

# Bottlenecks in the development of topical analgesics: molecule, formulation, dose-finding, and phase III design

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**Abstract:** Topical analgesics can be defined as topical formulations containing analgesics or co-analgesics. Since 2000, interest in such formulations has been on the rise. There are, however, four critical issues in the research and development phases of topical analgesics: 1) The selection of the active pharmaceutical ingredient. Analgesics and co-analgesics differ greatly in their mechanism of action, and it is required to find the most optimal fit between such mechanisms of action and the pathogenesis of the targeted (neuropathic) pain. 2) Issues concerning the optimized formulation. For relevant clinical efficacy, specific characteristics for the selected vehicle (eg, cream base or gel base) are required, depending on the physicochemical characteristics of the active pharmaceutical ingredient(s) to be delivered. 3) Well-designed phase II dose-finding studies are required, and, unfortunately, such trials are missing. In fact, we will demonstrate that underdosing is one of the major hurdles to detect meaningful and statistically relevant clinical effects of topical analgesics. 4) Selection of clinical end points and innovatively designed phase III trials. End point selection can make or break a trial. For instance, to include numbness together with tingling as a composite end point for neuropathic pain seems stretching the therapeutic impact of an analgesic too far. Given the fast onset of action of topical analgesics (usually within 30 minutes), enrichment designs might enhance the chances for success, as the placebo response might decrease. Topical analgesics may become promising inroads for the treatment of neuropathic pain, once sufficient attention is given to these four key aspects.

**Keywords:** topical, analgesics, cream, gel, dose-finding, formulation, ketamine, amitriptyline, baclofen, enrichment

## Introduction

In this article, we will review four critical issues related to the research and development of topical formulations containing analgesics such as amitriptyline, phenytoin, ketamine, and baclofen in neuropathic pain. They are as follows: the selection of the analgesic proper, formulation issues, dose-finding aspects, and phase III, especially related to the selected clinical end points. There are a number of advantages of using topical analgesics over oral analgesics, such as the following:

1. Local application only on the pain area where relief is needed
2. Fast onset of action
3. Higher concentration of the analgesic in the pain area
4. Low or no systemic drug levels
5. Absence of systemic side effects

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6. Absence of drug–drug interactions
7. Ease of implementing in multimodal therapies
8. Ease of combining more analgesics in one vehicle to obtain synergies
9. Improvement of compliance
10. No risk of dependency or abuse

The fundamentals enabling the development of topical analgesic formulations were identified at the end of the last century. The first hints of the efficacy of such topical formulations can be found in an article from 1981, where topical alcoholic solutions containing 5% amitriptyline or 5% doxepin were found to be effective against experimentally induced pruritus.<sup>1</sup> Somewhat later, there were also some indications that tricyclic antidepressants (TCAs) could exert an analgesic effect via a peripheral mechanism of action, as TCAs could inhibit inflammatory pain in arthritis models.<sup>2</sup> Subsequent experiments to determine the analgesic mechanism of action of clomipramine in a rat model for inflammation (inflamed carrageenan paw model) excluded peripheral mechanisms.<sup>3</sup> Though, further experiments from different groups supported a peripheral mechanism of action of TCAs, and thus a neurophysiological foundation for the use of topical creams containing TCAs emerged.<sup>4,5</sup> In 1999, on the basis of these experiments, it was suggested that such findings supported the development of cream formulations against pain due to the fact that such creams could increase the local concentration of amitriptyline without increasing the plasma levels, leading to systemic side effects.<sup>6,7</sup> The peripheral mechanisms of action of TCAs could be understood while observing the receptor affinities of the TCAs. For example, amitriptyline acts on many targets in the skin; it blocks Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>2+</sup> voltage-gated ion channels as well as the muscarinic, cholinergic, nicotinic, histaminergic,  $\alpha^2$ -adrenergic, opioid, adenosine, and *N*-methyl-d-aspartate receptors.<sup>8</sup> The fact that peripheral mechanisms contribute to neuropathic pain and that locally applied active pharmaceutical ingredient (API) could reduce such pain led to clinical trials to support the development of topical analgesics for the treatment of neuropathic pain.<sup>9</sup> The documented therapeutic effects of capsaicin and lidocaine in neuropathic pain further supported the case for exploring the targeting of peripheral pathomechanisms in neuropathic pain.<sup>10,11</sup> The complex interactions between nociceptors, immunocompetent cells, and epithelial cells, creating a pathogenetic network in neuropathic pain, support the use and evaluation of combining different APIs in topical formulations to target these three components.<sup>12,13</sup> As there are again a multitude of pharmacological targets related to these components, topical formulations containing a rational

selection of a number of APIs are in need of in-depth evaluation. Here, we need to also clarify regulatory hurdles, as the competent authorities European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), in general, recommend proving efficacy and safety for one API at a time. This suggests that when developing a topical formulation with two or more APIs, the combination should be better compared to the single topical APIs. Such a philosophy is not optimal because even combinations between one established active drug together with another drug that on its own accord would not lead to efficacy can result in a superior therapeutic principle owing to synergistic mechanisms. Single compound approaches might have worked in the past for a number of disorders, although for the treatment of complex disorders based on interactive networks of factors, we definitely need combinations of drugs to enhance the chances of finding a good therapeutic response. Many studies examining oral medication for neuropathic pain support combination of analgesics of different classes.<sup>14–17</sup> Nevertheless, some case studies and clinical trials have already supported the efficacy and safety of creams or gels containing one API only; we will discuss, for the sake of simplicity, in this article only topical formulations containing phenytoin, ketamine, amitriptyline, and/or baclofen alone or as combinations. These drugs act on many different targets (eg, NMDA receptors, ion channels, and GABA<sub>B</sub> receptors) located on dermal cells such as nerve endings, keratinocytes, and immunocompetent cells, and this may enhance the chances of synergism.<sup>8,18,19</sup>

However, since some conflicting results have been reported in this field, we will raise four critical issues that are not often considered in clinical trials on the efficacy and safety of topical analgesics published so far.

## First patent on topical formulations containing ketamine and amitriptyline

Patents are interesting and important sources to study issues related to drug development, as formulations selected are specified and, mostly, a rationale is given for the key aspects of the invention. The first patent in the field of topical formulations of TCAs and of ketamine, priority date of September 22, 1995, is “The preparation of topical regional compositions for the relief of pain” (patent WO 1997/010815). In this patent, a number of vehicles were claimed, such as lecithin composition, aloe vera gel, cocoa butter, aquafor, petroleum jelly, and/or a standard cold cream. The preferred base in this patent was a lecithin matrix gel. The selection was based on its ability to enhance transport of the API across the dermis

and into the tissues below to exert the effects of these agents on the nerves in the region below the site of application. A clinical trial was performed in 34 patients using three different APIs, alone or in combination, in preparations of lecithin matrix gels. The contents of these compositions were placebo (with no APIs), a composition containing ketamine 0.5%, a composition containing amitriptyline 0.05%, a composition containing guanethidine 0.05%, a composition containing a combination of ketamine 0.5% and amitriptyline 0.05%, and a composition containing a combination of ketamine 0.5% and guanethidine 0.05%. A total of 97% of the patients achieved >50% reduction in their rest pain 2–3 hours following application of lecithin matrix gel containing the combination of 0.5% ketamine plus 0.05% amitriptyline. In the placebo arm, none of the patients reported more than a 20% pain reduction. The ketamine 0.5% composition produced significant pain relief in 82% of patients at 2 hours and 62% at 3 hours following application. The data, however, were never published. In this patent, we can identify two key issues that we will discuss in more detail in the sections that follow:

1. The absence of dose finding: only one dose was defined for each compound (amitriptyline 0.05% and ketamine 0.5%)
2. No testing for the suitability of various vehicles: lecithin matrix gel was chosen without justification

## Selecting the API

The selection of the API is one of the key issues leading to success or failure of any topical drug formulation. Analgesics and co-analgesics differ greatly in their mechanism of action and their physicochemical properties, and it is mandatory to find the most optimal fit between such aspects and the pathogenesis of the targeted neuropathic pain. Furthermore, the physicochemical properties of any API selected for a topical formulation (eg, whether the molecule selected is hydrophilic, lipophilic, or amphoteric) will strongly influence the choice of a proper vehicle. The concentration of an API can influence the stability of the formulation.<sup>20</sup>

Remarkably, a specific analysis of the pathogenesis of a certain type of neuropathic pain and the mechanisms of action of a selected API is often missing in the literature. The pathogenesis of pain in hereditary motor and sensory neuropathies, and in diabetic neuropathy, and pain due to small fiber neuropathy (SFN) will perhaps have some similarities, but most probably more differences.<sup>21</sup> For instance, we have found that SFN pain patients, in which pathology resides mainly in the skin, are good responders to phenytoin

cream. Elsewhere, we have outlined the pathogenesis of neuropathic pain syndromes related to the skin, pointing out the pathological triad of keratinocytes, immune-competent cells, and nociceptors targeted by topical creams containing sodium channel blockers such as phenytoin.<sup>22,23</sup>

Many more pathophysiological mechanisms can be involved in the development and maintenance of a specific neuropathic pain syndrome. For example, for both capsaicin and lidocaine plasters, the approved indication is postherpetic neuralgia. The two APIs have entirely different mechanisms of action and thus influence different parts of the multifactorial pathophysiological mechanism. It would therefore not be surprising that synergism might occur when combined together. However, both in the preclinical models for neuropathic pain and in clinical trials, a rational approach to the analysis of optimal combinations is missing.

First, a good match is needed between the selected APIs and the indication. There are a multitude of neuropathic pain states, which most certainly differ in pathogenesis. SFN in sarcoidosis will have many different pathogenetic characteristics compared to chemotherapy-induced peripheral neuropathy (CIPN), and diabetic neuropathy will differ from postherpetic neuropathy and chronic inflammatory demyelinating polyradiculoneuropathy. For instance, many inflammatory markers are upregulated in the skin of chronic inflammatory demyelinating polyradiculoneuropathy patients, just as in Lyme disease, but not in the skin of diabetic patients.<sup>24</sup> The same holds true for complex regional pain syndrome (CRPS), where keratinocyte and mast cell activation and proliferation as well as inflammatory mediator release can be found in the skin.<sup>25</sup> In diabetes patients, the epidermal neuropilin-1 receptor expression is high in the epidermal layer of diabetic subjects suffering from polyneuropathy, compared to controls. Neuropilin-1 receptor trafficking toward the membranes of all epidermal cells in diabetes might play an important role in the development of SFN.<sup>26</sup> An understanding of the exact pathogenesis in the skin in a variety of neuropathic pain syndromes is still preliminary, but, clearly, it will differ considerably in various syndromes. Topical ketamine and/or clonidine, for instance, might be more suitable and more directly linked to the pathogenesis in CRPS compared to topical baclofen.<sup>27–30</sup> Second, the selected end points can make or break the study. In the amitriptyline-ketamine study, the primary analysis as defined in the protocol was an analysis of covariance (ANCOVA) to assess changes in pain, numbness, and tingling from baseline to week 6.<sup>31</sup> To expect analgesics to influence numbness, without any indications of such an effect from past studies, seems unrealistic. The selection of

allodynia in CRPS patients for a study evaluating the effects of topical ketamine alone or in combination with other APIs would be a better example of how to handle issues related to the selection of end points.<sup>29,30</sup>

## Optimization of formulation

In the literature, pharmaceutical aspects related to the selected topical formulation with APIs, such as ketamine, amitriptyline, and baclofen, are, with only a few exceptions, not described in detail. We will discuss two of those examples to illustrate that even seemingly comparable formulations, based on pluronic organogels, can differ owing to different ways of preparation. The first description is from a case report. Here, the composition of amitriptyline 7.5% gel was applied to a depressed patient who could not tolerate orally administered amitriptyline.<sup>32</sup> A transdermal preparation was compounded with a Pluronic Lecithin Organogel (PLO) base. The recipe was given in the study: a solution was prepared by dissolving soy lecithin granules in isopropyl palmitate. A 20% water-based gel was prepared by dissolving pluronic F-127 (Sigma Aldrich, St Louis, MO, USA) in distilled water. Amitriptyline was then dissolved in the liquid pluronic F-127 gel, and the resulting mixture was added to the lecithin-isopropyl palmitate. These two were stirred vigorously to form a gel. Apparently, this study might have set the standard for compounding topical amitriptyline formulations on the base of PLO. However, the goal of this gel was to create clinically relevant plasma levels, and with success: serum amitriptyline and nortriptyline concentrations were reported as total tricyclic concentrations were within the therapeutic range: 50–250 ng/mL.

A second recipe of a PLO gel can be found in the description of a ketamine 5% gel: soybean lecithin granules were mixed with 150 mL isopropyl palmitate. The mixture was stirred for at least 12 hours until a uniformly dark, amber-colored solution was obtained. Ketamine (10 mL; Ketalar [Parke-Davis (India) Ltd., Mumbai, India], 50 mg/mL) was added to reach a final concentration of 5 mg ketamine/mL gel.<sup>33</sup> It remains quite unclear; however, why this gel formulation was selected as a base vehicle for ketamine. Lecithin organogel has certain physicochemical properties enabling the dissolution of lipophilic, hydrophilic, and amphoteric molecules, and these gels are regarded as suitable for transdermal transport of APIs.<sup>34</sup> The fact that PLO described in the first case noted earlier did indeed lead to high amitriptyline plasma concentrations indicates its use for transdermal absorption for APIs. Furthermore, no information was given

on aspects such as the stability or pH of the selected PLO or on the convenience after application on the skin. If we compare the recipes of both PLOs, we can see that although both approaches lead to a PLO, the procedures are quite different, and thus the pharmaceutical and physicochemical properties of the gels might also be different, possibly leading to different clinical effects.

In a placebo-controlled study, 17 patients were randomized into either the treatment ketamine 5% cream or placebo cream.<sup>35</sup> The selected vehicle was based on Aquaphor gel, and subsequently the gel was compounded into a cream. Also here, no further details related to pH or stability were given. Neither was there any explanation why this specific base was selected. The effect of the placebo was as robust as the effect of the ketamine 5% cream.

In a recent pivotal trial with 462 patients, evaluating the efficacy and safety of a combination of 2% ketamine and 4% amitriptyline cream for reducing CIPN symptoms, no details were given on the selected cream base (nor a rationale for the selected dose).<sup>31</sup> The study was negative, and without discussing formulation issues, the authors came to the conclusion that topical formulations containing amitriptyline together with ketamine are not recommended for reducing CIPN symptoms. This is an example of jumping to conclusions in the absence of arguments related to key drug development issues such as the pharmaceutical properties and the requirements of the selected formulation.

A comparable randomized placebo-controlled trial in CIPN patients (n=203) for the efficacy and safety of baclofen 0.75%, amitriptyline 3%, and ketamine 1.5% in PLO was performed. The gel had 1-year stability data, but no rationale for the choice of this specific gel was given, nor a detailed composition.<sup>36</sup> The authors, however, indicated that the selected gel was not optimal: patients had difficulty in applying the gel owing to suboptimal smearability and poor absorption into their skin. The authors recommended using a different liposomal transdermal base in the future, making it easier for participants to rub the formulation into the skin. Whether transdermal absorption is indeed preferable compared to purely topical application was not further discussed.

Clearly, in none of the studies a thorough line of arguments was given to support the choice of the vehicle. In most cases, a PLO base was selected, although such a gel seems to induce patient compliance issues owing to lack of convenience in applying. No studies have ever been published comparing different vehicles. This comparison is also missing in the patents we reviewed.

## Phase II trial design and concentration

Which concentration should be selected for a topical formulation of an analgesic? It seems a simple question, but it is not, and one cannot throw a dice. In drug development, there is a generalized tendency to shortcut development lines and avoid full-powered dose-finding phase II trials. Such a flawed strategy, sadly enough, seems to be quite popular in the development of topical formulations. Such shortcuts, however, are always counterproductive, because the results of small trials are inconclusive, or because of false-positive findings one enters phase III without sufficient proof of principle.

In one of the first studies on topical formulations against pruritus, an alcoholic solution containing 5% amitriptyline or 5% doxepin was tested.<sup>1</sup> No reasons were given for the choice of concentration. Interestingly, doxepin 5% cream was registered by Xepin-Bioglan, Malmö, Sweden, and is included in the British National Formulary for the relief of itching associated with eczematous dermatitis – interesting, because we cannot find any published data to support the choice of concentration.

The analysis of the aforementioned development of the ketamine/amitriptyline and the baclofen/amitriptyline/ketamine formulations demonstrates a number of development flaws and shortcuts. The selection of a gel containing a maximum of 2% ketamine and 4% amitriptyline, with or without 0.75% baclofen, has not been backed up by sufficient dose-finding data. Or, to put it even more strongly, dose-finding data are missing. Related to the gel containing baclofen 0.75%, amitriptyline 3%, and ketamine 1.5%, the FDA apparently prohibited higher doses than initially proposed by the investigators owing to the lack of data on systemic absorption of this triple combination. Instead of starting a small study to evaluate the systemic absorption of the three components of the API combination gel, the authors followed the FDA specification and tested much lower concentrations of the APIs than initially proposed, although they had to know that most probably there was insufficient clinical data available to back up that specific low dose selection. Logically, by selecting a low dose for all active components, the study runs a great risk of ending as a negative study owing to underdosing. This was quite an expensive experiment leading to a new working hypothesis proposed by the authors: next time, select a higher concentration of APIs. This insight actually should have been clear from the beginning of the study.

A higher concentration might indeed have led to a better clinical effect, as documented earlier in a study on the

effects of topical ketamine 10% in allodynia in CRPS patients in a double-blind crossover placebo-controlled trial in 20 patients.<sup>29</sup> Ketamine reduced the allodynia significantly. Plasma levels of ketamine and its active metabolite norketamine were below the limits of detection after application.

## Phase III trial design and selection of primary end point

Apart from the issues discussed above, improvements in selecting the target indication, the end points, and other aspects of clinical trial design will contribute to the development of topical analgesics.

Owing to the fast onset of action of topical analgesics, responders can be identified quickly with a test application.<sup>37</sup> Meanwhile, we gathered experience using this responder identification method in our clinic. We test patients in a single-blind fashion, for instance patients suffering from SFN pain, by applying a finger-tip unit of placebo cream or the same amount of phenytoin 10% cream on burning and painful areas. Patients mostly indicate within 10 minutes a 50% reduction of baseline pain on phenytoin cream, while placebo cream does not lead to relevant pain reduction.

With this responder identification method, the most optimal API, the optimal concentration for a specific API, and various other formulations, can subsequently be tested in an enrichment design phase II study.<sup>38</sup> Also, combinations of APIs formulated in different bases can be tested by using a simple test design (blinded placebo or comparator-controlled crossover testing). This procedure can also be followed for a phase III study, an enrichment design strategy.<sup>39</sup> Before entering the study, patients will receive a test application with the analgesic cream. When the patient responds in a clinically meaningful way and reports relevant pain reduction, ie, a decrease of two points on the NRS or 33% pain reduction,<sup>40</sup> responders will be randomly assigned to the active arm or placebo arm, after baseline assessment. After applying the cream, patients will be assessed for a certain period again. To enhance the sensitivity of the clinical trial, a crossover design could be selected. After 1 week washout, patients receive the other cream. In this design also, an inpatient evaluation could be made. This type of enrichment randomized double-blind crossover trial is now being executed in the Netherlands for ketamine 10% cream and amitriptyline 10% cream.

## Conclusion

In evaluating the efficacy and safety of topical analgesics, many issues related to drug development are neglected. We pointed out the relevance of selecting the correct API, based

on the mechanisms of action of the API related to what we know about the pathogenesis of the neuropathic pain state. We also highlighted how details related to the pharmaceutical form are missing, dose-finding studies are missing, and the selection of end points and other aspects of clinical trial design are suboptimal. In order to test the efficacy and safety of an API such as phenytoin, amitriptyline, ketamine, or baclofen, one needs to compare the suitability of the selected vehicle in well-designed pilot trials. Furthermore, one cannot skip well-designed phase II studies in order to specifically define the active concentration range of the selected topical and the lowest effect dose. Such phase II studies need to be well powered, but seldom are. Most pilot studies are only suited for feasibility testing, whether one can find patients for inclusion, and whether the selected vehicle is acceptable and convenient for patients to “smear”. We presented a simple phase II test design in a limited group of patients (blinded placebo or comparator-controlled crossover n=1 testing) to quickly test the pain relief of various formulations and concentrations and compare and select the best. In addition to this explorative phase, we presented an enrichment design for a phase III study to decrease placebo responses and increase the chances of finding and including responders. Within this context, we developed a quick single-blinded responder identification method as a key element for such an enrichment study.

Topical analgesics are promising inroads for the treatment of neuropathic pain, once we learn to avoid development mistakes and shortcuts from the past.

## Disclosure

The authors JMKH and DJK are holders of two patents: 1) topical phenytoin for use in the treatment of peripheral neuropathic pain and 2) topical pharmaceutical composition containing phenytoin and a (co-)analgesic for the treatment of chronic pain. The authors report no other conflicts of interest in this work.

## References

- Bernstein JE, Whitney DH, Soltani K. Inhibition of histamine-induced pruritus by topical tricyclic antidepressants. *J Am Acad Dermatol*. 1981;5(5):582–585.
- Butler SH, Weil-Fugazza J, Godefroy F, Besson JM. Reduction of arthritis and pain behaviour following chronic administration of amitriptyline or imipramine in rats with adjuvant-induced arthritis. *Pain*. 1985; 23(2):159–175.
- Ardid D, Eschalier A, Lavarenne J. Evidence for a central but not a peripheral analgesic effect of clomipramine in rats. *Pain*. 1991;45(1): 95–100.
- Su X, Gebhart GF. Effects of tricyclic antidepressants on mechanosensitive pelvic nerve afferent fibers innervating the rat colon. *Pain*. 1998; 76(1–2):105–114.
- Sawynok J, Reid AR, Esser MJ. Peripheral antinociceptive action of amitriptyline in the rat formalin test: involvement of adenosine. *Pain*. 1999;80(1–2):45–55.
- Esser MJ, Sawynok J. Acute amitriptyline in a rat model of neuropathic pain: differential symptom and route effects. *Pain*. 1999;80(3):643–653.
- Sawynok J, Esser MJ, Reid AR. Peripheral antinociceptive actions of desipramine and fluoxetine in an inflammatory and neuropathic pain test in the rat. *Pain*. 1999;82(2):149–158.
- Kopsky DJ, Hesselink JM. High doses of topical amitriptyline in neuropathic pain: two cases and literature review. *Pain Pract*. 2012;12(2): 148–153.
- 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(5):323–328.
- Rains C, Bryson HM. Topical capsaicin. A review of its pharmacological properties and therapeutic potential in post-herpetic neuralgia, diabetic neuropathy and osteoarthritis. *Drugs Aging*. 1995;7(4):317–328.
- Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*. 1999;80(3):533–538.
- Keppel Hesselink JM, Kopsky DJ, Sajben N. New topical treatment of vulvodinia based on the pathogenetic role of cross talk between nociceptors, immunocompetent cells, and epithelial cells. *J Pain Res*. 2016; 9:757–762.
- Keppel Hesselink JM, Kopsky DJ. Topical analgesic creams and nociception in diabetic neuropathy: towards a rationale fundament. *Clin Case Rep Rev*. 2016;2(7):500–502.
- Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet*. 2009;374(9697):1252–1261.
- Gilron I, Baily J, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352(13):1324–1334.
- Gilron I, Chaparro LE, Tu D. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. *Pain*. 2016; 157(7):1532–1540.
- Gilron I, Tu D, Holden RR, Jackson AC, DuMerton-Shore D. Combination of morphine with nortriptyline for neuropathic pain. *Pain*. 2015; 156(8):1440–1448.
- Kopsky DJ, Keppel Hesselink JM, Bhaskar A, Hariton G, Romanenko V, Casale R. Analgesic effects of topical ketamine. *Minerva Anesthesiol*. 2015;81(4):440–449.
- Kopsky DJ, Keppel Hesselink JM. Neuropathic pain as a result of acromegaly, treated with topical baclofen cream. *J Pain Symptom Manage*. 2013;46(4):e4–e5.
- Mugglestone CJ, Mariz S, Lane ME. The development and registration of topical pharmaceuticals. *Int J Pharm*. 2012;435(1):22–26.
- Vanotti A, Osio M, Mailland E, Nascimbene C, Capiluppi E, Mariani C. Overview on pathophysiology and newer approaches to treatment of peripheral neuropathies. *CNS Drugs*. 2007;21:3–12.
- Kopsky DJ, Keppel Hesselink JM. Topical phenytoin for the treatment of neuropathic pain. *J Pain Res*. 2017;10:469–473.
- Keppel Hesselink JM, Kopsky DJ, Bhaskar AK. Skin matters! The role of keratinocytes in nociception: a rational argument for the development of topical analgesics. *J Pain Res*. 2016;10:1–8.
- Lee G, Xiang Z, Brannagan TH 3rd, Chin RL, Latov N. Differential gene expression in chronic inflammatory demyelinating polyneuropathy (CIDP) skin biopsies. *J Neurol Sci*. 2010;290(1–2):115–122.
- Birklein F, Drummond PD, Li W, et al. Activation of cutaneous immune responses in complex regional pain syndrome. *J Pain*. 2014;15(5): 485–495.
- Van Acker N, Ragé M, Vermeirsch H. NRP-1 Receptor expression mismatch in skin of subjects with experimental and diabetic small fiber neuropathy. *PLoS One*. 2016;11(9):e0161441.
- Drummond ES, Maker G, Birklein F, Finch PM, Drummond PD. Topical prazosin attenuates sensitivity to tactile stimuli in patients with complex regional pain syndrome. *Eur J Pain*. 2016;20(6):926–935.
- 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;6:239–245.

29. 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(1–2):18–25.
30. Russo MA, Santarelli DM. A novel compound analgesic cream (Ketamine, Pentoxifylline, Clonidine, DMSO) for complex regional pain syndrome patients. *Pain Pract*. 2016;16(1):E14–E20.
31. Gewandter JS, Mohile SG, Heckler CE, et al. A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study of 462 cancer survivors. *Support Care Cancer*. 2014;22(7):1807–1814.
32. Scott MA, Letrent KJ, Hager KL, Burch JL. Use of transdermal amitriptyline gel in a patient with chronic pain and depression. *Pharmacotherapy*. 1999;19(2):236–239.
33. Quan D, Wellish M, Gilden DH. Topical ketamine treatment of postherpetic neuralgia. *Neurology*. 2003;60(8):1391–1392.
34. Willimann H, Walde P, Luisi PL, Gazzaniga A, Stroppolo F. Lecithin organogel as matrix for transdermal transport of drugs. *J Pharm Sci*. 1992; 81(9):871–874.
35. 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(3):178–183.
36. Barton DL, Wos EJ, Qin R, et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer*. 2011;19(6): 833–841.
37. Kopsky DJ. Extending the therapeutic scope for the treatment of neuropathic pain with topical analgesics. *J Pain Relief*. 2016;5(3):251–252.
38. Keppel Hesselink JM. Thinking out of the pillbox: the relevance to topicals in the treatment of neuropathic pain. *J Pain Relief*. 2016;6(5):1–3.
39. Dworkin RH, Turk DC, Peirce-Sandner S. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2010;149(2):177–193.
40. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain*. 2000; 88(3):287–294.

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