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The Use of Ketamine for the Management of Acute Pain in the Emergency Department

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ABSTRACT
Ketamine has been used as an anesthetic agent for over 50 years. At the upper end of the dosing range, it displays dissociative anesthetic and amnestic effects, while at lower doses, it acts as an analgesic and demonstrates opioid-sparing capabilities. Ketamine is unique in its preservation of hemodynamic stability and respiratory function, and is used extensively in the emergency department (ED) for procedural sedation and the facilitation of brief painful procedures. Despite evidence supporting its safety and efficacy as an analgesic agent at sub-dissociative doses, its use in the ED for the management of acute pain remains uncommon. New guidelines were published in July 2018 by the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists that provide a framework for identifying patients who are likely to benefit from the use of Ketamine in an acute pain setting. **Key words:** ketamine for acute pain, ketamine in emergency care, ketamine in ED, ketamine guideline

KETAMINE HAS BEEN USED globally for more than 50 years as an anesthetic agent and is extensively utilized in the emergency department (ED) for procedural sedation and as an induction agent for rapid sequence intubation (Hopper et al., 2015; Pourmand, Royall, Alhawas, & Shesser, 2017). Initially synthesized in the early 1960s as an alternative to phencyclidine, ketamine is unique in its preservation of respiratory reflexes at therapeutic doses and was utilized in remote combat zones during the Vietnam War (Cohen et al., 2018). Shortly after its anesthetic properties were identified, ketamine was also found to act as an analgesic when administered in lower doses, also known as subanesthetic or nondissociative doses.

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Despite its declining use as a general anesthetic for surgical procedures, ketamine use remains common for the facilitation of painful procedures in the ED, for both adult and pediatric patients (Green, Roback, Kennedy, & Krauss, 2011). Current ED practice relies heavily on opioids for pain management (American College of Emergency Physicians, 2018), but adverse effects such as sedation, respiratory depression, and hypotension make this drug class suboptimal for many patient populations. In addition, recent examination of opioid shortages, misuse, and dependence has led to a renewed focus on multimodal pain management and the use of ketamine for pain control has become an area of increasing interest.

KETAMINE: WHAT IS IT AND HOW IS IT USED?

Ketamine is a distinct pharmacological agent that demonstrates dissociative, analgesic, and amnestic properties while maintaining hemodynamic stability and preserving spontaneous respirations and protective airway reflexes (Green et al., 2011; Sinner & Graf, 2008; Vadivelu et al., 2016). It is listed as a Schedule III controlled substance under the U.S. Controlled Substance Act because of its potential for abuse, dependence, and diversion (Drug Enforcement Administration, 1999). Despite numerous studies demonstrating the safety and efficacy of ketamine as an analgesic and its growing popularity in the treatment of chronic pain and refractory depression (Schwenk et al., 2018), the use of nondissociative ketamine still remains relatively uncommon in the ED (Ahern, Herring, Miller, & Frazee, 2015).

Pharmacology and Pharmacokinetics

Ketamine is a phenylpiperidine derivative, and its primary mechanism of action is as a noncompetitive antagonist at the phencyclidine binding site of *N*-methyl-D-aspartate (NMDA) receptors located in the central nervous system ([CNS]; Gupta, Devi, & Gomes, 2011). Glutamate, the primary excitatory neurotransmitter in the CNS, is the endogenous ligand for NMDA receptors and plays a major role in cognition, chronic pain, opioid tolerance, and mood regulation. Inhibition of this pathway is considered a major mechanism by which ketamine produces its analgesic effects (Gorlin, Rosenfeld, & Ramakrishna, 2016). Ketamine also acts on a variety of opioid receptors and has been shown to delay desensitization and improve resensitization of opioid receptors, which may potentiate the effects of opioids resulting in an opioid-sparing effect (Gupta et al, 2011; Laskowski, Stirling, McKay, & Lim, 2011; Lester, Braude, Niles, & Crandall, 2010). In addition, ketamine exerts effects on nicotinic and muscarinic cholinergic receptors, monoaminergic receptors, γ-aminobutyric acid receptors, and D_2 dopamine receptors, but relatively little is known about the role of these receptors in the analgesic effects of ketamine.

Ketamine is water- and lipid-soluble, allowing for administration in various routes and rapid crossing of the blood–brain barrier. It is initially distributed to highly perfused tissues such as the brain, lungs, and heart (Pourmand et al., 2017). Bioavailability following an intramuscular dose is 93%, whereas oral bioavailability is estimated to be only 17%–24% (Fanta, Kinnunen, Backman, & Kalso, 2015). When administered intramuscularly, the onset of analgesia is approximately 4 min and the peak effect is seen within 5–10 min. When administered intravenously, onset is within 10–30 sec and the peak effect is typically seen within 1–5 min. This rapid onset is different from what is observed with morphine, which has an onset of 5–10 min and takes approximately 20 min to reach peak analgesic effect (Majidinejad, Esmailian, & Emadi, 2014; Pourmand et al., 2017). The effects of ketamine generally last 30–45 min if no further dosing is administered, often resulting in the need for repeat boluses after an initial dose (Ahern et al., 2015; Sinner & Graf, 2008). Ketamine undergoes significant first-pass metabolism, which limits its bioavailability when administered orally. Therefore, ketamine has the best effect when

administered by the intravenous or intramuscular route. Metabolites of ketamine maintain a third of the activity of the parent compound and are excreted in the urine and bile (Fanta et al., 2015; Niesters, Martini, & Dahan, 2014).

Indications

Ketamine is currently only U.S. Food and Drug Administration (FDA) approved for use as an anesthetic agent, either as monotherapy or as an induction agent prior to the use of other general anesthetics (FDA, 2017). However, numerous off-label uses for ketamine have been studied since its discovery in the 1960s. Recent literature suggests that there may be a role for ketamine in managing depression (Cohen et al., 2018; Sanacora et al., 2017), bipolar disorder, posttraumatic stress disorder, suicidal ideation (Gao, Rejaei, & Liu, 2016), refractory chronic headache (Pomeroy, Marmura, Nahas, & Viscusi, 2017), status epilepticus (Fang & Wang, 2015), and acute agitation in the ED (Hopper et al., 2015). Ketamine has shown benefit in the management of both chronic pain and acute pain and may display anti-inflammatory effects as well (De Kock, Loix, & Lavand'homme, 2013). The role of nondissociative ketamine in the treatment of pain has been the subject of intense interest, especially as pressure mounts to curb opioid misuse and abuse.

The majority of studies evaluating ketamine use in the acute pain setting have focused on the perioperative period where ketamine decreases postoperative pain, reduces opioid consumption, and delays time to first opioid dose when given either intraoperatively or postoperatively in both opiate-naive and opiate-tolerant patients (Elia & Tramer, 2005; Loftus et al., 2010). As the use of ketamine continues to increase, more studies are being conducted to assess its efficacy in acute pain management outside of the surgical setting (Halpern, 2018).

In the ED setting specifically, there is a growing body of evidence to support the safety and efficacy of ketamine for acute pain. Numerous case reports suggest that ketamine alleviates pain and reduces opioid consumption in patients presenting with abdominal pain, back pain, chest pain, sickle cell pain, burns, fractures, dislocations, and other trauma (Ahern et al., 2015; Lester et al., 2010; Majidinejad et al., 2014; Richards & Rockford, 2013; Sin, Ternas, & Motov, 2015). In cases involving long bone fractures, one study showed that the analgesic effect of ketamine was very similar to that of morphine (Majidinejad et al., 2014). Because NMDA receptors have been implicated in the central sensitization involved in chronic pain, treatment with ketamine may also help prevent the chronification of acute pain related to surgery or trauma (Gorlin et al., 2016). Furthermore, ketamine provides an option for acute pain treatment of the opioid-tolerant patient (Ahern et al., 2015).

Sin et al. (2015), through a qualitative analysis, performed a systematic review of four studies, which enrolled a total of 428 patients, assessing the use of nondissociative doses of ketamine for treatment of acute pain in the ED. This systematic review was limited by the methodological limitations of the four trials, including small sample sizes, varying doses, and varying pain scales used to evaluate efficacy (e.g., numeric rating scale, visual scale). Moreover, there were variations in the types of pain in the patient populations and the doses of ketamine administration. Even with the methodological limitations, Sin et al. noted that nondissociative doses of ketamine appear to have a low incidence of adverse events, result in satisfactory pain control, and may reduce the need for opioid use in the ED. Although the review provides evidence that ketamine may be useful in the ED, the authors concluded that more rigorous investigations and studies are needed to either support or refute the use of nondissociative ketamine for acute pain management in the ED.

Opioids have long been the mainstay of treatment of moderate to severe acute pain in the ED (American College of Emergency Physicians, 2018). However, new evidence suggests that ketamine may not only reduce the need for opioids but also treat pain more

effectively than opioids alone (Laskowski et al., 2011). In a randomized clinical trial that enrolled 60 participants and compared ketamine with morphine monotherapy, patients in the ketamine group reported decreased pain intensity at 2 hr and required less rescue analgesia than patients in the morphine group (Beaudoin, Lin, Guan, & Merchant, 2014). In the Beaudoin et al. study, there were several important limitations to consider. First, the number of patients ($n = 60$) enrolled in the study was small. In addition, there was variability among the painful conditions in each of the treatment groups that could have led to confounding. Despite these limitations, Beaudoin et al. concluded that ketamine dosing at 0.3 mg/kg is an acceptable adjunct to morphine in the treatment of moderate to severe acute pain in patients with pain refractory to opioids. This dose of ketamine is consistent with other guidelines as discussed later.

Contraindications

The major contraindications for ketamine use are primarily derived from studies in which anesthetic doses were used (Schwenk et al., 2018). According to the drug monograph, the only absolute contraindications are hypersensitivity to ketamine and conditions where a significant increase in blood pressure would be hazardous, such as hypertensive emergency (FDA, 2017). In their clinical practice guideline, Green et al. (2011) also included conditions such as schizophrenia and other forms of psychosis as absolute contraindications due to the potential of ketamine to reactivate psychosis in these patients and stated that ketamine should not be used in children younger than 3 months because of an increased risk of respiratory complications.

Many relative contraindications remain the subject of clinical controversy and investigation. These include pregnancy, hepatic dysfunction, elevated intracranial or intraocular pressure, globe injury, moderate to severe hypertension, congestive heart failure, and acute alcohol intoxication (Gorlin et al., 2016; Green et al., 2011; Pourmand et al., 2017; Schwenk et al., 2018). Despite early concerns that ketamine could cause increased intracranial pressure, recent studies have demonstrated that cerebral perfusion pressure is not adversely affected and indicate that this potential contraindication is not as clinically relevant as initially thought (Green, Andolfatto, & Krauss, 2015; Zeiler, Teitelbaum, West, & Gillman, 2014). In addition, the potential for impairment of cerebral autoregulation after traumatic brain injury, and subsequent dependence on mean arterial pressure to perfuse the brain, suggests that ketamine's ability to maintain cardiovascular stability may in fact be beneficial in this patient population (Ahern et al., 2015).

Some studies have reported elevated liver enzymes following ketamine treatment, and hepatic dysfunction is subsequently listed as a relative contraindication in some of the literature (Kiefer et al., 2008; Noppers et al., 2011). However, these reports are mostly focused on patients requiring chronic administration of ketamine for indications such as depression and chronic pain. For the short duration that patients are likely to receive ketamine in the ED, the risk of hepatic injury appears to be minimal (Niesters et al., 2014).

Protective airway reflexes are maintained and, in some cases, exaggerated after ketamine administration, and the risk of laryngospasm may be increased in patients with upper respiratory tract infection, those with a history of airway instability or deformity, and those undergoing procedures that stimulate the posterior pharynx such as endoscopy (Green et al., 2011). Most ED procedures such as intraoral laceration repair, dental procedures, and oropharyngeal and esophageal foreign body removal have not been shown to increase the risk of laryngospasm (Green et al., 2009).

Some literature suggests that a history of substance abuse should be considered a contraindication to ketamine treatment (Schwenk et al., 2018). Recreational use of ketamine began shortly after its psychostimulatory properties were identified, and ketamine saw a rise in popularity as a "club drug" in

the 1990s and again in recent years (Vadivelu et al., 2016). When used for the short-term treatment of acute pain, the risk of developing an addiction to ketamine appears to be remote. In evaluating the available treatment options, it is also important to consider that patients who have a history of substance abuse may not be suitable candidates for treatment with opioids because of both abuse potential and tolerance. In this population, ketamine may be a better alternative, given its ability to reduce or eliminate the need for opioid administration (Schwenk et al., 2018).

General Administration Guidelines for Acute Pain

Ketamine can be administered via a variety of routes including intravenous bolus injection, continuous intravenous infusion, intramuscular injection, subcutaneous injection, intranasal solution, oral elixir, and rectal solution. However, it is currently only FDA approved for parenteral administration and there are no commercially available nonparenteral formulations (FDA, 2017). Administration of these products requires off-label compounding in compliance with USP-797 to ensure stability, sterility, and correct dosing. Despite these regulations, compounded products still carry a risk of contamination and dose variability, and few studies have been conducted to determine their optimal dosing and role in clinical practice (Schwenk et al., 2018).

Ketamine can be given as an intravenous bolus or as an intermittent or continuous infusion. Although it is well established that one of the hallmarks of ketamine is the preservation of respiratory function, the exception is when it is administered too rapidly. In these cases, transient respiratory depression and apnea can occur (Gao et al, 2016). Current emergency medicine guidelines recommend administering ketamine boluses over 30–60 sec to mitigate this potential risk (Green et al., 2011). However, a randomized, double-dummy study demonstrated that administering ketamine over 10–15 min using an infusion pump significantly reduced the rate of adverse effects related to feelings of unreality and sedation compared with intravenous push administration (Motov et al., 2017). Administration via intramuscular injection has been shown to be safe and effective with predictable pharmacokinetics, but when access is available, the intravenous route is preferred because of an increased incidence of vomiting and longer recovery time when the intramuscular route is used (Gao et al., 2016).

Institutions vary in their prescribing limitations, but it is common to require that only clinicians trained in the induction and maintenance of ketamine infusions such as pain specialists and anesthesiologists, critical care-trained physicians, and emergency department clinicians be responsible for decisions regarding the administration of ketamine, especially when combined with opioids for increased analgesia or benzodiazepines such as midazolam for attenuation of adverse events (Cohen et al., 2018; Vadivelu et al., 2016).

Potential Adverse Effects

Based on dissociative dosing ranges, the adverse effect profile of ketamine has limited the widespread acceptance of its routine use as an analgesic due to apprehension about psychomimetic effects and emergence reaction symptoms such as hallucinations, visual disturbances, vivid dreams, and agitation (Ahern et al., 2015; Elia & Tramer, 2005; Laskowski et al., 2011; Sin et al., 2015). However, much of the literature reports that these side effects are generally well-tolerated and patient satisfaction is typically high, with some studies proposing that these effects may be dose-related and less likely to occur at nondissociative doses (Gorlin et al., 2016; Richards & Rockford, 2013). In one study, 84% of patients ($n = 32$) reported that they would be willing to receive ketamine therapy again for the treatment of pain despite 34% of patients ($n = 13$) experiencing psychomimetic side effects (Ahern et al., 2015). Although not extensively studied, the use of benzodiazepines such as midazolam and diazepam as either

premedication or rescue medication may decrease the incidence of adverse psychomimetic effects or treat the symptoms of emergence agitation with no increase in recovery time or other adverse effects (Strayer & Nelson, 2008).

The most commonly reported adverse effects are nausea, vomiting, dizziness, increased salivary secretions, and mild neuropsychological reactions such as hallucinations or agitation (Schwenk et al., 2018). Additional side effects are listed in Table 1. The majority of adverse events reported in studies resolve spontaneously. However, antiemetics, such as ondansetron, can be given as an adjunctive agent to help ameliorate nausea and vomiting (Green et al., 2011). Large meta-analysis have shown no benefit from prophylactic atropine administration to reduce hypersalivation associated with ketamine administration, and its use as an adjunctive agent is not recommended in current guidelines (Green et al., 2011). Although it is difficult to draw a direct comparison, adverse event rates with ketamine have been reported to be lower than those associated with opioid administration (Ahern et al., 2015). Of note, ketamine has not been shown to cause increased levels of sedation and may in fact decrease sedation due to opioid-sparing effects (Gorlin et al., 2016).

At nondissociative doses, ketamine often results in transient tachycardia, hypertension, and bronchodilation due to its sympathomimetic effects (Gorlin et al., 2016; Strayer & Nelson, 2008). These cardiopulmonary effects may be preferable to those of opioids, which are more likely to cause hypoxia and hypotension (Lee & Lee, 2016). Clonidine, an α-2 adrenergic receptor agonist, has been proposed as a potential agent to counteract both the cardiovascular stimulatory effects and the undesirable psychedelic effects of ketamine, but further study is needed to determine whether such use is warranted in practice (Niesters et al., 2014; Schwenk et al., 2018). Despite the arguably safer cardiopulmonary profile of ketamine than of opioids, caution must still be used in patients with an underlying cardiovascular disease.

Table 1. Short-term side effects of ketamine

Increase in heart rate	Confusion
Slurred speech	Out-of-body experience
Euphoria	Shift in perception of reality
Numbness	Loss of sensory perception
Ataxia	Nausea and vomiting
Change in perception of time	Visual hallucinations
Double-vision	Hypertension

Note. Information obtained from Schwenk et al. (2018) and FDA (2017).

Some patients may report psychomimetic effects of ketamine as negative simply because they are not adequately prepared for them. It is recommended that patients be advised about the possibility of these effects prior to administration and that this preemptive education may reduce the likelihood that a patient will perceive these effects as negative (Ahern et al., 2015).

Dissociative Doses of Ketamine Versus Ketamine for Acute Pain

The effects of ketamine are dose dependent, with low doses producing analgesia and sedation and high doses producing general anesthesia. Specific guidelines for what is considered nondissociative dose versus anesthetic dose are not consistent, and this is one of the areas that the new guideline sought to clarify. The FDA (2017) lists the anesthetic dose as 1–4.5 mg/kg, with an average dose of 2 mg/kg. Nondissociative doses of ketamine are reported from 0.1 to 0.5 mg/kg as an intravenous bolus, with or without a subsequent intravenous infusion, usually started between 0.15 and 0.2 mg/kg/hr (American College of Emergency Physicians Emergency Medicine Practice Committee, 2017). The Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management recommends bolus dosing not to exceed

0.35 mg/kg and infusions not to exceed 1 mg/kg/hr except in rare circumstances and on a case-by-case basis (Schwenk et al., 2018). As mentioned previously, Beaudoin et al. (2014) recommended ketamine dosing at 0.3 mg/kg as an adjunct to opioid therapy.

Monitoring Recommendations for Nondissociative Doses

Although ketamine is unlikely to impact respiratory function or render a patient unresponsive at the doses used to treat acute pain, some authors recommend that a clinician should be present who is trained in airway management and Advanced Cardiac Life Support ([ACLS]; Schwenk et al., 2018). In the ED setting, monitoring may be managed by a registered nurse with an ACLS certification and who is trained in the administration of and familiar with the pharmacology of ketamine (Niesters et al., 2014; Pourmand et al., 2017; Schwenk et al., 2018). Monitoring parameters may include pulse oximetry, end-tidal carbon dioxide, blood pressure, telemetry, and mental status. However, the American College of Emergency Physicians (2017), in an Emergency Nurses Association-approved policy statement, indicates that special administration procedures and monitoring are not required and fall under the same policies and procedures as other typical analgesics such as morphine. Specific guidelines outlining discharge criteria and instructions are lacking, especially in patients receiving nondissociative ketamine.

A GUIDELINE FOR KETAMINE USE IN ACUTE PAIN

In July 2018, the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM), and the American Society of Anesthesiologists (ASA) published an evidence-based guideline for the use of intravenous ketamine infusions for acute pain management. The guideline was prepared by members of the Ketamine Guidelines Committee who were selected by the ASRA and the AAPM, along with the chair of the ASRA Guidelines Committee. It was determined early in the process that individual guidelines would be necessary for the treatment of acute and chronic pain, as the pathophysiology and approach to treatment differs (Cohen et al., 2018). The guideline focusing on acute pain was written by 10 specialists in anesthesiology and pain management. The organizations provided 14 graded recommendations. Grading was performed on the basis of magnitude and certainty of benefit using a modified version of the U.S. Preventive Services Task Force (USPSTF) guidelines (Schwenk et al., 2018).

Levels/Grades of Evidence for the Recommendations

Clinical practice guidelines are based on research studies and current evidence-based practice. To ensure the quality of the evidence and the strength of recommendations, the GRADE system was developed (Atkins et al., 2004). The GRADE system utilizes a step approach that considers the quality of evidence, outcomes importance, and balance of benefits and harms. Levels of certainty are based on the overall net benefit of the evidence. The GRADES scale includes A, B, C, D, and I, with A being highly recommended and D against the recommendation. In addition, I indicates that there is insufficient evidence to support the evidence (USPSTF, 2018). The levels of certainty range from high to low. High means that the level of evidence is consistent, whereas moderate means there is sufficient evidence to support the practice; however, the evidence is limited by factors such as study size or inconsistencies between studies. A low recommendation means that the evidence is insufficient to support the practice.

The Guideline Recommendations

The recommendations answered six key questions about ketamine and included information regarding indications, contraindications, use of ketamine as an adjunct to opioids,

and evaluation of the optimal nondissociative dose. Although the guideline does not specifically mention the use of ketamine in the emergency setting, the authors recommend that clinicians consider ketamine for the treatment of acute pain in opioid-dependent patients, in opioid-tolerant patients with chronic pain exacerbation, and in patients undergoing painful procedures (Schwenk et al., 2018). The guideline recommendations are summarized in Table 2.

Schwenk et al. (2018) note that the creation of the guideline was challenged by lack of literature without methodological flaws and therefore many of the recommendations are based on expert opinion. Guidelines based on expert opinion, such as this guidelines recommendation for intravenous ketamine bolus dosing not to exceed 0.35 mg/kg, may be incorrect for individual patients. Furthermore, expert opinion may be biased to the beliefs to which the experts subscribe and therefore misrepresent population norms (Pacini, Murana, Leone, Marco, & Pantaleo, 2016). In the guidelines' conclusion, the authors mentioned that larger, more rigorous studies are needed to evaluate the treatment parameters, to determine appropriate patient selection criteria, and to develop safety protocols for ketamine use.

Is There a Role for Nondissociative Dosed Ketamine in the ED to Treat Acute Pain?

Ketamine is a unique drug with many potential applications in the ED. Benefits of ketamine have been demonstrated as an analgesic in a variety of settings, including analgesia prior to awake procedures, acute exacerbations of chronic conditions, and in the setting of hemodynamic instability. Ketamine may also be a safer and more effective alternative, either as monotherapy or in combination with opioids, than treatment with opioids alone in patients who are opioid dependent or opioid tolerant (Beaudoin et al., 2014). The low cost and large therapeutic window of ketamine make it a good choice for the ED setting (Vadivelu et al., 2016).

A Proposal for Future Research

Interest in ketamine and the number of publications centered around its use have

Table 2. Summary of guideline recommendations

	Level of evidence (grade, level of certainty)
Recommendations for ketamine use	
Ketamine use at nondissociative doses in opioid-dependent or opioid-tolerant patients with acute or chronic sickle cell pain and in patients with sleep apnea, as an adjunct to limit opioids	Grade C, low
Intravenous bolus not to exceed 0.35 mg/kg	Grade C, moderate
Intranasal ketamine for acute pain	Grade C, low-to-moderate
Oral ketamine for acute pain	Grade C, low
Ketamine for use as sole analgesic	Grade C, low
Ketamine for use in addition to opioid-based intravenous PCA	Grade B, moderate
Contraindications for ketamine use	
Avoid use in pregnancy or psychosis	Grade B, moderate
Avoid use in poorly controlled cardiovascular disease	Grade C, moderate
Avoid use in severe hepatic disease and elevated intracranial or intraocular pressure, and use with caution in moderate hepatic disease	Grade C, low

Note. Information obtained from Schwenk et al. (2018). PCA = patient-controlled analgesia.

increased dramatically in recent years (Cohen et al., 2018). From this large body of literature, certain areas have been identified that most likely would not benefit from repeated review. For example, the ability of ketamine to act as an analgesic with opioid-sparing effects at nondissociative doses has been thoroughly investigated and identified.

Randomized controlled trials evaluating the use of ketamine for specific indications such as sickle cell pain, polytrauma, opioid-induced hyperalgesia, and pancreatitis in the ED would be helpful in identifying the patients who would most benefit from nondissociative ketamine. In addition, studies focused on patients who are traditionally excluded from ketamine trials, such as those with cardiovascular disease, kidney disease, and hepatic dysfunction, would help guide clinicians in understanding the applicability of these relative contraindications in the ED setting. Much of the available literature on this topic is in the form of retrospective case series or systematic reviews of small studies, and heterogeneity among studies is often cited as a limitation in such reviews.

Data from large prospective, randomized, blinded trials are needed to definitively elucidate the answers to some of the remaining clinical questions surrounding the use of nondissociative ketamine, particularly in the ED where its implementation has lagged behind other areas of practice. However, the ethical and practical concerns related to conducting clinical trials of this type are a limitation (Cohen et al., 2018).

CONCLUSION

Nondissociative ketamine is safe and effective for the treatment of a wide range of acute pain syndromes. The new ketamine guideline for acute pain provides a framework to guide clinicians in its optimal use and provides a dosing guideline that until its publication had been lacking. In addition, there is evidence to suggest that the ED may be an ideal setting for nondissociative ketamine, given its rapid onset, preservation of cardiopulmonary stability, and multiple available routes of administration. A major barrier to its use is a lack of familiarity on the part of both clinicians and patients and the long-standing practice of using opioids as first-line treatment of moderate to severe pain. As the popularity of ketamine continues to increase, many institutions are adopting protocols to identify patients who may benefit the most from its unique mechanism of action and to ensure its safe administration. Although ketamine may not be suitable for all patients, it is worth adding to the arsenal of tools available to treat acute pain.

REFERENCES

Ahern, T. L., Herring, A. A., Miller, S., & Frazee, B. W. (2015). Low-dose ketamine infusion for emergency department patients with severe pain. *Pain Medicine*, *16*(7), 1402–1409. doi:10.1111/pme.12705

American College of Emergency Physicians. (2017). *Sub-dissociative dose ketamine for analgesia*. Retrieved from https://www.acep.org/patient-care/policy-statements/sub-dissociative-dose-ketamine-for-analgesia/#sm.001yvre1rcubedj10lq2glnej92i4

American College of Emergency Physicians. (2018). *Opioid prescribing in the ED*. Retrieved from https://www.acep.org/by-medical-focus/mental-health–substance-abuse/opioids/Opioid-Prescribing-in-the-ED/#sm.001yvre1rcubedj10lq2glnej92i4

American College of Emergency Physicians Emergency Medicine Practice Committee. (2017). *Sub-dissociative ketamine for analgesia: Policy resource and education paper*. Retrieved from https://www.acep.org/globalassets/new-pdfs/preps/prep—sub-dissociative-dose-ketamine-for-analgesia-120717.pdf

Atkins, D., Best, D., Briss, P. A., Eccles, M., Falck-Ytter, Y., Flottorp, S., & Zaza, S. (2004). Grading quality of evidence and strength of recommendations. *BMJ (Clinical Research Ed.)*, *328*(7454), 1490. doi:10.1136/bmj.328.7454.1490

Beaudoin, F. L., Lin, C., Guan, W., & Merchant, R. C. (2014). Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: Results of a randomized, double-blind, clinical trial. *Academic Emergency Medicine*, *21*(11), 1193–1202. doi:10.1111/acem.12510

Cohen, S. P., Bhatia, A., Buvanendran, A., Schwenk, E. S., Wasan, A. D., Hurley, R. W., & Hooten, W. M. (2018). Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists.

Regional Anesthesia and Pain Medicine, *43*(5), 521–546. doi:10.1097/AAP.0000000000000808

De Kock, M., Loix, S., & Lavand'homme, P. (2013). Ketamine and peripheral inflammation. *CNS Neuroscience and Therapeutics*, *19*(6), 403–410. doi:10.1111/cns.12104

Drug Enforcement Administration. (1999). *Schedules of controlled substances: Proposed placement of ketamine into schedule III*. Retrieved from https://www.deadiversion.usdoj.gov/fed_regs/rules/1999/fr0409a.htm

Elia, N., & Tramer, M. R. (2005). Ketamine and postoperative pain—A quantitative systemic review of randomised trials. *Pain*, *113*(1–2), 61–70. doi:10.1016/j.pain.2004.09.036

Fang, Y., & Wang, X. (2015). Ketamine for the treatment of refractory status epilepticus. *Seizure*, *30*, 14–20. doi:10.1016/j.seizure.2015.05.010

Fanta, S., Kinnunen, M., Backman, J. T., & Kalso, E. (2015). Population pharmacokinetics of S-ketamine and norketamine in healthy volunteers after intravenous and oral dosing. *European Journal of Clinical Pharmacology*, *71*(4), 441–447. doi:10/1007/s00228-015-1826-y

Gao, M., Rejaei, D., & Liu, H. (2016). Ketamine use in current clinical practice. *Acta Pharmacologica Sinica*, *37*(7), 865–872. doi:10.1038/aps.2016.5

Gorlin, A. W., Rosenfeld, D. M., & Ramakrishna, H. (2016). Intravenous sub-anesthetic ketamine for perioperative analgesia. *Journal of Anaesthesiology Clinical Pharmacology*, *32*(2), 160–167. doi:10.4103/0970-9185.182085

Green, S. M., Andolfatto, G., & Krauss, B. S. (2015). Ketamine and intracranial pressure: No contraindications except hydrocephalus. *Annals of Emergency Medicine*, *65*(1), 52–54. doi:10.1016/j.annemergmed.2014.08.025

Green, S. M., Roback, M. G., Kennedy, R. M., & Krauss, B. (2011). Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Annals of Emergency Medicine*, *57*(5), 449–461.

Green, S. M., Roback, M. G., Krauss, B., Brown, L., McGlone, R. G., Agrawal, D., . . . Losek, J. D. (2009). Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: An individual-patient data meta-analysis of 8,282 children. *Annals of Emergency Medicine*, *54*(2), 158–168. doi:10.1016/j.annemergmed.2008.12.011

Gupta, A., Devi, L. A., & Gomes, I. (2011). Potentiation of μ-opioid receptor-mediated signaling by ketamine. *Journal of Neurochemistry*, *119*(2), 294–302. doi:10.1111/j.1471-4159.2011.07361.x

Halpern, P. (2018). *Comparison of treatment by IN ketamine to IV morphine in acute pain*. (Clinical Trials.gov Identifier NCT03511833). Retrieved from https://clinicaltrials.gov/ct2/show/NCT03511833?cond=ketamine+for+pain&rank=9

Hopper, A. B., Vilke, G. M., Castillo, E. M., Campillo, A., Davie, T., & Wilson, M. P. (2015). Ketamine use for acute agitation in the emergency department. *Journal of Emergency Medicine*, *48*(6), 712–719. doi:10.1016/j.jemermed.2015.02.019

Kiefer, R. T., Rohr, P., Ploppa, A., Dietrich, H. J., Grothusen, J., Koffler, S., . . . Schwartzman, R. J. (2008). Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: An open-label Phase II study. *Pain Medicine*, *9*(8), 1173–1201. doi:10.1111/j.1526-4637.2007.00402.x

Laskowski, K., Stirling, A., McKay, W. P., & Lim, H. J. (2011). A systematic review of intravenous ketamine for postoperative analgesia. *Canadian Journal of Anaesthesia*, *58*, 911–923. doi:10.1007/s12630-011-9560-0

Lee, E. N., & Lee, J. H. (2016). The effects of low-dose ketamine on acute pain in an emergency setting: A systematic review and meta-analysis. *PLoS One*, *11*(10), e0165461. doi:10.1037/journal.pone.0165461

Lester, L., Braude, D. A., Niles, C., & Crandall, C. S. (2010). Low-dose ketamine for analgesia in the ED: A retrospective case series. *American Journal of Emergency Medicine*, *28*(7), 820–827. doi:10.1016/j.ajem.2009.07.023

Loftus, R. W., Yeager, M. P., Clark, H. A., Brown, J. R., Abdu, W. A., Sengupta, D. K., & Beach, M. L. (2010). Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology*, *113*(3), 639–646. doi:10.1097/ALN.0b013e3181e90914

Majidinejad, S., Esmailian, M., & Emadi, M. (2014). Comparison of intravenous ketamine with morphine in pain relief of long bone fractures: A double blind randomized clinical trial. *Emergency*, *2*(2), 77–80. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26495351

Motov, S., Mai, M., Pushkar, I., Likourezos, A., Drapkin, J., Yasavolian, M., & Fromm, C. (2017). A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. *American Journal of Emergency Medicine*, *35*(8), 1095–1100. doi:10.1016/j.ajem.2017.03.004

Niesters, M., Martini, C., & Dahan, A. (2014). Ketamine for chronic pain: Risks and benefits. *British Journal of Clinical Pharmacology*, *77*, 357–367. doi:10.1111/bcp.12094

Noppers, I. M., Niesters, M., Aarts, L. P., Bauer, M. C., Drewes, A. M., Dahan, A., & Sarton, E. (2011). Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS Type 1 patients: A report of 3 cases. *Pain*, *152*(9), 2173–2178. doi:10.1016/j.pain.2011.03.026

Pacini, D., Murana, G., Leone, A., Di Marco, L., & Pantaleo, A. (2016). The value and limitations of guidelines,

expert consensus, and registries on the management of patients with thoracic aortic disease. *The Korean Journal of Thoracic and Cardiovascular Surgery*, *49*(6), 413–420. doi:10.5090/kjtcs.2016.49.6.413

Pomeroy, J. L., Marmura, M. J., Nahas, S. J., & Viscusi, E. R. (2017). Ketamine infusions for treatment refractory headache. *Headache*, *57*(2), 276–282. doi:10.1111/head.13013

Pourmand, A., Royall, C., Alhawas, R., & Shesser, R. (2017). Low dose ketamine use in the emergency department, a new direction in pain management. *American Journal of Emergency Medicine*, *35*(6), 918–921. doi:10.1016/j.ajem.2017.03.005

Richards, J. R., & Rockford, R. E. (2013). Low-dose ketamine analgesia: Patient and physician experience in the ED. *American Journal of Emergency Medicine*, *31*(2), 390–394. doi:10.1016/j.ajem.2012.07.027

Sanacora, G., Frye, M. A., McDonald, W., Mathew, S. J., Turner, M. S., Schatzberg, A. F., & Nemeroff, C. B. (2017). A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*, *74*(4), 399–405. doi:10.1001/jamapsychiatry.2017.0080

Schwenk, E. S., Viscusi, E. R., Buvanendran, A., Hurley, R. W., Wasan, A. D., Narouze, S., & Bhatia, A. (2018). Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Regional Anesthesia and Pain Medicine*, *43*(5), 456–466. doi:10.1097/AAP.0000000000000806

Sin, B., Ternas, T., & Motov, S. M. (2015). The use of subdissociative-dose ketamine for acute pain in the emergency department. *Academic Emergency Medicine*, *22*(3), 251–257. doi:10.111/acem.12604

Sinner, B., & Graf, B. M. (2008). Ketamine. *Handbook of Experimental Pharmacology*, *182*, 313–333. doi:10.1007/978-3-540-74806-9_15

Strayer, R. J., & Nelson, L. S. (2008). Adverse events associated with ketamine for procedural sedation in adults. *American Journal of Emergency Medicine*, *26*(9), 985–1028. doi:10.1016/j.ajem.2007.12.005

U.S. Food and Drug Administration. (2017). *Ketalar (ketamine hydrochloride) injection*. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pdf

U.S. Preventive Services Task Force. (2018). *Grade definitions*. Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions

Vadivelu, N., Schermer, E., Kodumudi, V., Belani, K., Urman, R. D., & Kaye, A. D. (2016). Role of ketamine for analgesia in adults and children. *Journal of Anaesthesiology Clinical Pharmacology*, *32*(3), 298–306. doi:10.4103/0970-9185.168149

Zeiler, F. A., Teitelbaum, J., West, M., & Gillman, L. M. (2014). The ketamine effect on intracranial pressure in nontraumatic neurological illness. *Journal of Critical Care*, *29*(6), 1096–1106. doi:10.1016/j.jcrc.2014.05.024

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