

Topical treatments for diabetic neuropathic pain (Review)

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Received June 4, 2018; Accepted November 22, 2018

DOI: 10.3892/etm.2019.7173

Abstract. Diabetic neuropathic pain (DNP) has a huge impact on quality of life and can be difficult to treat. Oral treatment is the most frequently used method for DNP, but its use is often limited by systemic side effects. Topical use of drugs as an alternative option for DNP treatment is currently gaining interest. In the present review, a summary is provided of the available agents for topical use in patients with DNP, including lidocaine plasters or patches, capsaicin cream, gel or patches, amitriptyline cream, clonidine gel, ketamine cream, extracts from medicinal plants including nutmeg extracts and *Citrullus colocynthis* extract oil, and certain compounded topical analgesics. Furthermore, the potential efficacy of these treatments is addressed according to the available clinical research literature. It has been indicated that these topical drugs have the potential to be valuable additional options for the management of DNP, with adequate safety and continuous long-term treatment efficacy. Compounded topical agents are also effective and safe for patients with DNP and could be another area worthy of further investigation based on the strategy of using low-dose, complementary therapies for DNP. The findings indicate that developing topical drugs acting on different targets in the process of DNP is a valuable area of future research.

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Key words: topical treatments, diabetes, diabetic neuropathy, diabetic neuropathic pain

1. Introduction

According to the International Diabetes Federation, there are 425 million adults with diabetes worldwide (1). Diabetic neuropathy is the most common complication of diabetes mellitus, becoming symptomatic after 14.5 years of chronic prolonged high blood glucose in type 1 diabetes, and after only 8.1 years in type 2 diabetes (2). A population-based study indicated that up to 50% of patients with either type 1 or type 2 diabetes develop diabetic neuropathy (3), and 15-30% of those manifestations are painful (4). Diabetic neuropathic pain (DNP) is among the most common, expensive and disabling complications of diabetes, affecting approximately 30% of patients with diabetes who are hospitalized and 25% of those in the community (5,6).

DNP is characterized by sensations of numbness, burning pain and prickling or stinging around the hands and feet, and the pain is more severe at night (7). The more severe occurrences of DNP can be intractable (8,9). Neuropathic pain can be constant and accompanied by cutaneous allodynia, which significantly influences quality of life (QOL) and prevents patients from performing their daily activities and roles of employment. The pain may also be associated with depression and may be a reason for withdrawal from recreational and social life (7,10,11). Thus, treating this debilitating condition appropriately is important, particularly because of the impact on QOL and the associated depression and anxiety (12).

The management of DNP is challenging and can require a multi-modal approach involving early recognition, glycemic control and psychological therapy, as well as therapies for symptomatic pain relief (13-15). At present, the pharmacological treatments for DNP include oral and topical therapies (16). Oral agents, such as amitriptyline, duloxetine, pregabalin and gabapentin, are recommended as first-line drug treatments (17). However, oral therapy requires multiple medications taken at varying times of the day and is often associated with a significantly elevated risk of systemic side effects, which may be severe (18). Some patients do not tolerate these drugs and some find them ineffective, which may cause a significant drop in patient compliance. With the potential to provide the same level of analgesic efficacy provided by oral analgesics, but relatively fewer systemic adverse events and drug-drug interactions (19,20), topical use of drugs as another treatment option for DNP is currently gaining interest (16,21). A variety of agents are used in the topical treatments of DNP, including

lidocaine, capsaicin, amitriptyline, clonidine, nutmeg extracts, *Citrullus colocynthis* extract oil and even a combination of various compounds, and so far offer promising results (22-28). Given the trend towards using topical medications to treat DNP, the present review provides an overview of the current knowledge regarding the physiopathology of DNP and the existing topical pharmacological treatments. A recent review, focusing on topical treatment for localized neuropathic pain, including post-herpetic neuralgia (PHN), complex regional pain syndrome, diabetic peripheral neuropathy and human immunodeficiency virus distal sensory polyneuropathy, has been published (29). In the current review, an overview is provided of the current understanding of the pathogenesis of DNP and the mechanism of drug action. Furthermore, the clinical data on available agents for topical use in patients with DNP is summarized, their potential efficacy addressed, and the potential for use of compounded topical agents in the future is highlighted.

2. Pathogenesis of DNP

The exact pathogenic mechanisms involved in the generation of DNP are not fully established (8). A variety of potential factors have been postulated to elicit the pain associated with diabetic neuropathy, including hyperglycemia, advanced glycation end-products (AGEs)/AGE receptor (RAGE) activity, oxidative stress, neuroinflammation and endoneural hypoxia (30,31). A schematic summarizing the potential mechanisms underlying the pathogenesis of DNP is presented in Fig. 1.

There is a consensus that hyperglycemia serves a crucial role in the development of DNP (2,32-36). Studies in non-diabetic individuals and in animals have demonstrated that hyperglycemia can cause a decrease in pain thresholds (34,35). Hyperglycemia is correlated with the progression of neuropathy pain; approximately 50% of patients who have had diabetes for more than 25 years will develop neuropathy and the majority of symptomatic patients will complain of pain (2,36).

Other factors besides hyperglycemia may result in the generation of DNP (37). An increase in AGE production and a decrease in the regeneration of glutathione may be caused by hyperglycemia (38,39). Depletion of glutathione could be the primary cause of oxidative stress and related to the accumulation of toxic species (40). In addition, when the disposal of intracellular glucose is impaired, alternate pathways are activated, which may also lead to oxidative stress and nerve injury (41-43). Hyperglycemia serves a key role in oxidative stress in diabetic nerves (41). Nerve hypoxia may be evoked by hyperglycemia, particularly in sensory nerves, altering their function and electrical stability (44). AGEs, oxidative stress and hypoxia thereby cause the production of inflammatory cytokines and growth factors, which in turn cause neuroinflammation and nerve injury (45-47). Neuropathic pain has been associated with neurological damage to the function of sensory fibers, including fast-conducting myelinated A δ fibers and slow-conducting unmyelinated C fibers, which conduct nerve impulses, and changes in voltage-gated ion channel distribution and expression (48,49). In addition, the upregulation of transient receptor potential vanilloid 1 (TRPV1) expression has been identified to be associated with

neuropathic pain (50). Hyperglycemia, AGEs, hypoxia and oxidative stress-mediated damage in neurons and glial cells, as well as the subsequent activation of proinflammatory cascades and crosstalk between these disease processes, may ultimately result in abnormal ectopic discharges and abnormal synaptic neurotransmitter release, including of serotonin and norepinephrine (8), and thereby trigger development of neuropathic pain (51).

3. Topical pharmacological treatment of DNP

The analgesic effect and safety of various topical agents including lidocaine plasters and patches, capsaicin cream, capsaicin gel, capsaicin patches, amitriptyline cream, clonidine gel, ketamine cream, extracts from medicinal plants including nutmeg extracts and *Citrullus colocynthis* extract oil, and some compounded topical analgesics, have been assessed in patients affected by DNP. Topical agents evaluated in clinical trials are discussed in detail herein and their targets of action are presented in Fig. 2.

Topical lidocaine. Lidocaine, a blocker of voltage-gated sodium channels (particularly Nav 1.7 and 1.8), can stabilize the neuronal membrane potential on abnormally excitable A δ and C fibers, resulting in a reduction of ectopic discharges (52,53). This raises the peripheral ectopic discharge threshold and reduces the pain transduction. Topical lidocaine has been demonstrated to be effective in the treatment of neuropathic pain conditions, including DNP (54-57). A network meta-analysis compared 5% lidocaine-medicated plaster for the relief of DPN with other relevant drugs, including amitriptyline (30, 75 and 125 mg/day), pregabalin (300 and 600 mg/day), capsaicin (0.075% cream, four times a day), gabapentin (≤ 900 and 1,200 mg/day) and placebo. It was indicated that all interventions were effective in comparisons with a placebo. Notably, lidocaine medicated plasters were comparable to all of the other interventions (58).

Here, five reports that assessed the effectiveness of topical lidocaine for DNP have been reviewed (Table I). A 4-week, randomized, open-label, multicenter, non-inferiority study, which compared lidocaine plaster with pregabalin in patients with DNP, was reported as an interim analysis (59) and published in full (52,60). The interim analysis revealed that patients administered with 5% lidocaine plasters experienced similar analgesic efficacy, fewer drug-related adverse events (DRAEs; 3.9 vs. 39.2%) and substantially fewer discontinuations due to DRAEs (1.3 vs. 20.3%) than pregabalin (59). In the full analysis the investigators also reported results for EuroQol-5D (EQ-5D) QOL evaluation. In line with the aforementioned results, 5% lidocaine-medicated plaster exerted comparable efficacy, greater improvements in the QOL based on EQ-5D, and fewer adverse events, DRAEs and related discontinuations compared with pregabalin (52). To our knowledge this was the only study that has assessed the lidocaine plaster as a monotherapy for DNP. An 8-week combination phase of this study also demonstrated additional decreases in recalled average pain intensity scores over the previous 3 days (numeric rating scale-3 scores) (60). Another open-label study on patients with DPN who experienced pain following a stable analgesic drug regimen and dosages for at least a week, and

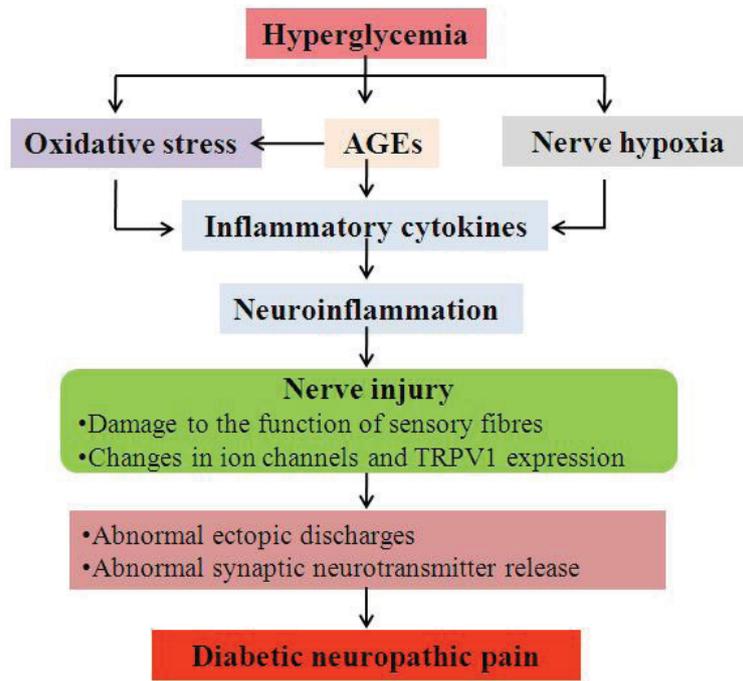


Figure 1. A summary of the pathogenesis of DNP. DNP, diabetic neuropathic pain; AGEs, advanced glycation end-products; TRPV1, transient receptor potential vanilloid 1.

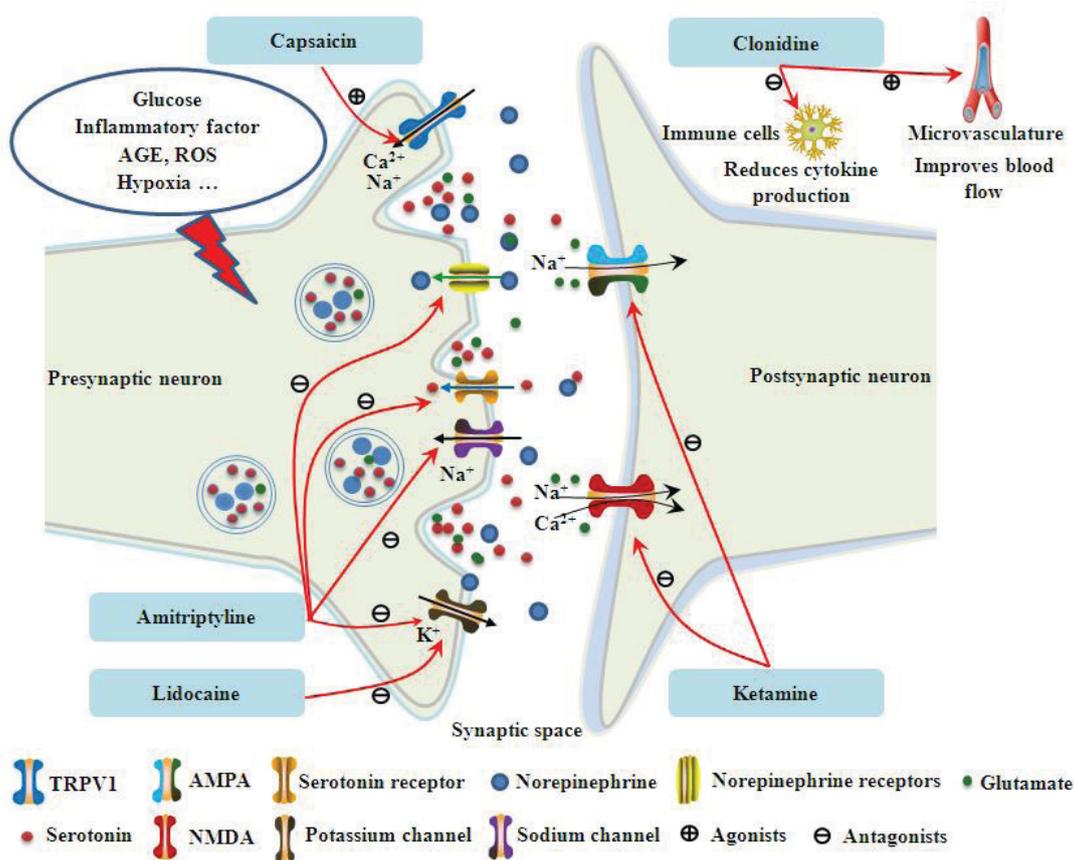


Figure 2. Therapeutic targets of topical agents for DNP. AGEs, advanced glycation end-products; ROS, reactive oxygen species; TRPV1, transient receptor potential vanilloid 1; AMPA, a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; NMDA, N-methyl-D-aspartate; DNP, diabetic neuropathic pain.

presented with an average daily pain diary rating of ≥ 4 on the brief pain inventory, exhibited significant improvements in pain

and QOL outcome measures during a 3-week 5% lidocaine patch treatment period. These benefits were maintained during

Table I. Summary of clinical studies on topical lidocaine for the treatment of DNP.

Author, year	Topical agent(s)	Study design	No. of patients (% male)	Age, years (mean \pm standard deviation)	Duration of pain	Outcomes	(Refs.)
<i>Comparisons with oral pregabalin</i>							
Baron <i>et al.</i> , 2009	5% Lidocaine plaster	Two-stage, adaptive, randomized, controlled, open-label, 4-week, multicenter trial that incorporated a drug wash-out phase of up to 2 weeks prior to the start of the comparative phase	Lidocaine: 47 (48.9) Pregabalin: 44 (54.5)	Lidocaine: 60.2 \pm 9.9 Pregabalin: 59.8 \pm 8.4	≥ 3 months	Showed similar analgesic efficacy, fewer DRAEs (3.9% vs. 39.2%) and fewer substantial discontinuations due to DRAEs (1.3 vs. 20.3%) than pregabalin.	(59)
Baron <i>et al.</i> , 2009	5% Lidocaine plaster	Two-stage adaptive, randomized, open-label, 4-week, multicenter, non-inferiority study	Lidocaine: 105 (42.9) Pregabalin: 105 (46.7)	Lidocaine: 60.9 \pm 10.0 Pregabalin: 60.9 \pm 8.8	≥ 3 months	Showed comparable efficacy, greater improvements in QOL, and fewer AEs, DRAEs and related discontinuations compared with pregabalin. An 8-week combination phase of this study demonstrated additional decreases in NRS-3 scores.	(52,60)
<i>Noncomparative studies</i>							
Barbano <i>et al.</i> , 2004	5% Lidocaine patch	Open-label, flexible-dosing, 3-week study with a 5-week extension	56 (NA)	NA	≥ 3 months	Significantly reduced pain and improved QOL. These benefits were maintained during an additional 5 weeks with tapering of concomitant analgesics.	(56)
Argoff <i>et al.</i> , 2004	5% Lidocaine patch	Open-label, non-randomized, prospective, 2-week study	41 (41.5)	56.7 \pm 12.6	NA	Effectively reduced the intensity of pain in patients with DNP. Well tolerated in combination with other analgesic regimens. No serious AEs or adverse drug interactions.	(55)
White <i>et al.</i> , 2003	5% Lidocaine patch	Open-label, non-randomized, 2-week multicenter pilot trial.	49 (46.9)	57.7 \pm 12.6	NA	Improved pain intensity and pain relief scores.	(61)

DNP, diabetic neuropathic pain; AE, adverse event; DRAE, drug-related adverse event; QOL, quality of life; NA, not available.

an additional 5-week period with a tapering of concomitant analgesics (56). A further two studies also included patients with PHN or lower back pain (55,61). The 5% lidocaine patch could effectively reduce the intensity of pain in patients with various pain-related conditions, including DNP. A reduction in pain intensity was also observed with topical 5% lidocaine in a double-blind, randomized, placebo-controlled crossover study including patients with DNP (62). These results of clinical trials indicated that administration with a topical lidocaine 5% patch or plaster could relieve pain symptoms, including in DNP.

Topical capsaicin. Capsaicin, the active agent of the dried fruits or ground powder (paprika) of chili peppers, is a naturally occurring alkaloid (63). Capsaicin has been used with some success in the treatment of patients with DNP (6,64). These effects are thought to be caused by selective binding to TRPV1 expressed on A δ and C fibers (65). Once capsaicin binds to the receptor and the TRPV1 channel is opened, sodium and calcium influx and substance P release occurs (66). Repeated TRPV1 exposure to capsaicin causes substance P depletion and TRPV1 desensitization and defunctionalization (7). Two forms of capsaicin are available for DNP, a low-dose cream and a high-dose patch, both of which should be used under specialist supervision (67). Capsaicin creams with concentrations of 0.025-0.250% must be applied multiple times per day for several weeks before analgesic effects become obvious (68). A single application of the Qutenza patch (capsaicin patch with an 8% concentration) following an appropriate local analgesia may provide up to 3 months of pain relief (23). Seven double-blind controlled studies and one open-label study of topical capsaicin in the treatment of DNP are summarized in Table II. No study specifically examined topical capsaicin as a monotherapy for DNP.

The action of low concentration capsaicin (0.025 or 0.075%) in the treatment of DNP was reported in a series of the studies reviewed. The Capsaicin Study Group attempted to define the efficacy and safety of topical 0.075% capsaicin in patients with painful diabetic neuropathy. Improvement in pain relief, pain intensity and daily activities, including sleeping, walking and the ability to work and participate in recreational activities, were observed in significantly more patients treated with capsaicin than with a vehicle (69,70). Compared with oral amitriptyline, topical 0.075% capsaicin cream was equally effective but considerably safer according to the results of a comparative study in patients with painful diabetic neuropathy (71). A double-blind, 8-week vehicle-controlled study with either 0.075% capsaicin cream or a vehicle cream over the painful area further confirmed the value and safety of capsaicin for pain relief in subjects with DNP (72,73). By contrast, Chad *et al* (74) and Kulkantrakorn *et al* (75) observed that low concentration topical capsaicin had little effect in the treatment of DNP. After 4 weeks of 0.075% capsaicin cream treatment, there was no notable difference between capsaicin and the vehicle in terms of their beneficial effects on DNP (74). Meanwhile, 0.025% capsaicin gel was determined safe and well tolerated, but it did not provide significant pain relief in patients with DNP compared with a placebo (75). Due to the inconsistencies between the aforementioned studies and their small sample sizes, it is difficult to conclude on the efficacy of low-concentration topical capsaicin in the treatment of DNP.

An 8% capsaicin patch, which is optimized for rapid delivery of a high concentration of capsaicin directly to the skin, contains 179 mg or 8% w/w capsaicin. One double-blind study that assessed the efficacy of an 8% capsaicin patch compared with a placebo and one open-label study that provided long-term safety and tolerability data on patients with painful diabetic peripheral neuropathy (PDPN) were available. In the double-blind trial that assessed efficacy, 369 patients were randomized to an 8% capsaicin patch (Qutenza) or a placebo patch regimen. The capsaicin patch provided modest but statistically significant improvements in pain relief and improved sleep quality compared with the placebo patch, was well tolerated, and was not associated with any sensory deterioration or new safety concerns (76). In the 52-week open safety study, 468 DNP patients were randomized to a capsaicin 8% patch repeat treatment for 30 or 60 min plus standard of care (SOC), or SOC alone. No worsening in sensory perception tested with sharp, cold, warm or vibration stimuli was observed with topical capsaicin. Compared with SOC therapy alone, SOC plus capsaicin 8% patch repeat treatment over 52 weeks was well tolerated, had no neurological or negative functional effects and raised no new safety concerns (77). An article from the Drug and Therapeutics Bulletin proposed that there is a limited role for topical capsaicin in the treatment of DNP due to the uncertain efficacy of low-concentration topical capsaicin and the considerably more expensive cost of the 8% capsaicin patch compared with oral therapies (67). However, topical 0.075% capsaicin was recommended as a likely effective treatment option for DNP in the American Academy of Neurology evidence-based guidelines (78). A network meta-analysis performed in patients with PDPN suggested that the 8% capsaicin patch was only as effective as oral centrally acting agents but offered superior systemic tolerability benefits (18). Either low concentration or high concentration capsaicin may provide a degree of pain relief to some patients with neuropathic conditions that cause different degrees of pain. Further developments in methods of application and formulation may lead to improved clinical efficacy.

Topical amitriptyline. Amitriptyline is a tricyclic anti-depressant that acts centrally by blocking Na⁺, K⁺, and Ca²⁺ voltage-gated ion channels (79-81), inhibiting neuronal reuptake of norepinephrine and serotonin. It is effective in treating various types of neuropathic pain (82). A topical form of this drug has been investigated in certain previous studies for the treatment of DNP (24,62,83) (Table III), however its adverse effects in oral administration have limited the higher doses needed to achieve adequate analgesia.

In a double-blind, randomized, placebo-controlled crossover study, 35 patients with postsurgical neuropathic pain, PHN or DNP were included to examine the analgesic effect of topical 5% amitriptyline. This study failed to show efficacy of topical amitriptyline in alleviating neuropathic pain, though the results were based on a small sample size of DNP patients (62). Inconsistent with these results, a double-blind, 12-week, randomized and non-inferiority trial revealed that topical 2% amitriptyline was effective in managing DNP. The results were similar to 0.75% capsaicin cream, with fewer adverse effects and improved patient compliance. However, the study only measured the median pain score using the visual

Table II. Summary of clinical studies on topical capsaicin for the treatment of DNP.

Author, year	Topical agent(s)	Study design	No. of patients (% male)	Age, years (mean \pm standard deviation)	Duration of pain	Outcomes	(Refs.)
<i>Comparisons with placebo or vehicle</i>							
Chad <i>et al</i> 1990	0.075% Capsaicin cream	Double-blind, 4-week, multicenter, vehicle-controlled, randomized study	Capsaicin: 24 (NA) Vehicle: 22 (NA)	NA	NA	No obvious effects on pain relief	(74)
The Capsaicin Study Group, 1991-1992	0.075% Capsaicin cream	Double-blind, 8-week, multicenter, vehicle-controlled parallel randomized study	Capsaicin: 138 (51.4) Vehicle: 139 (48.9)	Capsaicin: 60.1 (27-92) ^a Vehicle: 60.3 (22-81) ^a	NA	Well tolerated Effective for reducing pain Improved daily activities Enhanced QOL	(69,70)
Tandan <i>et al.</i> , 1992	0.075% Capsaicin cream	Double-blind, 8-week, vehicle-controlled study with either 0.075% capsaicin cream or vehicle cream over the painful areas	Capsaicin: 11 (54.5) Vehicle: 11 (45.5)	Capsaicin: 55.1 \pm 7.6 Vehicle: 53.3 \pm 11.8	NA	Decreased mean pain intensity Relieved mean pain scores No adverse effects on sensory thresholds Approximately 50% of subjects reported improved pain control or were cured in a follow-up open-label study	(72,73)
Kulkantrakorn <i>et al.</i> , 2013	0.025% Capsaicin gel	Double-blind, 20-week, crossover, randomized, single-center study enrolling subjects with DNP	33 (48.5)	58.0 (35-76) ^a	\geq 1 month	Safe and well tolerated Did not provide significant pain relief	(75)
Simpson <i>et al.</i> , 2017	8% Capsaicin patch	Phase 3, randomized, double-blind, 12-week, placebo-controlled, multicenter trial	Capsaicin: 186 (61.3) Placebo: 183 (55.2)	Capsaicin: 63.9 \pm 10.6 Placebo: 62.0 \pm 10.8	\geq 1 year	Provided modest and statistically significant improvements in pain relief Improved sleep quality Well tolerated Did not cause any sensory deterioration or new safety concerns	(76)

Table II. Continued.

Author, year	Topical agent(s)	Study design	No. of patients (% male)	Age, years (mean ± standard deviation)	Duration of pain	Outcomes	(Refs.)
<i>Comparisons with oral amitriptyline</i>							
Biesbroeck et al, 1995	0.075% Capsaicin cream	Double-blind, 8-week, multicenter, parallel study compared the safety and efficacy of topical capsaicin and oral amitriptyline in patients with painful diabetic neuropathy	NA	NA	NA	Equally effective Considerably safer	(71)
<i>Comparisons with SOC alone</i>							
Vinik et al, 2016	8% Capsaicin patch	Phase 3, multinational, open-label, randomized, controlled, 52-week safety study	Capsaicin 8% patch (30 min) + SOC: 156 (47.4) Capsaicin 8% patch (60 min) + SOC: 157 (50.3) SOC: 155 (45.8)	Capsaicin 8% patch (30 min) +SOC: 60.9±10.9 Capsaicin 8% patch (60 min) +SOC: 61.0±10.3 SOC: 59.1±10.3	≥1 year	In patients with PDPN, capsaicin 8% patch repeat treatment plus SOC over 52 weeks was well tolerated with no negative functional or neurological effects compared with SOC alone	(77)

^aMean age (range). SOC, standard of care; DNP, diabetic neuropathic pain; PDPN, painful diabetic peripheral neuropathy; QOL, quality of life; NA, not available.

Table III. Summary of clinical studies on other topical agents for the treatment of DNP.

Author, year	Topical agent(s)	Study design	No. of patients (% male)	Age, years (mean \pm standard deviation)	Duration of pain	Outcomes	(Refs.)
<i>Comparisons with topical 5% lidocaine and placebo</i>							
Ho <i>et al.</i> , 2008	5% Amitriptyline cream	Double-blind, randomized, placebo-controlled crossover study	35 (45.7)	57.4 \pm 13.8	≥ 6 months	No significant change in pain intensity was observed with topical amitriptyline or placebo Topical lidocaine and placebo each reduced pain more than topical amitriptyline	(62)
<i>Comparisons with topical 0.75% capsaicin cream</i>							
Kiani <i>et al.</i> , 2015	2% Amitriptyline cream	Double-blind, 12-week, randomized, and non-inferiority trial	Amitriptyline: 51 (33.3) Capsaicin: 51 (31.4)	Amitriptyline: 57.5 \pm 10.8 Capsaicin: 55.4 \pm 10.6	≥ 3 months	Both drugs significantly relieved pain in 12 weeks compared with baseline values. Well tolerated	(24)
<i>Comparisons with placebo</i>							
Campbell <i>et al.</i> , 2009 and Wrzosek <i>et al.</i> , 2015	0.1 and 0.2% Clonidine gels	Double-blind, 8-week, randomized placebo-controlled trial	0.1% clonidine: 54 (NA) 0.2% clonidine: 54 (NA) Placebo: 57 (NA)	NA	NA	The reduction in mean aggregate pain score from week 8 to baseline in subjects who received 0.1% gel was significantly greater compared with the placebo group. The reduction in pain for the 0.2% group was less impressive Adverse events were similar between the three groups.	(25,87)
Campbell <i>et al.</i> , 2012	0.1% Clonidine gel	Double-blind, 12-week, randomized, placebo-controlled, parallel-group, multi-center trial	Clonidine: 89 (49) Placebo: 90 (47)	Clonidine: 59.4 \pm 9.9 Placebo: 57.6 \pm 9.5	≥ 6 months	Significantly reduced the level of pain Safe and without the problematic side effects typically associated with systemic therapies	(88)

Table III. Continued.

Author, year	Topical agent(s)	Study design	No. of patients (% male)	Age, years (mean \pm standard deviation)	Duration of pain	Outcomes	(Refs.)
Motilal and Maharaj, 2013	Nutmeg extract	Double-blind, 4-week, randomized, placebo- controlled trial.	Nutmeg extract: 37 (32.4) Placebo: 37 (32.4)	Nutmeg extracts: 60.7 \pm 11.5 Placebo: 59.7 \pm 8.1	NA	Reduced worst and mean pain scores Improved QOL No statistically significant differences between the groups for all outcome measures	(26)
Heydari <i>et al</i> , 2016	Topical <i>Citrullus colocynthis</i> extract oil	Two-arm, double-blind, randomized, placebo-controlled, parallel study	<i>Citrullus colocynthis</i> extract oil: 30 (39.3) Placebo: 30 (55.6)	<i>Citrullus colocynthis</i> extract oil: 57.4 \pm 10.0 Placebo: 52.7 \pm 10.5	\geq 3 months	Decreased mean pain score Improved nerve function Improved physical domain of QOL	(27)
Mahoney <i>et al</i> , 2012	Topical ketamine cream	Double-blind, randomized, placebo-controlled, study	Ketamine: 10 (40.0) Placebo: 7 (57.1)	Ketamine: 64.0 \pm 9.5 Placebo: 65.4 \pm 15.0	NA	No more effective than placebo	(100)
ClinicalTrials. govNCT00476151, 2006	Topical 4% amitriptyline and 2% ketamine	Phase 2, multicenter, randomized, placebo- controlled, parallel group study	Ami/Ket: 114 (57.0) Placebo: 112 (50.9)	Ami/Ket: 56.1 \pm 9.4 Placebo: 55.1 \pm 11.0	\geq 6 months	Showed a strong trend toward pain reduction in painful diabetic neuropathy	(28)

DNP, diabetic neuropathic pain; QOL, quality of life; NA, not available.

analogue scale (24). In addition, two cases treated with high doses of topical amitriptyline in neuropathic pain have been described to record the effect of topical amitriptyline (83). One of the cases reported a 39-year-old patient suffering from severe neuropathic pain in the feet and hands, due to type II diabetes mellitus (83). Following the use of 5% amitriptyline, the pain in the hands was markedly relieved, and following application of amitriptyline 10% to the feet, a total reduction of pain occurred within 20 min and lasted the whole day. These effects reportedly lasted for 7 months and the patient did not experience any amitriptyline-related side effects (83). Amitriptyline could also improve the quality of sleep for the patients by reducing severe pins and needles in the feet at night (83). Therefore, high dose topical amitriptyline at 5 and 10% may be a useful adjunct to treat severe and intractable DNP. However at present, the therapeutic effect of amitriptyline on DNP is still unclear. Given the conflicting results of the reports, more studies are required to confirm the efficacy and safety of this topical compound as a treatment for DNP.

Topical clonidine. Clonidine is used to treat hypertension and other conditions, including intraocular pressure rise (84) and attention deficit syndrome (85), but it also has actions on sensory neurons by reducing excitability, acts on the microvasculature by improving blood flow, and acts on immune cells by reducing cytokine production (86). It is a presynaptic α_2 -adrenergic receptor agonist; thus adverse events associated with systemic use of this drug have limited its application. As such, topical clonidine formulations have been investigated in clinical studies. Two randomized placebo-controlled studies for the treatment of DNP have been conducted in the USA by Wrzosek *et al* (25) and Campbell *et al* (87) (Table III). Both studies evaluated the efficacy and safety of topical clonidine gel in DPDN patients. In the first of the studies, 54 patients received 0.1% clonidine gel (650 μ l) and another 54 patients were treated with 0.2% clonidine gel (500 μ l). The control group (57 patients) was given a placebo gel. Participants remained on their existing pain management treatments and these gels were applied to both feet twice daily for 2 weeks, then 3 times daily to a total of 8 weeks (25). Over the 8-week study interval, the reduction in mean aggregate pain score when compared with baseline in subjects who received 0.1% gel was significantly greater compared with the placebo group, while the reduction in pain for the 0.2% group was less notable. Investigators suggested the possible reason leading to such difference was the amount applied to the skin (500 μ l at 0.2% vs. 650 μ l at 0.1%). Campbell *et al* (88) subsequently performed a 12-week study to examine further the efficacy of topical 0.1% clonidine in treating DNP. In the clonidine group, the decrease in average pain from baseline to week 12 was greater than in the placebo group. For safety, only a low concentration of clonidine (<10 pg/ml) was aimed for in the plasma during topical application (88), and it was considerably lower than the threshold for treating hypertension, suggesting that topical use will be associated with few of the adverse effects of clonidine. The results of these two clinical trials indicated that the topical use of clonidine may relieve DNP, but it is not known from these studies if clonidine is safe for long-term use. The use of active treatment rather than placebo may reveal more information about the comparative efficacy of topical clonidine vs. other drugs.

Topical nutmeg extracts. Nutmeg is the dried kernel of the broadly ovoid seed of *Myristica fragrans*. Certain animal studies support nutmeg as a potential analgesic for DNP (89,90). A double-blind, 4-week, randomized, placebo-controlled trial further tested the ability of topical nutmeg extracts to reduce pain or improve QOL in patients with DNP (26) (Table III). A total of 74 participants who met the criteria for painful diabetic neuropathy were recruited. Subjects were instructed to apply four sprays of either topical nutmeg extract or placebo to the affected area 3 times a day followed by gentle massage for 4 weeks. The topical nutmeg extract preparation significantly reduced the worst and mean pain scores, and improved QOL by the end of the 4-week study, but the effects were not superior to the placebo. Due to the limited clinical research data, it is not possible to conclude on the efficacy of topical nutmeg extracts for the treatment of painful diabetic neuropathy.

Topical Citrullus colocynthis (bitter apple) extract oil. Bitter apple, or *Citrullus colocynthis*, is a medicinal plant originating from Africa and Asia, where it has traditionally been used for various medicinal purposes, including pain relief (91). *Citrullus colocynthis* has been demonstrated to have anesthetic (92), anti-oxidant (93) and anti-ulcerogenic effects (94). These properties are considered important in the pathophysiology and/or progression of diabetic neuropathy. Heydari *et al* (27) examined its efficacy and safety in DNP patients (Table III): 60 patients with DNP were randomized to receive topical *Citrullus colocynthis* or placebo twice daily for 3 months. There was a significantly greater decrease in mean pain score after 3 months in the *Citrullus colocynthis* group than with the placebo. It also significantly improved nerve function and the mean score in the physical aspect of QOL (95). Therefore, topical *Citrullus colocynthis* may be a potential agent for use in the treatment of DNP and should be investigated further in studies with larger sample sizes performed over longer duration.

Topical ketamine. Ketamine is a non-barbiturate anesthetic agent that acts through blocking glutamate receptors, including peripheral N-methyl-D-aspartate receptors and α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (86,96-98), and also as an inhibitor of voltage-gated Na⁺ and K⁺ ion channels (99). A recent study evaluated the effects of topical ketamine in relieving DNP (Table III): 17 patients with DNP were randomly divided into a 5% ketamine cream group or a placebo group. The 5% topical ketamine cream was no more effective than the placebo in relieving pain caused by diabetic neuropathy (100). A limitation of this study was the sample size; therefore the clinical efficacy of ketamine needs to be further evaluated.

Compounded topical agents. Mixtures of two or more medicated forms of compounded topical agent have been developed into potentially valuable treatment options for DNP. The authors of the current study concluded that these may be effective due to the multiple complementary effects at lower doses of each individual medication. It is apparent that only one study with compounded topical agents has been performed in patients with DNP only (28) (Table III); 4 other related studies also selected patients with other types

of neuropathic pain (96,101-103). In a pilot study and its follow-up studies of mixed neuropathic pain, including DNP, patients who were treated with topical low-dose combinations of amitriptyline (1-2%) and ketamine (0.5-1%) did not experience significant pain relief effect compared with those receiving placebo for 1-3 weeks (96,101). However, the treatment was associated with long-term perceived analgesic effectiveness for 12 months (102). As for higher concentrations of these combined agents (4% amitriptyline and 2% ketamine), a phase 2, multi-center, double-blind, randomized, placebo-controlled, parallel group study indicated a trend towards pain reduction in painful diabetic neuropathy (16,28). Somberg and Molnar (103) conducted a retrospective study on the analgesic activity of a topical (TT-CTAC) cream in patients with diabetic neuropathy and other chronic pain conditions. Two versions of TT-CTAC cream were evaluated: cream 6B and cream 7B. Both creams contain ketamine (10%), baclofen (2%), gabapentin (6%), amitriptyline (4%), bupivacaine (2%) and clonidine (0.2%). Additionally, one cream (7B) contained nifedipine (2%). Both creams provided considerable pain relief in the majority of the patients studied and were thus suggested to be useful modalities for pain therapy. Due to a lack of comparative studies between compounded topical agents and single drugs for DNP, it is not possible to conclude on the drug cost, efficacy and side effects of compounded agent compared with single-agent topical treatment of DNP. However, given the advantages of formula diversity, drug economy and safety, it may be that compounded topical agents have promising market prospects and clinical application value.

4. Conclusion and perspectives

DNP is a distressing consequence of diabetes that may be present in as many as one in five diabetic patients (104). The pain may be severe and management challenging. Oral treatment is the most frequently used and among the most convenient for pain medication, but is also associated with risk of adverse systematic effects (105,106), particularly in vulnerable patients with multiple comorbidities and altered pharmacokinetics and pharmacodynamics that may alter drug metabolism (107). This may decrease the patient's compliance. With this concern for the systematic side effects of oral agents, topical preparations for the treatment of DNP have gained increasing interest. Numerous clinical studies have evaluated the analgesic effect and safety of various topical agents, including topical anesthetic agent lidocaine, general anesthetic agent ketamine, antidepressant agent amitriptyline, α_2 adrenergic agent clonidine, capsaicin, nutmeg extracts, *Citrullus colocynthis* extract oil, and some compounded topical analgesics. Overall topical agents are easy to administer, offer significant improvement in patient compliance and reduce the burden of multiple drug regimens.

For the topical treatments of DNP discussed here, a 5% lidocaine patch has been found to significantly reduce pain in DNP patients with 2-3 weeks of treatment and the benefits were maintained during an additional 5 weeks with tapering of concomitant analgesics. Furthermore, the 5% lidocaine plaster was reported to exhibit similar analgesic efficacy and fewer DRAEs compared with oral pregabalin. It is difficult to draw

conclusions about the efficacy of low-concentration topical capsaicin in the treatment of DNP due to the inconsistencies among related research findings. The 8% capsaicin patch was as effective as oral centrally acting agents but offered systemic tolerability benefits, provided modest but statistically significant improvements in pain relief and was well tolerated. There is conflicting evidence regarding the effect of topical amitriptyline and it needs to be confirmed by further studies. Topical clonidine, nutmeg extract preparation, *Citrullus colocynthis* extract and some compounded topical agents may provide significant though less notable or only long-term improvements in pain relief. For instance, study demonstrated that 5% topical ketamine cream was no more effective than a placebo in relieving pain caused by diabetic neuropathy, but the study only included 17 patients with DNP.

Since published studies suggest that these drugs have the potential to be a valuable additional option for the management of DNP, with adequate safety and continuous long-term treatment efficacy, these topical drugs should be given further consideration for the treatment of DNP. Furthermore, as described in several studies, compounded agents are not only effective but also safe for patients with DNP. Therefore, the use of low-dose, complementary therapies with compounded agents is another area worthy of further investigation. Additionally, topical drugs that act on different targets in the process of DNP, including anti-inflammatory and abnormal ectopic discharge therapies, or anti-oxidant and AGE/RAGE therapies, should be studied in the future.

Acknowledgements

Not applicable.

Funding

The authors would like to thank the Natural Science Foundation of China (grant no. 81603171), the Natural Science Foundation of Hunan Province (grant no. 2018JJ3743) and the Open-End Fund for the Valuable and Precision Instruments of Central South University (grant no. CSUZC201734) for the financial support.

Availability of data and materials

Not applicable.

Authors' contributions

PFF, XDY and YYY designed the present study. XDY, PFF, DXX and YYY collected the literature and performed the literature review. XDY and YYY wrote the manuscript. YYY, PFF and XDY revised the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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