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REVIEW

Diabetic Peripheral Neuropathy: Pathophysiology and New Insights into the Mechanism of Action of High-Concentration Topical Capsaicin

David G Armstrong[1], Keith Bley[2], David M Simpson[3], Peter Staats[4], Samuel Allen[5], Audrey Carnevale[5], Lizandra Marcondes[5]

[1]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [2]Pyrotech Therapeutics, Inc., Beijing, People's Republic of China; [3]Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [4]Vagus Nerve Society, Atlantic Beach, FL, USA; [5]Averitas Pharma, Inc., Morristown, NJ, USA

Correspondence: Samuel Allen, Medical Affairs, Averitas Pharma, 360 Mt Kemble Ave Third Floor, Morristown, NJ, 07960, USA, Tel +1 901-659-1371, Email Samuel.Allen@averitaspharma.com

Abstract: Diabetic peripheral neuropathy (DPN) is a chronic, progressive complication of diabetes. Pain in DPN can be severe and detrimental to the patient's quality of life. In this review, we provide an update on the mechanism of action (MOA) of high-concentration capsaicin topical system (HCCTS) for treatment of painful DPN, with an emphasis on neuroregeneration. In diabetes, hyperglycemia and other metabolic imbalances lead to oxidative stress and inflammation, which result in degeneration of the axons of afferent neurons (particularly C and Aδ fibers) within the peripheral nervous system. Dysfunction of the microvasculature supporting the nerves further exacerbates neural damage. As a result, epidermal nerve fiber density (ENFD) diminishes, and physical and chemical changes to the remaining afferent fibers render them hypersensitive to painful stimuli and hyposensitive to normal stimuli. As the longest axons are usually damaged first, DPN normally begins in the feet, then legs, and finally the hands. HCCTS incorporates a matrix technology that forcibly diffuses a high concentration of capsaicin (a TRPV1 agonist) to the dermis and epidermis, targeting TRPV1 receptors that are upregulated in DPN and play a key role in pain generation. HCCTS activates TRPV1 receptors expressed on the neuron cell membrane and endoplasmic reticulum, leading to cytoplasmic calcium ion overload, and then a cascade of cellular events resulting in reversible neurolysis of these afferent terminals. After 1–3 months, the terminals regenerate with a "healthier" phenotype, increasing ENFD, resulting in vasodilation, which may lead to a microenvironment conducive to improved neuroregeneration. This MOA is supported by clinical evidence demonstrating that repeated HCCTS treatment provides cumulative benefits in pain and improvements in sensory function of the feet compared with baseline. If effects on sensory function are confirmed in large-scale clinical studies, HCCTS could help slow the progression of DPN to more severe forms of diabetic foot syndrome.

Plain Language Summary: Diabetic peripheral neuropathy, or DPN, is a long-term complication of diabetes that gets worse over time if left untreated. People with DPN may experience severe pain and poor physical and mental health. DPN occurs when elevated blood sugar levels progressively damage sensory nerve fibers in the skin and their supporting blood vessels. As a result, the number of nerve fibers in the skin decreases, and the remaining nerve fibers undergo changes that heighten their sensitivity. These changes can also lead to loss of normal feeling in the skin and slow wound healing, especially in the feet. High-concentration capsaicin topical system (HCCTS) is a treatment that is placed directly onto the skin, and approved in many countries to manage peripheral neuropathic pain; in the United States, it is approved for treatment of pain associated with DPN in the feet. HCCTS is applied by a healthcare professional to the feet for 30 minutes, and this medicine works by targeting and silencing pain receptors on nerve fibers, which leads to pain relief. After 1–3 months, nerve fibers grow back and are "healthier" than before, responding more normally to stimuli. Improved nerve functioning increases blood flow, which may help improve regeneration of healthier nerves. Repeated treatment of DPN with HCCTS is needed because diabetes is a long-term condition in which the nerves are constantly under attack from high blood sugar levels. Studies in patients with DPN have shown that HCCTS can provide long-lasting pain relief and improve quality of life.

Keywords: capsaicin, degeneration, DPN, hyperalgesia, neurolysis, TRPV1

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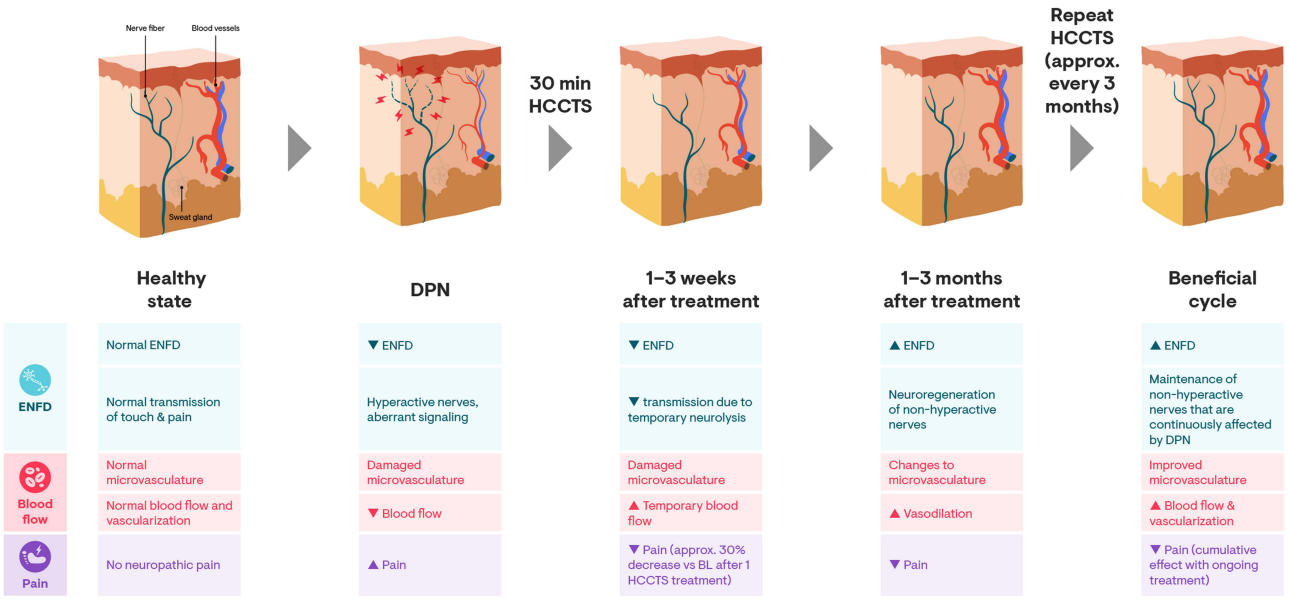
Graphical Abstract



BL, baseline; DPN, diabetic peripheral neuropathy; ENFD, epidermal nerve fiber density; HCCTS, high-concentration capsaicin topical system.

Introduction

Diabetic peripheral neuropathy (DPN) is a chronic and progressive complication of diabetes mellitus, often resulting in bilateral limb pain, numbness, and paresthesia, which can also lead to foot ulcers and amputation in severe cases.[1–5] The pain associated with DPN can be severe and negatively impact patients' quality of life (QOL), sleep, mental health, and ability to perform day-to-day activities.[1–5] In addition to the burden of pain, DPN is associated with a high pill burden, socioeconomic costs, and mortality associated with complications of the diabetic foot.[5–8]

Interconnecting pathologic pathways triggered by metabolic imbalances result in neuronal damage, decreased blood flow, and abnormal sensory perception in the affected area.[9] These pathologic changes begin distally, usually in the foot, where the combination of sensory, neuronal, and autonomic neuropathies result in altered sensory function that causes the feet to be painful, slow to heal, and prone to injuries.[10] Disease progression, lack of treatment, and sensory loss often lead to the skin on pedal prominences becoming damaged, infected, and even ulcerated.[3,9,10] In severe cases, the damaged areas—one or more toes or even the entire foot—require amputation.[10] In the United States, diabetes is regarded as the most common cause of non-traumatic lower limb amputation, accounting for nearly 100,000 amputations each year.[11]

Clinical guidelines and recommendations include several treatments for painful DPN, ranging from lifestyle modifications to non-invasive and invasive options.[12–16]

The most commonly used oral therapies are calcium channel α2-δ ligands (gabapentin and pregabalin), the selective serotonin and norepinephrine reuptake inhibitor duloxetine, and tricyclic antidepressants (amitriptyline, nortriptyline, desipramine).[12–15] Commonly used oral medications for painful DPN can be suboptimal, being associated with a poor risk–benefit ratio, low adherence, and high rates of discontinuation and dissatisfaction.[1,3,5,17,18] In addition, the well-known risks of opioid addiction and abuse mean that chronic use of opioids is problematic and not recommended.[14,19]

Commonly used topical therapies are lidocaine 5% transdermal patch (but this is not licensed for use in DPN in the USA) and the subject of this review, high-concentration capsaicin topical system (HCCTS).[12–15] Spinal cord stimulation (SCS) and magnetic peripheral nerve stimulation (mPNS) devices have recently been approved by the US Food and Drug Administration (FDA) as non-pharmacological therapies for managing chronic pain, including painful DPN (PDPN).[20,21] SCS involves the surgical implantation of electrodes and a power source that delivers electrical currents to the spinal

cord, effectively reducing the perception of pain in chronic pain conditions such as PDPN.[20] mPNS generates lower electric fields at the body's surface, allowing for greater penetration and the stimulation of deep nerves without pain.[22] SCS is supported by the American Diabetic Association and American Society of Pain and Neuroscience (ASPN) guidelines as a viable treatment option for patients with refractory PDPN who do not respond to pharmacological therapies.[13,14] mPNS is briefly mentioned by the ASPN as an emerging therapy for DPN/PDPN, where it may provide intermediate-term relief.[13]

The management of DPN requires improvement in several areas to enhance patients' QOL compared with current practices and to reduce risk of progression to more severe forms of diabetic foot. Firstly, there is a need for early detection and diagnosis so that appropriate intervention may be started in a timely manner.[23,24] Secondly, pain management needs to be more effective to increase response rates, with a longer duration of response than the current standard of care. Thirdly, treatments should focus on restoring sensory function. Finally, patients report that reducing their pill burden should be a priority;[5] therefore, non-systemic options should be made available.

Locally applied, topical therapy may play a role in meeting many of these needs. A HCCTS (Qutenza®, Averitas, Morristown, NJ, USA) has been approved by the FDA for the treatment of neuropathic pain associated with painful DPN of the feet and postherpetic neuralgia. In the European Union, HCCTS is indicated for the treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for pain. At the time of writing, HCCTS has been approved in 26 countries. In this review, we will discuss how repeated use of HCCTS can provide a range of benefits in DPN, with a focus on its potentially neuroregenerative mechanism of action.

Pathophysiologic Mechanisms of DPN

Diabetic neuropathy primarily affects the sensory neurons of the peripheral nervous system in the skin, and disease progression is characterized by the degeneration and loss of their nerve endings. The characteristic "stocking and glove" pattern of DPN arises from a tendency to damage the longest sensory axons first—that is, those that communicate to the feet, and then the hands.[25] Most of the early symptoms of DPN are mediated by damage to small fibers, which transmit pain via transient receptor potential vanilloid subtype 1 (TRPV1) and also are responsible for fine touch and detection of cold and warm stimuli.[25] As DPN progresses, there are also symptoms mediated by damage to large fibers responsible for gross mechanoreception and proprioception.

DPN affects people with type 1 and type 2 diabetes, as well as those with prediabetes.[26] However, evidence suggests that the close association between type 2 diabetes, metabolic syndrome, and obesity creates imbalances that contribute to a unique pathophysiology of DPN in type 2 diabetes.[25] A meta-analysis of 17 randomized studies showed that improved glycemic control can reduce the risk of development of clinical neuropathy in type 1 diabetes; in type 2 diabetes, however, improved glycemic control numerically reduced the risk but this did not reach statistical significance.[27] In type 2 diabetes, the progression of the pathology caused by prolonged hyperglycemia and other metabolic changes is not reversible without substantial changes to diet and lifestyle.[25,28,29] The pathology of DPN in type 2 diabetes is not fully understood, but involves metabolic imbalances and microvascular complications, ultimately causing neural damage and an altered response to pain and sensory stimulation.

Metabolic Imbalances

Hyperglycemia, dyslipidemia, and altered insulin signaling have wide-ranging, deleterious effects on multiple cell types, including neurons.[14,25] These metabolic imbalances trigger multiple pathways within neurons, leading to oxidative stress, inflammation, axonal injury, and degeneration, which result in progressive nerve injury (Figure 1).[25]

Hyperglycemia disrupts normal cellular metabolism, ultimately leading to a vicious cycle in which dysregulated production of reactive oxygen species (ROS), advanced glycation end products (AGEs), and other factors contribute to the poor and progressively neurotoxic environment in diabetes.[28,30,31] Increased generation of AGEs leads to their accumulation in the mitochondria, causing considerable strain to the electron transport chain, impaired energy production, and increased ROS generation.[31] As discussed in detail later, mitochondria play a key role in regulating proliferation and destruction of sensory neurons. Mitochondria are found at increased densities in response to the neurotrophin nerve growth factor (NGF), a known sensitizer of sensory neurons and potential mechanism of hyperexcitability.[32] The

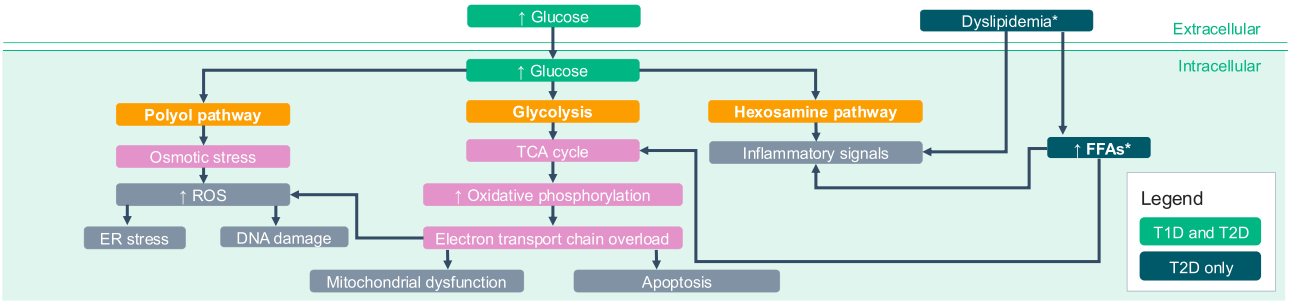


Figure 1 Mechanisms of neuronal damage caused by hyperglycemia and dyslipidemia in type 1 and type 2 diabetes. Asterisks indicate mechanisms in type 2 diabetes only. Adapted from Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Primers*. 2019;5(1):41. With permission from SNCSC.[25]
Abbreviations: ER, endoplasmic reticulum; FFA, free fatty acid; ROS, reactive oxygen species; TCA, tricarboxylic acid.

analgesic potential of anti-NGF antibodies demonstrated in animals[25] and two Phase II clinical trials have shown some efficacy of such agents in treatment of humans with painful DPN.[33,34] At the time of writing, no anti-NGF antibody is licensed for treatment of painful DPN.

Mitochondrial dysregulation and subsequent inflammatory events induce peripheral neuropathy and nerve dysfunction[35] while oxidative stress plays a central role in neuropathic pain,[36] leading to either apoptosis or pyroptosis not only in neurons but also in other cell types such as fibroblasts and epithelial cells.[30]

Microvascular Complications

Owing to their high metabolic activity, peripheral sensory nerves have a rich blood supply in the skin and are critically dependent on oxygen and nutrients from microvessels surrounding, and within, the nerve for proper functioning.[25] Hyperglycemia and its downstream effects damage the microvasculature.[25] Peripheral artery disease, vasoconstriction, and associated vascular abnormalities restrict blood supply to the periphery.[25,37,38] Diabetes also leads to decreased concentrations of mediators of blood vessel formation, such as vascular endothelial growth factor, associated with capillary basement thickening, endothelial hyperplasia, and neural dysfunction.[17,24,25] These vascular effects lead to diminished oxygen tension and hypoxia, which in turn contribute to distal nerve fiber damage.[37]

Neuronal Damage

A combination of damage, loss, and hyperactivity of peripheral sensory nerve fibers in the diabetic foot underlies the symptoms of painful DPN, which include numbness, burning, and stabbing pains (Figure 2).[39] Experiments using skin punch biopsies show that, as DPN progresses, there is a reduction in the epidermal nerve fiber (ENF) density, as assessed by immunohistochemistry using the pan-neuronal marker protein gene product 9.5 (PGP 9.5).[40] The nociceptive fibers that remain intact undergo physical and chemical changes that can make them hypersensitive to stimuli,[39] causing patients with DPN to experience spontaneous pain and sensitivity to stimuli that would have previously been characterized as innocuous.[25] Furthermore, an imbalance between excitatory and inhibitory sensory signals results in a loss of useful sensation (ie, hypoesthesia) and gain in unpleasant sensations (eg, paresthesia, allodynia, and hyperalgesia), leading to a seeming paradox in which the feet of patients with DPN can be described as simultaneously numb and continuously painful.[25,41]

Peptidergic, TRPV1-Expressing Afferent Fibers May Be Central to Pain in DPN

The TRPV1 receptor mediates integrated responses to painful stimuli, heat, and acidosis, and is expressed on C and Aδ nociceptive fibers.[36] TRPV1 is part of the large transient receptor channel superfamily of ion channels involved in somatosensory signaling.[44,45]

When dermal TRPV1-expressing, peptidergic C fibers are excited, they release calcitonin gene-related peptide (CGRP), which triggers vasodilation (a reaction known as axon reflex vasodilation).[46] Biopsies taken from patients

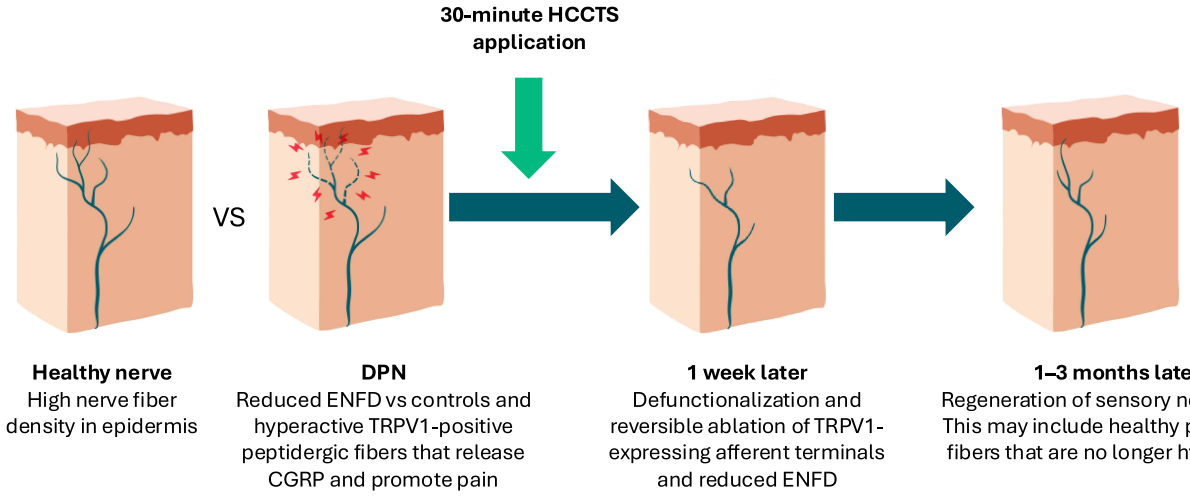


Figure 2 Proposed model for the effect of the HCCTS on nerve fiber anatomy and function via localized neurolysis and regeneration of TRPV1-positive nerve fibers. Nerve fiber density is reduced in the epidermis of patients with DPN, and the remaining fibers may exhibit an altered pain response. Following treatment with the HCCTS, the localized neurolysis of epidermal nerve fiber endings is followed by regeneration with potential restoration of a more normal phenotype and response to external stimuli. Based on findings from Kennedy et al, 2010[42] and Anand & Bley, 2022.[43]

Abbreviations: CGRP, calcitonin gene-related peptide; DPN, diabetic peripheral neuropathy; ENFD, epidermal nerve fiber density; HCCTS, high-concentration capsaicin topical system; TRPV1, transient receptor potential vanilloid subtype 1.

with DPN show a decreased density of nerve fibers compared with other peripheral neuropathies (Figure 2),[42,47,48] and it is plausible that the remaining hyperexcitable peptidergic fibers are responsible for pain in DPN.

Animal data show that both peptidergic and non-peptidergic intraepidermal innervation is reduced compared with innervation before the nerve damage.[49] Patients with DPN have a lower concentration of peptidergic C-fibers compared with healthy controls.[50] CGRP release from peripheral terminals of primary afferents in the early stages following nerve injury increases expression of voltage-gated Na^+ channels and TRPV1, and this may contribute to peripheral sensitization and maintenance of neuropathic pain.[51] Upregulation of TRPV1 in damaged nerve fibers contributes to a reduced stimulation threshold in DPN; in this hyperexcitable state, TRPV1 activation can lead to spontaneous pain and hyperalgesia.[32,39,52]

CGRP also contributes to maintenance of neuron viability, perhaps counteracting the oxidative stress that is part of DPN pathophysiology. While CGRP levels are elevated at the terminals, CGRP appears to be downregulated in the dorsal root ganglia of the peripheral sensory neurons.[53] The downregulation may be due to reduced density of C-fibers. This downregulation of CGRP is linked to an imbalance in mitochondrial metabolism and the production of ROS and is associated with impaired viability, regeneration, and function of these neurons.[53,54] In a murine model of DPN, increasing CGRP using gene transfection or exogenous CGRP led to improvements in neuron survival and outgrowth of neurites.[53]

CGRP activity leads to vasodilation, increases in local blood flow, local edema, and erythema – a process known as neurogenic inflammation.[55] This process acts to promote regeneration of damaged neurons (we will return to this concept later in this review). If peptidergic fibers are damaged in DPN, this could create a self-perpetuating cycle, where poor circulation exacerbates nerve damage and vice versa.[38] The significance of the microvascular component is highlighted by the fact that angiogenic and vasculogenic agents are proposed therapies for DPN.[38]

Mechanism of Action of HCCTS

Capsaicin is a highly potent and selective TRPV1 agonist. Following many years of work, researchers investigating TRPV1 as the receptor for capsaicin were awarded the Nobel Prize in 2021.[44] This fueled advancements in the understanding of pain and the mechanisms underlying capsaicin-induced analgesia.

When applied topically, capsaicin binds selectively to TRPV1-positive nociceptive neurons present in the skin (reviewed in Anand and Bley, 2011).[32] A significant challenge has been to optimize the mode of delivery of capsaicin

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for therapeutic purposes; as capsaicin is lipophilic and hydrophobic, there is limited potential for cutaneous delivery unless very high concentrations are applied. Topical formulations of low-concentration capsaicin, such as creams and lotions, have limited medical utility because of the need for frequent applications. The lack of acute pain relief, inconvenient application, and frequent associated discomfort results in poor compliance and, therefore, poor efficacy of these products.[39]

For the HCCTS, an optimized delivery system overcomes such issues; by delivering high local concentrations of capsaicin into the epidermis and dermis within a short time, capsaicin acts directly on TRPV1-expressing nerve fibers. The negligible diffusion of capsaicin into the blood also ensures limited effects beyond the skin and, therefore, few unwanted systemic effects.[56,57]

The HCCTS incorporates a matrix technology (Figure 3) made up of individual liquid micro-reservoir droplets that contain capsaicin solubilized in diethylene glycol monoethyl ether (DGME).[58,59] When applied to the skin, DGME from the topical system enters the stratum corneum, causing this barrier layer to become more permeable not only due to reduction of tight junction strength but also increased hydration. The penetration of DGME from the topical system into the skin leads to a change in osmotic gradient and allows water to enter the topical system. Owing to the occlusive backing of the topical system, the water that accumulates in the HCCTS along with the decrease of DGME decreases the osmotic gradient of capsaicin in the skin, which helps drive the diffusion into the epidermal layers. The reservoir of capsaicin created in the outer layers of the skin (the stratum corneum and epidermis, where nociceptive fibers terminate) serves to drive capsaicin into the dermis following removal of the topical system.[58,59]

Upon application directly onto the skin that is affected by PDPN, capsaicin activates TRPV1 receptors on the nerve fibers in the epidermis and dermis, which may be in a hypersensitive state (Figures 2 and 4).[32] Since the concentration of capsaicin is sufficiently high, a cascade of events is initiated that involves TRPV1 receptor activation, which leads to the influx of calcium ions (Ca^{2+}) through TRPV1 receptors on the cell membrane. The resulting cytoplasmic Ca^{2+} overload has multiple effects within the cell, affecting intracellular organelles and structural elements, which ultimately lead to localized axonal degeneration.[60] Capsaicin binds to TRPV1 expressed intracellularly on the endoplasmic reticulum membrane, stimulating further release of Ca^{2+} into the cell.[32]

Effects on the mitochondria are central to promoting apoptosis. As noted above, mitochondrial density is highest within parts of the neuron that are involved in sensory transduction (for which increased energy production is required).[61] Here, the excessive Ca^{2+} levels following TRPV1 activation stimulate opening of the mitochondrial permeability transition pore in the mitochondrial inner membrane.[62,63] This can lead to pro-apoptotic events including mitochondrial swelling, loss of membrane potential, release of cytochrome c and ROS, and further release of Ca^{2+} into the cytoplasm.[62,64,65] The downstream effects include oxidative damage to mitochondrial proteins, lipids, and DNA.

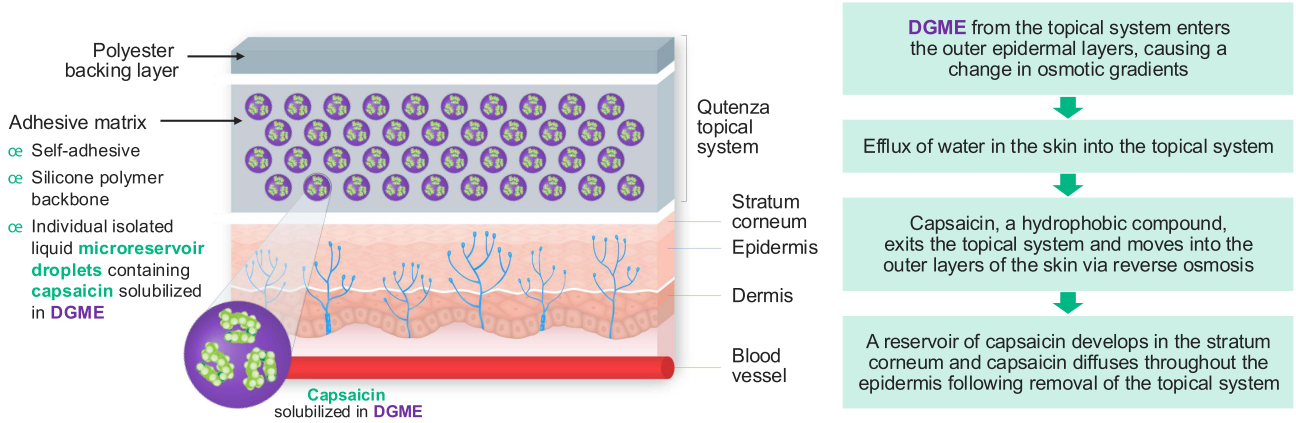


Figure 3 Structure of the HCCTS matrix technology and capsaicin delivery system. Therapeutic patch for transdermal delivery of capsaicin. Patent: US-8821920-B2. 2014. https://pubchem.ncbi.nlm.nih.gov/patent/US-8821920-B2.[59]
Abbreviations: DGME, diethylene glycol monoethyl ether; HCCTS, high-concentration capsaicin topical system.

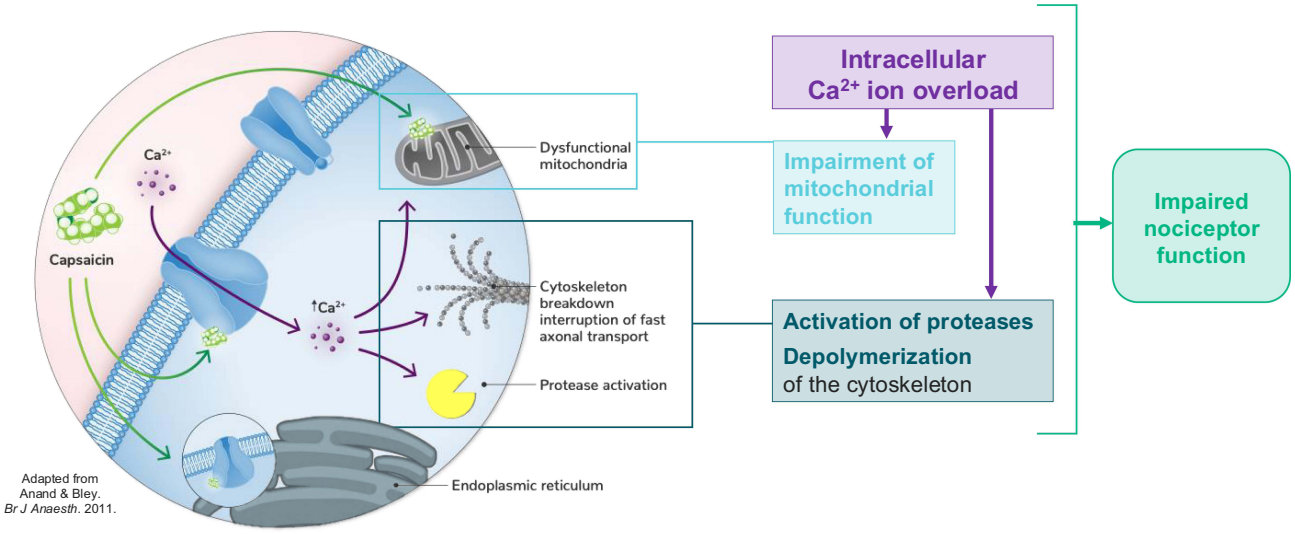


Figure 4 Molecular changes occurring following activation of TRPV1 by high-dose capsaicin. Adapted from Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth*. 2011;107(4):490–502. Creative Commons.[32]
Abbreviations: Ca^{2+}, calcium ions; TRPV1, transient receptor potential subtype vanilloid 1.

Caspases 3 and 9, which are activated by cytochrome c and ROS from the mitochondria, cause apoptosis via DNA fragmentation and condensation in the nucleus.[62] Other Ca^{2+}-dependent proteases depolymerize cytoskeletal components and break down the cytoskeleton.[61] In addition, high-dose capsaicin directly inhibits mitochondrial respiration independently of TRPV1 activation.[32] Sensory neurons are not killed by capsaicin, but the peripheral tips of the affected neurites are "trimmed", resulting in reduced spontaneous activity and loss of responsiveness to a range of painful stimuli.[32]

Thus, the intracellular effects of high-concentration capsaicin go beyond transient activation of the TRPV1 receptor. In contrast to low-concentration capsaicin, HCCTS activates the pathways described above that lead to high levels of intracellular Ca^{2+} and the consequent enzymatic, cytoskeletal, mitochondrial, and osmotic effects. The net effect of a single high-concentration capsaicin exposure is a localized denervation of TRPV1-expressing afferent terminals in the epidermis and dermis. A study in healthy human volunteers showed the loss and the recovery of ENFs in skin biopsies following a single HCCTS application.[42] While the study did not examine the time of onset of the neurolysis following one application, its effects were apparent 1 week later, when an approximately 80% reduction in ENF density was observed compared with untreated sites. By post-treatment week 24, there was almost a full recovery of ENF density to ~93% of the levels in the untreated sites, demonstrating the reversibility of this drug effect in healthy subjects.

In this way, HCCTS can induce long-lasting analgesic effects that are not achievable with the low-concentration capsaicin in patches and creams.[32]

Regeneration of Damaged Nerve Fibers

In a healthy state, peripheral neurons activate multiple signaling pathways to promote nerve regeneration after injury, largely through the expression of regeneration-associated genes like *GAP-43*.[66] However, these repair mechanisms are impaired in diabetes,[67] which may contribute to the poor recovery seen in DPN. Among peripheral neurons, unmyelinated nociceptors (C fibers and Aδ fibers) show a greater capacity for regeneration, driven by unique molecular responses, including heightened sensitivity to neurotrophic factors such as NGF and brain-derived neurotrophic factor.[66] This suggests that targeting these pathways and cell types may offer an effective strategy for promoting nerve repair in DPN.

Beyond localized neurolysis induced by HCCTS, evidence is mounting for a regenerative mechanism of action, whereby the "trimmed" nerve fiber endings (i) regenerate to higher densities versus HCCTS pretreatment levels, and (ii) demonstrate functional improvements versus HCCTS pretreatment levels.[43,47,68] Together, these data support the

hypothesis that regenerated nerve fibers can grow back with a different phenotype, which results in a more normalized response to painful and sensory stimuli (Figure 2).[32]

In the context of DPN, a demonstration of these regenerative effects of the HCCTS came from a single-center study in patients with painful DPN who were randomized to receive either standard of care (SOC; 12 patients) or SOC plus a single treatment with HCCTS (25 patients).[43] A separate arm investigated the effect of HCCTS as an addition to SOC in patients with non-painful DPN (24 patients). In line with other studies, both groups of patients with DPN showed significantly reduced ENF densities at baseline versus a control group of healthy patients. Three months following the HCCTS application, the patients with painful DPN showed significant reductions in pain scores on both the Numeric Pain Rating Scale and the Short-Form McGill Pain Questionnaire compared with patients receiving SOC. Patients with non-painful DPN did not display any pain throughout the study. At the 3-month follow-up timepoint, there were significant increases in intraepidermal nerve fiber (IENF) and subepidermal nerve fiber (SENF) densities in both the group with painful DPN and the group with non-painful DPN.

In analyses of punch biopsies of the skin, it is possible to determine subpopulations using different fluorescent markers: GAP43 is a marker of regenerating neurons, PGP9.5 is a marker of nerve structure. In the study described above, following an initial reduction in IENF density, regenerating nerve fibers positive for GAP43 were detected 3 weeks after HCCTS treatment, which correlates with the time when pain relief tends to become significant.[43] PGP9.5- and TRPV1-positive IENFs regenerated more gradually. This time course agrees with that shown by Kennedy et al in healthy volunteers: HCCTS application led to loss of IENF density and return of PGP9.5-positive fibers at 12 weeks and IENF density was nearly normal at 24 weeks.[42]

Similar results have been shown in patients with neuropathy following non-freezing cold injury[47] and in chemotherapy-induced neuropathic pain.[68] In the latter study, the return of IENF density and SENF density was accompanied by increased expression of NGF by basal keratinocytes, decreased expression of NT-3 by suprabasal keratinocytes, and decreased numbers of Langerhans cells.[68]

Regeneration of Peptidergic C Fibers That are Less Hyperexcitable Than at Baseline

Anand and Bley (2011) demonstrated improved axon reflex vasodilation in patients with non-painful DPN within 3 months of HCCTS treatment, which correlated positively with increasing ENF density.[32] As previously mentioned, this refers to the activation of peptidergic nerve fibers, which release CGRP and induce vasodilation.[46]

Sendel et al (2023) conducted a non-interventional exploratory trial in 23 patients with a range of (non-diabetic) peripheral neuropathic pain conditions who were treated with one application of HCCTS.[39] Functional laser speckle contrast analysis was used to test heat-evoked neurogenic vasodilation as a measure of function of peptidergic nerve fibers. Half of all patients demonstrated an improvement in vasodilation compared with baseline; there was a strong correlation between the degree of vasodilation and pain reduction (ie, the non-responders tended to have minimal changes in vasodilation compared with pretreatment values, and the responders tended to have greater changes in vasodilation).

The authors hypothesized that neuroregeneration of the peptidergic C fibers was incomplete in the non-responders, leading to persistence of hyperexcitable terminals. In responders, however, regeneration of healthy peptidergic C-fiber terminals was more complete and they had improved function (as indicated by increased vasodilation and thus increased perfusion).[43] According to this theory, it is not nerve ablation but the regeneration of the peptidergic afferents that constitutes the key mechanism responsible for continued analgesia following HCCTS application.

The regenerative response to capsaicin may also involve non-neuronal cells such as keratinocytes, which can release a variety of peptides and cytokines. While TRPV1 expressed on keratinocytes does not appear to contribute directly to initial pain responses,[45,69] these cells present another pathway for TRPV1 agonists to stimulate the release of neuroactive peptides, such as CGRP, corticotropin-releasing hormone, and urocortin. As mentioned above, a study of HCCTS application in chemotherapy-induced peripheral neuropathy found that normalization of IENF and SENF densities was accompanied by increased NGF expression by basal keratinocytes and decreased NT-3 expression by suprabasal keratinocytes.[35] Thus, while the pain-relieving effects of capsaicin in DPN are primarily mediated by neuronal pathways, non-neuronal cell types may contribute in other ways to aid healing responses to capsaicin.

Short-Term Increases in Local Blood Flow May Lead to an Environment That Encourages Neuroregeneration

Axon reflex vasodilation is a measure of neurogenic inflammation, in which peptidergic afferent activity leads to increases in local blood flow, local edema, and erythema.[55] These increases in local blood flow may lead to an environment that encourages neuroregeneration of more peptidergic C fibers and, more generally, improves the tissue microenvironment. As mentioned above, CGRP contributes to maintenance of neuron viability. The literature suggests that CGRP and NGF interact not just in pain signaling, but also in promoting neuroregeneration and inducing structural and functional changes in epidermal tissue.[70,71] While NGF is the primary driver of neuronal growth, CGRP supports its effects through vascular, inflammatory, and epidermal modulation, particularly in tissue injury and repair contexts. This relationship may be of particular relevance in patients with DPN for outcomes such as wound healing and peripheral nerve regeneration.

This hypothesis is supported by recent findings in murine models showing that CGRP released by peptidergic afferents acts via receptor activity-modifying protein 1 (RAMP1) on neutrophils and macrophages to inhibit recruitment, enhance efferocytosis, and polarize macrophages toward an anti-inflammatory, pro-repair phenotype.[72] CGRP inhibits release of pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL) 1β, and IL-6 from macrophages and dendritic cells, and this is an important part of the neuroregeneration process.[54] In diabetic mice with peripheral neuropathy, delivery of an engineered version of CGRP accelerated wound healing.[72]

The increasing population of peptidergic C fibers could lead to more long-term hemodynamic changes, counteracting the endothelial and poor microcirculation dysfunction associated with nerve damage in diabetes (discussed above and reviewed by Eid et al 2023[73]). This would hypothetically lead to a beneficial cycle in which, on each successive application of HCCTS, the population of nerve fibers is more responsive to capsaicin and generates further vasodilation. This could explain the phenomenon of progressive response (detailed below) in which patients appear to derive cumulative benefit from multiple HCCTS applications. Such effects may be the first step toward addressing the need for long-term DPN treatment that mitigates further disease progression.

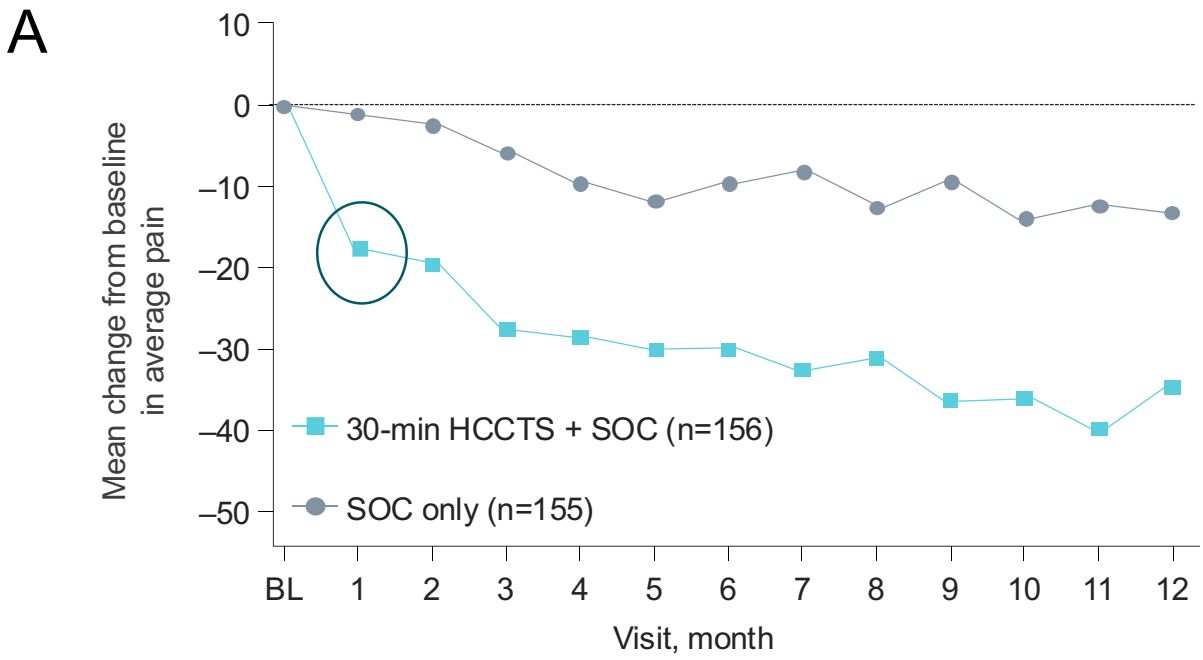
Clinical Data Showing Continual Improvement Suggestive of Neuroregeneration

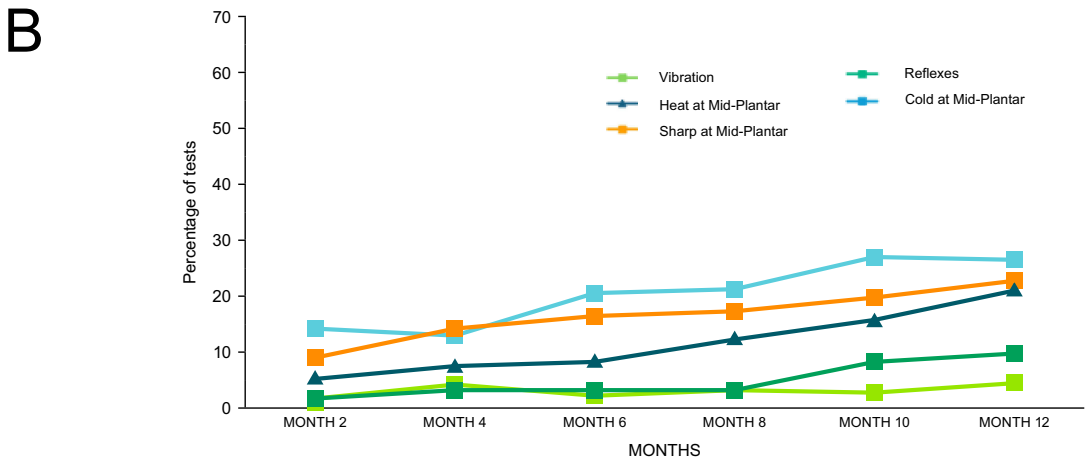
Clinical studies support a regenerative mode of action, as the number of responders and the extent of pain relief increase with each application of the HCCTS.[74,75]

The open-label, Phase III PACE trial was conducted in patients with painful DPN of the feet, and studied long-term safety and efficacy of repeated treatments with HCCTS plus SOC versus SOC alone over 1 year.[74,75] Compared with SOC alone, the 30-minute application was associated with a greater mean change in score from baseline using the Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) questionnaire, signifying no deterioration in QOL related to small-fiber neuropathy.[74,75] A reduction in average pain (measured by the Brief Pain Inventory–Diabetic Neuropathy questionnaire) with HCCTS plus SOC versus SOC alone was observed as early as 1 month and continually improved to the end of study (Figure 5A).[74,75] A post-hoc analysis showed that, among patients who received seven applications, there were progressive improvements in average daily pain: the proportion of patients who received seven 30-minute applications and achieved a ≥30% reduction from baseline increased from 34.5% after the first application to 77.1% after the seventh.[76]

Despite patients with DPN having reduced ENF density at baseline, repeated application of HCCTS did not have deleterious effects on sensory function, as measured using the Utah Early Neuropathy Scale and the Brief Sensory Pain Examination (BSPE).[75] Progressive improvements in pain intensity among patients in PACE were accompanied by improved QOL, sleep, and patients' satisfaction with treatment.[78] A post-hoc analysis showed notable improvements in sensory perception and reflex testing following repeated application of HCCTS (Figure 5B).[77] In patients with below-normal sensation (as determined using the BSPE) at baseline, an increase in the percentage of tests showing normal results was observed with the repeated application of HCCTS. After the sixth application, scores were normalized in 21–25.5% of tests. In patients with no sensation at baseline (baseline score of zero), an increase in the percentage of sensory tests that showed a positive shift was also observed with repeated applications. At the end of the study, there was

a slightly greater increase in glycated hemoglobin (HbA1C) in the SOC alone arm compared with both HCCTS arms (at end of study with last observation carried forward, the change in HbA1c in SOC alone arm was 0.24% compared with 0.06% for the patients in both the 30-minute and 60-minute HCCTS arms). It is possible, therefore, that glycemic control was a confounding factor; however, HbA1c levels were generally controlled throughout the study.





Vibration	1	4.2	2	2.9	2.5	4.2
n (number of tests	283	265	247	240	239	235
Reflexes	1.5	3.2	2.6	3	7.9	9.8
n (number of tests	265	253	235	231	228	224
Heat at Mid-Planter	5.4	7.5	8.6	12.4	15.8	21.1
n (number of tests	259	239	222	217	221	218
Cold at Mid-Planter	14	13	20.5	21.1	27	26.4
n (number of tests	207	192	176	175	178	174
Sharp at Mid-Planter	8.8	14.1	16.1	17.1	19.5	22.8
n (number of tests	227	213	199	193	195	193

Figure 5 Continued.

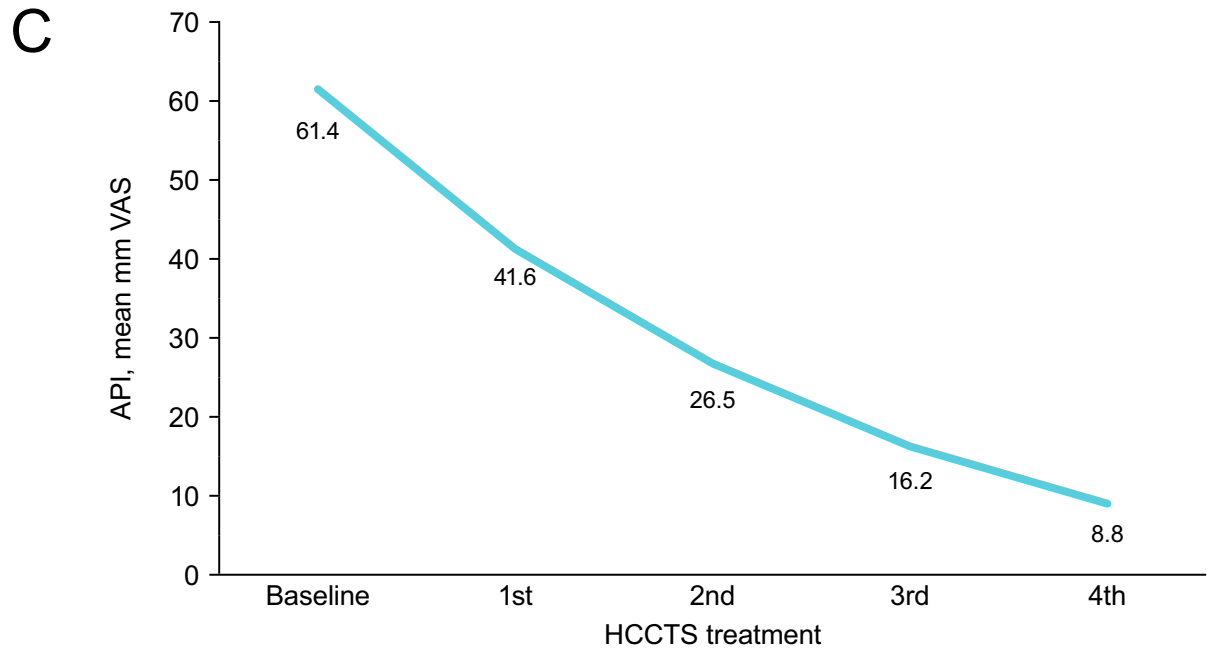


Figure 5 Data demonstrating benefit of continued HCCTS treatment on the feet in patients with DPN. (**A**) Data from PACE: Mean 24-hour pain intensity over 12 months following seven applications of HCCTS with ≥8-week intervals. SOC was optimized for each patient at the discretion of each investigator and was assessed at clinic visits and on days 1 to 5 post treatment by completion of a rescue pain medication diary. Adapted from Vinik AI, Perrot S, Vinik EJ, et al. Repeat treatment with capsaicin 8% patch (179mg capsaicin cutaneous patch): effects on pain, quality of life, and patient satisfaction in painful diabetic peripheral neuropathy: an open-label, randomized controlled clinical trial. J CurrMed Res Opinion. 2019;2(12):388–401. Creative Commons.[74] (**B**) Post-hoc analysis of PACE: Sensory perception in patients with abnormally low sensation at baseline (measured via the Brief Sensory Pain Examination), using five sensory modalities. Data indicate patients who experienced a shift from "below normal" to "normal" after up to six 30-minute applications of HCCTS at the months indicated. (**C**) Data from CASPAR, a retrospective observational study: Average 24-hour pain intensity (measured via a VAS; 0 = no pain; 100 = worst possible pain) among patients who received four HCCTS treatments (n=108). Adapted with permission from Katz N, Allen S, Carnevale A, Gordon K. Impact of treatment with high-concentration capsaicin (8%) (QTZ) topical system on sensory testing in patients living with painful diabetic peripheral neuropathy of the feet: a post-hoc analysis of the PACE trial. In: American Podiatric Medical Association (AMPA) Annual Scientific Meeting. Washington DC; 2024.[77]
Abbreviations: API, average pain intensity; BL, baseline; DPN, diabetic peripheral neuropathy; HCCTS, high-concentration capsaicin topical system; min, minutes; SOC, standard of care; VAS, visual analog scale.

The findings of PACE are supported by real-world data. Retrospective data from 365 patients with PDPN in the CASPAR study revealed cumulative benefits of repeated applications of HCCTS.[79] Average pain intensity and other measures of affective distress and QOL improved with a single application, and additional improvements were observed with each subsequent application (up to four over 12 months; Figure 5C). This registry included follow-up data from patients who stopped taking HCCTS: in these patients, discontinuation was associated with a cessation of the beneficial effect in average pain intensity, sleep, and QOL; in many cases, the data trended back toward baseline values. The greatest benefit in all outcomes was seen in patients who had received four applications. Repeated applications and monitoring are important to reveal the scale of response to HCCTS: in the Phase III safety study PACE (mentioned earlier), some patients who exhibited little or no improvement after a single application responded well to subsequent applications.[74,78]

These data from randomized clinical trials and real-world studies highlight several important features of the HCCTS mode of action. First, the pain-relieving effects are long-lasting and measurable for several months after a single 30-minute application. Second, the effects of repeated applications appear to be cumulative, with pain relief and QOL improving with each subsequent treatment.[74,75,78] Third, HCCTS appears to have beneficial effects on peripheral sensory function and vasodilation. Together, these effects correlate with a mode of action in which aberrant TRPV1-positive nociceptive fibers are pruned and replaced by healthier nerves that contribute to a more normative state in the diabetic foot.

The best evidence we have regarding long-term safety of repeat HCCTS in DPN is from PACE - the Phase III safety study.[27] In the primary analysis, repeat HCCTS (up to seven treatments) was not associated with deterioration in nerve function, as indicated by the Norfolk QOL-DN total score, compared with SOC alone. HCCTS was generally well tolerated and the most common treatment-emergent adverse events (TEAEs) included application-site pain and burning sensation, both of which were transitory and manageable. No patient treated with HCCTS 30 min + SOC had a drug-related TEAE leading to discontinuation.

Summary and Directions for Future Research

In summary, the HCCTS causes a cessation of hyperactivity and lysis of sensory nerve fiber terminals in the skin area treated, which lead to analgesic effects. The affected nerve fibers then appear to regenerate in the following months and likely contribute to the longer-term pain relief.[39,43] The evidence suggests that these regenerated fibers are phenotypically reset or "normalized" such that they have a reduced hypersensitivity and improved functional activity that contributes to a more normative sensory state and reduction in pain. Data from both large open-label and real-world evidence studies suggest an analgesic and functional benefit from repeated HCCTS applications, which may be related to cycles of nerve fiber regeneration resulting in functionally healthier neurons and an improved local tissue microenvironment. As impaired sensory function in the feet can contribute to progression of DPN and ulceration, it is plausible that capsaicin-mediated regeneration of the sensory neurons could result in both restorative and enduring effects. This may in turn prevent amputations, which are associated with great cost to healthcare systems and society. Approximately 10.5% of diabetic foot ulcer cases eventually require amputations, and in 2015, each case requiring major amputation was estimated to cost $115,9574.[80] The effect of HCCTS on sensory function needs to be evaluated in a prospective trial with a measure of sensory function as the primary outcome.

Amid the mounting evidence, further research is needed to fully understand the complex pathologic mechanisms of peripheral neuropathy in type 1 and type 2 diabetes. This will also allow us to identify when capsaicin can best intervene, possibly at earlier stages of the disease, to prevent the progressive deterioration in the periphery as well as the complications associated with diabetic foot syndrome.

There are several avenues for future research about HCCTS. One relates to developing a deeper understanding of the analgesic mechanism of action of capsaicin and the role of peptidergic nerve fibers and other non-neuronal TRPV1-expressing cell types. It will be necessary to determine the effects of repeated HCCTS on ENF density and other neuronal markers, vasodilation, and blood flow in the feet. In addition, it would be interesting to determine whether repeated treatments with HCCTS have any effects on long-term clinical outcomes such as a reduction in development of ulcers or infections, which can ultimately lead to amputations.

Abbreviations

AGE, advanced glycation end product; ASPN, American Society of Pain and Neuroscience; BSPE, Brief Sensory Pain Examination; Ca^{2+}, calcium ions; CGRP, calcitonin gene-related peptide; DGME, diethylene glycol monoethyl ether; DPN, diabetic peripheral neuropathy; ENF, epidermal nerve fiber; FDA, US Food and Drug Administration; HbA1C, glycated hemoglobin; HCCTS, high-concentration capsaicin topical system; IENF, intraepidermal nerve fiber; IL, interleukin; mPNS, magnetic peripheral nerve stimulation; NGF, nerve growth factor; PDPN, painful diabetic peripheral neuropathy; PGP 9.5, protein gene product 9.5; QOL, quality of life; RAMP1, receptor activity-modifying protein 1; ROS, reactive oxygen species; SCS, spinal cord stimulation; SENF, subepidermal nerve fiber; SOC, standard of care; TRPV1, transient receptor potential vanilloid subtype 1.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

SA, AC, and LM were employees of Averitas Pharma at the time of writing this review. DS reports personal fees from Averitas and Grunenthal, outside the submitted work. PS reports royalties for patent on high-dose capsaicin; grants from Nalu, and Saluda, outside the submitted work. The authors report no other conflicts of interest in this work.

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