Vehicles and Formulas:

Neuropathic Pain Review

Sarah Taylor, PharmD
Updated February 2025

Neuropathic pain impacts a large number of middle age and older adults. Specific prevalence data is difficult to come by, but one large cross-sectional analysis of patients from the UK suggests a prevalence of 7-10% in the general population and 20-30% in those with diabetes.[1] These estimates may increase in the future given that some researchers link COVID-19 with an increase in neurological complications including neuropathic pain.[2] Neuropathic pain refers to pain arising from the nervous system and is commonly caused by conditions such as diabetes, viral infection, medications (such as chemotherapy medications), surgery, stroke, and spinal cord injury among other factors.[1,2] First-line treatments for neuropathic pain typically involve oral tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), or gabapentinoids. Alternative treatments when these options fail include serotonin specific reuptake inhibitors (SSRIs), N-methyl-D-aspartate (NMDA) receptor antagonists, and even opioid pain medications.[3] For those who are not sufficiently treated on first-line therapies or for whom systemic medications are not desired for safety or efficacy reasons, topical treatment is often considered.

Given the adverse effect profile of medications such as TCAs, SNRIs, and gabapentinoids, some patients cannot take or choose to avoid these options as systemic therapies. For these patient groups topical preparations are sometimes considered. Unfortunately, commercially available topical options for neuropathic pain are limited. Lidocaine and capsaicin are both available in FDA approved topical forms for the treatment of neuropathic pain and diclofenac sodium or doxepin HCl topical products are also sometimes used off label for neuropathic pain. For patients for whom these options do not satisfactorily address pain, compounded options (especially in combination) are sometimes considered. Though combination topical pain creams are commonly prescribed for the management of conditions such as neuropathic pain, they have recently come under scrutiny given the *Compounding Topical Pain Creams: Review of Select Ingredients for Safety, Efficacy, and Use* published in 2020 by the National Academies of Sciences, Engineering, and Medicine and analyzed by the FDA. The report concludes that given limited evidence caution must be considered by prescribing physicians when writing for compounded pain medications.[4] Given this increased scrutiny, a review of evidence-based treatments is essential. Small studies and case reports often give conflicting information or are difficult to extrapolate and draw conclusions from. This review will focus mainly on available high-quality data, such as randomized controlled trials where available.

Active ingredients with a relatively robust body of evidence regarding topical use for pain include ketamine and amitriptyline. Ketamine is an NMDA receptor antagonist that also inhibits reuptake of norepinephrine and 5-hydroxytryptamine. The inhibition of these receptors helps to prevent sensitization and activation responses.[5] Amitriptyline is a TCA that inhibits reuptake of norepinephrine and serotonin in the central nervous system and may impact NMDA as well.[6] Efficacy of ketamine and amitriptyline for management of neuropathic pain may be dose related. One high quality randomized, double-blind, placebo-controlled trial comparing placebo to 2%

amitriptyline, 1% ketamine, and combination 2% amitriptyline and 1% ketamine (4mL applied three times daily) did not find statistically significant benefit between groups. Another similar study looked at higher concentrations did note benefit. This randomized placebo-controlled trial first treated patients with 4% amitriptyline and 2% ketamine for 1 week. Of the 250 patients in the trial 52% were considered responders to the cream. This group was then subdivided into three groups, one continuing to receive 4% amitriptyline and 2% ketamine, another receiving a lower concentration of 2% amitriptyline and 1% ketamine, and a third receiving placebo. The study found that the percentage of subjects reporting 30% or superior reduction in pain was 46% in the higher dose group, 26% in the lower dose group, and 19% in the placebo group. The difference between higher dose and lower dose therapy was statistically significant (suggesting dose related efficacy) and plasma levels were detected in less than 10% of subjects. Those that did have detectable levels still had levels far below what would be considered therapeutic, suggesting a superior safety profile for transdermal use as compared to oral use.[7] Another high quality double-blind, placebo-controlled trial of baclofen 10mg, amitriptyline 40mg, and ketamine 20mg in pluronic lecithin organogel (PLO) applied twice daily found statistically significant improvement in chemotherapy-induced peripheral neuropathy without evidence of systemic toxicity. The authors originally intended to test with the application of 60mg amitriptyline, 30mg ketamine, and 30mg baclofen, but ended up using a lower concentration due to direction from the FDA. The authors hypothesize that a larger treatment effect may be possible with a higher dose of applied drug.[8] Another study of 2% ketamine and 4% amitriptyline had patients apply up to 4g applied twice daily for chemotherapy-induced peripheral neuropathy. This study did report improved pain, numbness, and tingling scores with the treatment group, but the results did not reach the level of statistical significance.[9] It is possible that standardizing the amount applied (given that patients were permitted to apply however much cream they desired so long as it was 4g or less) may impact reported outcome. The authors of this study state that concentration and dose may impact clinical benefit for this condition.[9]

Higher concentrations of ketamine as a solo agent have also been evaluated specifically for complex regional pain syndrome (CRPS). One double-blind placebo-controlled trial evaluated the safety and efficacy of ketamine 10% cream for reduction of allodynia in patients suffering from CRPS. In this study 20 patients applied ketamine 10% cream and found that allodynia decreased significantly after ketamine cream application. The study also checked plasma levels one hour after application of the cream and found them to be below detectable limits, suggesting that systemic ketamine absorption was not responsible for the noted clinical benefit.[10] Though results are not yet available, studies continue to investigate amitriptyline and ketamine for neuropathic pain. With one double-blind, placebo controlled, cross over study planning to evaluate higher strengths (amitriptyline 10% or ketamine 10%) vs placebo in neuropathic pain in the near future.[18]

In addition to being studied in combination with amitriptyline and ketamine, baclofen has also been studied as a solo agent for peripheral neuropathic pain. One placebo-controlled, double-blinded clinical trial evaluated baclofen 5% topical cream (applied twice daily) for management of diabetic peripheral neuropathy. After initial treatment and after treatment for the 3-week duration of the study those in the baclofen group scored better on the neuropathic pain diagnostic questionnaire as compared to placebo patients.[19] Other lower quality evidence has evaluated baclofen in combination products. A retrospective study evaluating baclofen 2%, ketamine 10%, gabapentin 6%, amitriptyline 4%, bupivacaine 2%, and clonidine 0.2% with or without nifedipine 2% found patients who used the preparation reported reduced pain score, reduced need for oral medications, and reduced need for referral to a pain specialist, though there was no significant difference between the cream with and the cream without nifedipine.[18,20] A case series evaluating a combination of baclofen 2% with diclofenac 5%, ibuprofen 2%, cyclobenzaprine 2%, bupivacaine 2%, gabapentin 6%, and pentoxifylline 1% (referred to as T7 by the authors) had patients suffering from radicular pain apply 1-2 grams 3-4 times daily.

Treated patients demonstrated a decrease in pain scores with treatment as well as a delay in the need for surgery.[18,21] Though the evidence on these multi-ingredient combinations with baclofen are promising, further high-quality data in the form of randomized placebo-controlled trials are needed to assess their efficacy.

Amitriptyline is not the only TCA evaluated for topical use for neuropathic pain. Doxepin, commercially available as a 5% topical product for management of conditions such as pruritus, has also been studied for neuropathic conditions. One large randomized, double-blind, placebo-controlled trial evaluated 3.3% doxepin HCl vs 0.025% capsaicin vs 3.3% doxepin and 0.025% capsaicin in combination for chronic neuropathic pain. Patients applied a small amount (the size of a grain of rice) topically three times daily. The study found similar pain control with all three treatments compared to placebo, though the combination treatment caused less burning and was associated with more rapid analgesia as compared to the individual treatments or placebo.[23]

Another ingredient evaluated in high quality studies for management of neuropathic pain includes clonidine. Clonidine is commercially available in an FDA approved patch form for management of hypertension for systemic API delivery, but no commercially available product for topical or local use exists. In addition to its benefit for hypertension, clonidine is thought to improve neuropathic pain as an alpha-2 adrenergic receptor agonist. These alpha-2 receptors are present on nociceptors in the epidermis, activation of these receptors is thought to play a role downstream in maintaining normal excitability of nociceptors, which are thought to be abnormally sensitized in neuropathic pain models. One randomized, double-blind, placebo-controlled, parallel-group trial had patients apply 0.1% clonidine gel or placebo three times daily for 12 weeks to evaluate efficacy for diabetic neuropathy of the feet. The study found a statistically significant benefit for pain as compared to the placebo group.[11] Other studies have evaluated varying strengths of clonidine for topical use. For example, one study of clonidine 0.1% or 0.2% vs placebo found benefit with both clonidine 0.1% and 0.2% over placebo. The study noted statistically significant benefit with the 0.1% treatment while the 0.2% group had improvement just shy of the desired p value, the authors attributed this potentially to the increased skin coverage with the 0.1% vs the 0.2% applied product. Clonidine was detected in the serum of patients, but levels were well below the threshold needed for treatment of hypertension, suggesting that topical clonidine has a favorable safety profile for treatment of neuropathic pain.[12]

Another double-blind randomized controlled study in a model of neuropathic pain (induced in healthy volunteers) found topical clonidine and pentoxifylline at low and high concentrations (0.04%/2% and 0.1%/5%) to improve allodynia compared to the placebo group and recommended the combination for further evaluation in patients with CRPS and neuropathic pain.[13] Pentoxifylline is thought to be beneficial for management of neuropathy via its ability to inhibit inflammatory cytokines such as tumor necrosis factor (TNF) alpha. Other combination products, such as the T7 combination discussed previously have added pentoxifylline for this proposed mechanism, but further randomized clinical controlled trials on pentoxifylline as a single ingredient for management of neuropathic pain are not available.[18,21]

Some medications commonly studied for neuropathic pain, such as gabapentin or pregabalin have been evaluated in a variety of randomized controlled trials and found effective for neuropathic pain such as postherpetic neuralgia.[14] Despite the robust evidence for oral use, there is limited high quality data to support topical use. Though some case studies and observational studies have evaluated gabapentin either in combination or as a solo treatment at concentrations typically ranging from 2-10% have noted benefit, high quality evidence on topical gabapentin specifically for neuropathic pain is not currently available.[15,18]

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac sodium are commonly used for management of a variety of pain conditions. One randomized, placebo-controlled, double-blinded trial of

diclofenac sodium 1.5% solution (20 to 40 drops applied three times daily) in patients with CRPS or postherpetic neuralgia found a decrease in burning pain and improved visual pain score.[16] Other NSAIDs such as ibuprofen, ketoprofen, or indomethacin transdermal among others may also be useful for management of neuropathic pain, but randomized controlled trials evaluating these medications specifically for neuropathic pain are not currently available.

Anesthetics such as lidocaine are FDA approved for topical use for neuropathic pain, though some high-quality studies have evaluated the efficacy of alternative strengths and formulations. One study on a topical lidocaine 8% spray for management of posttraumatic peripheral neuropathy evaluated a dose up to 3mL per application and found lidocaine to perform significantly better than placebo for management of pain and tactile allodynia for a median of up to 5 hours after application.[17]

Another API of interest for management of neuropathic pain is phenytoin. Phenytoin has been evaluated primarily in observational studies at concentrations ranging from 5-30% for neuropathic pain.[18] One single-blind, placebo-controlled trial of phenytoin 10% cream in patients with neuropathic pain found 71.45% of patients responded to the cream (noted a reduction in pain numerical score of at least 2 points on an 11 point scale within 30 minutes) and the absolute score was significantly reduced in the phenytoin group as compared to the placebo group. Even with this relatively high percentage of phenytoin, plasma levels were not detected at 1.5hrs or 3hrs after last application after 1-2 weeks of regular application.[22] A recently completed randomized placebo-controlled trial evaluated phenytoin at both 10 and 20% vs placebo for neuropathic pain, though results are not yet available.[24]

A wide variety of therapeutic agents with varied mechanisms of action are commonly utilized for topical management of neuropathic pain. However, of these agents only a limited subset have been studied in high quality clinical trials. Agents with data to support their use include ketamine, amitriptyline, doxepin, baclofen, diclofenac, pentoxifylline, capsaicin, lidocaine and phenytoin. When designing combination creams for patients suffering from neuropathic pain, the use of these agents should be considered.

Vehicle	Water Activity	Transdermal Use for Pain
Salt Stable LS Advanced	>0.6	Salt Stable LS Advanced is an extremely durable and robust transdermal cream base. Various APIs commonly used topically in pain preparations including diclofenac, ibuprofen, pentoxifylline, ketamine, gabapentin, clonidine, and baclofen among others have demonstrated transdermal potential in in vitro studies in Salt Stable LS Advanced. This vehicle is capable of holding common pain APIs in concentrations up to 40%.
Versatile Anhydrous	<0.6	Versatile Anhydrous allows for extended BUD up to 180 days for transdermal preparations given its water activity below 0.6. This vehicle contains penetration enhancers to improve delivery of various APIs into the skin and can tolerate high API load up to 50%.
Pentravan Plus	>0.6	Pentravan Plus is a medium API load transdermal cream base. The Pentravan line has demonstrated transdermal potential in numerous peer reviewed publications with a variety of APIs including some commonly used in topical pain preparations such as ketoprofen. This vehicle is capable of holding common pain APIs in concentrations up to 30%.
Salt Durable	>0.6	Salt Durable is a thicker transdermal cream base option. Salt Durable contains a variety of common penetration enhancers and can tolerate concentrations of common pain APIs up to 40%. Salt Durable also does well with high concentrations of base forms of anesthetics.

Formula ID	Formula Name
FA-13769	Ketamine HCl 10% - Gabapentin 6% - Diclofenac Sodium 5% - Ibuprofen 3% - Pentoxifylline 3% - Baclofen 2% - Cyclobenzaprine HCl 2% - Bupivacaine HCl 1% Cream (Salt Durable)
FA-23662	Lidocaine 5%- Diclofenac 3% - Baclofen 5% Cream (Pentravan Plus)
FA-23780	Lidocaine 5% - Amitriptyline HCl 2% - Baclofen 2% Cream (Versatile™ Anhydrous Cream)
FA-23627	Ketamine HCl 10% - Gabapentin 6% - Ketoprofen 3% - Baclofen 2% - Cyclobenzaprine HCl 2% - Tetracaine 2% Cream (Versatile™ Anhydrous Cream)
FA-23609	Diclofenac Sodium 5% - Gabapentin 10% - Lidocaine 10% Cream (Versatile™ Anhydrous Cream)
FA-23931	Ketamine 10% - Amitriptyline HCl 5% - Lidocaine 5% Cream (Salt Stable LS Advanced)
FA-22456	Ketoprofen 10% - Baclofen 2% - Amitriptyline HCl 2% - Lidocaine 5% Cream (Salt Stable LS Advanced)
FA-23943	Diclofenac Sodium 3% - Baclofen 2% - Cyclobenzaprine HCl 2% - Gabapentin 6% - Bupivacaine HCl 2% Cream (Salt Stable LS Advanced)
FA-23942	Ketamine 10% - Baclofen 2% - Cyclobenzaprine HCl 2% - Diclofenac Sodium 3% - Gabapentin 6% - Bupivacaine HCl 2% Cream (Salt Stable LS Advanced)
FA-23944	Ketamine 2% - Amitriptyline HCl 4% - Baclofen 1% Cream (Pentravan® Plus)

References:

1. Baskozos G, Hébert HL, Pascal MM, et al. Epidemiology of neuropathic pain: an analysis of prevalence and associated factors in UK Biobank. Pain Rep. 2023;8(2):e1066. doi:10.1097/PR9.0000000000001066
2. Attal, Nadinea,*; Martinez, Valériaa,b,c; Bouhassira, Didiera,b. Potential for increased prevalence of neuropathic pain after the COVID-19 pandemic. PAIN Reports 6(1):p e884. DOI: 10.1097/PR9.0000000000000884
3. Bates D, Schultheis BC, Hanes MC, et al. A Comprehensive Algorithm for Management of Neuropathic Pain [published correction appears in Pain Med. 2023 Feb 1;24(2):219. doi: 10.1093/pm/pnac194.]. *Pain Med*. 2019;20(Suppl 1):S2-S12. doi:10.1093/pm/pnz075
4. Compounded Topical Pain Crams: Review of Select Ingredients for Safety, Effectiveness, and Use. 2020. Compounded Topical Pain Creams: Review of Select Ingredients for Safety, Effectiveness, and Use | The National Academies Press. Accessed 2/14/2025.
5. Bruna-Mejias A, Baeza V, Gamboa J, Baez Flores B, San Martin J, Astorga C, Leyton J, Nova-Baeza P, Orellana-Donoso M, Suazo-Santibañez A, et al. Use of Ketamine in Patients with Multifactorial Neuropathic Pain: A Systematic Review and Meta-Analysis. Pharmaceuticals. 2024; 17(9):1165. https://doi.org/10.3390/ph17091165
6. Lynch, M.E.; Clark, A.J.; Sawynok, J.; Sullivan, M.J.L. Topical 2% Amitriptyline and 1% Ketamine in Neuropathic Pain Syndromes: A Randomized, Double-blind, Placebo-controlled Trial. Anesthesiology 2005, 103, 140–146.
7. Lockhart E: Topical combination of amitriptyline and ketamine for post herpetic neuralgia (abstract). J Pain 2004; 5 (suppl 1):82
8. 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. doi:10.1007/s00520-010-0911-0
9. 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. doi:10.1007/s00520-014-2158-7
10. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a doubleblind placebo-controlled trial of topical ketamine. Pain. 2009;146(1–2):18–25.

11. Campbell C, Kipnes M, Stouch B et al. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. Pain. 2012; 153(9): 1815-1823.
12. Campbell C, Campbell J, Schmidt W, Brady K, Stouch B. Topical clonidine gel reduces pain caused by diabetic neuropathy: Results of a multicenter, placebo-controlled clinical trial. 2009; 10(4): DOI: 10.1016/j.jpain.2009.01.293
13. Ragavendran J, Laferriere A, Bennett G et al. Effects of topical combinations of clonidine and pentoxifylline on capsaicin-induced allodynia and postcapsaicin tourniquet-induced pain in healthy volunteers. 2015; 10: 2366-2374.
14. Cao X, Shen Z, Wang X et al. A Meta-analysis of Randomized Controlled Trials Comparing the Efficacy and Safety of Pregabalin and Gabapentin in the Treatment of Postherpetic Neuralgia. 2022: 1-18.
15. Ergisi M, Law A, Chaudhari N et al. Effectiveness of topical gabapentin in the treatment of vulvodynia: a narrative synthesis. Front. Pain Res. 2023; 4: https://doi.org/10.3389/fpain.2023.1159268
16. Ahmed S, Zhang Y, Chen L et al. Effect of 1.5% diclofenac on clinical neuropathic pain. Anesthesiology. 2015; 123(1): 191-198.
17. Kanai A, Segawa Y, Okamoto T, Koto M, Okamoto H. The analgesic effect of a metered-dose 8% lidocaine pump spray in posttraumatic peripheral neuropathy: a pilot study. *Anesth Analg*. 2009;108(3):987-991. doi:10.1213/ane.0b013e31819431aa
18. Kocot-Kępska M, Zajączkowska R, Mika J, Kopsky DJ, Wordliczek J, Dobrogowski J, Przeklasa-Muszyńska A. Topical Treatments and Their Molecular/Cellular Mechanisms in Patients with Peripheral Neuropathic Pain—Narrative Review. *Pharmaceutics*. 2021; 13(4):450. https://doi.org/10.3390/pharmaceutics13040450
19. Ala, S., Enayatifard, R., Monajati, M. et al. The Analgesic Effects of Baclofen 5% Topical Cream for Treatment of Diabetic Peripheral Neuropathy: a Placebo-Control and Double-Blinded Clinical Trial. SN Compr. Clin. Med. 4, 87 (2022). https://doi.org/10.1007/s42399-021-01108-7
20. Somberg, J.C.; Molnar, J. Retrospective Study on the Analgesic Activity of a Topical (TT-CTAC) Cream in Patients With Diabetic Neuropathy and Other Chronic Pain Conditions. *Am. J. Ther.* **2015**, *22*, 214–221.
21. Safaeian, P.; Mattie, R.; Hahn, M.; Plastaras, C.T.; McCormick, Z.L. Novel Treatment of Radicular Pain with a Multi-Mechanistic Combination Topical Agent: A Case Series and Literature Review. Anesthesiol. Pain Med. 2016, 6, e33322
22. Kopsky, D.J.; Hesselink, J.M.K. Single-Blind Placebo-Controlled Response Test with Phenytoin 10% Cream in Neuropathic Pain Patients. Pharmaceuticals 2018, 11, 122.
23. Kopsky DJ, van Eijk RPA, Warendorf JK, Keppel Hesselink JM, Notermans NC, Vrancken AFJE. Enriched enrollment randomized double-blind placebo-controlled cross-over trial with phenytoin cream in painful chronic idiopathic axonal polyneuropathy (EPHENE): a study protocol. *Trials*. 2022;23(1):888. Published 2022 Oct 22. doi:10.1186/s13063-022-06806-8
24. McCleane G. Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. *Br J Clin Pharmacol*. 2000;49(6):574-579. doi:10.1046/j.1365-2125.2000.00200.x