The Role of the Capsaicin 8 % Patch (Qutenza®) in the Treatment of Post-herpetic Neuralgia

Gordon Irving, MD

Medical Director, Swedish Pain Center, Seattle, Washington, US

Abstract

Post-herpetic neuralgia (PHN) occurs as a complication of acute herpes zoster. The capsaicin 8 % (w/w) dermal patch (Qutenza®) is a transient receptor potential vanilloid agonist that increases intracellular calcium concentration, triggering calcium-dependent protease enzymes to cause cytoskeletal breakdown. This action is thought to lead to loss of cellular integrity and defunctionalization of nociceptor epidermal nerve fibers. The capsaicin 8 % patch is indicated in the US for the treatment of neuropathic pain associated with PHN. In pivotal, randomized, double-blind, multicenter trials in patients with PHN, a single 60-minute application of the capsaicin 8 % dermal patch reduced mean numeric pain rating scale scores between baseline and weeks 2–8 to a significantly greater extent than the low-dose comparator patch (capsaicin 0.04 % w/w). The capsaicin 8 % (w/w) dermal patch was found to be safe and generally well-tolerated. Most commonly reported side effects were local, comprising dermal irritation, erythema, and pain at the site of application. These effects were transient and mild to moderate in severity. Transient patch application-related pain was not a barrier to use and was managed with local cooling or oral analgesics in nearly all cases. Thus, the capsaicin 8 % dermal patch appears to have a good safety profile, is well tolerated, and offers effective topical therapy in some patients with PHN. This review aims to characterize the use of the capsaicin 8 % dermal patch in the treatment of PHN.

Keywords

Neuropathic pain, post-herpetic neuralgia (PHN), capsaicin 8 % patch, Qutenza®

Post-herpetic neuralgia (PHN), a neuropathic pain disorder resulting from nerve fiber damage following herpes zoster (HZ) infection, is caused by reactivation of the varicella zoster virus (VZV).[1–3] VZV reactivation leads to the symptom complex commonly known as shingles.[4] PHN is defined as VZV-associated pain persisting for more than 3 months after resolution of a VZV infection.[5] PHN symptoms often include allodynia, whereby normally innocuous stimuli, such as the light brushing of the skin, can elicit pain, paresthesia, and dysesthesia.[6]

The incidence of PHN increases with age.[7,8] In population-based data from 1996 to 2005, out of 1,669 adult residents (≥22 years) of Olmsted County, MN, US, the proportion of individuals who developed PHN increased from 5 % in those aged <60 years to 10 % in those aged between 60 and 69 years, 17 % in those aged 70 to 79 years, and 20 % in individuals aged ≥80 years.[8] Apart from age, other risk factors for PHN include severe acute pain related to the VZV infection, rash severity (>50 lesions), and the presence of a prodrome.[9,10]

Pharmacologic Treatments and Unmet Needs

Guidelines issued by the American Academy of Neurology,[11] the International Association for the Study of Pain,[12] and the European Federation of Neurological Societies[13] categorize tricyclic antidepressants (TCAs), anticonvulsants such as gabapentin and pregabalin, and the lidocaine 5 % topical patch as first-line treatments for PHN. TCAs,[14–16] gabapentin,[17] pregabalin,[18] and topical lidocaine[19–21] have demonstrated efficacy in reducing the pain of PHN and have mostly acceptable tolerability profiles. In a recent systematic review and meta-analysis of 229 studies,[22] the use of TCAs, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin were strongly recommended.

The use of TCAs in treating PHN, however, is hampered by a slow onset of action and systemic adverse events such as urinary retention, weight gain, constipation, and sedation.[23] TCAs have also been associated with cardiotoxic events, including myocardial infarction and cardiac dysthymias.[23–26] Elderly patients appear particularly susceptible to these

events.[23] Adverse events associated with anticonvulsants likewise limit their use in some patients. The most common adverse events with gabapentin or pregabalin reported in clinical studies included somnolence, weight gain, and dizziness.[27,28]

Pathophysiologic Mechanisms Underlying Post-herpetic Neuralgia

The pathophysiology of PHN, although not fully understood, is believed to be rooted in neuronal injury affecting both the peripheral and central nervous system (CNS).[29] This injury leads to peripheral and central neurons generating spontaneous discharges while also lowering the activation threshold to cause pain with nonpainful stimuli (allodynia). At the cellular level, there is evidence to indicate that nerve fiber membrane receptors associated with pain, such as the transient receptor potential vanilloid 1 (TRPV1), are upregulated.[30]

Unique Mechanism of Action

The transient receptor potential (TRP) family of ion channels are selective for calcium and magnesium over sodium ions.[31] TRPV1 channels are expressed in the CNS in areas that process pain signals.[32] TRPV1, a member of the TRP family of ion channels, is a calcium-permeable channel, which is modulated by a diverse range of exogenous noxious stimuli including pH changes, high temperatures, and irritant and pungent compounds.[33]
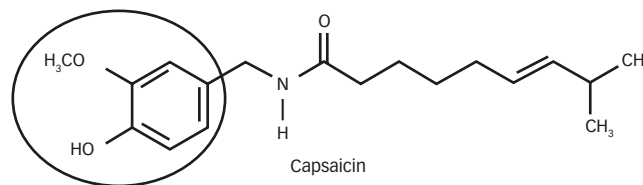
The capsaicin 8 % w/w; 640 µg/cm² patch (Qutenza®) is indicated in the US for the management of neuropathic pain associated with PHN.[34] Capsaicin, 8-methy-*N*-vanillyl-6-nonenamide (see *Figure 1*),[35] is the active ingredient in chili peppers that evokes burning and "flare and weal" responses and is a highly selective agonist for the TRPV1 receptor.[31,36] TRPV1 receptors are found on a portion of primary sensory neurons with cell bodies in the dorsal root ganglion and are selectively expressed in the epidermis cutaneous nociceptors making them accessible to local treatment.[36,37] In general, the TRPV1-expressing neurons are peptidergic, small diameter, and give rise to thin, unmyelinated C fibers,[37–39] which may play an essential role in the chronic pain-induced plastic changes in the CNS.[38] Natural stimuli such as tissue burns, noxious heat, and spider toxins can activate TRPV1 expressing C-fibers.[31]

Inactivation of voltage-gated sodium ion channels and direct pharmacologic desensitization of plasma membrane TRPV1 receptors may contribute to an immediate reduction in neuronal excitability and pain, while more persistent effects may be due to sustained increased levels of intracellular calcium.[39] Such raised levels can activate calcium-dependent enzymes, such as proteases,[40] which can induce depolymerisation of cytoskeletal components, including microtubules.[41,42] Thus, multiple mechanisms are believed to be important for capsaicin-induced analgesia (see *Figure 2*). Capsaicin-induced local depletion of substance P is not thought to be crucial for capsaicin's mechanism of action.[43] Intra-epidermal nerve fibers degenerate following high-dose capsaicin application;[44] these nerve fiber endings have been shown to recover after 24 weeks in healthy volunteers.[45]
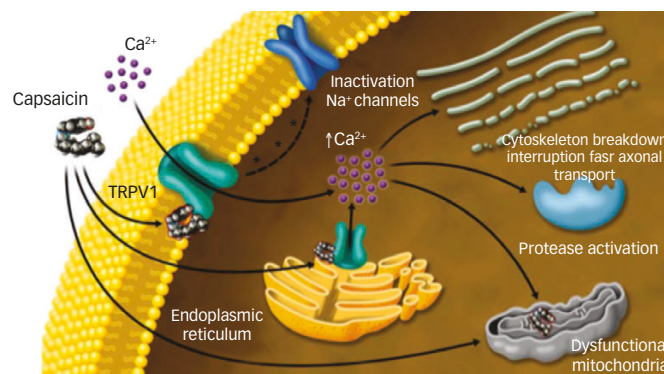
Pharmacokinetic Profile

The capsaicin 8 % dermal patch measures 280 cm² and contains 179 mg of capsaicin (640 µg/cm²).[34] Capsaicin is extremely lipophilic, having little affinity for the aqueous blood phase and is readily absorbed into the epidermal and dermal layers. To determine systemic capsaicin exposure

Figure 1: The Chemical Structure of Capsaicin, which Consists of a Vanilloid Ring (Circled) and an Alkyl Side Chain

Source: QUTENZA (capsaicin) 8 % patch FULL PRESCRIBING INFORMATION 2009.[35]

Figure 2: Multiple Mechanisms Underlying Defunctionalization Induced by Capsaicin

TRPV1 = transient receptor potential vanilloid 1. Reproduced with permission 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;107:490–502.[43]

after single 60 or 90 minute applications, plasma samples were collected in 173 patients with PHN at varying intervals after patch removal (0, 1, 3, 6, and 24 hours).[46] Overall, the majority of plasma concentrations of capsaicin were lower than 10 ng/ml; capsaicin plasma levels were found to decline rapidly, with a mean elimination half-life after patch removal of 1.64 hours. After a 60-minute application, the mean area under the plasma concentration time curve was 7.42 ng.h/ml and the maximum plasma concentration (C_{max}) value was 1.86 ng/ml. The primary metabolites of capsaicin,[47,48] hydroxycapsaicin, 17-hydroxycapsaicin, and 16,17-dehydrocapsaicin, as observed in *in vitro* hepatic and skin metabolism studies, were not detected in patients in this study.

Capsaicin is metabolized readily in the liver by various cytochrome P450 enzymes.[49] During *in vitro* incubation with human skin, [14C]capsaicin was metabolized slowly over 20 hours.[47] As only small quantities of drug reach the systemic circulation, there are no recommendations for dose adjustments in cases of hepatic or renal failure.[50]

Clinical Experience

The capsaicin 8 % patch clinical development program comprised phase I, II, and III studies and is summarized in *Tables 1*, *2*, and *3*,[45,51–59] respectively. For treatment of PHN, the capsaicin 8 % patch is applied for 60 minutes and then removed. In order to more fully blind patients in the trials, a low-concentration capsaicin 0.04% patch was used as an active control; this dose was selected because it induced erythema and a sensation of heat. In one

Table 1: Phase I Studies Investigating the Capsaicin 8 % Patch

Study/Reference	Design	Parameter Investigated	Outcome
Malmberg et al., 2004[51]	Randomized controlled open-label study comparing C8P with capsaicin 0.04 % patch and control patch (n=20)	Epidermal nerve fiber density	Significant reduction in epidermal nerve fiber density observed in the C8P
Kennedy et al. 2010[45] (ClinicalTrials.gov identified: NCT00254449)	Randomized controlled open-label study of long-term effects (n=36)	Epidermal nerve fiber density and quantitative sensory testing	Significant reduction in epidermal nerve fiber density

C8P = capsaicin 8 % patch.

multicenter, randomized controlled trial (RCT), 42 % of PHN patients treated with the capsaicin 8 % patch reported a ≥30 % reduction in pain intensity compared with 32 % in the active control group (odds ratio [OR] 1.56, 95 % confidence interval [CI] 1.03 to 2.37; p=0.03; see *Table 2*).[56] In this same study, the mean percent change in numerical pain rating scale (NPRS) score between baseline and weeks 2–12 was –29.9 % in the capsaicin 8 % patch group versus –20.4 % in the active control group. In another multicenter RCT in PHN, the mean percent change in NPRS score between baseline and weeks 2–8 was –32.0 % in the capsaicin 8 % patch group versus –24.4 % in the active control group (p=0.011).[58] In the same study, a ≥30 % reduction in NPRS score was achieved in 46 % of capsaicin 8 % patch-treated patients compared with 34% of active controls (p=0.02; see *Table 3*).[58]

A meta-analysis that included seven RCTs of similar design investigated the capsaicin 8 % patch (1,120 with PHN; 338 with HIV-associated neuropathy [AN]).[60] This meta-analysis was based on pooled individual patient data, for identical end-points, as if all patients were part of one large study. The percent change from baseline to weeks 2–12 was –30.7 % in the capsaicin 8 % patch and –22.7 % in the control group, which yielded a group difference of 8.0 % (95 % CI 4.6, 11.5) (p<0.001); the proportion of patients achieving a 30 % reduction in pain intensity was 44 % for the capsaicin 8 % patch-treated patients compared with 34 % for control-treated patients.[60] In a separate meta-analysis of combined individual patient data (1,313 participants with PHN) from seven double-blind RCTs,[61] 44 % of patients had a ≥ 30 % reduction in pain intensity, and 11 % of patients achieved complete pain relief 2–12 weeks after capsaicin 8 % patch treatment. In those responding to treatment, analgesia started within a few days of treatment and was sustained for an average of 5 months. In a Cochrane review[62] of six studies involving 1,272 participants with PHN and 801 with HIV-AN, it was concluded that capsaicin 8 % patch treatment generated greater levels of pain relief than the active control in both PHN and HIV-AN. Point estimates of the numbers needed to treat were 8.8 (95 % CI 5.3–26) at 8 weeks and 7.0 (95 % CI 4.6–15) at 12 weeks.

The Qutenza Safety and Effectiveness in Peripheral neuropathic Pain (QUEPP) study evaluated 1,044 patients without diabetes with peripheral neuropathic pain, who received a single application of the capsaicin 8 % patch.[63, 64] PHN was the most frequent diagnosis (31.9 %) followed by postsurgical neuralgia (22.8 %), post-traumatic neuropathy (12.4 %), polyneuropathy (14.3 %), and mixed pain syndromes (16.6 %). Mean relative pain intensity during weeks 1–12 decreased by 24.7 % (1.1 standard error of the mean [SEM]) and significant improvements in pain attacks (p≤0.001), sleep duration (p≤0.001), and sleep quality (p≤0.001) were reported in the peripheral neuropathic pain patients. The ≥30 % responder rate was 42.7 % and the ≥50 % responder rate was 23.7 %. The use of opioids and anti-convulsants decreased significantly (p<0.001) in capsaicin 8 % patch-treated patients. In the QUEPP study, 146 adverse drug reactions were reported in 106 of 1,063 patients of the safety population (10.0 %); the most common among these were application site reactions, such as erythema and pain.[63] In total, 27 serious adverse event (SAE) drug reactions were reported in 17 patients (1.6 %) and five SAEs resulted in death, none of which were treatment-related.[64] The highest treatment response, relative change of numeric pain rating score on days 7–14 to week 12 compared with baseline, was seen in patients with a history of pre-existing peripheral neuropathic pain of <6 months, suggesting that early initiation of treatment may be advantageous.[62] In patients with pre-existing peripheral neuropathic pain for <6 months, the mean relative change of the NPRS score on days 7–14 to week 12 versus baseline was –36.6 % (4.6 SEM; n=105).

Longitudinal analysis from four double-blind RCTs of the topical capsaicin 8 % patch has suggested that there are different response groups to treatment, which may be related to different pain mechanisms despite a presumed common underlying disease process.[65] In this analysis, five distinct response subgroups were detected from data of 1,248 patients treated with the capsaicin 8 % patch, including a group of nonresponders, a group with partial response, and a group exhibiting full analgesic effect.

Overall, the clinical studies showed the capsaicin 8 % patch to be generally safe and well-tolerated (see *Tables 1–3*). The most commonly reported side effects were dermal irritation, erythema, and pain at the site of application. These effects were transient and mild to moderate in severity. This was emphasized by an integrated analysis of tolerability data from the capsaicin 8 % patch clinical program, including 1,696 patients with peripheral neuropathic pain related to PHN, HIV-AN, and painful diabetic neuropathy. Almost all (≥98 %) of the patients completed ≥90 % of the full treatment duration, regardless of the number of treatments given.[66] NPRS score increases returned, on average, to baseline within 85 minutes following treatment.[60] Transient patch application-related pain with the capsaicin 8 % patch was managed with local cooling or oral analgesics in nearly all cases. This indicated that patch application-related pain was not a barrier to use.

Role of Lidocaine Pre-treatment
To mitigate any discomfort, prior to treatment with the capsaicin 8 % patch, the product prescribing information states that patients should be pre-treated with topical anesthetic cream, such as lidocaine, for 60 minutes.[35] Lidocaine reduces pain transmission through inhibition of sodium ion channels; sodium channels act independently of the TRPV1 receptors.[67] Capsaicin can induce axonal depolarization and dysfunction even in the presence of sodium channel blockade.[68] There are potential advantages in avoiding pre-treating patients with topical lidocaine including a reduction in total treatment time and a potential cost benefit. This was supported by a comparison of 32 pre-treated patients with 26 non-pre-treated patients receiving capsaicin 8 % patch treatment in which there was no significant

Table 2: Phase II Studies Investigating the Capsaicin 8 % Patch

Reference	ClinicalTrials.gov Identifier	Design	Treatment (Patient Numbers)	Main Efficacy Outcomes	Key Safety/Tolerability Outcomes (%)
Backonja et al., 2010[52]	NCT00034710	Randomized, double-blind, controlled study with an open-label extension in PHN	C8P (n=32) or control patch* (n=12)	During days 8–28 after the double-blind treatment, C8P-treated patients had a mean change in NPRS score from baseline of –32.7 % versus –4.4 for control (p=0.003) Open-label extension: mean change from baseline morning and evening NPRS score during weeks 2–12 was –33.8 % for C8P and +4.9 % for control	TEAEs occurred in 42 % of C8P group and 17 % of control group
Simpson et al., 2010[53]	NCT00233155	Open label, randomized repeat treatments up to four patches, in PNP	54 PHN patients, 52 with HIV-DSP		96 % of patients reported ≥1 TEAE. Most-frequently reported TEAEs were transient, mild-to-moderate application site erythema, pain, edema, and papules
Webster et al., 2011[54]	NCT00916942	Open label in PNP	C8P (n=24) following lidocaine 2.5/prilocaine 2.5 % cream		All patients completed >90 % of intended patch application duration. Pain during application was transient
Webster et al., 2012[55]	NCT00082316	Open label, randomized in PNP	117 patients (25 with PHN, 91 PDN, and 1 HIV-DSP) with three topical anesthetic formulations: (L.M.X.4®), Topoicaine® Gel or Betacaine Enhanced Gel 4		Treatment with any of the topical anesthetics tested appeared to have a good safety profile and generally well tolerated. >97 % of patients completed ≥90 % of the planned treatment

*C8P = capsaicin 8 % patch; HIV-DSP = human immunodeficiency virus-associated distal sensory polyneuropathy; NPRS = numerical pain rating scale score; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; PNP = peripheral neuropathic pain; TEAE = treatment-emergent adverse event. *Control patch = capsaicin low dose (0.04 %) patch*

Table 3: Phase III Studies Investigating the Capsaicin 8 % Patch

Reference	ClinicalTrials.gov identifier	Design	Treatment	Main Efficacy Outcomes	Key Safety/Tolerability Outcome (%)
Backonja et al., 2008[56]	NCT00115310	Multicenter, double-blind, parallel-group in PHN	C8P (n=206) or control patch* (n=196)	From baseline to weeks 2–8, a ≥30 % reduction in pain intensity was achieved in 42 % of the C8P group versus 32 % of the control group (p=0.03). Mean change in NPRS score: –29.6 % in C8P group versus –19.9 % in control group (p=0.001)	TEAEs occurred in 99 % of C8P group versus 88 % of control group
Webster et al., 2010[57]	NCT00061776	Multicenter, randomized, double-blind, controlled dose finding study in PHN	C8P (n=222) or control patch* (n=77)	Mean percent reductions in NPRS score from baseline to weeks 2–8 was significantly greater in the total C8P group (26.5 %; p=0.0286) and the 90-minute C8P group (27.8 %; p=0.0438) compared with the pooled control group (17.3 %)	99 % completed ≥90 % of the intended patch application. 59 % of the C8P group reported an TEAE versus 56 % of the control group
Irving et al., 2011[58]	NCT00300222	Multicenter, randomized double-blind study in PHN	C8P (n=212) or patch control* (n=204)	From baseline to weeks 2–8, a ≥30 % reduction in NPRS score seen in 46 % of the C8P group versus 34 % of the control group Overall, there was a 32.0 % mean reduction from baseline in NPRS score in the C8P group versus a 24.4 % reduction the in control group	Most TEAEs were application site specific (notably erythema and pain), transient, and generally mild to moderate in severity
Webster et al., 2011[59]	NCT00068081	Multicenter, randomized double-blind, controlled study in PHN	C8P (n=102) or control patch* (n=53)	36.5 % mean reduction in NPRS scores from baseline to weeks 2–8 in the C8P group versus 29.9 % reduction in controls (p=NS)	Reported in 75 % of C8P patients and 53 % of control patients. Most TEAEs were application-site specific

*C8P = capsaicin 8 % patch; NPRS = numerical pain rating scale score; PHN = post-herpetic neuralgia. *Control patch = capsaicin low dose (0.04 %) patch.*

difference in mean NPRS at any time during or after capsaicin patch treatment.[67] Furthermore, the same proportions (57 %) of pre-treated and non-pre-treated patients were willing to receive capsaicin re-treatment.

Topical lidocaine-induced analgesia itself is transient (lasting 1–2 hours); statistically significant pain relief compared with the vehicle patch was not achieved in clinical trials until 4 hours post-application.[69] This suggests

that 60-minute pre-treatment does not allow sufficient time for topical lidocaine to act on the nerve endings. Further study is therefore warranted to explore whether lidocaine pre-treatment confers any overall benefit in the application of the capsaicin 8 % patch.

Repeat Application of the 8 % Capsaicin Patch

The effects of repeated 8 % capsaicin patch treatment were shown in an open label extension of a PHN trial.[52] Fifteen patients who received at least two treatments had similar reductions in their pain score from baseline, 28.4 % after the first treatment; 29.7 % after the second treatment. Nine patients who received three treatments achieved a mean reduction from baseline in NPRS score of 34.1 ± 24.2 (95 % CI 52.7–15.6). These results demonstrated that a mean decrease of approximately 30 % was maintained during each treatment cycle of the capsaicin 8 % patch regardless of the number of treatments received.

Cost-effectiveness

A review of high-concentration topical capsaicin for the treatment of chronic neuropathic pain highlighted that although the treatment is similar to other available therapies in terms of efficacy, it is likely to be used when other available therapies have failed owing to reasons of cost.[62] However, in a cost-effectiveness analysis using a 1-year Markov model that compared the 8% capsaicin patch to existing PHN therapies, measures showed that 8% capsaicin and topical lidocaine patches had significantly higher rates of effectiveness than oral agents.[70] The analysis also found that the 8 % capsaicin patch was comparable to the topical lidocaine patch and within an accepted cost per quality-adjusted life-year gained threshold compared with the oral treatments.

Concluding Remarks

Initially the topical administration of capsaicin, a highly selective agonist for TRPV1, resulted in localized burning sensations, hyperalgesia, allodynia, and erythema.[36] Over time, TRPV1-expressing cutaneous nociceptors become less sensitive to a variety of stimuli, including capsaicin itself, and exhibit a protracted decrease in spontaneous and evoked firing known as defunctionalization.[36,43] Capsaicin-induced defunctionalization of cutaneous nociceptors results in a reversible retraction of epidermal nerve fibers while leaving the majority of the neuron and cell body in the dorsal root ganglion unaffected.[71–73]

At present, it is unclear why only a proportion of patients respond to capsaicin treatment and how response to treatment may be predicted. Questions also persist as to whether lidocaine pre-treatment is beneficial, how deep the capsaicin from the capsaicin 8 % patch penetrates the skin layers, and how much capsaicin reaches the nociceptors.

Overall, the clinical evidence indicates that the capsaicin 8 % patch has a good safety and tolerability profile and offers effective topical therapy in PHN. The episodic treatment application of every 3 months or longer makes the capsaicin 8 % patch a convenient option for patients. The capsaicin 8 % patch is therefore a valuable addition to the armamentarium of analgesic options for PHN. ■

1. Lungu O, Annunziato PW, Gershon A, et al., Reactivated and latent varicella-zoster virus in human dorsal root ganglia, Proc Natl Acad Sci U S A, 1995;92:10980–4.
2. Hope-Simpson RE, Postherpetic neuralgia, J R Coll Gen Pract, 1975;25:571–5.
3. Schmader K. Herpes zoster in older adults, Clin Infect Dis, 2001;32:1481–6.
4. Gnann JW Jr, Varicella-zoster virus: atypical presentations and unusual complications, J Infect Dis, 2002;186(Suppl. 1):S91–8.
5. Ryan-Cebula S, Groninger H, Postherpetic neuralgia #272, J Palliat Med, 2013;16:1143–4.
6. Baron R, Peripheral neuropathic pain: from mechanisms to symptoms, Clin J Pain, 2000;16(Suppl. 2):S12–20.
7. Opstelten W, Mauritz JW, de Wit NJ, et al., Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database, Fam Pract, 2002;19:471–5.
8. Yawn BP, Saddier P, Wollan PC, et al., A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction, Mayo Clin Proc, 2007;82:1341–9.
9. Nagasako EM, Johnson RW, Griffin DR, Dworkin RH, Rash severity in herpes zoster: correlates and relationship to postherpetic neuralgia, J Am Acad Dermatol, 2002;46:834–9.
10. Jung BF, Johnson RW, Griffin DR, Dworkin RH, Risk factors for postherpetic neuralgia in patients with herpes zoster, Neurology, 2004;62:1545–51.
11. Dubinsky RM, Kabbani H, El-Chami Z, et al., Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology, Neurology, 2004;63:959–65.
12. Dworkin RH, O'Connor AB, Backonja M, et al., Pharmacologic management of neuropathic pain: evidence-based recommendations, Pain, 2007;132:237–51.
13. Attal N, Cruccu G, Baron R, et al., EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision, Eur J Neurol, 2010;17:1113–e88.
14. Watson CP, Chipman M, Reed K, et al., Amitriptyline versus maprotiline in postherpetic neuralgia: a randomized, double-blind, crossover trial, Pain, 1992;48:29–36.
15. Kishore-Kumar R, Max MB, Schafer SC, et al., Desipramine relieves postherpetic neuralgia, Clin Pharmacol Ther, 1990;47:305–12.
16. Watson CP, Vernich L, Chipman M, Reed K, Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial, Neurology, 1998;51:1166–71.
17. Rice AS, Maton S, Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study, Pain, 2001;94:215–24.
18. Dworkin RH, Corbin AE, Young JP Jr, et al., Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial, Neurology, 2003;60:1274–83.
19. Rowbotham MC, Davies PS, Verkempinck C, Galer BS, Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia, Pain, 1996;65:39–44.
20. Galer BS, Jensen MP, Ma T, et al., The lidocaine patch 5 % effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale, Clin J Pain, 2002;18:297–301.
21. Galer BS, Rowbotham MC, Perander J, Friedman E, Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study, Pain, 1999;80:533–8.
22. Finnerup NB, Attal N, Haroutounian S, et al., Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis, Lancet Neurol, 2015;14:162–73.
23. Nalamachu S, Morley-Forster P, Diagnosing and managing postherpetic neuralgia, Drugs Aging, 2012;29:863–9.
24. Sampathkumar P, Drage LA, Martin DP, Herpes zoster (shingles) and postherpetic neuralgia, Mayo Clin Proc, 2009;84:274–80.
25. Argoff CE, Review of current guidelines on the care of postherpetic neuralgia, Postgrad Med, 2011;123:134–42.
26. Saarto T, Wiffen PJ, Antidepressants for neuropathic pain: a Cochrane review, J Neurol Neurosurg Psychiatry, 2010;81:1372–3.
27. Moore RA, Wiffen PJ, Derry S, et al., Gabapentin for chronic neuropathic pain and fibromyalgia in adults, Cochrane Database Syst Rev, 2014;4:Cd007938.
28. Moore RA, Straube S, Wiffen PJ, et al., Pregabalin for acute and chronic pain in adults, Cochrane Database Syst Rev, 2009(3):Cd007076.
29. Kost RG, Straus SE. Postherpetic neuralgia-pathogenesis, treatment, and prevention, N Engl J Med, 1996;335:32–42.
30. Baron R, Binder A, Wasner G, Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment, Lancet Neurolo, 2010;9:807–19.
31. Peppin JF, Pappagallo M, Capsaicinoids in the treatment of neuropathic pain: a review, Ther Adv Neurol Disord, 2014;7:22–32.
32. Giordano C, Cristino L, Luongo L, et al., TRPV1-dependent and -independent alterations in the limbic cortex of neuropathic mice: impact on glial caspases and pain perception, Cereb Cortex, 2012;22:2495–518.
33. Morales-Lazaro SL, Simon SA, Rosenbaum T, The role of endogenous molecules in modulating pain through transient receptor potential vanilloid 1 (TRPV1), J Physiol, 2013;591 (Pt 13):3109–21.
34. Acorda Therapeutics I. QUETENZA Full Prescribing Information 2013 [cited 2014 3 November]. Available at: http://www.qutenza.com/_docs/qutenza_full_PI_.pdf (accessed March 16, 2015).
35. QUTENZA (capsaicin) 8 % patch FULL PRESCRIBING INFORMATION 2009. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022395lbl.pdf (accessed February 5, 2014).
36. Szallasi A, Blumberg PM. Vanilloid (Capsaicin) receptors and mechanisms, Pharmacol Rev, 1999;51:159–212.
37. Uçeyler N, Sommer C, High-dose capsaicin for the treatment of neuropathic pain: What we know and what we need to know, Pain Ther, 2014 [Epub ahead of print].
38. Nakao A, Takahashi Y, Nagase M, et al., Role of capsaicin-sensitive C-fiber afferents in neuropathic pain-induced synaptic potentiation in the nociceptive amygdala, Mol Pain, 2012;8:51.
39. Huang W, Wang H, Galligan JJ, Wang DH, Transient receptor potential vanilloid subtype 1 channel mediated neuropeptide secretion and depressor effects: role of endoplasmic reticulum associated Ca^{2+} release receptors in rat dorsal root ganglion neurons, J Hypertens, 2008;26:1966–75.
40. Chard PS, Bleakman D, Savidge JR, Miller RJ, Capsaicin-induced neurotoxicity in cultured dorsal root ganglion neurons: involvement of calcium-activated proteases, Neuroscience, 1995;65:1099–108.
41. Han P, McDonald HA, Bianchi BR, et al., Capsaicin causes protein synthesis inhibition and microtubule disassembly through TRPV1 activities both on the plasma membrane and intracellular membranes, Biochem Pharmacol, 2007;73:1635–45.
42. Goswami C, Schmidt H, Hucho F, TRPV1 at nerve endings regulates growth cone morphology and movement through cytoskeleton reorganization, FEBS J, 2007;274:760–72.
43. 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;107:490–502.
44. Simone DA, Nolano M, Johnson T, et al., Intradermal injection of capsaicin in humans produces degeneration and subsequent reinnervation of epidermal nerve fibers: correlation with sensory function, J Neurosci, 1998;18:8947–59.
45. Kennedy WR, Vanhove GF, Lu SP, et al., A randomized, controlled, open-label study of the long-term effects of NGX-4010, a high-concentration capsaicin patch, on epidermal nerve fiber density and sensory function in healthy volunteers, J Pain, 2010;11:579–87.

46. Babbar S, Marier JF, Mouksassi MS, et al., Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration capsaicin patch to patients with peripheral neuropathic pain, *Ther Drug Monit*, 2009;31:502–10.

47. Chanda S, Bashir M, Babbar S, et al., *In vitro* hepatic and skin metabolism of capsaicin, *Drug Metab Dispos*, 2008;36:670–5.

48. Beaudry F, Vachon P, Quantitative determination of capsaicin, a transient receptor potential channel vanilloid 1 agonist, by liquid chromatography quadrupole ion trap mass spectrometry: evaluation of *in vitro* metabolic stability, *Biomed Chromatogr*, 2009;23:204–11.

49. Reilly CA, Yost GS, Metabolism of capsaicinoids by P450 enzymes: a review of recent findings on reaction mechanisms, bio-activation, and detoxification processes, *Drug Metab Rev*, 2006;38:685–706.

50. Baranidharan G, Das S, Bhaskar A, A review of the high-concentration capsaicin patch and experience in its use in the management of neuropathic pain, *Ther Adv Neurol Disord*, 2013;6:287–97.

51. Malmberg AB, Mizisin AP, Calcutt NA, et al., Reduced heat sensitivity and epidermal nerve fiber immunostaining following single applications of a high-concentration capsaicin patch, *Pain*, 2004;111:360–7.

52. Backonja MM, Malan TP, Vanhove GF, Tobias JK, NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled study with an open-label extension, *Pain Med*, 2010;11:600–8.

53. Simpson DM, Gazda S, Brown S, et al., Long-term safety of NGX-4010, a high-concentration capsaicin patch, in patients with peripheral neuropathic pain, *J Pain Symptom Manage*, 2010;39:1053–64.

54. Webster LR, Nunez M, Tark MD, et al., Tolerability of NGX-4010, a capsaicin 8 % dermal patch, following pretreatment with lidocaine 2.5 %/prilocaine 2.5 % cream in patients with post-herpetic neuralgia, *BMC Anesthesiol*, 2011;11:25.

55. Webster LR, Peppin JF, Murphy FT, et al., Tolerability of NGX-4010, a capsaicin 8 % patch, in conjunction with three topical anesthetic formulations for the treatment of neuropathic pain, *J Pain Res*, 2012;5:7–13.

56. Backonja M, Wallace MS, Blonsky ER, et al., NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study, *Lancet Neurol*, 2008;7:1106–12.

57. Webster LR, Malan TP, Tuchman MM, et al., A multicenter, randomized, double-blind, controlled dose finding study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia, *J Pain*, 2010;11:972–82.

58. Irving GA, Backonja MM, Dunteman E, et al., A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia, *Pain Med*, 2011;12:99–109.

59. Webster LR, Tark M, Rauck R, et al., Effect of duration of postherpetic neuralgia on efficacy analyses in a multicenter, randomized, controlled study of NGX-4010, an 8 % capsaicin patch evaluated for the treatment of postherpetic neuralgia, *BMC Neurol*, 2010;10:92.

60. Mou J, Paillard F, Turnbull B, Tet al., Efficacy of Qutenza(R) (capsaicin) 8 % patch for neuropathic pain: a meta-analysis of the Qutenza Clinical Trials Database, *Pain*, 2013;154:1632–9.

61. Mou J, Paillard F, Turnbull B, et al., Qutenza (capsaicin) 8 % patch onset and duration of response and effects of multiple treatments in neuropathic pain patients, *Clin J Pain*, 2014;30:286–94.

62. Derry S, Sven-Rice A, Cole P, et al., Topical capsaicin (high concentration) for chronic neuropathic pain in adults, *Cochrane Database Syst Rev*, 2013;2:Cd007393.

63. Maihofner CG, Heskamp ML, Treatment of peripheral neuropathic pain by topical capsaicin: Impact of pre-existing pain in the QUEPP-study, *Eur J Pain*, 2014;18:671–9.

64. Maihofner C, Heskamp ML, Prospective, non-interventional study on the tolerability and analgesic effectiveness over 12 weeks after a single application of capsaicin 8 % cutaneous patch in 1044 patients with peripheral neuropathic pain: first results of the QUEPP study, *Curr Med Res Opin*, 2013;29:673–83.

65. Martini CH, Yassen A, Krebs-Brown A, et al., A novel approach to identify responder subgroups and predictors of response to low- and high-dose capsaicin patches in postherpetic neuralgia, *Eur J Pain*, 2013;17:1491–501.

66. Peppin JF, Majors K, Webster LR, et al., Tolerability of NGX-4010, a capsaicin 8 % patch for peripheral neuropathic pain, *J Pain Res*, 2011;4:385–92.

67. Kern KU, Nowack W, Poole C, Treatment of neuropathic pain with the capsaicin 8 % patch: is pretreatment with lidocaine necessary?, *Pain Pract*, 2014;14:E42–50.

68. Lam VY, Wallace M, Schulteis G, Effects of lidocaine patch on intradermal capsaicin-induced pain: a double-blind, controlled trial, *J Pain*, 2011;12:323–30.

69. Lidoderm (Lidocaine Patch 5 %) label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020612s007lbl.pdf (February 25, 2015).

70. Armstrong EP, Malone DC, McCarberg B, et al., Cost-effectiveness analysis of a new 8 % capsaicin patch compared to existing therapies for postherpetic neuralgia, *Curr Med Res Opin*, 2011;27:939–50.

71. McMahon SB, Lewin G, Bloom SR, The consequences of long-term topical capsaicin application in the rat, *Pain*, 1991;44:301–10.

72. Nolano M, Simone DA, Wendelschafer-Crabb G, et al., Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation, *Pain*, 1999;81(1–2):135–45.

73. Polydefkis M, Yiannoutsos CT, Cohen BA, et al., Reduced intraepidermal nerve fiber density in HIV-associated sensory neuropathy, *Neurology*, 2002;58:115–9.