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Alexandru DP Papoiu & Gil Yosipovitch

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Expert Opinion

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Topical capsaicin. The fire of a ‘hot’ medicine is reignited

Alexandru DP Papoiu & Gil Yosipovitch†
†*Wake Forest University Health Sciences, Department of Dermatology, Winston-Salem, North Carolina, USA*

Importance of the field: Capsaicin and its receptor, TRPV1, occupy a central place in current neurophysiological studies regarding pain transmission and have opened new avenues for understanding the role of transient receptor potential (TRP) receptors in itch processing. Substantial efforts in drug discovery are at present directed at vanilloid receptors for finding new remedies for pain and itch.
Areas covered in this review: We provide an overview of the major clinical indications of capsaicin, primarily targeting pain and itch of various origins, with an emphasis on the usefulness of capsaicin in treating pruritus and dermatological conditions. In particular, we cover the most relevant findings in recent years, from 2000 onward (although seminal discoveries and studies are discussed irrespective of their date of publication if deemed essential for understanding capsaicin’s actions).
What the reader will gain: Readers are offered a broad perspective on the areas of clinical application of capsaicin, emphasizing its usefulness in the treatment of neurophatic pain and pruritus of various origins.
Take home message: Capsaicin has been proven a truly exciting molecule and remains a valuable drug for alleviating pain and itch, widely surpassing its role as a simple spicy ingredient.

Keywords: itch therapy, pain, topical capsaicin, TRPV1

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1. Introduction: historical notes

Capsaicin, the active pungent ingredient in hot chilli peppers has been in use for ages as a spicy additive, according to some reports as far back as 7000 BCE. Its pharmacological adaptation, which started in the middle of the 19th century, is now being revived by the emergence of new FDA-approved, high-concentration patches.

Capsaicin is a water-insoluble derivative of homovanillic acid, first extracted (in impure form) in 1816 by Christian F. Bucholz and obtained in a pure form in 1876 by John C. Thresh, who gave it the current name. The structure of capsaicin was elucidated by E. K. Nelson in 1919 (see **Figure 1**) and capsaicin was synthesized in 1930 by Spath and Darling (**Box 1**) [1].

Closely related analogs of capsaicin were isolated from chili peppers by Kosuge and Inagaki, who named them capsaicinoids. Capsaicin is the main capsaicinoid in hot chili peppers, seconded by dihydrocapsaicin and they are about twice as potent in pungency as the minor capsaicinoids nordihydrocapsaicin, homodihydrocapsaicin and homocapsaicin. There are at least six natural capsaicinoids and one synthetic member of this family. Several natural and synthetic analogs, agonists and antagonists of the capsaicin receptor (TRPV1) have been obtained and investigated because of the potential of these molecules in the treatment of pain and itch.

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Box 1. Drug summary.

Drug name (generic)	Capsaicin
Indications	Neuropathic pain Joint disease (arthritis) Neuropathic itch Dermatological and localized itch Systemic itch (uremic pruritus)
Route of administration	Topical cream or patch Intranasal Intravesical Oral (dietary-culinary)
Pharmacology description/ mechanism of action	TRPV1 receptor agonist initially produces nerve excitation, substance-P release and then prolonged depletion of substance P and desensitization, ultimately blocking nerve transmission in capsaicin-sensitive unmyelinated polymodal C nociceptors. Decreases density of TRPV1-positive epidermal nerve endings
Chemical structure/name	*Trans*-8-methyl-*N*-vanillyl-non-6-enamide
Molecular formula	$C_{18}H_{27}NO_3$
Molar mass	305.41 g/mol
Physico-chemical properties	Melting point: 62 – 65°C Boiling point: 210 – 220°C @ 0.01 Torr Water-insoluble, lipophilic, soluble in ethanol
Analogs and related compounds	Dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin (from *Capsicum* extract) RTX (resiniferatoxin, a more potent TRPV1 agonist than capsaicin) Capsazepine (TRPV1 antagonist) Rutaecarpine

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2. Chemical structure

Capsaicin is an acylamide of homovanillic acid presenting three functional moieties: vanillyl, acylamide and alkenyl. Capsaicin molecule contains a double bond; therefore, it can theoretically present *cis* and *trans* isomers. *trans*-Capsaicin is the naturally predominant isomer due to steric hindrance factors; made via rational synthesis the '*trans*' form is the active compound used in high-potency NGX-4010 patches (Qutenza®, NeurogesX, Inc., San Mateo, CA). An intranasal formulation of the *cis* isomer called 'zu-capsaicin' (Civamide) is investigated as a therapy for cluster headache and in a topical cream formulation for osteoarthritis.

3. Mechanism of action

Capsaicin's actions can be classified into TRPV1-mediated actions and TRPV1-independent effects and mechanisms.

The specific action of capsaicin occurs via its interaction with TRPV1 receptors in primary sensory neurons found in polymodal C and Aδ mechano-heat nociceptors. Since TRPV1 is expressed in many cell types other than primary sensory neurons (keratinocytes, mast cells, glial cells, platelets) other biological actions of capsaicin could also work via a TRPV1-mediated mechanism (see [2]). Capsaicin selectively activates TRPV1 receptors present on polymodal mechano- and heat-sensitive C nerve fibers and mechano heat-sensitive Aδ-fibers, which are referred to as 'capsaicin-sensitive' neurons. These nerve fibers can transmit both pain and itch; more specifically, C polymodal nociceptors can transmit experimental itch induced by cowhage spicules via release of the protease mucunain.

Initially, capsaicin binds cation channel TRPV1 receptor, which leads to channel opening, Ca^{2+} and Na^{+} entry and nerve depolarization, stimulating substance-P (SP) release and swiftly producing an intense burning and stinging sensation that can be perceived as painful or itchy (in the majority of subjects). Capsaicin induces an initial hypersensitization followed by a long-lasting nerve desensitization, which constitutes the basis of its therapeutic use. Substance P is not the only neuropeptide released, but TRPV1 activation induces the release of somatostatin, calcitonin gene related peptide (CGRP) and other neuromediators (neurokinin A, kassinin), leading to neurogenic inflammation. Capsaicin releases neuropeptides from sensory nerve endings via two mechanisms: (a) a secretory efferent function of TRPV1 neurons releases neuropeptides by exocytosis upon their depolarization; and (b) via an antidromic reflex stimulation of dorsal root ganglia (DRG) neurons [3]. The long-term analgesic and antipruritic effects of prolonged capsaicin application are paradoxical, since capsaicin can induce initially both (burning) pain and itch. The beneficial analgesic action is explained by the subsequent, lasting desensitization. The stimulated release of substance P is soon followed by an exhaustion of substance P reserves which renders neurons desensitized or refractory. The mechanisms of desensitization may involve several stages and are not completely understood. The short-term desensitization is related to capsaicin's ability to block the intra-axonal transport of nerve growth factor (NGF), substance P and somatostatin [4-6]. NGF controls the expression of neuropeptides via a NGF-responsive element in the preprotachykinin gene encoding substance P and neurokinin A (NKA) [7], which explains how the depletion of NGF from the perykarya of sensory neurons induces a depletion of substance P (and neurokinin A; see [2]).

4. Molecular mechanism of TRPV1 desensitization by capsaicin

To explain the relationship between substance P depletion and the ensuing desensitization, one has to examine the

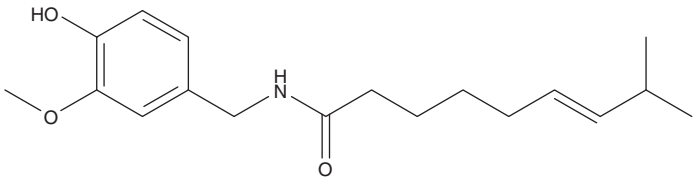

Figure 1. The chemical structure of capsaicin.

regulation of the TRPV1 receptor channel at the molecular level. TRPV1 activation by capsaicin binding induces an amplified release of substance P and CGRP upon neuronal depolarization, via exocytosis and antidromic reflexes. Substance P acts upon neurokinin-1 (NK-1) receptors (a G-protein-coupled receptor), which colocalize with TRPV1 receptors in $TRPV1^+$ neurons**.** NK-1 receptors regulate the translocation and activation of PKCε, a kinase that is essential for the activation of TRPV1 via phosphorylation [8]. Therefore, there is a positive feedback loop that increases the (hyper)sensitization of TRPV1 (manifested as hyperalgesia) and the sustained release of mediators, which in turn activates further the $TRPV1^+$ neurons. The depletion of substance P is a consequence of this amplified response, which continues until the neuropeptide reserves are exhausted. The activation of TRPV1 is a result of complex regulatory mechanisms controlling phosphorykation/dephosphorylation states at two critical Serine residues and are dependent on intracellular calcium concentration, Ca–CaM binding to TRPV1, levels of IP_3, ATP, CaM kinase II and the action of calcineurin (the latter deactivating TRPV1), among other factors [9-11]. A depletion of SP induces a deactivation of TRPV1 due to the loss of phosphorylation primarily via downregulating the PKCε pathway, a major regulatory mechanism for TRPV1. When the activating factors are depleted, the equilibrium is shifted towards the dephosphorylated state and TRPV1 becomes inactivated (desensitized).

The short-term effect of vanilloid application is a downregulation of TRPV1 itself, a phenomenon labeled 'phenotypic switch' or defunctionalization [2,12]. Ultimately, capsaicin induces a substantial decrease in the density of TRPV1-positive epidermal nerve endings, which explains the analgesia induced by capsaicin over extended periods of time (lasting up to several weeks). The significant neuronal degeneration observed following extended application of capsaicin is probably caused by vanilloid-mediated neuronal apoptosis and by capsaicin's direct neurotoxicity, reversible upon discontinuation of the drug. Topical capsaicin (0.075% or the 8% *trans*-capsaicin patch) produced a degeneration of epidermal nerve fibers that was correlated with the diminished pain sensation; upon discontinuation of the drug, the return of nociception in about 6 weeks was found to coincide with reinnervation. [13,14].

The potential spectrum of action of capsaicin is wider than the effects elicited via TRPV1 interaction. Capsaicin exerts several other pharmacodynamic actions by targeting other molecular entities by vanilloid-independent mechanisms. We briefly note below the other mechanisms by which capsaicin may exert secondary actions, side-effects and (neuro)toxicity (**Table 1**).

5. The significance of capsaicin receptor (TRPV1) in physiology

Besides its use in alleviating pain and itch in clinical practice, capsaicin has a significant theoretical value. Capsaicin became a useful pharmacological tool for basic research helping to unearth the physiological function of the receptor it is acting upon. The discovery of a capsaicin-sensitive receptor has opened new avenues in pain and itch research. Now it is widely accepted that TRPV1 and the related vanilloid receptors are important relays for pain transmission ('pain sensors'), and they play several physiological roles.

The cloned TRPV1 is a 95-kDa protein with intracellular N- and C-termini and the N-terminus presents three ankyrin domains. The structure of TRPV1 has six transmembrane domains with an additional intramembrane loop connecting the fifth and sixth transmembrane domains [15]. TRPV1 can be activated by (noxious) temperature above 43°C (mediates pain hyperalgesia), low extracellular pH, eicosanoids and diverse endogenous lipid derivatives [16-18]. TRPV1 is now found to be expressed at lower levels in the spinal cord, brain and a wide-range of non-neuronal cells such as epithelial cells (keratinocytes, urothelium, gastric epithelial cells, enterocytes, pneumocytes), in platelets, in vascular endothelium and cells of the immune system (T cells, mast cells) in smooth muscle, fibroblasts and hepatocytes [19].

Insights for a physiological role of TRPV1 came from earlier studies that were linked to substance P dysregulation. A sequel of the treatment with vanilloid agonists was loss of hair and skin ulcerations [20,21]; the damage was attributed to the depletion of substance P from dermal nerve endings [22,23]. Alopecia areata was linked to a defect in vanilloid-sensitive nerve function and, indeed, recently a couple of studies have uncovered capsaicin's positive effect in stimulating hair growth. A capsaicin cream induced vellus hair regrowth in some patients with alopecia areata [24,25], while a controlled randomized trial found capsaicin action in this regard superior to clobetasol (see below) [26]. Substance P was also shown to facilitate hair growth in mice [27]. TRPV1 agonists cause pain and itch in humans and pain behavior in animals, while the disruption of TRPV1 gene

Table 1. TRPV1-independent pharmacological actions of capsaicin.

Mechanism of action	Studies
Blockade of K1 ion channels	Dubois 1982 [128]; Petersen *et al.* 1987 [129]; Kehl 1994 [130]; Kuenzi and Dale 1996 [131]
Inhibition of NADH-oxidoreductase and other enzymes	Shimomura *et al.* 1989 [132]
Alters membrane fluidity/elasticity	Meddings *et al.* 1991 [133]; Aranda *et al.* 1995 [134]
Inhibitory effect of capsaicin on thrombocyte aggregation (anticoagulant effect)	Hogaboam and Wallace 1991 [135]
Inhibition of activity of clotting factors VIIIc and IX	Murray *et al.* 2009 [115]
Competitive inhibitor of tyrosyl-tRNA synthetase	Cochereau *et al.* 1996 [136,137]
Causes degeneration in neurons *not* expressing TRPV1	Ritter and Dinh 1993 [138]

or a block of TRPV1 receptor by antagonists ameliorates thermal hyperalgesia [28,29].

After more than 12 years of intense research on TRPV1 receptor since its discovery as capsaicin's primary target, the current general consensus is that TRPV1 plays a significant role in pain signaling; but it is not limited to sensory functions [30,31]. TRPV1 is now considered to be involved in the following physiological or pathophysiological functions: it plays a major role in body-temperature maintenance [32], regulation of feeding and body weight [33], respiratory inflammation and disease [34,35]; interestingly, the activation of TRPV1 by agonists exerts beneficial effects on cardiovascular and gastrointestinal functions [36-39].

Endogenous ligands for TRPV1 have been recently identified that may indicate that capsaicin therapeutic action may depend on a competition with a range of endogenous players. Arachidonic acid derivatives and lypoxygenase products exert potent stimulatory effect on TRPV1 (e.g., arachidonyl-ethanolamide, anandamide previously known as a cannabinoid receptor 1 agonist; *N*-arachidonoyl dopamine and *N*-oleoyldopamine [17]).

6. Absorbtion, pharmacokinetics and metabolism

When used in a topical formulation the lipophilic capsaicin penetrates the stratum corneum and is slowly delivered through the skin into systemic circulation at a rate of ~ 2.71 μg/cm^2/h [40]. Capsaicin is metabolized by cytochromes P450 in the liver to dihydrocapsaicin and other hydroxylated metabolites (9 metabolites in total). Serum concentrations following the 8% dermal patch application are remarkably low and are detectable only in a small fraction of human subjects to whom capsaicin was applied topically. The maximum plasma concentration observed in any patient studied was 17.8 ng/ml. Capsaicin serum concentrations decline rapidly, with a mean population elimination half-life ($t_{1/2}$) of 1.64 h. The mean area under the curve (AUC) and C_{max} values after a 60-min application were 7.42 ng/h/ml and 1.86 ng/ml, respectively [41]. Capsaicin is thought to be primarily eliminated via the renal route. A very slow inactivation by cleavage of the amide bond also occurs in the human skin following topical administration to yield vanillylamide and vanillic acid, but this process is considered largely inconsequential [42].

7. Analogs of capsaicin

Topical capsaicin *per se* has a rather low therapeutic index by inducing a characteristic, initially strong, unpleasant burning and stinging sensation (irritation). Being not very well tolerated, capsaicin can easily render itself impractical to use, causing a high withdrawal rate during treatment (up to 30%) [2,43]. Therefore several analogs are being sought and evaluated as safer, better-tolerated alternatives, both as agonists or antagonists of TRPV1.

Resiniferatoxin (RTX) is an improved TRPV1 agonist, first isolated in 1975, which was subsequently described as a highly potent vanilloid [44,45]. Animal studies performed with RTX found a more favorable ratio of desensitization to irritation than capsaicin [46-48]. RTX is more potent than capsaicin to induce nerve desensitization.

Rutaecarpine, a major quinazolinocarboline alkaloid isolated from Chinese herbal drug Wu-Chu-Yu, has long been used for the treatment of gastrointestinal disorders, headache, amenorrhea and postpartum hemorrhage in traditional Chinese medicine [49]. The multiple pharmacological actions of rutaecarpine seem to be mediated by the released neurotransmitters such as CGRP and substance P through the activation of TRPV1 [50].

Capsazepine was evaluated as one of other potential alternatives to capsaicin, serving as a TRPV1 antagonist, and was found to be beneficial in animal models of pain and inflammation [51,52]. Several synthetic TRPV1 agonists and antagonists have been investigated and reviewed recently [53].

8. Current clinical uses of capsaicin

8.1 Overview

The counterirritation and the extended desensitization that follows topical capsaicin application are used in clinical practice in the amelioration of pain and itch. The recently FDA-approved use of 8% *trans*-capsaicin via dermal patches (NGX-4010, Qutenza) in single application is reviving the therapeutic use of capsaicin (see Section 8.5). Pharmacological 'ablation' of C-fibers by perineural capsaicin injection was also tried in cancer patients with untractable pain [54].

We briefly list below the conditions for which capsaicin has been clinically tested and proven effective as an analgesic. We refer the reader to excellent reviews available on the use of capsaicin for neuropathic pain for a more in-depth analysis [15,30,55] to emphasize the benefits of capsaicin in the relief of itch.

A particularly challenging condition, dually painful and pruritic, is postherpetic neuralgia (PHN), which presents pain and itch both generally and refractory to therapy [56,57]. The recent Phase III trial using 8% synthethic *trans*-capsaicin patch has documented the amelioration of pain scores by 30%, 2 – 12 weeks after a single patch application for 1 h [58]. However, the effect on the accompanying itch of PHN – which can be very severe and sometimes intractable – was not reported, apparently not being an end point of this study. We can only speculate that the positive results obtained in relieving pain of PHN promises this formulation can be effective as an antipruritic to a comparable degree.

Therapeutic application of the long-lasting desensitization induced by capsaicin has been documented since 1850. The first medicinal indication of capsaicin on record was for toothache [59]. Eugenol and guaiacol, other vanilloid receptor ligands commonly used in dentistry, also seem to exert their analgesic activity via TRP receptors [60,61]. Capsaicin is effective in 'atypical odontalgia' [62], in 'burning mouth' syndrome [63] and in vasomotor rhinitis [64,65]. The intranasal application of a single dose of 30 mM capsaicin solution relieves nasal congestion in patients with allergic rhinitis [66,67]. Capsaicin could reduce the size of nasal polyps and the intranasal administration is also reportedly effective in cluster headache [68-71].

Capsaicin is used to relieve muscle pain in a variety of over-the-counter (OTC) formulations (Capsazin® Capsoderma®, Stimurub®, Heat®); their therapeutic effect is due to the secondary neurogenic inflammation, which produces an increase in microcirculation in the respective area; the mediators of this action seem to be CGRP and somatostatin [72,73]. However, the full mechanism of 'counterirritation' is not well elucidated.

8.2 Major indications for capsaicin

Used as an adjuvant analgesic, capsaicin acts locally by inducing a lasting desensitization of peripheral nerve fibers. In topical formulations, capsaicin has been used in a variety of neuropathic pain conditions such as postherpetic neuralgia, a condition that presents severe, sometimes intractable itching [74-77]; painful diabetic neuropathy [78-79], postmastectomy pain syndrome [80,81] and in joint disease (osteoarthritis and rheumatoid arthritis [82,83]; see **Table 2**).

A condition considered until recently refractory to topical capsaicin was HIV-related neuropathy. However, the high-concentration 8% dermal patch NGX-4010 (Qutenza) in a single 60-min administration was able to induce a 30% amelioration of pain, to a duration of up to 12 weeks [84].

In a Phase III, placebo-controlled trial, 99 cancer patients with postsurgery neuropathic pain were given capsaicin cream 0.075% (or placebo) four times a day for 8 weeks. At the end of the 8 weeks, there was a 53% reduction in pain in the capsaicin group compared with 17% in the placebo group. As main adverse effects, there was significant burning and redness [85].

8.2.1 *Joint disease*

It has been discovered that substance P and CGRP are important mediators for arthralgia. Since capsaicin has the long-term effect of depleting substance P and CGRP, it could therefore attenuate pain signaling in arthritis. It is also possible that counterirritation contributes to the analgesic effect. In experimental models of arthritis, capsaicin was able to reduce joint inflammation, although it is not totally clear whether topical capsaicin penetrates well to affect sensory nerve endings in joint structures. In a controlled study of 21 patients, a 0.075% capsaicin cream improved tenderness and pain in joints with osteoarthritis (a degenerative form of arthritis), but had no effect in patients with rheumatoid arthritis (an inflammatory form of arthritis) [86]. However, in a similar study in which 70 patients with osteoarthritis and 31 patients with rheumatoid arthritis were treated with capsaicin 0.025% cream (or placebo) four times a day for 4 weeks, 80% of patients experienced a reduction in knee pain during treatment with capsaicin cream, while the placebo response was 48%; burning occured in 44% of patients [82].

8.3 Topical capsaicin for the relief of itch

Since itch sensation is mediated by unmyelinated polymodal C nociceptors/pruritoceptors that can equally transmit pain, capsaicin can be rationally used as an antipruritic owing to the lasting desensitization of sensory nerve fibers it induces [87-90]. In a similar fashion to relieving pain, capsaicin can block peripheral nerve transmission of itch. In such a way, capsaicin offers the advantage of a local therapy, practically 'numbing' the peripheral neuronal pathways transmitting itch, without the notable side effects associated with systemic agents, tricyclic antidepressants, opiate antagonists and neuroleptics. Capsaicin has been shown to have a beneficial antipruritic effect in different types of itch (**Table 3**), neuropathic itch (itch arising from damaged peripheral nerve fibers) [91,92], in systemic itch (uremic pruritus in patients undergoing hemodialysis), as well as relieving pruritus of dermatological origin: psoriasis, lichen simplex chronicus and prurigo nodularis. In the majority of the placebo-controlled studies, capsaicin's effect was consistently more potent than the placebo.

8.3.1 *Neuropathic itch*

Topical capsaicin has been used successfully for the amelioration of itch of notalgia paresthetica, a condition characterized by pruritus in the scapular area caused by entrapment of the posterior branches of T_2 – T_6 nerves [93-95], and in brachioradial pruritus, a peripheral neuropathic form of itch caused by entrapment of C_4 – C_7 cervical nerve fibers [91].

Table 2. Clinical indications of topical capsaicin for pain relief.

Disease type	Condition	Study
Neuropathies	Meralgia paraesthetica	[84]
	Burning mouth syndrome	
	Postherpetic neuralgia	
	Diabetic neuropathy	
	Oral neuropathic pain	
	Trigeminal neuralgia	
	Reflex sympathetic dystrophy	
	HIV-related neuropathy	
Joint disease	Osteoarthritis	
	rheumatoid arthritis (mixed results)	
Other painful conditions	Guillain-Barre syndrome	Morgenlander *et al.* 1990 [139]
	Fibromyalgia	Kroenke *et al.* 2009 [140]
	Postmastectomy pain syndrome	Watson *et al.* [80,81]
	Stump pain	Rayner *et al.* 1989 [141]
		Weintraub *et al.* 1990 [142]

Table 3. Indications of topical capsaicin to relieve itch and improve dermatological disorders.

Source of itch	Condition
Neuropathic itch	Notalgia paraesthetica
	Brachioradial pruritus
	Post-herpetic neuralgia (PHN)
Dermatological conditions	Itch of psoriasis
	Lichen simplex chronicus
	Prurigo nodularis
	Lipodermatosclerosis, lobular panniculitis*
	Alopecia areata
Systemic itch	Uremic pruritus (patients on hemodialysis)
Localized itch	Vulvar vestibulitis
	Perianal pruritus
Miscellaneous forms of itch	Aquagenic pruritus
	Pruritus sine materia (idiopathic, itch with no apparent cause)

*Case reports.

8.3.2 Systemic itch

The cause of itch of uremic patients on hemodialysis is still not completely understood. Interestingly, capsaicin is effective in treating systemic itch occurring in chronic kidney patients undergoing hemodialysis [100,101]. In a double-blind, placebo-controlled, crossover study, 19 hemodialysis patients with moderate to severe pruritus were examined. Fourteen out of the 17 patients who completed the study reported a marked relief and five patients had a complete remission of pruritus. Capsaicin was significantly more effective than placebo and the therapeutic effect antipruritic lasted 8 weeks.

8.3.3 Relief of itch of dermatological origin

8.3.3.1 Lichen simplex chronicus

Lichen simplex chronicus is a condition where chronic itching and scratching lead to thickening of the skin with potential scaling (lichenification). Patients with this condition reported improvement of the pruritus following capsaicin cream application; interestingly, however, 75% of patients who reported beneficial effects actually preferred placebo to capsaicin, probably because of the intense irritation induced by capsaicin [98].

8.3.3.2 Prurigo nodularis

Prurigo nodularis, a typical pruritic disease characterized by appearance of itchy nodules or papules benefits from topical capsaicin therapy. In a double-blind, placebo-controlled study, 33 patients with prurigo nodularis were treated with varied doses of capsaicin cream 4 – 6 times daily for 2 weeks up to 10 months, and a complete remission was observed in all patients within 12 days. Sixteen out of 33 patients observed recurrence of pruritus within 2 months of completing treatment [99].

8.3.3.3 Other dermatological indications

Topical capsaicin reduces not only the severity of pruritus in psoriasis but also reduced scaling and erythema, possibly improving the overall progression of this disease [100,101], presumably due to its synergistic anti-inflammatory effects. We have also documented cases where capsaicin was effective in the treatment of refractory, painful lipodermatosclerosis and lobular panniculitis, in which other treatments failed [102].

A recent randomized study of 50 patients compared the efficacy of capsaicin versus clobetasol in the treatment of alopecia areata and found that capsaicin was superior to the potent corticosteroid, although the differences were not statistically significant. It is postulated that capsaicin works by blocking the inhibition of hair growth [26].

8.3.4 Miscellaneous forms of itch

Topical capsaicin is also successful in the relief of idiopathic itch (pruritus sine materia) [103] in the alleviation of localized itch (e.g., perianal pruritus, vulvar vestibulitis) [104,105] and of aquagenic pruritus [106].

8.4. Placebo effect, blinding and compliance issues

8.4.1 The difficulty of "blinding" participants in controlled studies

In general, the therapeutic value of capsaicin in neuropathic itch and pain was considered difficult to evaluate since controlled capsaicin trials versus placebo are difficult to impossible to blind owing to the typical intense burning and stinging sensation elicited by capsaicin [2]. An interesting

solution was used in Phase II and III trials testing the efficacy of high-concentration NGX-4010 (*trans*-capsaicin dermal patches 8%), whereby, instead of placebo, a positive control of 0.04% capsaicin formulation (patch) was used to ensure 'blinding' [58,84]. Previously, a high placebo response rate (17 – 48%) was reported in several controlled trials and, paradoxically, the placebo may induce a better response than capsaicin in isolated cases (see [2]).

8.4.2 *Compliance issues*

A low compliance rate is a serious drawback hampering the beneficial long-term action of topical capsaicin, since a high number of patients discontinue treatment because of the irritation, which is not easily tolerable. The documented withdrawal rates are approximately 30% or higher [43,107-109]. The mixed results reported previously with capsaicin are basically due to an unfavorable ratio of irritation ('burning' sensation) to desensitization [2]. New capsaicin derivatives with an improved desensitization-to-irritation ratio would be of higher clinical relevance. To overcome the initial burning sensation, pretreatment with local anesthetic EMLA (eutectic mixture of lidocaine and prilocaine) cream has been successfully used. EMLA reduced the burning sensation from capsaicin also attenuating heat hyperalgesia. EMLA-pretreated skin after 1 and 5 days of treatment displayed a significantly higher warmth sensation detection threshold [110].

8.5 Recent studies

The recent FDA approval of high-concentration (8%) dermal patches indicates a revival in the use of capsaicin for pain therapy. A practical approach to increase the effectiveness of capsaicin is to use high doses (8 – 10%) following regional anesthesia [111] or to deliver capsaicin via a single-application dermal patch – the NGX-4010 formulations (Qutenza), preceded by local anesthesia induced with lidocaine ointments [58,84].

NGX-4010, a high-concentration (8%) synthetic *trans*-capsaicin dermal patch, was recently developed to treat patients with neuropathic pain. In a randomized, double-blind, multicenter, 12-week study testing the efficacy and safety of one application of Qutenza, patients with PHN received one 60-min application of (8%) capsaicin or a low-concentration control patch (0.04% capsaicin). Patients who received NGX-4010 had a significantly greater reduction of pain during weeks 2 – 8 and weeks 2 – 12 than did the patients who received the control patch. A 'rapid and sustained' pain relief in patients with postherpetic neuralgia was documented, the mean changes of pain scores reported being -29.6 versus -19.9% (positive control). No adverse events were associated with the treatment, except for local reactions at the site of application and those related to treatment-associated pain [58,112].

In a related placebo-controlled, double-blind, multicenter trial, NGX-4010 was found effective in the treatment of painful HIV-associated distal sensory polyneuropathy (HIV-DSP). Participants with painful HIV-DSP received either NGX-4010 or a control (a low-concentration capsaicin patch). NGX-4010 or control was applied once to painful areas on the feet. A single 90-min application resulted in a mean pain reduction of 23% during weeks 2 – 12, compared with an 11% reduction for control. One-third of NGX-4010-treated patients reported 30% pain decrease from baseline compared with 18% for controls. The single NGX-4010 application was considered safe and provided at least 12 weeks of pain reduction in patients with HIV-DSP [84]. These findings improved capsaicin's record, since the efficacy of 0.075% capsaicin in patients with HIV-associated distal symmetrical peripheral neuropathy (DSPN), studied earlier in a multicenter, controlled trial indicated that a 0.075% capsaicin cream was ineffective in relieving this type of neuropathic pain [113].

9. Potential ethnic factors involved in the efficacy and mechanism of action of capsaicin

We have noticed for many years in our practice that African Americans seem not to respond well to topical capsaicin and neither do they complain of burning or stinging sensations. Examining the effect of capsaicin on thermal detection thresholds and skin blood flow, we recently confirmed that capsaicin 0.075% produced a limited hyperalgesia and neurogenic inflammation in African Americans, in sharp contrast with three other ethnic groups. Rating continuously the intensity of pain, burning and stinging intensity post-capsaicin, we found that African Americans displayed the lowest intensity ratings for pain, burning or stinging [114]. Intriguingly, capsaicin did significantly increase the warmth detection threshold in African Americans, a sensation mediated via TRPV3 receptors, but significantly decreased this threshold in Hispanics, the latter being the only group reporting significant itching after capsaicin application, which could suggest an involvement of TRPV3 receptors in the modulation of itch.

10. Other biological actions and potential uses of capsaicin

Capsaicin has been proposed as a therapeutic agent in several other areas (e.g., prevention of aspiration pneumonia, etc.). It exerts several effects on lipid and carbohydrate metabolism and may have a positive role in weight control, decreasing the excess caloric intake in humans. Capsaicin provides protection against gastroduodenal ulcer in experimental models and it is bactericidal against *Helicobacter pylori*. The intravesical instillation of capsaicin solution is successfully used in the treatment of neurogenic hyperactive bladder disorder. TRPV1 antagonists have been suggested as cough-suppressing agents.

Capsaicin could have a potential role as an anticoagulant as it inhibits platelet aggregation and the activity of clotting

factors VIIIc and IX *in vitro* [115]. However, the overall effect on blood clotting in humans remains disputed.

Interestingly, capsaicin could exert an anticarcinogenic action [116]. It seems that capsaicin's action may consist in blocking the metabolic activation of pro-carcinogens. A recent observation is that capsaicin can inhibit the growth of a number of transformed cell lines [117]. Another mechanism proposed for capsaicin's antitumor activity is via induction of apoptosis [118].

11. Adverse effects, toxicity and mutagenesis

11.1 Adverse effects

The most obvious adverse effects of capsaicin are the initial pain, itch, burning and stinging sensation and the erythema that arises from the neurogenic inflammation [43,107]. Capsaicin also typically produces a hypersensitivity to heat stimuli and heat pain (thermal hyperalgesia). High-concentration dermal patches can also induce pain and itch (42 and 6% of cases, respectively) [58,84,112]. Sweat and heat aggravate the burning sensation induced by capsaicin. The unpleasant sensations can be minimized by lidocaine administration or pretreatment with EMLA without compromising the desired long-term therapeutic effect (i.e., desensitization) [110].

The possibility of respiratory symptoms (coughing and sneezing) has been raised [119,120], which could be eliminated by bathing after the topical application [121]. Capsaicin may induce airway congestion, coughing and shortness of breath in healthcare workers applying capsaicin cream (especially in asthmatics), who were therefore advised to wear masks or respirators. Capsaicin is hazardous in cases of direct skin or eye contact, ingestion or inhalation. Special care has to be given to application of capsaicin in the proximity of mucosal areas (especially eyes), in perianal and perigenital areas where irritation can be unbearable. Capsaicin is notably used as the active repellent agent in pepper spray, which represents a significant source of exposure in the field of law enforcement. Severe overexposure to pure capsaicin can result in death [122-124]. Because of its documented neurotoxicity and intense hyperalgesic effects, agonists of TRPV1 with lower toxicity are intensively sought as better alternatives to capsaicin.

11.2 Mutagenesis

Since humans are broadly exposed to capsaicin (from diet) the possibilities that capsaicin could be mutagenic, tumorigenic or carcinogenic were exhaustively investigated and critically reviewed [2]. There seems to be a consensus that capsaicin's liver metabolites may be the actual hazardous species [125,126]; however, topical capsaicin is considered safe to use. Following long-term intravesical instillation of capsaicin, no premalignant or malignant changes were found [127]. Capsaicin is not mutagenic unless it is metabolized in liver microsomes. Capsaicin metabolites are weak mutagens and only at high concentration. In regard to capsaicin's carcinogenetic potential, many studies have focused on this topic, but have yielded conflicting results.

12. Conclusion

Although pharmacological treatment for neuropathic pain and itch has improved over the last decade, many patients do not reach full analgesia from systemic therapies (such as tricyclical antidepressants, neuroleptics and opioids), which are marred by potentially serious adverse effects. Therefore, topical capsaicin, by targeting peripheral nerves, provides a local approach for the relief of pain and itch exerting a complementary therapeutic action through a *sui generis* mechanism. A current drawback is the low compliance rate for commercial over-the-counter preparations due to the high incidence of burning sensation elicited. Based on our experience, we recommend EMLA as a pretreatment to limit the occurrence of burning sensation and pain.

13. Expert opinion

The recently FDA-approved, high-concentration dermal patches showed an increased therapeutic benefit over the low-concentration formulations, for relieving pain of neuropathic origin including PHN and notably HIV neuropathy, a condition where low-dose capsaicin was shown previously ineffective. In light of recent findings regarding ethnic differences in hyperalgesic and neurogenic inflammatory responses to capsaicin [114], it would be of interest to examine whether there are functional gene polymorphisms in the TRPV1 genes affecting the response to this drug, which would enable assessment of which individuals would respond well to this therapy. New analogs of capsaicin, not inducing pain themselves but having potent analgesic and antipruritic effects, may further ignite the excitement for the therapeutic potential of this medicine, for the benefit of millions of patients with neuropathic pain and itch.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Alexandru DP Papoiu[1] MD PhD
Gil Yosipovitch[†1,2,3] MD
[†]Author for correspondence
[1]Wake Forest University Health Sciences, Department of Dermatology, Winston-Salem, North Carolina, USA
[2]Wake Forest University Health Sciences, Department of Neurobiology and Anatomy, Winston-Salem, North Carolina, USA
[3]Wake Forest University Health Sciences, Department of Regenerative Medicine, Winston-Salem, North Carolina, USA
Tel: +1 336 716 2901; Fax: +1 336 716 7732; E-mail: gyosipov@wfubmc.edu