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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

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Background: Over the past 2 decades, the use of intravenous ketamine infusions as a treatment for chronic pain has increased dramatically, with wide variation in patient selection, dosing, and monitoring. This has led to a chorus of calls from various sources for the development of consensus guidelines.

Methods: In November 2016, the charge for developing consensus guidelines was approved by the boards of directors of the American Society of Regional Anesthesia and Pain Medicine and, shortly thereafter, the American Academy of Pain Medicine. In late 2017, the completed document was sent to the American Society of Anesthesiologists' Committees on Pain Medicine and Standards and Practice Parameters, after which additional modifications were made. Panel members were selected by the committee chair and both boards of directors based on their expertise in evaluating clinical trials, past research experience, and clinical experience in developing protocols and treating patients with ketamine. Questions were developed and refined by the committee, and the groups responsible for addressing each question consisted of modules composed of 3 to 5 panel members in addition to the committee chair. Once a preliminary consensus was achieved, sections were sent to the entire panel, and further revisions were made. In addition to consensus guidelines, a comprehensive narrative review was performed, which formed part of the basis for guidelines.

Results: Guidelines were prepared for the following areas: indications; contraindications; whether there was evidence for a dose-response relationship, or a minimum or therapeutic dose range; whether oral ketamine or another *N*-methyl-D-aspartate receptor antagonist was a reasonable treatment option as a follow-up to infusions; preinfusion testing requirements; settings and personnel necessary to administer and monitor treatment; the use of preemptive and rescue medications to address adverse effects; and what constitutes a positive treatment response. The group was able to reach consensus on all questions.

Conclusions: Evidence supports the use of ketamine for chronic pain, but the level of evidence varies by condition and dose range. Most studies evaluating the efficacy of ketamine were small and uncontrolled and were either unblinded or ineffectively blinded. Adverse effects were few and the rate of serious adverse effects was similar to placebo in most studies, with higher dosages and more frequent infusions associated with greater risks. Larger studies, evaluating a wider variety of conditions, are needed to better quantify efficacy, improve patient selection, refine the therapeutic dose range, determine the effectiveness of nonintravenous ketamine alternatives, and develop a greater understanding of the long-term risks of repeated treatments.

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INTRODUCTION AND JUSTIFICATION

Chronic pain and depression are both leading causes of years lost to disability worldwide, as they are typically refractory to conventional treatments.[1] There is considerable overlap between chronic pain and depression in terms of coprevalence

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Because this document has neither been presented to nor approved by either the American Society of Anesthesiologists Board of Directors or House of Delegates, it is not an official or approved statement or policy of the Society. Variances from the recommendations contained in the document may be acceptable based on the judgment of the responsible anesthesiologist.

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and treatment, with many therapies typically used to treat one being effective for the other.[2] One such treatment that intersects with both conditions is ketamine, which has generated enormous interest among health care providers, patients and their caregivers, and patient advocacy groups. Systematic and evidence-based reviews have found ketamine to be effective for both chronic pain and depression, and recent years have witnessed a dramatic increase in research and publications, clinical use, and publicity as determined by Internet traffic.[3] But because ketamine has been clinically available for almost 50 years, it has not been subject to the same scrutiny by the US Food and Drug Administration (FDA) or postmarketing surveillance as drugs that remain on patent protection. In fact, a recent symposium on its use compared its unbridled rise in clinical use as analogous to the "Wild West."[4]

Ketamine is classified by most pharmacological sources as an "anesthetic agent," being able to induce general anesthesia and ablate protective airway reflexes. Consequently, most hospitals prohibit its use as a "bolus" by nonanesthesiologists, and many require an anesthetist to oversee its use in any context. Yet, similar to other drugs used in anesthesia, the physiological effects are dose related, which has led to variations in policies. The surge in use; lack of large-scale, methodologically sound studies to guide treatment; and absence of treatment standards, to include safe-use recommendations, strongly portend the need for guidelines to inform safe practice. Previous consensus guidelines have been published on the use of ketamine for mood disorders, but these guidelines did not discuss mechanisms, address safe use, or provide guidance for pain management.[5] The objectives of this consensus statement are to provide an overview on the literature supporting ketamine for chronic pain, depression, and posttraumatic stress disorder (PTSD); determine appropriate patient selection for the use of ketamine infusions to treat acute and chronic pain; establish a framework for standardization of use during intravenous (IV) infusions; and establish safety parameters regarding monitoring, personnel, and dosing, which can be used for the treatment of chronic pain and psychiatric disorders. These recommendations are based on the US Preventive Services Task Force grading of evidence, updated in July 2012.[6]

METHODS OF DEVELOPMENT

This was a joint effort undertaken by the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the American Academy of Pain Medicine (AAPM), which commenced in November 2016; the boards of directors of these groups approved the documents in December 2017 and February 2018, respectively. In December 2017, on direction from the American Society of Anesthesiologists (ASA) president, the preliminary draft document was sent to the chairpersons of the ASA's Committees on Pain Medicine and Standards and Practice Parameters, who consulted with select members of the those committees. After incorporating minor revisions, the ASA Administrative Council approved the guidelines for both acute and chronic pain.

The Ketamine Guidelines Committee was charged with preparing guidelines on the use of ketamine as an analgesic that would enhance patient selection and safe practice, guide institutional protocol development, serve as a resource for information, and function as a template for regulatory bodies and payers. Members were selected by ASRA and AAPM, as well as the chair of the ASRA Guidelines Committee, who was selected by the 2 organizations as chairperson of the Consensus Guidelines Committee on Ketamine for Pain Management. Committee members were chosen based on their expertise and experience with the use of ketamine to treat pain; evaluating the literature; statistical background; and developing protocols to govern its oversight. The various sections of the review portion of the manuscript, as well as for the questions and answers that comprised the chronic pain guidelines, were separated into modules composed of 3 to 5 authors and the committee chair, with 1 panel member designated as "lead." These questions were selected by the committee chair based on input from the Guidelines Committee and refined by the group based on discussion during conference calls and e-mail correspondence. The answers to the questions were composed by the author modules based on consensus, with discrepancies resolved by the chair and his designee(s). All sections of the review portion and the acute and chronic pain guidelines were then reviewed by the entire committee and revised by consensus as needed through discussion. A consensus was originally deemed to be greater than 75% panel agreement with dissenting opinions noted, but we were able to reach complete concurrence on all issues considered.

Search engines used during composition of the various sections included MEDLINE, EMBASE, Google Scholar, and Cochrane Database of Systematic Reviews, as well as by examination of the reference sections of all manuscripts. Articles considered for inclusion were animal and experimental studies, systematic and other types of reviews, meta-analyses, clinical trials, and, for certain sections in which high-grade evidence was lacking (eg, treatment, complications), case reports and series. Key words used for the review section included "ketamine," "*N*-methyl-D-aspartate receptor," "central sensitization," whereas those used to address the specific guideline topics were tailored to the individual questions (eg, dose-response, dextromethorphan, intranasal, complex regional pain syndrome [CRPS]). Protocols from various institutions including academic, private practice, military, and Veterans Administration were also reviewed to gauge community standards. Conclusions for each question were graded from A to D or as insufficient, according to the US Preventive Services Task Force grading of evidence guidelines, with the level of certainty rated as high, medium, or low.[6] This system, which has been modified for use by the American Society of Interventional Pain Physicians in guidelines for pain treatment therapies,[7] was chosen over several others because of the wide range and greater flexibility it affords.[8,9] For example, unlike other systems, it allows for high-grade recommendations in the absence of systematic reviews or consistent level I studies (ie, which would be beneficial for recommendations concerning safety issues such as monitoring or rescue therapy for refractory cases).

DISCUSSION

History

Ketamine, originally labeled as CI-581, is a chemical derivative of phencyclidine. It was first administered to 20 volunteers from a prison population in 1964 and produced dissociative anesthesia, providing effective analgesia in doses ranging from 1 to 2 mg/kg.[10] As early as 1958, phencyclidine (CI-395) was administered to humans under a different name and was reported to cause increased blood pressure and nystagmus while maintaining respiration.[11]

The story of ketamine began with 2 scientists from Parke-Davis (now a subsidiary of Pfizer, Detroit, Michigan). A medicinal chemist, V. Harold Maddox, discovered a new chemical organic Grignard reaction, which led to the synthesis of phencyclidine (later given the clinical investigation number CI-395) on March 26, 1956.[12] Parke-Davis pharmacologist Graham Chen and his associates obtained the compound from Maddox in 1958. In animal studies, it caused an excited drunken state in rodents, but a cataleptoid immobilized state in pigeons. They extended the studies to a large variety of animals and concluded that the pharmacology of this compound was unusually complex.[13]

After sufficient animal toxicity testing, phencyclidine was given to humans undergoing surgery. John E. Gajewski, MD, at Parke-Davis was responsible for its clinical development. Phencyclidine proved to be a relatively safe anesthetic in humans, as it had been with monkeys. However, some patients developed severe and prolonged postsurgery emergence delirium.[14] The first human was given ketamine via an IV subanesthetic dose on August 3, 1964. Guenter Corssen, MD, an anesthesiologist at the University of Alabama at Birmingham and author on that pivotal first manuscript,[10] subsequently increased the dose in a stepwise fashion from no effect to "conscious but spaced out" and finally to a dose sufficient to produce general anesthesia. The findings were described as "remarkable!" The overall incidence of adverse effects was approximately 1 in 3 volunteers, and frank emergence delirium was minimal. Most of the subjects described strange experiences such as a feeling of floating in outer space and having no feeling in their arms or legs. Encouraged by its anesthetic effect, Parke-Davis filed for FDA approval of the drug and carried out further clinical studies. Ketamine was approved by the FDA in 1970. During the Vietnam War, it became a widely used anesthetic in theaters of operation where concerns about hemodynamic instability are paramount in wounded service members and has now been in clinical use for more than 50 years.

Epidemiology of Chronic Pain

Chronic pain is a worldwide epidemic. Among the leading causes of years lost to disability worldwide in 2013, 4 of the top 10 (low-back pain, neck pain, migraine, musculoskeletal disorders), including the perennial top cause—low-back pain—are pain related.[1] In the United States and other industrialized countries, the impact of chronic pain is even more pronounced, with 3 of the top 4 causes constituting chronic pain conditions (eg, low-back and neck pain and musculoskeletal disorders).[15] The socioeconomic burden due to chronic pain is enormous and cannot be overestimated. In a 2010 report, the Institute of Medicine estimated that chronic pain afflicts 1 of 3 Americans, costing between \$560 billion and \$635 billion annually.[16] In Europe, the reported burden of chronic pain is nearly equally steep, with the point prevalence estimated to be 25% to 30%.[17]

Classification of Chronic Pain and the Effects of Ketamine for Nonneuropathic Pain

There are numerous ways to classify and categorize chronic pain, but perhaps the most meaningful is by "type" or "location" (eg, neuropathic, nociceptive, central, peripheral, or mixed), as this informs treatment at every level of care. For example, nonsteroidal anti-inflammatory drugs are widely considered to be ineffective for neuropathic pain, whereas ketamine and gabapentinoids are generally acknowledged to be less effective for nonneuropathic pain than they are for neuropathic pain.[18] However, clinical reality is different than theoretical constructs based on animal studies, and drugs previously considered to be useful for only 1 type of pain (eg, ketamine for neuropathic pain, nonsteroidal anti-inflammatory drugs for nonneuropathic pain) have been shown in clinical trials to be efficacious for other types.[19–23] Many experts consider the distinction between different pain types to be a continuum, rather than discrete classification categories.[18] Although the preponderance of preclinical evidence supporting an antinociceptive effect for ketamine has been conducted using peripheral neuropathic and central pain models,[24–26] there are a handful of studies demonstrating an analgesic benefit in inflammatory and other nonneuropathic animal models.[27,28]

Pain categorization is important for determining diagnostic workup, guiding treatment decisions, and predicting outcomes. Among chronic pain patients, between 15% and 25% are estimated to have a predominantly neuropathic etiology.[29–31] For CRPS type I, which fails to meet the most recent International Association for the Study of Pain definition of neuropathic pain[32] but is the most common indication for ketamine treatment, the estimated prevalence rates vary between 20 and 30 per 100,000 person years.[33,34] Yet, these statistics may belie the true burden of neuropathic pain, as studies have shown that neuropathic pain may be associated with a poorer quality of life than comparable degrees of nonneuropathic pain.[35] A recent review found the strongest evidence for IV ketamine to be for the treatment of neuropathic pain and CRPS, although the nonneuropathic pain condition they compared them to was fibromyalgia.[36] In addition to fibromyalgia being a particularly challenging condition to treat, the studies cited also utilized lower dosages. Anecdotal evidence also supports intermediate-term benefit for ketamine infusions for nonneuropathic pain conditions such as refractory headaches and back pain.[37]

Mechanisms of Action

Ketamine exerts its analgesic, antidepressant, and psychomimetic effects via myriad pathways. Its primary mechanism is as a noncompetitive antagonist at the phencyclidine binding site of *N*-methyl-D-aspartate (NMDA) receptors residing in the central nervous system (CNS), particularly in the prefrontal cortex and hippocampus,[38] where it decreases the frequency of channel opening and duration of time spent in the active, open state.[39] The NMDA receptor is a ligand-gated channel whose major endogenous agonist is glutamate, the predominant excitatory neurotransmitter in the CNS. When this receptor is inhibited, decreased neuronal activity ensues. Activation of the NMDA channel plays a major role in cognition, chronic pain, opioid tolerance, and mood regulation and is considered the principal receptor involved in phenomena of central sensitization and windup.[38,40–43] Although some studies suggest a role for peripheral mechanisms in the analgesic effect of ketamine,[44] reviews have mostly found topical ketamine to be ineffective.[45]

Yet, NMDA-receptor antagonism is not the sole mechanism for its analgesic and antidepressant effects. In high doses, ketamine activates a variety of opioid receptors (mu > kappa > sigma), although the observation that its pain-relieving effects are not reversed by naloxone indicates this is not the major source of antinociception.[46,47] Ketamine also acts on a multitude of other non-NMDA pathways that play integral roles in pain and mood regulation, including antagonistic effects on nicotinic and muscarinic cholinergic receptors, the blockade of sodium and potassium (ie, hyperpolarization-activated cyclic nucleotide–gated [HCN]) channels, activation of high-affinity D_2 dopamine receptors and L-type voltage-gated calcium channels, facilitation of γ-aminobutyric acid A (GABA-A) signaling, and the enhancement of descending modulatory pathways.[48–51] Collectively, these other pathways may explain why ketamine may be beneficial in nonneuropathic pain conditions and provide a rationale for its use as a topical analgesic agent.[18,38,52,53]

The recent surge in opioid use and overdoses has led to a rise in non–opioid-based treatment options. In preclinical studies, ketamine has been shown to reduce opioid tolerance and hyperalgesia.[24,54] Although a recent meta-analysis demonstrated a small effect size for ketamine and other NMDA-receptor antagonists in reducing opioid consumption and improving analgesia in the perioperative setting,[55] the results of clinical studies have not been uniformly positive, which may in part be due to the multitude of factors that contribute to postsurgical pain and opioid consumption.[55–57]

The antidepressant effects of ketamine have generated intense interest in recent years in the psychiatric community. Given the high coprevalence rate of chronic pain and depression and other psychiatric morbidities, as well as the requirement of some institutions for patients being administered ketamine to be monitored by anesthesia providers, this has important ramifications for pain medicine providers.[58] Despite the recent surge in use in the context of mood disorders, there is a relative paucity of clinical data compared with its use as an anesthetic and analgesic agent, but the mood-enhancing effects appear to emerge in approximately 4 hours, after most of the drug has been cleared from circulation, and persist for up to 2 weeks, long after the acute analgesic effects dissipate.[59] Similar to its use as an analgesic, a variety of routes of administration have been successfully used for treatment of depression, including oral, intramuscular, and intranasal.[38,60–62]

Several mechanisms have been postulated to explain the rapid-acting antidepressant effects of ketamine. These include: (1) blockade of interneuronal and excitotoxic extrasynaptic NMDA receptors; (2) disinhibition of pyramidal cells leading to a glutamate surge; (3) activation of prosynaptogenic AMPA (α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid) receptors; (4) activation of synaptogenic intracellular signaling, including TORC1 (mammalian target of rapamycin complex 1) and brain-derived neurotrophic factor pathways; (5) increased GABA-B levels; and (6) inhibition of brain glycogen synthase kinase 3 (GSK-3B).[63–68] Inhibition of GSK-3 is a mechanism shared by the mood-stabilizing drug lithium, and the use of adjunct GSK-3B inhibitors such as lithium may augment and prolong ketamine's antidepressant effects.[69] Clinical trials and anecdotal experience have demonstrated efficacy not only for depression, but also for the treatment and prevention of PTSD.[70,71] Yet despite these other physiological effects, similar to its anticociceptive properties, the primary mechanism for its psychiatric effects is believed to be via the NMDA receptor. In preclinical and clinical studies, ketamine's antidepressant effects appear to follow a glutamate surge that leads to a cascade of events resulting in synaptogenesis and subsequent reversal of the negative effects of chronic stress and depression, particularly within the prefrontal cortex.[59] For PTSD, the potential beneficial effects of ketamine may derive from its ability to inhibit the glutamate-activated NMDA receptor, as glutamate plays a pivotal role in stress reactivity and formation of traumatic memories.[72,73] However, more research is needed to better elucidate these mechanisms and to determine the long-term effects of ketamine on depression and PTSD.

Pharmacodynamics and Pharmacokinetics

Ketamine exists as a racemic mixture of R(−) and S(+) stereoisomers. The S(+) stereoisomer is approximately 3 to 4 times more potent than its R(−) cousin consequent to its greater affinity for the PCP binding site on the NMDA receptor.[49] The S(+) stereoisomer has a shorter duration of action and possesses greater neuroprotective and analgesic properties than its R(−) counterpart, which might potentially make it a more ideal analgesic,[49,74] but preclinical and clinical analgesic studies comparing the 2 enantiomers have thus far yielded conflicting results.[75–77] Regarding the incidence of psychomimetic effects and abuse potential, studies comparing the different enantiomers have also produced mixed results.[78,79] For depression, 2 animal studies demonstrated more sustained antidepressant effects for the R(−) stereoisomer, but there are no clinical studies to guide treatment.[78,80]

Ketamine exhibits a unique combination of hypnotic, analgesic, and amnestic effects, which makes it ideal for treating post-traumatic and procedure-related pain. The hypnotic effects are likely secondary to inhibition HCN1 nonspecific cation channels that mediate "sag" currents, which help regulate and stabilize membrane potential.[81] The mechanisms behind the amnestic effects of ketamine are multifactorial in nature and probably the result of interactions at an assortment of receptors that include NMDA, serotonin, and nicotinic cholinergic.[82,83]

There is growing evidence for ketamine as a treatment for refractory seizures as well as for its use during electroconvulsive therapy. The anticonvulsant effects may be attributable not only to its effects on the NMDA receptor, but also to agonistic effects at the sigma and GABA-A and GABA-B receptors.[84,85] In electroconvulsive therapy, the propensity to induce seizures may be mitigated by the anticonvulsive effects of general anesthesia. Perhaps because of its interactions with the nicotinic receptor, the ability of ketamine to elevate the seizure threshold is less than that for other induction agents.[86] In animal studies, ketamine has been shown to decrease seizure threshold when given sequentially after aminophylline[87] and paradoxically to decrease enflurane-induced seizure activity.[88] In humans, ketamine has been shown to enhance epileptic discharges, which may explain the rare occurrence of seizures.[89,90]

Ketamine is a versatile drug that can be administered via many routes including IV, intramuscular, insufflation/intranasal, inhalational (smoked), oral (elixir or compounded pills), topical (minimal systemic absorption), and rectal (Table 1). It is both water and lipid soluble, which allows for extensive rapid distribution throughout the body and rapid crossing of the blood-brain barrier. Its predominant route of metabolism is via hepatic microsomal enzymes, most notably cytochrome P450, with approximately 12% remaining protein bound in plasma.[49] Although genetic polymorphisms of P450 isoforms (2B6, 2C9) may affect metabolism and clearance,[92,93] 1 study found that a genetic variant associated with decreased CYP2B6 expression and metabolism (CYP2B6*6) did not alter pharmacokinetics following single, low-dose (0.4 mg/kg) oral administration.[92] Thus, the effects of these polymorphisms in studies evaluating higher, IV dosages remains unknown.

Ketamine's half-life in plasma is approximately 2.3 ± 0.5 hours. The drug is rapidly metabolized to norketamine, hydroxynorketamine and dehydronorketamine, with norketamine possessing one-fifth to one-third of activity at the NMDA receptor as its parent compound, and 2R,6R hydroxyketamine, once considered to be an inactive metabolite, being an active inhibitor at the AMPA glutamate and α7 subtype of the nicotinic cholinergic receptor, which may contribute to antidepressant effects.[94–96] The excretion of unchanged ketamine (4%) and its metabolites is via the urine.

In low doses, ketamine causes analgesia and sedation, whereas in high doses, it produces general anesthesia. The clinical effects of ketamine result from both direct and indirect actions, with the latter predominating in most clinical contexts. Ketamine administration generally results in increases in heart rate, systolic and diastolic blood pressure, salivary and tracheobronchial secretions, and bronchodilation due to its stimulatory effects on the sympathetic nervous system. In clinically administered dosages, it has minimal effects on airway reflexes (ie, upper airway skeletal tone and responsiveness remain intact) and respiratory rate; paradoxically, some studies have shown an increased respiratory response to hypercapnea.[38,49,97] These effects make ketamine an ideal drug for trauma victims in the setting of hypovolemia, septic shock, or pulmonary disease and have led some experts to recommend and utilize ketamine as a potential first-line treatment for battlefield injuries.[98] The direct, dose-dependent negative inotropic effects on cardiac muscle are typically realized only in catecholamine depleted individuals (eg, long-term trauma or intensive care patients).[99]

The dissociative properties associated with ketamine are thought to result from the combination of reduced activation of the thalamocortical system and increased activity in the limbic system

TABLE 1. Pharmacokinetics of Ketamine for Different Routes of Administration[38,91]

Route of Administration	Typical Dosing	Bioavailability, %	Time of Onset	Duration of Action After Dosing
Intravenous	1–4.5 mg/kg for general anesthesia induction; 1–6 mg/kg per hour for anesthesia maintenance; 0.5–2 mg/kg for 1-d outpatient or 3- to 5-d inpatient awake ketamine infusions in chronic pain (higher dosages titrated to effect from lower doses); 0.2–0.75 mg/kg for procedural analgesia, can be repeated; 0.1 mg/kg for IV infusion test; 5- to 35-mg/h continuous infusion for acute traumatic or postoperative pain, 1–7 mg/demand dose mixed with opioids in patient-controlled analgesia	N/A	30 s	5–10 min for bolus doses
Intramuscular	2–4 times IV dosing; 5–10 mg/ kg for surgical anesthesia; 0.4–2 mg/kg for procedural analgesia; bolus and treatment dosing 0.10–0.5 mg/kg for chronic pain	75–95	2–5 min	30–75 min
Intranasal	0.2–1 mg/kg for chronic pain and sedation; 3–6 mg/kg for procedural analgesia and anesthetic premedication	25–50	5–10 min	45–120 min
Subcutaneous	0.1–1.2 mg/kg per hour for chronic pain; bolus and treatment dosing 0.10–0.6 mg/kg	75–95	10–30 min	45–120 min
Oral	0.3–1.25 mg/kg for chronic pain; up to 3 mg/kg for procedural analgesia and anesthetic premedication	10–20	5–20 min	2–4 h
Rectal	5–10 mg/kg for anesthesia premedication and procedural analgesia	25–30	5–15 min	2–3 h
Topical	1%–10% cream for chronic pain	<5	<2 d	NA

and hippocampus.[49] To a large extent, these effects may be reduced or eliminated with the concurrent use of benzodiazepines or α2 agonists, which act to reduce the psychomimetic effects by diminishing the cholinergic effects, which in turn mitigates the excessive stimulation of downstream corticolimbic neurons.[100,101]

The analgesic effects of ketamine are usually experienced when plasma concentrations approach 100 ng/mL. One advantage for using ketamine over opioid therapy for chronic pain is that long-term use is associated with less tolerance and tachyphylaxis.[102,103] This, in conjunction with the preliminary evidence touting its ability to prevent and reverse opioid tolerance and hyperalgesia, has led to its growing use as a rescue treatment in opioid-tolerant individuals (Table 1).[104–107]

Evidence

Preclinical Evidence and Challenges in Translation: Can Ketamine Reverse or Halt Central Sensitization?

The predominant therapeutic effect for ketamine is believed to involve its antagonistic effects at the NMDA receptor, which plays a major role in neuroplasticity and excitotoxicity. Hence, the NMDA receptor has been implicated in such diverse phenomena as memory and cognition, central sensitization and windup, and opioid tolerance and hyperalgesia.[18,108,109] Central sensitization may accompany any chronic pain condition but is most frequently linked to neuropathic pain.[110] Not surprisingly, although the preponderance of preclinical studies demonstrating an antinociceptive effect for ketamine have been conducted in neuropathic pain models, ketamine has also demonstrated analgesic effects in animal studies simulating inflammatory conditions.[111,112]

The simplest and most elegant explanation proposed for ketamine's chronic pain–relieving properties is that it "resets the CNS," in essence reversing the deleterious effects of central sensitization by virtue of its NMDA-receptor antagonistic effects.[113] However, the evidence for this hypothesis is inconsistent. Functional magnetic resonance imaging studies have shown that it is possible to reverse pathoanatomical changes associated with chronic pain with effective treatment,[114,115] but the effects of ketamine have not been extensively studied using functional imaging or instruments validated for measuring central sensitization.[116] Studies that have sought to measure quantitative sensory testing and conditioned pain modulation after ketamine administration have for the most part yielded negative findings.[48,117–123] Yet, an animal study showing that ketamine is more efficacious in chronic stages of CRPS, when central mechanisms predominate, than in acute stages, when peripheral mechanisms are more prominent, supports the reversal of central sensitization theory as the principal mode of analgesia.[124] Whereas most of ketamine's analgesic effects may be mediated via NMDA-receptor antagonism, it is likely that its effects on other systems including HCN1, cholinergic, aminergic, and opioid pathways also play a role.[125] Ketamine may exert its profound analgesic effects by not only affecting the sensory-discriminative system, but also modulating the affective-motivational component of pain.

As noted above, there is a preponderance of preclinical evidence supporting ketamine as an antidepressant and more mixed evidence supporting it as a treatment for PTSD.[59,69,126–128] The myriad physiological changes that mediate these benefits predominate in the CNS and are associated with enhanced neural activity in the prefrontal cortex and reduced activity in the amygdala and hippocampus.[129,130] Whereas animal models of pain use antinociception as a surrogate for analgesia, animal models of depression utilize tangible characteristics such as locomotor activity, aggression, preference for sucrose, and physiological responses (eg, electroencephalography to measure disturbances in circadian rhythm, laboratory tests to measure stress response, neuroimaging to measure CNS changes) to measure the subjective variable of mood.[131] For PTSD, the inherent challenges in translating a subjective condition to objective measures are equally challenging.[131] These factors may explain why most drugs shown to be beneficial in preclinical models of pain, depression, and PTSD fail in clinical trials.[18,131,132]

Clinical Evidence for Use in Acute Pain Management

When used for chronic pain, many physicians will administer the highest dose tolerated in an effort to "reverse central sensitization" or "unwind windup," attempting to pharmacologically counteract adverse effects, rather than tapering down the infusion. In contrast, in an acute pain setting, ketamine dosages are titrated to effect, carefully balancing analgesia with adverse effects, the latter of which may require a reduction in dosage.

Most studies evaluating ketamine in an acute pain setting have focused on the perioperative environment and a few other specific painful disease states, such as sickle cell pain crises. For patients outside the perioperative setting, evidence is limited to mostly case reports. The evidence suggests that most patients who benefit from ketamine in the acute pain setting fall into several categories. The first group of patients is those who are undergoing painful surgery, after which the expected postoperative pain rating is considered to be in the severe range.[133] Examples of surgical procedures in which the benefits seem to be the greatest include upper abdominal surgery and thoracic surgery; orthopedic limb, spine, intra-abdominal, and lower abdominal procedures also appear to be painful enough to warrant consideration of ketamine. Multiple reviews have demonstrated that ketamine reduces opioid consumption, pain levels, or both for a minimum of 24 hours after surgery and possibly 48 hours or more.[134–136] No (preincisional bolus only or very low dose) or only a very minor preventive effect on persistent postsurgical pain (number needed to treat >10) for ketamine is evident from existing studies, with 1 review suggesting that higher total dosages may be more likely to demonstrate a modest preventive effect (effect sizes −0.59 for dosages ≤0.5 mg/kg, −0.04 for dosages between 0.5 and 1 mg/kg, and −0.81 for dosages exceeding 1 mg/kg).[133]

Opioid-tolerant and opioid-dependent patients are frequently cited as groups that should receive ketamine, primarily because it makes conceptual sense given the role of the NMDA receptor in hyperalgesia and opioid tolerance.[55,137] Despite recommendations from several groups[138,139] for consideration of ketamine, the clinical evidence is limited to a few randomized controlled trials (RCTs). Loftus and colleagues[140] found ketamine reduced postoperative and long-term opioid use in opioid-dependent patients undergoing spine surgery, whereas another study reported that opioid-tolerant patients undergoing multiple different surgeries who received ketamine experienced improved average pain ratings postoperatively.[141] There are also less impressive[142] and negative studies[143,144] in this patient population. In studies examining the use of low-dose ketamine added to opioid patient-controlled analgesia for postsurgical pain, systematic reviews have found evidence for reduced pain scores and opioid consumption for up to 72 hours.[145,146]

Evidence for ketamine in acute painful exacerbations of chronic diseases such as sickle cell disease and nonoperative trauma (eg, rib fractures) is limited to mostly case reports and small case series.[147–151] In many of these conditions, limited numbers of patients and ethical considerations make prospective studies challenging. There is a clear need for well-designed, prospective studies in sickle cell disease and other painful disease states that acute pain physicians confront. The feasibility of performing such large-scale randomized studies, however, remains questionable.

Clinical Evidence for Use in Chronic Pain

The efficacy of ketamine for chronic neuropathic pain and conditions with features of neuropathic pain has been investigated in double-blind RCTs.[44,117–119,123,152–169] Several of these trials found that ketamine, administered under ideal clinical conditions, was associated with significantly greater reductions in pain compared with the control condition. However, statistical measures of the treatment effect, or effect size, were not used in these studies. In the absence of measures of effect size, a comparison of pain scores between the ketamine and control groups could help guide decisions about the use of ketamine in clinical practice. For example, 4[117,123,160,162] of 7[117,123,155,160–162,164] double-blind RCTs reported that ketamine infusions were associated with significantly greater reductions in pain compared with placebo in patients with mixed chronic neuropathic pain diagnoses. The difference in pain reduction between the ketamine and control groups measured during the ketamine infusions ranged from 25% to 45% in 3 studies.[44,118,152] However, in the study by Kvarnström and colleagues,[118] the significant group difference measured during the 0.4-mg/kg infusion was no longer present 110 minutes following completion of the infusion. In the study by Max and colleagues,[152] in which ketamine provided (mean dose, 58 mg over 2 hours) superior pain relief to both alfentanil and placebo, the pain relief disappeared before the adverse effects resolved. In the study by Leung et al,[44] the authors attributed part of the analgesic benefit to peripheral mechanisms. In another study, patients in the ketamine group (0.24 mg/kg over 30 minutes) experienced a 10-point greater pain score reduction on a 0- to 100 mm visual analog scale (VAS) measured during the infusion compared with placebo.[153]

In 2 double-blind RCTs that involved patients with traumatic spinal cord injury pain, ketamine infusions (0.06-mg/kg bolus followed by 0.36 mg/kg per hour and 0.4 mg/kg over 40 minutes) were associated with a 35% to 40% reduction in pain measured during the infusion compared with placebo.[119,154] In a third RCT that involved patients with traumatic spinal cord injury pain, IV ketamine 80 mg infused over 5 hours was associated with a 22-point reduction in VAS pain scores compared with placebo at 2-week follow-up, but not afterward.[155] Among patients with phantom limb pain (PLP), greater than 90% pain reduction was observed 30 minutes following an IV ketamine infusion of 0.4 mg/kg over 1 hour compared with placebo in 1 RCT,[117] and in another trial, IV ketamine (0.1-mg/kg bolus followed by 0.42 mg/kg per hour) was associated with a 2-point reduction (10-cm VAS) in pain scores 48 hours following completion of the infusion compared with placebo.[156] In a single RCT that involved patients with postherpetic neuralgia (PHN), IV ketamine 0.15 mg/kg over 10 minutes was associated with a 50% reduction in pain measured 15 to 45 minutes following ketamine administration compared with placebo.[157]

For conditions with features of neuropathic pain, ketamine has been investigated in several RCTs, but the treatment effects are mixed. In patients with fibromyalgia, a condition often associated with central sensitization, the findings of 2 RCTs demonstrated a 20- to 25-point reduction in VAS pain scores 90 to 120 minutes following IV ketamine 0.3 mg/kg compared with placebo.[158,159] In 2 other RCTs that involved patients with fibromyalgia, ketamine (0.3 mg/kg over 30 minutes and 0.5 mg/kg for 3 hours) was associated with a 0.5- to 0.9-point reduction in pain scores (10-cm VAS) at 90 to 180 minutes following IV ketamine compared with placebo.[21,160] However, in the study by Noppers and colleagues[160] that enrolled 24 patients with fibromyalgia who received a ketamine infusion of 0.5 mg/kg for 3 hours, no differences were found in pain scores or quality of life during the 8-week follow-up period. In patients with CRPS, 1 RCT reported a 1.2-point (0- to 10-point numerical rating scale) difference in pain scores between the ketamine (0.43 mg/kg per hour continuously over 4.2 days) and placebo infusion groups at 11-week follow-up, but no group difference was observed at 12-week follow-up.[161] This study was limited to patients with CRPS type I, which does not meet the most recent International Association for the Study of Pain definition of neuropathic pain because of the absence of an identifiable nerve injury.[32] A second RCT that

TABLE 2. Randomized Placebo-Controlled Trials Evaluating Intravenous Ketamine for Chronic Pain With a Minimum of 48 Hours of Follow-Up

First Author, Year	Patients	Ketamine Regimen	Follow-Up	Results	Comments
Amr,[155] 2010	40 patients with neuropathic pain after spinal cord injury	80 mg over 5 h per day × 1 wk	4 wk	Ketamine better than placebo for 2 wk	All patients also received gabapentin
Eichenberger,[117] 2008	20 patients with PLP	0.4 mg/kg over 1 h with 48 h minimum interval between infusions	48 h	Ketamine better than placebo and calcitonin. No difference between ketamine alone and combination for worst pain reduction, but combination superior for mean pain reduction. Mixed results for QST	Crossover study comparing ketamine to calcitonin to combination of both to placebo
Schwartzman,[123] 2009	19 patients with CRPS types 1 and 2	Up to 100 mg over 4 h for 10 consecutive weekdays	9–12 wk	Ketamine better than placebo for pain, but no improvement in QST and no correlation between response and serum levels	Study halted at midpoint because of lack of improvement in ketamine group
Sigtermans,[161] 2009	60 patients with CRPS type 1	0.43 mg/kg per hour continuously over 4.2 d	12 wk	Ketamine better than placebo, but results were not statistically significant beyond 11 wk	Blinding ineffective
Noppers,[160] 2011	24 patients with fibromyalgia	0.5 mg/kg over 30 min	8 wk	Ketamine better than placebo only up to 3 h	Blinding ineffective
Mitchell,[162] 2002	35 patients with ischemic limb pain	0.6 mg/kg over 4 h	2–9 d (mean, 5 d)	Ketamine better than placebo	All patients also received opioids
Salas,[164] 2012	20 patients with cancer pain	0.5 mg/kg per day increased to 1 mg/kg per day × 2 d for persistent pain	48 h	No difference between treatment groups	All patients received morphine

QST indicates quantitative sensory testing.

included individuals with both CRPS types I and II reported a 14-point difference on the short-form McGill Pain Questionnaire between the ketamine (up to 100 mg over 4 hours for 10 consecutive weekdays) and placebo infusion groups at 9- to 12-week follow-up (Table 2).[123]

In individuals with nociceptive pain, the results have been mixed. Among patients with ischemic pain attributed to severe peripheral vascular disease, 1 RCT reported a 19% difference in pain relief between the ketamine infusion of 0.6 mg/kg over 4 hours and a placebo infusion at 5-day follow-up,[162] but a second RCT reported no significant differences in pain scores between ketamine (0.15–0.45 mg/kg over 5 minutes) and morphine 10 mg when measured at the time of each drug's peak effect following completion of the infusions.[163] In a small, double-blind study evaluating an IV ketamine infusion (0.5 mg/kg per day increased to 1 mg/kg per day for 2 days) for persistent pain as an add-on treatment to morphine for cancer pain, no difference between treatment groups was found during the 48-hour follow-up period.[164]

The use of ketamine in headache disorders has surged over the past few years in light of several studies demonstrating benefit.[165–167] In a single RCT that involved patients with migraine headache, a bolus of subcutaneous ketamine 80 μg/kg was associated with an approximately 50% reduction in acute migrainous pain compared with placebo and an approximate 75% reduction in chronic migrainous pain at 7- to 10-day follow-up when administered in thrice-a-day dosing for 3 weeks.[168] However, a second RCT that investigated the effects of intranasal ketamine 25 mg compared with intranasal midazolam 2 mg found that ketamine reduced the severity but not the duration of migrainous aura, with no significant group differences in pain scores observed.[169] In a retrospective study that involved 49 patients diagnosed with 7 different chronic pain conditions with neuropathic pain features, a 5.9-point (10-cm VAS) reduction in pain scores was observed following a ketamine infusion (median dose, 0.9 mg/kg over 30–45 minutes; median number of infusions, 4), with 38% of patients reporting greater than 3 weeks of relief (Table 3).[37]

When interpreting controlled trials evaluating ketamine, one must consider that because of ketamine's psychomimetic effects, blinding can be difficult. In the study by Noppers and colleagues,[160] 75% of participants correctly guessed which group they were allocated to, and in the study by Sigtermans and colleagues,[161] 28 of 30 patients who received ketamine correctly guessed their treatment group. Systematic reviews and clinical studies have found that the absence of blinding exaggerates the effect size by approximately 35% and that unclear blinding increases the treatment effect by 13% to 25%.[170–172]

Adverse Effects and Pathophysiology

Cardiovascular and Pulmonary Effects

The challenge in describing the physiologic effects of ketamine used at subanesthetic doses are that: (1) many of the studies that reported these effects focused on anesthetic doses, which are typically 1.5 to 2 mg/kg or higher given as a bolus; and (2) there is no standard definition of what dose is considered "subanesthetic." Practitioners are left to make assumptions about the severity and frequency of these effects at lower doses based on limited evidence. Nevertheless, early work by Gooding and colleagues[173] in 1977 suggests that ketamine has greater effects on the pulmonary vasculature than the systemic vasculature. Furthermore, they note no significant changes in cardiac output, stroke volume, systemic vascular resistance, and other cardiovascular parameters. However, in critically ill patients, there appears to be a negative inotropic effect as demonstrated in a 1980 study.[174] Reviews have noted that ketamine has both a negative inotropic effect and

TABLE 3. Clinical Outcomes for Ketamine Therapy in Headaches

First Author, Year	Study Design and Patients	Treatments	Results	Comments
Granata,[165] 2016	Observational study in 29 patients with cluster headache	Low-dose IV ketamine (0.5 mg/kg over 1 h) every 2 wk up to 4 times	Cluster attacks were completely aborted in 100 % of patients with episodic headaches and in 54% of patients with chronic cluster headaches for a period of 3–18 mo	13 had chronic cluster, and 16 had the episodic form
Moisset,[166] 2017	Case report in 2 patients with cluster headache	Single IV ketamine infusion (0.5 mg/kg over 2 h) combined with magnesium sulfate (3000 mg over 30 min)	Complete relief in 1 patient and 50% for the other patient, for 6 wk in both cases	Both had chronic cluster headache
Pomeroy,[167] 2017	Retrospective study in 77 patients with migraine or NDPH	IV subanesthetic ketamine infusion (0.1–1 mg/kg per hour); mean length of infusion, 4.8 d	71.4% of patients were classified as acute responders; sustained response did not achieve statistical significance	Patients had chronic migraine or NDPH; acute responders defined as those with at least 2-point improvement in headache pain at discharge
Afridi,[169] 2013	Randomized, double-blind, placebo-controlled, parallel study in 30 patients with migraine	25 mg intranasal ketamine with 2 mg intranasal midazolam as an active control; each subject recorded data from 3 episodes of migraine	Ketamine reduced the severity but not duration of aura, whereas midazolam had no effect	Patients had migraine with prolonged aura. 18 subjects completed the study
Nicolodi,[168] 1995	Randomized, double-blind crossover in 34 patients with migraine headache (17 each received acute and chronic therapy)	Acute therapy: SC ketamine hydrochloride (80 μg/kg) or SC saline (control); chronic therapy: SC ketamine (80 μg/kg) TID for 3 wk	Marked relief of pain both as an acute treatment and as a prophylactic therapy	Migraine headaches not diagnosed using the International Classification of Headache Disorders criteria; mild adverse effects in the majority of patients in both ketamine and placebo groups

NDPH indicates new daily persistent headaches; SC, subcutaneous; TID, 3 times daily.

simultaneous indirect sympathetic nervous system stimulation, which is due to systemic release of catecholamines, vagal nerve inhibition, inhibition of norepinephrine reuptake at peripheral nerves, and other mechanisms.[175–177] Parameters such as heart rate, blood pressure, cardiac output, and myocardial oxygen consumption increase even with subanesthetic doses.[175,176] In the pulmonary system, ketamine causes bronchodilation that appears to be due to circulating catecholamines.[176,177] Pharyngeal and laryngeal reflexes are mostly preserved, as is respiratory function, and there are increased secretions.[176,177] The speed of injection may play a role in maintenance of respiratory function,[176] implying that subanesthetic infusions for analgesia may carry a lower risk of respiratory depression than when ketamine is administered as a bolus dose for use as an anesthetic, although no direct evidence exists to support this.

Spinal Cord Effects

Several studies in animals suggest that ketamine may cause pathological changes when given intrathecally.[178–180] However, several other studies report that no histopathologic changes are observed when the preservative is omitted.[181,182] High-quality data are lacking in humans, but it seems prudent to avoid intrathecal ketamine given the lack of evidence showing clear benefit, except in rare circumstances. Currently, the use of intrathecal ketamine is listed as a sixth-line adjuvant to be used in conjunction with other neuraxial analgesics in individuals with refractory cancer or other terminal chronic pain conditions.[183]

Psychomimetic Adverse Effects

Reviews and meta-analyses of perioperative ketamine have come to different conclusions regarding ketamine's adverse psychomimetic effects including hallucinations, visual disturbances, unpleasant dreams, and dysphoria, when it is used in subanesthetic doses.[133–135,175–177] Based on 37 RCTs that studied perioperative ketamine, Bell and colleagues[134] concluded that the incidence of psychomimetic adverse effects was similar in ketamine and placebo groups. After evaluating 10 studies examining intraoperative ketamine and 15 assessing postoperative infusions, a review also concluded that psychomimetic adverse effects were not increased by ketamine, with the exception of 1 study that reported a higher incidence of hallucinations.[135] These findings are in contrast to those of Laskowski and colleagues,[133] who reported that in 70 studies analyzing IV ketamine for postoperative analgesia, "neuropsychiatric effects" were increased in the ketamine treatment groups compared with placebo. A retrospective study analyzing 321 patients who received subanesthetic ketamine infusions for various acute pain indications reported an incidence of 16% for CNS excitation symptoms.[184] Although there was no control group, 35 of the 37 patients whose infusions were stopped because of CNS symptoms had resolution of symptoms upon cessation, suggesting that ketamine was responsible. Based on the totality of evidence, it appears that subanesthetic ketamine administered only intraoperatively is unlikely to cause major psychomimetic adverse effects; however, postoperative infusions are associated with limited and reversible psychomimetic adverse effects.

The issue of dosing as it relates to the occurrence of psychomimetic adverse effects is not clearly established in the literature. One review addressed this and found that safety is not correlated to the dose given when it comes to subanesthetic ketamine.[135] Another noted that, "psychedelic adverse effects occur in a dose-dependent fashion" but did not provide a reference for the claim.[175] Although CNS effects do seem to be dose-dependent when ketamine is used in anesthetic doses,[177] the evidence is not as clear for subanesthetic regimens, beyond a yet-to-be determined threshold. In a retrospective study by Schwenk and colleagues,[184] discontinuation of ketamine infusions secondary to adverse effects was unrelated to the maximum infusion rate, which further questions the notion that adverse effects at low doses are dose related.

Hepatic, Genitourinary, and Gastrointestinal Effects

There are few studies that directly address the issues of hepatotoxicity and cystitis with subanesthetic ketamine use. Data must be extrapolated from animal studies and studies in ketamine abusers. Animal studies have demonstrated the potential of ketamine to cause hepatotoxicity as well as cystitis.[185] In humans, the incidence of hepatotoxicity and cystitis may be increased with higher doses and repeated exposure, although liver enzyme levels return to normal after discontinuation of the drug.[186] One study found that illicit ketamine had a greater propensity to induce urological pathology than legal ketamine, which the authors attributed to adulterants enhancing the inflammatory response.[187] Wong and colleagues[188] assessed a group of 297 chronic ketamine abusers with liver biopsy and magnetic resonance cholangiopancreatography and found the prevalence of liver injury to be 9.8%, all cases of which involved cholestatic pathology. Another study by Noppers and colleagues[189] reported that 3 patients being treated with ketamine for CRPS developed hepatotoxicity during their second exposure to the drug. All 3 had elevated liver enzymes that took several months to return to reference range.[189]

Ketamine-induced cystitis has been documented primarily in abusers of ketamine.[190] It typically presents as painful hematuria, dysuria, frequency, and postmicturition pain.[191] The entity was first described in 2007 in a case series of 9 patients who were ketamine abusers.[192] Treatment begins with cessation of ketamine use[191] and may also consist of mucosal protective agents such as hyaluronic acid or anticholinergic drugs.[191,193] More severe disease may require surgical intervention.[191] Almost all of the available literature on this topic involves ketamine abusers, with a single case report documenting a pediatric patient who developed cystitis while taking ketamine chronically for pain.[194] Therefore, the risk of developing cystitis with brief ketamine infusions or short-term therapy at subanesthetic doses is largely unknown but may be increased with repeated or frequent exposures.[190]

Nausea and vomiting appear to decrease in patients receiving ketamine in the perioperative period.[133,134] It is not clear whether this effect is due to ketamine itself or its opioid-sparing properties. It has been suggested that ketamine may have a higher propensity to cause nausea than other sedative hypnotics,[176] and several retrospective analyses reported rates of 2.8% to 6.5% for nausea and vomiting.[167,184] However, the overall findings from available meta-analyses demonstrate either no difference between ketamine and placebo groups in nausea and vomiting[136] or a reduction in nausea and vomiting (Table 4).[133,134,146]

Monitoring

Ketamine is associated with adverse psychomimetic, cardiovascular, and gastrointestinal effects resulting from its action on a variety of substrate receptors including NMDA, acetylcholine, opioid, monoamine, and histamine. Monitoring methods for these possible adverse events have not been directly examined in clinical studies. In the available literature (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/AAP/A249),[21,44,117–119,123,152–163,197–199] the most common parameter reported is blood pressure measurement followed by monitoring of electrocardiogram (ECG), level of sedation/consciousness, and pulse oximetry. The use of capnography has not been reported in the literature, and psychomimetic adverse events have been collected as self-report measures.

TABLE 4. Adverse Effects and Pathophysiology Associated With Subanesthetic Ketamine

Key Studies	Adverse Effects	Comments
Laskowski,[133] 2011; Bell,[134] 2005; Jouguelet-Lacoste,[135] 2015; Elia,[136] 2005; Drayna,[195] 2012	• Psychomimetic (dysphoria, hallucinations, nightmares, and vivid dreams)	• Unlikely to occur with intraoperative use alone; may occur if used postoperatively • If they occur, discontinuation of infusion often improves symptoms; benzodiazepines or α2 agonists may be effective
	• Blurry vision or diplopia	• Reported incidence 6.2% • Dose-response relationship unclear at subanesthetic doses • Incidence of intraocular pressure, a possible cause of visual symptoms, not known with subanesthetic dosages
Laskowski,[133] 2011; Bell,[134] 2005; Elia,[136] 2005	• Nausea and/or vomiting	• PONV no worse with ketamine than placebo and may be decreased
Wai,[185] 2012; Bell,[186] 2012; Wong,[188] 2014; Noppers,[189] 2011	• Hepatic toxicity	• Occurs mostly in ketamine abusers • Reported upper incidence 9.8% • Typically presents with elevated liver enzymes • Mechanism may be cholestatic • Resolves after ketamine cessation in most patients
Schwartzman,[123] 2009; Goldberg,[196] 2005;	• Headache	• Although reported at >10% in some studies, most report similar incidence to placebo • At higher doses, serious causes such as elevated intracranial pressure should be considered • Considered a treatment for headaches
Morgan,[190] 2011; Jhang,[191] 2015; Shahani,[192] 2007; Chen,[193] 2011	• Cystitis	• Occurs mostly in ketamine abusers • Typically presents with painful hematuria, dysuria, increased frequency, and pain postmicturition • Mechanism may involve direct toxic effect, bladder barrier dysfunction, neurogenic inflammation, immunoglobulin E–mediated inflammation, overexpression of carcinogenic genes, abnormal apoptosis, and nitric oxide synthase–mediated inflammation • First-line treatment is ketamine cessation; hyaluronic acid or anticholinergic agents may be helpful
Gomes,[178] 2011; Walker,[179] 2010; Vranken,[180] 2006; Rojas,[181] 2012; Errando,[182] 1999	• Spinal cord injury	• Reported only with intrathecal use • Weak evidence exists in animal studies; unknown effects in humans • Toxicity may be more likely if preservative used but may still occur with preservative-free formulation

PONV indicates postoperative nausea and vomiting.

Similar to other procedural interventions that are performed using sedation or monitored anesthetic care, the monitoring used during administration of ketamine should depend on the likelihood of deleterious signs (eg, elevated blood pressure and heart rate, ECG changes, loss of consciousness, psychotomimetic), symptoms (eg, chest pain, airway obstruction, hallucinations), and the potential for adverse consequences. The monitoring practices for ketamine infusions in the literature vary considerably and are not always consistent with ASA recommendations for the delivery of medications for moderate and deep sedation.[200] These recommendations include basic safety measures such as ensuring nil-per-os status, the use of supplemental oxygen during deep sedation, and monitoring the patient's level of consciousness, ventilation, oxygenation, and hemodynamic status prior to sedation, after the infusion has begun, periodically throughout the infusion, and prior to discharge, whereby certain discharge criteria must be met. The frequency and extent of monitoring depend in part on the presence and severity of associated medical comorbidities. For example, in patients with relative contraindications to ketamine such as poorly controlled angina, an infusion may still be indicated in refractory cases if the perceived benefits outweigh the risks. In patients with a history of angina, the physician might consider utilizing more frequent blood pressure monitoring (or continuous monitoring with an arterial line) in an intensive care unit setting.

Guidelines

Guideline Question 1: Which Patients and Chronic Pain Conditions Should Be Considered for Ketamine Infusions?

Chronic neuropathic pain is the most widely investigated indication for IV ketamine. Specific diagnostic categories that have been studied in RCTs include neuropathic pain of mixed diagnoses, traumatic spinal cord injury, PHN, and PLP. Conditions with features of neuropathic pain have also been studied including CRPS, fibromyalgia, and chronic ischemic pain.

In 7 double-blind RCTs, 78 patients with mixed neuropathic pain diagnoses were administered IV ketamine.[44,118,152,153,197–199] In 4 studies, significant reductions in pain during the ketamine infusion were observed compared with placebo.[44,118,152,153] However, in 3 studies, no significant differences in pain were observed between the ketamine and placebo groups.[197–199] The dose of the ketamine infusions ranged from 0.006 to 0.75 mg/kg per hour,[118,152,153,197–199] and the duration of the infusions ranged from 5 minutes to 2 hours.[44,118,152,153,197–199] The variations in dose and duration of infusion limited the identification of a definitive dose-response relationship between ketamine and pain scores. In the study by Leung and colleagues,[44] the dose of the ketamine infusion was not specified, but rather the authors titrated the infusion rate to achieve 3 target serum concentrations (50, 100, and 150 ng/mL). In this study, the pain scores decreased in a stepwise manner as the targeted plasma level increased, consistent with a dose-response relationship.[44] In the study by Backonja and colleagues,[197] the duration of pain relief persisted for 2 to 3 hours following the infusion; otherwise, the duration of pain relief was not assessed beyond completion of the infusion in the remaining 6 studies.[44,118,152,153,198,199]

In 3 double-blind RCTs, the effects of IV ketamine were studied in 69 patients with traumatic spinal cord injury pain.[119,154,155] Significant reductions in pain scores during the ketamine infusion were observed in all 3 studies compared with placebo.[119,154,155] In 2 of these studies, the duration of pain relief was not assessed beyond the duration of the infusion.[119,154] In the study by Amr,[155] which added gabapentin to both treatment arms, a significant difference in pain scores was observed between the ketamine and placebo groups through 2 weeks following the infusions, but not afterward. There was considerable variation in the dose and duration of the ketamine infusions, which ranged from 6 μg/kg/min (0.42 mg/kg per hour) to 0.4 mg/kg for 17 minutes to 5 hours for 7 consecutive days.[119,154,155] Notably, less than 1 year after Amr's double-blind study evaluating IV ketamine for spinal cord injury neuropathic pain, Amr[201] performed a similar study comparing a single bolus of epidural ketamine (0.2 mg/kg) plus gabapentin to epidural saline on 40 patients with the same condition. The results were more auspicious in that short-term benefit was observed through 30 days, although not at longer follow-up periods.[201] However, the analgesic mechanisms behind a single neuraxial bolus and high-dose IV administration given over several days may be different, which makes generalizability difficult.

In 2 double-blind RCTs, the effects of IV ketamine were assessed in 21 patients with PLP,[117,156] with significant reductions in pain scores during the infusion observed in both studies compared with placebo. In the study by Nikolajsen and colleagues,[156] significant reductions in pain scores compared with placebo were observed up to 35 minutes following completion of the ketamine regimen, which consisted of a 0.1-mg/kg bolus administered over 5 minutes followed by an infusion of 7 μg/kg per minute (0.5 mg/kg per hour) for not more than 45 minutes.[156] In the other study, no significant differences in pain scores between placebo and ketamine (0.4-mg/kg infusion over 1 hour) or calcitonin as stand-alone treatments were found at 48-hour follow-up, although ketamine and calcitonin in combination was associated with significant improvements in average and worst pain.[117]

In a single double-blind RCT, the effects of IV ketamine (0.15 mg/kg administered over 10 minutes) were investigated in 8 patients with PHN.[157] Between 15 and 45 minutes following the ketamine infusion, significant reductions in pain scores were observed compared with placebo.

The clinical outcomes of several studies are available for conditions often associated with features of neuropathic pain including fibromyalgia, ischemic pain, migraine headache, low-back pain, and cancer. In 4 double-blind RCTs, the effects of IV ketamine infusions ranging from 0.3 to 0.5 mg/kg for 10 to 30 minutes were compared with placebo in 97 patients with fibromyalgia. In all 4 trials, significant improvements in pain were found during and immediately following the infusions.[21,158–160] Sustained improvements in pain compared with placebo were observed for up to 120 minutes in the 1997 study by Sorensen and colleagues.[159] However, in the study by Noppers and colleagues,[160] there were no significant differences in pain reduction between the ketamine and placebo groups at 2.5 hours, 1 week, or 8 weeks following the infusion.

The effects of IV ketamine on ischemic pain was assessed in 2 double-blind RCTs that involved 26 patients with severe peripheral vascular disease.[162,163] In the study by Mitchell and Fallon,[162] significant differences in pain relief between the ketamine (0.6 mg/kg administered over 4 hours) and placebo groups were reported 24 hours and 5 days following the infusions. In the study by Persson and colleagues,[163] 3 IV doses of ketamine (0.15, 0.3, 0.45 mg/kg) were compared with 10 mg of IV morphine, with both drugs infused over 5 minutes. No significant group differences in the analgesic effects of ketamine and morphine were observed when assessed at the time of the peak effects of each drug (5 minutes for ketamine and 20 minutes for morphine).[163]

In a double-blind study evaluating the effect of an add-on, low-dose IV ketamine infusion (up to 1 mg/kg per day or 0.025 mg/kg per hour) to morphine in 20 patients with cancer-related pain, which often has a neuropathic component, no benefit was observed in the treatment group during the 48-hour follow-up period.[164]

The effects of ketamine on migraine headache and chronic low-back pain have not been widely studied. In a single double-blind RCT that involved 17 patients with migraine headache, significant improvements in pain were observed compared with placebo for acute pain (<1 hour) and for at least 15 days in 12 subjects following administration of subcutaneous ketamine (80 μg 3 times daily for 3 weeks.).[168] However, a retrospective study failed to demonstrate prolonged benefit for migraine and new daily persistent headache following a multiday IV ketamine infusion.[167] For chronic low-back pain, the evidence supporting IV ketamine is purely anecdotal and derived from a retrospective study that included 7 patients.[37]

The effects of ketamine on CRPS were investigated in 2 double-blind RCTs involving 79 patients.[123,161] In the study by Sigtermans and colleagues,[161] significant improvements in pain were observed with S(+) ketamine (mean ketamine infusion dose, 22 [SD, 2.0] mg/h; mean duration, 4.2 days) compared with placebo at weeks 1 through 11 following the ketamine infusion. However, at the week 12 follow-up, the difference in pain scores between groups was no longer statistically significant.[161] In the study by Schwartzman and colleagues,[123] a significant difference in the short-form McGill Pain Questionnaire scores was observed between the ketamine (0.35 mg/kg per hour over 4 hours daily for 10 days) and placebo groups at 4 time points following the infusions (weeks 1–2, weeks 3 to 4, weeks 5–8, and weeks 9–12). However, the pretreatment McGill Pain Questionnaire total score in the ketamine group was lower compared with the placebo group, and among the 7 other parameters of pain assessed, few significant differences were observed between groups and none after 8 weeks. This trial failed to enroll the planned number of individuals, in part because the authors determined that higher dosages were necessary.[123]

In summary, for spinal cord injury pain, there is weak evidence supporting ketamine infusions (0.42 mg/kg per hour to 0.4 mg/kg ranging from 17 minutes to 5 hours for 7 consecutive days) for short-term improvements in pain (grade C recommendation, low level of certainty). For CRPS, there is moderate evidence supporting ketamine infusions (22 mg/h for 4 days or 0.35 mg/kg per hour over 4 hours daily for 10 days) to provide improvements in pain for up to 12 weeks (grade B recommendation, low to moderate level of certainty). For mixed neuropathic pain, PLP, PHN, fibromyalgia, cancer pain, ischemic pain, migraine headache, and low-back pain, there was weak or no evidence supporting ketamine infusions for immediate improvements in pain (grade D, low level of certainty). Excluding CRPS, there was no evidence supporting ketamine infusions for intermediate or long-term improvements in pain.

Guideline Question 2: What Are the Contraindications for Ketamine Infusions?

When contraindications for ketamine are listed in textbooks and sources such as the Prescribers' Digital Reference, ketamine is classified as a Drug Enforcement Administration Schedule III, nonbarbiturate, sedative hypnotic.[202] It is FDA-approved for induction of general anesthesia, and as an anesthetic agent, it is given in higher dosages than for use in acute and chronic pain. In the subanesthetic doses used for acute or chronic pain, the IV ketamine boluses and infusion dosages are generally well tolerated.[203,204] In the majority of patients, ketamine is associated with minimal physiological effects on the neurologic, cardiovascular, respiratory, gastrointestinal, and ophthalmic systems.[205] Ketamine is metabolized by the liver and excreted by the kidney, but in the vast majority of cases, prolonged effects on hepatic or renal function have not been noted with subanesthetic doses.[189,206,207] Thus, the contraindications for anesthetic doses of ketamine may be relative contraindications or precautions when using subanesthetic doses, although definitive evidence is often lacking. In other words, patients with certain preexisting morbidities involving these systems are likely at a greater risk of complications when used at subanesthetic doses. Consequently, there are metabolic contraindications to the use of IV ketamine for chronic pain based on “best practices” noted in the literature.[205] Because ketamine is used as an elective treatment for a non–life-threatening condition (ie, pain), it is prudent to heed these relative contraindications and precautions, even though the likelihood of complications is low. Similarly, although there is evidence to indicate that some adverse effects are dose-dependent when ketamine is used in an anesthetic context, the evidence is less clear-cut for subanesthetic regimens beyond an unknown threshold dose. This is illustrated by a study from Schwenk and colleagues[184] in which discontinuation of ketamine related to adverse effects in a perioperative setting was unrelated to the infusion rate.

Medical contraindications and precautions regarding use of ketamine are listed in Table 5. In most instances, the evidence base for these recommendations is not robust enough to distinguish between absolute and relative contraindications except for elevated intracranial and intraocular pressure, brain tumor, and traumatic brain injury, which appear to be weak relative contraindications.[195,208,209] For example, there appears to be little to no risk of developing increased intracranial pressure when IV ketamine is used as an anesthetic induction agent prior to intubation in an operating room or intensive care unit setting in patients with brain tumors or traumatic brain injuries.[208,209] The same applies to concerns regarding elevated intraocular pressure when ketamine is used for sedation.[195] For cardiovascular events such as precipitation of angina, both anesthetic dosages and subanesthetic dosages used to treat chronic pain have been implicated.[210,211]

The American Psychiatric Association (APA) recently published consensus guidelines regarding the use of IV ketamine for treatment-resistant depression.[5] These guidelines as well as other reports[203,205,212] suggest few psychiatric contraindications. Large case series and systematic reviews indicate that there is an approximately 3.5% to 7.4% incidence of psychomimetic or dysphoric effects with IV ketamine.[134,136,203,205] The majority of these effects involve transient hallucinations or dissociative, out-of-body sensations, none of which lead to self-injurious behavior, extreme agitation, or extended psychosis. It is unclear from these studies if there is a dose-response relationship between ketamine and the incidence or intensity of psychiatric adverse effects, although adverse effects for most medications that act in the CNS are dose related. It is noteworthy that the treatment of choice to prevent or abort ketamine-induced hallucinations or dissociative effects is low-dose benzodiazepines (such as IV lorazepam or midazolam) or α2 agonists (clonidine), and not antipsychotics. As such, individuals with a history of serious psychomimetic effects and relative contraindications to rescue medications such as benzodiazepines (eg, use of some human immunodeficiency virus retroviral drugs, poorly controlled myasthenia gravis, history of adverse reaction) may not be good candidates for ketamine treatment. A history of psychosis as a contraindication is based on reports that the administration of subanesthetic IV ketamine to schizophrenics has caused reactivation of hallucinations and/or delusions.[213] It is also possible that patients with delirium can experience an exacerbation of symptoms with ketamine infusion.

Considering the growing recognition of its abuse potential,[214–217] a history of alcohol or other substance abuse is mentioned in several Web sites, drug monographs, and case reports as a relative contraindication to ketamine use. Unlike for acute pain in which there is a widely accepted mandate for urgent treatment, infusions are generally given on a 1-time basis, and the therapeutic alternatives (ie, high-dose opioids in an opioid-dependent individual) are often less appealing than ketamine; for chronic

TABLE 5. Contraindications to and Precautions for Use of Subanesthetic Doses of Ketamine for Chronic Pain

Category	Contraindication/Precaution
Cardiovascular	• Unstable angina • Poorly controlled hypertension • High-risk coronary vascular disease
Neurological and ophthalmic	• Elevated intracranial pressure, including secondary traumatic brain injury or tumor • Elevated intraocular pressure, acute globe injury, or glaucoma
Endocrinological (due to possible potentiation of sympathomimetic effects)	• Hyperthyroidism • Pheochromocytoma
Metabolic	• Severe liver disease
Gastrointestinal	• Full stomach aspiration risk
Pregnancy	• Lack of data on safety
Psychiatric	• Intoxication with alcohol or other substances • Active substance abuse • Delirium • Psychosis • Refusal or inability to consent

pain treatment, the use of a drug with abuse potential in a high-risk population may carry significant risks that outweigh the benefits. Risk stratification using instruments validated for opioid use such as Revised Screener and Opioid Assessment for Patients with Pain and Opioid Risk Tool may provide some information regarding abuse potential, although the instruments have not been validated for ketamine abuse, and unlike chronic opioid therapy, ketamine infusions are not typically accompanied by outpatient prescriptions.[218] In general, because repeated use (ie, serial infusions) for chronic pain often involves higher dosages given more frequently than when ketamine is administered for acute pain, the possible cumulative risks (drug-induced cystitis) and effects (hepatic dysfunction) of chronic administration should be taken into consideration when embarking on a scheduled multiday infusion regimen.

In summary, ketamine should not be used in patients with poorly controlled cardiovascular disease and should be avoided in individuals with certain poorly controlled psychoses (grade B evidence, moderate level of certainty). For hepatic dysfunction, it should be avoided in individuals with severe impairment but may be administered judiciously with proper monitoring in people with moderate disease (grade C evidence, low level of certainty). In patients with elevated intracranial and intraocular pressure, there is grade C evidence that ketamine should not be used or used only in lower dosages with extreme caution (low level of certainty). Serial ketamine infusions should not be undertaken in patients with an active substance abuse problem and should be used along with universal precautions to monitor for abuse (grade C evidence, low level of certainty).

Guideline Question 3: Is There Any Evidence for a Therapeutic Dose Cutoff Threshold, a Dose-Response Relationship, Longer (ie, Continuous Versus Boluses), More Frequent (repeat) Infusions, or Higher Dosages to Be More Effective for Chronic Pain?

Adjuvants used to treat chronic pain are always associated with a therapeutic dose range, which may vary from patient to patient. Dosing below the therapeutic range is unlikely to result in significant benefit.[219] For depression, systematic reviews have concluded that repeat infusions have a larger effect size than single infusions and that a ketamine dosage of 0.5 mg/kg over 40 minutes was more effective than very low dosages, although the small numbers of patients involved and significant heterogeneity in study design limited the conclusions.[220,221] However, a recent consensus statement on ketamine use for depression found that alternative lower dosage schemes could be appropriate in different contexts.[5] In 1 case series, 3 patients received a total of 74 infusions over a 12-month period.[222]

Similar heterogeneity in treatment conditions and study design limits the conclusions one can draw for chronic pain, although the trends seem to suggest that higher dosages afford longer benefit. One small, randomized study that compared a single low-dose bolus of 0.4 mg/kg IV ketamine, calcitonin, ketamine plus calcitonin, and placebo for PLP found benefit that persisted through 48-hour follow-up.[117] Among RCTs for refractory pain that evaluated patients for longer time periods, the study by Noppers and colleagues,[160] which used a single, low-dose bolus (0.5 mg/kg) for fibromyalgia, reported benefits lasting only 3 hours, whereas a study on ketamine for spinal cord injury, which used an intermediate dose (80 mg/d for 1 week), reported benefits lasting 2 weeks.[155] For ischemic limb pain, the study by Mitchell and Fallon,[162] which administered a low-dose infusion of 0.6 mg/kg over 4 hours, described benefits that persisted for 5 days. However, in the only RCT evaluating IV ketamine for cancer-related pain, a low-dose, 24-hour infusion of 1 mg/kg found no benefit in individuals who were receiving concomitant opioid therapy.[164] In RCTs evaluating higher dosages administered as either serial outpatient infusions[123] or an inpatient infusion[161] for CRPS, significant improvement compared with placebo persisted for over 2 months.

In other studies, a small, retrospective analysis that administered IV ketamine titrated to a pain score of 3 or less out of 10 for at least 8 hours in 6 patients with refractory migraine headaches found no evidence of a dose-response relationship.[223] In a randomized study performed in patients with neuropathic pain, Huge and colleagues[224] reported a 38% reduction in pain score with 0.4 mg/kg of intranasal S(−) ketamine versus a 31% reduction with fewer adverse effects when 0.2 mg/kg was administered. Although this difference was not statistically significant, the study was underpowered (n = 16) to detect a dose-response relationship.

In 2 RCTs that examined the relationship between serum blood levels and postinfusion pain scores, no correlation was noted,[118,123] although a third RCT that compared 3 doses of ketamine to morphine did find a dose-response relationship.[163] An experimental study evaluating quantitative sensory testing in 12 subjects with neuropathic pain also found a dose-response relationship, with higher plasma levels resulting in greater reductions in cold pain and brush-evoked pain.[44] Multiday anesthetic-dose infusions of ketamine in dosages up to 7 mg/kg per hour have been successfully reported to alleviate severe, refractory CRPS and other chronic pain conditions, but require intensive care unit monitoring and intubation or other precautions to protect against aspiration.[225] The rationale for high-dose infusions is that subanesthetic dosages were anecdotally found to be less effective for advanced CRPS; however, no randomized studies have compared low- and high-dose infusions. A recent review by Maher and colleagues[36] concluded that higher total infused dosages of ketamine and longer infusions were associated with longer durations of pain relief. In an analysis accompanying a review by Noppers and colleagues,[226] the authors concluded that infusions less than 2 hours in duration were unlikely to provide benefit lasting more than 48 hours. They found that infusions longer than 10 hours, which resulted in higher dosages, were associated with an almost 95% probability of a patient attaining greater than 50% pain relief for more than 48 hours, whereas infusions over 30 hours increased that probability to almost 99%.[226] Although the authors did not specify whether the infusions should be continuous or cumulative hours, one might reasonably use the latter interpretation provided the serial infusions are performed before the analgesic benefit dissipates.

Overall, we conclude that there is moderate evidence to support higher dosages of ketamine over longer time periods, and more frequent administration, for chronic pain. Similar to the strategy used for opioids and other analgesic drugs with significant adverse effect profiles, it is reasonable to start dosing with a single, outpatient infusion at a minimum dose of 80 mg lasting more than 2 hours and reassess before initiating further treatments, similar to what is widely recommended for epidural steroid injections (grade C recommendation, low level of certainty) (Fig. 1).

Guideline Question 4: Is There Any Role for Oral Ketamine or Another NMDA Receptor Antagonist as a Follow-Up Treatment in Lieu of Repeat Infusions?

The resources required for IV ketamine treatment have led to many attempts at utilizing oral ketamine and other NMDA-receptor antagonists, which are often used because of the lack of a readily available oral formulation for ketamine and concern for adverse effects, including those associated with compounding.

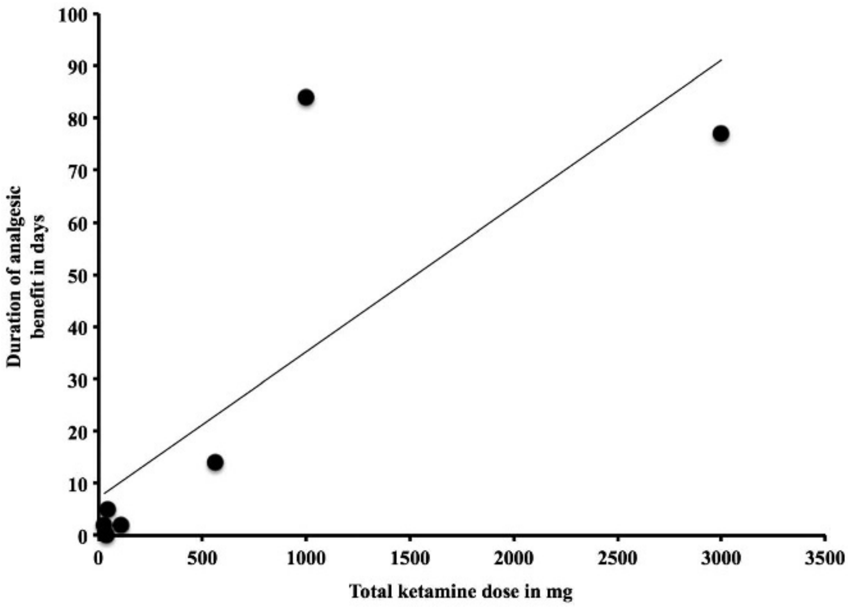

FIGURE 1. Graphical depiction of the relationship between ketamine dose and duration of analgesic benefit in randomized placebo-controlled trials that evaluated IV ketamine for chronic pain with a minimum of 48 hours' follow-up.[117,123,155,160–162,164] A trend line is been plotted to indicate the nature of this relationship.

Oral ketamine has been evaluated in several placebo-controlled trials,[227–230] with studies generally demonstrating no significant benefit, although 1 well-designed study found a significant opioid-sparing effect.[229] However, oral ketamine has poor bioavailability, and the relative dosages used in these studies were considerably less than in the studies evaluating IV administration. In 1 study that used oral ketamine (median dose, 150 mg/d) as a follow-up treatment after 10-day inpatient infusions, the authors reported that oral ketamine was effective (≥50% pain relief and/or improvement in quality of life) in 44% of patients, partially effective in 20%, and was associated with an opioid-sparing effect in the absence of pain reduction in 14% of 55 cases. Two-thirds of these patients obtained relief lasting longer than 6 months. Sixty percent of patients in this study had neuropathic pain, and those receiving opioids fared better than individuals not on opioid therapy.[231] In a small, placebo-controlled crossover trial performed in 8 patients with neuropathic pain who had responded to IV ketamine, oral ketamine syrup (0.5 mg/kg every 6 hours for 1 week) resulted in significantly better pain relief than saline, with 4 patients continuing treatment for longer than 9 months.[232]

Intranasal ketamine has a higher bioavailability than oral ketamine and has been studied in several randomized trials in individuals with chronic pain. These studies have demonstrated efficacy for breakthrough pain for a variety of chronic pain conditions in individuals with opioid tolerance (1–5 sprays of 10 mg ketamine),[52] neuropathic pain ((S)-ketamine 0.2 mg/kg compared with 0.4 mg/kg without a control group),[224] and the severity but not duration of aura in migraineurs (25 mg).[169] However, none of these studies demonstrated analgesia lasting more than a few hours, indicating the need for continued treatment. One issue that must be considered when starting a patient on oral or intranasal ketamine is the potential for accidents, as ketamine may cause hallucinations and impairments in judgment, visual and perceptual functions, and psychomotor ability. This is particularly relevant for motor vehicle collisions, such that if ketamine is considered as a treatment for incident or breakthrough pain, proper safety precautions must be exercised.[233]

Cohen and colleagues[234–236] performed a series of studies evaluating the use of a brief IV ketamine test (0.1 mg/kg) to predict subsequent treatment with oral dextromethorphan in patients with neuropathic pain, opioid tolerance, and fibromyalgia. When data for all 3 studies were pooled, the overall sensitivity, specificity, positive predictive value, and negative predictive value were 76%, 78%, 67%, and 85%, respectively.[237] One criticism of these studies is that expectation bias, which is an integral part of the placebo effect, may have enhanced the effect in infusion responders. In general, the use of nonketamine NMDA-receptor antagonists. such as dextromethorphan (conflicting), amantadine (conflicting), magnesium (positive findings in small studies), memantine (mostly negative), and carbamazepine, which may possess some NMDA antagonistic properties (positive), has yielded mixed results for neuropathic pain and possibly other chronic pain conditions characterized by central sensitization.[238,239]

Overall, we conclude that there is low-level evidence to support the use of oral ketamine (150 mg/d or 0.5 mg/kg every 6 hours) and other NMDA-receptor antagonists such as dextromethorphan (0.5–1 mg/kg every 8 hours) as follow-up therapy following IV infusions, and moderate evidence to support intranasal ketamine (1–5 sprays of ketamine 10 mg, 0.2–0.4 mg/kg (S)-ketamine, and single dose ketamine 25 mg every 6 hours as needed) as a treatment for breakthrough pain. From a clinical practice perspective, oral ketamine has significant abuse potential and a high street value. For these reasons, in patients with a history of abuse or who are at high risk of abuse, the risks of prescribing it chronically in a community-based setting should be weighed against the potential benefits, and proper surveillance, similar to what is done for patients on chronic opioid therapy, should be used. More research should also be conducted regarding the long-term effects of ketamine. Considering the costs and resources involved with IV infusions, it is reasonable to try a follow-up intranasal ketamine, oral ketamine, or oral dextromethorphan treatment regimen in lieu of serial treatments (grade B recommendation, low level of certainty for oral preparations, moderate level of certainty for intranasal ketamine).

Guideline Question 5: What Tests Should Be Ordered Prior to an Infusion of Ketamine?

Although ketamine has direct negative inotropic effects that may be evidenced in individuals who are catecholamine depleted, in clinical practice the use of ketamine is generally associated with increased heart rate and blood pressure, owing to its sympathomimetic properties. In a randomized study evaluating the hemodynamic effects of propofol and ketamine in 16 individuals undergoing total hip replacement, the use of anesthetic ketamine dosages (1.5-mg/kg induction dose followed by 50 μg/kg per minute [3 mg/kg per hour]; mean dose, 157.5 mg/h) was associated with significant increases in mean arterial and pulmonary artery pressures, resulting in a 100% increase in myocardial oxygen consumption.[240] Of note, the maintenance dose of ketamine used in this study was similar to the high-end dosages used to treat chronic pain in some settings.[241]

The use of preinfusion testing to minimize risks is an important clinical consideration prior to IV ketamine administration for pain management. In a case report involving a patient with terminal disease with cancer-related pain and a history of angina, subendocardial myocardial infarction, and chronic obstructive pulmonary disease who received a subcutaneous ketamine infusion of 150 mg per day to supplement opioid analgesia for back pain related to spine metastases, angina was precipitated 15 days after the start of the infusion, requiring escalating doses of sublingual nitroglycerin.[211] This persisted even after his baseline antianginal medication was restarted and necessitated discontinuation of the infusion. However, in 21 double-blind RCTs that involved 395 patients with chronic neuropathic pain–related conditions,[21,44,117–119,123,152–163,197–199] 12-lead ECGs were obtained prior to the administration of IV ketamine in only 1 study.[153] This particular RCT included 20 patients with nerve injury pain who received a 0.1-mg/kg ketamine bolus over 10 minutes followed by an IV ketamine infusion 0.007 mg/kg per minute (0.4 mg/kg per hour) for 20 minutes. No adverse cardiovascular effects were reported.[153] In the remaining 20 RCTs, 9 studies used continuous ECG monitoring during the ketamine infusions.[21,44,117,123,155,156,158,159,163] No data were reported regarding changes in heart rate during the ketamine infusion in 5 studies,[21,123,156,158,159] and no significant changes in heart rate were reported in 2 studies.[44,117] In a randomized study conducted in 80 patients with spinal cord injury pain who received 80 mg of IV ketamine or placebo over 5 hours, a "15% increase" in heart rate was observed in 2 patients.[155] In another randomized, double-blind study involving 8 patients given ketamine dosages ranging from 0.15 to 0.45 mg/kg on 4 separate days to treat ischemic pain from arteriosclerosis obliterans, changes in heart rate were observed to stay "within the limits of ±10 beats/min in all patients."[163] Although ketamine has been anecdotally associated with cardiac arrhythmias,[242] no arrhythmias were reported in any of the 9 studies that used continuous ECG monitoring.[21,44,117,123,155,156,158,159,163] A literature review evaluating the use of ketamine for procedural sedation in more than 70,000 patients found the incidence of cardiovascular and other adverse events to be exceedingly low, reporting 1 case of hypoxic cardiac arrest secondary to respiratory depression in a debilitated adult.[243]

Ketamine undergoes extensive hepatic metabolism, and although short-term use of the drug has been infrequently associated with elevated liver function tests, clinically apparent liver damage has not been reported. In one of the earliest reports evaluating the effect of ketamine on liver function, Dundee and colleagues[206] found that 14 of 34 patients receiving 3 to 4 mg/kg of ketamine for anesthesia experienced significant elevations in liver function tests. Lower dosages used for chronic pain may also be associated with liver toxicity. In a randomized trial by Noppers et al,[189] 13 patients were randomized to a second exposure to ketamine 16 days following a 100-hour infusion (maximum infusion rate of 7.2 μg/kg per minute or 0.4 mg/kg per hour for a mean dose of 1813 mg), a second exposure 12 weeks after the initial exposure, or a first exposure of ketamine following treatment with midazolam. In the 6 patients who received their second treatment 16 days after the first, 1 patient developed severe hypertension, and 3 patients developed dramatic elevations (≥3 times baseline) in liver enzymes that returned to normal within 3 months; none of the patients in the other 2 groups experienced abnormal liver function tests.[189] Other studies have reported that approximately 10% of individuals receiving high-dose ketamine infusions will experience significant increases in liver enzymes.[225] In another RCT that included 60 patients with CRPS, patients received daily "liver function tests" during a continuous ketamine infusion that was on average 4.2 days in duration. The average ketamine dose was 22 mg/h, and no adverse hepatic effects were reported.[161]

In summary, there is insufficient evidence supporting preinfusion testing prior to the administration of IV ketamine for chronic neuropathic pain conditions in healthy individuals. In individuals at high risk of cardiovascular events or symptoms suggestive of cardiovascular disease, baseline ECG testing may be considered to exclude individuals with uncontrolled ischemic heart disease. In individuals with baseline liver dysfunction, at risk of liver toxicity (eg, alcohol abusers, people with chronic hepatitis), or who are expected to receive high doses of ketamine at frequent intervals, baseline and postinfusion liver function tests should be considered on a case-by-case basis (grade C evidence, low level of certainty).

Guideline Question 6: What Training Is Prudent for Personnel Who Administer Boluses and Infusions and Oversee Dose Titration? Does This Recommendation Change With Dosage (That Is, Subanesthetic Versus Anesthetic Range) or Route of Administration?

The administration of ketamine as a bolus and/or infusion for the treatment of pain requires a knowledge and understanding of pain, familiarity with the drug's pharmacodynamic and pharmacokinetic effects, and the effects ketamine has on the symptoms and signs of pain (eg, allodynia, hyperalgesia). Ketamine is a dissociative anesthetic associated with significant neuropsychiatric, gastrointestinal, cardiovascular, and respiratory adverse effects that can vary depending on the dose and subject.[238,244] These neuropsychiatric adverse events include sedation, vivid dreams or nightmares, hallucinations, out-of-body experiences, headache, dizziness, fatigue, changes in mood, altered vision and hearing, light-headedness, paresthesias, changes in taste, dysarthria, euphoria, and inebriation. Hemodynamic adverse effects include tachycardia, arrhythmias, and hypertension, whereas possible respiratory events include hypoventilation or hyperventilation, oxygen desaturation, and hypoxia.[37,123,156,157,161,196,225,245] The majority of these adverse effects are transient and can be treated by lowering the rate of infusion or stopping it. Medications including benzodiazepines, α2 agonists, β-blockers, and antiemetics can be administered to counter these effects. Although none of the published studies have reported serious adverse events, it should be acknowledged that the number of participants in these studies was relatively small, and the risk of serious adverse events cannot be ruled out.

There are no published guidelines or recommendations outlining the specific training requirements for physicians involved in the administration of ketamine at dosages above those typically given for depression (>0.5 mg/kg), although its classification as an anesthetic agent has resulted in some institutions mandating that boluses be given only by anesthesiologists or anesthetists. It has been suggested that credentialing in moderate (conscious) sedation should be a prerequisite for staff administering ketamine and the health care providers involved in caring for patients.[246] Staff and clinicians overseeing the care of patients receiving this medication should be trained in responding to cardiovascular and respiratory emergencies.[247] Health care providers involved in administration of ketamine should also have adequate training in titrating the dose of ketamine while ensuring the safety of the recipient and the availability of treatments to address adverse effects. Furthermore, it is also recommended that ketamine infusions should be performed in settings with appropriate monitoring and resuscitation facilities under the care of an appropriately trained physician.[248]

The APA guidelines for administration of ketamine to treat depression in dosages that are significantly lower (usually a single dose of 0.5 mg/kg administered over 40 minutes) than those used for chronic pain syndromes[247] recommend that hemodynamic (ECG, blood pressure) and respiratory monitoring (end-tidal carbon dioxide and oxygen saturation) be available during infusion.[5] The APA guidelines also recommend that an on-site clinician be available to evaluate and emergently treat potential behavioral risks including suicidal ideation, severe anxiety, and marked mental status changes before discharge home and that rapid follow-up evaluations of patients' psychiatric symptoms be provided as needed.[5]

This panel agrees with the APA recommendation that only a licensed physician who can administer a Drug Enforcement Administration Schedule III medication with Advanced Cardiac Life Support certification be in charge of administering ketamine, but because of the higher dosages used for chronic pain, we believe that person should also meet ASA requirements for the delivery of moderate sedation. For the person who actually administers subanesthetic IV bolus sedation, recommended credentials include a registered nursing degree with Advanced Cardiac Life Support certification, along with training in the administration of moderate sedation and specifically the pharmacology of ketamine. The training can be via courses given internally or by accredited organizations (eg, American Association of Moderate Sedation Nurses).

Although the APA consensus statement did not find any cases of clinically relevant respiratory depression at the low dosages given for depression, they did mention several instances of patients becoming unresponsive, putting them at risk of aspiration. Because the doses and/or duration of ketamine infusions used to treat pain are higher than those used to treat depression and the sedative midazolam is often given preemptively or as a rescue medication, it is appropriate to recommend that only those trained in the induction and maintenance of ketamine infusions, such as anesthesiologists, critical care–trained physicians, and pain physicians with appropriate credentials to include training in airway management, be responsible for decisions regarding administration of this medication in doses that may render a patient unresponsive. An appropriately trained health care provider[246] can monitor the patient receiving ketamine infusion in subanesthetic doses and change the infusion rate based on directions from the responsible physician who, for single-day infusions, should be immediately available.

Individuals respond with great variability to ketamine, so there is wide variation in hospital-based practices. Specific concerns regarding the monitoring of ketamine administration include airway protection, cardiovascular stimulation, the potential interaction of ketamine with concomitantly administered medications that may enhance certain effects (eg, midazolam), and the treatment of adverse effects.

Ketamine doses at levels that may result in serious adverse sequelae (bolus dose of ≥0.35 mg/kg and/or infusion of ≥1 mg/kg per hour) should be administered by clinicians experienced in ketamine administration in a unit that contains trained nurses available for monitoring and individuals trained in airway management and Advanced Cardiac Life Support (eg, anesthesiologist, nurse anesthetist, emergency department physician) who are immediately available to address any potential emergencies.[225] For some individuals (ie, elderly individuals and those with significant comorbidities), lower thresholds should trigger the requirements for more intensive monitoring and safety measures. Higher cutoffs using subanesthetic dosages may also be utilized in appropriately resourced environments in both inpatient and outpatient settings when patients have been "stabilized" or previously treated with higher dosages.[123,161] The basic monitoring requirements (hemodynamic and respiratory parameters, sedation levels using a validated scale) remain the same irrespective of the route of administration or dose in individuals receiving ketamine in a nonchronic treatment regimen. Availability of personnel and equipment for resuscitation at all times is also mandatory irrespective of the level of infusion (grade A recommendation, low level of certainty).

Guideline Question 7: What Preemptive Medications Should Be Available for Administration as Rescue Medications to Treat Possible Adverse Events Related to Ketamine Infusions?

Ketamine is associated with myriad adverse effects including psychomimetic, cardiovascular, and gastrointestinal effects, resulting from its action on a variety of receptors, which include NMDA, acetylcholine, opioid, ion channels, monoamine, and histamine. For the treatment of CRPS, an open-label study found anesthetic doses (up to 117 μg/kg/min or 7 mg/kg per hour) resulted in 90% of patients experiencing moderate to severe psychomimetic effects including anxiety, dysphoria, and nightmares despite premedication and maintenance infusions of midazolam and clonidine.[225] These adverse effects were dose-dependent and persisted following infusion discontinuation. One pilot study using a subanesthetic infusion of S(+)-ketamine (up to 5 μg/kg per minute or 0.3 mg/kg per hour) produced mild psychomimetic effects including euphoria and disorientation[122]; however, a double-blind RCT using a modestly higher but still subanesthetic dosage (up to 7.2 μg/kg per minute or 0.4 mg/kg per hour) reported 93%, 63%, and 47% rates of mild psychomimetic effects, nausea, and emesis, respectively.[161] These last 2 studies also did not administer premedication to mitigate adverse effects, and neither specifically addressed the differential effects of the R and S enantiomers, as some studies suggest that the more potent S(+)-ketamine contains more psychedelic effects.[249] A double-blind RCT using subanesthetic doses of racemic ketamine (up to 5.2 μg/kg per minute or 0.3 mg/kg per hour), in combination with midazolam and clonidine premedication, reported no psychomimetic adverse effects.[123]

The literature evaluating the benefit or harm of premedication prior to ketamine use is primarily limited to pediatric sedation and general anesthesia for surgical procedures; therefore, it suffers from the bias of pediatric physiology or concomitant procedures and medications, which limit the conclusions that can be drawn for chronic pain. In a single RCT, midazolam and dexmedetomidine were found to reduce psychomimetic and cardiovascular adverse events when ketamine was used as a sole general anesthetic (2 mg/kg, once) in very brief surgical cases.[250] In populations receiving subanesthetic ketamine, the number-needed-to-harm, with "harm" defined as ketamine-induced psychomimetic adverse effects, has been calculated. A meta-analysis of sedated and awake pediatric and adult patients estimated the number-needed-to-harm for hallucinations to be 21 when ketamine is used without coadministration of a benzodiazepine; when patients are given a benzodiazepine prior to ketamine administration, the number increases to 35, suggesting premedication may lessen but not eliminate psychomimetic events.[136]

Further indirect evidence of the benefits afforded by preemptive treatment with mitigating medications in adults includes double-blind RCTs evaluating premedicants in patients receiving subanesthetic dosages of IV ketamine (<70 mg/h) for sedation. In 1 study, lorazepam was found to decrease the emotional distress caused by ketamine but not the incidence of psychosis,[251] whereas another study reported that midazolam reduced agitation.[252]

Ketamine overdose is associated with loss of consciousness, respiratory depression, tachycardia, hypertension, and severe psychomimetic events including positive and negative signs of schizophrenia. No RCT directly addresses the use of rescue medications, and the recommendations for management of severe toxicity include supportive care addressing untoward signs and symptoms.[253] Treatment recommendations include the use of a benzodiazepine such as midazolam or diazepam to prevent or attenuate psychomimetic symptoms, mitigate sympathomimetic symptoms, and reduce the incidence of nausea; the butyrophenone haloperidol for its antiemetic properties, sedative effects, and reduction of psychomimetic symptoms and emergence reactions; and clonidine for its ability to reduce sympathomimetic effects and decrease the incidence of psychomimetic reactions. Dystonia is not commonly experienced but can be treated with the antihistamine, diphenhydramine. Seizures, although rare, should be treated with benzodiazepines followed by barbiturates or propofol if persistent.

Overall, we conclude there is limited direct evidence supporting the preemptive use of benzodiazepines and α2 agonists and no evidence to support antidepressant, antihistamine, or anticholinergic premedicants prior to the initiation of subanesthetic ketamine for chronic pain treatment (grade C recommendation, low level of certainty).

Guideline Question 8: What Constitutes a Positive Treatment Response for Chronic Pain?

Guidelines have been published on what constitutes a clinically meaningful benefit for an individual for specific metrics, which can differ from what constitutes a significant improvement in a clinical trial.[254] Farrar and colleagues[255] analyzed data on more than 2500 patients from 10 clinical trials for a variety of different chronic pain conditions and found that a 2-point or 30% decrease in pain score corresponded to a patient rating of "much improved." Because pain scales are not linear,[256] a 30% decrease in pain would appear to be a reasonable benchmark. For acute pain, a systematic review found a 17-mm (interquartile range, 14–23 mm, on a 0- to 100-mm VAS) decrease to be the median "minimal clinically important difference" in terms of absolute pain reduction, with 23% (interquartile range, 18%–36%) being the median relative diminution.[257] The 23% reduction is similar to what Bicket et al[258] found to constitute the threshold for patient satisfaction when they analyzed the results of 3 RCTs evaluating epidural steroid injections for subacute and chronic radiculopathy. Besides pain, other factors that should be considered when identifying treatment responders include function, psychological and emotional well-being, sleep, and satisfaction.[259] Pain is subjective, and pain scores should never be considered in isolation. For example, a 1-point decrease in pain that is accompanied by cessation of analgesic use and return-to-work would be considered by most to constitute a better outcome than a 2-point decrease in pain in the context of a significant increase in opioid consumption and corresponding decrease in activity. The IMMPACT guidelines provide recommendations on the core outcome domains for chronic pain clinical trials, which can be adapted for individual use (ie, Oswestry Disability Index for a patient with back pain, Western Ontario and McMaster Universities Osteoarthritis Index for a patient with osteoarthritis, Beck Depression Inventory for a patient with a mood disorder, a sleep scale for a patient with a sleep disorder).[259]

Studies evaluating ketamine for chronic pain have generally enrolled patients refractory to conventional treatments, who may be less likely to respond to any intervention; this reflects clinical practice. In the RCTs that have designated specific pain reduction cutoffs for what constitutes a responder, 50% or greater pain relief is the most common,[117–119,160] with only the study by Salas and colleagues[164] noting the proportion of individuals who experienced 30% or greater benefit. In the placebo-controlled studies that evaluated intermediate- and long-term follow-up periods, none specified a time frame threshold for what was considered a positive response.[123,155,160,161]

The duration of a clinical trial and by extension the duration of relief required to designate a response as positive correlate with the cost and risks of the treatment. When balancing these factors, one must consider not only the perceived and objective benefits (eg, return to work, medication reduction), but also the need for repeat or additional treatments and the potential for long-term complications. In general, the required benefit for surgery exceeds that of nonsurgical procedural interventions, which in turn is greater than that for medications and alternative treatments. Along this spectrum, an IV ketamine infusion in an outpatient setting most closely resembles nonsurgical pain management procedures in terms of risks, costs, and the need for repeat treatments.

In conclusion, given the refractory nature of patients who receive ketamine infusions, we recommend that a positive outcome be considered as 30% pain relief or greater in conjunction with patient satisfaction and/or more objective indicators of meaningful benefit, such as a 12.8% improvement in Oswestry Disability Index score in a patient with back pain or a 20% or greater reduction in opioid use.[260,261] In terms of duration of benefit, patient expectations and satisfaction should be considered, but based on the cumulative risks and costs of treatment, greater than 3 weeks following a single outpatient infusion and greater than 6 weeks following an inpatient or series of infusions are a reasonable designation. Similar to multiple guidelines for epidural steroid injections,[262] a consecutive "series" of infusions should not be administered by rote, but rather tailored to patient response. Considering the risks of long-term ketamine treatment, limiting these to no more than 6 to 12 treatments per year is reasonable, although deviations may be made in exceptional circumstances (grade C recommendation, low to moderate level of certainty).

Future Research

The use of ketamine has skyrocketed for chronic pain and depression, but many questions remain unanswered. The most prominent among these revolve around durability of benefit and implications of repeated administrations (ie, the development of pharmacodynamic, metabolic, and behavioral tolerance leading to tachyphylaxis and loss of analgesic benefit), standardization of treatment (ie, optimum dosages and infusion parameters), and acute and chronic adverse effects, including remote neuropsychiatric effects. Given the poor translational reproducibility and validity of preclinical chronic pain research to humans, only robust clinical trials with long-term follow-up will provide answers to these questions.

Identifying individuals likely to respond to treatment or those predisposed to significant adverse effects based on phenotypes and possibly genotypes can shift the risk-benefit ratio toward greater benefit. In an era characterized by an increased emphasis on precision medicine and efforts to contain spiraling health care costs, refining selection criteria can reduce risks and costs and improve treatment outcomes. Because back pain, neck pain, and other musculoskeletal disorders, along with depression, comprise the 4 leading causes of disability in the United States,[15] determining the effectiveness of ketamine in these predominantly nonneuropathic and mixed conditions[263,264] is of paramount importance. Although there is stronger evidence in preclinical and clinical studies evaluating ketamine for neuropathic pain and CRPS, there is a growing body of evidence in animals for inflammatory pain and for humans in nonneuropathic spine pain.[27,28,37] A role for ketamine infusions in other common chronic pain syndromes such as fibromyalgia and headaches has also been suggested and been explored in prospective case series with mixed results.[37,160,167,265]

TABLE 6. Summary of ASRA/AAPM/ASA Recommendations for Ketamine Infusions for Chronic Pain

Recommendation Category	Recommendation	Level of Evidence*
Indications	(1) For spinal cord injury pain, there is weak evidence to support short-term improvement	(1) Grade C, low certainty
	(2) In CRPS, there is moderate evidence to support improvement for up to 12 wk	(2) Grade B, low to moderate certainty
	(3) For other pain conditions such as mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, and spinal pain, there is weak or no evidence for immediate improvement	(3) Grade D, low certainty
Dosing range and dose response	(1) Bolus: up to 0.35 mg/kg	(1) Grade C, low certainty
	(2) Infusion: 0.5 to 2 mg/kg per hour, although dosages up to 7 mg/kg per hour have been successfully used in refractory cases in ICU settings	(2) Grade C, low certainty
	(3) There is evidence for a dose-response relationship, with higher dosages providing more benefit. Total dosages be at least 80 mg infused over a period of >2 h	(3) Grade C, low certainty
Relative contraindications	(1) Poorly controlled cardiovascular disease, pregnancy, active psychosis	(1) Grade B, low certainty
	(2) Severe hepatic disease (avoid), moderate hepatic disease (caution)	(2) Grade C, low certainty
	(3) Elevated intracranial pressure, elevated intraocular pressure	(3) Grade C, low certainty
	(4) Active substance abuse	(4) Grade C, low certainty
Role of oral NMDA receptor antagonist as follow-on treatment	(1) Oral ketamine or dextromethorphan, and intransal ketamine can be tried in lieu of serial infusions in responders	(1) Grade B, low certainty for oral preparations, moderate certainty for intranasal ketamine
Preinfusion tests	(1) No testing is necessary for healthy individuals	(1) Grade C, low certainty
	(2) In individuals with suspected or at high risk of cardiovascular disease, baseline ECG testing should be used to rule out poorly controlled ischemic heart disease.	(2) Grade C, low certainty
	(3) In individuals with baseline liver dysfunction or at risk of liver toxicity (eg, alcohol abusers, people with chronic hepatitis), and those who are expected to receive high doses of ketamine at frequent intervals, baseline and postinfusion liver function tests should be considered on a case-by-case basis	(3) Grade C, low certainty
Positive response	(1) A positive response should include objective measures of benefit in addition to satisfaction such as ≥30% decrease in pain score or comparable validated measures for different conditions (eg, Oswestry Disability Index for back pain)	(1) Grade C , low-to-moderate certainty
Personnel and monitoring	(1) Supervising clinician: a physician experienced with ketamine (anesthesiologist, critical care physician, pain physician) who is ACLS certified and trained in administering moderate sedation	(1) Grade A, low certainty
	(2) Administering clinician: registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation	(2) Grade A, low certainty
	(3) Setting: at dosages exceeding 1 mg/kg per hour, a monitored setting containing resuscitative equipment and immediate access to rescue medications and personnel who can treat emergencies should be used, although this dose may vary based on individual characteristics	(3) Grade A, low certainty

*Evidence was evaluated according to the US Preventive Services Task Force grading of evidence, which defined levels of evidence based on magnitude and certainty of benefit.[5]

ACLS indicates Advanced Cardiac Life Support; ICU, intensive care unit.

One of the biggest questions surrounding ketamine is whether the drug can prevent the transition from acute to chronic pain by virtue of its NMDA antagonist and opioid-sparing properties. Given the high prevalence rates of surgery and acute pain, and the growing use of ketamine in the context of posttraumatic (including postsurgical) pain, designing large, multicenter studies should be given high priority.

Finally, in addition to preventing the chronification of acute pain, another top National Institutes of Health chronic pain research priority is the establishment of registries. Unlike placebo-controlled clinical trials, which gauge efficacy in small, well-selected populations, registries can provide a better measure of effectiveness in large populations treated under real-life conditions and may provide important information regarding who is likely to benefit from a specific treatment (ie, phenotyping or precision medicine). In the absence of large, randomized studies, the establishment of ketamine treatment-based registries can help guide treatment decisions.

CONCLUSIONS

The growing body of literature, both peer reviewed and aimed at lay audiences, recommending ketamine for chronic pain and depression has led to a surge in its use, with the growth in utilization outpacing the development of standards governing practice. This unrestrained growth has led to a chorus of calls from patient advocacy groups, physicians, payers, regulatory bodies and pain medicine organizations for the development of guidelines. Similar to other consensus statements, the guidelines contained here do not represent "edicts" aimed at establishing definitive standard of care, but rather provide a structural framework that should be considered when devising institutional protocols and developing individualized care plans. We appreciate that medicine is an art as well as a science and that evidence-based medicine considers not only scientific literature, but also clinical judgment based on physician experience and patient values and preferences.[266] Therefore, what may be warranted in some scenarios may prove to be suboptimal in other circumstances, and reasonable individuals may come to different conclusions based on the same data. In the current guidelines, we were able to come to a full consensus without dissension on all questions, although several questions required multiple revisions before agreement could be reached (Appendix 2, Supplemental Digital Content 2, http://links.lww.com/AAP/A250).

The recommendations in response to the questions we have addressed are often based on small randomized trials, observational and retrospective studies, clinical experience, and evidence extrapolated from the use of ketamine in other contexts and thus may change as better evidence emerges. This may be more relevant for the sections concerned with indications and, to a lesser extent, contraindications, which continue to evolve with more information. For example, adverse effects such as ketamine-induced psychosis may result from either 1-time use or cumulative effects (eg, psychosis, urinary tract dysfunction, liver disease),[189,267,268] and as the serial use of ketamine for chronic conditions such as depression and pain continues to rise, and the prevalence of abuse increases commensurately, the indications, contraindications, and surveillance recommendations may change in concert.

Based on specific requests, we tried to provide recommended dosing ranges whenever possible. Although these recommendations are based on the existing literature, which is characterized by a lack of large, high-quality studies, one must recognize that the mechanisms of pain are strikingly similar for certain conditions (eg, deafferentation and cortical reorganization for PLP and spinal cord injury) and share considerable overlap even in widely disparate conditions (eg, central sensitization for fibromyalgia and neuropathic pain). Therefore, one could reasonably extrapolate ketamine dosing schemes for a condition that has been adequately investigated to another condition that has not been well researched, as is typically done for other analgesic medications. Differences not only in disease features but also patient characteristics, and practice settings and capabilities, further highlight the need for dosing flexibility. As is true for all aspects of medicine, the decisions as to when a treatment is indicated, what setting and parameters to use, how to monitor its effects, and how to minimize risks should be made on an individualized basis after sufficient discussion with the patient (Table 6).

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REFERENCES

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:743–800.
2. Chopra K, Arora V. An intricate relationship between pain and depression: clinical correlates, coactivation factors and therapeutic targets. *Expert Opin Ther Targets*. 2014;18:159–176.
3. Radvansky BM, Puri S, Sifonios AN, Eloy JD, Le V. Ketamine-a narrative review of its uses in medicine. *Am J Ther*. 2016;23: e1414–e1426.
4. Anderson P. Ketamine for chronic pain on the rise. http://www.medscape.com/viewarticle/878159. Published April 4, 2017. Accessed November 3, 2017.
5. Sanacora G, Frye MA, McDonald W, et al. American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017;74:399–405.
6. U.S. Preventive Task Force. Grade definitions. Available at: https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions. Accessed November 3, 2017.
7. Helm Ii S, Simopoulos TT, Stojanovic M, Abdi S, El Terany MA. Effectiveness of thermal annular procedures in treating discogenic low back pain. *Pain Physician*. 2017;20:447–470.
8. Oxford Centre for Evidence-Based Medicine—Levels of Evidence (March 2009). Available at: http://www.cebm.net/blog/2009/06/11/oxford-centre-evidence-based-medicine-levels-evidence-march-2009. Accessed January 15, 2018.
9. The GRADE Working Group. GRADE. Available at: http://www.gradeworkinggroup.org. Updated April 2016. Accessed January 18, 2018.
10. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther*. 1965;6: 279–291.
11. Greifenstein FE, DeVault M, Yoshitake J, et al. A study of a 1-aryl cyclo hexyl amine for anesthesia. *Anesth Analg*. 1958:37:283–294.
12. Maddox VH, Godefroi EF, Parcell RF. The synthesis of phencyclidine and other 1-arylcyclohexylamines. *J Med Chem*. 1965;8:230–235.
13. Chen G, Ensor CR, Russell D, Bohner B. The pharmacology of 1-(1-phenylcyclohexyl) piperidine HCl. *J Pharmacol Exp Ther*. 1959;127:241–250.
14. Mion G. History of anaesthesia: the ketamine story—past, present and future. *Eur J Anaesthesiol*. 2017;34:571–575.

15. Murray CJ, Atkinson C, Bhalla K, et al. U.S. Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013;310:591–608.

16. Institute of Medicine Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research*. Washington, DC: The National Academies Press; 2011. Available at: http://books.nap.edu/openbook.php?record_id=13172. Accessed November 3, 2017.

17. Leadley RM, Armstrong N, Lee YC, Allen A, Kleijnen J. Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain. *J Pain Palliat Care Pharmacother*. 2012;26:310–325.

18. Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. *BMJ*. 2014;348:f7656.

19. Clarke H, Bonin RP, Orser BA, Englesakis M, Wijeysundera DN, Katz J. The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. *Anesth Analg*. 2012;115:428–442.

20. Cohen KL, Harris S. Efficacy and safety of nonsteroidal anti-inflammatory drugs in the therapy of diabetic neuropathy. *Arch Intern Med*. 1987;147:1442–1444.

21. Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain*. 2000;85:483–491.

22. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage*. 2000;20:246–252.

23. Vo T, Rice AS, Dworkin RH. Non-steroidal anti-inflammatory drugs for neuropathic pain: how do we explain continued widespread use? *Pain*. 2009;143:169–171.

24. Mak P, Broadbear JH, Kolosov A, Goodchild CS. Long-term antihyperalgesic and opioid-sparing effects of 5-day ketamine and morphine infusion ("burst ketamine") in diabetic neuropathic rats. *Pain Med*. 2015;16:1781–1793.

25. Castel A, Hélie P, Beaudry F, Vachon P. Bilateral central pain sensitization in rats following a unilateral thalamic lesion may be treated with high doses of ketamine. *BMC Vet Res*. 2013;9:59.

26. Mehta AK, Halder S, Khanna N, Tandon OP, Singh UR, Sharma KK. Role of NMDA and opioid receptors in neuropathic pain induced by chronic constriction injury of sciatic nerve in rats. *J Basic Clin Physiol Pharmacol*. 2012;23:49–55.

27. Le Roy C, Laboureyras E, Gavello-Baudy S, Chateauraynaud J, Laulin JP, Simonnet G. Endogenous opioids released during non-nociceptive environmental stress induce latent pain sensitization via a NMDA-dependent process. *J Pain*. 2011;12:1069–1079.

28. Rivat C, Laulin JP, Corcuff JB, Célèrier E, Pain L, Simonnet G. Fentanyl enhancement of carrageenan-induced long-lasting hyperalgesia in rats: prevention by the *N*-methyl-D-aspartate receptor antagonist ketamine. *Anesthesiology*. 2002;96:381–391.

29. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain*. 2008;136:380–387.

30. Harifi G, Amine M, Ait Ouazar M, et al. Prevalence of chronic pain with neuropathic characteristics in the Moroccan general population: a national survey. *Pain Med*. 2013;14:287–292.

31. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain*. 2006;7:281–289.

32. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain*. 2016;157:1599–1606.

33. De Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. *Pain*. 2007;129:12–20.

34. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted County, a population-based study. *Pain*. 2003;103:199–207.

35. Smith BH, Torrance N, Bennett MI, Lee AJ. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. *Clin J Pain*. 2007;23:143–149.

36. Maher DP, Chen L, Mao J. Intravenous ketamine infusions for neuropathic pain management: a promising therapy in need of optimization. *Anesth Analg*. 2017;124:661–674.

37. Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. *Pain Med*. 2012;13:263–269.

38. Cohen SP, Liao W, Gupta A, Plunkett A. Ketamine in pain management. *Adv Psychosom Med*. 2011;30:139–161.

39. Orser BA, Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade of *N*-methyl-D-aspartate receptors. *Anesthesiology*. 1997;86:903–917.

40. Chang CH, Hsiao YH, Chen YW, Yu YJ, Gean PW. Social isolation-induced increase in NMDA receptors in the hippocampus exacerbates emotional dysregulation in mice. *Hippocampus*. 2015;25:474–485.

41. Duman RS, Li N, Liu RJ, Duric V, Aghajanian G. Signaling pathways underlying the rapid antidepressant actions of ketamine. *Neuropharmacology*. 2012;62:35–41.

42. Trujillo KA, Akil H. Inhibition of opiate tolerance by non-competitive *N*-methyl-D-aspartate receptor antagonists. *Brain Res*. 1994;633:178–188.

43. Zhou HY, Chen SR, Pan HL. Targeting *N*-methyl-D-aspartate receptors for treatment of neuropathic pain. *Expert Rev Clin Pharmacol*. 2011;4:379–388.

44. Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain*. 2001;91:177–187.

45. Casale R, Symeonidou Z, Bartolo M. Topical treatments for localized neuropathic pain. *Curr Pain Headache Rep*. 2017;21:15.

46. Sarton E, Teppema LJ, Olievier C, et al. The involvement of the mu-opioid receptor in ketamine-induced respiratory depression and antinociception. *Anesth Analg*. 2001;93:1495–1500.

47. Smith DJ, Perrotti JM, Mansell AL, et al. Ketamine analgesia is not related to an opiate action in the periaqueductal gray region of the rat brain. *Pain*. 1985;21:253–265.

48. Niesters M, Aarts L, Sarton E, Dahan A. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo-controlled cross-over proof-of-concept study. *Br J Anaesth*. 2013;110:1010–1016.

49. Sinner B, Graf BM. Ketamine. *Handb Exp Pharmacol*. 2008;182:313–333.

50. Seeman P, Ko F, Tallerico T. Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. *Mol Psychiatry*. 2005;10:877–883.

51. Sleigh J, Harvey M, Voss L, Denny B. Ketamine-more mechanisms of action than just NMDA blockade. *Trends Anaesth Crit Care*. 2014;4:76–81.

52. Carr DB, Goudas LC, Denman WT, et al. Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. *Pain*. 2004;108:17–27.

53. Rabi J. Topical ketamtene: a review of the history, mechanisms, uses, safety and future. *Int J Pharm Compd*. 2016;20:107–113.

54. Lilius TO, Jokinen V, Neuvonen MS, Niemi M, Kalso EA, Rauhala PV. Ketamine coadministration attenuates morphine tolerance and leads to increased brain concentrations of both drugs in the rat. *Br J Pharmacol*. 2015;172:2799–2813.

55. Wu L, Huang X, Sun L. The efficacy of *N*-methyl-D-aspartate receptor antagonists on improving the postoperative pain intensity and satisfaction after remifentanil-based anesthesia in adults: a meta-analysis. *J Clin Anesth*. 2015;27:311–324.

56. Leal PC, Salomão R, Brunialti MK, Sakata RK. Evaluation of the effect of ketamine on remifentanil-induced hyperalgesia: a double-blind, randomized study. *J Clin Anesth*. 2015;27:331–337.

57. Pestieau SR, Finkel JC, Junqueira MM, et al. Prolonged perioperative infusion of low-dose ketamine does not alter opioid use after pediatric scoliosis surgery. *Paediatr Anaesth*. 2014;24: 582–590.

58. Velly AM, Mohit S. Epidemiology of pain and relation to psychiatric disorders [published online ahead of print May 15, 2017]. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017.

59. Abdallah CG, Adams TG, Kelmendi B, Esterlis I, Sanacora G, Krystal JH. Ketamine's mechanism of action: a path to rapid-acting antidepressants. *Depress Anxiety*. 2016;33:689–697.

60. Schoevers RA, Chaves TV, Balukova SM, Rot MA, Kortekaas R. Oral ketamine for the treatment of pain and treatment-resistant depression. *Br J Psychiatry*. 2016;208:108–113.

61. Chilukuri H, Reddy NP, Pathapati RM, Manu AN, Jollu S, Shaik AB. Acute antidepressant effects of intramuscular versus intravenous ketamine. *Indian J Psychol Med*. 2014;36:71–76.

62. Lapidus KA, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry*. 2014;76:970–976.

63. Beurel E, Song L, Jope RS. Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. *Mol Psychiatry*. 2011;16:1068–1070.

64. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010;329:959–964.

65. Li N, Liu RJ, Dwyer JM, et al. Glutamate *N*-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry*. 2011;69: 754–761.

66. Garcia LS, Comim CM, Valvassori SS, et al. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:140–144.

67. Maeng S, Zarate CA Jr., Du J, et al. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry*. 2008;63: 349–352.

68. Lener MS, Niciu MJ, Ballard ED, et al. Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. *Biol Psychiatry*. 2017;81:886–897.

69. Scheuing L, Chiu CT, Liao HM, Chuang DM. Antidepressant mechanism of ketamine: perspective from preclinical studies. *Front Neurosci*. 2015; 9:249.

70. Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2014;71:681–688.

71. Burbiel JC. Primary prevention of posttraumatic stress disorder: drugs and implications. *Mil Med Res*. 2015;2:24.

72. Nair J, Singh AS. The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectr*. 2008;13:585–591.

73. Riaza Bermudo-Soriano C, Perez-Rodriguez MM, Vaquero-Lorenzo C, Baca-Garcia E. New perspectives in glutamate and anxiety. *Pharmacol Biochem Behav*. 2012;100:752–774.

74. Himmelseher S, Pfenninger E. The clinical use of S-(+)-ketamine—a determination of its place. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 1998;33:764–770.

75. Pees C, Haas NA, Ewert P, Berger F, Lange PE. Comparison of analgesic/sedative effect of racemic ketamine and S(+)-ketamine during cardiac catheterization in newborns and children. *Pediatr Cardiol*. 2003; 24:424–429.

76. Peterbauer C, Larenza PM, Knobloch M, et al. Effects of a low dose infusion of racemic and S-ketamine on the nociceptive withdrawal reflex in standing ponies. *Vet Anaesth Analg*. 2008;35:414–423.

77. Guará Sobrinho H, Garcia JB, Vasconcelos JW, Sousa JC, Ferro LS. Analgesic efficacy of the intra-articular administration of S(+)-ketamine in patients undergoing total knee arthroplasty. *Rev Bras Anestesiol*. 2012; 62:665–675.

78. Yang C, Shirayama Y, Zhang JC, et al. R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. *Transl Psychiatry*. 2015;5:e632.

79. Engelhardt W. [Recovery and psychomimetic reactions following S-(+)-ketamine]. *Anaesthesist*. 1997;46(suppl 1):S38–S42.

80. Zhang JC, Li SX, Hashimoto K. R(−)-ketamine shows greater potency and longer lasting antidepressant effects than S(+)-ketamine. *Pharmacol Biochem Behav*. 2014;116:1371–41.

81. Chen X, Shu S, Bayliss DA. HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine. *J Neurosci*. 2009;29: 600–609.

82. Coates KM, Flood P. Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant alpha7 and alpha4beta2 neuronal nicotinic acetylcholine receptors in *Xenopus* oocytes. *Br J Pharmacol*. 2001;134:871–879.

83. Liy-Salmeron G, Meneses A. Effects of 5-HT drugs in prefrontal cortex during memory formation and the ketamine amnesia-model. *Hippocampus*. 2008;18:965–974.

84. Synowiec AS, Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM. Ketamine use in the treatment of refractory status epilepticus. *Epilepsy Res*. 2013;105:183–188.

85. Manocha A, Sharma KK, Mediratta PK. Possible mechanism of anticonvulsant effect of ketamine in mice. *Indian J Exp Biol*. 2001;39: 1002–1008.

86. Gálvez V, McGuirk L, Loo CK. The use of ketamine in ECT anaesthesia: a systematic review and critical commentary on efficacy, cognitive, safety and seizure outcomes. *World J Biol Psychiatry*. 2017;18:424–444.

87. Hirshman CA, Krieger W, Littlejohn G, Lee R, Julien R. Ketamine-aminophylline-induced decrease in seizure threshold. *Anesthesiology*. 1982;56:464–467.

88. Darimont PC, Jenkins LC. The influence of intravenous anaesthetics on enflurane-induced central nervous system seizure activity. *Can Anaesth Soc J*. 1977;24:42–56.

89. Celesia GG, Chen RC, Bamforth BJ. Effects of ketamine in epilepsy. *Neurology*. 1975;25:169–172.

90. Dimitrov A, Despodova TS. Case of convulsions with late onset after Ketalar anesthesia. [in Bulgarian]. *Akush Ginekol (Sofiia)*. 1976;15: 229–230.

91. Ketalar (ketamine hydrochloride) injection. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pdf. Accessed on November 11, 2017.

92. Rao LK, Flaker AM, Friedel CC, Kharasch ED. Role of cytochrome P4502B6 polymorphisms in ketamine metabolism and clearance. *Anesthesiology*. 2016;125:1103–1112.

93. Zheng X, Fang P, Bao SS, Lin D, Cai JP, Hu GX. Function of 38 variants CYP2C9 polymorphism on ketamine metabolism in vitro. *J Pharmacol Sci*. 2017;135:8–13.

94. Singh NS, Zarate CA Jr, Moaddel R, Bernier M, Wainer IW. What is hydroxynorketamine and what can it bring to neurotherapeutics? *Expert Rev Neurother*. 2014;14:1239–1242.

95. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature*. 2016;533: 481–486.

96. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. *Anesth Essays Res*. 2014;8:283–290.

97. Soliman MG, Brindle GF, Kuster G. Response to hypercapnia under ketamine anaesthesia. *Can Anaesth Soc J*. 1975;22:486–494.

98. Fisher AD, Rippee B, Shehan H, Conklin C, Mabry RL. Prehospital analgesia with ketamine for combat wounds: a case series. *J Spec Oper Med*. 2014;14:11–17.

99. Sprung J, Schuetz SM, Stewart RW, Moravec CS. Effects of ketamine on the contractility of failing and nonfailing human heart muscles in vitro. *Anesthesiology*. 1998;88:1202–1210.

100. MacPherson RD, Woods D, Penfold J. Ketamine and midazolam delivered by patient-controlled analgesia in relieving pain associated with burns dressings. *Clin J Pain*. 2008;24:568–571.

101. Lenze EJ, Farber NB, Kharasch E, et al. Ninety-six hour ketamine infusion with co-administered clonidine for treatment-resistant depression: a pilot randomised controlled trial. *World J Biol Psychiatry*. 2016;17:230–238.

102. White MC, Karsli C. Long-term use of an intravenous ketamine infusion in a child with significant burns. *Paediatr Anaesth*. 2007;17:1102–1104.

103. Domino EF. Taming the ketamine tiger. 1965. *Anesthesiology*. 2010;113: 678–684.

104. Laulin JP, Maurette P, Corcuff JB, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. *Anesth Analg*. 2002;94:1263–1269.

105. Richebé P, Rivat C, Rivalan B, Maurette P, Simonnet G. Low doses ketamine: antihyperalgesic drug, non-analgesic. [in French]. *Ann Fr Anesth Reanim*. 2005;24:1349–1359.

106. Tawfic QA. A review of the use of ketamine in pain management. *J Opioid Manag*. 2013;9:379–388.

107. Prommer EE. Ketamine for pain: an update of uses in palliative care. *J Palliat Med*. 2012;15:474–483.

108. Ghasemi M, Phillips C, Trillo L, de Miguel Z, Das D, Salehi A. The role of NMDA receptors in the pathophysiology and treatment of mood disorders. *Neurosci Biobehav Rev*. 2014;47:336–358.

109. Lin CH, Huang YJ, Lin CJ, Lane HY, Tsai GE. NMDA neurotransmission dysfunction in mild cognitive impairment and Alzheimer's disease. *Curr Pharm Des*. 2014;20:5169–5179.

110. Alshuft HM, Condon LA, Dineen RA, Auer DP. Cerebral cortical thickness in chronic pain due to knee osteoarthritis: the effect of pain duration and pain sensitization. *PLoS One*. 2016;11:e0161687.

111. De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. *CNS Neurosci Ther*. 2013;19:403–410.

112. Vranken JH. Elucidation of pathophysiology and treatment of neuropathic pain. *Cent Nerv Syst Agents Med Chem*. 2012;12:304–314.

113. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain*. 1991;44:293–299.

114. Seminowicz DA, Wideman TH, Naso L, et al. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci*. 2011;31:7540–7550.

115. Čeko M, Shir Y, Ouellet JA, Ware MA, Stone LS, Seminowicz DA. Partial recovery of abnormal insula and dorsolateral prefrontal connectivity to cognitive networks in chronic low back pain after treatment. *Hum Brain Mapp*. 2015;36:2075–2092.

116. Kregel J, Vuijk PJ, Descheemaeker F, et al. The Dutch Central Sensitization Inventory (CSI): factor analysis, discriminative power, and test-retest reliability. *Clin J Pain*. 2016;32:624–630.

117. Eichenberger U, Neff F, Sveticic G, et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg*. 2008;106:1265–1273.

118. Kvarnström A, Karlsten R, Quiding H, Emanuelsson BM, Gordh T. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. *Acta Anaesthesiol Scand*. 2003;47:868–877.

119. Kvarnström A, Karlsten R, Quiding H, Gordh T. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. *Acta Anaesthesiol Scand*. 2004;48:498–506.

120. Baad-Hansen L, Juhl GI, Jensen TS, Brandsborg B, Svensson P. Differential effect of intravenous S-ketamine and fentanyl on atypical odontalgia and capsaicin-evoked pain. *Pain*. 2007;129:46–54.

121. Nickel FT, Ott S, Möhringer S, et al. Effects of different anesthetics on pain processing in an experimental human pain model. *Pain Pract*. 2016; 16:820–830.

122. Kiefer RT, Rohr P, Ploppa A, et al. A pilot open-label study of the efficacy of subanesthetic isomeric S(+)-ketamine in refractory CRPS patients. *Pain Med*. 2008;9:44–54.

123. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain*. 2009;147:107–115.

124. Tajerian M, Leu D, Yang P, Huang TT, Kingery WS, Clark JD. Differential efficacy of ketamine in the acute versus chronic stages of complex regional pain syndrome in mice. *Anesthesiology*. 2015;123:1435–1447.

125. Zhang LM, Zhou WW, Ji YJ, et al. Anxiolytic effects of ketamine in animal models of posttraumatic stress disorder. *Psychopharmacology (Berl)*. 2015;232:663–672.

126. Juven-Wetzler A, Cohen H, Kaplan Z, Kohen A, Porat O, Zohar J. Immediate ketamine treatment does not prevent posttraumatic stress responses in an animal model for PTSD. *Eur Neuropsychopharmacol*. 2014;24:469–479.

127. Morena M, Berardi A, Peloso A, et al. Effects of ketamine, dexmedetomidine and propofol anesthesia on emotional memory consolidation in rats: consequences for the development of post-traumatic stress disorder. *Behav Brain Res*. 2017;329:215–220.

128. Scheidegger M, Henning A, Walter M, et al. Ketamine administration reduces amygdalo-hippocampal reactivity to emotional stimulation. *Hum Brain Mapp*. 2016;37:1941–1952.

129. Li CT, Chen MH, Lin WC, et al. The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: a randomized controlled study. *Hum Brain Mapp*. 2016;37:1080–1090.

130. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology*. 2004; 29:1765–1781.

131. Stewart AM, Nguyen M, Poudel MK, et al. The failure of anxiolytic therapies in early clinical trials: what needs to be done. *Expert Opin Investig Drugs*. 2015;24:543–556.

132. Khan A, Schwartz K. Study designs and outcomes in antidepressant clinical trials. *Essent Psychopharmacol*. 2005;6:221–226.

133. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth*. 2011; 58:911–923.

134. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). *Acta Anaesthesiol Scand*. 2005;49:1405–1428.

135. Jouguelet-Lacoste J, LaColla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med*. 2015; 16:383–403.

136. Elia N, Tramèr MR. Ketamine and postoperative pain—a quantitative systematic review of randomised trials. *Pain*. 2005;113:61–70.

137. Elliott K, Minami N, Kolesnikov YA, Pasternak GW, Inturrisi CE. The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, NG-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids. *Pain*. 1994;56:69–75.

138. Wenzel JT, Schwenk ES, Baratta JL, Viscusi ER. Managing opioid-tolerant patients in the perioperative surgical home. *Anesthesiol Clin*. 2016;34:287–301.

139. Mahathanaruk M, Hitt J, de Leon-Casasola OA. Perioperative management of the opioid tolerant patient for orthopedic surgery. *Anesthesiol Clin*. 2014;32:923–932.

140. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology*. 2010;113: 639–646.

141. Barreveld AM, Correll DJ, Liu X, et al. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. *Pain Med*. 2013;14: 925–934.

142. Urban MK, Ya deau JT, Wukovits B, Lipnitsky JY. Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. *HSS J*. 2008;4:62–65.

143. Vaid P, Green T, Shinkaruk K, King-Shier K. Low-dose ketamine infusions for highly opioid-tolerant adults following spinal surgery: a retrospective before-and-after study. *Pain Manag Nurs*. 2016;17:150–158.

144. Subramaniam K, Akhouri V, Glazer PA, et al. Intra- and postoperative very low dose intravenous ketamine infusion does not increase pain relief after major spine surgery in patients with preoperative narcotic analgesic intake. *Pain Med*. 2011;12:1276–1283.

145. Assouline B, Tramèr MR, Kreienbühl L, Elia N. Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. *Pain*. 2016; 157:2854–2864.

146. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. *Can J Anaesth*. 2016;63:311–325.

147. Uprety D, Baber A, Foy M. Ketamine infusion for sickle cell pain crisis refractory to opioids: a case report and review of literature. *Ann Hematol*. 2014;93:769–771.

148. Jennings CA, Bobb BT, Noreika DM, Coyne PJ. Oral ketamine for sickle cell crisis pain refractory to opioids. *J Pain Palliat Care Pharmacother*. 2013;27:150–154.

149. Meals CG, Mullican BD, Shaffer CM, Dangerfield PF, Ramirez RP. Ketamine infusion for sickle cell crisis pain in an adult. *J Pain Symptom Manage*. 2011;42:e7–e9.

150. Tawfic QA, Faris AS, Kausalya R. The role of a low-dose ketamine-midazolam regimen in the management of severe painful crisis in patients with sickle cell disease. *J Pain Symptom Manage*. 2014;47: 334–340.

151. Losing AK, Jones JM, Keric A, Briggs SE, Leedahl DD. Ketamine infusion therapy as an alternative pain control strategy in patients with multi-trauma including rib fracture; case report and literature review. *Bull Emerg Trauma*. 2016;4:165–169.

152. Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. *Clin Neuropharmacol*. 1995;18:360–368.

153. Gottrup H, Bach FW, Juhl G, Jensen TS. Differential effect of ketamine and lidocaine on spontaneous and mechanical evoked pain in patients with nerve injury pain. *Anesthesiology*. 2006;104:527–536.

154. Eide PK, Stubhaug A, Stenehjem AE. Central dysesthesia pain after traumatic spinal cord injury is dependent on *N*-methyl-D-aspartate receptor activation. *Neurosurgery*. 1995;37:1080–1087.

155. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. *Pain Physician*. 2010;13:245–249.

156. Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain*. 1996;67:69–77.

157. Eide PK, Jørum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the *N*-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain*. 1994;58:347–354.

158. Sorensen J, Bengtsson A, Backman E, Henriksson KG, Bengtsson M. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. *Scand J Rheumatol*. 1995;24: 360–365.

159. Sorensen J, Bengtsson A, Ahlner J, Henriksson KG, Ekselius L, Bengtsson M. Fibromyalgia—are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. *J Rheumatol*. 1997;24:1615–1621.

160. Noppers I, Niesters M, Swartjes M, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. *Eur J Pain*. 2011;15:942–949.

161. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. *Pain*. 2009;145:304–311.

162. Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. *Pain*. 2002;97:275–281.

163. Persson J, Hasselstrom J, Wiklund B, Heller A, Svensson JO, Gustafsson LL. The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. *Acta Anaesthesiol Scand*. 1998;42:750–758.

164. Salas S, Frasca M, Planchet-Barraud B, et al. Ketamine analgesic effect by continuous intravenous infusion in refractory cancer pain: considerations about the clinical research in palliative care. *J Palliat Med*. 2012;15: 287–293.

165. Granata L, Niebergall H, Langner R, Agosti R, Sakellaris L. Ketamine I.V. for the treatment of cluster headaches: an observational study [in German]. *Schmerz*. 2016;30:286–288.

166. Moisset X, Clavelou P, Lauxerois M, Dallel R, Picard P. Ketamine infusion combined with magnesium as a therapy for intractable chronic cluster headache: report of two cases. *Headache*. 2017;57:1261–1264.

167. Pomeroy JL, Marmura MJ, Nahas SJ, Viscusi ER. Ketamine infusions for treatment refractory headache. *Headache*. 2017;57:276–282.

168. Nicolodi M, Sicuteri F. Exploration of NMDA receptors in migraine: therapeutic and theoretic implications. *Int J Clin Pharmacol Res*. 1995;15: 181–189.

169. Afridi SK, Giffin NJ, Kaube H, Goadsby PJ. A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. *Neurology*. 2013; 80:642–647.

170. Hrobjartsson A, Thomsen AS, Emanuelsson F, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *BMJ*. 2012;344:e1119.

171. Savovic J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med*. 2012;157:429–438.
172. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ*. 2008;336:601–605.
173. Gooding JM, Dimick AR, Tavakoli M, Corssen G. A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients. *Anesth Analg*. 1977;56:813–816.
174. Waxman K, Shoemaker WC, Lippmann M. Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg*. 1980;59:355–358.
175. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. *Br J Clin Pharmacol*. 2014;77:357–367.
176. Craven R. Ketamine. *Anaesthesia*. 2007;62(suppl 1):48–53.
177. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth*. 1989;36:186–197.
178. Gomes LM, Garcia JB, Ribamar JS Jr, Nascimento AG. Neurotoxicity of subarachnoid preservative-free S(+)-ketamine in dogs. *Pain Physician*. 2011;14:83–90.
179. Walker SM, Westin BD, Deumens R, Grafe M, Yaksh TL. Effects of intrathecal ketamine in the neonatal rat: evaluation of apoptosis and long-term functional outcome. *Anesthesiology*. 2010;113:147–159.
180. Vranken JH, Troost D, de Haan P, et al. Severe Toxic damage to the rabbit spinal cord after intrathecal administration of preservative-free S(+)-ketamine. *Anesthesiology*. 2006;105:813–818.
181. Rojas AC, Alves JG, Moreira EL, et al. The effects of subarachnoid administration of preservative-free S(+)-ketamine on spinal cord and meninges in dogs. *Anesth Analg*. 2012;114:450–455.
182. Errando CL, Sifre C, Moliner S, et al. Subarachnoid ketamine in swine—pathological findings after repeated doses: acute toxicity study. *Reg Anesth Pain Med*. 1999;24:146–152.
183. Deer TR, Pope AJ, Hayek SM, et al. The Poly-Analgesic Consensus Conference (PACC): recommendations for intrathecal drug delivery: guidance for improving safety and mitigating risks. *Neuromodulation*. 2017;20:155–176.
184. Schwenk ES, Goldberg SF, Patel RD, et al. Adverse drug effects and preoperative medication factors related to perioperative low-dose ketamine infusions. *Reg Anesth Pain Med*. 2016;41:482–487.
185. Wai MS, Chan WM, Zhang AQ, Wu Y, Yew DT. Long-term ketamine and ketamine plus alcohol treatments produced damages in liver and kidney. *Hum Exp Toxicol*. 2012;31:877–886.
186. Bell RF. Ketamine for chronic noncancer pain: concerns regarding toxicity. *Curr Opin Support Palliat Care*. 2012;6:183–187.
187. Rajandram R, Yap NY, Ong TA, et al. Oral ketamine induced pathological changes of the urinary tract in a rat model. *Malays J Pathol*. 2017;39: 47–53.
188. Wong GL, Tam YH, Ng CF, et al. Liver injury is common among chronic abusers of ketamine. *Clin Gastroenterol Hepatol*. 2014;12: 1759–1762.
189. Noppers IM, Niesters M, Aarts LP, et al. 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*. 2011;152:2173–2178.
190. Morgan CJ, Curran HV. Ketamine use: a review. *Addiction*. 2011;107: 27–38.
191. Jhang JF, Hsu YH, Kuo HC. Possible pathophysiology of ketamine-related cystitis and associated treatment strategies. *Int J Urol*. 2015;22:816–825.
192. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology*. 2007;69:810–812.
193. Chen CH, Lee MH, Chen YC, Lin MF. Ketamine-snorting associated cystitis. *J Formos Med Assoc*. 2011;110:787–791.
194. Grégoire MC, MacLellan DL, Finley GA. A pediatric case of ketamine-associated cystitis (letter-to-the-editor re: Shahani R, Streutker C, Dickson B, et al. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007;69: 810–812). *Urology*. 2007;71: 1232–1233.
195. Drayna PC, Estrada C, Wang W, Saville BR, Arnold DH. Ketamine sedation is not associated with clinically meaningful elevation of intraocular pressure. *Am J Emerg Med*. 2012;30:1215–1218.
196. Goldberg ME, Domsky R, Scaringe D, et al. Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome. *Pain Physician*. 2005;8:175–179.
197. Backonja M, Arndt G, Gombar KA, Check B, Zimmermann M. Response of chronic neuropathic pain syndromes to ketamine: a preliminary study. *Pain*. 1994;56:51–57.
198. Felsby S, Nielsen J, Arendt-Nielsen L, Jensen TS. NMDA receptor blockade in chronic neuropathic pain: a comparison of ketamine and magnesium chloride. *Pain*. 1996;64:283–291.
199. Jørum E, Warncke T, Stubhaug A. Cold allodynia and hyperalgesia in neuropathic pain: the effect of *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine—a double-blind, cross-over comparison with alfentanil and placebo. *Pain*. 2003;101:229–235.
200. American Society of Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002;96: 1004–1017.
201. Amr YM. Epidural ketamine in post spinal cord injury–related chronic pain. *Anesth Essays Res*. 2011;5:83–86.
202. Ketamine hydrochloride—drug summary. Available at: http://www.pdr.net/drug-summary/Ketalar-ketamine-hydrochloride-1999. Accessed January 31, 2017.
203. Ahern TL, Herring AA, Anderson ES, Madia VA, Fahimi J, Frazee BW. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. *Am J Emerg Med*. 2015;33:197–201.
204. Ahern TL, Herring AA, Miller S, Frazee BW. Low-dose ketamine infusion for emergency department patients with severe pain. *Pain Med*. 2015;16:1402–1409.
205. Gorlin AW, Rosenfeld DM, Ramakrishna H. Intravenous sub-anesthetic ketamine for perioperative analgesia. *J Anaesthesiol Clin Pharmacol*. 2016;32:160–167.
206. Dundee JW, Fee JP, Moore J, McIlroy PD, Wilson DB. Changes in serum enzyme levels following ketamine infusions. *Anaesthesia*. 1980;35: 12–16.
207. Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. *Anaesth Intensive Care*. 2005;33: 311–322.
208. Cohen L, Athaide V, Wickham ME, Doyle-Waters MM, Rose NG, Hohl CM. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. *Ann Emerg Med*. 2015;65:43–51.
209. Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on intracranial pressure in nontraumatic neurological illness. *J Crit Care*. 2014;29:1096–1106.
210. Guerra F. Ketamine and angina. *Anesthesiology*. 1978;155.
211. Ward J, Standage C. Angina pain precipitated by a continuous subcutaneous infusion of ketamine. *J Pain Symptom Manage*. 2003;25:6–7.
212. Kraus C, Lanzenberger R, Kasper S. Ketamine for the treatment of depression. *JAMA Psychiatry*. 2017;74:970.
213. Lahti AC, Holcomb HH, Medoff DR, Tamminga CA. Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuroreport*. 1995;6:869–872.

214. Epocrates. Ketamine: contraindications/cautions. Available at: https://online.epocrates.com/u/1031970/ketamine/Contraindications+Cautions. Accessed January 18, 2018.

215. WebMD. Who should not take ketamine HCL syringe? Available at: https://www.webmd.com/drugs/2/drug-156554/ketamine-intravenous/details/list-contraindications. Accessed January 18, 2018.

216. Davis FA. Ketamine drug monograph. Available at: https://davisplus.fadavis.com/3976/meddeck/pdf/ketamine.pdf. Accessed January 18, 2018.

217. Pal HR, Berry N, Kumar R, Ray R. Ketamine dependence. *Anaesth Intensive Care*. 2002;30:382–384.

218. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009;10:131–146.

219. Yang M, Qian C, Liu Y. Suboptimal treatment of diabetic peripheral neuropathic pain in the United States. *Pain Med*. 2015;16:2075–2083.

220. Xu Y, Hackett M, Carter G, et al. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2016;19:1–15.

221. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. *Hum Psychopharmacol*. 2015;30:152–163.

222. Szymkowicz SM, Finnegan N, Dale RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. *J Affect Disord*. 2013;147:416–420.

223. Lauritsen C, Mazuera S, Lipton RB, Ashina S. Intravenous ketamine for subacute treatment of refractory chronic migraine: a case series. *J Headache Pain*. 2016;17:106.

224. Huge V, Lauchart M, Magerl W, et al. Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. *Eur J Pain*. 2010;14:387–394.

225. Kiefer RT, Rohr P, Ploppa A, et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. *Pain Med*. 2008;9:1173–1201.

226. Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan A. Ketamine for the treatment of chronic non-cancer pain. *Expert Opin Pharmacother*. 2010;11:2417–2429.

227. Jafarinia M, Afarideh M, Tafakhori A, et al. Efficacy and safety of oral ketamine versus diclofenac to alleviate mild to moderate depression in chronic pain patients: a double-blind, randomized, controlled trial. *J Affect Disord*. 2016;204:1–8.

228. Ishizuka P, Garcia JB, Sakata R, Issy A, Mülich SL. Assessment of oral S+ ketamine associated with morphine for the treatment of oncologic pain. *Rev Bras Anestesiol*. 2007;57:19–31.

229. Lauretti G, Lima I, Reis M, Prado W, Pereira N. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. *Anesthesiology*. 1999;90:1528–1533.

230. Haines DR, Gaines SP. N of 1 randomised controlled trials of oral ketamine in patients with chronic pain. *Pain*. 1999;83:283–287.

231. Marchetti F, Coutaux A, Bellanger A, Magneux C, Bourgeois P, Mion G. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: a retrospective 5-year study of 51 patients. *Eur J Pain*. 2015;19:984–993.

232. Furuhashi-Yonaha A, Iida H, Asano T, Takeda T, Dohi S. Short- and long-term efficacy of oral ketamine in eight chronic-pain patients. *Can J Anaesth*. 2002;49:886–887.

233. Giorgetti R, Marcotulli D, Tagliabracci A, Schifano F. Effects of ketamine on psychomotor, sensory and cognitive functions relevant for driving ability. *Forensic Sci Int*. 2015;252:127–142.

234. Cohen SP, Chang AS, Larkin T, Mao J. The intravenous ketamine test: a predictive response tool for oral dextromethorphan treatment in neuropathic pain. *Anesth Analg*. 2004;99:1753–1759.

235. Cohen SP, Verdolin MH, Chang AS, Kurihara C, Morlando BJ, Mao J. The intravenous ketamine test predicts subsequent response to an oral dextromethorphan treatment regimen in fibromyalgia patients. *J Pain*. 2006;7:391–398.

236. Cohen SP, Wang S, Chen L, et al. An intravenous ketamine test as a predictive response tool in opioid-exposed patients with persistent pain. *J Pain Symptom Manage*. 2009;37:698–708.

237. Cohen SP, Kapoor SG, Rathmell JP. Intravenous infusion tests have limited utility for selecting long-term drug therapy in patients with chronic pain: a systematic review. *Anesthesiology*. 2009;111:416–431.

238. Collins S, Sigtermans M, Dahan A. NMDA receptor antagonists for the treatment of neuropathic pain. *Pain Med*. 2010;11:1726–1742.

239. Aiyer R, Mehta N, Gungor S, Gulati A. A systematic review of NMDA receptor antagonists for treatment of neuropathic pain in clinical practice. *Clin J Pain*. 2018;34:450–467.

240. Maneglia R, Cousin MT. A comparison between propofol and ketamine for anaesthesia in the elderly. Haemodynamic effects during induction and maintenance. *Anaesthesia*. 1988;43(suppl):109–111.

241. Kiefer RT, Rohr P, Ploppa A, Altemeyer KH, Schwartzman RJ. Complete recovery from intractable complex regional pain syndrome, CRPS-type I, following anesthetic ketamine and midazolam. *Pain Pract*. 2007;7:147–150.

242. Stukus KS, Przybylowicz RW, Backes CH Jr, Cohen DM. Ventricular tachycardia after ketamine sedation for fracture reduction. *Pediatr Emerg Care*. 2014;30:730–732.

243. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med*. 2008;26:985–1028.

244. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst Rev*. 2013;30:CD009416.

245. Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Med*. 2004;5:263–275.

246. American Society of Anesthesiologists. Statement on granting privileges for administration of moderate sedation to practitioners who are not anesthesia professionals (approved by the ASA House of Delegates on October 25, 2005, and reaffirmed on October 26, 2016). Available at: http://www.asahq.org/~/media/Sites/ASAHQ/Files/Public/Resources/standards-guidelines/statement-on-granting-privileges-for-administration-of-moderate-sedation-to-practitioners.pdf. Accessed July 19, 2017.

247. Zorumski CF, Conway CR. Use of ketamine in clinical practice: a time for optimism and caution. *JAMA Psychiatry*. 2017;74:405–406.

248. Mailis A, Taenzer P. Evidence-based guideline for neuropathic pain interventional treatments: spinal cord stimulation, intravenous infusions, epidural injections and nerve blocks. *Pain Res Manag*. 2012;17:150–158.

249. Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol*. 1997;7:25–38.

250. Trivedi S, Kumar R, Tripathi AK, Mehta RK. A comparative study of dexmedetomidine and midazolam in reducing delirium caused by ketamine. *J Clin Diagn Res*. 2016;10:UC01–UC04.

251. Krystal JH, Karper LP, Bennett A, et al. Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. *Psychopharmacology (Berl)*. 1998;135:213–229.

252. Sener S, Eken C, Schultz CH, Serinken M, Ozsarac M. Ketamine with and without midazolam for emergency department sedation in adults: a randomized controlled trial. *Ann Emerg Med*. 2011;57:109–114.

253. National Library of Medicine Toxnet. Ketamine casrn:6740-88-1. Available at: https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+2180. Accessed July 29, 2017.

254. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105–121.

255. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.

256. Beilin Y, Hossain S, Bodian CA. The numeric rating scale and labor epidural analgesia. *Anesth Analg*. 2003;96:1794–1798.

257. Olsen MF, Bjerre E, Hansen MD, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med*. 2017;15:35.

258. Bicket MC, Pasquina PF, Cohen SP. Which regional pain rating best predicts patient-reported improvement in lumbar radiculopathy? *Pain Pract*. 2017;17:1058–1065.

259. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106:337–345.

260. Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study questionnaire Short Form 36, and pain scales. *Spine J*. 2008;8:968–974.

261. Cohen SP, Hurley RW, Buckenmaier CC 3rd, Kurihara C, Morlando B, Dragovich A. Randomized placebo-controlled study evaluating lateral branch radiofrequency denervation for sacroiliac joint pain. *Anesthesiology*. 2008;109:279–288.

262. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. *Reg Anesth Pain Med*. 2013;38:175–200.

263. Fishbain DA, Cole B, Lewis JE, Gao J. What is the evidence that neuropathic pain is present in chronic low back pain and soft tissue syndromes? An evidence-based structured review. *Pain Med*. 2014;15:4–15.

264. Liu R, Kurihara C, Tsai HT, Silvestri PJ, Bennett MI, Cohen SP. Classification and treatment of chronic neck pain: a longitudinal cohort study. *Reg Anesth Pain Med*. 2017;42:52–61.

265. Littlejohn G, Guymer E. Modulation of NMDA receptor activity in fibromyalgia. *Biomedicines*. 2017;5:pii:E15.

266. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312:71–72.

267. Myers FA Jr, Bluth MH, Cheung WW. Ketamine: a cause of urinary tract dysfunction. *Clin Lab Med*. 2016;36:721–744.

268. Zuccoli ML, Muscella A, Fucile C, et al. Paliperidone for the treatment of ketamine-induced psychosis: a case report. *Int J Psychiatry Med*. 2014;48:103–108.