Section Editor: **Spencer S. Liu**

REVIEW ARTICLE

Topical and Peripheral Ketamine as an Analgesic

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Ketamine, in subanesthetic doses, produces systemic analgesia in chronic pain settings, an action largely attributed to block of *N*-methyl-D-aspartate receptors in the spinal cord and inhibition of central sensitization processes. *N*-methyl-D-aspartate receptors also are located peripherally on sensory afferent nerve endings, and this provided the initial impetus for exploring peripheral applications of ketamine. Ketamine also produces several other pharmacological actions (block of ion channels and receptors, modulation of transporters, anti-inflammatory effects), and while these may require higher concentrations, after topical (e.g., as gels, creams) and peripheral application (e.g., localized injections), local tissue concentrations are higher than those after systemic administration and can engage lower affinity mechanisms. Peripheral administration of ketamine by localized injection produced some alterations in sensory thresholds in experimental trials in volunteers and in complex regional pain syndrome subjects in experimental settings, but many variables were unaltered. There are several case reports of analgesia after topical application of ketamine given alone in neuropathic pain, but controlled trials have not confirmed such effects. A combination of topical ketamine with several other agents produced pain relief in case, and case series, reports with response rates of 40% to 75% in retrospective analyses. In controlled trials of neuropathic pain with topical ketamine combinations, there were improvements in some outcomes, but optimal dosing and drug combinations were not clear. Given orally (as a gargle, throat swab, localized peritonsillar injections), ketamine produced significant oral/throat analgesia in controlled trials in postoperative settings. Topical analgesics are likely more effective in particular conditions (patient factors, disease factors), and future trials of topical ketamine should include a consideration of factors that could predispose to favorable outcomes. (Anesth Analg 2014;119:170–8)

Ketamine was synthesized in the early 1960s as part of the search for an ideal anesthetic, and introduced into clinical medicine as a dissociative anesthetic in 1965.[1,2] As a general anesthetic, it provides cardiac stability but is limited by psychotropic and other central effects. In the early 1980s, ketamine was recognized to block glutamate *N*-methyl-D-aspartate (NMDA) receptors,[3] which were emerging as important contributors to central sensitization within the spinal cord and to chronic pain.[4] By 2000, a literature search identified 378 animal studies and 132 human studies that had evaluated NMDA receptors in pain and provided convincing evidence for a role of these receptors in chronic pain states.[5] A 2003 review on the use of ketamine for management of chronic pain in clinical populations reported 11 controlled trials and many uncontrolled trials and case reports[6]; subsequent reviews published in 2009 to 2010 extended the number of controlled trials to 22–29[7,8] and 36.[9] Most trials have examined effects of IV boluses and infusions, subcutaneous (SC) or IM injections, and oral ketamine. Three trials have evaluated the efficacy of long-term IV infusions of ketamine (4–5 hours daily for 7–10 days or continuously over 4 days) and demonstrated promising long-term effects.[9] Paralleling this clinical development, the pharmacology of low-dose ketamine in relation to analgesia has continued to be explored on a mechanistic basis.[10,11] As the molecular biology of the NMDA receptor has become better understood, there also has been a focus on development of novel NMDA receptor blocking drugs, both for chronic pain and other conditions involving central nervous system dysfunction.[12,13]

Since the mid-1990s, it was recognized that glutamate receptors are located on peripheral nerve endings and can contribute to pain signaling.[14,15] Key observations include: (1) glutamate is present within sensory nerve endings and is released extracellularly by noxious stimulation; (2) NMDA and other glutamate receptors are present on sensory nerve endings, and on cells adjacent to nerve endings (e.g., keratinocytes, immune cells); (3) inflammation and tissue damage cause elevated glutamate release from primary afferent nerve endings and keratinocytes; and (4) peripheral applications of glutamate receptor agonists lead to activation of sensory nerves, with electrophysiological and behavioral manifestations.[14,15] In accord with these developments, there has been an emerging interest in the potential for NMDA receptor antagonists to be applied topically, or peripherally by other means, to represent a novel strategy for pain management. Clinical case reports of the efficacy

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Accepted for publication January 16, 2014.

Funding: No funding related to this article.

Conflicts of Interest: See Disclosures at the end of the article.

Reprints will not be available from the author.

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DOI: 10.1213/ANE.0000000000000246

of topical ketamine for relieving pain began to appear in the late 1990s.[16,17] Topical approaches to analgesia have the potential to produce pain relief with minimal adverse systemic effects due to low plasma levels, and, as mechanisms involved in peripheral pain signaling have come to be better understood, there has been considerable interest in exploration of novel topical agents as analgesics.[18,19]

The purpose of this review is: (1) to consider mechanisms potentially involved in peripheral actions of ketamine; (2) to summarize clinical studies using topical and peripheral ketamine for pain management; and (3) to identify areas for further development. In constructing the review, standard methodologies using keyword searches relevant to particular sections and attentive reading of the literature were used; this is not a systematic review, and is best characterized as a narrative and interpretive review.

PERIPHERAL MECHANISMS OF ACTION OF KETAMINE

Plasma concentrations associated with analgesic actions of ketamine in humans are in the low micromolar range (0.3–1.0 μM, 100–300 ng/mL) and are consistent with concentrations that block NMDA receptors; this has provided the main foundation for understanding the pharmacology of ketamine as a systemic analgesic drug.[5,11,20] During the 1990s, additional pharmacological actions produced by ketamine were recognized, and their potential contributions to analgesia considered.[21–23] However, many of these actions occur at higher concentrations (10–100 μM and beyond) and were not considered to account for systemic analgesia that occurs with low doses of ketamine.[5,11,20] Additional actions of ketamine are summarized in Table 1. These include: (1) binding to multiple opioid receptors (ORs)[24]; (2) binding to monoamine transporters[23,25]; (3) binding to muscarinic and nicotinic cholinergic receptors and inhibition of function[23]; (4) binding to D_2 and 5-HT_2 receptors[26]; (5) inhibition of ion channels (Na^+, Ca2+, K^+)[20–22,27,28]; (6) decreased activation and migration of microglia.[28] Additional actions of ketamine seen at higher concentrations were suggested to contribute to the pharmacological profile of ketamine at higher systemic doses in preclinical studies, high and near-anesthetic doses in humans,[11] and after spinal administration.[27] When ketamine is administered topically or injected locally into tissue, higher local tissue concentrations may occur compared with systemic dosing, and lower affinity actions also may contribute to the pharmacology of peripheral ketamine. Thus, 0.5% to 5.0% ketamine (Tables 2 and 3) is 5 to 50 mg/mL and is a solution of approximately 18 to 180 mM, while 0.5 mg/kg in 2 mL injected locally (peritonsillar)[29,30] is a solution of approximately 30 mM. These solutions undergo dilution after dermal penetration and tissue distribution after topical applications, or tissue distribution and systemic absorption after localized injections. Although tissue concentrations after such applications have not been assessed directly, it is conceivable that local concentrations are within ranges that can recruit several lower affinity mechanisms of action of ketamine noted above. In direct mechanistic studies, when a drug action is to recruit a mechanism, antagonists can provide direct evidence for involvement of that mechanism; however, when a drug action is to interfere with that mechanism, it is more difficult to definitively implicate that mechanism because mimicry by agents that clearly engage that mechanism provide necessary, but not sufficient, information to implicate that mechanism. Few preclinical studies have directly addressed mechanisms involved in peripheral antinociception by ketamine, but some recent studies have implicated the nitric oxide/cyclic guanosine monophosphate

Table 1. Summary of Pharmacological Actions of Ketamine

Action	Potency	Reference
NMDA receptor block	Ki 0.4–46 μM	Fisher et al.[5]
	IC_{50} 1.6–6.2 μM	Chiz et al.[11]
Opioid receptors (ORs)		Smith et al.[24]
μ-ORs	Ki 27 μM	
δ-ORs	Ki 101 μM	
κ-ORs	Ki 85 μM	
Block of monoamine uptake		
Noradrenaline transporter	Ki 67 μM	Kohrs and Durieux[23]
Dopamine transporter	Ki 63 μM	
Serotonin transporter	Ki 162 μM	Nishimura et al.[25]
Receptors actions		
Block of muscarinic, nicotinic cholinergic receptors	IC_{50} 10–80 μM	Kohrs and Durieux[23]
Receptor binding		
Dopamine D_2	Ki 0.5 μM	
Serotonin 5-HT_2	Ki 15 μM	Kapur and Seeman[26]
Ion channels		
Block of Na^+, Ca^{2+} channels	Ki >50 μM or >100 μM	Eide et al.[20] Hirota and Lambert[21]
Block of Na^+, voltage-gated K^+ channels	IC_{50} 130–270 μM	Meller[22]
Block of Ca^{2+}-activated K^+ channels	100 μM	Schnoebel et al.[27] Hayashi et al.[28]
Functional effects		
Decreased activation, migration of microglia	100 μM	Hayashi et al.[28]
Inhibition of production of inflammatory mediators	≥ 2 μM, ≥ 50 μM, ≥100 μM depending on mediator and test system	DeKoch and Loix[41] See also Liu et al.[40]

Ki refers to binding studies, IC_{50} to functional effects. See references for further details.

Table 2. Reports on the Effects of Topical Ketamine for Neuropathic Pain in Clinical Case Studies and Controlled Trials

Agent, dose	Condition (*N*), study design	Outcome, comments	Reference
A. Case reports			
Ketamine 0.5%–5%	Sympathetically maintained pain (*N* = 5); case series	Improvements in pain; maintained at follow-up	Crowley et al.[16]
Ketamine 1%	Reflex-sympathetic dystrophy (*N* = 3), postherpetic neuralgia (*N* = 1), lumbar radiculopathy (*N* = 1); case series	All report pain some relief at application site within hours	Gammaitoni et al.[17]
Ketamine 0.25%–1.5%	CRPS type 1 (*N* = 5); CRPS type 2 (*N* = 2); case series[a]	After 1 to 2 wk, improvements in early dystrophic stage but not in chronic atropic stage	Ushida et al.[70]
Ketamine 0.5%	Postherpetic neuralgia (*N* = 23); case series	10 of 16 (60%) note some analgesia with ketamine; response within days	Quan et al.[71]
Ketamine 10%	Nerve entrapment (*N* = 1); case report	Topical ketamine reduced pain; if not applied, pain returns; effective for months; >50% pain relief; slight derealisation reported (oral cannabis also used)	Keppel Hesselink and Kopsky[72]
B. Controlled trials			
Ketamine 0.5%	Mixed neuropathic pain vs placebo (*N* = 20); subjects received each treatment for 2 d	No difference from placebo over 1 to 2 days; no plasma ketamine levels detected	Lynch et al.[73]
Ketamine 1%	Mixed neuropathic pain vs placebo (*N* = 47), 3 wk	No difference from placebo at 1 to 3 wk	Lynch et al.[75]
Ketamine 1%	Postherpetic neuralgia vs placebo (*N* = 12); 15 d; crossover trial after 7 d washout	No difference from placebo in initial phase or in crossover phase	Barros et al.[74]
Ketamine 5%	Painful diabetic neuropathy vs placebo (*N* = 27); 4 wk; controlled trial	No difference from placebo on any pain measure following treatment	Mahoney et al.[76]
C. Experimental trial			
Ketamine 10%	CRPS vs placebo (*N* = 20); crossover trial; acute assessment of sensory thresholds at 30 min	Ketamine reduced allodynia & hyperalgesia on symptomatic limb but not on healthy limb; systemic levels undetectable	Finch et al.[59]

Reports are listed chronologically within blocks.

[a]CRPS = complex regional pain syndrome, formerly known as reflex sympathetic dystrophy, sympathetically maintained pain or causalgia; type 1 is without demonstrable nerve lesions, and involves tissue trauma, inflammation and vascular changes; type 2 involves demonstrable nerve damage.[45,46]

pathways and adenosine triphosphate-sensitive K^+ channels in such actions.[31,32]

Many of the above mechanisms primarily have been considered in relation to neuronal sites of action with implications for influencing pain signaling in the periphery via actions on nociceptors. It is now appreciated that keratinocytes in the epidermis can contribute to pain signaling via interactions with nerve endings and that these undergo changes after inflammation and injury.[33–35] Keratinocytes express NMDA receptors and release L-glutamate in the epidermis, and these play a role in the differentiation of keratinocytes.[36–39] Given the tissue plasticity involving keratinocytes that occurs after injury and in disease states, a potential role for actions of ketamine at NMDA receptors on keratinocytes, as well as via other mechanisms, is feasible.

A further set of actions that contribute to the pharmacological profile of ketamine is regulation of inflammatory and immune responses both in vitro and in vivo, which leads to decreased levels of several proinflammatory mediators (e.g., interleukin-1β, interleukin-6, interleukin-8, tumor necrosis factor-α).[40,41] These actions result from ketamine interacting with toll-like receptors on immune cells and repression of nuclear factors (NF-κB, AP-1). A clinical correlation to this anti-inflammatory effect is that ketamine inhibits early postoperative inflammatory responses[42]; the functional consequences of this are not clear but could involve reduction in postoperative adverse effects (e.g., cognitive dysfunction).[43] With respect to peripheral actions of ketamine, nebulized ketamine delivered directly to the airways resulted in suppression of allergen-mediated airway hyperreactivity, reduction in airway inflammation and inflammatory cell infiltration, and decreased levels of inflammatory mediators in airway lavage in a model of allergen-induced asthma in rats.[44] These peripheral anti-inflammatory actions of ketamine could contribute to the peripheral analgesic actions of ketamine in several clinical settings. For example, complex regional pain syndrome (CRPS) type 1 involves several mechanisms, including peripheral inflammation, peripheral vascular changes, and peripheral hypersensitivity,[45,46] and ketamine's actions on inflammatory processes, as well as on neurons, keratinocytes, and other cell types, could account for unique actions in this condition (Table 2).

PERIPHERAL ADMINISTRATION OF KETAMINE IN EXPERIMENTAL TRIALS

Reports that peripheral NMDA receptors contribute to pain signaling in preclinical models[47–49] stimulated experimental studies whereby ketamine was administered locally by acute SC injection. In rodents, peripheral delivery of ketamine was reported to produce antinociception in the formalin test,[50] in a thermal hyperalgesia model,[51] and a prostaglandin E_2-hyperalgesia model.[31,32] In humans, Warncke et al.[52] demonstrated that SC ketamine 5 mg reduced primary hyperalgesia and development of secondary hyperalgesia after thermal injury in healthy volunteers. Pedersen et al.[53] reported a transient reduction in heat and mechanical thresholds immediately after injection of SC ketamine 7.5 mg but no effect at other times or on secondary hyperalgesia in healthy volunteers. In the intradermal capsaicin (10 μg)-induced hyperalgesia model in humans, SC ketamine 1 mg had no effect on transient pain but inhibited secondary hyperalgesia; it also increased mechanical thresholds when given in the absence

Table 3. Topical Ketamine Given in Combination with Other Agents for Neuropathic Pain

Agent, dose	Condition (*N*), study design	Results, comments	Reference
A. Controlled trials			
Ketamine (KET) 0.5%, amitriptyline (AMI) 1%, KET 0.5% + AMI 1%	Mixed neuropathic pain (*N* = 20); all subjects received all treatments for 2 d; *N* = 11 entered 7 d open-label phase of KET/AMI	No differences in pain between groups over 1 to 2 d; reduction in pain at 3 to 7 d in open-label group; minimal plasma levels of amitriptyline and ketamine	Lynch et al.[73]
Ketamine 1%, amitriptyline 2%, (KET 1% + AMI 2%)	Mixed neuropathic pain (*N* = 92); factorial trial of 4 groups for 3 wk	No difference in pain between groups at 1 and 3 wk; minimal plasma levels; well-tolerated	Lynch et al.[74]
KET 1% + AMI 2%	Peripheral neuropathic pain (*N* = 28); 12 mo open-label study; 75% completed trial	34% pain reduction at 6 mo (*N* = 5≥50%); 37% pain reduction at 12 mo (*N* = 7≥50%); minimal plasma levels; well-tolerated	Lynch et al.[77]
KET 1% +AMI 2% (L) KET 2%+ AMI 4% (H)	Postherpetic neuralgia; enriched enrollment; *N* = 118 responders randomized to L, H, or placebo for 2 wk	46% (H) vs 26% (L) vs 19% placebo with ≥30% pain reduction; minimal plasma levels; well-tolerated	Lockhart[78] Everton et al.[79]
Ketamine 20 mg (1.5%), amitriptyline 40 mg (3%), baclofen 10 mg (0.8%) (drugs in 1.31 g gel)	Chemotherapy-induced peripheral neuropathy (*N* = 203); parallel trial vs placebo for 4 wk	Improvement in motor subscale; trend in sensory subscale; minimal plasma levels; well-tolerated	Barton et al.[80]
Ketamine 1%, amitriptyline 2%, lidocaine 5%	Radiation skin reaction (*N* = 16); open-label study for 2 wk following radiation therapy	Several measures of pain reduced at 30 min; reduced burning pain in long term (at 2 wk)	Uzaraga et al.[81]
B. Case reports			
Ketamine 0.5%, amitriptyline 1%	Erythromelalgia (*N* = 1); note *N* = 5 other cases	Pain relief within 2 d, maintained 2 mo; 4 others with >50% relief	Sandroni and Davis[82]
Ketamine 0.5%, amitriptyline 1%–2%, lidocaine 2% (most KET + AMI)	Erythromelalgia (*N* = 36); retrospective of cases between 2004 and 2011	75% have some pain relief, 42% have substantial relief	Poterucha et al.[83]
Ketamine 0.5%, amitriptyline 2.5%	Proctodynia (*N* = 1); refractory to treatment	Substantial analgesia in 2 d, well maintained	Lehman, Sciallis[84]
Ketamine 0.5%, amitriptyline 1%–2%	Rectal, genital, perineal pain (*N* = 13) [neuropathic component not well defined]; retrospective of cases between 2004 and 2011	85% have some relief, 54% substantial relief	Poterucha et al.[85]
Ketamine 0.5%, amitriptyline 1%	Neuropathic itching (brachioradial pruritis) (*N* = 1); refractory; also *N* = 3 other cases	Complete relief with topical treatment for 4 y; 2 other with some relief, 1 with no relief	Poterucha et al.[86]
Ketamine 0.5%, amitriptyline 1% or 2%	Localized pruritis [includes neuropathic origins] (*N* = 16); retrospective of cases between 2004 and 2011	15 of 16 had failed other therapies; 62% have some relief with topicals	Poterucha et al.[87]
Amitriptyline 5%, ketamine 10%, dimethylsulfoxide or DMSO 50%, 1 mo each	CRPS type 1 (*N* = 1); severe, intractable	Sequential applications (AMI, KET, DMSO); each addition reduced pain; substantial effect for 8 mo; no adverse effects	Kopsky and Keppel Hesselink[88]
Ketamine 10%, palmitoylethanolamide or PEA (orally)	CRPS type 1 (*N* = 1); severe, intractable	Treatment reduced pain >50%, marked reduction in swelling and skin discoloration after 1 mo; from wheelchair to walking without cane	Keppel Hesselink and Kopsky[89]
Ketamine 10%, lidocaine 8%, clonidine 0.2%, ketoprofen 5%	PHN (*N* = 1)	Pain reduction in 3 to 4 d, further reduction in 7 to 10 d; pain resolved after 1 mo	Zur[90]
Ketamine 4%, carbamazepine 4%, lidocaine 4%, ketoprofen 4%, gabapentin 4%	Orofacial neuropathic pain (*N* = 12); also *N* = 10 systemic only and *N* = 17 topical + systemic; retrospective case series	Topical application reduced pain ≥30% in 41% of cases; similar effect with systemic only (41%) or topical + systemic (52%)	Heir et al.[91]
Ketamine 5%–10%, lidocaine 2%–10%	Neuropathic pain (*N* = 21); clear and suggested diagnosis groups; retrospective case series	Considered effective in 7 of 8 clear, and 1 of 3 suggested diagnosis; 8 of 11 or 73% benefitted	Tam and Furlan[92]

Reports are generally listed chronologically, except for some clustering around disease conditions.
CRPS = complex regional pain syndrome.

of capsaicin; a dose of 0.1 mg ketamine had no such effects.[54] In other such studies, SC injection of 5 mg ketamine had no effect on either transient pain or secondary hyperalgesia in response to capsaicin 100 μg[55,56]; the difference in results was perhaps due to use of a higher capsaicin dose in the latter studies. In each of these studies, ketamine consistently inhibited the vascular flare response (axon reflex) to capsaicin, indicating involvement of different mechanisms in such

responses compared with pain.[54–56] Side effects consistent with systemic effects (central actions) were reported after SC injections of 5 mg ketamine (in 25%)[53] and 7.5 mg ketamine (in 67%).[55] Local injection of 6 mg ketamine SC (0.3%, 2 mL) produced local anesthetic actions to von Frey filament testing in volunteers; this action was proposed to account for enhancement of analgesia by other local anesthetic drugs.[57]

Ketamine has also been administered topically as a gel in humans, and acute sensory effects determined. In healthy volunteers, topical ketamine (1 mL of 50 mg/mL, 5%) had no effect on the immediate burning response to capsaicin 250 μg but reduced mechanical hyperalgesia over 1 hour.[58] The same response was seen with topical application of ketamine to the other side of the body, and the effect was attributed to a systemic action.[58] Another study examined topical ketamine (0.5 mL of 10%, 50 mg) in patients with CRPS[59] and reported reduction in allodynia and punctate responses on the symptomatic side 30 minutes after application of topical ketamine; this was due to a local action because application to the healthy limb had no such effect. The latter study also examined plasma levels of ketamine and norketamine after topical administration (blood sampled 1 hour after administration) and reported no detectable plasma levels (limit 0.5–0.7 ng/mL).[59] Plasma levels of 150 ng/mL are needed for analgesia after IV or IM administration of ketamine.[60–63] It is not clear why one study implicated systemic[58] while the other implicated local ketamine actions,[59] because both used the same dose and vehicle; whether tissue conditions encountered in CRPS influence skin absorption and local tissue distribution compared with healthy volunteers remains to be determined.

TOPICAL KETAMINE FOR NEUROPATHIC PAIN

Neuropathic pain results from injury (lesion, disease) to the somatosensory system and can involve peripheral and central sites; manifestations include spontaneous (paresthesia, pain), negative (hypoesthesia, hypoalgesia), and positive (allodynia, hyperalgesia) sensory symptoms.[64] Mechanisms involved in neuropathic pain occur at multiple levels of the pain neuraxis and include peripheral sensitization, central sensitization in the spinal cord, and central changes.[65] Several classes of analgesics exhibit efficacy in neuropathic pain (antidepressants, anticonvulsants, opioids, other adjuvants), but oral treatments exhibit partial efficacy and can be limited by adverse effects.[66,67] Two topical analgesics are approved for use in neuropathic pain, lidocaine medicated plaster,[68] and the high-concentration capsaicin patch,[69] indicating the usefulness of this approach for such conditions.

Since 1998, with publication of several cases reporting efficacy of topical ketamine for neuropathic pain,[16] additional cases and case series reports have been published (Table 2, 2A). These describe cases of sympathetically maintained pain, reflex-sympathetic dystrophy, CRPS, postherpetic neuralgia, and other conditions.[17,70–72] The amount of ketamine applied varied, with concentrations ranging mostly from 0.5% to 5.0% (applications of 1–2 mL, 2–4 × day). Several controlled trials have compared topical ketamine with placebo groups in clinical populations (Table 2, 2B). Ketamine 0.5% to 1.0% had no effect compared with placebo over 2 days,[73] 2 weeks,[74] or 3 weeks[75] in several neuropathic pain conditions. Furthermore, ketamine 5% had no effect on painful diabetic neuropathy over 4 weeks.[76] These controlled trials of topical ketamine do not generally recapitulate case report observations. In an experimental trial in CRPS subjects, acute application of topical ketamine 10% had no effect on spontaneous pain, but reduced evoked sensory thresholds 30 minutes after application.[59] This trial differed from other efficacy trials in that it determined effects of acute applications rather than chronic applications for condition-related pain. Neither topical application of ketamine 0.5% to 1% (daily)[73,75] nor 10% (acute application)[59] produced detectable levels of ketamine or the active metabolite, norketamine, in plasma. There are no data on plasma ketamine levels after repeated doses of higher concentrations of ketamine (5%–10%).

TOPICAL KETAMINE IN COMBINATION WITH OTHER DRUGS FOR NEUROPATHIC PAIN

There are several controlled trials of topical ketamine administered in combination with other drugs for neuropathic pain (Table 3, 3A). When compared with placebo, topical ketamine 0.5% + amitriptyline 1% had no effect on mixed neuropathic pain over 2 days,[73] and topical ketamine 1% + amitriptyline 2% had no effect over 3 weeks.[75] In an open-label study over 12 months, pain was reduced 34% to 47% with this topical combination.[77] In a dose-range comparison of ketamine + amitriptyline (1%/2%, 2%/4%), only the higher combination produced a significant reduction in pain compared with placebo.[78,79] When ketamine 1.5% + amitriptyline 3% + baclofen 0.8% was compared with placebo for chemotherapy-induced neuropathy, there was a significant improvement in motor subscales and a trend toward improvement in sensory effects.[80] When ketamine 1% + amitriptyline 2% was evaluated in an open-label trial for radiation skin reactions, there were acute reductions in several measures of pain at 30 minutes and reductions in burning pain at 2 weeks.[81]

There are several case studies, including several case series reports, indicating the effects of topical ketamine in combination with other drugs (Table 3, 3B). Ketamine 0.5% + amitriptyline 1% produced marked improvements in pain and function in a case of erythromelalgia, a disorder characterized by redness, increased skin temperature and pain in the extremities that has vascular and neuropathic elements; a further 4 of 5 cases reported improvements in pain >50%.[82] A subsequent retrospective analysis of 36 cases of erythromelalgia treated with topical ketamine + amitriptyline indicated 75% had some relief of symptoms.[83] A report of successful treatment of proctodynia with ketamine 0.5% + amitriptyline 2.5%[84] was followed by a retrospective analysis of 13 cases of rectal, genital, or perineal pain where 85% reported some relief of symptoms.[85] Finally, a case of neuropathic itching relieved by ketamine 0.5% + amitriptyline 1%[86] was followed by retrospective analysis of 16 cases; 62% had some relief from localized pruritis (including neuropathic) with topical regimens.[87] Each of the retrospective analyses recognized inherent limitations to the approach; however, each noted a high response rate in conditions that are challenging to treat and encouraged further clinical exploration. Finally, there are several case reports of good outcomes with ketamine given in combination with several other ingredients for neuropathic pain. Thus, amitriptyline 5%, ketamine 10%, and dimethyl sulfoxide

50% (given sequentially in that order) produced stepwise improvements in CRPS;[88] ketamine 10% along with oral palmitoylethanolamide relieved CRPS,[89] and ketamine 10% along with lidocaine 8%, clonidine 0.2%, and ketoprofen 5% provided pain relief in postherpetic neuralgia.[90] A retrospective survey of ketamine in combination with several other drugs indicates a response rate of 41% for orofacial pain,[91] and when combined with lidocaine, 73% in cases of neuropathic pain.[92]

These case reports provide promising observations that suggest topical ketamine in combination with other drugs, and in particular with amitriptyline, is useful in cases of neuropathic pain. While controlled trials do not provide consistent data for efficacy, there may be a concentration–response relationship,[78,79] and placebo-controlled trials generally have examined lower concentrations.[73,75] Topical analgesics are not universally effective, and open-label trials of 5% lidocaine medicated plaster (which is approved for use) indicate response rates of 50% to 70%.[93,94] Future controlled trials of topical analgesics will need to attend to factors that might predict responses to topical analgesics, such as pain or sensory characteristics, patient characteristics, and disease duration and severity.[95] For example, post hoc analysis indicates catastrophizing can contribute to outcomes in topical analgesic trials, including formulations containing ketamine.[96]

TOPICAL AND LOCALIZED DELIVERY OF KETAMINE FOR ORAL INDICATIONS

After recognition of the peripheral effects of NMDA receptors on pain signaling, ketamine was administered orally as a mouthwash for oral pain. Thus, Slatkin and Rhiner[97] reported a case of oral cancer and radiation-induced mucositis that was treated with ketamine oral rinse (20 mg/5 mL, swished for 1 minute then expectorated); this led to an immediate reduction in pain; with continued use over a week, pain was reproducibly reduced, and benefit lasted hours; the condition improved over several months with further use. Subsequently, ketamine gargle was explored for postoperative sore throat resulting from endotracheal intubation for surgery. There are now several placebo-controlled studies (N = 40–46 subjects) reporting ketamine gargle (40–50 mg/30 mL, for 30–40 seconds), given after arrival in the operating room before surgery, reduces postoperative sore throat scores 2 to 24 hours after surgery.[98–101] Plasma levels of ketamine and norketamine were low, and the effect of the gargle was considered to be due to a local peripheral action.[100]

Ketamine also has been applied topically to the tonsillar fossa after tonsillectomy in children.[102,103] In one trial, ketamine 20 mg (in 10 mL vehicle) was applied directly to the tonsillar fossa, after surgery and control of bleeding, and then aspirated after 5 minutes; ketamine (as well as morphine and ketamine + morphine) produced analgesia and reduced rescue medication intake over 24 hours after surgery compared with artificial saliva.[102] In another trial, ketamine 20 mg (in 5 mL, soaked in a swab) was applied to the fossa for 5 minutes; this produced significant analgesic effects compared with placebo in the postsurgical interval.[103] Both trials concluded topical ketamine seemed a safe, effective, and easy approach for decreasing tonsillectomy pain. Other studies used peritonsillar injections of ketamine (0.5–1 mg/kg, 2 mL) and reported lower pain after surgery, less postoperative dysphagia, and reduced analgesic use.[29,30,104,105] Side effects were not observed after local injections of ketamine, and preincisional injection of ketamine into the tonsils was considered safe and effective for pain after tonsillectomy. In these latter studies, plasma levels of ketamine after local injections into tonsils were not determined. While outcomes might reflect systemic actions, a peripheral action also is likely in view of the effects of topical ketamine applications noted above, and postsurgical effects may well have resulted from both peripheral and central actions.

SUMMARY AND CONCLUSIONS

Ketamine, in anesthetic doses, produces dose-related unconsciousness and profound analgesia, but use is limited by adverse central nervous system effects (psychotropic effects, abuse liability). At subanesthetic doses, systemic ketamine produces analgesia, an action largely attributed to block of NMDA receptors in the spinal cord and inhibition of central sensitization (although other actions likely also contribute). Since the recognition of NMDA receptors on sensory afferent nerve endings in the mid-1990s, ketamine has been applied to the peripheral compartment as gels and creams at somatic cutaneous sites, and, more recently, as mouthwashes, gargles, swabs, or local injections for oral indications. When given peripherally, ketamine can achieve higher local tissue concentrations than when given systemically, and recruit more of the pharmacological actions that have been reported for ketamine; such actions include neuronal effects as well as actions on other cell types (keratinocytes, immune cells). The evidence supporting peripheral analgesic actions of topical ketamine given alone consists of case reports; controlled trials have not replicated those observations. Ketamine also has been administered topically in combination with other drugs (amitriptyline, baclofen, lidocaine, ketoprofen, clonidine, gabapentin). Controlled trials provide some data supporting efficacy, but optimal doses and drug combinations are not clear. Individual case reports indicate benefits in individuals that have often been refractory, and case series reports indicate a favorable rate of pain relief. When applied to the oral cavity, ketamine produced statistically significant benefits in pain measures in controlled trials. This collective body of information provides support for further clinical exploration of ketamine as a peripherally active analgesic when given alone in certain settings (especially oral indications) and as a topical analgesic in combination with other drugs for cutaneous somatic sites in neuropathic pain. Topical analgesics probably will be most effective in subpopulations of individuals, and it will be important to address factors (e.g., pain or sensory characteristics, patient characteristics, disease duration, and severity) that might better predict those who will respond to topical analgesics.

DISCLOSURES

Name: Jana Sawynok, PhD.
Contribution: Sole contributor.
Conflicts of Interest: Author has received license fees from Epicept.
This manuscript was handled by: Spencer S. Liu, MD.

REFERENCES

1. White PF, Way WL, Trevor AJ. Ketamine–its pharmacology and therapeutic uses. Anesthesiology 1982;56:119–36
2. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 1989;36:186–97
3. Lodge D. The history of the pharmacology and cloning of ionotropic glutamate receptors and the development of idiosyncratic nomenclature. Neuropharmacology 2009;56:6–21
4. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993;52:259–85
5. Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management. Preclinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage 2000;20:358–73
6. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. Anesth Analg 2003;97:1730–9
7. Bell RF. Ketamine for chronic non-cancer pain. Pain 2009;141:210–4
8. Blonk MI, Koder BG, van den Bemt PM, Huygen FJ. Use of oral ketamine in chronic pain management: a review. Eur J Pain 2010;14:466–72
9. Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan A. Ketamine for the treatment of chronic non-cancer pain. Expert Opin Pharmacother 2010;11:2417–29
10. Chizh BA, Headley PM. NMDA antagonists and neuropathic pain–multiple drug targets and multiple uses. Curr Pharm Des 2005;11:2977–94
11. Chizh BA. Low dose ketamine: a therapeutic and research tool to explore N-methyl-D-aspartate (NMDA) receptor-mediated plasticity in pain pathways. J Psychopharmacol 2007;21:259–71
12. Koller M, Urwyler S. Novel N-methyl-D-aspartate receptor antagonists: a review of compounds patented since 2006. Expert Opin Ther Pat 2010;20:1683–702
13. Santangelo RM, Acker TM, Zimmerman SS, Katzman BM, Strong KL, Traynelis SF, Liotta DC. Novel NMDA receptor modulators: an update. Expert Opin Ther Pat 2012;22:1337–52
14. Carlton SM. Peripheral excitatory amino acids. Curr Opin Pharmacol 2001;1:52–6
15. Miller KE, Hoffman EM, Sutharshan M, Schechter R. Glutamate pharmacology and metabolism in peripheral primary afferents: physiological and pathophysiological mechanisms. Pharmacol Ther 2011;130:283–309
16. Crowley KL, Flores JA, Hughes CN, Iacono RP. Clinical application of ketamine ointment in the treatment of sympathetically maintained pain. Int J Pharm Compd 1998;2:122–7
17. Gammaitoni A, Gallagher RM, Welz-Bosna M. Topical ketamine gel: possible role in treating neuropathic pain. Pain Med 2000;1:97–100
18. Sawynok J. Topical and peripherally acting analgesics. Pharmacol Rev 2003;55:1–20
19. Cairns BE. Peripheral Receptor Targets for Analgesia: Novel Approaches to Pain Management. Hoboken, NJ: John Wiley & Sons, Inc., 2009
20. Eide PK, Stubhaug A, Breivik H, Oye I. Reply to S.T. Meller: Ketamine: relief from chronic pain through actions at the NMDA receptor. Pain 1997;72:289–91
21. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth 1996;77:441–4
22. Meller ST. Ketamine: relief from chronic pain through actions at the NMDA receptor? Pain 1996;68:435–6
23. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg 1998;87:1186–93
24. Smith DJ, Bouchal RL, deSanctis CA, Monroe PJ, Amedro JB, Perrotti JM, Crisp T. Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. Neuropharmacology 1987;26:1253–60
25. Nishimura M, Sato K, Okada T, Yoshiya I, Schloss P, Shimada S, Tohyama M. Ketamine inhibits monoamine transporters expressed in human embryonic kidney 293 cells. Anesthesiology 1998;88:768–74
26. Kapur S, Seeman P. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. Mol Psychiatry 2002;7:837–44
27. Schnoebel R, Wolff M, Peters SC, Bräu ME, Scholz A, Hempelmann G, Olschewski H, Olschewski A. Ketamine impairs excitability in superficial dorsal horn neurones by blocking sodium and voltage-gated potassium currents. Br J Pharmacol 2005;146:826–33
28. Hayashi Y, Kawaji K, Sun L, Zhang X, Koyano K, Yokoyama T, Kohsaka S, Inoue K, Nakanishi H. Microglial Ca(2+)-activated K(+) channels are possible molecular targets for the analgesic effects of S-ketamine on neuropathic pain. J Neurosci 2011;31:17370–82
29. Siddiqui AS, Raees US, Siddiqui SZ, Raza SA. Efficacy of preincisional peritonsillar infiltration of ketamine for post-tonsillectomy analgesia in children. J Coll Physicians Surg Pak 2013;23:533–7
30. Ugur KS, Karabayirli S, Demircioğlu Rİ, Ark N, Kurtaran H, Muslu B, Sert H. The comparison of preincisional peritonsillar infiltration of ketamine and tramadol for postoperative pain relief on children following adenotonsillectomy. Int J Pediatr Otorhinolaryngol 2013;77:1825–9
31. Romero TR, Galdino GS, Silva GC, Resende LC, Perez AC, Côrtes SF, Duarte ID. Ketamine activates the L-arginine/nitric oxide/cyclic guanosine monophosphate pathway to induce peripheral antinociception in rats. Anesth Analg 2011;113:1254–9
32. Romero TR, Duarte ID. Involvement of ATP-sensitive K(+) channels in the peripheral antinociceptive effect induced by ketamine. Vet Anaesth Analg 2013;40:419–24
33. Zhao P, Barr TP, Hou Q, Dib-Hajj SD, Black JA, Albrecht PJ, Petersen K, Eisenberg E, Wymer JP, Rice FL, Waxman SG. Voltage-gated sodium channel expression in rat and human epidermal keratinocytes: evidence for a role in pain. Pain 2008;139:90–105
34. Radtke C, Vogt PM, Devor M, Kocsis JD. Keratinocytes acting on injured afferents induce extreme neuronal hyperexcitability and chronic pain. Pain 2010;148:94–102
35. Hou Q, Barr T, Gee L, Vickers J, Wymer J, Borsani E, Rodella L, Getsios S, Burdo T, Eisenberg E, Guha U, Lavker R, Kessler J, Chittur S, Fiorino D, Rice F, Albrecht P. Keratinocyte expression of calcitonin gene-related peptide β: implications for neuropathic and inflammatory pain mechanisms. Pain 2011;152:2036–51
36. Genever PG, Maxfield SJ, Kennovin GD, Maltman J, Bowgen CJ, Raxworthy MJ, Skerry TM. Evidence for a novel glutamate-mediated signaling pathway in keratinocytes. J Invest Dermatol 1999;112:337–42
37. Fischer M, Glanz D, William T, Klapperstück T, Wohlrab J, Marsch WCh. N-methyl-D-aspartate receptors influence the intracellular calcium concentration of keratinocytes. Exp Dermatol 2004;13:512–9
38. Nahm WK, Philpot BD, Adams MM, Badiavas EV, Zhou LH, Butmarc J, Bear MF, Falanga V. Significance of N-methyl-D-aspartate (NMDA) receptor-mediated signaling in human keratinocytes. J Cell Physiol 2004;200:309–17
39. Fischer M, Glanz D, Urbatzka M, Brzoska T, Abels C. Keratinocytes: a source of the transmitter L-glutamate in the epidermis. Exp Dermatol 2009;18:1064–6
40. Liu FL, Chen TL, Chen RM. Mechanisms of ketamine-induced immunosuppression. Acta Anaesthesiol Taiwan 2012;50:172–7
41. De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. CNS Neurosci Ther 2013;19:403–10
42. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg 2012;115:934–43
43. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Hudetz AG, Pagel PS, Warltier DC. Ketamine attenuates postoperative cognitive dysfunction after cardiac surgery. Acta Anaesthesiol Scand 2009;53:864–72
44. Zhu MM, Zhou QH, Zhu MH, Rong HB, Xu YM, Qian YN, Fu CZ. Effects of nebulized ketamine on allergen-induced airway hyperresponsiveness and inflammation in actively sensitized Brown-Norway rats. J Inflamm (Lond) 2007;4:10
45. Bruehl S. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology 2010;113:713–25
46. Coderre TJ, Bennett GJ. A hypothesis for the cause of complex regional pain syndrome-type I (reflex sympathetic dystrophy):

pain due to deep-tissue microvascular pathology. Pain Med 2010;11:1224–38
47. Carlton SM, Hargett GL, Coggeshall RE. Localization and activation of glutamate receptors in unmyelinated axons of rat glabrous skin. Neurosci Lett 1995;197:25–8
48. Zhou S, Bonasera L, Carlton SM. Peripheral administration of NMDA, AMPA or KA results in pain behaviors in rats. Neuroreport 1996;7:895–900
49. Davidson EM, Coggeshall RE, Carlton SM. Peripheral NMDA and non-NMDA glutamate receptors contribute to nociceptive behaviors in the rat formalin test. Neuroreport 1997;8:941–6
50. Davidson EM, Carlton SM. Intraplantar injection of dextrorphan, ketamine or memantine attenuates formalin-induced behaviors. Brain Res 1998;785:136–42
51. Oatway M, Reid A, Sawynok J. Peripheral antihyperalgesic and analgesic actions of ketamine and amitriptyline in a model of mild thermal injury in the rat. Anesth Analg 2003;97:168–73
52. Warncke T, Jørum E, Stubhaug A. Local treatment with the N-methyl-D-aspartate receptor antagonist ketamine, inhibits development of secondary hyperalgesia in man by a peripheral action. Neurosci Lett 1997;227:1–4
53. Pedersen JL, Galle TS, Kehlet H. Peripheral analgesic effects of ketamine in acute inflammatory pain. Anesthesiology 1998;89:58–66
54. Koppert W, Zeck S, Blunk JA, Schmelz M, Likar R, Sittl R. The effects of intradermal fentanyl and ketamine on capsaicin-induced secondary hyperalgesia and flare reaction. Anesth Analg 1999;89:1521–7
55. Gottrup H, Bach FW, Arendt-Nielsen L, Jensen TS. Peripheral lidocaine but not ketamine inhibits capsaicin-induced hyperalgesia in humans. Br J Anaesth 2000;85:520–8
56. Gottrup H, Bach FW, Jensen TS. Differential effects of peripheral ketamine and lidocaine on skin flux and hyperalgesia induced by intradermal capsaicin in humans. Clin Physiol Funct Imaging 2004;24:103–8
57. Tverskoy M, Oren M, Vaskovich M, Dashkovsky I, Kissin I. Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: a study in postoperative patients. Neurosci Lett 1996;215:5–8
58. Pöyhiä R, Vainio A. Topically administered ketamine reduces capsaicin-evoked mechanical hyperalgesia. Clin J Pain 2006;22:32–6
59. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. Pain 2009;146:18–25
60. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth 1981;53:805–10
61. Clements JA, Nimmo WS, Grant IS. Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. J Pharm Sci 1982;71:539–42
62. Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. Pain 2001;91:177–87
63. Wallace MS, Ridgeway B 3rd, Leung A, Schulteis G, Yaksh TL. Concentration-effect relationships for intravenous alfentanil and ketamine infusions in human volunteers: effects on acute thresholds and capsaicin-evoked hyperpathia. J Clin Pharmacol 2002;42:70–80
64. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010;9:807–19
65. von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron 2012;73:638–52
66. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T; European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113–e88
67. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2010;85:S3–14
68. Mick G, Correa-Illanes G. Topical pain management with the 5% lidocaine medicated plaster–a review. Curr Med Res Opin 2012;28:937–51
69. Haanpää M, Treede RD. Capsaicin for neuropathic pain: linking traditional medicine and molecular biology. Eur Neurol 2012;68:264–75
70. Ushida T, Tani T, Kanbara T, Zinchuk VS, Kawasaki M, Yamamoto H. Analgesic effects of ketamine ointment in patients with complex regional pain syndrome type 1. Reg Anesth Pain Med 2002;27:524–8
71. Quan D, Wellish M, Gilden DH. Topical ketamine treatment of postherpetic neuralgia. Neurology 2003;60:1391–2
72. Keppel Hesselink JM, Kopsky DJ. Intractable neuropathic pain due to ulnar nerve entrapment treated with cannabis and ketamine 10%. J Clin Anesth 2012;24:78–9
73. Lynch ME, Clark AJ, Sawynok J. A pilot study examining topical amitriptyline, ketamine, and a combination of both in the treatment of neuropathic pain. Clin J Pain 2003;19:323–8
74. Barros GA, Miot HA, Braz AM, Ramos F, Borges MA. Topical (S)-ketamine for pain management of postherpetic neuralgia. An Bras Dermatol 2012;87:504–5
75. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Anesthesiology 2005;103:140–6
76. Mahoney JM, Vardaxis V, Moore JL, Hall AM, Haffner KE, Peterson MC. Topical ketamine cream in the treatment of painful diabetic neuropathy: a randomized, placebo-controlled, double-blind initial study. J Am Podiatr Med Assoc 2012;102:178–83
77. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. J Pain 2005;6:644–9
78. Lockhart E. Topical combination of amitriptyline and ketamine for post herpetic neuralgia. J Pain 2004;5:S82
79. Everton D, Bhagwat D, Damask M: A multicenter, double-blind, randomized, placebo controlled study of the efficacy/safety of two doses of amitriptyline/ketamine topical cream in treating post-herpetic neuralgia (PHN). J Pain 2007;8:S47
80. Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD 3rd, Kugler JW, Hoff KL, Reddy PS, Rowland KM Jr, Riepl M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer 2011;19:833–41
81. Uzaraga I, Gerbis B, Holwerda E, Gillis D, Wai E. Topical amitriptyline, ketamine, and lidocaine in neuropathic pain caused by radiation skin reaction: a pilot study. Support Care Cancer 2012;20:1515–24
82. Sandroni P, Davis MD. Combination gel of 1% amitriptyline and 0.5% ketamine to treat refractory erythromelalgia pain: a new treatment option? Arch Dermatol 2006;142:283–6
83. Poterucha TJ, Weiss WT, Warndahl RA, Rho RH, Sandroni P, Davis MD, Murphy SL. Topical amitriptyline combined with ketamine for the treatment of erythromelalgia: a retrospective study of 36 patients at Mayo Clinic. J Drugs Dermatol 2013;12:308–10
84. Lehman JS, Sciallis GF. Effective use of topical amitriptyline hydrochloride 2.5% and ketamine hydrochloride 0.5% for analgesia in refractory proctodynia. J Drugs Dermatol 2008;7:887–9
85. Poterucha TJ, Murphy SL, Rho RH, Sandroni P, Warndahl RA, Weiss WT, Davis MD. Topical amitriptyline-ketamine for treatment of rectal, genital, and perineal pain and discomfort. Pain Physician 2012;15:485–8
86. Poterucha TJ, Murphy SL, Davis MD, Sandroni P, Rho RH, Warndahl RA, Weiss WT. Topical amitriptyline-ketamine for the treatment of brachioradial pruritus. JAMA Dermatol 2013;149:148–50
87. Poterucha TJ, Murphy SL, Sandroni P, Rho RH, Warndahl RA, Weiss WT, Davis MD. Topical amitriptyline combined with topical ketamine for the management of recalcitrant localized

pruritus: a retrospective pilot study. J Am Acad Dermatol 2013;69:320–1
88. Kopsky DJ, Keppel Hesselink JM. Multimodal stepped care approach involving topical analgesics for severe intractable neuropathic pain in CRPS type 1: a case report. Case Rep Med 2011;2011:319750
89. Keppel Hesselink JM, Kopsky DJ. Treatment of chronic regional pain syndrome type 1 with palmitoylethanolamide and topical ketamine cream: modulation of nonneuronal cells. J Pain Res 2013;6:239–45
90. Zur E. Topical treatment of neuropathic pain using compounded medications. Clin J Pain 2014;30:73–91
91. Heir G, Karolchek S, Kalladka M, Vishwanath A, Gomes J, Khatri R, Nasri C, Eliav E, Ananthan S. Use of topical medication in orofacial neuropathic pain: a retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:466–9
92. Tam E, Furlan AD. Transdermal lidocaine and ketamine for neuropathic pain: a study of effectiveness and tolerability. Open Neurol J 2012;6:58–64
93. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. Curr Med Res Opin 2009;25:1663–76
94. Binder A, Bruxelle J, Rogers P, Hans G, Bösl I, Baron R. Topical 5% lidocaine (lignocaine) medicated plaster treatment for post-herpetic neuralgia: results of a double-blind, placebo-controlled, multinational efficacy and safety trial. Clin Drug Investig 2009;29:393–408
95. Sawynok J. Topical analgesics for neuropathic pain: Preclinical exploration, clinical validation, future development. Eur J Pain 2014;18:465–81
96. Mankovsky T, Lynch M, Clark A, Sawynok J, Sullivan MJ. Pain catastrophizing predicts poor response to topical analgesics in patients with neuropathic pain. Pain Res Manag 2012;17:10–4
97. Slatkin NE, Rhiner M. Topical ketamine in the treatment of mucositis pain. Pain Med 2003;4:298–303
98. Canbay O, Celebi N, Sahin A, Celiker V, Ozgen S, Aypar U. Ketamine gargle for attenuating postoperative sore throat. Br J Anaesth 2008;100:490–3
99. Rudra A, Ray S, Chatterjee S, Ahmed A, Ghosh S. Gargling with ketamine attenuates the postoperative sore throat. Indian J Anaesth 2009;53:40–3
100. Chan L, Lee ML, Lo YL. Postoperative sore throat and ketamine gargle. Br J Anaesth 2010;105:97
101. Shrestha SK, Bhattarai B, Singh J. Ketamine gargling and postoperative sore throat. JNMA J Nepal Med Assoc 2010;50:282–5
102. Canbay O, Celebi N, Uzun S, Sahin A, Celiker V, Aypar U. Topical ketamine and morphine for post-tonsillectomy pain. Eur J Anaesthesiol 2008;25:287–92
103. Tekelioglu UY, Apuhan T, Akkaya A, Demirhan A, Yildiz I, Simsek T, Gok U, Kocoglu H. Comparison of topical tramadol and ketamine in pain treatment after tonsillectomy. Paediatr Anaesth 2013;23:496–501
104. Dal D, Celebi N, Elvan EG, Celiker V, Aypar U. The efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy. Paediatr Anaesth 2007;17:263–9
105. Honarmand A, Safavi MR, Jamshidi M. The preventative analgesic effect of preincisional peritonsillar infiltration of two low doses of ketamine for postoperative pain relief in children following adenotonsillectomy. A randomized, double-blind, placebo-controlled study. Paediatr Anaesth 2008;18:508–14