Journal of Diabetes & Metabolic Disorders
https://doi.org/10.1007/s40200-024-01459-7

REVIEW ARTICLE

Assessing the efficacy of topical formulations in diabetic neuropathy: a narrative review

Ali Elbeddini[1] · Azasma Tanvir[2] · Orhan Yilmaz[2] · Yusra Rahman[3] · Renata Mongon[4]

Received: 22 May 2024 / Accepted: 19 June 2024

Abstract

Background We conducted a review of topical medications available for alleviation of diabetic neuropathic pain (DNP) and compared their efficacy with oral medications for pain relief. We also explored the feasibility of compounding topical medications.

Methods Searches on PubMed, Medline Ovid, and Embase databases were conducted and findings were presented as a narrative review.

Results and discussion 8% Capsaicin patches and 5% Lidocaine patches had the most evidence. The literature also showed evidence for topical clonidine, gabapentin, and amitriptyline.

Conclusion Topical formulations are a potential substitute to oral medications in patients suffering from DNP. Potential options include 8% Capsaicin patch, 5% Lidocaine patch, Clonidine gel, Topical gabapentin, and an amitriptyline and ketamine combination. A promising area of research that requires further study is the effect of a combination of topicals in alleviated DNP.

Keywords Localized neuropathic pain · Compounding services · Patient safety

Introduction

Diabetes is a chronic, prevalent and multi-faceted chronic condition characterized by high blood glucose. It increases patients' risk of cardiovascular comorbidities and may progress to serious and debilitating complications, such as diabetic kidney disease, retinopathies and diabetic neuropathic pain (DNP) [1, 2] that can affect patients' quality of life and result in significant morbidity and mortality.

The prevalence of diabetes is rapidly increasing across North America and worldwide [3], with more than 422 million adults living with diabetes in 2014, compared to 108 million in 1980 [4]. In Canada, more than 7.3% of the population over the age of 12 have been diagnosed with diabetes, and many more carry risk factors, given that 64% of adults and 30% of children in Canada are either overweight or obese [3, 5]. It is estimated that around 50% of diabetic patients suffer from symptoms of neuropathy, with an increasing prevalence correlated with increasing age among people with diabetes [1–4]. According to a meta-analysis in 2019, the risk factors associated with DNP are older age, longer duration of diabetes, higher HbA1c levels, and the presence of diabetic retinopathy [6]. DNP is more prevalent

✉ Ali Elbeddini
Elbeddini.a@gmail.com

Azasma Tanvir
azt292@usask.ca

Orhan Yilmaz
orhan.yilmaz@usask.ca

Yusra Rahman
rahmay3@mcmaster.ca

Renata Mongon
renatamongon@gmail.com

1 Family Medicine Department, University of Ottawa, School of Medicine, 600 Peter Morand Crescent Suite 201, Ottawa, ON K1G 5Z3, Canada

2 College of Medicine, University of Saskatchewan, 107 Wiggins Rd, Saskatoon, SK S7N 5E5, Canada

3 Faculty of Health Sciences, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada

4 Anesthesiology Department, State University of Campinas, Campinas, Brazil

Published online: 03 July 2024

in older individuals and has a higher burden in the elderly as it affects mobility, quality of life and is associated with other comorbidities [7].

Another issue prevalent in the elderly population is the issue of polypharmacy, which is defined as the regular use of at least five medications [8]. Many patients who experience DNP are elderly individuals suffering from other comorbidities for which they are taking medications. Adding on another oral medication to their treatment regimen not only increases the risk of side effects, but also the risk of drug-drug interactions. Combining this with the fact that many elderly patients may have memory impairments and thus may struggle to accurately take their medications, adding on another oral pill may create a significant hindrance associated with medication compliance for these individuals.

The standard clinical practice guidelines in North America for managing DNP recommend managing the hyperglycemia, along with a variety of oral medications for symptom control, including antidepressants, anticonvulsants, and opioids, among others [9–12]. Unfortunately, while these treatments do provide pain relief, they come with numerous adverse effects and require a lengthy titration period to reach optimal doses [13].

Given these multiple issues, it is important to explore alternative treatment options for DNP, especially in the elderly population. One possible solution is to investigate the use of topical formulations for pain relief.

This narrative review focuses on existing literature surrounding the use of topical formulations for the management of DNP. Research shows that a variety of topical formulations show promise for pain management without the systemic side effects associated with oral medications. This review focuses on five specific topical formulations: capsaicin patch, lidocaine patch, clonidine gel, topical gabapentin, and topical ketamine and amitriptyline formulations.

Aims and objectives

Our overall goal of this research is to present one of the many ways in which pharmacy services contribute to positive patient outcomes. This review paper aims to evaluate the use of pharmacy compounding services in the management of DNP. Here are the key objectives:

- To compare topical gabapentin, amitriptyline and ketamine gel with oral gabapentin in treating DNP

  Based on their efficacy, safety, adherence, and onset of action

- To explore the feasibility of compounding topical medications for DNP

Methods

Keywords used in databases included “diabetes”, “diabetic neuropathic pain”, “topical”, “clinical trial”, “capsaicin”, “clonidine”, “lidocaine”, “ketamine”, “amitriptyline”, and “gabapentin”. Databases used included PubMed, Medline Ovid, and Embase. Searches were limited to articles published in the English language and human trials. The time frame included articles published from 1945 to December 2023. The findings from the search are presented as a narrative review. As in all narrative reviews, a selection bias cannot be excluded. The article presented here is a literature review, and does not require any ethical approval.

Results and discussion

Existing oral treatments for DNP

Standard North American clinical practice guidelines for treating DNP mainly recommend the management of hyperglycemia and the use of oral medications such as antidepressants (e.g. tricyclic antidepressants, SSRIs, and SNRIs), anticonvulsants (gabapentinoids, topiramate) and opioids painkillers for symptomatic relief as first- and second-line options [2, 9–12]. One of the most common first-line treatments are the gabapentinoids, including pregabalin and gabapentin. However, gabapentinoids require a long titration period to reach the optimal dose [13] and are associated with numerous undesirable side effects, including effects on the central nervous system, weight gain and uncoordinated movements. FDA has also issued warnings about significant breathing problems, especially in the elderly population associated with pregabalin and gabapentin [14].

The FDA has approved pregabalin for DNP, but gabapentin is often used off-label for this condition. Cohort studies have found that the median dose used for pregabalin in DNP patients was lower than the FDA recommended dose. Given the range of side effects, sub-therapeutic doses and off-label use in patients who are likely presenting with polypharmacy, gabapentinoids are potential candidates for deprescribing [15].

Existing literature for use of topical medications in the management of DNP

A summary of the literature findings on topical medications for the management of neuropathic pain is presented in Table 1.

Table 1 Summary of the evidence for the use of topical formulations in neuropathic pain

Study	Findings
Amitriptyline 4%/ketamine 2% cream vs. placebo	• 30% pain reduction was achieved in 60% of patients • Superior to placebo in patients with DNP • Early irritation and skin rash associated with treatment
Topical gabapentin vs oral gabapentin	• Topical effective at much lower plasma concentrations • Much less systemic side effects • Studied in post-herpetic neuralgia
Clonidine 0.1% gel vs. placebo	• Better pain score improvement of DNP with clonidine gel • No adverse effects associated with clonidine gel
Topical lidocaine 5% vs. oral pregabalin	• Comparable analgesic efficacy in DNP 1. Less systemic side effects with topical lidocaine 2. Less discontinuation due to side effects with topical lidocaine
Topical capsaicin vs. placebo	• Capsaicin associated with superior pain relief, improving quality of life, and treatment satisfaction in patients with DNP

Capsaicin patch

Topical Capsaicin is a potential alternative to centrally acting oral neuropathic medications. Capsaicin is the active ingredient found in red peppers and it contains both antioxidant and antiinflammatory properties [16]. Binding to the transient receptor potential vanilloid 1 receptor (TRPV1) results in initial burning experienced with capsaicin, however prolonged activation of the receptor depletes associated neurotransmitters which in turn dampens the ability of neurons to transmit pain signals [17].

Currently, there are two formulations of capsaicin available for analgesia; topical 0.025 to 0.075% capsaicin cream and a capsaicin 8% high concentration patch. The capsaicin dermal patch was recently approved by the United States Food and Drug Administration for treatment of DPN [18].

Two major clinical trials were undertaken to assess the efficacy of capsaicin for DPN. The STEP trial was a randomized controlled trial which assessed the efficacy of 30 min application of topical 8% capsaicin for treatment of DPN [19]. According to this study, patients with DPN in their feet had up to 12 weeks of sustained pain relief with 30 min applications of topical 8% capsaicin. In addition to modest pain relief, patients also sustained improvement in sleep compared to the placebo group. These benefits were comparable to other efficacious treatments for DPN, but without the associated side effects.

The PACE trial was a long term randomized study assessing the efficacy of up to seven applications of topical 8% capsaicin in patients with DPN [20]. Patients in the treatment group received 30 min applications of topical 8% capsaicin in addition to the standard of care treatment, whereas the control group received just the standard of care alone. Patients in the treatment group had self reported improvements in quality of life, pain, and activity levels. Similarly, a study which compared topical 8% capsaicin to oral amitriptyline in patients with DPN also supported the improvements in sleep, fatigue, depression, and quality of life, in addition to moderate to substantial pain relief compared to participants using low concentration capsaicin creams [21].

When comparing to other available analgesics for DPN, a network meta analysis including 25 randomized control trials indicated that the topical 8% capsaicin is comparable in efficacy to oral agent such as pregabalin, duloxetine and gabapentin for treatment of DPN [22].

In addition to capsaicin patches, capsaicin lotions may also be prescribed for analgesia. However the evidence for capsaicin lotions are less promising. According to Kulkantronr et al.,the 0.075% capsaicin lotion had an efficacy that was similar to placebo [23]. Similarly, a less potent 0.025% capsaicin lotion, although well tolerated, did not seem to result in appreciable analgesia in this population [24]. The capsaicin patch in comparison not only is more efficacious in terms of analgesia, but also results in lower application frequency compared to less potent topical formulations [25].

The most common adverse drug effects of topical capsaicin included localized discomfort, erythema, and burning [21]. These side effects may be a potential limitation to treatment. However, local anesthetics may be given to avoid the initial intense burning associated with application [21]. Moreover, compared to oral systemically absorbed medication, capsaicin bypasses issues pertaining to polypharmacy, high side effect profile and time to effect [18, 25]. That being said, it may be used either alone or in combination to oral medications for DPN pain relief [18].

Given its clinical efficacy, low side effect profile, tolerability, the topical 8% capsaicin formulation was recently deemed a first line option for DPN treatment according to the American Association of Clinical Endocrinology and Clinical Compendia American Diabetes Association [26].

Topical lidocaine

Topical lidocaine relieves pain by stabilizing neuronal membranes and blocking nerve conduction in the soft tissue under the skin [27]. There are two common types of topical lidocaine used for the treatment of diabetic neuropathic pain (DNP): (1) lidocaine patch 5%, and (2) lidocaine medicated plaster. The lidocaine patch is applied to intact skin directly on or near the area in pain, and the recommended dosage is a maximum of 3 patches within a 12-h period, after which the patches would be removed for 12 h (27; 28). 5% of the drug is absorbed by the body and the patch has a half-life of six to eight hours [28]. Systemic absorption is minimized by the function of the lidocaine patch, which reduces the risk of systemic side effects and clinically significant drug interactions [28]. Also, there are limited side effects involved in using the patch, with mild skin reaction being the most common side effect [28]. Studies suggest that the patch may be a good candidate for polypharmacy in patients who respond partially to single treatments [29].

In terms of effectiveness, many studies suggest that the lidocaine patch reduces pain and improves quality of life (QoL), among other benefits. White et al. (2003) reports significant improvements in "pain interference with general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life" in patients experiencing pain from a series of conditions including DNP, and who had incomplete responses to their current analgesic treatment (p. 321) [30]. Similarly, Argoff et al. (2004) found that the lidocaine patch reduces the intensity of pain for DNP and is well tolerated in combination with other analgesic treatments [29]. An open-label study by Barbano et al. (2004) demonstrated that using up to 4 5% lidocaine patches for up to 18 h per day was well tolerated, which is a more flexible use of the recommended dosage mentioned above [31].

Similarly, lidocaine medicated plaster (LMP) is associated with fewer adverse effects (i.e., system toxicity, side effects, drug reactions) than its systemically acting counterparts [32], with the most common side-effect being skin irritation at the application site [33]. The plaster provides a barrier that protects the skin from mechanical stimuli and is suggested to increase compliance with long-term therapy due to ease of use and application [33].

In addition to demonstrating the effectiveness of LMP, many researchers seek to compare it to other analgesics. In a series of studies, Baron et al. found that LMP improves QoL, has fewer adverse and drug-related events, and fewer patient discontinuations compared to pregabalin [32]. LMP provides similar levels of pain relief for patients experiencing DNP when compared to pregabalin [34]. Finally, combining LMP with pregabalin provides clinically relevant pain relief and is well-tolerated for those who did not respond to monotherapy [35]. Most recently, LMD was found to be safer and more effective than oral medications in the treatment of LMP [36].

Topical clonidine

Another topical formulation which shows promise in alleviating DNP is clonidine gel. Clonidine, a presynaptic alpha 2 adrenergic receptor agonist, has historically been used for managing hypertension; However, adverse effects associated with its systemic use have limited its application [37]. When applied topically as a gel, clonidine may act locally to modulate pain pathways, which offers a more targeted approach as compared to systemic administration. There exist studies which demonstrate the utility of topical clonidine gel, as outlined below.

A double blind placebo controlled multicentre trial was conducted in 2009 which looked at the analgesic efficacy of a topical clonidine gel in painful diabetic neuropathy over 8 weeks [38]. Researchers found that the mean pain score was significantly less in the group that received 0.1% or 0.2% clonidine as compared to placebo. They also noted that while patients with detectable clonidine in their blood had more pain reduction than patients whose serum clonidine was not detected ($p < 0.05$), the serum clonidine levels were still well below the threshold than that used to treat hypertension.

The researchers followed up this study with another randomized, double-blind, placebo-controlled, multi-center trial in 2012 which spanned 12 weeks [8]. Subjects in this trial applied either 0.1% Clonidine gel or placebo TID to their feet for 12 weeks. The average pain score improvement after 12 weeks of clonidine 0.1% gel application was 2.6 for those receiving the treatment and 1.4 for those receiving the placebo ($p = 0.01$). There were no side effects observed with this treatment [8].

A third randomized, double blind trial conducted in 2015 studied 0.1% clonidine gel and 0.75% capsaicin cream in type 2 diabetic patients over the course of 12 weeks [39]. This trial found that although clonidine gel had a comparable efficacy with capsaicin cream in the treatment of DNP ($p < 0.001$), dermatological complications were more common in the capsaicin group ($p = 0.001$), with the clonidine group having less adverse effects. These studies point to the clinical utility of topical clonidine as a potential therapeutic for DNP and more trials should be conducted to further determine its role as a therapeutic.

Topical gabapentin

Another potential topical formulation for DNP is topical gabapentin. Various topical gabapentin formulations have been shown to have good skin penetration [40] and have been studied with favorable outcomes in the management of DNP [41]. One noteworthy finding was that all patients

in the trial reported pain improvement within 1 h of topical gabapentin application. This finding is in stark contrast to oral gabapentin, which requires up to 2 weeks of titration to the optimal dose [42]. Previous studies have shown that topical gabapentin was effective for pain relief at peak plasma concentrations of 0.01 µg/mL in patients with DNP and post-herpetic neuralgia. In comparison, oral gabapentin needs to achieve plasma concentrations of 2–20 µg/mL to achieve desired pain relief in the same population groups [41]. In a Cochrane review meta-analysis (22 studies, $n=3948$) of oral gabapentin used for various neuropathic indications [43], 11% of patients reported adverse-event medication discontinuations with oral gabapentin, with 3.2% experiencing severe adverse events. Most notably, the most common side effects reported were dizziness (19%), somnolence (14%), peripheral edema (7%), and gait disturbance (14%).

The use of topical gabapentin for pain management has previously been studied in patients with post-herpetic neuralgia (PHN), DNP and other neuropathic pain syndromes in a small non-controlled study with 23 subjects, wherein 87% of subjects noted pain score improvement with topical gabapentin after one month [41]. Interestingly, all patients who responded to topical gabapentin treatment experienced pain relief within 1 h of topical medication administration. Within this study, only one patient reported loss of balance, sleep disturbance, and generalized skin irritation, and no other patient-reported systemic or localized adverse effects. Meanwhile, oral gabapentin and pregabalin have been associated with many adverse effects due to their systemic bioavailability [42]. Numerous case studies have associated chorea, weight gain and adverse CNS effects with the use of oral gabapentin [13], which can be of concern given the chronic and progressive nature of DNP affecting elderly patients who may already be at high risk of falls given their age and other comorbidities that often co-present with diabetes.

Topical amitriptyline & ketamine

Lastly, a combined formulation of topical amitriptyline/ketamine cream also shows promise in alleviating DNP. In a large, multi-center phase II clinical trial conducted in 2006 with patients with DNP, amitriptyline 4%/ketamine 2% (AK) cream was shown to be superior to placebo. Over 30% pain reduction was achieved in 60% of patients using AK cream as compared to 48% in placebo ($p=0.102$), while over 50% pain reduction was achieved in 31% of patients compared to 21% in placebo ($p=0.056$) [44].

A randomized, double blind, placebo controlled trial comparing AK cream to oral gabapentin was conducted in 2007 [45]. The study showed oral gabapentin showed no significantly greater reduction in pain than the AK cream, which was measured via average pain scores after 4 weeks of treatment [45]. The results for AK cream and oral gabapentin were similar. This study also noted that after 4 weeks, the AK cream resulted in more pain relief than placebo, and this was statistically significant ($p=0.044$). AK cream also resulted in significantly greater reduction in sleep interference as compared to placebo ($p=0.027$).

The most common adverse effects noted with the AK cream in the trials were application site irritation, such as erythema, rashes, and burning; However, this was a mild and transient effect [45]. In the trial from 2006, patients had vital sign monitoring, physical exams, electrocardiograms, and laboratory monitoring for adverse effects. No serious adverse effects were reported in the trial and the cream was well tolerated, thus this topical formulation shows promise as a safer alternative to oral medications.

Compounding topical formulations

Drug compounding is the process of modifying or mixing ingredients to create a medication. It often involves the combination of two or more drugs, through which medications are customized to fit the needs of individual patients [46]. Although several studies explore the efficacy of compounded topical formulations for neuropathic pain, only one study has been performed examining patients with only DNP [47]. This study evaluates a combined formulation of topical amitriptyline/ketamine, outlined in Section "Conclusion".

Additional studies have explored the use of compounded topical formulations for neuropathic pain. A 4-week randomized placebo-controlled trial conducted in 2010 investigated the use of a compounded gel consisting of 0.76% baclofen, 1.5% ketamine, and 3% amitriptyline in Pluronic-Lecithin Organogel. The study included patients with chemotherapy-induced peripheral neuropathy, which commonly presents with sensory symptoms such as pain, numbness, and tingling [48]. The results showed a greater advantage of the compounded formulation compared to placebo in both sensory ($p=0.053$) and motor ($p=0.021$) subscales, with the largest improvement being in neuropathic symptoms of shooting/burning pain, tingling, and cramping in the hands [47]. No systemic adverse effects were noted. The improvement of neuropathic pain symptoms in this study points towards promising therapeutic potential in patients with DNP, which should be further explored.

Another compounded topical formulation found to alleviate neuropathic pain is a 3.3% doxepin hydrochloride/0.025% capsaicin cream. Doxepin hydrochloride is a tricyclic antidepressant (TCA) with analgesic effects for neuropathic pain in addition to its antidepressant properties [49]. Capsaicin is a selective TRPV1 agonist that has shown to provide analgesic effects for neuropathic pain [50], as outlined in Section "Introduction". A randomized, double-blind, placebo-controlled study compared the effect of this compounded cream against each drug individually and a placebo.

Although all treatment groups (except placebo) similarly reduced overall pain over the 4-week trial, the 3.3% doxepin hydrochloride/0.025% capsaicin cream had the fastest onset of pain relief (week 1) [49]. Side effects for this compounded cream included burning discomfort after application (61%), drowsiness (5.5%), and headache (2.8%) [49]. The burning discomfort was notably experienced by participants in all 3 treatment groups. The therapeutic benefit of this formulation should be weighed with its clinical application through further investigation to indicate its potential use for patients with DNP.

Although some compounded topical formulations for neuropathic pain have been studied, considerable research is yet to be conducted exploring the vast potential for treatment using these therapies. The appreciable pain relief, minimal systemic side effects, and impact specifically on neuropathic pain symptoms are just some of the clinical benefits of these treatments determined thus far. Therefore, this provides promising potential for the investigation and development of additional compounded topical formulations for DNP.

Conclusion

A narrative review was conducted to assess the therapeutic effectiveness of topical medications in the alleviation of DNP and to compare their efficacy to oral medications. Two major clinical trials demonstrated that an 8% capsaicin topical formulation can lead to moderate and sustained pain relief with side effects such as localized discomfort, erythema and burning. Significantly, it was found that topical 8% capsaicin had comparable efficacy to oral medications and a much lower side effect profile. A breadth of studies has demonstrated that a lidocaine patch can lead to significant reductions in pain and improvements in quality of life, with limited side effects. A LMP has also shown to be effective at reducing pain with significantly less adverse side effects compared to pregabalin. Topical clonidine has also shown promise as a potential therapy for DNP with significantly reduced pain compared to a placebo. More studies are needed to further determine its efficacy. As compared to oral gabapentin, topical gabapentin has a much more favorable side effect profile, faster onset of action, lower required concentration for pain relief and fewer adverse events associated with discontinuation. A combined formulation of topical amitriptyline/ketamine cream has also been shown to be significantly more effective than a placebo and has comparable efficacy to oral gabapentin in reducing pain with mild and transient side effects. Finally, a promising therapeutic intervention for DNP is compounded topical formulations with a randomized placebo-controlled trial demonstrating pain reduction in chemotherapy-induced peripheral neuropathy. 3.3% doxepin hydrochloride/0.025% capsaicin cream has also been found to be effective but side effects such as burning discomfort may limit use. More research is needed to better understand the role these formulations can play in managing DNP.

Acknowledgements The authors recognize the support of Subha Mustufa for her invaluable contribution to this research project in writing a subsection of this manuscript.

Funding No funding received from any third party.

Data availability Not applicable.

Declarations

Ethical approval Non applicable.

Conflict of interest The authors declared that they have no conflict of interest.

References

1. American Diabetes Association. 9. Microvascular complications and foot care. Diabetes Care. 2015;38(Supplement_1):S58–66. https://doi.org/10.2337/dc15-S012.
2. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–72. https://doi.org/10.1056/NEJMoa0802987.
3. Millar WJ, Young TK. Tracking diabetes: prevalence, incidence and risk factors. Health Rep. 2003;14(3):35–47.
4. World Health Organization. World health organization global report on diabetes. Geneva: World Health Organization; 2016.
5. Statistics Canada. Health fact sheets: chronic conditions, 2016. 2016. http://www.statcan.gc.ca/pub/82-625-x/2017001/article/54858-eng.htm. Accessed 20 Jan 2024
6. Liu X, Xu Y, An M, Zeng Q. The risk factors for diabetic peripheral neuropathy: a meta-analysis. PLoS ONE. 2019;14(2):e0212574. https://doi.org/10.1371/journal.pone.0212574.
7. Hicks CW, Selvin E. Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. Curr DiabRep. 2019;19:1–8. https://doi.org/10.1007/s11892-019-1212-8.
8. Campbell CM, Kipnes MS, Stouch BC, Brady KL, Kelly M, Schmidt WK, Petersen KL, Rowbotham MC, Campbell JN. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. Pain. 2012;153(9):1815–23. https://doi.org/10.1016/j.pain.2012.04.014.
9. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D, American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, & American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011;76(20):1758–65. https://doi.org/10.1212/WNL.0b013e3182166ebe.
10. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol.

2005;96(6):399–409. https://doi.org/10.1111/j.1742-7843.2005.pto_96696601.x.
11. American Diabetes Association. Standards of medical care in diabetes 2016. Diabetes Care. 2016;42(Suppl 1):S124–38.
12. Houlden RL. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada: introduction. Can J Diabetes. 2018;42(Suppl 1):S1-5. https://doi.org/10.1016/j.jcjd.2017.10.001.
13. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther. 2003;25(1):81–104.
14. U.S. Food and Drug Administration. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). United States: FDA. 2019. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin. Accessed 20 Jan 2024
15. Gingras MA, Lieu A, Papillon-Ferland L, Lee TC, McDonald EG. Retrospective cohort study of the prevalence of off-label gabapentinoid prescriptions in hospitalized medical patients. J Hosp Med. 2019;14(9):547–50. https://doi.org/10.12788/jhm.3203.
16. Dludla PV, Nkambule BB, Cirilli I, Marcheggiani F, Mabhida SE, Ziqubu K, Ntamo Y, Jack B, Nyambuya TM, Hanser S, Mazibuko-Mbeje SE. Capsaicin, its clinical significance in patients with painful diabetic neuropathy. Biomed Pharmacother. 2022;153:113439. https://doi.org/10.1016/j.biopha.2022.113439.
17. Baranidharan G, Das S, Bhaskar A. A review of the high-concentration capsaicin patch and experience in its use in the management of neuropathic pain. Ther Adv Neurol Disord. 2013;6(5):287–97. https://doi.org/10.1177/1756285613496866.
18. Abrams RMC, Pedowitz EJ, Simpson DM. A critical review of the capsaicin 8% patch for the treatment of neuropathic pain associated with diabetic peripheral neuropathy of the feet in adults. Expert Rev Neurother. 2021;21(3):259–66. https://doi.org/10.1080/14737175.2021.1874920.
19. Simpson DM, Robinson-Papp J, Van J, Stoker M, Jacobs H, Snijder RJ, Schregardus DS, Long SK, Lambourg B, Katz N. Capsaicin 8% patch in painful diabetic peripheral neuropathy: a randomized, double-blind, placebo-controlled study. J Pain. 2017;18(1):42–53. https://doi.org/10.1016/j.jpain.2016.09.008.
20. Vinik AI, Perrot S, Vinik EJ, Pazdera L, Jacobs H, Stoker M, Long SK, Snijder RJ, van der Stoep M, Ortega E, Katz N. Capsaicin 8% patch repeat treatment plus standard of care (SOC) versus SOC alone in painful diabetic peripheral neuropathy: a randomised, 52-week, open-label, safety study. BMC Neurol. 2016;16(1):251. https://doi.org/10.1186/s12883-016-0752-7.
21. Derry S, Rice AS, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017;1(1):CD007393. https://doi.org/10.1002/14651858.CD007393.pub4.
22. van Nooten F, Treur M, Pantiri K, Stoker M, Charokopou M. Capsaicin 8% patch versus oral neuropathic pain medications for the treatment of painful diabetic peripheral neuropathy: a systematic literature review and network meta-analysis. Clin Ther. 2017;39(4):787-803.e18. https://doi.org/10.1016/j.clinthera.2017.02.010.
23. Kulkantrakorn K, Chomjit A, Sithinamsuwan P, Tharavanij T, Suwankanoknark J, Napunnaphat P. 0.075% capsaicin lotion for the treatment of painful diabetic neuropathy: a randomized, double-blind, crossover, placebo-controlled trial. J Clin Neurosci. 2019;62:174–9. https://doi.org/10.1016/j.jocn.2018.11.036.
24. Kulkantrakorn K, Lorsuwansiri C, Meesawatsom P. 0.025% capsaicin gel for the treatment of painful diabetic neuropathy: a randomized, double-blind, crossover, placebo-controlled trial. Pain Pract. 2013;13(6):497–503. https://doi.org/10.1111/papr.12013.
25. Leavell Y, Simpson DM. The role of the capsaicin 8% patch in the treatment of painful diabetic peripheral neuropathy. Pain Manag. 2022;12(5):595–609. https://doi.org/10.2217/pmt-2021-0025.
26. Landrum O, Marcondes L, Egharevba T, Gritsenko K. Painful diabetic peripheral neuropathy of the feet: integrating prescription-strength capsaicin into office procedures. Pain Manag. 2023;13(10):613–26. https://doi.org/10.2217/pmt-2023-0028.
27. Pasero C. Lidocaine Patch 5%: how to use a topical method of controlling localized pain. AJN Am J Nurs. 2003;103(9):75–7.
28. Forde G. Adjuvant analgesics for the treatment of neuropathic pain: evaluating efficacy and safety profiles. J Fam Pract. 2007;56(2 Suppl Pain):3–12.
29. Argoff CE, Galer BS, Jensen MP, Oleka N, Gammaitoni AR. Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the Neuropathic Pain Scale. Curr Med Res Opin. 2004;20 Suppl 2(dux, 0351014):S21-8. https://doi.org/10.1185/030079904X12960.
30. White WT, Patel N, Drass M, Nalamachu S. Lidocaine patch 5% with systemic analgesics such as gabapentin: a rational polypharmacy approach for the treatment of chronic pain. Pain Med (Malden, Mass). 2003;4(4):321–30. https://doi.org/10.1111/j.1526-4637.2003.03045.x.
31. Barbano RL, Herrmann DN, Hart-Gouleau S, Pennella-Vaughan J, Lodewick PA, Dworkin RH. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. Arch Neurol. 2004;61(6):914–8. https://doi.org/10.1001/archneur.61.6.914.
32. 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. 2009a;25(7):1663–76. https://doi.org/10.1185/03007990903047880.
33. Wolff RF, Bala MM, Westwood M, Kessels AG, Kleijnen J. 5% lidocaine medicated plaster in painful diabetic peripheral neuropathy (DPN): a systematic review. Swiss Med Wkly. 2010;140(21–22):297–306. https://doi.org/10.4414/smw.2010.12995.
34. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an open-label, two-stage adaptive, randomized, controlled trial. Clin Drug Investig. 2009b;29(4):231–41. https://doi.org/10.2165/00044011-200929040-00002.
35. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of combination therapy with 5% lidocaine medicated plaster and pregabalin in post-herpetic neuralgia and diabetic polyneuropathy. Curr Med Res Opin. 2009c;25(7):1677–87. https://doi.org/10.1185/03007990903048078.
36. Überall M, Bosl I, Hollanders E, Sabatschus I, Eerdekens M. Painful diabetic peripheral neuropathy: real-world comparison between topical treatment with lidocaine 700 mg medicated plaster and oral treatments. BMJ Open Diabetes Res Care. 2022;10(6). https://doi.org/10.1136/bmjdrc-2022-003062.
37. Serednicki WT, Wrzosek A, Woron J, Garlicki J, Dobrogowski J, Jakowicka-Wordliczek J, Wordliczek J, Zajaczkowska R. Topical clonidine for neuropathic pain in adults. Cochrane Database Syst Rev. 2022;5(5):CD010967. https://doi.org/10.1002/14651858.CD010967.pub3.
38. 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. J Pain. 2009;10(4):S55.
39. Kiani J, Sajedi F, Nasrollahi SA, Esna-Ashari F. A randomized clinical trial of efficacy and safety of the topical clonidine and

capsaicin in the treatment of painful diabetic neuropathy. J Res Med Sci. 2015;20(4):359–63.
40. Martin CJ, Alcock N, Hiom S, Birchall JC. Development and evaluation of topical gabapentin formulations. Pharmaceutics. 2017;9(3):31. https://doi.org/10.3390/pharmaceutics9030031.
41. Hiom S, Patel GK, Newcombe RG, Khot S, Martin C. Severe postherpetic neuralgia and other neuropathic pain syndromes alleviated by topical gabapentin. Br J Dermatol. 2015;173(1):300–2. https://doi.org/10.1111/bjd.13624.
42. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol. 2006;6(1):108–13.
43. Wiffen PJ, Derry S, Bell RF, Rice AS, Tölle TR, Phillips T, Moore RA. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6(6):CD007938. https://doi.org/10.1002/14651858.CD007938.pub4.
44. National Library of Medicine (U.S.). A Phase 3 multicenter, randomized, double-blind, placebo-controlled 14-week study of DS-5565 in Chinese patients with diabetic peripheral neuropathic pain. Identifier NCT04094662. 2019. https://clinicaltrials.gov/ct2/show/NCT04094662. Accessed 20 Jan 2024
45. Sawynok J, Zinger C. Topical amitriptyline and ketamine for postherpetic neuralgia and other forms of neuropathic pain. Expert Opin Pharmacother. 2016;17(4):601–9. https://doi.org/10.1517/14656566.2016.1146691.
46. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on the Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams; Jackson LM, Schwinn DA, editors. Compounded topical pain creams: review of select ingredients for safety, effectiveness, and use. Washington: National Academies Press (US); 2020. Appendix D, Glossary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560340/. Accessed 20 Jan 2024
47. Yang XD, Fang PF, Xiang DX, Yang YY. Topical treatments for diabetic neuropathic pain. Exp Ther Med. 2019;17(3):1963–76. https://doi.org/10.3892/etm.2019.7173.
48. Gupta R, Bhaskar A. Chemotherapy-induced peripheral neuropathic pain. BJA Educ. 2016;16(4):115–9. https://doi.org/10.1093/bjaed/mkv044.
49. 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):574–9. https://doi.org/10.1046/j.1365-2125.2000.00200.x.
50. Groninger H, Schisler RE. Topical capsaicin for neuropathic pain #255. J Palliat Med. 2012;15(8):946–7. https://doi.org/10.1089/jpm.2012.9571.