

# Ketamine as Rescue Treatment for Difficult-to-Sedate Severe Acute Behavioral Disturbance in the Emergency Department

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**Study objective:** We investigate the effectiveness and safety of ketamine to sedate patients with severe acute behavioral disturbance who have failed previous attempts at sedation.

**Methods:** This was a prospective study of patients given ketamine for sedation who had failed previous sedation attempts. Patients with severe acute behavioral disturbance requiring parenteral sedation were treated with a standardized sedation protocol including droperidol. Demographics, drug dose, observations, and adverse effects were recorded. The primary outcome was the number of patients who failed to sedate within 120 minutes of ketamine administration or requiring further sedation within 1 hour.

**Results:** Forty-nine patients from 2 hospitals were administered rescue ketamine during 27 months; median age was 37 years (range 20-82 years); 28 were men. Police were involved with 20 patients. Previous sedation included droperidol (10 mg; 1), droperidol (10+10 mg; 33), droperidol (10+10+5 mg; 1), droperidol (10+10+10 mg; 11), and combinations of droperidol and benzodiazepines (2) and midazolam alone (1). The median dose of ketamine was 300 mg (range 50 to 500 mg). Five patients (10%; 95% confidence interval 4% to 23%) were not sedated within 120 minutes or required additional sedation within 1 hour. Four of 5 patients received 200 mg or less. Median time to sedation postketamine was 20 minutes (interquartile range 10 to 30 minutes; 2 to 500 minutes). Three patients (6%) had adverse effects, 2 had vomiting, and a third had a transient oxygen desaturation to 90% after ketamine that responded to oxygen.

**Conclusion:** Ketamine appeared effective and did not cause obvious harm in this small sample and is a potential option for patients who have failed previous attempts at sedation. A dose of 4 to 5 mg/kg is suggested, and doses less than 200 mg are associated with treatment failure. [Ann Emerg Med. 2016;■:1-7.]

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### INTRODUCTION

The sedation of agitated and aggressive patients in the emergency department (ED) and other acute care areas is a major problem for health care workers. Patients with acute behavioral disturbance may respond to verbal de-escalation or oral sedation, but a substantial proportion of this group requires parenteral sedation and mechanical restraint.<sup>1-5</sup> The majority of these patients will be sedated or tranquilized with parenteral sedation with an antipsychotic or benzodiazepine.<sup>1,3-6</sup> In a recent study, only 8% of patients were not sedated with 1 or 2 doses of droperidol, and only 3% after 3 doses.<sup>6</sup> However, this small number of patients with acute behavioral disturbance who remain difficult to sedate despite multiple doses of parenteral medications are highly problematic.<sup>7</sup> Although such patients are uncommon, they cause a significant

disruption and danger to the ED and consume time and resources required for other patients.

There is limited evidence available on the effective management of patients with acute behavioral disturbance when standard approaches to sedation with sedating antipsychotics and benzodiazepines have failed. Clinical practice guidelines do not cover the treatment options to manage repeatedly failed sedation. A number of agents have been suggested, including barbiturates, propofol, sedating antihistamines (diphenhydramine or promethazine), dexmedetomidine, and ketamine,<sup>7-10</sup> but there is little evidence to support one over another. Some clinicians may simply opt to intubate the patient, which is a last resort, resource intensive, and fraught with potential complications. To our knowledge, no previous studies have explored an alternative management for failed sedation of acute behavioral disturbance.

**Editor's Capsule Summary***What is already known on this topic*

Violent patients with agitated delirium can endanger themselves and emergency department staff.

*What question this study addressed*

Is ketamine a safe and effective rescue option when droperidol has failed to tranquilize violent, delirious patients?

*What this study adds to our knowledge*

In this prospective observational study, 49 of 1,296 agitated adults failed initial tranquilization attempts (usually with 2 doses of droperidol 10 mg intramuscularly) and received ketamine intramuscularly (median 300 mg). All but 5 were then adequately sedated, with minimal adverse effects.

*How this is relevant to clinical practice*

Ketamine is an effective rescue therapy for violent agitated delirium; however, this sample is too small to confirm its safety for this purpose.

The success of ketamine for the sedation of out-of-hospital patients<sup>11,12</sup> and those retrieved with psychiatric illness<sup>13</sup> suggests it may be a useful medication for difficult-to-sedate patients in the ED. We hypothesized that ketamine may be a safe and useful agent for the management of difficult-to-sedate patients in the ED.

**Goals of This Investigation**

The aim of the study was to investigate the effectiveness and safety of ketamine in severely agitated and aggressive patients in the ED when other parenteral sedation had failed on at least 2 occasions.

**MATERIALS AND METHODS****Study Design and Setting**

This was a subgroup analysis of difficult-to-sedate patients with severe acute behavioral disturbance, included from the Droperidol or Midazolam<sup>1</sup> (DORM II) study,<sup>6</sup> a prospective observational study of ED patients with acute behavioral disturbance who required parenteral sedation and physical restraint. Ethics approval was obtained from the Hunter New England Area Health Service Human Research Ethics Committee and the Metro South Health Service District Human Research Ethics Committee to cover all hospitals involved. Patients required immediate sedation for

patient and staff safety, and because of the lack of the patients' decisionmaking capacity, consent was waived because medical treatment was provided as a duty of care.

Both this analysis and DORM II were observational studies of a clinical protocol in which ketamine (this analysis) or droperidol (DORM II) was administered as part of that protocol. They were not clinical trials, so a clinical trials notification was not required. Although this analysis used a subgroup of patients from the DORM II study, it was not simply a retrospective review of the DORM II data. Ketamine was introduced by clinicians at the 2 hospitals in December 2011, with the intention of prospectively analyzing patients who received ketamine.

Patients were included in this analysis from 2 adult metropolitan hospitals of the 6 hospitals involved in the DORM II study.<sup>6</sup> These 2 hospitals were used because they are teaching hospitals that have clinical toxicology services providing advice on difficult-to-sedate patients, and the clinician investigators at these 2 hospitals made a decision to use ketamine if droperidol failed. In addition, both hospitals had the highest recruitment rate to DORM II, and in one there was consecutive recruitment of all cases. The first hospital is a medium-sized urban hospital with a tertiary toxicology unit and drug and alcohol service, and has twice the number of patients presenting with acute behavioral disturbance compared with most EDs.<sup>5</sup> The second hospital is a large tertiary adult referral hospital with 60,000 presentations each year, has a dedicated toxicology service, and has a similar number of presentations with acute behavioral disturbance.

**Selection of Participants**

Patients (>16 years) with acute behavioral disturbance were recruited as part of the DORM II study from the 2 EDs if they required physical restraint and parenteral sedation and had a score of 2 to 3 on the Sedation Assessment Tool (Table E1, available online at <http://www.annemergmed.com>).<sup>14</sup> Patients who could be settled (ie, Sedation Assessment Tool score 0 or 1) with verbal de-escalation or oral medication were excluded. Any patients who then remained agitated and aggressive after their initial sedation and received ketamine as additional sedation were included in this analysis. A standardized protocol was used for all patients with acute behavioral disturbance in the 2 EDs, which recommended two 10-mg doses of droperidol. However, in a minority of cases the protocol was not followed, so either fewer doses of droperidol were given or benzodiazepines were used. In some cases, after consultation with the on-call clinical toxicologist a third dose of droperidol was given before ketamine. The aim was to review ketamine as a rescue treatment, so we included all

cases in which there was an initial failure of sedative medication. Patients were included from December 2011 until February 2014.

### Interventions

In the DORM II study, all patients with acute behavioral disturbance were managed with a standardized protocol that included the administration of intramuscular sedation and the assessment of the level of sedation or agitation with the Sedation Assessment Tool.<sup>6,14</sup> The protocol recommended starting with a 10-mg dose of intramuscular droperidol for parenteral sedation, and if the patient is not sedated within 15 minutes a second dose of 10 mg droperidol was given. Patients who were not sedated after 30 minutes were discussed with the on-call clinical toxicologist at each site, and from December 2011 ketamine was used in the majority of cases as the third-line agent. The clinical toxicologists decided on an intramuscular dose of ketamine of 4 to 6 mg/kg, based on intramuscular use in other settings.<sup>10,15,16</sup> Rarely, droperidol was not used as the first-line agent. This usually occurred when new junior or training medical staff did not consult the clinical toxicologist. In one case, only a single dose of droperidol was given before ketamine.

All patients were observed in a critical care area and had pulse rate, pulse oximetry, respiratory rate, and blood pressure recorded every 5 minutes for the first 20 minutes and then every 30 minutes for the next 2 to 4 hours. The level of agitation or sedation was measured with the Sedation Assessment Tool score.<sup>14</sup> This score is used routinely in both EDs and assesses the degree of agitation or sedation as a score of 3 (physically violent) to -3 (unconscious).

### Data Collection and Processing

All observations were recorded on a purpose-designed acute behavioral disturbance chart by the treating medical and nursing staff, which was part of the patient's medical record. It included patient demographics (age and sex), reason for presentation, method of arrival, drug administration details (dose and timing), sedation scores, vital signs (pulse rate, blood pressure, respiratory rate, and oxygen saturations), and adverse effects. This information was then entered into a relational database (Microsoft Access 2010; Microsoft, Redmond, WA) by a single researcher who collected all cases for DORM II daily for data entry. This researcher identified all cases of ketamine administration prospectively as they were entered into the database.

### Primary Data Analysis

The primary outcome for the study was the number of patients who failed to achieve sedation within 120 minutes of ketamine administration or required further sedation within 1 hour of ketamine. A number of other outcomes were included: (1) the time to sedation from the initial onset of acute behavioral disturbance, defined as a decrease in the Sedation Assessment Tool score by 2 levels or a score of zero or less; (2) the time to sedation after the administration of ketamine; and (3) any adverse effects (airway obstruction, oxygen saturation less than 90%, respiratory rate less than 12 breaths/min, new-onset arrhythmia, and systolic blood pressure less than 90 mm Hg). In addition, the change in pulse rate and blood pressure after ketamine administration was measured.

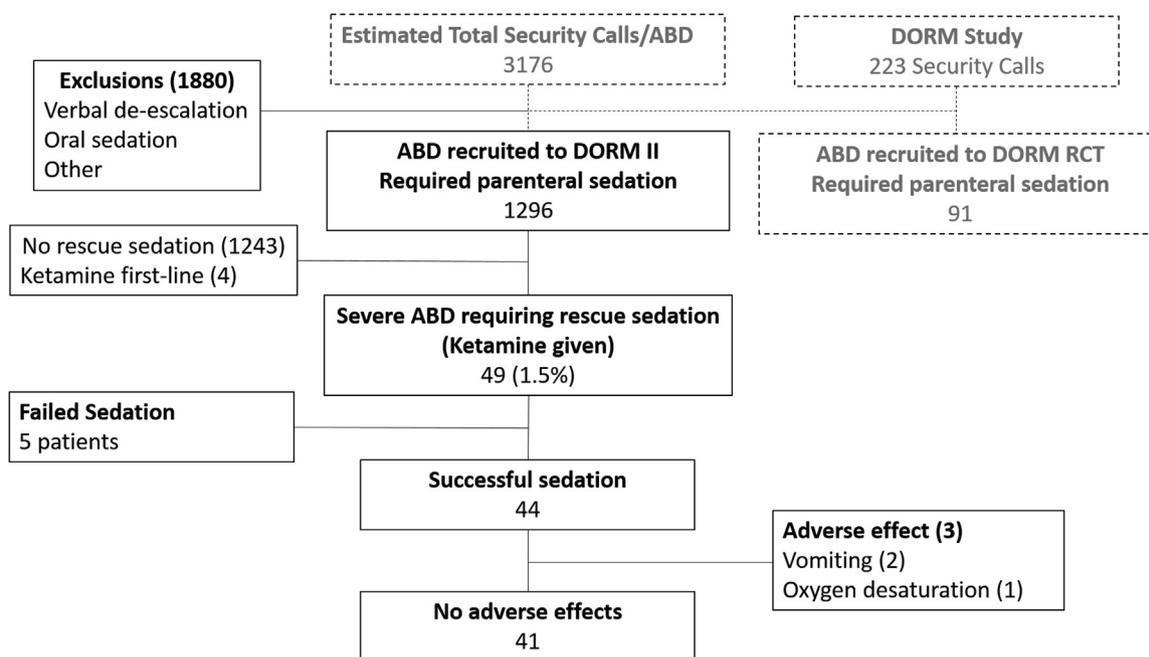
Continuous variables were summarized as medians, interquartile ranges (IQRs), and ranges, and dichotomous outcomes were reported with 95% confidence intervals. All analyses and graphics were conducted with GraphPad Prism (version 6.03; GraphPad Software, San Diego, CA).

### RESULTS

There were 1,296 patients sedated as part of the DORM II protocol at the 2 hospitals during the 27-month period. Of these, 53 patients (4%) received ketamine as part of their sedation. Four of these patients received ketamine without any previous sedation, leaving 49 patients who received ketamine after the failure of previous parenteral sedation (Figure). Three of the 4 patients were sedated by ketamine, 2 at 10 minutes and 1 at 20 minutes. The fourth patient received only 30 mg ketamine and then a further 30 mg 85 minutes later and did not settle for 5 hours. One of the 4 patients had a dystonic reaction after droperidol, but none had any adverse effects after ketamine.

Of the 49 patients, there were 28 men (57%) and the median age was 37 years (range 20 to 82 years). Police were required to assist with the transport of 20 patients to the hospital (41%). Droperidol alone was administered before ketamine in 46 patients (10 mg [1], 10+10 mg [33], 10+10+10 mg [11], and 10+10+5 mg [1]), whereas a combination of droperidol, diazepam, and midazolam was given in 2 patients and midazolam alone in 1 (Table). The median dose of ketamine used was 300 mg (IQR 200 to 400 mg; range 50 to 500 mg).

Five patients (10%; 95% confidence interval 4% to 23%) were not sedated within 120 minutes (1), required additional sedation within 1 hour (1), or both (3). The doses administered in these 5 patients were 100, 150, 150, 200, and 400 mg. One of the 5 patients receiving 200 mg ketamine remained severely agitated for



**Figure.** Flowchart of the patients recruited to DORM II and those included in this subgroup analysis. An estimate of the total number of patients with acute behavioral sedation is included according to the number reported in the DORM study and then randomized to parenteral sedation.<sup>1</sup> ABD, Acute behavioral disturbance; RCT, randomized controlled trial.

12 hours (overnight) and was given no further sedation. Unfortunately, the clinical toxicologist was not notified about this patient again until the following morning.

The median time to sedation from the onset of acute behavioral disturbance was 60 minutes (IQR 40 to 140 minutes; range 20 to 540 minutes). The median time

**Table.** Baseline characteristics and sedative medications given to the patients.

Demographics/Characteristics	Number	%
Age, median (IQR), y	37 (20–82)	
Male patient (%)	28	57
<b>Reason for presentation</b>		
Deliberate self-poisoning*	16	33
Psychosis	14	29
Intoxicated	8	16
Psychostimulants	7	14
Medical cause	3	6
Dementia	1	2
Brought in by police	20	41
<b>Sedation before ketamine (mg)</b>		
Droperidol (10)	1	2
Droperidol (10×2)	33	67
Droperidol (10×3)	11	22
Droperidol (25)	1	2
Droperidol (30)+midazolam (75)	1	2
Droperidol (20)+diazepam (10)+midazolam (10)	1	2
Midazolam (15)	1	2

IQR, Interquartile range.

\*Intentional overdose.

to sedation postketamine was 20 minutes (IQR 10 to 30 minutes; range 2 to 500 minutes). Three patients were re-sedated with ketamine 4 to 24 hours after the initial dose.

There were adverse effects in 3 patients after ketamine (6%). Two patients had vomiting (one treated with intramuscular metoclopramide 10 mg) and the third had an episode of oxygen desaturation to 90% without airway obstruction 40 minutes after ketamine, which immediately responded to oxygen, with no further problems. No patient had laryngeal spasm. One patient developed hypotension before ketamine but after droperidol.

There were 43 patients who had a preadministration systolic blood pressure with a median of 130 mm Hg (IQR 115 to 146 mm Hg; range 100 to 195 mm Hg). Blood pressures were measured a median of 15 minutes (2 to 120 minutes) postadministration, with a median change in systolic blood pressure of +5 mm Hg (IQR –3 to 23 mm Hg; range –47 to 38 mm Hg). No patients were hypotensive and 3 patients had a systolic blood pressure greater than 180 mm Hg (181, 183, and 198 mm Hg), but all had blood pressure greater than 140 mm Hg before ketamine (181, 149, and 174 mm Hg). There were 45 patients with pre- and post-pulse rate measurements with a median change of 0 beats/min (IQR –13 to 11 beats/min; range –60 to 30 beats/min).

## LIMITATIONS

Our study is limited by its sample size. Although ketamine administration was associated with no serious adverse events, larger samples would be required to reliably confirm its safety profile. The study had a relatively small heterogeneous patient sample and the inability to prevent the occasional variation in the treatment protocol. Although the majority of patients had 2 administrations of droperidol before ketamine, this was not always the case, with some receiving 1 or 3 doses and some receiving benzodiazepines. However, the aim was to assess ketamine as a rescue medication, not only after droperidol.

There was also some variability in the timing between droperidol doses and ketamine administration. This meant that it is not possible to determine whether the ultimate sedation of the patient was a result of the ketamine, delayed response to the initial medication (mainly droperidol), or both. There is some support for the sedation being due to ketamine because the median total time to sedation (from the initial onset of acute behavioral sedation) was 55 minutes, which is much longer than the median time in the DORM II study of 20 minutes.<sup>6</sup> However, the median time to sedation after ketamine administration in this analysis was 20 minutes, the same as the median time to sedation in DORM II, suggesting that the sedation was due to ketamine.

Another potential limitation was that we present a subgroup analysis of patients from the DORM II study, and therefore the outcomes and data collection were designed to assess droperidol and not ketamine. However, after the introduction of ketamine in the 2 hospitals, the investigators planned a priori to prospectively assess the safety and effectiveness of ketamine by using the DORM II study infrastructure.

The study environment of the ED is a limitation of our study, and caution should be exercised in regard to generalizing it to areas that do not have ready access to critical care monitoring and medical staff. It would not be appropriate for ketamine to be used for acute behavioral disturbance on general wards or in psychiatric settings. However, recent reports have demonstrated the safety and effectiveness of ketamine for sedation in other environments, such as out-of-hospital transport, as well as in retrieval of psychotic patients.<sup>11-13,17,18</sup>

## DISCUSSION

This study reports the clinical use of ketamine in 49 patients with severe acute behavioral disturbance who could not be sedated with high-dose droperidol or, in a few cases, droperidol and benzodiazepines. Only 10% of the 49

patients could not be sedated within 2 hours or required additional sedation, which is only a very small proportion of the initial 1,296 patients who required sedation. There were only 3 adverse effects, 2 minor and the other easily treated with oxygen.

The major reason for failure of ketamine appeared to be the use of smaller doses, with 4 of 5 patients receiving 200 mg or less. The aim was to use 4 to 6 mg/kg, but in some cases staff decided to administer only half of the dose because of concerns about oversedation. However, larger doses of ketamine are not necessarily associated with oversedation, although they are associated with other adverse effects such as emergence phenomena.<sup>19</sup>

Although “nightmares” and recovery agitation are commonly reported in adult patients when ketamine has been administered for other indications, this was not reported in our series.<sup>16,19</sup> It is possible that it was difficult to distinguish agitation associated with ketamine from the agitation already present in the patient. However, in the majority of cases no more medication was given to the patient after ketamine, and the patient settled for more than an hour and in most cases woke normally. The other concern with ketamine is the well-reported increase in blood pressure and pulse rate after administration. However, in our study there were only minor increases in both after administration. This may be due to an excess of endogenous sympathomimetic substances being present because of the agitation, therefore limiting further release of endogenous monoamines by ketamine. Hopper et al<sup>20</sup> also reported only minor increases in blood pressure and pulse rate.

Benzodiazepines are the other obvious choice for difficult-to-sedate patients. However, there is increasing evidence that benzodiazepines alone<sup>3,21,22</sup> and combinations of benzodiazepines and antipsychotics are associated with higher rates of adverse effects.<sup>1,6</sup> Both the DORM and DORM II studies found a higher rate of adverse effects with airway obstruction, oxygen desaturation, and hypotension than antipsychotics alone.<sup>1,6</sup> A systematic review found that the addition of a benzodiazepine to haloperidol for psychosis-induced aggression provided no additional benefit but was associated with increased risk of harm.<sup>23</sup> The additional use of ketamine after droperidol for difficult-to-sedate patients with severe acute behavioral disturbance appears to provide a safer option in this patient group compared with the combination of droperidol and benzodiazepines.

There is one other recent study of ketamine in the ED by Hopper et al.<sup>20</sup> This study reviewed 32 patients given ketamine for acute agitation from 459 patients given ketamine in the ED during a 7-year period. Ketamine was

administered intravenously and intramuscularly, and in almost half of the patients it was given without previous sedative medication. The median dose administered intramuscularly was 200 mg, with an IQR of 150 to 200 mg. There was a much higher failure rate in this study, with 16 of 32 patients (50%) requiring further sedation within an hour. The results of this study support our suggestion that lower doses of ketamine are associated with a higher failure rate. In addition, Hopper et al<sup>20</sup> reported a similar low adverse event rate.

The major difference between our study and that by Hopper et al<sup>20</sup> was that ketamine was not administered as part of a standardized sedation protocol. Our study was undertaken as part of a much larger study of more than 1,000 patients requiring parenteral sedation. The majority of the patients were sedated with droperidol, which was safe and effective.<sup>6</sup> We then focused on the small group of patients who were not sedated, and this study now provides evidence that ketamine is an appropriate third-line agent to be used in these patients. There is one recent study of 5 adolescents (aged 14 to 18 years) who were sedated with intramuscular or intravenous ketamine, which again had similar outcomes. Ketamine was administered initially in some cases or after other attempts had failed.

There are an increasing number of studies of ketamine use in the out-of-hospital setting for agitated and difficult-to-sedate patients.<sup>11,12,17,18</sup> These include a variety of reasons to sedate, most commonly trauma, and a mixture of intravenous and intramuscular use. These studies provide further support for the safety of ketamine. However, a significant proportion of patients receiving out-of-hospital ketamine have to be intubated on arrival to the ED.<sup>12</sup>

Ketamine appears to be a reasonable third-line agent in the sedation of patients with acute behavioral disturbance. The recommended dose is 4 to 6 mg/kg, which should be administered intramuscularly in a critical care area. Further research is required to define its use in settings outside of the ED for severe behavioral disturbance.

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Author contributions: GKI, LAC, and CBP designed the study. LAC entered the data. All authors recruited or supervised recruitment of patients and were responsible for data collection. GKI performed a data audit, analyzed the data, and wrote the first draft of the article. All authors contributed to the final article. GKI takes responsibility for the paper as a whole.

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**Table E1.** Sedation Assessment Tool.

<b>Score</b>	<b>Responsiveness</b>	<b>Speech</b>
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/cooperative	Speaks normally
-1	Asleep but rouses if name is called	Slurring or prominent slowing
-2	Responds to physical stimulation	Few recognizable words
-3	No response to stimulation	Nil