



Ketamine for pain management

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1. Background

1.1. Basic pharmacology and mechanisms of action of ketamine

Ketamine is commonly used as an analgesic in emergency medicine and as an adjuvant drug in the perioperative setting. In addition, it is used as a third-line adjuvant drug for opioid-resistant pain in palliative care and for intractable chronic noncancer pain. More recently, ketamine is increasingly being used to treat major depression and other mood disorders.

Ketamine is a phencyclidine derivative that was developed in the 1960s as an anaesthetic agent. The most important pharmacological properties of ketamine are due to it being a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, and its analgesic action at subanaesthetic dose is believed to be primarily due to NMDA receptor antagonism in the brain and spinal cord.³³ The NMDA receptor is important for learning, memory, and synaptic plasticity. Regarding pain, the NMDA receptor is involved in the amplification of pain signals, the development of central sensitization, and opioid tolerance.⁴⁹ Ketamine has been shown to have antihyperalgesic effects and to reduce or reverse opioid tolerance.^{22,24}

Ketamine also interacts with other receptors and channels, including nicotinic and muscarinic acetylcholine receptors, opioid receptors, monoaminergic receptors, and voltage-sensitive sodium channels.⁴¹ It enhances endogenous antinociceptive systems, increasing the descending inhibitory serotonergic pathway.³³ Recent research indicates that ketamine may also

Key Points

1. There is good evidence that perioperative ketamine decreases postoperative pain scores and opioid requirements, but there is a lack of consensus on dose, for both bolus and infusion.
2. Despite limited evidence, a trial of low-dose intravenous or subcutaneous ketamine adjuvant to morphine may be warranted in refractory cancer pain.
3. There is only very limited evidence for the use of ketamine in chronic noncancer pain and concerns and a lack of safety data concerning long-term or repeated treatment. Importantly, there is no strong evidence to support the current practice of treating chronic noncancer pain with repeated intravenous infusions.
4. Ketamine has dose-dependent adverse effects, and there are good arguments for avoiding high doses.
5. Spinal administration is associated with neurotoxicity, whereas oral ketamine has low bioavailability and is associated with adverse effects.

modulate (suppress) pain transmission by limiting astrocyte and microglial activation.⁴⁶

Ketamine gives robust and rapid relief of major depression and suicidal ideation.¹ The mechanism for this effect is as yet not fully elucidated, but major depressive disorder is associated with synaptic downregulation in the prefrontal cortex and hippocampus, and it is believed that ketamine causes a glutamate surge that leads to a series of events resulting in synaptogenesis and reversal of the negative effects of depression and chronic stress.¹ A recent functional magnetic resonance imaging study in patients with treatment-resistant depression compared with healthy volunteers demonstrated that ketamine normalized depression-related prefrontal dysconnectivity.²

Ketamine has anti-inflammatory effects, modulating the production of different proinflammatory mediators. A recent study using a rabbit model of gonarthrosis found that ketamine suppressed the inflammatory response in osteoarthritis,²⁸ whereas a systematic review concluded that intraoperative ketamine reduces the postoperative IL-6 inflammatory response in surgical patients.¹⁵

The most commonly reported adverse effects of ketamine are psychotomimetic (hallucinations, agitation, anxiety, dysphoria, and euphoria). Administration of ketamine may also cause dizziness, nausea, sedation, and tachycardia. Ketamine's

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adverse effects are dose-dependent. At low dose, it acts as an NMDA receptor antagonist, providing an analgesic effect; but at higher doses, it acts on other receptors and channels including dopamine D₂ receptors, monoaminergic receptors, and opioid receptors.⁶² Ketamine dose dependently inhibits monoamine transporters, and it has been suggested that this may be one mechanism behind its psychotomimetic adverse effects.⁴¹ Chronic abuse of ketamine is associated with a range of adverse effects, some of which have also been reported in pain patients treated with ketamine (Tables 1 and 2).

1.2. Pharmacokinetics and administration of ketamine

Ketamine is available as a racemic mixture or as the S(+) enantiomer that is approximately twice as potent as racemic ketamine and about 4 times as potent as the R(−) enantiomer.³³ Ketamine is N-demethylated by liver microsomes into the major metabolite of racemic ketamine, norketamine, which is rapidly metabolized to ketamine's major secondary metabolite, 6-hydroxynorketamine, and to the lesser metabolites 4-hydroxyketamine and 6-hydroxyketamine.³³ Ketamine has been shown to have antinociceptive effects and to reduce opioid tolerance, whereas norketamine has been shown to have antinociceptive properties in animal studies, but little is known about its analgesic effects in humans. A study in healthy volunteers found that S(+)-norketamine after S(+) ketamine dosing did not have significant antinociceptive properties and even made a negative contribution to S(+) ketamine analgesia.³⁹ Six-hydroxynorketamine in an animal model failed both to demonstrate antinociceptive properties and to attenuate opioid tolerance.²⁶

Ketamine may be given by multiple routes of administration including intravenous (IV), subcutaneous, oral, intranasal, transdermal, and spinal (epidural and intrathecal). Spinal administration of ketamine has been shown to be associated with neurotoxicity, safety data are lacking and no NMDA receptor antagonists have been approved for neuraxial use in humans.⁵⁷ The oral bioavailability of ketamine is low, reportedly 17% to 24% for oral racemic ketamine and 8% to 11% for oral S(+)-ketamine.⁴¹ After oral intake of ketamine, norketamine plasma concentrations are much higher than those of the parent drug.⁴¹

Ketamine does not cause respiratory depression and does not decrease blood pressure, making it a useful drug in emergency

medicine and intensive care, although there are certain concerns because of its effect on intracranial pressure and ocular pressure. The use of ketamine in emergency medicine and intensive care is beyond the scope of this review.

Ketamine's antihyperalgesic, antidepressant, and anti-inflammatory effects, together with its beneficial interactions with opioids, including reduction of opioid tolerance, make it an especially interesting drug to use in pain management. However, depending on the clinical setting, the extent to which ketamine is clinically useful depends not only on its efficacy and tolerability but also on other factors such as ease of administration, costs, and long-term safety.

The best evidence for efficacy and tolerability comes from systematic reviews of randomized controlled trials (RCTs), whereas case reports provide valuable information on adverse effects. In this review, we will examine the current evidence for the benefits and harms of ketamine and its clinical usefulness in pain management.

2. Ketamine for acute postoperative pain

There is a large body of literature addressing the use of ketamine in the perioperative setting. Adjuvant treatment with IV racemic, or S(+) ketamine is common, to improve postoperative pain relief and reduce opioid requirements. Epidural ketamine has also been used in this setting. In some cases, ketamine has been used with the aim of preventing chronic postoperative pain.

2.1. Evidence for efficacy and adverse effects

A search of PubMed on February 23, 2018, using the terms "ketamine" AND "postoperative pain" and the filter "systematic reviews" yielded 56 hits, 11 of which were systematic reviews addressing perioperative ketamine for acute or chronic postoperative pain^{4,8,16,21,30,36,42,55,59,60,63} (Table 3). A recently completed Cochrane review,¹⁴ currently under review, has also been included.

Perioperative ketamine decreased postoperative pain scores,^{4,8,16,21,30,36,42,55,60,63} increased the time to first analgesic request,^{21,60} and reduced postoperative opioid requirements.^{4,8,16,21,42,55,59,60,63} Ketamine also reduced postoperative nausea and/or vomiting.^{4,21,36,55,60,63} Interestingly, Laskowski et al.²¹ found that ketamine had significant analgesic benefit for major procedures involving the upper abdomen and thorax,

Table 1
Adverse effects of ketamine, other than psychotomimetic, reported in cancer/palliative care pain management.

Adverse effect	Authors	Comment
Neurotoxicity (subpial vacuolar myelopathy)	Karpinski et al., 1997 ²⁰	Intrathecal ketamine with preservative (benzethonium chloride) 5 mg/d
Neurotoxicity (focal lymphocytic vasculitis in medullary tissue, nerves, and leptomeninges of the thoracic and lumbar spinal cord)	Stotz et al., 1999 ⁴⁸	Intrathecal ketamine with preservative (benzethonium chloride), mean dose 67.2 mg/d
Neurotoxicity (severe histological abnormalities: central chromatolysis, nerve cell shrinkage, neuronophagia, microglial upregulation, and gliosis)	Vranken et al., 2005 ⁵⁴	Intrathecal preservative-free S(+) ketamine 20–50 mg/d
Generalized hyperalgesia and allodynia	Mitchell, 1999 ³⁴	After abrupt cessation of 3-wk subcutaneous infusion 200 mg/24 h.
Urotoxicity	Storr et al., 2009 ⁴⁷	Oral administration 50–170 mg × 4. 3 cases
Needle site irritation	Mitchell, 1999 ³⁴ ; and Oshima et al., 1990 ⁴⁰	Subcutaneous infusion 60–360 mg/24 hrs; and subcutaneous infusion 200 mg/24 h
Angina	Ward et al., 2003 ⁵⁶	Subcutaneous infusion of ketamine 150 mg/24 h

Table 2**Adverse effects of ketamine, other than psychotomimetic, reported in chronic noncancer pain management.**

Adverse effect	Authors	Comments
Urotoxicity	Grégoire et al., 2008 ¹⁷	CRPS-1. Oral ketamine titrated to 8 mg/kg/d. Urological symptoms (dysuria, frequency, urgency, and incontinence) noted after 9 d of treatment. Symptoms decreased when ketamine reduced to 6 mg/kg/d, disappeared at dose of 2 mg/kg/d, but reappeared when dose increased to 5 mg/kg/d
Hypertension	Van Hecke et al., 2014 ⁵²	Chronic back pain. Oral ketamine, initially 20 mg × 4, increased to 20 + 20 + 20 + 30 mg daily. Reduction in ketamine dose led to reduction in blood pressure
Hepatotoxicity	Noppers et al., 2011 ³⁸	CRPS-1. One or 2 continuous intravenous 100-h S(+)-ketamine infusions (infusion rate 10–20 mg/h), with a 16-d interval between infusions
Anosmia	Mayell et al., 2009 ²⁹	Chronic pelvic/abdominal pain after surgery and radiotherapy. Intranasal ketamine. Dose: 14 mg per spray, up to 4 sprays 4 hourly, as required
Dependency	Bonnet, 2015 ¹²	See supplemental digital content 2, http://links.lww.com/PR9/A26 .

CRPS, complex regional pain syndrome.

associated with high pain scores or high opioid requirements. This finding was also reported by the most recent Cochrane review.¹⁴

One review that focused on ketamine for persistent post-surgical pain³⁰ did not find an overall reduced risk of developing chronic postoperative pain in the ketamine group compared with placebo. However, when exclusively IV ketamine studies were analysed, they demonstrated statistically significant risk reduction at 3 and 6 months. According to the authors, this could have been due to spinal NMDA receptors playing only a minor role as targets for ketamine in postoperative pain, or due to ketamine having lower systemic efficacy when it is administered by the epidural route.

Most systematic reviews report that perioperative ketamine was well tolerated, with adverse effects being mild or absent. Most studies provided dichotomous data on central nervous system adverse events.¹⁴

2.1.1. Clinical considerations

Although most trials investigated ketamine given by the IV route, clinical regimens differed, especially regarding dose. Data from the review by Brinck et al.¹⁴ indicate that 77 of the 130 trials used racemic ketamine as an IV bolus, with 35 of these studies using a dose less than 0.25 mg/kg. Twenty-one studies used a bolus dose of 0.5 to 1 mg/kg. Forty-two trials used racemic ketamine as a continuous IV infusion, with the most common dose being 2 to 5 µg/kg/min. Ten trials used S(+) ketamine, of these 8 used a preincisional IV bolus (0.075–0.5 mg/kg), followed by an IV infusion (0.25–6.7 µg/kg/min). One trial used R(–) ketamine as an IV bolus (1 mg/kg).

Ketamine seems most beneficial when pain scores are high, suggesting that it is primarily useful for surgery associated with high levels of postoperative pain. Given that ketamine reduces opioid requirements, it may also be indicated for subgroups such as opioid tolerant or opioid-dependent patients.

3. Ketamine for opioid-resistant pain in palliative care

Ketamine is widely used as a third-line drug for cancer pain, when the pain has not responded to opioid in combination with drugs

such as nonsteroidal anti-inflammatory drugs, amitriptyline, and gabapentinoids. Published case reports demonstrate that ketamine is used for refractory pain in palliative care in many countries, and that treatment regimens differ widely using IV, subcutaneous, oral, intrathecal, and topical routes of administration. A Cochrane review on ketamine as an adjuvant to opioid for cancer pain,⁹ first published in 2003, described 32 case reports involving 246 patients treated with ketamine. Doses ranged from 1 mg/kg/d as a subcutaneous infusion, to 600 mg/d as an IV infusion and 67.2 mg/d intrathecally.

3.1. Evidence for efficacy and adverse effects

A simple search of PubMed using the terms “ketamine” AND “cancer” and the filter “systematic reviews” yielded 14 hits, 4 of which were systematic reviews on ketamine for cancer pain. Three of the 4 titles were different versions of the Cochrane review on ketamine as an adjuvant to opioid in cancer pain in adults, which has been twice updated, most recently in 2017.⁹ The fourth title was a comprehensive review of all available English language literature on ketamine for cancer pain in children and adults¹³ (Table 4).

The recently updated Cochrane review included 3 RCTs. Two small cross-over trials investigated IV ketamine in 2 doses³¹ or intrathecal ketamine⁵⁸ as an adjuvant to morphine. Both trials found that ketamine reduced pain intensity and morphine requirements. A third larger trial with a parallel-group design and 185 participants investigated rapid titration of subcutaneous ketamine to high dose (500 mg) in participants who were using different opioids.¹⁸ In this trial, there was no difference between groups regarding patient-reported pain intensity, and there was almost twice the incidence of adverse effects in the ketamine group. Two serious adverse events (bradyarrhythmia and cardiac arrest) believed to be related to ketamine were reported in this trial. The update concluded that current evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for refractory cancer pain, and that rapid dose escalation of ketamine to high dose (500 mg) does not seem to have clinical benefit and may be associated with serious adverse events.

The review by Bredlau et al.,¹³ which used a comprehensive approach and less stringent methodology than the Cochrane review included 5 RCTs and 6 prospective uncontrolled trials on

Table 3**Systematic reviews of ketamine for postoperative pain.**

Type of surgery	Authors	No. of RCTs/ participants (N)	Outcomes	Comments
All	Brinck et al., 2018 ¹⁴	130, N = 8341	Postoperative opioid consumption; pain intensity; time to first analgesic request; hyperalgesia; and adverse effects	IV ketamine. Cochrane review
Spinal	Pendi et al., 2018 ⁴²	14, N = 649	Postoperative opioid consumption; and pain intensity	Searched for all routes of administration, but all included studies used IV ketamine
Laparoscopic cholecystectomy	Zhu et al., 2018 ⁶³	6, N = 294	Pain intensity; postoperative opioid consumption; length of stay; and adverse effects	IV ketamine
Thoracotomy	Moyse et al., 2017 ³⁶	15, N = 360	Postoperative opioid consumption; pain intensity; and adverse effects	IV, IM, and ED ketamine
Laparoscopic cholecystectomy	Ye et al., 2017 ⁶¹	5, N = 212	Pain intensity; postoperative opioid consumption; and adverse effects	IV ketamine
All	Assouline et al., 2016 ⁴	19, N = 1453 (1349 adults and 104 children)	Percent decrease in cumulative 24-h morphine consumption; pain intensity; PONV; and respiratory adverse effects	IV ketamine added to an opioid in a PCA device
All	Wang et al., 2016 ⁵⁵	36, N = 2502	Pain intensity; cumulative morphine consumption; patient satisfaction; PONV; and adverse effects	IV ketamine added to PCA containing morphine or hydromorphone
All	McNicol et al., 2014 ³⁰	17, N = 1800	Prevalence of PPSP; intensity or severity of PPSP; and adverse effects	Ketamine given by any route
All	Yang et al., 2014 ⁵⁹	5, N = 266	Pain intensity; postoperative morphine consumption; time to first analgesic; and adverse effects	Ketamine given preoperatively
All	Laskowski et al., 2011 ²¹	70, N = 4701	Total postoperative opioid consumption pain intensity; time to first analgesic; and adverse effects	IV ketamine. Included trials performed in children
All	Bell et al., 2006 ⁸	37, N = 2240	Postoperative PCA opioid consumption; pain intensity; rescue medication; time to first analgesic request; and adverse effects	Ketamine by any route or added to a PCA device. Cochrane review*
All	Elia et al., 2005 ¹⁶	53, N = 2839	Pain intensity; cumulative morphine consumption; time to first analgesic request; and adverse effects	Ketamine by any route or added to a PCA device. Included trials performed in children

* Cochrane review by Bell et al.⁸ not updated since 2006, therefore marked "Withdrawn" in Cochrane Library.

ED, epidural; IM, intramuscular; IV, intravenous; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting; PPSP, persistent postsurgical pain; RCT, randomized controlled trial.

ketamine for cancer pain in adults. No RCTs in children were identified, but the authors considered 5 retrospective studies. The review found that ketamine reduced opioid requirements, and may improve pain control, at the same time noting the significant limitations of the current evidence and the wide variation in dosages, routes, duration, and frequency of ketamine administration in the published literature. The authors also expressed concerns regarding ketamine's neurotoxic effects, recommending that intrathecal administration and epidural administration should be avoided. The review concludes that "*In children and adults with cancer pain that has not responded adequately to*

standard therapy, the literature supports considering ketamine as an adjuvant therapy."

Several reports have described neurotoxicity when ketamine was administered intrathecally in the palliative care setting.^{20,48,54} Abrupt cessation of a continuous subcutaneous infusion was reported to result in generalized hyperalgesia.³⁴ Storr et al. reported 3 patients treated by a palliative care team who developed urological symptoms (frequency, haematuria, dysuria, and bladder pain) after oral ketamine.⁴⁷ For reports of adverse effects of ketamine, other than psychotomimetic, in the management of refractory cancer pain, see **Table 1**.

Table 4**Systematic reviews on ketamine for refractory cancer pain.**

Pain condition	Authors	No. of trials/ participants	Outcomes	Comments
Cancer pain	Bell et al., 2017 ⁹	3, N = 215	Patient-reported pain intensity; total opioid consumption; rescue medication; adverse events; patient satisfaction/preference; function; and distress	Included only randomized, double-blinded, placebo-controlled trials addressing ketamine given by any route and in any dose as adjuvant to preexisting opioid
Cancer pain	Bredlau et al., 2013 ¹³	16, N = 483 adult participants	Aimed to provide a synthesis of the data on ketamine for refractory cancer pain in children and adults, including dose, route of administration, duration of treatment, effect, and adverse effects	Included 5 RCTs and 6 prospective, uncontrolled trials in adults. No RCTs in children were identified, but 5 retrospective studies were reviewed

RCT, randomized controlled trial.

3.1.1. Clinical considerations

We concur with the review by Bredlau et al.¹³ that although the evidence is limited, ketamine may be useful as a third-line drug for selected patients with refractory cancer pain. Many of the case studies describe a dramatic effect of ketamine, but as yet, we are unable to identify characteristics of responders. The choice of opioid may be of importance because recent animal studies have shown that ketamine and norketamine attenuate morphine tolerance more effectively than oxycodone tolerance.²⁵

There seem to be good arguments for keeping the ketamine dose low. Ketamine has dose-dependent adverse effects. Terminally ill cancer patients may have reduced hepatic function because of metastases and diminished liver perfusion. Hepatic impairment can cause reduced drug metabolism and significantly impaired clearance.³⁷ Increased age has also been shown to be associated with substantially reduced ketamine clearance.²³ Examples of low-dose regimens adjuvant to opioid, primarily morphine, are racemic ketamine 1 mg/kg/24 hours per day,⁷ or S(+) ketamine (0.5–2 mg/kg/24 hours) as an IV infusion, with careful individual titration.¹⁰

The evidence for efficacy and tolerability for ketamine in this setting is limited. It is undeniably challenging to conduct RCTs in this patient group. What then in theory could be the indications for ketamine treatment? When cancer pain or pain in a palliative care patient is refractory to opioid and adjuvant drugs, then ketamine may be an option. There are many reasons for pain in this patient group. Ketamine could be especially relevant when there are problems of opioid tolerance, a significant neuropathic pain component, inflammatory pain, depression, or any combination of these factors. In fact, this may be the pain patient group that is most likely to need a trial of ketamine and where the risk benefit ratio is the most beneficial. A trial of ketamine does not need to be lengthy and if there is no clear benefit, then ketamine treatment should be terminated.

4. Ketamine for chronic noncancer pain

It is more difficult to formulate clear indications for the use of ketamine in chronic noncancer pain. Given ketamine's range of adverse effects and the lack of safety data concerning long-term treatment, there is good reason to be cautious when treating complex chronic pain problems with this drug. Possible indications could be refractory neuropathic or inflammatory pain with, or without, depression in carefully selected patients.

Ketamine is increasingly being used as a third-line drug for refractory chronic noncancer pain. In this setting, it is commonly administered as intermittent IV infusions. Patients may be offered hospital admission and infusion treatment over several days.

However, outpatient treatment seems to be on the increase, and in the United States, a large number of "ketamine clinics" have been established offering infusions for a variety of conditions, including chronic pain, depression, and other mood disorders. A Medscape report suggests that there may be more than 1000 such clinics currently operating in the United States.⁵¹ For chronic pain, these clinics offer a series of infusions on an outpatient basis, followed by "maintenance therapy" for example, involving monthly ketamine infusions.⁵ Although racemic ketamine is an inexpensive drug, patient costs associated with this treatment are high (supplemental digital content 1, <http://links.lww.com/PR9/A25>).⁵

4.1. Evidence for efficacy and adverse effects

A search of PubMed on February 23, 2018, using the terms "ketamine" AND "chronic pain" and the filter "systematic reviews" yielded 20 hits, of which 4 were systematic reviews on ketamine for chronic noncancer pain in adults^{6,19,32,61} (**Table 5**).

Of the 2 reviews published in 2018, Michelet et al.³² included only randomized, placebo-controlled, double-blinded trials on ketamine for chronic pain in adults (**Table 6**). The authors found low-level evidence (GRADE) demonstrating that ketamine was ineffective regarding the primary outcome of the review, failing to decrease pain intensity at 4 weeks after the beginning of treatment. When only trials not judged to have a high risk of bias were analyzed, they found moderate-level evidence that ketamine was effective at 4 weeks after treatment, suggesting a long-lasting effect. However, the clinical implications of this finding are uncertain because trial sequential analysis found the meta-analysis to be underpowered and methodological shortcomings in several of the included trials have been noted. The authors judged the trials by Mitchell et al.³⁵ and Amr³ to be at high risk of bias, whereas the methodology and conclusions of the trial by Schwartzman et al.,⁴⁴ which was prematurely terminated before even half of the planned number of patients had been included, have also been challenged.¹¹ The carefully performed trial by Sigtermans et al.⁴⁵ found that ketamine infusions gave pain relief for patients with complex regional pain syndrome (CRPS) type I but did not result in functional improvement. As the authors pointed out, blinding in this trial was possibly compromised by ketamine-related adverse effects. Follow-up times in these chronic pain RCTs were 1 week,⁵³ 9 days,³⁵ 11 weeks,⁴⁵ and 3 months.^{43,44}

Ketamine was generally associated with more adverse effects than placebo. The studies were heterogenous regarding dose, route of administration, and duration of treatment, and the authors of the review were unable to recommend any treatment regimen, noting the need for further trials.

Table 5
Systematic reviews of ketamine for chronic noncancer pain.

Pain condition	Authors	No. of trials/ participants	Outcomes	Comments
Chronic noncancer pain	Michelet et al., 2018 ³²	6, N = 149	Pain intensity; and adverse effects	Included only randomized and placebo-controlled trials (Table 6).
CRPS	Zhao et al., 2018 ⁶¹	15, N = 258	Pain intensity; and percentage participants achieving 30% or higher pain relief	One RCT. Included cohort/retrospective studies
CRPS	Azari et al., 2012 ⁶	19, N = NA	Efficacy and safety	Included 3 randomized, placebo-controlled trials, 7 observational studies, and 9 case reports
Chronic noncancer pain	Hocking et al., 2003 ¹⁹	24 published reports, N = 198	No clearly defined outcomes	Assessment of all published evidence, including case reports

CRPS, complex regional pain syndrome; NA, not available; RCT, randomized controlled trial.

Table 6**Randomized, placebo-controlled, double-blinded trials on ketamine for chronic pain in adults (Michelet et al., 2018³²).**

Condition	Authors	No. of participants	Outcomes	Comments
Neuropathic pain secondary to spinal cord injury	Amr, 2010 ³	40	Pain intensity; and adverse effects	Ketamine infusion as an adjuvant to oral gabapentin
Limb ischaemia secondary to peripheral vascular disease	Mitchell and Fallon, 2002 ³⁵	35 (28 completed the study)	BPI; total opioid requirements past 24 h; and sensory changes	Single IV infusion of low-dose ketamine (0.6 mg/kg over 4 h). Thirty-three patients treated with morphine, 2 with dextropropoxyphene. 7 withdrawals, 5 due to a surgical procedure, and 2 due to an acute medical event
Neuropathic pain	Rigo et al., 2017 ⁴³	42	Pain intensity	Oral ketamine 30 mg × 3 vs oral methadone 3 mg × 3 vs (oral ketamine 30 mg + oral methadone 3 mg) × 3
CRPS (not specified whether CRPS-I or CRPS-II)	Schwartzman et al., 2009 ⁴⁴	19	Overall pain level (NRS); activity; QoL; and sensory changes	4-h IV infusion of racemic ketamine daily for 10 d. Maximum 0.35 mg/kg/h, not to exceed 25 mg/h (100 mg of ketamine over a 4-h period). "CRPS medications" continued
CRPS-I	Sigtermans et al., 2009 ⁴⁵	60	Pain intensity; sensibility; and function	S(+) ketamine 4.2-d IV infusion, 1.2 µg/kg/min (or 5 mg/h for a 70-kg patient), titrated at regular intervals to a maximum of 7.2 µg/kg/min (or 30 mg/h for a 70-kg patient). Participants using strong opioids were excluded from the study.
Central pain	Vranken et al., 2005 ⁵³	33	Pain relief; health status; and QoL	Iontophoretic S(+) ketamine 50 and 75 mg. 30% of participants were using strong opioids

BPI, Brief Pain Inventory; CRPS, complex regional pain syndrome; IV, intravenous; NRS, numeric rating scale; QoL, quality of life.

Zhao et al.⁶¹ addressed ketamine infusions for CRPS-I and CRPS-II and analyzed data from 258 participants in 15 trials. However, only one of the 15 included studies was an RCT, and retrospective studies were also included. Fourteen of the 15 studies used S(+) ketamine infusions, whereas one used racemic ketamine. The authors concluded that that ketamine may provide short-term pain relief, but that further studies are required to confirm this conclusion.

4.1.1. Clinical considerations

Sigtermans et al.⁴⁵ when discussing the lack of functional improvement in the ketamine group speculated whether more prolonged treatment, possibly in combination with physical therapy or rehabilitation strategies, could be necessary. Combining ketamine treatment with rehabilitation strategies is an important aspect, which as yet, has not been addressed by any RCT.

The addiction literature contains numerous reports on the neurotoxic, hepatotoxic, and urotoxic adverse effects of ketamine. There are also case reports concerning similar ketamine-related adverse effects in patients with chronic pain (Table 2). Grégoire et al.¹⁷ described cystitis in a 16-year-old patient treated for CRPS-I with oral ketamine. A patient with chronic back pain developed uncontrolled hypertension (blood pressure 224/124 mm Hg), 1 week after starting treatment with oral ketamine.⁵² Noppers et al.³⁸ described 3 of 6 CRPS-I patients treated with ketamine who developed hepatotoxicity after S(+)-ketamine infusions. A patient with chronic pain after cancer therapy and with no detected recurrence who received treatment with intranasal ketamine developed permanent anosmia 6 months after starting treatment.²⁹

Liu et al.²⁷ have recently reported ketamine-related upper gastrointestinal (GI) tract toxicity, such as epigastric pain

("K-cramps," "K-belly"), vomiting, anaemia, and GI bleeding, in 25% of inhalational abusers of ketamine seeking treatment for urotoxicity, and advise that young patients presenting with upper GI symptoms should be questioned about the recreational use of ketamine. It is not common knowledge that repeated administration of ketamine may cause GI symptoms. Whether such symptoms could arise in relation to repeated infusions of ketamine is unknown, but there is a possibility that ketamine-related GI toxicity could be overlooked in the clinical setting.

Ketamine's potential for addiction should also be considered when patients are treated with intermittent IV infusions. Ketamine is a popular club drug. In animal models, repeated administration in subanaesthetic doses causes sensitisation, a characteristic of drugs such as cocaine. Trujillo found the results of his rodent studies to be sufficiently concerning as to advise caution regarding the repeated use of ketamine, both recreationally and in the clinical setting.⁵⁰ Bonnet¹² report a patient initially treated for back pain and recurrent depression who subsequently abused and developed an addiction to ketamine (supplemental digital content 2, <http://links.lww.com/PR9/A26>).

Because ketamine's adverse effects are dose-dependent, high doses should be avoided. Adding a low dose of ketamine to an opioid, especially morphine, seems to improve pain relief. However, combination treatment with potentially addictive drugs such as ketamine and opioid in a patient group with normal life expectancy and where treatment may be long term or repeated multiple times may cause problems in susceptible individuals.

5. Conclusions

Ketamine is a drug with complex mechanisms of action and many properties which make it interesting for pain management. However, treatment regimens differ widely and there are

concerns regarding adverse effects. High doses of ketamine are reported to cause a range of adverse effects and should be avoided. Ketamine has low oral availability, and oral administration seems to be associated with a high rate of adverse effects. Spinal and epidural routes are not recommended because of issues of neurotoxicity. Although ketamine is a drug of addiction, safety data regarding long-term and/or intermittent treatment are lacking.

There is good evidence that ketamine in the perioperative setting reduces pain scores and opioid requirements. Adverse effects are mild or absent, and perioperative ketamine may decrease postoperative nausea and vomiting. It seems most beneficial for surgery associated with high levels of postoperative pain.

The evidence for the use of ketamine in palliative care is limited, and it is not possible to recommend any specific treatment regimen. However, despite the limited evidence, a trial of low-dose ketamine, adjuvant to opioid (morphine), may be warranted in refractory cancer pain or pain in palliative care.

The evidence regarding ketamine for chronic noncancer pain is extremely limited, and there is a lack of safety data concerning long-term or repeated treatments. Importantly, there seems to be no strong evidence for the current widespread use of intermittent ketamine infusions.

Disclosures

R.F. Bell has nothing to disclose. E.A. Kalso reports personal fees from Pierre Fabre and personal fees from Grunenthal, outside the submitted work.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PR9/A25> and <http://links.lww.com/PR9/A26>.

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