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The Reemergence of Ketamine for Treatment in Critically Ill Adults

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Objectives: To assess the evidence and discuss the risks and clinical relevance of ketamine for the treatment of various disease states impacting the adult critically ill population.

Data Sources: A literature review was performed using PubMed evaluating primary literature published until August 2018.

Study Selection: Case reports, observational studies (cohort, case-control), and randomized controlled trials involving patients 18 years and older in a nonperioperative setting using either IV or intramuscular ketamine were included for analysis. Uses of ketamine discussed focused on critically ill patients in the ICU and emergency department settings.

Data Extraction: Included studies were evaluated for dosing, outcomes, and adverse effects of ketamine. For each study, the design, population, intervention, investigated outcomes, and results were assessed.

Data Synthesis: The evidence was organized according to use of ketamine, which included pain, sedation, status asthmaticus, alcohol withdrawal syndrome, status epilepticus, and acute behavioral psychologic disturbances. Evaluation of the evidence was based on the included primary literature along with any related guideline recommendations.

Conclusions: Ketamine has suggested potential benefit in several disease states impacting critically ill patients including pain, alcohol withdrawal syndrome, status epilepticus, and acute agitation. Further supporting evidence is needed to validate its use in the setting of critical illness. (*Crit Care Med* 2020; XX:00–00)

Key Words: alcohol withdrawal; ketamine; mechanical ventilation; pain; status asthmaticus; status epilepticus

BACKGROUND

Ketamine is a well-known anesthetic with sedative and analgesic properties historically used during medical procedures and in the postoperative setting. Clinical experience in humans began in the 1960s when ketamine was used during surgical interventions at the University of Michigan. It attained U.S. Food and Drug Administration approval in 1970, gaining popularity for its profound analgesia and preservation of airway reflexes (1). A short-acting derivative of phencyclidine, ketamine is one-tenth the potency of its parent compound and exhibits dissociative effects by perpetuating a dream-like detachment from the environment (1, 2). Despite potential for abuse and adverse neuropsychiatric reactions, recent literature has expanded our understanding of ketamine's unique pharmacology and explores utilizing its analgesic, sedative, anti-inflammatory, and antidepressant effects for many off-label indications (3). This review aims to summarize several of the emerging off-label indications for ketamine in the critically ill. The more familiar uses of rapid sequence intubation and procedural sedation are beyond the scope of this review and will not be discussed. Utilization of the Strength of Recommendation Taxonomy criteria will be applied for ketamine use in each disease state discussed (**Appendix**, Supplemental Digital Content 1, http://links.lww.com/CCM/F375) (4).

PHARMACODYNAMICS

Commonly marketed as a racemic mixture, the S(+) and R(–) enantiomers of the parent compound, as well as its primary metabolites ([R,S]-norketamine and [2R,6R;2S,6S]-hydroxynorketamine), play important roles in ketamine's pharmacology. Although incompletely understood, ketamine's versatility may be owed to its numerous sites of activity with most of its known therapeutic properties—particularly anesthesia and analgesia—largely the result of noncompetitive inhibition of N-methyl-D-aspartate (NMDA) receptors (NMDARs) (1, 2). S(+)-ketamine is twice as potent as the racemic mixture and exhibits four times the affinity for the phencyclidine binding site of NMDAR compared with R(–)-ketamine. The result is dissociation manifesting as catatonia and amnesia

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while preserving laryngeal reflexes at subanesthetic IV doses. Antagonism of NMDAR also results in analgesic and antidepressant effects, the latter influenced more by R (–)-ketamine and the hydroxynorketamine metabolites. Analgesia may also be mediated through serotonin and norepinephrine activation and opioid-receptor agonism by ketamine (S[+] > R[–]) and norketamine, and is useful in opioid-induced hyperalgesia by decreasing the so-called "wind-up" phenomenon associated with repeated stimuli (5). Gamma-aminobutyric acid (GABA) activity may be either enhanced or antagonized by ketamine through augmentation of $GABA_A$ receptors and decreasing GABA uptake or by disinhibition of GABA release via NMDAR blockade, respectively (2, 5). The relevance of GABAergic effects is uncertain since doses larger than those used clinically are needed; however, premedication with benzodiazepines may attenuate ketamine-associated delirium suggesting an antagonistic effect on GABA. Ketamine binds both nicotinic and muscarinic acetylcholine receptors (AChRs). Blockade of the α7 nicotinic AChR, as well as direct and indirect effects on monoamines (dopamine, serotonin, norepinephrine), are proposed to be involved in its role as an antidepressant (2).

Blockade of catecholamine reuptake makes ketamine a favorable alternative to anesthetics with negative hemodynamic profiles; however, hypertension and tachycardia can also occur. As such, providers should exercise caution in patients with coronary artery disease, preexisting hypertension, and certain neurologic conditions where elevations in intracranial pressure (ICP) would be harmful (6–8). Despite the sympathomimetic potential, ketamine's myocardial depressant effects can be unmasked in states of catecholamine depletion (e.g., acute heart failure) resulting in hypotension and bradycardia (1, 9). Furthermore, neurologic effects (e.g., delirium, hallucinations, nightmares) are common and associated with well-described emergence reactions.

TABLE 1. Pharmacokinetic Properties of Ketamine (1–3, 5, 58, 59)

Properties	Values
Bioavailability	
Intramuscular	93%
Intranasal	25–50%
Oral	20–25%
Onset of action	
Intramuscular	3–4 min
IV	30 s
Intranasal	10 min
Half-life	
Distribution	10 min
Elimination	2–3 hr
Duration	
Intramuscular	12–25 min; recovery 3–4 hr
IV	5–10 min; recovery 1–2 hr
Intranasal	Up to 60 min
Distribution	
Volume of distribution	2.4 L/kg
Protein binding	20–50%
Metabolism/elimination	
Hepatic	N-demethylation to norketamine (20–30% activity; half-life 5.32 hr) via CYP3A4 (major) and CYP2B6, CYP2C9 (minor)
Excretion	Urine (91%); feces (3%)

PHARMACOKINETICS

Its pharmacokinetic properties make ketamine an attractive agent for use in the critical care setting (**Table 1**). Depending on the route of administration, ketamine typically exhibits a rapid onset of action (1, 5, 10). It undergoes clearance via cytochrome P450-mediated mechanisms (CYP 2B6, 2C9, 3A4), which can be altered in the setting of hepatic impairment and interacting medications. In the general population, the elimination half-life is approximately 2–3 hours. Once metabolized hepatically via N-dealkylation, norketamine can be 33% as potent as the parent compound, leading to potential prolonged clinical effects. Ketamine is lipophilic with limited protein binding, allowing for easier distribution into the CNS (5).

POTENTIAL USES FOR KETAMINE

Evidence for each off-label use is displayed within **Table 2**.

Acute Pain Management

Rationale. Many studies investigating ketamine for pain management include patients presenting to the emergency department (ED). There are limited pain management recommendations for ketamine in nonoperative settings in the ICU, outside of those resulting from a randomized, double-blind study, which demonstrated a reduction in morphine consumption ($p < 0.05$) without a significant difference in pain score at 24 or 48 hours compared with morphine (11–13). Additionally, there was lower mean morphine equivalent use ($p = 0.015$) in a retrospective, case-control cohort involving 30 ICU patients (14). Due to ketamine's effects on delta-, kappa-, and mu-opioid receptors in addition to NMDA inhibition, there is increasing interest in its utilization for acute pain.

Evidence. The majority of studies use a variety of ketamine doses, including weight-based and fixed-dosed, for pain (15–23), showing it may reduce pain scores by at least 3 on a numeric pain scale out of 10 (19, 21–24). Ketamine has demonstrated pain score reduction similar to morphine, although duration of effect may be shorter (22–24).

Risks. Although multiple studies discussed report more adverse effects with ketamine compared with control groups, the low severity of these effects did not require an

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TABLE 2. Primary Literature Reviewing Ketamine

References	Study Design	Patient Population	Intervention	Comparison	Outcomes
Pain (level 2 evidence for ED setting)					
Guillou et al (12)	RCT, DB	Adult surgical ICU patients following major abdominal surgery requiring postoperative and ventilation management on morphine 1 mg/mL PCA	Ketamine 0.5 mg/kg followed by 0.12 mg/kg/hr for first 24 hr then 0.06 mg/kg/hr for following 24 hr ($n = 41$)	Placebo ($n = 52$) Morphine 1 mg every 7 min was allowed in both groups	Mean morphine consumption 58 ± 35 mg in ketamine group vs 80 ± 37 mg in morphine group at 48 hr, with mean consumption of morphine between group of 22 ± 8 mg ($p < 0.05$) No significant differences in pain using Visual Analog Scale (on 100 mm scale) at 24 and 48 hr
Walters et al (14)	RR	Adult ICU patients receiving standard-of-care hydromorphone PCA with any level of pain (on a 10-point scale), ≥ 1 rib fracture, and Injury Severity Score > 15	Ketamine 0.1 mg/kg/hr with optional 0.1 mg/kg bolus every 2 hr for severe pain (group selected at provider's discretion; $n = 15$)	Standard-of-care ($n = 15$) All patients received additional analgesic therapies	Average pain score 5.8 vs 2.1 in ketamine group ($p < 0.001$). Average pain score was 7 pre-ketamine vs 4.1 post-ketamine ($p < 0.001$) Mean morphine equivalent 3.5 ± 0.8 mg/hr vs 2.5 ± 0.5 mg/hr in ketamine group ($p = 0.015$) No significant difference for ICU or hospital LOS
Ahern et al (18)	Prospective, observational	Adult ED patients with moderate to severe pain (score 5 or higher on NRS on 10-point scale) ($n = 38$)	Ketamine 15 mg IV push then 20 mg IV infusion over 1 hr Adjunctive 4 mg IV morphine if pain reported	None	Median reduction in pain scores were by 3 in 10 min, and 5 in 30 min. At 60 min, the median pain score was 5 and 4 in 120 min from a baseline score of 9 For 12 patients receiving ketamine alone, percentage of patients experiencing clinically significant decrease of 3 or more was 75% at 10 min, 100% at 60 min, and 83% at 120 min. Ketamine group had lower median NRS pain scores
Beaudoin et al (19)	DB, PC, RCT	Adult ED patients (20 in each group) with at least moderate pain score (score ≥ 5 on NRS on a 10-point scale) with pain duration < 7 d ($n = 60$)	Group 1: morphine + 0.15 mg/kg ketamine Group 2: morphine + 0.3 mg/kg ketamine All morphine doses were 0.1 mg/kg up to 10 mg. Rescue morphine was dosed at 0.05–0.1 mg/kg as frequently as every hour	Standard care: morphine + 0.9% NS placebo	Summed pain-intensity difference was 7 (4.3–10.8) and 7.8 (4.8–12.8) in groups 1 and 2, respectively, compared with 4 (1.8–6.5) in standard care group. Greater number of patients in groups 1 and 2 were treatment responders

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TABLE 2. (*Continued*). Primary Literature Reviewing Ketamine

References	Study Design	Patient Population	Intervention	Comparison	Outcomes
Bowers et al (20)	DB, PC, RCT	Adult ED patients reporting pain score ≥ 6 (on a 10-point scale) after initial dose of opioid analgesia ($n = 116$)	Ketamine 0.1 mg/kg over 1 min ($n = 53$) Rescue medication was 0.05 mg/kg morphine or equivalent dose	0.9% normal saline ($n = 63$)	Ketamine patients had a 0.65 lower mean pain score ($p < 0.05$) Mean satisfaction score (on a 4-point Likert scale with 0 being "completely unsatisfied" and 3 being "very satisfied") was 2.66 ± 0.67 in the ketamine group vs 2.52 ± 0.5 in the control group (p = not reported) Total opioid usage was 9.95 ± 5.83 mg in the ketamine group vs 12.81 ± 6.81 ($p = 0.02$)
Motov et al (21)	DB, RCT	Adult ED patients with acute abdominal, flank, back, traumatic chest, or musculoskeletal pain with pain score ≥ 5 on a 10-point scale ($n = 48$)	Group 1: ketamine 0.3 mg/kg IV push over 5 min ($n = 24$) Rescue medication was morphine 0.1 mg/kg	Group 2: ketamine 0.3 mg/kg IV infusion over 15 min ($n = 24$)	Adverse effect rates via the Side Effects Rating Scale for Dissociative Anesthetics were similar between groups except regarding unreality which was higher in the push group (91.7% vs 54.2%; $p = 0.008$) Mean pain decreased by 5.17 ± 3.53 in group 1 compared with 5.75 ± 3.48 in group 2 ($p = 0.026$)
Miller et al (22)	DB, RCT	Adult ED patients with abdominal, flank, low back, or extremity pain with moderate to severe pain on a 10-point scale ($n = 45$)	Ketamine 0.3 mg/kg (maximum dose 25 mg) IV infusion over 5 min ($n = 21$) Could receive second rescue dose 20 min later	Morphine 0.1 mg/kg (maximum dose 8 mg) IV infusion for 5 min ($n = 24$)	Maximum change in NRS pain score, from baseline, was 4.9 (95% CI, 5.8–4) in ketamine vs 5 (95% CI, 6.6–3.5) in morphine group Time to achieve maximum change in NRS score was 5 min in ketamine vs 100 min in morphine group Second dose was administered in 54% of ketamine and 38% in morphine group ($p = 0.37$)
Motov et al (23)	DB, RCT	Adult ED patients with acute (≤ 7 d) abdominal, flank, back, or musculoskeletal pain ≥ 5 on a 11-point scale ($n = 45$)	Ketamine 0.3 mg/kg IV over 3 to 5 min ($n = 45$) Rescue medication was fentanyl 1 μg/kg IV if score ≥ 5	Morphine 0.1 mg/kg IV over 3 to 5 min ($n = 45$)	Comparative difference in pain score at 30 min was 0.2 (95% CI, −1.19 to 1.46; $p = 0.97$) Complete resolution of pain was achieved in 44% for ketamine vs 13% for morphine group at 15 min (difference, 31 min; 95% CI, 13.1–49.2 min); however, similar rates between groups for 30, 60, 90, and 120 min Higher number of patients in morphine group had reduction of ≥ 3 NRS points No significant difference between group for rescue medication use; except at 120 min (29% in ketamine vs 12% in morphine group [difference, 17; 95% CI, 0.8–43.2])

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TABLE 2. (*Continued*). Primary Literature Reviewing Ketamine

References	Study Design	Patient Population	Intervention	Comparison	Outcomes
Mitchell and Fallon (24)	DB, RCT	Patients diagnosed with critical limb ischemia secondary to peripheral vascular disease if no further vascular reconstruction was possible was possible or if there was unavoidable delay in proposed surgical intervention of at least 7 d with "average pain in last 24 hr" score ≥ 3 (on a 10-point scale) on Brief Pain Inventory scale ($n = 35$)	Ketamine 0.6 mg/kg IV over 4 hr ($n = 18$) Opioid received prior to study: 34% codeine-based product, 6% tramadol, 43% morphine, and 11% morphine with codeine products	0.9% NS over 4 hr ($n = 17$)	Mean decrease from baseline to 24 hr after infusion was 0.8 in ketamine group vs 0 in placebo (0.9; 95% CI, −0.6 to 2.3; $p = 0.233$) Significant difference in patient estimation of pain relief favoring ketamine (15% vs −2%; $p = 0.047$) and on enjoyment of life ($p = 0.004$)
Adjunctive analgosedation in mechanical ventilation (level 3 evidence)					
Buchheit et al (29)	RR	Mechanically ventilated adults receiving continuous infusion opioids that met a safety screen for spontaneous breathing trial ($n = 40$)	Median ketamine maintenance dose was 0.3 mg/kg/hr (IQR, 0.21–0.3 mg/kg/hr) for a median of 1.89 d (IQR, 0.96–3.06 d)	Pre- and post-ketamine initiation	Average ME infusion rate significantly decreased from 6.66 mg/hr (IQR, 3.33–10 mg/hr) to 0 mg/hr (IQR, 0–3.33 mg/hr) 24 hr after ketamine infusion ($p < 0.001$) Phenylephrine equivalent decreased from 70 mg/hr (25–95 mg/hr) to 40 mg/hr (0–80 mg/hr) 6 hr after ketamine ($p = 0.019$). Propofol requirements decreased from 150 mg/hr (80–200 mg/hr) to 32.5 mg/hr (0–150 mg/hr) 24 hr after ketamine ($p = 0.002$)
Pruskowski et al (30)	RR	Mechanically ventilated adult trauma patients ($n = 36$)	Average ketamine rate was 0.64 ± 0.39 mg/kg/hr during first 24 hr and 0.94 ± 0.62 mg/kg/hr between 48 and 72 hr	Pre- and post-ketamine initiation	Difference in median IV ME received before ketamine was 431.3 mg (IQR, 206.3–1012.4 mg) vs 272.5 mg (IQR, 52.5–772.5 mg; $p = 0.026$) 72 hr after ketamine initiation Difference in median dexmedetomidine dose was 0.5 μg/kg/hr before compared with 0.9 μg/kg/hr ($p = 0.002$), propofol 35.4 μg/kg/min before vs 22.8 μg/kg/min ($p = 0.002$), and midazolam 14.25 mg before compared with 17.25 mg ($p = 0.735$) at 72 hr

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TABLE 2. (*Continued*). Primary Literature Reviewing Ketamine

References	Study Design	Patient Population	Intervention	Comparison	Outcomes
Groetzinger et al (31)	RR	Mechanically ventilated adults receiving continuous sedation and SAS score of 3 or 4 at ketamine initiation ($n = 91$)	Median bolus dose was 30 mg (IQR, 25–50 mg) with a median starting dose was 0.1 mg/kg/hr (IQR, 0.2–0.25 mg/kg/hr). The median dose was 0.41 mg/kg/hr (IQR, 0.20–0.52 mg/kg/hr) Duration of infusion was 2.8 d (IQR, 1.9–4.9 d)	Pre- and post-ketamine initiation	Alternative sedatives were reduced or discontinued in 63% of patients within 24 hr of ketamine initiation Total fentanyl dose changed from 4,918 μg (IQR, 2,978–7,205 μg) before to 4,725 μg (IQR 2,350–7,500 μg) 48 hr after ketamine initiation Ketamine use had an increased number of Riker Sedation-Agitation Scale scores at goal compared with prior to initiation (61% vs 55%; $p = 0.001$)
Status asthmaticus (level 3 evidence)					
Howton et al (32)	DB, PC, RCT	Adult patients (18–65 yr), without a history of chronic obstructive pulmonary disease, hypertension, coronary artery disease, hyperthyroidism, or a psychiatric disorder, presenting to the ED with an acute asthma exacerbation and peak expiratory flow < 40% predicted following three albuterol 0.5 mg nebulizer treatments ($n = 44$)	Ketamine 0.1 mg/kg IV bolus over 5 min, followed by IV continuous infusion at 0.5 mg/kg/hr plus standard therapy ($n = 23$) Standard therapy: oxygen, continuous nebulized albuterol at 10 mg/hr, and methylprednisolone sodium succinate 125 mg IV	Normal saline placebo plus standard therapy ($n = 21$)	No significant between group difference in the primary outcome of change in forced expiratory volume in 1 s over 3 hr (absolute difference and associated p not reported)
Alcohol withdrawal syndrome (level 3 evidence)					
Wong et al (34)	RR	ICU patients ($n = 23$) Resistant AWS 19 (82.6%) Mechanically ventilated 6 (75.0%) DTs 10 (43.5%)	Ketamine initiated at ICU discretion Adjunct to symptom-triggered benzodiazepine (Riker SAS) Median Bolus: 0.3 mg/kg (38.1% of patients) Infusion: 0.2 mg/kg/hr (0.12–0.23 mg/kg/hr)	Pre- and post-ketamine initiation	No difference in 12- and 24-hr pre-post benzodiazepine requirements (−40 mg; $p = 0.11$ and −13.3 mg; $p = 0.33$, respectively) Mean ICU LOS 6.3 d Mean hospital LOS 12.3 d
Pizon et al (35)	RR	Nonintubated ICU patients diagnosed with DT ($n = 63$)	At DT diagnosis: Ketamine initiated at 0.15–0.3 mg/kg/hr + Symptom-triggered benzodiazepine (Withdrawal Assessment Scale protocol) ± Ketamine bolus 0.3 mg/kg	Pre- and post-guideline including Ketamine for DT	Decreased ICU LOS 2.83 d with ketamine (95% CI, −5.58 to −0.089; $p = 0.043$) Decreased likelihood of intubation with ketamine (OR, 0.14; 95% CI, 0.04–0.49) Decreased total benzodiazepine requirements in diazepam equivalent with ketamine (1,508.5 vs 2,525.1 mg; $p = 0.02$)

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TABLE 2. (*Continued*). Primary Literature Reviewing Ketamine

References	Study Design	Patient Population	Intervention	Comparison	Outcomes
Shah et al (36)	RR	ICU patients with resistant AWS ($n = 30$) (Clinical Institute Withdrawal Assessment for Alcohol ≥ 20 AND diazepam equivalent > 40 mg in 1 hr) Mechanically ventilated 16 (53.3%)	Ketamine initiated at 0.5 mg/kg/hr (maximum dose of 4.5 mg/kg/hr) Adjunct to lorazepam infusion (± mechanical ventilation) ICU discretion	Pre- and post-ketamine initiation	Decreased benzodiazepine requirement 24 hr post-ketamine (14.3 vs 10 mg/hr; $p < 0.05$) Initial symptom control within 1 hr of ketamine initiation 30 (100%) Six patients intubated after ketamine; median time to intubation 8.5 hr (IQR, 5–12 hr) ICU LOS 8.2 ± 2.4 d Hypertension 2 (6.7%)
Status epilepticus (level 3 evidence)					
Gaspard et al (39)	RR	Refractory status epilepticus ($n = 60$) 46 (80%) adults 34 (57%) unknown etiology 11 (18%) nonanoxic brain injury 7 (12%) postanoxic brain injury	No standard intervention Median infusion: 2.75 mg/kg/hr (0.05–10 mg/kg/hr) ± Bolus (median 1.5 mg/kg; max 5 mg/kg)	None	Likely response 7 (12%) Possible response 12 (20%) Higher likelihood of response found with fewer concomitant antiepileptic present at ketamine initiation (4 vs 8; $p < 0.01$) Decreased mortality in younger age and patients achieving response to ketamine ($p = 0.001$ and $p < 0.001$, respectively)
Agitation/excited delirium (level 3 evidence)					
Keseg et al (44)	RR	Adult patients who received ketamine for sedation in a prehospital setting ($n = 35$)	Ketamine 4 mg/kg intramuscular ($n = 29$)	Ketamine 2 mg/kg IV ($n = 4$) Two patients received intramuscular followed by IV	Prehospital records noted improvement in patient condition in 91% (95% CI, 77–98%) of patients
Riddell et al (45)	Prospective, observational	Acutely agitated ED patients 18–65 yr old requiring chemical sedation ($n = 98$)	Ketamine (IV or intramuscular) ($n = 24$) Mean doses: ketamine 0.87 mg/kg IV, 2.97 mg/kg intramuscular	Midazolam (IV or intramuscular) ($n = 17$) vs lorazepam (IV or intramuscular) ($n = 33$) vs haloperidol (intramuscular) ($n = 14$) or haloperidol + benzodiazepine ($n = 10$) Mean doses: midazolam 3.08 mg IV, 2.25 mg/g intramuscular; lorazepam 1.9 mg IV, 2.4 mg intramuscular; haloperidol 5.71 mg intramuscular	Patients who received ketamine had significantly lower agitation scores at 5, 10, and 15 min after receiving medication ($p = 0.001$, $p \leq 0.001$, $p = 0.032$)

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TABLE 2. (*Continued*). Primary Literature Reviewing Ketamine

References	Study Design	Patient Population	Intervention	Comparison	Outcomes
Cole et al (46)	Prospective, observational	Adult patients requiring chemical sedation for profound agitation defined as AMSS +4 (combative, very violent, or out of control) in a prehospital setting. AMSS scale ranges from +4 (combative/violent) to −4 (no response to mild shaking) ($n = 49$)	Ketamine 5 mg/kg intramuscular	None	Median time to sedation (AMSS ≤ +1 or anxious/restless) was 4.2 min (95% CI, 2.5–5.0 min; range, 1–25 min)
Parsch et al (47)	RR	Adult patients with acute severe mental illness and agitation requiring transport in a prehospital setting ($n = 78$)	Ketamine IV 0.25–0.5 mg/kg followed by 1–2 mg/kg/hr titrated to clinical response (post-guideline implementation; $n = 28$)	No ketamine (pre-guideline implementation; $n = 50$)	Patients requiring intubation before and after the implementation of the ketamine guideline was 36% of patients intubated before compared with 7.14% after (OR, 0.14; 95% CI, 0.02–0.81; $p < 0.01$)
Cole et al (48)	Prospective, observational	Adult patients requiring chemical sedation for severe acute undifferentiated agitation defined as AMSS +2 (anxious, agitated) or +3 (very anxious, agitated, mild physical element of violence) in a prehospital setting ($n = 146$)	Ketamine 5 mg/kg intramuscular ($n = 64$)	Haloperidol 10 mg intramuscular ($n = 82$)	Median time to sedation (AMSS ≤ +1 or anxious/restless) was 5 min for ketamine and 17 min for haloperidol ($p < 0.0001$)
Olives et al (49)	RR	Patients ≥ 18 yr old who received intramuscular ketamine for profound agitation in a prehospital setting ($n = 135$)	Ketamine 5 mg/kg intramuscular (based on estimated weight) "High dose" (> 5 mg/kg) or "low dose" (≤ 5 mg/kg)		63% of all patients were intubated; ketamine dose did not significantly differ between intubated and nonintubated patients (median 5.25 mg/kg and 5.14 mg/kg, respectively)

AMSS = Altered Mental Status Scale, AWS = alcohol withdrawal syndrome, DB = double-blind, DT = delirium tremens, ED = emergency department, IQR = interquartile range, LOS = length of stay, ME = morphine equivalents, NRS = Numerical Rating Scale, NS = not significant, OR = odds ratio, PC = placebo controlled, PCA = patient controlled analgesia, RCT = randomized controlled trial, RR = retrospective review, SAS = Riker Sedation-Agitation Scale.

intervention, and many patients received concomitant opioids which could confound findings. Ahern et al (18) found that 53% of patients reported weak to modest side effects, and 34% reported bothersome effects. Most common side effects were dizziness, fatigue, nausea, and feelings of unreality. Bowers et al (20) reported more patients experienced adverse effects with ketamine compared with placebo (27 vs 12 patients), with the majority experiencing lightheadedness or dizziness (30%). Mitchell and Fallon (24) found that 33% of patients receiving ketamine compared with 6% in placebo reported feeling emotional at 24 hours, with no other differences in adverse effects.

Clinical Application. Despite the majority of evidence resulting from an ED population, low-dose ketamine for acute pain has demonstrated reduced pain scores. However, most included trials had a small sample size, prior receipt of opioids, were single-center, and used convenience sampling for enrollment. Given the quality of evidence from these studies, ketamine can reasonably be used as an adjunctive agent for acute pain in the ED (level 2 evidence); however, further evidence is needed to extrapolate results to the ICU setting. There are several ongoing trials continuing to investigate ketamine for acute pain management (25–28).

Adjunctive Analgosedation in Mechanical Ventilation

Rationale. There are limited data on the use of ketamine as an adjunctive agent for sedation outside of procedural or general anesthesia, with no formal recommendation from guidelines (1, 4, 5). Ketamine may be an ideal adjunctive agent in mechanically ventilated patients since it can reduce opioid requirements while not depressing hemodynamic parameters like alternative sedative medications.

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Evidence. Buchheit et al (29) observed the use of subanesthetic doses of ketamine as an adjunctive option for intubated patients and found significant reductions in opioid and propofol requirements 24 hours post-ketamine introduction ($p \leq 0.001$ and $p = 0.02$, respectively). Additionally, vasopressor requirements were significantly reduced 6 hours after initiating ketamine ($p = 0.019$), however, not at 24 hours ($p = 0.236$) (29). Another retrospective review of mechanically ventilated patients investigated ketamine as an alternative agent and found, the utilization of ketamine significantly reduced opioid and propofol requirements ($p < 0.05$) (30). A third retrospective cohort reduced or discontinued alternative sedatives in 63% of patients within 24 hours of adding ketamine infusion (31).

Risks. Rates and severity of adverse effects were not reported in all included studies. No significant difference in blood pressure or respiratory rates (RRs) before and 24 hours after ketamine was noted; however, there was a significant increase in heart rate ($p = 0.01$) (29). Another study found no significant difference in heart rate after ketamine initiation (31). However, reported adverse effects included dysphoria, nystagmus, tachycardia, and increased agitation. Only one study reported increased amounts of dexmedetomidine and ziprasidone following ketamine initiation (30).

Clinical Application. Despite limited data, retrospective studies suggest efficacy and opioid-sparing properties of ketamine as an adjunctive sedative in mechanically ventilated patients (level 3 evidence). Considering its limited evidence, the role of ketamine as a continuous infusion should be reserved as an adjunctive agent in refractory situations. Given the retrospective study designs, small sample size, and varying dosing regimens, larger, prospective, randomized studies with traditional sedation are warranted to further assess clinical outcomes.

Status Asthmaticus

Rationale. Ketamine causes bronchodilation by increasing circulating catecholamines, inhibiting vagal outflow, and relaxing airway smooth muscle (1, 32). Given this effect, ketamine has been considered a potential treatment for severe asthma exacerbations refractory to standard therapy.

Evidence. Experimental use of ketamine in adult patients presenting with status asthmaticus is limited to one randomized controlled trial. Howton et al (32) evaluated the safety and efficacy of ketamine in nonintubated adults with an acute, severe asthma exacerbation. Fifty-three patients with a peak expiratory flow less than 40% of the predicted value following initial albuterol therapy were randomized to receive a ketamine 0.2 mg/kg IV bolus over 5 minutes, followed by an IV continuous infusion at a rate of 0.5 mg/kg/hr or placebo; both groups received standard therapy. Due to dysphoria that occurred in three of the initial six ketamine patients, subsequent bolus doses were decreased to 0.1 mg/kg IV and the first nine patients were eliminated from the analysis. There was overall improvement seen in peak flow, Borg score, RR, and forced expiratory volume in 1 second among both patient groups; however, there were no statistically significant differences detected between the two groups when comparing changes in these parameters over a 3-hour time period. Noting the possibility of β-error, the authors concluded that ketamine at a dose low enough to avoid dysphoria demonstrated no clinical benefit in treating refractory asthma exacerbations in an adult population when compared with standard therapy.

Risks. There were no statistically significant differences in terms of safety, although overall adverse effect rates were numerically higher with ketamine compared with placebo. Rates of individual adverse effects were not reported; however, dysphoria and dizziness were noted to be the most common. One patient was intubated in the ketamine group compared with three in the placebo group, but this was stated to not be a statistically significant finding.

Clinical Application. The literature on ketamine use for status asthmatics in adults is sparse, and this study failed to show a significant difference in efficacy compared with standard therapy alone (level 3 evidence). Well-conducted, randomized controlled trials with a patient-oriented primary outcome are still needed to identify whether there is any clinical benefit of using ketamine in this population. Thus, ketamine should not be routinely used for status asthmaticus.

Alcohol Withdrawal Syndrome

Rationale. Chronic alcoholics experience a down-regulation in GABA receptors and an up-regulation of NMDA receptors (1, 9). Symptom-triggered benzodiazepine therapy is the mainstay in management of alcohol withdrawal syndrome (AWS), although there are no guidelines for the assessment and management of AWS in the critically ill population (33). Oftentimes, patients develop resistance to benzodiazepines, typically defined as needing greater than 40 mg of diazepam equivalents over the course of an hour. Major sequelae of uncontrolled AWS include seizure and delirium tremens (DTs), and therapies are needed to prevent these effects (33). Ketamine exhibits a mechanism of action similar to ethanol by blocking NMDA, a site of action that is uncommonly used in current AWS management.

Evidence. Two recent studies reported the use of ketamine infusions as an adjunct to symptom-triggered therapy in the ICU population (34, 36). Wong et al (34) were unable to find a difference in benzodiazepine requirements before and after initiation of ketamine in 23 ICU patients with AWS ($p = 0.11$). Conversely, Shah et al (36) found decreased lorazepam requirements 24 hours after ketamine initiation ($p < 0.05$), and all 30 patients achieved symptom control within 1 hour of ketamine. Despite this reporting, six of 14 nonintubated patients eventually required mechanical ventilation after initiation of ketamine. This study used higher infusion rates compared with Wong et al (34), possibly accounting for the difference in outcomes. The study populations differed between both analyses, reporting differences in rates of intubation prior to ketamine, and the reasons for initiation of ketamine (i.e., delirium tremens, benzodiazepine resistance).

Another recent study evaluated a protocol implemented for the management of nonintubated patients with DTs, where a

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ketamine infusion was immediately added to symptom-triggered therapy at the diagnosis of DTs (35). The authors found significant reductions in mean ICU length of stay by 2.83 days (95% CI, –5.58 to –0.089 d; $p = 0.043$), likelihood for intubation (odds ratio, 0.14; 95% CI, 0.04–0.49), and total benzodiazepine requirements ($p = 0.02$) when compared with symptom-triggered therapy with benzodiazepines alone (35).

Risks. Few adverse events are noted with ketamine in AWS. The need for intubation may be of concern, as it was exemplified by the more aggressive dosing strategy reported by Shah et al (36). Emergence reactions were not reported.

Clinical Application. Although ketamine appears to be a safe option to consider as an adjunct to AWS management in the ICU, current evidence is fairly discrepant concerning appropriate timing, dosing strategies, and monitoring of ketamine in AWS (level 3 evidence) (35, 36). There is a need for further well-designed studies to confirm ketamine's place in therapy in managing AWS.

Status Epilepticus

Rationale. Strong evidence exists for the administration of benzodiazepines for status epilepticus (SE), but evidence for other medications is based on very limited data. In many cases, patients develop refractory SE (RSE), or the failure to control seizures with benzodiazepines and a second antiepileptic drug (AED) (38). The down-regulation of GABA receptors and subsequent pharmacoresistance to benzodiazepines may contribute to disease progression from SE to RSE (37). Reduced response to common first-line drugs due to altered $GABA_A$ receptor and augmentation of p-glycoprotein-mediated export of phenytoin and phenobarbital can be seen 30 minutes after seizure onset (40). Coupled with increased excitotoxicity due to up-regulation of NMDA receptors at the synaptic membrane, ketamine presents itself as a possible treatment option.

Evidence. In a multicenter study, Gaspard et al (39) observed the use of ketamine for the management of RSE in adults and children. The authors assessed the impact of ketamine on seizure control, defining a "possible response" as permanent control of SE within 24 hours of starting of ketamine. In the study, 19 of 60 patients (32%) achieved a "possible response" to ketamine (39). Response rates were highest when ketamine was started early (at a median of 12 hr) after seizure onset and when fewer concurrent antiepileptics were present at the time of ketamine initiation (4 vs 8 AEDs; $p < 0.01$). The median infusion rate was 2.75 mg/kg/hr and administration of a bolus dose did not correlate with permanent seizure control. Variables associated with lower mortality included younger age and achieving a "possible response" to ketamine ($p = 0.001$ and $p \leq 0.001$, respectively). Other retrospective reviews describe success in controlling super-RSE (RSE persisting for 24 hr) with ketamine, although the quality of evidence remains low (40–42).

Risks. A case of cardiac arrest with possible association to ketamine was reported, although more data are needed to confirm this adverse event (43). Ketamine's effect on ICP while managing RSE has also not been fully assessed.

Clinical Application. It may be reasonable to consider ketamine in the management of RSE, especially in the setting of cardiac depression from other anesthetic agents (level 3 evidence). It is unclear at what point of therapy ketamine should be added and some have advocated to start ketamine early in the course of RSE due to the pharmacoresistance that can develop early in RSE (40). Nevertheless, further studies are needed to truly elucidate the place in therapy and optimal dosing strategy of ketamine in RSE.

Acute Agitation

Rationale. Patients may present in a prehospital or ED setting with acute agitation or excited delirium, defined as altered sensorium and aggressive behavior in which patients experience hyperadrenergic autonomic dysfunction and metabolic acidosis that may result in death (44–46). Ketamine may be an appropriate treatment option due to its rapid onset and duration, particularly when given intramuscularly (45).

Evidence. A prospective, observational study compared ketamine to a benzodiazepine or haloperidol (or combination) in 98 patients and found that those who received ketamine were less agitated at 5, 10, and 15 minutes ($p = 0.001$, $p \leq 0.001$, $p = 0.032$, respectively) based on an agitation score of less than or equal to 2 on a 6-point scale, indicating patients to be mildly aroused/pacing, settled, or asleep (scores 2, 1, and 0, respectively) (45). Other studies have described ketamine in the prehospital setting (44, 46–49).

Keseg et al (44) conducted a retrospective review of 35 patients who received ketamine for agitation and reported subjective improvement in 91% of patients without using a standardized assessment methodology. Cole et al (46) investigated intramuscular ketamine as first-line therapy in 49 patients with profound agitation defined as Altered Mental Status Scale (AMSS) of +4 and found that patients achieved adequate sedation in a median of 4.2 minutes (95% CI, 2.5–5.0 min; range, 1–25 min). Parsch et al (47) performed a retrospective review before and after implementation of ketamine practice guidelines for a transport team and found that intubation incidence decreased (36% vs 7.14%; $p < 0.01$). Another recent prospective, open-label trial compared ketamine 5 mg/kg intramuscular to haloperidol 10 mg intramuscular in patients with AMSS +2 or +3 and found that patients who received ketamine achieved adequate sedation within a median of 5 minutes versus 17 minutes for haloperidol ($p < 0.0001$) (48).

Risks. High intubation rates after ketamine administration have been reported, however, this may be related to individual provider practice as described in two studies (46, 49). Parsch et al (47) reported higher complication rates in the ketamine group (49% vs 5%; $p < 0.0001$), including intubation (39% vs 4%; $p < 0.0001$). A retrospective cohort study compared single ketamine doses related to intubation incidence and found that both "high dose" (> 5 mg/kg) and "low dose" (≤ 5 mg/kg) groups had similar rates (49). Other complications included hypersalivation, emergence reaction, laryngospasm, and vomiting (44–48).

Clinical Application. Although data are limited, studies suggest ketamine's efficacy for acute agitation in ED and

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TABLE 3. Ketamine Dosing and Safety From Primary Literature

Indication	Included Doses	Relative Safety
Subdissociative pain (18–24)	"Weight-based": 0.1–0.5 mg/kg IV over 3–5 min "Fixed dose": 15 mg IV followed by 20 mg infusion over 60 min	More adverse effects were reported in ketamine group (fatigue, dizziness, nausea, feelings of unreality)
Adjunctive analgosedation in mechanical ventilation (29–31)	0.06 to 0.94 mg/kg/hr continuous infusion	Well tolerated (8% experienced adverse effects requiring discontinuation of ketamine) Significant increase in median heart rate for ketamine group
Status asthmaticus (32)	0.1 mg/kg IV bolus over 5 min, followed by 0.5 mg/kg/hr continuous infusion	Numerically higher rate of adverse effects (17.4% vs 4.8%, respectively; $p = 0.1880$) and hospital admissions (87% vs 66.7%, respectively; $p = 0.1088$) with ketamine compared with standard therapy alone, although not statistically significant findings
Alcohol withdrawal (34–36)	0.15 to 3 mg/kg/hr continuous infusion ± 0.3 mg/kg initial IV bolus	Well tolerated (no patients experienced adverse effects requiring discontinuation of ketamine or major medical intervention)
Status epilepticus (39)	0.05 to 10 mg/kg/hr continuous infusion ± 1.5 mg/kg initial IV bolus	7% experienced adverse effects requiring discontinuation (arrhythmias and infusion-related reactions)
Agitation/excited delirium (44–49)	3–5 mg/kg intramuscular 2 mg/kg IV bolus 0.25–0.5 mg/kg IV bolus, followed by 1–2 mg/kg/hr IV continuous infusion	High rate of intubation in some studies (7–63%) Other complications included hypersalivation (18–38%), emergence reaction (4–10%), laryngospasm (4–5%), and vomiting (0–6%)

prehospital settings. However, given the higher reported incidence of adverse effects, ketamine could be considered as an adjunct agent with close monitoring until further prospective data are available (level 3 evidence).

CONCLUSIONS

As our understanding of ketamine expands, so does its role in the management of critically ill patients (**Table 3**). This review sought to summarize the use of ketamine in various disease states encountered in the ICU and ED, although most publications were limited by small sample sizes retrospective design. Further prospective, randomized controlled trials with standardized dosing and adjunctive therapies are needed to support ketamine use in these disease states for the critically ill population (50–57).

Dr. Hurth was designated as a primary author. Drs. Jaworski, Thomas, Kirsch, Rudoni, and Wohlfarth were responsible for verifying the literature search, evaluating studies, and reviewing through the publication in its entirety.

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This work was completed at ProMedica Toledo Hospital/Toledo Children's Hospital.

All authors disclosed off-label product use of ketamine.

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