REVIEW ARTICLE

Ketamine in Chronic Pain Management: An Evidence-Based Review

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Ketamine has diverse effects that may be of relevance to chronic pain including: *N*-methyl-D-aspartic acid, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, kainate, γ-aminobutyric $acid_A$ receptors; inhibition of voltage gated Na^+ and K^+ channels and serotonin, dopamine re-uptake. Ketamine has been in clinical practice for over 30 yr; however, there has been little formal research on the effectiveness of ketamine for chronic pain management. In this review we evaluate the available clinical data as a basis for defining the potential use of ketamine for chronic pain. Literature referenced in this review was obtained from a computer search of EMBASE and MEDLINE from 1966 through August, 2002. Search terms included ketamine, ketalar, pain, painful, analgesic, and analgesia. Abstracts were screened for relevance and publications relating to chronic pain use were obtained. Levels of evidence were stratified according to accepted guidelines (level I-IV). For central pain, there is level II and level IV evidence of efficacy for parenteral and oral ketamine. For complex regional pain syndromes, there is only level IV evidence of efficacy of epidural ketamine. For fibromyalgia, there is level II evidence of pain relief, reduced tenderness at trigger points, and increased endurance. For ischemic pain, a level II study reported a potent dose-dependent analgesic effect, but with a narrow therapeutic window. For nonspecific neuropathic pain, level II and level IV studies reported divergent results with questionable long-term effects on pain. For phantom limb pain and postherpetic neuralgia, level II and level II studies provided objective evidence of reduced hyperpathia and pain relief was usually substantial either after parenteral or oral ketamine. Acute on chronic episodes of severe neuropathic pain represented the most frequent use of ketamine as a "third line analgesic," often by IV or subcutaneous infusion (level IV). In conclusion, the evidence for efficacy of ketamine for treatment of chronic pain is moderate to weak. However, in situations where standard analgesic options have failed ketamine is a reasonable "third line" option. Further controlled studies are needed.

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When first and second-line drugs such as opioids, anticonvulsants, or antidepressants fail to provide satisfactory analgesia for the patient with chronic pain, third-line drugs such as ketamine may provide a suitable option. Ketamine has been available in clinical practice for over 30 yr, and the theory that *N*-methyl-D-aspartate (NMDA) receptor antagonists may be useful in pathological pain states has been known for at least the last 10 yr. Nevertheless, there has been little formal research on the effectiveness of the use of ketamine in chronic pain management. Whether the minimal research reflects a lack of confidence in the drug or a perceived adverse risk-benefit ratio is unclear. Although the use of ketamine is now generally accepted, the evidence base for this remains poor. We present the available clinical data as a basis for defining the potential role of ketamine.

Methods

The literature referenced in this review was obtained from a computer search of the EMBASE© and MEDLINE© database from 1966 through August, 2002. A number of different search strategies were used without language restriction. Search terms included "ketamine," "ketalar," "pain," "painful," "analgesic," and "analgesia." Abstracts were screened for relevance, and publications relating to chronic pain in humans were obtained. Additional reports were identified

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Table 1. Levels of Evidence Ratings

Level I	Evidence obtained from systematic review of relevant randomized controlled trials (with meta-analysis where possible).
Level II	Evidence obtained from one or more well designed randomized controlled trials.
Level III	Evidence obtained from well designed nonrandomized controlled trials OR from well designed cohort or case-control analytical studies, preferably multicenter or conducted at different times.
Level IV	The opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

from the reference lists of retrieved reports and from review articles. Unpublished reports and abstracts were not considered, and authors were not contacted. The levels of evidence have been stratified according to accepted guidelines (Table 1), and these have been applied to both the evidence and the conclusions. Although level I evidence is the desired standard on which to base clinical decision-making, treatment based on other levels of evidence can be used in appropriate circumstances. Level I evidence was not available for any aspect of this review. Also, there is only a small amount of level II evidence, all of which is borderline because of very small numbers of patients. The impact of many studies can be questioned because they often lack specific diagnoses. However, it is possible that considering symptomatology rather than the exact diagnosis may be more relevant in the chronic pain population.

This review is therefore based on evidence that would generally not be included in a systematic review. Because of the variation in the study objectives and design and the small number of level II studies, a meta-analysis of the published data was not deemed appropriate.

Pharmacology

This review will focus on the clinical aspects of ketamine. As the pharmacology has been discussed in detail in the literature (1–3), it will not be extensively repeated here. In summary, ketamine has an analgesic action at many sites both centrally and peripherally (4). These actions are mediated via multiple receptor subtypes, including opioid, NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate, kainate, and γ-amino butyric acid A receptors. Ketamine also inhibits serotonin and dopamine reuptake and inhibits voltage-gated Na^+ and K^+ channels. The mechanism of action in the reversal of opioid tolerance by ketamine is believed to involve an interaction between NMDA receptors, the nitric oxide pathway and μ-opioid receptors (5). With action at such a wide range of receptors, it could be perceived that ketamine has potential in a diverse spectrum of conditions. This, however, is likely at the possible cost of diverse side effects.

Clinical Studies

Details from the relevant reports are presented in Table 2.

Central Pain

The effectiveness of both parenteral and oral ketamine was studied in nine patients with central dysesthesia pain after spinal cord injury (level II) (6) and one with neuropathic pain after cauda equina trauma (level IV) (7). Ketamine reduced both continuous and evoked pain at the expense of only modest side effects. In one case it was used as the sole analgesic. A further case describes central poststroke pain after subarachnoid hemorrhage (level IV) (8), which was refractory to all conventional therapy. The authors used midazolam premedication, then incremental IV ketamine dosing to effect. Marked relief of pain, allodynia, and hyperalgesia was obtained, and oral dosing commenced at 50 mg nightly increasing to 50 mg 3 times a day. Increasing the dose further led to side effects without additional analgesic benefit. Oral ketamine allowed the opioids and anticonvulsants to be tapered and discontinued. Sustained analgesic benefit was still experienced after 9 mo without apparent tolerance.

Complex Regional Pain Syndromes

Two reports (level IV) (9,10) described complete pain relief using ketamine by the epidural route in three patients refractory to other treatments. In one patient, however, there was no comment regarding the use of concurrent physiotherapy or rehabilitation although the other two underwent "intensive rehabilitation" that could have, at least partly, explained the observed results (11). The use of ketamine by bolus administration caused severe headache and nausea in one patient, but ketamine was deemed acceptable in the other two cases. Resolution of the autonomic features occurred in the two patients treated by bolus administration and "intensive rehabilitation," but the autonomic features persisted in the other. Only one report (9) described ketamine administered as the sole analgesic drug.

Fibromyalgia

Two randomized controlled trials (level II) (12,13) reported 46 patients fulfilling the 1990 American College

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Table 2. Published Reports Concerning Ketamine Administration in Chronic Persistent Pain

Study	Design (Evidence level)	Regimen	Outcome	Withdrawals/Side Effects
Eide et al. (6)	9 Pts, R, DB, (II)	Spinal cord injury. K, AL or PL.	Severity of continuous and evoked pain ↓ by K and AL.	1—"bothersome dizziness."
Fisher and Hagen (7)	1 Pt, CR. 5-mo FU. (IV)	Postcauda equina trauma. Haloperidol pretreatment 0.5 mg PO 4 hrly. K 10 mg sc bolus then 3 mg/h ↑ to 5 mg/h. Changed to K 10 mg/8 h PO ↑ to 25 mg/8 h.	Pt self report. Pain relieved at 5 mg/h. Persistent benefit from K po—other analgesics stopped.	Bolus caused brief "floating/dreaming" sensation, sc sites changed daily because of erythema.
Vick and Lamer (8)	1 Pt, CR. 9-mo FU (IV)	Central poststroke pain. Midazolam pretreatment, IV boluses (0.1 mg/kg) K to effect. Converted to oral dosing 50 mg nightly then 50 mg/8 h.	VAS 9/10 pretreatment. VAS 3/10 posttreatment. Sustained effect. Other therapeutic drugs withdrawn.	Dysphoria, confusion and depression refractory to benzodiazepines if dose increased above 150 mg/day.
Takahashi et al. (9)	1 Pt, CR. 8-mo FU (IV)	CRPS 2 from sciatic n. injury. K 0.3 mg/kg IV ineffective and produced SE. Epidural K 0.3 mg/kg effective but SE—resolved after 24 h. Pain returned at same time. Continuous inf. 25 μg/kg/h effective without SE. Epidural removed after 10 days.	Pain relief and disappearance of mechanical allo persisted during FU. Autonomic features not abolished.	Initial SE not specified. Transient headache, nausea and discomfort after epidural administration.
Lin et al. (10)	2 Pts, CR (IV)	CRPS 1 of lower limbs K 7.5 mg, MO 0.75 mg and 0.1% B (6 mL) boluses via a lumbar epidural every 8 h—continued 9–11 days while epidural remained patent and free from signs of infection, intensive rehabilitation, 7 and 11 treatments over 3 and 6 mo.	Almost complete resolution of pain and autonomic dysfunction.	Not documented.
Sorensen et al. (12)	31 F Pts, 3 separate R, PLC, DB studies (II)	Gp 1 (n = 9) received PL × 2, MO 10 mg or naloxone 0.8 mg IV over 10 min–60 min between drugs. Gp 2 (n = 11) received L 5 mg/kg or PL infused over 30 min followed by 4 h observation—repeated daily for 1 wk—CO after 1 wk WOP. Gp 3 (n = 11) received K 0.3 mg/kg or PL in similar protocol to Gp2.	Gp 1—no significant changes. Gp 2—reduction in pain both during and after the inf. Gp 3—significant ↓ pain intensity, tenderness at tender points, ↑ endurance.	Gp 1: 7/9; Gp 2: 3/11; Gp 3: 10/11 had transient (<15 min) SE after K. Unreality, dizziness, auditory change.
Graven-Nielsen et al. (13)	29 F Pts, R, PLC, DB (II)	K 0.3 mg/kg IV or PL over 30 min on 2 separate days. Active drug >50% ↓ pain intensity at rest on 2 consecutive occasions identified 17 K responders. 15 received DB inf of K or PL on two sessions separated by 1 wk WOP. Plasma K and norK levels analyzed.	↓ referred pain, temporal summation, muscular hyperalgesia and muscle pain at rest.	2 withdrew—unrelated reasons, 12 failed to respond initially. SE not documented.
Persson et al. (15)	5F:3M Pts, R DB CO (II)	Lower extremity rest pain. K 0.15, 0.3, 0.45 mg/kg IV or MO 10 mg IV over 5 min on 4 study days—at least 24 h WOP.	Dose-dependent analgesic effect of K with transient complete pain relief in all at largest dose. 5-complete relief with M; 3—little or no relief.	Disturbed cognition and perception were pronounced and dose dependant.
Backonja et al. (16)	4F:2M Pts, DB, PLC (II)	Premedicated (lorazepam or midazolam). K 0.25 mg/kg IV or PL given over 5 min. CO after 4 h.	3/6 >50% ↓ pain, allo and hyperalgesia for 2–3 h. 1/6—no relief from pain but ↓ allo and hyperalgesia.	5/6 had SE during K; diplopia, nystagmus psychomimetic SE, ↑ HR/BP.
Max et al. (17)	8F Pts, R, PLC, DB CO (II)	Posttraumatic neuropath pain. K 0.75 mg/kg/h, AL 1.5 μg/kg/min or PL IV for 2 h—doubled at 60 min and 90 min if no benefit or minimal SE—halved if SE.	K signif. ↓ pain and allo (P < 0.01). AL ↓ allo (P < 0.01) but not background pain.	SE always preceded analgesia and persisted beyond return of pain after stopping inf.
Felsby et al. (18)	4F:6M Pts, R DB PLC (II)	3 sessions with 24 h WOP. K 0.2 mg/kg, MG 0.16 mmol/kg or PL IV over 10 min then continuous inf. K 0.3 mg/kg, MG 0.16 mmol/kg or PL.	K—signif ↓ pain (57%) and allo (33%). MG—non-signif ↓ pain (29%) and allo (18%).	HR and BP within ± 20% of baseline. Psychomimetic SE 7/10 after K. Heat and pain at injection site from MG.
Broadley et al. (19)	2M Pts, CR (IV)	Refractory neuropathic pain. 1 initially controlled on K 0.2 mg/kg/h SC then converted to PO dosing, ↑ as tolerated reaching 200 mg/6 h. 1 commenced 25 mg/8 h ↑ over 2 wk to 100 mg/6 h.	Pain free until GI illness prevented PO dosing—converted to SC until death 1 mo later. Pain free for 3 mo, then symptoms returned—flecainide used with success for 2 mo then K restarted—Pain free without SE until reporting (4 mo).	Vivid, not unpleasant dreaming.
Enarson et al. (20)	13F:8M Pts, CS (IV)	K 100 mg/day PO (40 mg in sensitive pts) given in divided doses, ↑ 40 mg every 2 days until effective or SE limiting. Final doses 40–500 mg/day (median, 220 mg).	Only 4 continued K over 1 yr with improved ↓ pain and ↓ analgesic use; even these eventually discontinued K because of an unfavourable benefit versus SE ratio.	9 discontinued within 2 wk—intolerable psychomimetic SE, 4—few SE but minimal benefit, 4—equivocal response.
Walker and Cousins (24)	1M, CR (IV)	K infusion 10 mg/h IV allowed intrathecal MO to be ↓ from 32 mg/day to 2 mg/day; K ceased at day 20. MO withdrawal anticipated; oral clonidine given.	Sustained reduction in hyperalgesia, intrathecal MO. Dose slowly increased over next 12 mo to half previous dose (15 mg/day).	Mild hallucinations on 3 occasions—controlled by temporary ↓ ketamine infusion rate.

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Table 2. Continued

Study	Design (Evidence level)	Regimen	Outcome	Withdrawals/Side Effects
Mathison et al. (25)	7F Pts, U (IV)	Nerve damage in trigeminal region. Nonstandardized regime—K (racemic K, (R)-K or (S)-K) various doses and various schedules (single IV bolus ± inf., IM dosing).	4 nonresponders >5 yr pain history, 3 pts with short pain histories consistently reported prolonged ↓ pain after K (>12 h). 3—no benefit despite dose ↑ to near anesthetic levels. 1—pain ↓ only during the inf.	Psychomimetic SE common, (R)-K > (S)-K.
Eide and Stubhaug (26)	1 Pt, *N* of 1, DB, PLC (II)	"Optimal" dose 60 mg PO admin 6 ×/day—observed in open dose escalating trial. *N* of 1 trial—K PO or PL on 10 2-day periods.	Stat. signif ↓ pain intensity on swallowing.	Some SE—fatigue, dizziness, "well tolerated."
Rabben et al. (27)	26F:4M Pts, DB, CO (II)	Secondary trigeminal neuralgia Pethidine 1 mg/kg or K 0.4 mg/kg with 0.05 mg/kg midazolam IM. Pts crossed after 1 wk WOP. 1 week after IM challenge, remaining 26 pts received K 4 mg/kg PO or PL for 3 nights then CO.	IM injections—9/30 no relief with either drug; 8/30 prolonged analgesia from both drugs but ↑ with K; 9/30 transient relief with K but minimal relief with Pethidine. PO dosing—5/8 with prolonged effect from IM dose obtained analgesia. 0/9 with transient effect IM obtained benefit.	4 withdrew; 3 nausea; 1 unrelated. Psychomimetic SE more marked after PO—only reported if sleep did not occur within 30 min. None reported hangover effect next day.
Nikolajsen et al. (28)	3F, 8M Pts, R, PLC, DB, CO (II)	Stump and phantom pain. K 0.1 mg/kg IV over 5 min then inf. of 7 μg/kg/min for 45 min, or PL. CO after 3 day WOP.	↓ stump and phantom pain assessed by VAS and MPQ. K significantly ↑ pressure thresholds and ↓ hyperpathia.	9/11—insobriety or discomfort.
Stannard and Porter (29)	2M:1F Pts, CS, U (III)	Phantom limb. K 0.125–0.3 mg/kg IV then cont. SC inf. 0.125–0.2 mg/kg/h for maintenance. Pts educated on SC inf. and discharged home with portable inf. pumps.	IV bolus—all described "warm feeling" and immediate pain ↓. 1—prolonged benefit over 6 months later reporting recurrence of symptoms on stopping K. 1—poor concentration—limited inf. to when pain was severe.	1—well for 4 days then became agitated, frightened and discontinued.
Nikolajsen et al. (30)	1M Pt, CR (IV)	Stump pain. Initial response to K assessed by DB PLC IV inf. at 2 test sessions separated by 1 wk WOP (total dose 0.42 mg/kg as bolus + inf over 50 min). Further single-blind PLC trial K 50 mg PO then K 50 mg/6 h PO.	Profound analgesia with initial IV inf. K 50 mg PO produced 6 h of complete relief of stump P.	Tolerance or adverse SE not observed during 3-mo treatment.
Eide et al. (32)	4F:4M Pts, R, DB, CO (II)	PHN at various sites. Single IV bolus K 0.15 mg/kg, MO 0.075 mg/kg or PL given over 10 min. 7 day WOP. No analgesics used in 48 h before testing.	No signif change in thresholds for warm, cold, heat, pain, or tactile sensation. K normalized abnormal heat pain sensations in 4 pts. K, but not MO, produced signif. pain relief. Both drugs ↓ allo; only K inhibited hyperpathia.	8/8 K pts had some SE—number distressed were dizziness (5), fatigue (4), unreality (3), altered visual (3) and auditory acuity (1), 6/8 MO and 1/8 PL had SE—none distressing.
Eide et al. (33)	3F:2M Pts, Open prospective (III)	Responders from Eide 1994. K SC inf. at ↑ing doses 0.05, 0.075, 0.1, 0.15 mg/kg/h. Each rate maintained for 7 days. Plasma levels K and norK before each dose change.	Relief of cont. pain (daily VAS) at smallest dose—most marked at largest. ↓ number and severity of spont pain in 5/5. Allo ↓ 60%–100% after 1-wk inf. of 0.05 mg/kg/h and hyperpathia ↓ after 1 wk of 0.15 mg/kg/h. K and norK levels ↑ throughout study without evidence of norK accumulation.	SE occurred in 5/5—itching/painful induration at injection site, nausea, fatigue, dizziness. 1 Pt discontinued after 2 wk because of SE.
Hoffmann et al. (34)	1M Pt, CR (IV)	Ophthalmic PHN Initial IM test dose 0.2 mg/kg then SC inf. 5 mg/h. Converted to PO dosing 40 mg/4 h gradually ↑ to 200 mg/5 h.	2 h relief from test dose, maintained by SC inf. Pain recurred at ↓PO dose but controlled at larger—able to return home—↓ daily dose to 400 mg after 2 wk, stopped at 4 wk without recurrence.	Local inflammation at SC inf. site required daily changes. No other SE reported.
Klepstad and Borchgrevink (35)	1M Pt, CR, 4-yr FU. (DB, PLC test period) (IV)	Initial bolus K 10 mg IV then SC inf. 100 mg/day. Changed to 10 mg IM daily for 4 mo then PO dosing 50 mg/4 h. 2 mo later reverted to 10 mg/12 h IM because of unrelated gastrointestinal pathology. Continued for 6 mo before commencing SC inf. 72 mg/day—continued until death.	Pain abruptly ↓ from VAS 100 to 0 after bolus—remained <20 for 12 h. VAS 5–30 during IM dosing. "Good" relief obtained with PO dosing.	Painful local induration from SC route initially—improved by topical heparin ointment. Transient "insobriety" after bolus. No signif. SE from K.

AL = alfentanil; Allo = allodynia; CO = crossover; CR = case report; CS = case series; DB = double-blinded; FU = follow-up; inf = infusion; IM = intramuscular; IV = intravenous; K = ketamine; L = lidocaine; MG = magnesium; MO = morphine; PL = placebo (saline); PLC = placebo controlled; PO = oral; pts = patients; R = randomized; SC = subcutaneous; SE = side effects; U = unblinded; WOP = washout period; CRPS = complex regional pain syndrome; VAS = visual analogue scale; HR = heart rate; BP = blood pressure; GI = gastrointestinal; MPQ = McGill Pain Questionnaire; PHN = Postherpetic neuralgia.

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of Rheumatology classification criteria for fibromyalgia (14). Ketamine was compared against morphine, lidocaine, naloxone, and placebo, although none of these are of significant benefit. These 2 studies showed that ketamine increased endurance and reduced pain intensity, tenderness at trigger points, referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest. Both studies suggested that central sensitization is present in fibromyalgia and that tender points represent areas of secondary hyperalgesia and deduced that relief of these symptoms by ketamine indicated a reduction in central sensitization.

Ischemic Pain

Both nociceptive and neuropathic components probably contribute to the ischemic pain of arteriosclerosis, which is often poorly responsive to opioids. Eight patients with rest pain in the lower extremity received either IV ketamine or morphine (level II) (15). Pain intensity, measured with a visual analog scale (VAS), was highly variable during and after all the infusions. The three patients who experienced little or no relief with morphine had higher baseline scores, and pooled data suggest that 0.15 mg/kg ketamine was approximately equipotent to morphine 10 mg, but this should be interpreted with caution because control experiments with a placebo were not performed. The authors concluded that ketamine has a potent dose-dependant analgesic effect in clinical ischemic pain but with a narrow therapeutic window.

Nonspecific Pain of Neuropathic Origin

Six publications present data from a heterogeneous group of patients with neuropathic pain. These include a wide variety of underlying diagnoses but with the common factor of neuropathic descriptors to their pain. Three double-blinded, placebo-controlled studies (level II) (16–18) showed a significant reduction in hyperalgesia and allodynia although the effect on continuous background pain was less marked. One case report (level IV) (19) described success with subcutaneous (SC) ketamine that was subsequently converted to oral dosing. This provided good analgesia with some vivid, though not unpleasant, dreaming. A case series, however, presented less favorable data (level IV) (20) in which 21 patients commenced ketamine. Only four had sufficient benefit to continue oral ketamine for long periods (over 1 yr), reporting improvements in pain and reduced analgesic usage. Even these, however, eventually discontinued ketamine because of side effects and minimal benefit. The authors comment that the analgesic benefit appeared to be more pronounced in patients with pain histories of less than 5 yr duration. A further study (level II) (21) determined ketamine responders by titration of oral ketamine. These were then entered into an *n* of 1 randomized trial, which made it possible to perform randomized blinded testing in a single patient (22). Only 9 of 21 patients showed sufficient benefit to be entered into the trial, and only 2 responded sufficiently to continue oral ketamine after the trial.

Acute on Chronic Neuropathic Pain

Currently the most frequent use of ketamine is in managing severe acute episodes of refractory neuropathic pain, often in a situation where large doses of opioids have contributed to the development of severe hyperalgesia. Both the neuropathic pain and large dose opioid-related hyperalgesia are at least partly related to NMDA receptor activation, and thus a NMDA blocker in the form of ketamine is theoretically a logical treatment option. However there has been no rigorous study of the effectiveness of a ketamine infusion in controlling chronic episodes. This contrasts with a significant literature demonstrating a reduction in opioid requirements when ketamine is used preemptively before surgery (23). However, well-documented case reports indicate that a ketamine infusion can be invaluable in severe acute on chronic pain, with (level IV) evidence of decreased hyperalgesia and progressive reduction in morphine or other opioid requirements. One case report (level IV) describes a patient receiving large-dose (32 mg/day) intrathecal morphine for mixed nociceptive/neuropathic pain (24). The patient presented with a severe exacerbation of pain and extensive hyperalgesia that was unresponsive to first- and second-line treatments and only briefly responsive to intrathecal bupivacaine. An IV infusion of ketamine was administered at a rate of 10 mg/h. Over the first 18 days the intrathecal dose of morphine was reduced from 32 mg/day to 2 mg/day, and ketamine was ceased at day 20. During this treatment a sustained reduction in hyperalgesia occurred (Fig. 1), and the intrathecal morphine dose remained at half the prior level 12 mo later. An additive analgesic effect or placebo response may have been responsible for the improved analgesia, but if these were the only factors involved, a more rapid increase in intrathecal morphine requirements after cessation of the IV ketamine would have been expected. In some situations of extremely severe acute exacerbations of neuropathic pain, ketamine infusion is combined with lidocaine infusion; however, there is no rigorous evaluation of this combined treatment. From a practical aspect we have found that the SC route of administration is a useful option for ketamine infusion in that it avoids potential delays in treatment caused by problems resiting IV cannulae. It may also be the case that blood concentrations are more stable with the SC route for reasons noted above. We have also found that side effects are less likely if boluses are avoided, presumably because blood "peaks" of increased ketamine concentration are avoided (level IV

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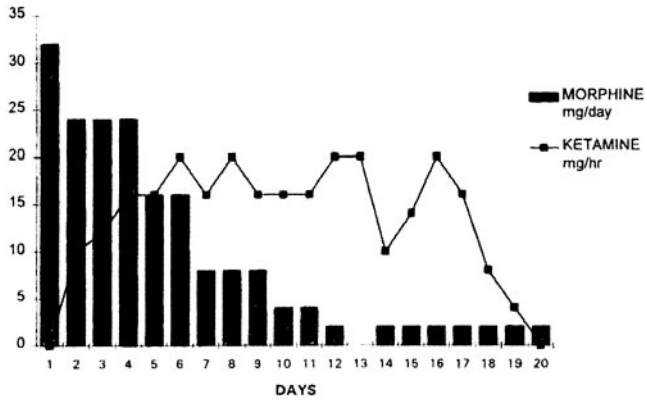

Figure 1. Intrathecal morphine and ketamine dose in a patient who presented with a severe acute on chronic episode of neuropathic pain. Reproduced with permission from The Journal of Pain and Symptom Management 1997;14:129–32 (24).

unpublished data). Local irritant effects, however, can sometimes complicate this route of administration.

Orofacial Pain

Seven female patients with a diagnosis of neuropathic pain attributable to "nerve damage in the trigeminal region" refractory to conventional therapies were given ketamine (racemic, (R) or (S)) (level IV) (25). Consistent prolonged pain relief (>12 h) was obtained in 3 patients who had suffered pain for <3 yr. Of the remaining 4, who had suffered pain for more than 5 yr, 3 reported no benefit despite dose escalation to near-anesthetic levels. One reported pain relief during the infusion that stopped shortly after it was terminated. An oral-dose escalation study in a patient with glossopharyngeal neuralgia followed by an *N* of 1 trial demonstrated statistically significant benefit. Relief of continuous and swallowing-induced pain was significant compared with placebo (level II) (26). In this patient, ketamine was commenced at 30 mg 6 times daily and increased to 100 mg 6 times daily, although the additional benefit from exceeding 60 mg 6 times daily was small. Pain relief was associated with some side effects; however, the treatment was well tolerated by the patient.

Ketamine has been compared to pethidine or placebo in 30 patients with secondary trigeminal neuralgia (level II) (27). Eight patients obtained prolonged relief (6–24 h) with IM ketamine, and five of these also had a good response with subsequent oral dosing. Nine patients obtained transient relief (<2 h) but did not then respond to oral therapy. The authors speculated that NMDA receptor inhibition, even for a short period, might annul the sensitization and thereby cause pain relief even after ketamine has been eliminated from the body. They also suggest those who responded poorly or not at all may have complete and irreversible excessive activation of the NMDA receptor. In this situation, ketamine is only likely to be of benefit in large concentration. The authors comment that nonresponders are likely to have mechanisms that are NMDA-independent. This assumes that there is continuing peripheral noxious input, or central sensitization mechanisms playing the sole or predominant role and seems to ignore the biopsychosocial model of pain.

Phantom/Stump Pain

A study of IV ketamine in 11 patients (level II) (28) reported a decrease in stump and phantom pain assessed by VAS and Magill Pain Questionnaire. Ketamine significantly increased pressure thresholds and reduced hyperpathia, although side effects (insobriety or discomfort) were observed in 9 patients. These results are supported by a case series (level III) (29); however, all 3 patients were given ketamine, unblinded, having been told that there were good reasons why it may have an impact on their phantom pain. This might have served to enhance the placebo response. A further case report described benefit in a patient with stump pain after bilateral amputation at knee level (30). Before surgery he had experienced severe ischemic pain despite large-dose opioid therapy. Conventional treatments were either ineffective or not tolerated by the patient, but ketamine IV proved very effective. A subsequent trial of oral ketamine produced complete relief of pain. Attempts to reduce the dosage resulted in recurrence of symptoms. Tolerance or problematic side effects did not seem to develop. The use of oral ketamine to control phantom pain is supported by other researchers (level IV) (31).

Postherpetic Neuralgia

One study (level II) (32) compared ketamine, morphine, and placebo in eight patients with postherpetic neuralgia at various anatomic sites. Ketamine produced significant pain relief and reduced allodynia and hyperpathia but caused side effects in all patients. Sensory thresholds were unaltered, although the quality of sensation may have been changed. The same authors go on to describe 5 patients from this article in an open prospective study of SC ketamine administration (level III) (33). Relief of continuous pain (daily VAS) was observed at the smallest dose but was most marked at the largest. All reported reduction in the number and severity of spontaneous pain attacks. Allodynia and hyperpathia were both maximally reduced after 1 wk of the largest dose. Side effects, most commonly induration at the injection site that caused one patient to discontinue treatment, occurred in all patients. None chose to discontinue treatment because of psychotomimetic effects, preferring the improved pain relief.

One case report (level IV) (34) described complete resolution of ophthalmic postherpetic neuralgia after

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ketamine administration at doses up to 1000 mg/day PO. The authors concluded that although the results could be explained simply by the natural history of the disease, the immediate and definite effect of ketamine in comparison with the other therapies was striking. One further report (level IV) (35) described the successful use of ketamine by various routes in a patient with multiple comorbidities. Unusually, they document continued benefit over a 4-yr period with minimal side effects. Ketamine was continued until the death of the patient from unrelated causes. The authors also performed a double-blinded comparison of SC ketamine versus placebo (12% glucose to mimic local effects) to confirm the observed benefit was not simply attributable to the natural history of the disease. Pain returned during the placebo days.

Discussion

We probably do not yet have sufficient evidence to advocate the routine use of ketamine in chronic pain. Despite the use of ketamine for over 30 years, there are few good-quality studies with adequate numbers of patients to clearly delineate the place of this drug in chronic pain medicine. We do, however, have much evidence that it can cause significant side effects. This is not surprising, given the abundance of NMDA receptors using glutamate as the main agonist in both the central and peripheral nervous systems. It is not possible to block such a widespread receptor without some adverse effect. This is in addition to the effect of ketamine on many other receptors, as alluded to earlier.

We also have little data regarding long-term administration by any particular route. The data suggest that ketamine may be used most effectively to reduce the symptoms of allodynia, hyperalgesia, and hyperpathia rather than acting as a traditional analgesic (level II). Thus, patients in whom this is a predominant feature may be more likely to benefit. This could be consistent with NMDA receptor blockade limiting or reducing central sensitization, although the ability of ketamine to interact with such a wide variety of receptors means that this is currently only speculative.

Ketamine can be given by multiple routes: IV, IM, SC, oral, rectal, nasal, transdermal (36), epidural, or intrathecal. Although experimental studies are often performed with parenteral ketamine, the optimal route of administration remains unclear. Some reports describe parenteral administration at home (level III) (29,33); however, this technique is probably impractical in the long term. In addition to the logistics of refills and sharps disposal, SC ketamine can be an irritant, requiring almost daily changing of the infusion site; heparin ointment (level IV) (35) has been used with some benefit. Data from studies using systemic administration are often extrapolated to other routes. Orally administered ketamine undergoes extensive first pass metabolism, primarily via *N*-demethylation, resulting in small ketamine concentrations and large nor-ketamine concentrations in blood and tissue (37). We do not know how this affects the therapeutic ratio between analgesia and side effects because nor-ketamine has significant analgesic properties (37) and may indeed play an important role. This would be supported by analysis of the reported data that confirm effective oral doses are often less than parenteral doses of ketamine (19). There is currently no readily available oral form of ketamine in the United Kingdom, and dosing relies on using the injectable solution, which has a bitter taste; an oral formulation to enable blinded studies has been suggested (21) (Appendix A). The safety of neuraxially administered ketamine remains unclear, with mixed data in the literature. Radicular demyelination has been observed in rats (38), subpial vacuolar myelopathy has been observed after intrathecal administration (level IV) (39), and focal lymphocytic vasculitis close to the catheter injection site has been observed without neurological deficit or other histological changes (level IV) (40). All reports used ketamine with benzethonium chloride as preservative. Animal studies report no inflammatory reactions when preservative-free drug is used. More recently, however, it has been suggested that the preservative is also an active receptor blocker (41), although the importance of this remains to be clarified. Although basic studies indicate a peripheral site of action of ketamine, evidence of efficacy in humans for peripheral analgesic effects of ketamine is conflicting and is restricted largely to acute pain. A controlled study of a transdermal ketamine patch reported significant adjuvant analgesic effects for postoperative pain after gynecologic surgery (36). However rigorous studies in volunteers, using inflammatory pain generated by an infrared burn, showed only brief analgesic effects of infiltrated ketamine (42). Although ketamine currently enjoys significant use in topical preparations for chronic pain, there are no published controlled studies.

Parenteral administration, IV or SC, in the range 0.125–0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ appears to be optimal (level II) but there are occasional reports of larger or smaller doses. Because this mode of administration is impractical in the long term as a result of the need for hospitalization or repeated changes of delivery site, the need for oral dosing has arisen. The doses reported in the literature for this route vary widely between 30–1000 mg/day (mean, 200 mg). If this is to be believed then the therapeutic window is massive and deserves comment. It could easily be speculated that the analgesic effect from ketamine at the smaller doses may result from action at different receptor sites than that caused by larger doses. Alternatively, this wide dose range reflects the variation in diagnoses within many study groups. Epidural administration has been

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reported as effective in complex regional pain syndrome with a dose of 20–30 mg/day (level IV). Therapeutic benefit is likely to be dose-dependent (26).

The role of the NMDA receptor and NMDA antagonists with respect to mechanisms of chronic pain conditions is a controversial subject that has been reviewed in detail elsewhere (5,6,42–45). In brief, much evidence points to involvement of NMDA receptors in persisting nociceptive and neuropathic pain. Thus, patients with pain conditions including nociceptive and/or neuropathic mechanisms may benefit.

However, not all patients with nociceptive and/or neuropathic pain respond to ketamine; there appear to be three different patterns of response: full response, partial response, and nonresponders. Several reports have suggested that the likelihood of response is increased in the younger patient with a shorter history of pain (<5 years) (25), whereas the best results in one study (21) were obtained in 2 patients with prolonged histories of 12–20 years (level II). In some studies, barely 30% had a beneficial effect; this is little more than can be obtained from a placebo response. The data also suggest a frequent incidence of intolerable side effects that does not seem to improve significantly with altered dose or route of administration. Therefore, even those patients who respond to ketamine may not continue treatment as a result of intolerable side effects. It is interesting to note that even those patients in whom the best results were obtained did not persist with ketamine in the long term.

Human pharmacological studies indicate that NMDA receptors are important for sensory perception, proprioception, cognition, and consciousness (43,44). It is therefore not surprising that NMDA-receptor antagonists commonly have psychotomimetic side effects, and this is one of the main disadvantages of ketamine administration. Clinical experience shows that anxious and apprehensive patients are more likely to exhibit psychotomimetic side effects. It is possible that this actually reflects a pharmacological mechanism, as ketamine is more likely to bind to NMDA receptors when the channel is in the activated or open state. The reduction in side effects associated with a quiet, relaxed atmosphere could therefore be explained by the fact that the NMDA receptor is more likely to be closed. Pretreatment with a benzodiazepine is said to minimize psychotomimetic effects; administration after they have developed is less successful. This could be explained by the same receptor state mechanism. A benzodiazepine given before ketamine may increase the likelihood of closing the NMDA receptor but may be less effective after ketamine has bound. The incidence of psychomimetic side effects, however, was not altered in the studies that routinely administered benzodiazepines, and most only used them as rescue medication. This is not in accordance with general thinking.

There was not a consistent dose response. One case using ketamine 1000 mg/day PO reported no psychomimetic side effects, yet they are commonly reported at smaller doses. It has been suggested that oral ketamine administration causes fewer side effects, perhaps because of the smaller plasma levels, improved side effect profile of nor-ketamine, or reduced peak effect (7). Night-time dosing can also reduce side effects (level IV), perhaps because of the fact that patients tend to be more relaxed (see discussion above) or perhaps because sleep intervenes.

Painful induration at the injection site is the most common problem with SC administration, as previously described, occurring both with and without preservative. Some patients experience positive side effects such as improved sleep and elevated mood. Rarely reported side effects include hepatic failure, which has been reported after daily doses of 900–1500 mg orally (46).

Clements et al. (47) found consistent increases of pain thresholds for plasma concentrations of racemic ketamine more than 160 ng/mL (0.36 μmol/L) in experimental ischemic pain, and subsequent studies have confirmed this value (15). These concentrations were obtained with SC infusion of $0.05\ \text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (3–5 mg/h for an average adult) (33). The same study demonstrated a significant positive correlation between pain relief and the serum ketamine concentration (% pain relief = 63.8 × ketamine concentration − 6.1, $r = 0.60$, $df = 16$, $P < 0.01$). There was also significant positive correlation between pain relief and the serum nor-ketamine concentration (% pain relief = 111.6 × nor-ketamine concentration − 7.8, $r = 0.49$, $df = 16$, $P < 0.05$). The usefulness of this in clinical practice is unclear and seems to ignore the highly subjective nature of the pain experience as a biopsychosocial phenomenon. There was no accumulation of either ketamine or nor-ketamine, nor did their relative concentrations change, during the 4-week treatment period of this study.

Summary

Patients with incapacitating, otherwise intractable, chronic pain may accept side effects from a treatment if pain relief is sufficiently effective. In some patients, ketamine has proved effective and, on this basis, a trial of ketamine is probably warranted for the patient with severe chronic pain that is incapacitating and refractory to other first- and second-line pharmacological therapies. However, apart from a few cases of complete resolution, this generally does not provide a long-term solution and should therefore be regarded as a temporary measure while other treatment options are considered. We suggest that the following may be a reasonable approach when considering ketamine administration:

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1. Ensure that there are no contraindications to the use of ketamine.
2. Educate the patient regarding the potential side effects and obtain fully informed consent (level IV).
3. Perform a fully monitored, placebo controlled IV trial of ketamine to assess therapeutic benefit. Available data suggest this should be a dose of 0.25–0.5 mg/kg given slowly over 30 min with pain assessments before and after administration (level II).
4. Poor responders or nonresponders are unlikely to benefit from oral ketamine. A good therapeutic response from systemic administration suggests a greater likelihood of benefit from oral dosing (level IV).
5. Commence oral ketamine 0.5 mg/kg taken immediately before going to bed to minimize the likelihood of side effects (level IV). Increase the dose by 0.5 mg/kg as tolerated until pain relief is obtained or intolerable side effects occur (level IV). The mean effective dose from the literature is 200 mg/day (level II) although there is a wide variation.
6. For severe acute on chronic episodes of neuropathic pain, administer ketamine by continuous infusion (IV or s.c.) at a rate of 0.14–0.4 $mg \cdot kg^{-1} \cdot h^{-1}$ (level IV).

This suggested approach is based on data reviewed in this article. As there are only a small number of studies and this evidence is weak, any recommendations based on it are also weak. They are, however, based on the only data that are available at present.

The magnitude of reported benefit from ketamine in chronic pain is often little more than what could be expected by a placebo effect. It is therefore unlikely that ketamine will become a regular treatment option for patients with chronic pain unless there is greater interest in performing good quality studies in this area to further delineate the target population and dose response for specific diagnoses. Until this takes place, ketamine will remain a third-line drug that is administered on the basis of weak evidence in patients who have failed to respond to routine pharmacotherapy.

Appendix

Formulations of Ketamine and Placebo Liquids

Oral Ketamine Liquid

5 mL ketamine injection 100 mg/mL
1.25 mL conc. peppermint water BP.
0.1 mL conc. anise water BP.
1.25 mL conc. chloroform water BPC.
20 mL syrup (preserved) BP.
Water for irrigation to 50 mL.

Placebo Liquid

2 mL conc. peppermint water BP
0.2 mL conc. anise water BP
1.25 mL conc. chloroform water BPC.
5 mL syrup (preserved) BP
Water for irrigation to 50 mL.

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