Chapter 4
Topical Capsaicin Formulations in the Management of Neuropathic Pain

Mark Schumacher and George Pasvankas

Abstract This chapter reviews the scientific and clinical evidence supporting the use of topical formulations containing the pungent principle of chili peppers—capsaicin, for the treatment of peripheral neuropathic pain. Given the limitations of current oral and parenteral therapies for the management of pain arising from various forms of nerve injury, alternate therapeutic approaches that are not associated with systemic adverse events that limit quality of life, impair function, or threaten respiratory depression are critically needed. Moreover, neuropathic conditions can be complicated by progressive changes in the central and peripheral nervous system, leading to persistent reorganization of pain pathways and chronic neuropathic pain. Recent advances in the use of high-dose topical capsaicin preparations hold promise in managing a wide range of painful conditions associated with peripheral neuropathies and may in fact help reduce suffering by reversing progressive changes in the nervous system associated with chronic neuropathic pain conditions.

4.1 Introduction

Physicians have faced a common dilemma over the ages, how to relieve a patient's pain without doing harm. Fortunately, long before the advent of clinical trials, early physicians successfully used native plant derivatives to provide pain relief. Although

M. Schumacher (✉)
Division of Pain Medicine, Department of Anesthesia and Perioperative Care, University of California, 513 Parnassus Ave, Box 0427, San Francisco, CA 94143-0427, USA
e-mail: schumacm@anesthesia.ucsf.edu

G. Pasvankas
Division of Pain Medicine, Department of Anesthesia and Perioperative Care, University of California, 2255 Post St., MZ Bldg N, San Francisco, CA 94143, USA
e-mail: pasvankasg@anesthesia.ucsf.edu

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Table 4.1 Peripheral neuropathic conditions treated with topical capsaicin

Peripheral neuropathic conditions treated with Topical capsaicin
Postherpetic neuralgia (PHN)
Painful diabetic polyneuropathy (PDPN)
HIV-associated distal symmetrical polyneuropathy (HIV-DSPN)
Persistent postsurgical pain

their preparations may have been crude by today's standards, they apparently provided effective pain relief for their time. Use of medicinal plant derivatives from hot chilies in South America dates as far back as 4000 BC. However, much of our modern accounts and written records of chili's irritant properties and medicinal use in the western hemisphere are derived from Aztec culture beginning in the twelfth century. Beyond their irritant use, Aztec physicians also realized chili's usefulness to treat painful maladies such as toothaches—perhaps one of the earliest recorded forms of "nerve pain."

Use of medicinal salves and balms used in ancient times appeared to reemerge in the 1800s with the isolation of the principle agent from hot chili peppers—capsaicin. Building on the realization that the experience of pain is based on specialized nerves, "nociceptors," that respond to noxious stimuli (Sherrington 1906), later Hungarian investigators in the 1940s observed that capsaicin both activates and subsequently inactivates sensory nerves. Following the confirmation of the "nociceptor" hypothesis by Bessou and Perl in 1969, the existence of a "capsaicin receptor" expressed on C-polymodal nociceptors was investigated and importantly the phenomenon of nociceptor "desensitization" due to repetitive exposure to capsaicin was formally investigated (Bessou and Perl 1969; Szolcsanyi and Jancso-Gabor 1975, 1976; Szolcsanyi et al. 1975).

As described in detail in this chapter, it was not until the 1980s that the broader use of topical capsaicin appeared in earnest in the medical literature as a therapy for difficult-to-manage pain syndromes—especially for the treatment of painful conditions associated with nerve injury, such as post-herpetic neuralgia (PHN). Conditions such as PHN describe one of a number of maladies that are associated with sensations of burning, shooting, and/or electrical-quality pain. Unfortunately, attempts to manage such painful conditions with therapies that rely primarily on opioid analgesics have been associated with well-known side effects such as nausea/vomiting, constipation, pruritus and at higher dosing, respiratory depression. Moreover, certain patient populations, such as those with advanced age, multiple medical problems, pulmonary disease, or those with increasing opioid requirements may have an unacceptably high risk of adverse events including urinary retention and life threatening respiratory depression. Such opioid-associated adverse events can rapidly degrade quality of life and level of function, limiting their usefulness in chronic painful conditions involving nerve injury.

This chapter reviews the application of topical formulations containing the pungent principle of chili peppers—capsaicin, for the treatment of neuropathic painful conditions (see Table 4.1). Given the limitations of current oral and parenteral

therapies for the management of pain arising from various forms of nerve injury, alternate therapeutic approaches that are not associated with adverse events that limit quality of life, impair function or threaten respiratory depression are critically needed. Moreover, neuropathic events can be complicated by progressive changes in the central nervous system, such as central sensitization leading to persistent reorganization of pain pathways and chronic pain. Recent advances in the use of high-dose topical capsaicin preparations hold promise in managing a wide range of painful conditions associated with nerve injury and may in fact help stop or reverse progressive changes in the nervous system associated with chronic neuropathic pain conditions.

4.2 Neuropathic Pain

Whether noted by clinician or patient, neuropathic pain can be one of the most disabling and challenging medical conditions to effectively manage. This is in part due to the diverse and poorly understood pathophysiological drivers that are associated with persistent neuropathic pain. Of the known sources of painful neuropathic pain, this chapter will focus on a subgroup of those of peripheral origin or manifested in a peripheral site of disease that have shown to be responsive to topical capsaicin. These include infectious (herpes zoster, HIV, metabolic (diabetes), and nerve entrapment/surgical/trauma). Although it is uncertain what specific property these diverse disease states or lesions share that engender the development of persistent painful neuropathic conditions, by definition, pain arising as a direct consequence of a lesion or disease affecting the somatosensory system either peripheral or central, now serves as the current definition of neuropathic pain by the International Association for the Study of Pain—Special Interest Group on Neuropathic Pain (NeuPSIG).

4.2.1 Pathways and Mechanisms

4.2.1.1 Nociceptors: The Site of Capsaicin Action

Since the early observations of Sherrington, who believed that the experience of pain was based on nerves that responded to specific types of noxious stimuli that cause tissue damage, the concept of “nociceptive nerves” and later the term “nociceptor” emerged to describe what we now refer to as primary afferent nociceptors (Sherrington 1906). Nociceptors represent that portion of the peripheral nervous system that is specialized for the detection of noxious stimuli. One of the principle benefits provided by nociceptors is their rapid detection of impending or actual tissue injury. Nociceptors accomplish this by being a part of an integrated system or “pain pathway” beginning with peripheral nociceptive terminals that function to detect multiple noxious stimuli (transduction), the relay of these signals to the

central nervous system through the conduction of action potentials (transmission) and finally their interpretation as a harmful or unpleasant experience (perception) (Fields 1990).

Within the peripheral nervous system, somatosensory detection of tissue damaging stimuli (thermal, mechanical, chemical) begins at the peripheral terminals of primary afferent nociceptors whose cell bodies reside primarily in the trigeminal (V) and dorsal root ganglia (DRG). In addition, cranial nerves V (innervation of the majority of the face, conjunctiva, mouth, and dura mater) as well as cranial nerves VII, IX, and X (innervation of the skin of the external ear, and mucous membranes of the larynx and pharynx) also participate in nociception (Carpenter 1985). Likewise, nerve terminals derived from nociceptors residing in spinal dorsal root ganglia (cervical, thoracic, and lumbar) innervate the somatotopic dermatomes of the skin and underlying tissue. Nociceptors derived from dorsal root ganglia then send central processes to laminae I, II, and V of the dorsal horn of the spinal cord and following synaptic connection with second-order dorsal horn neurons, nociceptive information is relayed to higher centers of the brain.

Detection of noxious stimuli of the skin and underlying deep tissues (somatic) has been divided into three modalities: noxious thermal, mechanical, and chemical. The behavioral and physiological responses following the application of one of these three painful modalities have served as the cornerstone for a classification scheme of nociceptors. Within this classification scheme, the threshold for evoking the sensation of pain has been determined in human volunteers with certain external forces applied to the skin such as noxious thermal stimuli (temperatures ≥43–45 °C) or intense mechanical stimuli. Criteria for detection of noxious chemical stimuli have also been applied and rely on the sensation of pain in response to certain compounds such as *capsaicin*, the pungent principle ingredient in hot chili peppers and the therapeutic focus of this chapter (Fields 1990).

Primary afferent nociceptors have been further classified based on their axon diameter, conduction velocity, degree of myelination, and more recently, cross-sectional area of neuronal soma. The axons of primary afferent neurons fall into three distinct groups, Aß (large-diameter, 6–22 μm, heavily myelinated with fast conduction velocities (CV) of 33–75 m/sec), Aδ (diameter 2–5 μm, thinly myelinated with CV 5–30 m/sec), and C fibers (diameter 0.3–3 μm, unmyelinated with CV of 0.5–2 m/sec) (Bessou and Perl 1969). Nociceptors activated by multiple noxious stimuli are referred to as "polymodal nociceptors." (McMahon and Koltzenburg 1990) Included in this category are C fiber type mechano-heat nociceptors and at least two types of A fiber type nociceptors: mechano-heat Type I (high heat threshold >49 °C) and mechano-heat Type II, (heat threshold ~43 °C) (Fields 1990). Finally, high threshold mechano-nociceptors that fail to respond to thermal stimuli have been characterized for both C and A fiber types as well as for nociceptors that respond only to noxious chemical stimuli.

The sensation of peripheral neuropathic pain arising from peripheral sites of pathology has been described as arising from both unmyelinated C-type (slowly conducting) nerve fibers associated with sensations of dull, aching, burning, and poorly localized pain as well as thinly myelenated Aδ nerve fibers which are more rapidly

conducting and signal sensations of sharp, stabbing, and often well-localized pain. However, despite this elegant classification of nociceptor subtypes, discharge patterns of polymodal nociceptors do not precisely correlate with stimulus-induced pain sensation (Adriaensen et al. 1984). Therefore, central processing of nociceptor impulses must be required for the discrimination of painful sensations. Although not proven, one may hypothesize that the selective destruction and/or functional silencing of a subset of polymodal nociceptors following topical capsaicin treatment, as discussed below, could disrupt the input of peripheral neuropathic pain signal processing of polymodal nociceptors.

Nociceptors also have the ability to adjust their sensitivity following repetitive noxious stimuli or tissue/nerve injury. Sensitization encompasses an increase in spontaneous nociceptor activity, a lowered threshold for activation, and an increase in action potential firing after suprathreshold stimuli (Fields 1990). Together with plasticity changes in the dorsal horn of the spinal cord, sensitization of nociceptors contributes to hyperalgesia. Nociceptor modulation is complex and multiple pathways exist to both detect noxious stimuli and modulate transducing element sensitivity. Under neuropathic conditions this complexity is increased, driven by overlapping biochemical processes—some common to both tissue and nerve injury. Examples of changes more prominent to experimental neuropathic pain models arising from peripheral nociceptor sensitization include increased small-afferent signaling arising from distal sprouting of injured nerves and aberrations in nociceptor channels/receptor expression (sodium and calcium channels, Nerve Growth Factor/NGF receptor-TrkA) in injured and uninjured (adjacent) sensory neurons.

One signaling molecule long associated with experimental neuropathic pain is the trophic factor "nerve growth factor" (NGF). Since its identification by Levi-Montalcini and Calissano, NGF has been distinguished from other neurotrophin family members (brain-derived neurotrophic factor NT-3, and NT-4/5) as being essential for normal nociceptor development and function (Koltzenburg 1999; Lewin and Mendell 1994; McMahon et al. 1995). NGF is synthesized and secreted by a wide variety of tissues including Schwann cells located within sensory ganglion and importantly, in the end-target tissues of nociceptive terminals—epidermal fibroblasts and keratinocytes. NGF is intimately involved in maintaining and modifying the phenotype of the nociceptor population. Adult sensory neurons lose their dependency on NGF for survival but retain expression of its high-affinity receptor TrkA primarily on the small-diameter primary afferent nociceptors (C and Aδ) (Koltzenburg 1999). Tissue and nerve injury are associated with increased NGF production and content at the site of the injury, serving as the driving signal for the associated pain and hyperalgesia (Woolf and Costigan 1999). Therefore, long-term exposure of nociceptive terminals to increased levels of NGF can result in long-term phenotypic changes in the repertoire of nociceptive transducing elements such as the capsaicin receptor. Such changes may lead to aberrations in pain signaling and in turn, may represent a molecular template for sustained peripheral neuropathic pain. Although the focus of this chapter is on peripheral mechanisms of neuropathic pain and its treatment with topical capsaicin, other more central changes associated with models of neuropathic pain also include the loss of the

blood brain barrier integrity surrounding the spinal cord, allowing migration of non-neuronal inflammatory cells into the dorsal horn (sensory) of the spinal cord and the DRG. Other changes associated with experimental models of neuropathic pain include activation of dorsal horn microglia that are known to be associated with chronic pain (Watkins et al. 2001).

4.2.2 Assessment

Neuropathic pain often goes unrecognized and therefore is under-reported being unsuccessfully treated with agents such as non-steroidal anti-inflammatory drugs (NSAIDS) and/or acetaminophen (Gore et al. 2007). Although there is no "gold standard," pathognomonic sign or symptom for the diagnosis of neuropathic pain, a focused history and sensory exam can often provide clinicians the critical insight for early recognition and subsequent treatment. A combination of signs (hypoesthesia, hyper/hypo-algesia, heat/cold hyperalgesia, allodynia) and symptoms (paraesthesias, sensation of burning, and/or shooting pain) together with the appropriate clinical context increases the likelihood of a reliable diagnosis of neuropathic pain (Haanpaa et al. 2009).

To assist the clinician, standardized screening tools have been developed to provide the practitioner a reliable and importantly, validated approach to forming an accurate diagnosis. Two such tools are the "Leeds assessment of neuropathic symptoms and signs" (LANSS) (Bennett 2001) and the "Douleur Neruopathiques 4 questions" (DN4) (Bouhassira et al. 2005). Although a clinical history may provide a high degree of suspicion about whether a particular patient indeed is suffering from pain of peripheral neuropathic origins, the incidence of neuropathic pain varies geographically. Whereas patients in developing countries with high rates of HIV or trauma due to war may be predisposed to neuropathic pain from these processes, patients from developed countries may be more likely to develop neuropathic pain as a consequence of diabetes or a herpes zoster infection predisposing to PHN (Haanpaa et al. 2009).

4.2.3 Treatment of Neuropathic Pain

Evidence-based guidelines for the treatment of painful neuropathic conditions continue to gain strength as additional randomized controlled trials are successfully completed. Expert opinion in the form of guideline recommendations have emerged and in many cases have been updated from societies dedicated to the evidence-based management of neuropathic pain such as NeuPSIG (Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain) (Dworkin et al. 2010, 2007). Therefore, guidelines intended to recommend any therapy as a "first-line" treatment for a particular type of neuropathic pain require that

efficacy has been established in multiple randomized clinical trials (RCT) (Oxford Center for Evidence-based Medicine, Grade A) and that these recommendations are consistent with the provider's experience/patient population. Unfortunately, few neuropathic pain therapies including those involving the topical application of capsaicin, fulfill such criteria. Nevertheless, an evolving list of first-line medications have been recommended that include: antidepressants with both norepinephrine and serotonin reuptake inhibition, calcium channel alpha 2 delta ligands (gabapentin and pregabalin), and topical lidocaine (Dworkin et al. 2010). Second-line therapies (which may be considered "first-line" under certain circumstances) include tramadol and opioid analgesics. Finally, so-called "third line" therapies include other anticonvulsants and "low-dose" capsaicin creams, as high-dose capsaicin-based patch studies were just emerging as these guidelines were reported. These recommendations are in line with other international expert groups (Attal et al. 2010). Among a collection of European countries that participated in comparison of their clinical practice guidelines on the treatment of neuropathic pain in cancer patients, all responded that the use of amitriptyline was a first-line recommendation (Piano et al. 2014). Second, the use of gabapentinoids was recommended. Within this report, the clinical practice guidelines across nine countries also included whether the use of capsaicin-containing plasters should be recommended for the treatment of conditions of "local (peripheral) neuropathic pain", presumably having a restricted pattern of distribution (dermatomal or non-dermatomal). Although four of the countries did not provide data, the remaining five countries all recommended that capsaicin-containing plasters should be utilized for the treatment of neuropathic conditions (Piano et al. 2014).

Therefore, providers are faced with a range of choices from pharmacologic therapies of nonopioid and opioid agents, adjuvant analgesics, topical preparations, and interventional techniques such as neuroblockade and intraspinal infusions to recently advancing neurostimulatory techniques. Unfortunately, there is even less evidence in support of interventional approaches to manage pain from neuropathic conditions refractory to pharmacologic interventions. Due to the paucity of RCT data in this area, only weak recommendations so far exist that include the use of epidural injections for herpes zoster, epidural steroid injections for radiculopathy, spinal cord stimulation (SCS) therapy for failed back surgical syndrome, and SCS for complex regional pain syndrome type 1 (CRPS type 1) (Dworkin et al. 2013). More invasive-ablative techniques are also sometimes used under conditions of compassionate care for patients with progressive malignant disease driving neuropathic symptoms (Kanpolat et al. 2009; Meyerson 2001; Turnbull et al. 2011) although these can also be associated with significant risks or unmasking other painful sensations.

As we await additional randomized clinical trials, a step-wise approach for the treatment of neuropathic pain is recommended where a combination of proven medications may represent a superior therapeutic plan. Nevertheless, clinical trials investigating the use of such combination therapies have yet to fully emerge. Just as one considers the application of multiple pharmacologic agents to a particular condition, patients suffering from chronic neuropathic pain will likely benefit from

a multimodal or multidisciplinary approach to their pain management. Importantly, multidisciplinary treatment programs compared with conventional treatment are effective in reducing the intensity of the pain reported by the patient for a period of four months to one year (evidence category A2). Although multimodal therapy has been shown to be efficacious for a number of conditions, its superiority over uni-modal therapies has not yet been fully supported in the literature due to the absence of sufficient high quality randomized controlled trials (category D evidence). Nevertheless, it is the recommendation of the American Society of Anesthesiologists—ASA task force in 2010 on practice guidelines for chronic pain management, that "a multimodal strategy be part of the treatment plan for patients with chronic pain" (2010). Moreover, such a multi-modal approach should ensure early recognition and treatment of psychosocial maladies that are critical for long-term success in any treatment plan and goal to improve functional status and overall quality of life.

4.3 The Action of Capsaicin on Primary Afferent Nociceptors

It has long been appreciated that initial applications of capsaicin are painful, but paradoxically, repeated application produces a topical analgesic effect. It has been proposed that a series of overlapping capsaicin-induced effects that include: desensitization, nociceptor dysfunction, neuropeptide depletion, (Cao et al. 1998; Yaksh et al. 1979), and nociceptive terminal destruction (Robbins et al. 1998; Simone et al. 1998) constitute critical elements producing pain relief. However, several aspects of topical capsaicin treatment appear to limit its overall effectiveness and application in clinical practice. The first is the requirement for repeated capsaicin application (up to 4–5 times daily) to establish and maintain an adequate degree of analgesia. Repeated use of capsaicin-containing topical creams leads to the loss of epidermal nerve fibers that can be detected as soon as 3 days following repeated application. In fact, after 3 weeks of capsaicin treatment on the volar forearm 4 times daily, there was an approximately 80 % reduction in epidermal nerve processes. Loss of the epidermal fibers (see Fig. 4.1) was concordant with a reduction in painful sensation to noxious heat and mechanical stimuli (Nolano et al. 1999). Similar findings were observed when capsaicin was injected subcutaneously in volunteers (Simone et al. 1998).

Yet in other clinical studies performed to better quantify the effects of low-dose capsaicin on expression of TRPV1 and neuropeptides in human nociceptive terminals, control human skin biopsies showed abundant immunoreactivity to the neuropeptides SP (substance-P) and CGRP (calcitonin gene related peptide). After 1 day of repeated topical application of capsaicin (five times daily) at a concentration of 0.025 %, a diminution of SP and CGRP immunoreactivity in nerve fibers was observed (Stander et al. 2004). Continuous application of capsaicin for 24 days, 1 and 8 months, respectively, resulted in a decrease of SP and CGRP

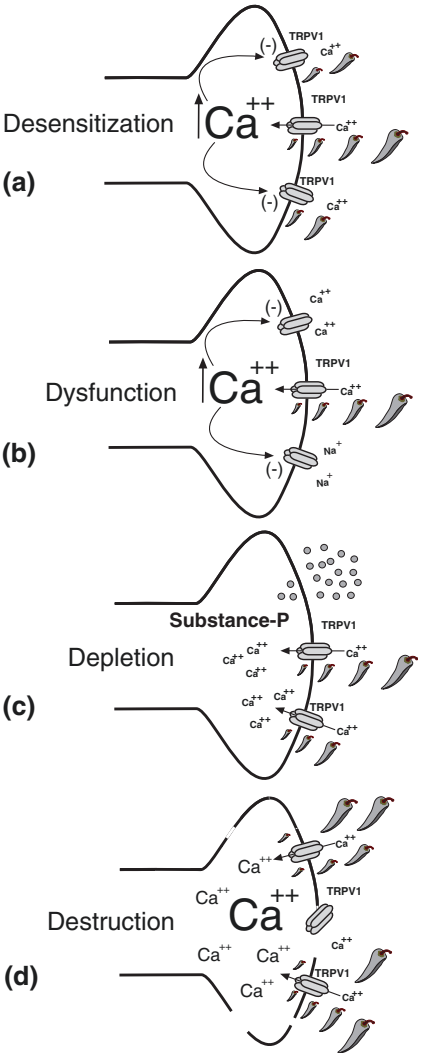

Fig. 4.1 Topical capsaicin-mediated analgesia. Topical application of capsaicin to the skin can produce concentration, dosing interval, and time-dependent changes to underlying sensory nerve terminals expressing the capsaicin receptor (*TRPV1*). As illustrated in panels (**a**–**d**), functional (**a**–**c**) and subsequently structural (**d**) changes in the *TRPV1*-expressing nociceptive terminals occur as a result of the magnitude and duration of *TRPV1* activation. Long-term analgesia may arise from selective destruction and/or functional silencing of a subset of polymodal nociceptors following topical capsaicin treatment disrupting central nociceptive input from peripheral neuropathic pain signal processes. **a** Desensitization is a calcium-dependent phenomenon where application of capsaicin leads to a decrease in inward current response during continued capsaicin application. When capsaicin is applied at repeated intervals, each subsequent response becomes smaller and is often referred to as tachyphylaxis. *TRPV1* may become refractory to the effect of endogenous inflammatory mediators and intracellular secondary messengers. **b** Repeated or prolonged application of capsaicin can also produce nociceptor dysfunction. Under this condition,

◀ which is dependent on the influx and/or excess of store-released calcium, other pain-transducing receptor–channels are inactivated. This may explain analgesic effects beyond the known function of TRPV1. **c** Depletion of neuropeptides (Substance-P, CGRP) from nociceptive terminal is evoked by capsaicin (low- and high-dose) or repeat applications. Substance-P has been show to play a key role in facilitating nociceptive neurotransmission in the dorsal horn of the spinal cord. **d** Destruction of TRPV1-expressing nociceptive terminals has been the most reliable marker correlating the application of capsaicin with analgesia

expression in superficial small nerve fibers of the papillary dermis, whereas, in nerve fibers of the deep dermis, the content of neuropeptides was unchanged. In contrast, the distribution and intensity of TRPV1 staining in nerve fibers and appendage structures was not changed as compared to untreated skin. Seven and 14 days after discontinuation of the capsaicin therapy, immunoreactivity to SP and CGRP was again detectable in small papillary nerve fibers. We, and others, hypothesize that capsaicin directs a dose-dependent effect, with low-dose capsaicin treatments associated with loss of neuropeptides in sensory terminals whereas the repetitive and/or highest capsaicin dosing being the most effective in directing the destruction of nociceptor terminals. What properties of nociceptors allow for their selective inactivation/destruction following capsaicin application?

With the isolation of a cDNA clone encoding a capsaicin-activated ion channel in 1997, the molecular basis of the capsaicin receptor, transient receptor potential cation channel subfamily V member 1 (TRPV1) was finally realized (Caterina et al. 1997). Termed TRPV1, it encodes a nonselective cation channel subunit of approximately 95 kDa that is highly expressed in the small-diameter sensory neurons of dorsal root, trigeminal, and vagal ganglion. Its structure mostly resembles that of members of the Kv 1.2 and store-operated channel family (Caterina et al. 1997). The TRPV1 subunit spans the plasma membrane six times, containing large N- and C-terminal intracellular regions, and is proposed to form tetrameric and/or heteromeric channel complexes (Eilers et al. 2007; Kedei et al. 2001; Kuzhikandathil et al. 2001). It is activated by capsaicin on the intracellular surface in a dose-dependent manner. Once activated, TRPV1 allows for the depolarization of the nociceptor through the conduction of cations. However it is not selective for monovalent cations but rather it preferentially conducts calcium through its channel pore, resulting in an increase in intracellular calcium and cellular depolarization. Thus, TRPV1 can be considered a cellular sensor and when expressed on sensory neurons, can confer specialized properties such as the detection of noxious stimuli and as explained below, detects changes in endogenous signaling molecules associated with tissue injury and inflammation.

Nerve and tissue injury result in the production and release of multiple inflammatory products that have been characterized and identified to directly activate TRPV1. These include products of inflammation and tissue injury such as NGF (Koltzenburg 1999; Mendell et al. 1999) as well as anandamide, the endogenous ligand for the cannabinoid receptor (CB1) (Smart et al. 2000; Julius and Basbaum 2001). Products of the lipoxygenase pathway of arachidonic acid, 12-(S)-hydroperoxyeicosatetranoic acid (12-(S)-HPETE), and leukotriene B4, (LTB_4) have also been found to activate

Table 4.2 Topical capsaicin formulations

Low concentration topical	High concentration topical
Over the counter	Prescription
Multiple formulations including cream, liquid, patch	Patch
Generally at or below 0.15 % capsaicin	8 % capsaicin
Applied by patient at any location	Applied by medical professional in an appropriate clinical venue
Application repeated multiple times daily for anywhere from weeks to indefinite time period	Applied once for one hour, repeated as needed at three month or greater intervals
Does not require pretreatment to the application area	Requires pretreatment with topical local anesthetic to the application area

TRPV1 in vitro (Shin et al. 2002). It has been reported that TRPV1 is expressed on large and small cutaneous nerve fibers in the human dermis and at the epidermal–dermal junction, while intraepidermal nerve fibers only occasionally stained for TRPV1. A similar staining pattern of TRPV1 immunoreactivity was also described in rat skin (Guo et al. 1999). Importantly, TRPV1 and SP are also co-localized in human cutaneous nerve fibers confirming previous reports in rat and mice. Therefore, beyond the ability of capsaicin to disrupt the function of polymodal nociceptors expressing TRPV1, capsaicin-induced inactivation could also result in blockade of endogenous activation of TRPV that is associated with pathophysiologic conditions giving rise to neuropathic pain symptoms.

4.3.1 Painful Neuropathic Conditions Treated with Topical Capsaicin Preparations

4.3.1.1 Overview

Early meta-analysis that included patients suffering from diabetic neuropathy and osteoarthritis concluded that topical capsaicin improved pain when compared with a placebo (Zhang and Li Wan Po 1994), the analysis includes a number of uncontrolled and/or underpowered trials, a concern that has weakened their influence on changing clinical practice over time. Moreover, if one applies a more “rigorous” standard for clinical trials (as exists presently) on trial data prior to 2004, topical capsaicin (0.025 or 0.075 %) showed poor to moderate efficacy in the treatment of either musculoskeletal or neuropathic symptoms (Mason et al. 2004). Coupled with one-third of these study patients experiencing mild to moderate adverse effects such as erythema, irritation, and transient increase in pain, (see Table 4.2) enthusiasm for widespread use of these agents in the absence of concurrent local anesthetic pretreatment appeared to plateau. Therefore, such treatments were considered for so-called “nonresponders” rather than as a first-line treatment option.

To obtain improved patient acceptance and analgesic efficacy using capsaicin-based creams, therapeutic trials have progressively shifted from repeated applications of a combination of local anesthetic pretreatment followed by low-dose capsaicin (Turnbull et al. 2011) to potentially a single application of high-dose topical capsaicin patch. This shift, in part, owes its origin to a case series that included 10 patients suffering from intractable lower extremity pain with neuropathic features. Application of capsaicin (5–10 %) under regional anesthesia resulted in a wide range of posttreatment pain relief (Robbins et al. 1998).

Therefore, the report of Robbins et al. suggested an alternative approach, a single application period of a high-dose capsaicin rather than the onerous task of repeat daily applications of low-dose formulations that are associated with a high dropout rate. Later, a high concentration capsaicin patch (8 %) was devised and its application to the skin for a period of 1–2 h produced longer term changes in epidermal nerve fibers that included loss of staining and reduction of heat sensitization. This illustrated that a short-term application of a high concentration of capsaicin can mimic those changes previously seen under repeat application (3–5 times/day for 1 week) of lower concentration capsaicin cream (Malmberg et al. 2004). Subsequently, a randomized double-blinded study for the treatment of PHN using a 1-hour application of a high-dose capsaicin (8 %) patch was found to provide significant pain relief between study weeks 2–12 (Backonja et al. 2008). However, just as repeated application of low-dose capsaicin creams has found limited acceptance by patients due to application-induced burning and/or irritation, application of a high-dose capsaicin patch must also overcome a similar therapeutic barrier. To address this additional therapeutic barrier, high-dose capsaicin patch administration requires a unique application protocol as compared with low-dose breams and a health care provider (see Table 4.2). Pilot studies indicated that pretreating the proposed application area with 4 % lidocaine jelly for one hour was reported to provide “acceptable” side effects following application of high-dose capsaicin patch, though such treatment was commonly associated with localized pain and erythema (Backonja et al. 2008).

4.4 Safety and Tolerability of High-Dose Capsaicin Patch

Beginning with a series of small, open label studies, more rigorous double-blinded randomized controlled studies focused on the safety and tolerability of high-dose capsaicin-containing patches following prior application of a topical local anesthetic. Importantly, it was studied whether the type of local anesthetic influenced the degree of tolerability of the subsequent capsaicin patch application. In a randomized prospective study of 117 patients suffering from a range of peripheral neuropathies including PHN and diabetic neuropathy, using LMX 4, Topicaine, or Betacaine, with endpoints of average pain score at baseline versus at 2–12 weeks, no significant difference in tolerability was found between the various local anesthetics (Webster et al. 2012). Although no serious adverse events

Table 4.3 Capsaicin application site adverse effects

Capsaicin application site adverse effects
Erythema
Pain
Pruritus
Papules

Adverse reactions occurring in clinical studies in ≥5 % of patients treated with high concentration capsaicin patch and of higher incidence than controls. Symptoms were generally rated as "mild" or "moderate" and generally resolved by postapplication day 0–2

(AE) related to high-dose capsaicin patch treatment were reported, 50–59 % of the study patients reported adverse effects (see Table 4.3), which were primarily local, mild to moderate in severity, and resolved within in 1–2 days. Furthermore, analgesic responses were not significantly different between local anesthetic pretreatment groups. Importantly, patients receiving a longer (90-min) patch application were associated with greater procedural discomfort and greater use of periprocedural analgesics without a proportional increase in analgesic effect. Thus a 60-min application period was largely adopted (Webster et al. 2012). Moreover, these results mirror a smaller study with a focus only on patients with PHN treated topically with lidocaine 2.5 %/prilocaine 2.5 % cream for 60 min before receiving a single 60-min application of topical high concentration capsaicin. Maximum mean change in NPRS score was +3.0 observed at 55-min postpatch application with scores gradually declining to near preanesthetic levels within 85 min of patch removal. However, half of the patients received analgesic medication on the day of treatment (Webster et al. 2011). More broadly, analysis of twelve studies of mixed experimental design and patients with various peripheral painful neuropathies (PHN, HIV-DSPN, and PDN) showed that the maximum increase in pain reporting score ranged from 2.3 to 2.8 with no difference in treatment-associated pain among the different neuropathies (Webster et al. 2012).

Despite the mild to moderate adverse effects described above (localized pain and irritation) topical capsaicin engenders an overall favorable safety profile due to several complementary factors. Capsaicin can be systemically absorbed through the skin as a function of its applied concentration and duration of exposure. When the kinetics of systemic capsaicin absorption were investigated in patients receiving a high-dose capsaicin (8 %) patch for pain arising from either PHN, HIV-associated neuropathy (HIV-AN), or from diabetes mellitus (PDN), patch application to the trunk (PHN) directed the greatest plasma levels (peak 17.8 ng/mL). Conversely, significantly lower plasma concentrations were detected when the patch was applied to the feet (diabetic neuropathy, HIV-AN). Likewise, if application time was increased from 60 to 90 min, the hourly plasma concentration was observed to double (Babbar et al. 2009). Ultimately following absorption, capsaicin is rapidly eliminated by the cytochrome P450 hepatic enzyme system, (Chanda et al. 2008) with a population elimination half-life of 1.64 h (Babbar et al. 2009).

In summary, the application of high-dose capsaicin in the treatment of a diverse range of peripheral neuropathic states results in significant postapplication pain (up to a change of +3 on the NPRS) but treatment-associated pain is independent of underlying neuropathic condition or type of pretreatment local anesthetic. Greater than half of patients appeared to require supplemental analgesics to manage the treatment-associated pain which may be greater with a longer (90-min) application period. Nevertheless, pain associated with patch treatments was relatively transient in duration with the majority of patients returning to baseline pain levels within 2 days and overall without report of severe adverse events. For these reasons, high-dose capsaicin patch therapy has been advanced and investigated for efficacy in the treatment of a number of chronic painful conditions arising from peripheral neuropathic states, but with an apparent majority of studies derived from patients suffering from PHN (Peppin et al. 2011; Simpson et al. 2010).

4.4.1 Postherpetic Neuralgia

PHN is one of the most prevalent painful conditions associated with neuropathy that clinicians may encounter. PHN is driven in the USA by some 800,000 cases of primary herpes zoster infection each year (Schmader 2002). In Germany by comparison, from 2004 to 2009, 403,625 herpes zoster infection cases were estimated per year with approximately 5 % of such cases developing PHN (Ultsch et al. 2013). Following a primary systemic infection, the herpes zoster virus remains dormant in the dorsal root (sensory) ganglion but may become reactivated under conditions of stress, infection, malignancy (especially lymphoma), or immune-suppression resulting in its renewed replication. As a result of increased herpes zoster viral transport to the skin via infected sensory nerves, eruption of painful lesions along dermatomal distributions are manifest resulting in an increased risk of developing PHN after age 55 (Ultsch et al. 2013).

Acute outbreaks of herpes zoster are treated with a combination of medications to suppress viral replication and if needed, to manage painful symptoms. Although pain is well known to be associated with a reactivation (shingles) event, it is when pain and discomfort persist for more than 1 month after the zoster rash has healed that the diagnosis of PHN is typically made. Symptoms can include perceptions of constant burning and gnawing as well as paroxysmal sharp shooting and/or shocking pain either at rest or induced by light tactile stimulation. A combination of antiviral therapy (Acyclovir) and multimodal analgesics (gabapentinoids, TCAs, topical capsaicin preparations, opioids, topical lidocaine preparations) are intended to decrease the duration of outbreak, promote healing, and manage pain. Unfortunately, despite the effective treatment of herpes zoster infection, PHN may still develop resulting in pain that is notoriously difficult to manage—degrading a patient's quality of life.

In response to this therapeutic dilemma, a variety of treatment options have been investigated including the use of topically applied agents, such as capsaicin.

Initially formulated as "low-dose" capsaicin creams, several large, double-blinded, vehicle-controlled studies of patients with chronic PHN-demonstrated efficacy of low-dose capsaicin creams (0.075 %). The authors of these studies suggested that they should be considered as part of the initial plan for PHN pain management (Watson et al. 1993). Given the modest success of low-dose capsaicin, the development of a high-dose capsaicin patch has more recently reinvigorated the idea that high-dose topical capsaicin preparations could one day take their place among first-line treatments of painful symptoms of PHN pain. In support of this effort and as previously introduced, a topical patch capable of delivering high-dose (8 %) capsaicin therapy was subsequently developed.

4.4.1.1 Efficacy of High-Dose Capsaicin Patch Therapy for the Treatment of PHN

Randomized controlled trials: building a case for the therapeutic efficacy of high-dose capsaicin treatment in peripheral neuropathies has required substantial evidence. What must be overcome is not only an analgesia endpoint, but that the increase in pain associated with a single patch treatment can be sufficiently tolerated and be of short duration such that the benefit of a long-term analgesia will outweigh the mild—moderate short-term adverse effects. Therefore, multiple randomized, double-blinded controlled multicenter trials were conducted. NPRS for weeks 2–8 post high-dose capsaicin patch application were compared with a low concentration (0.04 %) control patch. Initial results showed a 29.65 versus 19.9 % reduction of pain intensity in treatment versus control patients during weeks 2–8 and a similar 29.6 versus 19.9 % for weeks 2–12. Importantly, these findings held true regardless of whether or not patients were taking concomitant antineuropathic pain medications (Backonja et al. 2008).

In a dose finding study, 299 PHN patients received high-dose or low-dose capsaicin patch for 30, 60, or 90 min. Although the 30-min group did not meet statistical significance, the 60-min treatment was significant with the largest improvement for patients during weeks 2–8 was following the 90-min treatment (27.8 vs. 17.3 %) (Webster et al. 2010a). Notably, the degree of pain relief for PHN in these studies appeared independent of whether patients were treated within the first 6 months of PHN or later (after 6 months). Whereas, another report suggested a greater overall improvement (including patient satisfaction) in analgesic treatment profile for patients suffering from PHN for greater than 6 months (Webster et al. 2010b).

Beyond individual or multicenter-integrated data studies described previously, meta-analysis of high-dose capsaicin prospective randomized trials have been performed inclusive of PHN, painful diabetic neuropathy, and HIV-associated neuropathy. Such meta-analysis continued to demonstrate a significant decrease in reported pain between high-dose capsaicin patch treatments versus low-dose controls (30.7 % reduction from baseline during weeks 2–12 vs. 22.7 % drop in low-dose control patch). Overall, (all sub groups of neuropathic pain) there was a 30 % reduction

achieved in 44 % of high-dose patch versus 34 % control (low-dose patch), however, the overall magnitude of these differences is relatively small—approximately 8–10 %. Such meta-analysis were limited by a study period that was 12 weeks, and a neuropathic pain subgroup cohort that was insufficient in size to detect subgroup treatment benefits (Mou et al. 2013) (Irving et al. 2012). Subsequent meta-analysis was undertaken with a larger number of PHN patients (1313 PHN) studied with high-dose capsaicin patch treatment, and using a 30 % reduction in mean pain intensity score as characterizing a "responder." This analysis revealed a mean of 3.4 days until onset of analgesia, with duration of analgesic response of 5 months (Irving et al. 2012). Furthermore, in an attempt to identify patients that may have gained the greatest benefit from high-dose patch treatment, a study identified five types of "responders:" (1) a population showing worsening of response (i.e., pain increases during treatment) which were 1.5 and 0.8 % of patch versus control; (2) a population showing no analgesic response which were 22.7 % of patch and 39.1 % of control; (3) a population showing a partial or full analgesic response but with a return to pretreatment pain levels within 12 weeks (24.7 % patch vs. 17.6 % control); (4) a population showing a partial analgesic response at week 1 that remained constant during the study period (14.5 % patch and 14.3 % control); and (5) a population that showed an ongoing decline in pain rating during the 12 weeks of the study which were 36.6 % patch and 28.2 % control. Importantly, increasing age and duration of disease as well as concurrent opioid use all were negative predictors of resolution of the pain (Group 5), and generally, no analgesic response to the high-dose capsaicin patch treatment (Group 2) (Martini et al. 2013).

Taking a complementary approach, a systematic review of six studies including 2073 patients was performed by the Cochrane Database through December of 2012 that included RCT and controlled trials of at least 6-week duration. Four studies of 1272 participants for PHN showed numbers needed to treat (NNT) to attain "much improved or very much improved" of 8.8 and 7.0. Serious adverse events were no more common with high-dose treatment than controls nor were the rate of study withdrawals, however the "lack of efficacy" withdrawals were found to be greater in controls—supporting a beneficial effect of the high-dose patch. Overall, the systematic review of high-dose patch treatment for PHN (and HIV-associated neuropathy) generated more participants with high levels of pain relief than control—but the additional proportion of that benefit is not large. Nevertheless, for those who did respond, benefits in sleep, fatigue, depression, and quality of life were also seen (Derry et al. 2013).

4.4.1.2 Summary: Treatment of PHN with High-Dose Capsaicin

PHN can result in severe neuropathic pain and impaired functional status. The majority of oral analgesic treatments for PHN carry the risk of significant systemic side effects. This has been in large part responsible for the interest in topically administered therapies. Prior to the advent of a high-dose capsaicin patch, widespread acceptance of capsaicin in lower concentration forms were limited by

unimpressive evidence and compliance with the cumbersome and uncomfortable nature of chronic administration. With the advent of a high-dose patch, a capsaicin treatment option now exists that does not eliminate, but changes and potentially improves upon the limitations of its administration. There is now a modest but growing evidence base including several RCTs, meta-analysis, and systematic review supporting safety and efficacy in the use of high-dose capsaicin patch treatment for PHN. Interestingly, thus far only a single retrospective study has attempted to provide insight as to the financial impact of the use of the high concentration capsaicin patch in the treatment of PHN. Using a model based on monthly analgesic medication cycles, including analgesic dose titration and management of adverse events, the proportion of patients achieving at least a 30 % improvement in PHN pain with outcomes cost per quality-adjusted life-year (QALY) were calculated. Although no head-to-head studies were identified for comparison, they found that the high-dose (8 %) capsaicin patch (and topical lidocaine patch) were significantly more effective than oral analgesic medications prescribed for PHN. The incremental cost-effectiveness ratio for the capsaicin patch overlapped with the topical lidocaine patch and was within the accepted threshold of cost per QALY gained compared to tricyclic antidepressants (TCAs), duloxetine, gabapentin, and pregabalin. However, the frequency of the high-dose capsaicin patch retreatment could significantly impact its cost-effectiveness (Armstrong et al. 2011).

4.4.2 Diabetic Neuropathy

Diabetes mellitus affects more than 14 million people within the USA, and estimates predict that globally, rates will increase to 366 million by 2030 (Wild et al. 2004). Among this cohort, some estimate that between 18 and 24 % may suffer from some form of painful diabetic neuropathy (PDN) and a subset of patients suffering from diabetic polyneuropathy is termed PDPN (Schmader 2002; Spallone and Greco 2013). PDPN is thought to arise from the metabolic and microvessel consequences associated with chronic hyperglycemic exposure, as occurs in diabetes type I or II. PDPN represents the most bothersome of symptoms of diabetic polyneuropathy that develops into a chronic painful condition. Management of the painful neuropathic symptoms associated with PDNP has been difficult given limited choices of therapeutic agents (TCAs, gabapentinoids, topical lidocaine), and often less than 50 % pain reduction or high number-needed-to-treat—NNT.

Given the apparent widespread prevalence and difficulty in managing PDPN, use of preparations containing either low or high concentrations of capsaicin have been investigated. Early randomized studies using relatively low-dose capsaicin preparations (0.075 %) versus a vehicle control four times daily on patients suffering from PDPN, showed a small but statistically significant improvement in pain intensity scores (VAS) and pain relief (The Capsaicin Study Group 1991). More recently the idea that capsaicin-containing topical preparations may, in fact, have a therapeutic advantage in the treatment of diabetic neuropathy was advanced

due to over-expression of its natural target—the capsaicin receptor (TRPV1) in an experimental rodent model of diabetes (Rashid et al. 2003). Unfortunately, such a promising idea has not yet been observed to translate into therapeutic outcome. For example, in a noncontrolled, prospective observational study, 91 patients with PDPN were enrolled for single treatment with 1–4 high-dose topical capsaicin patches and pain scores were studied longitudinally over a 12-week period. Approximately one-third (34 %) of patients treated with a single application of the high-dose capsaicin patch showed a rapid and clinically relevant reduction in pain that persisted (70 ± 5 % pain reduction) by week 12. However, an equal percentage either had no improvement or a short-term benefit that peaked at 3 weeks following treatment (Martini et al. 2012). As observed in the treatment of other peripheral neuropathies, high-dose capsaicin patch therapy for PDNP was also associated with a mean increase in reported pain scores of 2.3–2.8 on night two, resulting in 14 % of treated patients requiring additional analgesics to manage their treatment-associated pain (Peppin et al. 2011). Therefore, although some patient's suffering from PDNP may indeed experience significant analgesic benefit, its overall lower response rate has made it problematic to consider high-dose capsaicin patch therapy as a first-line analgesic treatment until more convincing evidence from RCT is reported.

4.4.3 HIV-Associated Painful Neuropathy

Painful peripheral neuropathies as a result of HIV infection represent another therapeutic challenge for both patient and clinician. HIV-associated distal symmetrical polyneuropathy (DSPN), represents perhaps the most common neurologic complication (30–50 %) of HIV-infected patients. Although the mechanism of HIV-DSPN-associated pain remains unclear, it is presumably driven by a combination of cytotoxic HIV-viral protein product(s) and/or is exacerbated by certain antiretroviral therapies (Acharjee et al. 2010; Huang et al. 2013). Such pain can be refractory to standard pharmacologic treatment leading to major morbidity and disability. In response for the need of more effective treatments, early trials again focused on the use of low-dose capsaicin-containing topical preparations but with unsatisfactory results (Paice et al. 2000). With the development of the high-dose (8 %) capsaicin patch, a renewed effort was launched to demonstrate the efficacy of topical capsaicin for the treatment of HIV-DSPN without a detectable change in the perception of warmth, cold, sharp pain, or vibration sensation (Simpson et al. 2008). Although an initial RCT study showed a trend toward better pain relief for these patients, the study failed to meet its primary endpoint (Clifford et al. 2012). Subsequently, the combination of two similarly designed RCT revealed a reduction in pain with application of the high-dose patch treatment for 30 but not 60 min—missing significance due to an unusually high level of pain relief from the low-dose control patch application (Brown et al. 2013). Finally, with study of a greater number of subjects (801 HIV-DSPN patients) with pain of the lower extremities

(feet) showed modest pain relief with 41 % of HIV-DSPN patients having a 30 % reduction in symptoms and a mean duration of response of 5 months. Importantly, of those that were followed for the entire 12 months, 10 % had complete resolution of painful symptoms (Mou et al. 2013). Moreover, there was no apparent relationship between the duration of patch application, the number of patch applications or the degree of analgesia achieved. Numbers needed to treat (NNT) to achieve a patient report of "better or much better" was 5.8 and higher NNT for other outcome measures. Adverse events included short-term site swelling and burning sensation with 44 % of the patients requesting oxycodone/acetaminophen following capsaicin patch placement. A small number of patients also experienced itching or coughing (Derry et al. 2013). Given the NNT of HIV-DSPN patients to achieve even a modest analgesic result, use of high-dose capsaicin patch does not appear to be a first-line analgesic treatment for HIV-DSPN although an unpredictable subset of such patients may obtain significant long-term relief of painful symptoms.

4.4.4 Other Painful Conditions with Neuropathic Features

Just as postherpetic neuralgia, diabetic and HIV-associated neuropathies represent distinct disease entities they also share overlapping features of pain and dysfunction of the peripheral nociceptive system. Although less well known, there are a number of other painful conditions with neuropathic features arising from diverse pathophysiology. Of these, the more commonly known include: trigeminal neuralgia, complex regional pain syndrome type-II (causalgia) and persistent postsurgical pain. Paradoxically, despite sharing apparently similar mechanistic origins (partial nerve injury) they differ widely in terms of their therapeutic response to pharmacologic and interventional therapies but all are known to be difficult to effectively manage and generally resistant to opioid based analgesic strategies. Perhaps due to their complexity and relative scarcity, there does not appear to be any controlled studies for the treatment of trigeminal neuralgia or CRPS-II with topical capsaicin—except perhaps a case report of the successful treatment of PHN in the trigeminal (V1) distribution with a high-dose capsaicin patch (Sayanlar et al. 2012).

In contrast, the use of topical capsaicin for the management of postoperative incisional pain includes a series of case reports (McPartland 2002; Rayner et al. 1989; Weintraub et al. 1990). Controlled trials for the treatment of persistent postsurgical pain following mastectomy has been pursued with reasonable success and later in part confirmed by an open label trial (Dini et al. 1993; Watson and Evans 1992). Capsaicin-based topical applications were also investigated with a controlled trial on postsurgical neuropathic pain in cancer patients with the use of 0.075 % cream applied four times daily. Impressively, 53 versus 17 % (placebo control) of patients experienced a significantly greater pain relief while using topical capsaicin (Ellison et al. 1997). As concern of persistent postsurgical pain syndromes grow, additional trials utilizing capsaicin-containing preparations should be forthcoming.

4.5 Conclusions

As our understanding of the molecular basis of pain transduction has advanced, propelled with the isolation of the capsaicin receptor (TRPV1), there has been a renewed effort to leverage these discoveries to develop more effective treatment for persistent painful conditions. Despite the historic use of topical preparations containing capsaicin, the recent combination of neurobiology, biotechnology, and advances in clinical trial design has allowed concentrated forms of capsaicin to be safely applied to manage painful neuropathic conditions. Of the painful conditions described in this chapter, the strongest evidence exists for the use of high-dose capsaicin for the management of painful PHN. However, as with other therapeutic options for the treatment of painful neuropathic conditions, there appear to be patient responders and non-responders suffering from PHN and a range of other neuropathic conditions. Fortunately, there appears no advantage, nor disadvantage, of such patients taking concurrent anti-neuropathic/analgesic medications while undergoing high-dose capsaicin patch treatment. For those patients fortunate to receive analgesic benefit from a single application of the high-dose capsaicin patch, there is the potential of long-lasting relief of painful symptoms without the requirement of continued daily topical application. Nevertheless, analgesic response rates for peripheral neuropathic painful conditions tend to average approximately 30 % and rarely if ever exceed 50 %. Moreover, the magnitude of analgesic effect is typically modest (10–30 %). Beyond PHN, other painful neuropathic conditions sensitive to the analgesic effects of topical capsaicin (with decreasing level of evidence) include HIV-associated painful neuropathy (DSPN), painful diabetic neuropathy and postsurgical neuropathic pain. In these cases, there is not yet adequate evidence to support capsaicin-based topical therapies as first-line treatments. However, for some patients who are intolerant of standard pharmacologic approaches for the treatment of peripheral neuropathic pain syndromes, topical capsaicin preparations continue to offer a rational and often successful option—largely free of systemic side effects such as sedation, altered mental status, or risks of dependence and addiction.

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