

REVIEW

Ketamine in Pain Management

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SUMMARY

For ketamine's fiftieth birthday, a narrative review of this unique drug in pain management is presented. Its history is traced from its conception, and its heritage, as a phencyclidine off-spring, delineated. The earliest roots of the conceptions concerning the mechanisms of action are sought, and then followed in preclinical as well as clinical research. The major proposed mechanisms in the literature are commented on and evaluated. The growth of the clinical evidence for perioperative pain, acute pain, and chronic pain is followed from early attempts to systematic reviews. Finally, an attempt is made to foresee what the next 50 years might hold in store for our 50 years old.

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Introduction

Ketamine, at the ripe age of fifty, is still a newcomer in the pain field. Age-old drugs constitute our basic armamentarium for nociceptive pain. First, we have the cyclooxygenase inhibitors, to which group paracetamol, Non steroidal antiinflammatory drugs (NSAIDs) and the newer Cyclooxygenase-2 (COX-2) selective inhibitors can be counted. In the shape of salicylates, these drugs have been around for centuries. Second, we have the opioids that have been acknowledged for their analgesic properties for millennia. And, that about finishes the list of conventional antinociceptive drugs. Ketamine, only half a century old, is a new kid on the block, with basically a different mechanism of action. It has found use not only for nociceptive, but also for neuropathic pain. Ketamine was first presented in the literature in 1965 [1] and was approved for clinical use in 1970 [2]. Even though it does have an undisputed analgesic potential, the details of that potential are still not, after 50 years on the market, entirely clear. The forerunner of ketamine, Phencyclidine (PCP), under the brand name Sernyl, was noted to have analgesic properties quite distinct from the sedative ones [3]. Ketamine was thus expected to exhibit analgesia as well. At the outset the focus of interest was on ketamine's anesthetic benefits, however, and analgesia was considered just a facet of those benefits. Since then, the analgesic potential of low-dose ketamine has been explored as a clinical usage in its own right. Ketamine analgesia has now been reported in a number of pain states, in some cases convincingly so. In many situations, the

picture is far from clear, however, and the risk-benefit tradeoff even more uncertain. Ketamine being a unique drug, a host of different applications have been tried. As the mechanisms of action gradually have been uncovered, many of these therapies have found theoretical support, and the indications for analgesic ketamine therapy have expanded. As there are many unanswered issues concerning even the basic mechanisms, however, many therapies are experimental, with a lack of scientific evidence. A large "terra incognita" still calls for research [4].

A number of excellent systematic reviews on ketamine analgesia, in different pain conditions, have been published in recent years. This will not be a systematic review. I will instead present more of a narrative review, from a clinician's perspective, following the winding history of ketamine. I will highlight what we have learnt concerning its analgesic properties, as well as its place in clinical practice. First, I will try to cover how our understanding of the involvement of different mechanisms of action has evolved. Then, I will peruse the clinical evidence using a clinical classification: acute pain, perioperative pain, chronic pain, and cancer-related pain.

Analgesic Mechanisms

NMDA Receptor Antagonism

Before proceeding, a matter of terminology has to be cleared up. Ketamine was originally thought of mainly as an anesthetic, and

its purely analgesic qualities appear to have been part and parcel of its usefulness in that context. The characterization of the anesthetic state caused by ketamine thus has some relevance for our considerations of its analgesic potential. The anesthetic state brought about by ketamine is unique. The transition to anesthesia is considered to be an abrupt qualitative step of an "all or nothing" character [5]. An implication of this fact would be that as long as the patient is awake, we would, more or less, be dealing with analgesia without admixture of sedation.

Although the analgesic properties of ketamine were recognized at its introduction on the market, the possibility of using it only as an analgesic does not seem to have been initially entertained. Ideas about its usefulness were instead centered on its use as a sole anesthetic or an induction agent [3]. Systematic exploration of the analgesic properties, *per se*, that is, at low doses, was not performed until later. Sadove et al. [6] were among the first. They emphasized the analgesic effect at low doses and suggested the possibility of using ketamine, in subdissociative doses as an analgesic. Even though the analgesic effects were being explored, analgesic mechanisms of action were unknown for many years. There was, however, an indication in ketamine's Phencyclidine heritage, suggesting a common mode of action. Phencyclidine was known to interact with neurotransmitter systems, voltage-dependent ion channels, etc. There were also indications that dissociative anesthetics interacted with glutamate receptors [7]. The discovery of the N-methyl D-aspartate (NMDA) receptor provided an important milestone in uncovering the mechanisms [8]. In 1982, Lodge and his colleagues are said to have conclusively demonstrated that PCP and ketamine were selective NMDA receptor antagonists [9]. This result was confirmed for both enantiomers in 1991 [10]. Work with the ketamine enantiomers also revealed stereo-selective effects indicating a receptor-mediated pharmacological mechanism [11]. In the 40 years that have passed since the work of Lodge and his group, the mechanisms of action of ketamine have been shown to be extremely complex, meriting the term "The nightmare of the pharmacologist" [12].

Opioid Receptor Agonism

The early researchers were convinced that the "PCP site", that is, the NMDA receptor, was not the only mediator of the analgesic effects. Fink and Ngai were among the first to explore an opioid mechanism [13]. Using *in vitro* binding test systems and *in vivo* displacement of opioid by ketamine, they demonstrated a possible opioid analgesic mechanism. This interaction had also been shown to be stereoselective [14]. In 1987, Smith et al. [15], building on the antagonizing effects of naloxone in animal experiments, and effects on guinea-pig ileum, further investigated the interaction between ketamine and opiate-binding sites. In a rat model, a component of ketamine analgesia was shown to be related to an interaction with opiate receptors, preferably μ , as opposed to σ subtypes. Cross-tolerance between ketamine and morphine was later demonstrated in mice by Finck et al. [16]. The involvement of opioid receptors was studied in 1995 by Hustveit et al. [17] in a binding model using guinea-pig ileum. The authors conclude that ketamine analgesia most probably is mediated by PCP receptors although a κ -opioid receptor effect cannot be excluded. Maurset

et al. [18] also studied the effects of ketamine and pethidine in postoperative pain in patients, as well as ischemic pain in healthy volunteers. No antagonistic effect of naloxone was found on ketamine analgesia in either case. The authors speculate that the discrepancy in results might be due to a difference in dose, opioid effects being manifest only in the higher doses used in the animal experiments. Contradicting results were nonetheless arrived at by another group [19]. Stella and associates administered naloxone or placebo in clinically relevant doses to patients receiving a ketamine anesthetic induction. The induction dose was titrated to cause loss of consciousness in 50% of the patients. Naloxone reduced this percentage by almost one half. Even so, Amoit et al. reported that they were not able to replicate this finding [20]. The reason for the different results is unclear, but underlines our lack of understanding of this important mechanism of action. Furthermore, the effects mediating analgesia might be different from those mediating anesthesia. Evidence from animal experiments has indicated synergistic analgesic effects when combining opioids and ketamine [21]. There have even been suggestions that there might be a third ketamine dose range, apart from high-dose anesthesia and low-dose analgesia. In that dose range, ketamine *per se* would be devoid of analgesic effects, but would work in synergy with opioids [22]. As is often the case, clinical studies have not been confirmatory. In 1993, a Cochrane review looked at ketamine as an adjuvant to opioids in cancer-related pain [23]. The clinical evidence was considered insufficient to assess the benefits or harm of in that context. An update by the same authors in 2012 came to the same conclusion [24]. Yet another recent study found no benefit when adding ketamine to opioids in cancer-related pain [25]. In summary, the role of opioid mechanisms in ketamine analgesia in man is still undecided.

Local Anesthetic Action

In the mid-seventies, many other ideas concerning ketamine's mode of action were tested. In view of the progressive increase in threshold and decrease in conduction velocity seen in animal experiments, a stabilization of membranes was postulated as one possible mechanism. A local anesthetic effect could account for that property. Ketamine effects of local anesthetic character were consequentially found on nerve conduction in the sciatic nerve of the toad, as well as in human subjects. The latter were subjected to subcutaneous and ring blocks of the finger. The subjects seem to have been tested ad hoc, this was before the age of Consolidated Standards of Reporting Trials (CONSORT) statements [26]. Ketamine was later demonstrated to be an effective local anesthetic agent for intravenous regional anesthesia, providing sympathetic, sensory, and motor blockade [27]. The problem was unacceptably high incidences of psychotomimetic experiences in the patients when the tourniquet was released. As expected, the mechanism underlying the local anesthetic effect turned out to be a depression of sodium-channel function [28]. The required concentrations, in that study, were about 10–50 times greater than relevant concentrations during general anesthesia, but compatible with those for intravenous regional anesthesia. The well-established local anesthetic effects of ketamine therefore probably have no relevance for the systemic analgesic effects.

Sigma Receptor Interaction

Early on, sigma receptors were thought to be a type of opioid receptor, and some ketamine effects were hypothesized to be mediated by the sigma receptor [15]. It has since been well established that sigma receptors are distinct from opioid as well as all other known neurotransmitter receptors. Nevertheless, their physiological and pharmacological role is quite uncertain, and they may modulate other receptors such as the NMDA receptor [29]. It does not therefore appear as if the sigma receptor can be removed from the list of potential mechanisms for ketamine analgesia. Interestingly, R-ketamine has a greater affinity for the sigma receptor than S-ketamine, as opposed to other ketamine recognition sites, a fact that could be of importance for the differential side effects of the enantiomers [11].

Cholinergic Effects

Acetylcholine is considered to play an important role in pain inhibition in the spinal cord. Both ketamine and its metabolite, nor-ketamine, have been demonstrated to exert effects on the nicotinic acetylcholine system [30]. Ketamine has also been shown to inhibit muscarinic function. Although the muscarinic systems in the CNS have not been completely elucidated, the effect would probably be antalgic, not analgesic [31]. The contribution of cholinergic effects to ketamine analgesia is thus not clear. There might be both analgesic, nicotinic as well as antalgic, muscarinic effects.

Monoamine Effects

Yet another mechanism in the pain system where ketamine effects were explored was serotonin uptake. Ketamine was reported to inhibit this uptake [32–34]. The monoamines serotonin and norepinephrine are thought to be the principal mediators of endogenous descending pain inhibition [35]. At the present time, it is not clear to what extent the monoamine reuptake inhibition contributes to ketamine analgesia in man.

Supraspinal Mechanisms

Even though spinal mechanisms surely play a role in ketamine analgesia, much of the pain relief is arguably supraspinal. The rapid evolution of brain imaging technology has made exploration of the mechanisms involved possible. An early positron emission tomography (PET) study using (S)-(N-methyl-IlC) ketamine investigating specific binding, demonstrated high brain concentrations in regions of large density of NMDA receptors [36]. Brain concentrations were related to analgesia in human volunteers, using an ischemic pain model. Ketamine has also been shown to decrease pain activation in the secondary somatosensory cortex, insula, and anterior cingulate cortex. The mid-cingulate cortex has been implicated in the affective dimension of pain [37]. An interesting attempt to tease apart the analgesic from the anesthetic actions of ketamine has been reported by Rogers et al. [38]. The analgesic effect could be separately measured within a more global action of ketamine on the brain. In particular, the insular cortex and thalamus, regions that are activated by noxious stimuli, exhibited a decreased response.

Niesters et al. [39] have very recently used resting-state functional magnetic resonance imaging (fMRI), an exciting new technique to study ketamine-induced changes in brain connectivity. Such changes were observed in areas involved in pain and endogenous pain modulation.

Diverse Effects

Being the “The nightmare of the pharmacologist,” as stated above, numerous other tentative mechanisms pertaining to different ketamine effects have been explored. Many of them have little or no relevance for the analgesic effects. I will therefore not dwell on them here, other than mentioning them.

Ketamine depresses both myocardium and vascular smooth muscle at clinically relevant concentrations, presumably by inhibition of voltage-gated calcium channels as well as calcium release from intracellular stores [40,41]. This mechanism is probably not involved in pain transmission.

Ketamine has been shown to have dopamine agonistic effects [42]. These effects probably have behavioral consequences but do not seem to influence ketamine analgesia *per se*.

Antiinflammatory effects of ketamine have been consistently reported in recent years. Ketamine has been found to release adenosine in the periphery, leading to inhibition of proinflammatory cytokine secretion [43]. Ketamine also reduces the biosynthesis of tumor necrosis factor alpha (TNF- α) and Interleukin (IL-6) through suppression of toll-like receptor 4 (TLR-4) activation [44]. Although these antiinflammatory effects might play a role in long-standing pain conditions, they probably cannot contribute to the short-term analgesic effects.

Ketamine has been used topically, although it is often unclear whether the investigated effect is mainly on cutaneous structures, or if systemic effects of transdermal administration are involved [45]. Finch et al. have, however, found plasma concentrations below the threshold of determination after topical administration [46]. Peripheral pain-relieving effects of ketamine have also been demonstrated in a human inflammatory pain model [47]. Supposedly, the effects were mediated via ketamine's local anesthetic properties, locally. Several measures of pain and hyperalgesia were not affected, and the authors do not believe the peripheral effect is clinically relevant. The topical/peripheral treatment mode needs further exploration to judge its clinical potential.

Analgesia or Antihyperalgesia?

An important issue concerning ketamine as an analgesic is whether its analgesic effect is mainly a result of an antihyperalgesia, or if there is specific analgesia [48]. The difference might seem academic, but does have clinical and research implications. Some researchers [49] have presented results that could be interpreted as demonstrating that analgesia is poor if NMDA antagonistic effects are not in play [50]. The extent to which non-NMDA mechanisms significantly contribute to clinical analgesia remain to be established [51].

If the analgesic effects observed in the clinic mainly are attributable to an antihyperalgesia, we will have to carefully explore the dose – response characteristics of that effect. If there is a separate,

purely analgesic effect, it will supposedly have a different dose – response characteristic. In order to optimize our therapy, we will have to adapt to whichever is the case. See Table 1 for a summary of “Established and putative analgesic mechanisms of action for ketamine analgesia.”

Perioperative Pain

Ketamine was initially used as an anesthetic, but the analgesic effects postoperatively were quite naturally observed in the initial clinical studies. In view of the pronounced psychotomimetic side effects, emergence reactions often dominate discussion in the early reports [52]. The analgesic properties of ketamine, when used for postoperative pain relief were, however, at the same time, the mid-seventies, being explored [53]. Ketamine was also increasingly being mentioned in reviews on postoperative analgesia [54]. In an important review on the therapeutic use of ketamine, the specific use of ketamine as an analgesic is mentioned, but not elaborated on [55]. A recent review of perioperative ketamine uncovered 37 trials that met the inclusion criteria. Of these, 27 found that rescue analgesic requirements, pain intensity or both, were reduced by ketamine. In ten, there was no significant effect, and three were considered insensitive [56]. The authors conclude that “ketamine is effective in reducing morphine requirements in the first 24 h after surgery.” A tentative conclusion was also that increasing the dose above approximately 30 mg daily would not increase the morphine-sparing effect. A note of caution was furthermore added because the studies were heterogenous, not supporting any specific regimen. Some studied preincisional boluses, others boluses at wound closure, yet others perioperative infusions

with boluses. Administering ketamine preincisionally, preemptively, has been deemed efficacious in earlier reviews [57]. Preemptive trials with ketamine have, however, been declared uniformly negative in a later systematic review [58].

Several of the studies in the review by Bell et al. were performed with epidural ketamine, a practice I believe should be abandoned in view of the relatively strong indications of spinal cord pathology [59,60]. Furthermore, the clinical gains are probably marginal [22,61], making the risk-benefit trade-off not in favor of epidural use. I will therefore not further comment on studies on the spinal use of ketamine. Yet another recent systematic review of ketamine for postoperative analgesia restricted inclusion to intravenous ketamine without regional anesthesia [62]. A random effects model and subgroup analysis were used. Clinical benefit of ketamine was found in procedures involving more severe pain such as upper abdominal, thoracic, and major orthopedic surgery. These findings are in line with the results of an earlier review [63].

Over the years, it has turned out, as always when it comes to ketamine, that the hard facts of postoperative analgesia are elusive. The reasons are complex, the postoperative situation is multifaceted [64], and ketamine is, as we have seen above, the pharmacologists nightmare. Building on present evidence although there does seem to be a place for ketamine in our postoperative toolbox, and some practices are sufficiently supported by the evidence. Low-dose infusion of ketamine, perhaps as low as 18 $\mu\text{g}/\text{kg}/\text{h}$, during surgery is opioid sparing in some situations, although perhaps not if central or peripheral nerve blocks are used [65]. Adding ketamine to morphine in a patient controlled analgesia (PCA) regimen does not seem to improve analgesia in general

Table 1 Established and putative analgesic mechanisms of action for ketamine analgesia

Analgesic target	Comments	References
Receptor mediation	Shown by stereoselectivity	Klepstad [11]
NMDA receptor antagonism	Perhaps the main analgesic mechanism	Lodge [9], Oye [10]
Opioid receptors	Unclear role at present	Finck [13], Smith [15], Finck [16], Maurset [18], Hustveit [17]
NMDA – Opioid interaction	Insufficient evidence to decide	Bell [23]
Local anesthetic	Well established probably no relevance for systemic analgesia	Durrani [27], Frenkel [28]
Sigma receptors	May play a role in ketamine analgesia	Smith [15], Klepstad [11], Seeman [42]
Cholinergic, Nicotinic	Nicotinic effects may contribute to ketamine analgesia	Abelson [30]
Cholinergic, Muscarinic	Muscarinic effects are perhaps antalgic	Durieux [31]
Descending inhibition	Via monoaminergic descending inhibitory pathways, in rats	Koizuka [34]
Monoamine, Dopamine	Probably not involved in ketamine analgesia	Seeman [42]
Monoamine, Serotonin	Probably plays a role in ketamine analgesia	Martin [33], Crisp [32]
Pain-related brain areas	–	Rogers [38], Sprenger [37]
Intrinsic brain connectivity	–	Niesters [39]
VGCC block	Probably not involved in ketamine analgesia	Wong [41], Akata [40]
Antiinflammatory TLR-4-dependent activation	Probably not involved in acute ketamine analgesia may play a role in long-standing pain	Wu [44]
Antiinflammatory Adenosine receptors	Probably not involved in acute ketamine analgesia may play a role in long-standing pain	Mazar [43]
Peripheral effect	Probably no clinically relevant effect	Pedersen [47]

NMDA, N-methyl D-aspartate; TLR-4, toll-like receptor 4.

[63]. The picture here is varied although, perhaps there is some benefit in thoracic, but not in orthopedic or abdominal surgery [66].

The analgesic effect of interest can finally be primarily in the immediate postoperative phase, or more long term, postsurgically. Ketamine is of particular interest in this latter context, but the field is uncharted [67].

In conclusion, there probably is perioperative benefit of ketamine in surgery associated with more severe pain. Even for these indications, optimal dosing and timing of the ketamine administration remain to be determined. For other indications, the evidence is even scarcer.

Acute Pain

The early reports of potent analgesic effects, distinct from the anesthetic effect, led to an exploration of the usefulness of ketamine in acute pain situations [68]. It was reported to provide equivalent analgesia to opioids in war injuries [69], as well as entrapment after accidents [70]. The treatment of burns, where patients often are in severe pain, was a natural tentative indication for ketamine [71] [72].

In many reports on analgesia in acute pain, the administered doses have been quite large causing at least a temporary loss of consciousness. The clinical value of the purely analgesic effect as distinct from anesthesia is more difficult to evaluate in those situations [73]. The ketamine doses for acute pain in the subdissociative range have not been established, all we have to rely on is anecdotal reports and a few isolated studies. Bolus doses in the order of 0.1–0.2 mg/kg i.v. have been suggested [55]. Even larger doses, 0.2–0.5 mg/kg i.v. have also been advocated [68,74]. In an experimental study, however, almost half of the subjects lost consciousness at a dose of 0.25 mg/kg [75], illustrating the narrow therapeutic window for subdissociative ketamine. Titrating the dose, starting at 0.1 mg/kg i.v. with a limit of 0.5 mg/kg i.v. is a prudent approach that has been recommended [76].

Chronic Pain

Chronic neuropathic pain was one of the first reported indications for treating chronic pain with ketamine [77]. In general, reports about the specific use of ketamine in clinical chronic pain conditions were scarce before the late nineties [78]. A review in 2003 for chronic noncancer pain found 11 controlled trials as well as several uncontrolled trials and anecdotal reports [79]. The studied conditions were mainly in the neuropathic pain field; postherpetic neuralgia, phantom limb pain, and central pain. There were also a few studies on complex regional pain disorders (CRPS), ischemic pain, and fibromyalgia. There was no long-term follow-up in the controlled trials, but many of the case reports followed the patients for months and even years. In one case, there was continued benefit over 4 years. Due to the quality of the trials and data heterogeneity, the authors conclude that “the evidence for efficacy of ketamine for treatment of chronic pain is moderate to weak.” This first review was followed 6 years later by a second topical review on the subject of chronic noncancer pain [80]. In the intervening years, another 18 controlled trials had been published. These trials too mostly investigate neuropathic pain,

although whiplash-associated pain, temporomandibular joint arthralgia, atypical odontalgia, breakthrough pain, and migraine prophylaxis were also studied. The author concludes, “while the current literature provides evidence for acute relief of chronic noncancer pain, information supporting the efficacy and tolerability of ketamine in the long-term treatment of chronic pain is extremely limited.”

Pain in Cancer and Palliative Care

Intractable pain is often encountered in cancer and palliative pain management. Consequently, ketamine has surely been used early on in attempts to control pain in these situations [81]. Nevertheless, reports in the literature are rare before the early 1990s [82,83]. There is also a dearth of clinical studies on the subject. Existing studies have mainly looked at the combination of opioids and ketamine. Firm evidence for the benefit of ketamine has not been forthcoming in these studies [24,25,84]. There may well be pain mechanisms that are peculiar to cancer-related pain, particularly in osseous involvement [85,86]. Hypothetically, these mechanisms may be susceptible to ketamine, making ketamine indicated in specific pain states. Nonetheless, little is known about these effects of ketamine, and the majority of cancer-related pain is presumably mediated by the mechanisms outlined above. All in all, this is a field where extensive research, both on analgesic mechanisms and clinical effectiveness, is needed [87].

The Next 50 Years

So, which issues concerning ketamine can we hope will be resolved in the next 50 years, before its centenary? What cues are there in clinical practice, or experimental research, pointing the way to interesting innovations?

First, in view of the fact that we still have rudimentary knowledge about important aspects of ketamine, despite having researched its properties for 50 years, the acumen of our research, hitherto, can be questioned. In my mind, the issue of ketamine’s mechanism of action should be central in our endeavors. If there are different mechanisms of action in play in different dose ranges, with varying effectiveness in different pain conditions, we will never get an unobscured picture of the clinical drug effects without taking that into account. Administering ketamine in manifold ways also complicates matters. What we need is plasma concentration or effect site data over time, enabling us to compare different modes of administration [48,88].

Delving deeper into the differences between the enantiomers might potentially lead to more sophisticated therapy although the evidence for dramatic differences, that could be clinically relevant, are lacking at present [80]. A major concern for the future is toxicity, in particular neuroapoptosis, in children, and cystitis, in long-term use [48]. As mentioned above, my opinion is that the issue of spinal toxicity is already decided. In clinical practice, various innovative interventions are constantly being tried. Examples are intermittent infusions [80] and “burst” administration [89]. Creativeness of this kind is also important for the future although it has to be tempered by testing the new ideas in clinical studies. Further avenues of importance in future research are improving

the use of adjuvant drugs for mitigation of side effects, and technology development for drug administration.

Finally, on the horizon, there are some relatively novel developments that have the potential to significantly enhance our understanding of ketamine as a clinical tool. In the next 50 years, I believe our knowledge about the NMDA subtypes will enable a more differentiated and sophisticated therapy [90]. The new

imaging tools, resting-state networks, and functional connectivity can be expected to revolutionize our understanding of the clinical effects of ketamine [39].

Conflict of Interest

The author declares no conflicts of interest.

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