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REVIEW

Capsaicin 8% dermal patch in clinical practice: an expert opinion

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ABSTRACT

Introduction: Neuropathic pain (NP) is caused by a lesion or disease of the somatosensory system, which can severely impact patients' quality of life. The current-approved treatments for NP comprise of both centrally acting agents and topical drugs, including capsaicin 8% dermal patches, which is approved for the treatment of peripheral NP.

Areas covered: The authors summarize literature data regarding capsaicin use in patients who suffer from NP and discuss the clinical applications of this topical approach.

Expert opinion: Overall, the capsaicin 8% dermal patch is as effective in reducing pain intensity as other centrally active agents (i.e. pregabalin). Some studies have also reported fewer systemic side effects, a faster onset of action and superior treatment satisfaction compared with systemic agents. In our opinion, capsaicin 8% dermal patches also present additional advantages, such as a good systemic tolerability, the scarcity of adverse events, the possibility to combine it with other agents, and a good cost-effective profile. It is important to note that, as the mechanism of action of capsaicin 8% is the 'defunctionalization' of small afferent fibers through interaction with TRPV1 receptors, the peripheral expression of this receptor on nociceptor fibers, is crucial to predict patient's response to treatment.

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Neuropathic pain; topical treatment; capsaicin; TRPV1 receptors; fibers

1. Introduction

Neuropathic pain (NP) is caused by a lesion or disease of the somatosensory system [1]. Depending on the site of the lesion or the underlying disease, this type of pain can be classified as either central or peripheral [1,2]. The most relevant causes of peripheral NP (PNP) are painful diabetic peripheral neuropathy (PDPN), postherpetic neuralgia (PHN), HIV-associated neuropathy (HIV-AN) and chemotherapy-induced peripheral neuropathy, as well as trauma or surgical procedures [2]. In addition to pain, patients with PNP experience several symptoms that include, burning, tingling, numbness, allodynia and hyperalgesia, which collectively have a severe impact on quality of life [3]. NP is often poorly responsive to available treatments [2].

Transient receptor potential vanilloid-1 (TRPV1) acts as a thermal nociceptor; however, it plays an important role in detecting a number of painful stimuli, which include heat, acids and irritant chemicals [1]. Capsaicin, which is the main active ingredient in hot chili peppers, is a potent and highly selective TRPV1 agonist [1,4,5]. This molecule activates TRPV1-expressing nociceptors on the skin, causing the onset of pain and erythema [6]. Following this action, topical capsaicin attenuates cutaneous hypersensitivity and reduces pain through a process usually described as 'defunctionalization' of nociceptor fibers [5]. Defunctionalization is the cellular consequence of calcium influx triggered by capsaicin-activated TRPV1. High levels of intracellular calcium, its associated enzymatic, cytoskeletal and osmotic changes, and the disruption of mitochondrial respiration all lead to an impaired local nociceptor function for extended periods. This explains why the effects of capsaicin last well beyond its application and TRPV1 stimulation.

Capsaicin creams of low concentrations (0.025–0.075%) have shown moderate efficacy in the topical treatment of PNP [1]. Nevertheless, these creams require several applications per day, and the initial burning sensation is often poorly tolerated. Qutenza®, which is a high-concentration (8%) capsaicin dermal patch, has been developed with the aim of providing long-lasting pain relief resulting from a single application. The capsaicin 8% dermal patch is approved in the EU, either alone or in combination with other medicinal products (for pain), for the treatment of PNP in adults [6]. Overall, patients using the capsaicin dermal patch reported limited adverse events. The general incidence of serious adverse events that resulted from controlled trials was 6% compared to 4% with the control patch [7]. The most common adverse reactions were application site reactions, such as dryness, erythema, edema, pain, papules and pruritus. Nevertheless, those reactions were mild to moderate in severity, resolved spontaneously within 7 days and did not preclude the

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Article highlights

- Peripheral neuropathic pain (PNP) is a chronic condition arising from damaged fibers of the somatosensory system and involves the transient receptor potential vanilloid-1 (TRPV-1).
- Oral drugs are satisfactory to only a portion of patients.
- Topical treatment with capsaicin is efficient in attenuating pain and is characterized by few side effects.
- Capsaicin acts through pharmacological defunctionalization of the TRPV-1 receptor.
- Capsaicin is administered by a single application of a dermal patch; its efficacy has been tested both in clinical trials and in 'field-practice' experiences and it is cost-effective compared to other oral agents.
- Topical capsaicin dermal patch may represent a suitable choice for treatment for localized PNP.

This box summarizes key points contained in the article.

completion of the treatment (99% of the patients completed ≥90% of the treatment) [8].

Possible disadvantages of the use of capsaicin dermal patch are the fact that its application occurs under the supervision of a healthcare professional and that the treatment may be repeated after 3 months, in case of reappearance of the pain [3,4]. Despite the discomfort, the treatment is well tolerated by the patients.

However, real-life experiences, including well-grounded Expert Opinions, appear necessary for a further elucidation of the role of the high-concentration capsaicin dermal patch in clinical practice, including proper selection of patients most suitable to this therapy [1]. This article reviews available evidence on the pharmacological treatment of PNP, focusing on the use of the capsaicin 8% dermal patch: it presents clinical data on this drug, and discusses the role of high-dose capsaicin in clinical practice, according to the experience of a group of Experts.

2. Localized neuropathic pain: basic principles and treatment options

2.1. Molecular basis and pathophysiology

Localized NP is defined as 'a type of peripheral neuropathic pain characterized by a circumscribed and consistent area of maximum pain' [9–13]. All types of fibers can be damaged in this condition, but Aδ fibers and, particularly, C fibers have the greatest relevance [14,15]. Indeed, since multiple Aδ and C fiber populations converge onto different spinal neuronal populations, addressing pain mechanisms at the level of peripheral C fibers can result in high levels of analgesic control by attenuation of the drivers of central changes.

Voltage-gated sodium channels (NaV channels) are of paramount importance for nociception, since they generate and propagate action potentials [16,17]. Moreover, HCN channels have recently been associated with inflammatory, neuropathic and postoperative pain [18]. According to the above, targeting peripheral channels, and in particular sodium channels, prevents painful stimuli from reaching the CNS, although individual response may vary [19,20]. Sodium channels may not therefore be the only target to address.

For instance, the thermo-transient receptor potentials (TRPs), which provide information about thermal changes in the environment, are expressed in small primary sensory nerve terminals [21,22]. To date, six thermo-TRPs have been characterized: TRPV1, TRPV2, TRPV3, TRPV4, TRP melastatin 8 and TRP ankyrin (TRPA) 1. TRPV1 and TRPV2 are activated by painful levels of heat; TRPV3 and TRPV4 respond to non-painful warmth; TRP melastatin 8 is activated by non-painful cold temperatures; and TRP ankyrin (TRPA) 1 reacts to painful cold. The different thermal thresholds are controlled by extracellular mediators, which are released by tissue damage or inflammation (e.g., bradykinin, prostaglandins and growth factors).

Blockers of TRPs have been extensively researched, since they may be used as novel analgesics, but they are associated with unacceptable side effects. On the other hand, targeting inflammatory mediators to control the modulation of thermo-TRPs may be a different strategy to develop novel analgesics.

Central sensitization does have an essential role in the process of pain – that is, the exaggerated pain felt after nerve injury and inflammation that can be induced in healthy volunteers by acute intense peripheral stimulation and is observed in many pain conditions [23,24]. Central sensitization is also associated with windup and long-term potentiation and can be recruited by activation of TRPV1 using capsaicin [25].

2.2. Treatment

International guidelines and recommendations from the European Federation of Neurological Societies and the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain recommend oral medicines, such as tricyclic antidepressants, anticonvulsants (including gabapentin and pregabalin), and selective serotonin and noradrenaline reuptake inhibitors as first-line options [5,26,27]. However, these oral therapies provide satisfactory pain relief only in a minority 30–40% of patients. They are also associated with undesirable systemic side effects. As a consequence, many individuals with neuropathic pain still suffer from persistent pain and poor quality of life despite their use [9,28–30].

A pharmacologic treatment algorithm for localized NP has been suggested: primary care physicians and non-pain specialists should consider the use of topical analgesic agents as the first-line treatment [31]. Overall, topical agents targeting the peripheral nervous system can be effective at providing rapid, targeted pain relief of PNP without the side effects, which are sometimes associated with systemic, oral therapies. Topical agents may be especially useful when there are concerns about systemic side effects or compliance, and in frail/elderly patients [9]. Indeed, localized activity and low systemic absorption can prevent issues associated with oral or intravenous routes, such as gastric disturbances, CNS side-effects and variable serum concentrations, thus resulting in a low risk of drug–drug interactions [9].

Two topical treatments are currently licensed by the European Medicines Agency (EMA) for peripheral NP: lidocaine 5%-medicated plaster for PHN only and the capsaicin 179 mg 8% cutaneous patch (capsaicin 8% patch) for all types of peripheral neuropathic pain.

3. Capsaicin: pharmacodynamic and pharmacokinetic properties

Inactivation of NaV channels and pharmacological desensitization of TRPV1 receptors may contribute to an immediate reduction in neuronal excitability and responsiveness [5]. Capsaicin is an agonist at the TRPV1 ligand-gated cation channel, which is highly expressed in nociceptive nerve fibers (mainly C and Aδ fibers) [1]. Multiple mechanisms are involved in capsaicin-induced so-called 'defunctionalization' of the sensory nerve fibers [5].

Furthermore, topical exposure to capsaicin causes sensations of heat, burning, stinging or itching, since activation of TRPV1 results in sensory neuronal depolarization, and can induce local sensitization to receptor activation by heat, acidosis and endogenous agonists. However, high concentrations of capsaicin or repeated applications can lead to a persistent local effect on cutaneous nociceptors, constituted by reduced spontaneous activity and a loss of responsiveness to a wide range of sensory stimuli [5]. At concentrations higher than those required to activate TRPV1, capsaicin can also cause mitochondria dysfunction by directly inhibiting electron chain transport. At the same time, the peripheral fibers in the affected zone pull back from their cutaneous innervation territories rendering them less likely to be activated by peripheral stimuli. Thus, the peripheral fibers with their nociceptors and associated ion channels are no longer amenable to activation by stimuli applied to the treated area, and central sensitization is thereby attenuated. This retraction is due to several effects that include temporary loss of membrane potential, inability to transport neurotrophic factors and reversible retraction of epidermal and dermal nociceptive fiber terminals, which all block the transmission of nociceptive stimuli for a prolonged period [5,32]. This condition is temporary and reversible, and terminals are usually reconstituted within 3 months after the administration of capsaicin. Remarkably, due to the high selectivity of capsaicin for the TRPV1 receptor and the selective expression of TRPV1 in nociceptive sensory nerves, other skin sensory nerve endings may remain intact and functional, with no loss of tactile and vibratory sensations [33].

Topical capsaicin acts locally, and pain relief is not facilitated by transdermal systemic delivery. Indeed, due to its insolubility in water, capsaicin is not readily absorbed into the microvasculature [5,6]. Over a 60-min application of the capsaicin 8% dermal patch, ≈1% of capsaicin is estimated to be absorbed into the epidermal and dermal layers of the skin [6]. In patients with PHN, HIV-AN or PDPN, systemic exposure to capsaicin appeared to be low and transient following a single 60- or 90-min application of the capsaicin 8% dermal patch [34]. Capsaicin is rapidly metabolized *in vitro* by liver enzymes to form three major metabolites – that is, 16-hydroxycapsaicin, 17-hydroxycapsaicin and 16,17-dehydrocapsaicin. These metabolites were not detected in the plasma of patients with peripheral neuropathy treated with topical capsaicin and are not pharmacologically active on TRPV1 receptors [1].

4. Therapeutic efficacy of the Capsaicin 8% dermal patch

The therapeutic efficacy of the high-concentration 8% capsaicin dermal patch for the treatment of PNP has been assessed in patients with PDPN and in nondiabetic patients with PNP of various etiologies, including PHN and HIV-AN, both in large, randomized clinical trials (Tables 1 and 2) [35–47], and in 'field-practice' experiences (Tables 3-6) [8,48–67].

A detailed description of those trials is provided in an excellent recent review by Blair et al., and goes beyond the scopes of the present article [1]. We focus here on the studies comparing capsaicin with pregabalin, a centrally acting agent widely used for neuropathic pain.

In the open-label, randomized, multicenter, non-inferiority ELEVATE trial, 282 patients with PNP received capsaicin 8%, while 277 were assigned to pregabalin [36]. The primary endpoint was a ≥ 30% mean decrease in Numeric Pain Rating Scale (NPRS) score from baseline to week 8. Secondary endpoints were time-to-onset of pain relief and treatment satisfaction. Overall, the capsaicin 8% patch was non-inferior to pregabalin in the achievement of a ≥ 30% mean decrease in NPRS score at week 8 (55.7% vs 54.5%, respectively; odds ratio: 1.03 [95% CI: 0.72–1.50]). The median time-to-onset of pain relief was shorter for capsaicin 8% patch compared with pregabalin (7.5 vs 36.0 days; hazard ratio: 1.68 [95% CI: 1.35–2.08]; $p < 0.0001$). In addition, treatment satisfaction was greater with the capsaicin 8% patch compared with pregabalin. Capsaicin was also associated with a more favorable tolerability profile compared with pregabalin (incidence of systemic drug reactions with capsaicin: 0–1.1%; with pregabalin: 2.5–18.4%). All adverse events were of mild-to-moderate severity; treatment discontinuation only occurred with pregabalin (n = 24). The authors concluded that the capsaicin 8% patch provides non-inferior pain relief compared with an optimized dose of pregabalin in PNP, and showed a faster onset of action, fewer systemic side effects and greater treatment satisfaction. In a subsequent analysis of the same trial, the capsaicin 8% dermal patch was superior to pregabalin in reducing the intensity and area of dynamic mechanical allodynia (DMA), a common clinical manifestation of PNP and a consequence of central sensitization [11]. Indeed, the change in DMA intensity from baseline to study end was greater with the capsaicin 8% patch, as compared with pregabalin [−0.63 (95% CI: −1.04 to −0.23; $p = 0.002$)]. Similarly, the capsaicin 8% patch was superior over pregabalin in the reduction of DMA area [−39.5 cm^2 (95% CI: −69.1 to −10.0; $p = 0.009$)]. A greater number of patients experienced a complete resolution of allodynia with the capsaicin 8% patch treatment compared with pregabalin (24.1% vs 12.3%; $p = 0.001$).

A network meta-analysis of 25 randomized controlled trials showed that the capsaicin 8% dermal patch was just as effective as oral, centrally acting agents (i.e. pregabalin, duloxetine and gabapentin) in patients with PDPN; however, it demonstrated benefits of better tolerability due to a lack of systemic effects [68]. For the endpoint of ≥30% pain reduction, the capsaicin 8% patch was significantly more effective than placebo (OR: 2.28 [95% CI: 1.19–4.03]), showed a clear advantage over pregabalin (OR: 1.83 [95% CI: 0.91–3.34]) and gabapentin (OR: 1.66 [95% CI: 0.74–3.23]), and exhibited a similar efficacy

Table 1. Randomized short therapy (8–12 weeks) clinical trials on the efficacy of capsaicin 8% dermal patch.

Study	N° of patients (condition)	Treatment (duration [min] or dose)	Study duration	Pain reduction[a]	Response rate (%)[b]	Other efficacy results	Safety results
Cruccu 2018 [35]	253 (NP)	CAP (30–60)	8 weeks	DMA: −2.98	24.1	DMA area: −72.6 cm^2	Mild-to-moderate site pain, erythema, burning sensation Treatment-related discontinuation: 0%
	253 (NP)	Pregabalin (150–600 mg/day)		DMA: −2.35	12.3	DMA area −33.1 cm^2	Treatment-related discontinuation: 8.5%
Haanpaa 2016 [36]	282 (PNP)	CAP (30–60)	8 weeks	–	−55.7	OTE at w8: 52.1% TTR: 7.5 days	TEAE: 61.3% Pain: 23.8% Erythema: 20.9% Burning Sensation: 15.6% Treatment-related discontinuation: 0%
	277 (PNP)	Pregabalin (78–600 mg/day)		–	−54.5	OTE at w8: 44.8% TTR: 36 days	TEAE: 54.5% Dizziness: 18.4% Somnolence: 15.5% Nausea: 10.8% Treatment-related discontinuation: 8.5%
Simpson 2017 [37]	186 (PDPN)	CAP (30)	12 weeks	−27.4%	–	TTR: 19 days Sleep interference score*: −33.1%	TEAE: 46.8% Burning sensation: 14% Pain: 10.8%
	183 (PDPN)	Placebo		−20.9%	–	TTR: 72 days Sleep interference score*: −24.2%	TEAE: 33.9% Pain: 5.5% Burning sensation: 2.7%
Brown 2013 [38]	482 (HIV-DSP)	CAP (30–60)	12 weeks	−27.4%	40	PGIC[c]:	TEAE (77%)
	239	CAP (30)		-26.9%	40	67	Pain (65%)
	243	CAP (60)		-27.9%	40	65	Erythema (37%)
						69	
				−20.0%	31	PGIC[c]:	TEAE (52%)
				-15.8%	23	49	Pain (31%)
				-24.2%	37	41	Erythema (27%)
						57	
Clifford 2012 [39]	332 (HIV-DSP)	CAP (30–60)	12 weeks	−29.5%	43	PGIC[c]: CGIC[c]:	TEAE (93%)
	167	CAP (30)		-26.2%	39	67 66	Pain (83%)
	165	CAP (60)		-32.8%	48	65 65	Erythema (53%)
						69 66	
	162 (HIV-DSP)	CON (30–60)		−24.5%	36	PGIC[c]: CGIC[c];	TEAE (83%)
	73	CON (30)		-19.1%	26	55 52	Pain (38%)
	89	CON (60)		-30.0%	45	45 39	Erythema (36%)
						63 63	
Irving 2011 [40]	212 (PHN)	CAP (60)	12 weeks	−32.0%	46	PGIC[c]: 61 CGIC[c]: 63	TEAE (98%) Erythema (92%) Pain (63%)
	204 (PHN)	CON (60)		−24.4%	34	PGIC[c]: 47 CGIC[c]: 48	TEAE (87%) Erythema (69%) Pain (28%)
Simpson 2008 [41]	225 (HIV-DSP)	CAP (30–90)	12 weeks	−22.8%	34	PGIC[c]: CGIC[c]:	TEAE (72%)
	72	CAP (30)		-27.7%	42	67 66	Pain (21%)
	78	CAP (60)		-15.9%	24	66 65	Pruritus (17%)
	72	CAP (90)		-24.7%	36	70 63	
						65 70	
	82 (HIV-DSP)	Control (30–90)		−10.7%	18	PGIC[c]: 31 CGIC[c]: 37	TEAE (55%) Pain (9%) Swelling (9%)
Backonja 2008 [42]	206 (PHN)	CAP (60)	12 weeks	−29.6%	42	PGIC[c]: 55	TEAE: 99% Erythema: 94% Pain: 56%
	196 (PHN)	CON (60)		−19.9%	32	PGIC[c]: 43	TEAE: 88% Erythema: 65% Pain: 22%

Table 2. Randomized long therapy (48–52 weeks) clinical trials on the efficacy of capsaicin 8% dermal patch.

Study	N° of patients (condition)	Treatment (duration [min] or dose)	Study duration	Pain reduction[a]	Response rate (%)[b]	Other efficacy results		Safety results
Vinik 2016 [43]	156 (PDPN)	CAP (30) + SOC	52 weeks	–	–	QOL-DN[d]: −27.6% vs −32.8%		Pain: 28.2% vs 29.3%
	157 (PDPN)	CAP (60) + SOC				UENS[d]: −2.1 vs −3.0		Burning sensation: 9.0 vs 9.6%
								Erythema: 7.7% vs 8.9%
	155 (PDPN)	SOC		–	–	QOL-DN[d]: −6.7%		–
						UENS[d]: −1.2		
Perrot 2015 [44]	156 (PDPN)	CAP (30) + SOC	52 weeks	BPI-DN PSI: −1.9 vs −2.2	–	EQ-5DVAS[d]: 10.4 vs 11.2		–
	157 (PDPN)	CAP (60) + SOC		BPI-DN PII: −1.9 vs −2.0				
	155 (PDPN)	SOC		BPI-DN PSI: −0.9	–	EQ-5DVAS[d]: 5.5		–
				BPI-DN PII: −0.8				
Simpson 2014 [45]	272 (HIV-DSP)	CAP (60)	52 weeks	−25.8%	–	PGIC[c]:	CGIC[c]:	Administration site reaction:
	81	1 cycle		-27.1%		59	61	50%
	90	2 cycles		-24.6%		62	58	37%
	55	3 cycles		-22.7%		68	70	41%
	46	4 cycles				76	80	40%
Backonja 2010 [46]	26 (PHN)	CAP (60)	48 weeks	−32.7%	–	–		TEAE (42%)
								Fatigue (12%)
								Dizziness (12%)
	12 (PHN)	CON (60)		−4.4%	–	–		TEAE (17%)
								Pruritus NOS (8%)
Simpson 2010 [47]	54 (PHN)	CAP (60–90)	1 year	–	–	–		TEAE (98%)
								Erythema (96%)
								Pain (67%)
	52 (HIV-DSP)	CAP (90)						TEAE (90%)
								Erythema (75%)
								Pain (73%)

BL: baseline; BPI-DN: Brief Pain Inventory; CAP: Capsaicin 8% patch; CGIC: Clinical Global Impression of Change; CON: control; DMA: dynamic mechanical allodynia; EQ-5DVAS: EuroQol visual analogue scale; HIV-DSP: painful human immunodeficiency virus-associated distal sensory polyneuropathy; NOS: not otherwise specified; NP: neuropathic pain; OTE: optimal therapeutic effect; PDPN: painful diabetic peripheral neuropathy; PGIC: Patients' Global Impression of Change; PHN: postherpetic neuralgia; PII: Pain Interference Index; PNP: peripheral neuropathic pain; PSI: Pain Severity Index; QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy; SOC: standard of care; TEAE: treatment-emergent adverse event; TTR: time to treatment response; UENS: Utah Early Neuropathy Scale.

[a]Mean change in NPRS score from baseline to weeks 2–8 in PHN [40,42], weeks 1–4 in PHN [46] or weeks 2–12 in HIV-DSP38-42; mean change in DMA intensity from baseline to week 8 in NP [35]; mean change in BPI-DN PSI and PII from baseline to 52 weeks for PDPN [44].

[b]Percentage of patients who achieved ≥ 30% reduction from BL in NPRS mean score from baseline to weeks 2–8 in PHN [40,42], weeks 2–12 in HIV-DBS [38,39,41] week 8 in PNP [43], or complete resolution of DMA in NP [35].

[c]Very much, much or slightly improved at week 12 [38–41,45].

[d]Mean change from baseline to weeks 2–8 [37], to week 52 [43,44].

Table 3. Field practice experiences on the efficacy of capsaicin 8% dermal patch for short time therapy (2, 4 and 8 weeks).

Study	Study type	N° of patients (condition)	Treatment duration (min)	Study duration	Pain reduction[a]	Response rate (%)[b]	Other efficacy results	Safety results
Churruca 2018 [48]	Observational prospective	18 (NP due to scar after urological surgery)	CAP (60)	2 weeks	from 8.4 ± 0.8 to 4.4 ± 2.5 (NPRS)	– –	6.3 ± 1.7 to 3.3 ± 1.7 DN4	Pruritus & Burning: 44.4% Pruritus: 11.1% Burning sensation: 16.7%
Tenreiro-Pinto 2018 [49]	Observational prospective	43 (PONP, PHN)	CAP (30–60)	2 weeks	−40.0 (NPRS) -35.1 (PTA)	–	–	–
Churruca 2016 [50]	Observational prospective	14 (NP)	CAP (60)	2 weeks	from 8.4 ± 0.6 to 4.2 ± 2.7 (NRPS)	–	from 6.5 ± 1.7 to 3.3 ± 1.8 (DN4)	Erythema: Mild 54%, moderate 33%, severe 13% Burning sensation: 67%
Privitera 2017 [51]	Longitudinal	14 (amputation stump and phantom limb pain)	CAP (30–60)	4 weeks	NPRS: -1.01 (spontaneous stump pain) -2.03 (evoked stump pain) -1.41 (phantom limb pain)	-	Aallodynia/pinprick hypersensitivity area [d]: -165 cm^2 (spontaneous stump pain) -132 cm^2 (evoked stump pain) -80 cm^2 (phantom limb pain)	–
Bardo-Brouard 2018 [52]	Case series	8 (refractory NP with NF1)	CAP (60)	8 weeks	–	≥30% 37.5%	PGIC [c]: 100% responders	Local reactions (burning and pain) No systemic side effects
Mankowski 2017 [53]	Phase IV	420 (PNP, PONP, PHN, others)	CAP (30–60) 1st 2nd 3rd	8 weeks	−26.6% (NPRS) -28.7% -27.3%	≥30% ≥50% 44.4 26.2 49.1 30.4 49.2 30.5	EQ-5D [(d)]: +0.200 utils PGIC [c]: 62.8% Time to 2nd treatment: 191 days	Erythema: 8.1% Pain: 5.0% Pruritus: 1%
Levesque 2017 [54]	Observational prospective	60 (pelvic, perineal and gluteal neuralgia)	CAP (30–60)	8 weeks	−1.08 ± 2.6 (NRPS)	–	PGIC [c]: 24% Sitting duration [d]: +0.39 h Medication use [d]: −0.53 MQS	–

CAP: Capsaicin 8% patch; DN4: Douleur Neuropathique en 4 Questions; EQ-5D-3L, EuroQol five dimensions 3 level questionnaire; MQS: Medication Quantification Scale; NF1: neurofibromatosis 1; NP: neuropathic pain; NPRS: Numerical Pain Rating Scale; PGIC: Patients' Global Impression of Change; PHN: post-herpetic neuralgia; PONP: post-operative and post-traumatic neuropathic pain; PNP: peripheral neuropathic pain; PTA: pain treatment area.

[a]If not otherwise specified: mean change in pain score from baseline to week 2 [49]; weeks 2–8 [53]; weeks 2–12 [55,56,58,61,62,; week 4 [51]; week 8 [54]; week 12 [59,63], and month 6 [68].

[b]Reduction in pain mean score from baseline to days 7–10 [57], weeks 2–12 [38,45,53,61,62], week 8 [52], and 24 weeks [66].

[c]Very much or much improved at week 8 [52,53,54] and week 12 [55,56,63], and slightly, very much or much improved at 6 months [68].

[d]Mean change from baseline to week 2 [56], week 4 [51], week 8 [53], and week 52 [68].

Table 4. Field practice experiences on the efficacy of capsaicin 8% dermal patch for medium time treatment (12 weeks).

Study	Study type	N° of patients (condition)	Treatment duration (min)	Study duration	Pain reduction[a]	Response rate (%)[b]		Other efficacy results	Safety results
Perrot 2019 [55]	Observational prospective	495 (PNP)	CAP (30–60)	12 weeks	−3.0 ± 2.2 (BPI intensity) -2.5 ± 2.4 (BPI interference) -23.1 ± 19.7 (NPSI)	–	–	PGIC [(c)]: 23%	–
Hansson 2018 [56]	Observational prospective	382 (PNP)	CAP (30–60); first treatment	12 weeks	−0.97 ± 2.04 (NPRS)	≥30% 29	≥50% 16	EQ-5D-3 L[(d)]: +0.148 (52% pts) PGIC [(c)]:21%	Application site reaction: mild 14%, moderate 39%, severe 11%
		181 (PNP)	CAP (30–60); retreatment		−0.54 ± 1.87 (NPRS)	27	12	EQ-5D-3 L[(d)]: +0.126 (32% pts) PGIC[(c)]: 44%	Application site reaction: mild 40%, moderate 32%, severe 12%
Gustorff 2017 [57]	Observational prospective	54 (PNP)	CAP (30–60)	12 weeks	–	≥30%: 35.2		Responders vs non responders: Pressure pain threshold 320 kPa vs 480 kPa Significantly lower allodynia Significantly greater reduction in PAS	–
Filipczak-Bryniarska 2017 [58]	Observational prospective	18 (CIN) high sensitivity vs low sensitivity	CAP (30–60)	12 weeks	−1.16 vs −0.25 (NRPS)	−84 vs −97		–	–
Aitken 2017 [59]	Observational cohort	20 (NP from critical ischemia in ESRD)	CAP (30–60)	12 weeks	−20% (VAS)	–		EQ-5D: significant reduction in mobility and pain BPI: significant reduction in all 7 domains	Well tolerated, no significant side effect
Zis 2016 [60]	Phase IV	90 (lumbosacral pain)	CAP (30–60)	12 weeks	from 7.6 ± 0.7 to 2.6 ± 1.1 (VAS)	–		EQ-5D: significant improvement in all 5 dimensions	–
Maihofner 2014 [61]	Phase IV	1044 (PNP) Preexisting pain <6 months 6 months to2 years >2–10 years >10 years	CAP (30–60);	12 weeks	−36.6% (NPRS) -25.1% -22.3% -19.2%	≥30%: 61.7 42.3 40.9 32.3	≥50%: 39.3 23.3 21.6 14.1	–	ADR 11.1% 11.2% 9.4% 11.7%
Maihofner 2013 [62]	Phase IV	1044 (PNP)	CAP (30–60)	12 weeks	−24.7% (NPRS)	≥30%:42.7	≥50%: 23.7	Reduced number of pain attacks in 24 h: from 8.1 to 3.8 Improved sleep duration: +0.4 h/day Improved SF-12: +16.1% PCS; +11.7% MCS	ADR: 10% (pain, erythema) SAR: 1.6%
Peppin 2011 [8]	Integrated analysis	1696 (PNP)	CAP (30–90)	12 weeks	–	–		–	Patch-related pain (pain now): max +2.6 ± 2.7 Average 24 h pain returned to baseline after 1–2 days ≥98% of patients completed ≥90% treatment duration

CAP: Capsaicin 8% patch; ADR: adverse drug reaction; BPI: Brief Pain Inventory; CIN: chemotherapy-induced neuropathy; EQ-5D-3L, EuroQol five dimensions 3 level questionnaire; ESRD: end-stage renal disease; MCS: Mental Component Summary score; NP: neuropathic pain; NPRS: Numerical Pain Rating Scale; NPSI: Neuropathic Pain Symptom Inventory; PAS: painful area size; PCS: Physical Component Summary Score; PGIC: Patients' Global Impression of Change; PNP: peripheral neuropathic pain; SAR: serious adverse drug reaction; SF-12: short form 12 health survey; VAS: visual analog scale.

[a]If not otherwise specified: mean change in pain score from baseline to week 2 [49]; weeks 2–8 [53]; weeks 2–12 [55,56,58,61,62,; week 4 [51]; week 8 [54]; week 12 [59,63], and month 6 [68].

[b]Reduction in pain mean score from baseline to days 7–10 [57], weeks 2–12 [38,45,53,61,62], week 8 [52], and 24 weeks [66].

[c]Very much or much improved at week 8 [52,53,54] and week 12 [55,56,63], and slightly, very much or much improved at 6 months [68].

[d]Mean change from baseline to week 2 [56], week 4 [51], week 8 [53], and week 52 [68].

Table 5. Field practice experiences on the efficacy of capsaicin 8% dermal patch for long time treatment (6 months, 1 year).

Study	Study type	N° of patients (condition)	Treatment duration (min)	Study duration	Pain reduction[a]	Response rate (%)[b]	Other efficacy results	Safety results
Lantéri 2019 [63]	Phase IV	684 (PNP)	CAP (30–60)	6 months	−8.0 ± 18.2 (NPSI)	≥30% 26	PGIC[c]: 57.9%	Pain: 5.7%: Erythema 5.6%
Galvez 2017 [64]	Phase IV	306 (PNP, non-diabetic)	CAP (30–60)	52 weeks	−1.9 ± 1.89 (BPI)	–	Allodynia/hyperalgesia: from 241.9 cm^2 to 219.9 cm^2 PGIC [c]: 31.6%	TEAE: 82.4% Pain: 36.6% 50.4% sensory deterioration/loss in ≥1 modality
Rorbaek 2017 [65]	Case series	14 (PNP – feet or lower legs)	CAP (30–60)	–	−3 (VAS, 43% of the pts)	23	–	–
		13 (PNP – fingers, hand or arms)	CAP (60)	–		46	–	–
Marec 2016 [66]	Observational cohort	28 (CIN)	CAP (30)	24 weeks	–	≥30%: 18 30-50%: 7 50–70%: 36 70–90%: 36 >90%: 3	Time to 2nd treatment: 7 months	–
Reeves 2016 [67]	Phase IV	7 (PNP, ≥6/10 VNRS; ≥12/24 LANSS)	CAP + gabapentinoid	1 year	Average post-treatment VNRS: 1.5 ± 1.4	–	Improved sleep: 50% Improved QoL: 83% Improved ADL: 100% Good to excellent satisfaction: 100% Time to 2nd treatment: 8 months	–

CAP: Capsaicin 8% patch; ADR: adverse drug reaction; BPI: Brief Pain Inventory; CIN: chemotherapy-induced neuropathy; EQ-5D-3L, EuroQol five dimensions 3 level questionnaire; ESRD: end-stage renal disease; MCS: Mental Component Summary score; NP: neuropathic pain; NPRS: Numerical Pain Rating Scale; NPSI: Neuropathic Pain Symptom Inventory; PAS: painful area size; PCS: Physical Component Summary Score; PGIC: Patients' Global Impression of Change; PNP: peripheral neuropathic pain; SAR: serious adverse drug reaction; SF-12: short form 12 health survey; VAS: visual analog scale.

[a]If not otherwise specified: mean change in pain score from baseline to week 2 [49]; weeks 2–8 [53]; weeks 2–12 [55,56,58,61,62,; week 4 [51]; week 8 [54]; week 12 [59,63], and month 6 [68].

[b]Reduction in pain mean score from baseline to days 7–10 [57], weeks 2–12 [38,45,53,61,62], week 8 [52], and 24 weeks [66].

[c]Very much or much improved at week 8 [52,53,54] and week 12 [55,56,63], and slightly, very much or much improved at 6 months [68].

[d]Mean change from baseline to week 2 [56], week 4 [51], week 8 [53], and week 52 [68].

Table 6. Risk of adverse events for the different oral agents in comparison to placebo, data taken from [68].

Adverse event	Oral agent	Risk vs placebo; OR (95% CI)
Somnolence	Gabapentin	4.03 (95% CI:2.36–6.57)
	Pregabalin	4.14 (95% CI:3.00–5.60)
	Duloxetine	3.54 (95% CI:2.51–4.90)
	Amitriptyline	147.73 (95% CI:5.91–596.83)
Dizziness	Gabapentin	4.69 (95% CI:2.83–7.55)
	Pregabalin	4.63 (95% CI:3.44–6.16)
	Duloxetine	1.92 (95% CI:1.37–2.65)
	Amitriptyline	31.13 (95% CI:2.76–141.00)
Fatigue	Gabapentin	3.73 (95% CI:0.98–11.10)
	Pregabalin	2.21 (95% CI:0.25–8.98)
	Duloxetine	2.64 (95% CI: 1.32–4.95)
Discontinuation due to adverse events	Gabapentin	2.2 (95% CI:1.36–3.41)
	Pregabalin	2.03 (95% CI:1.5–2.71)
	Duloxetine	2.35 [95% CI, 1.68–3.2)]

compared with duloxetine (OR: 0.99 [95% CI: 0.5–1.79]). Compared with placebo, oral agents were correlated with a significant elevation in the risk of somnolence, dizziness, fatigue and discontinuation due to adverse events (Table 6).

Lastly, to date, published cost–effectiveness analyses of patients who suffer from PNP suggest that the capsaicin 8% dermal patch is cost-effective compared with oral agents, including tricyclic antidepressants, duloxetine, gabapentin and pregabalin (i.e. 59,919 USD vs tricyclic antidepressants; 43,908 USD vs duloxetine; 42008 USD vs gabapentin; 40241 USD versus pregabalin) [69].

5. Expert opinion

The activity of capsaicin is entirely dependent on the amount of TRPV1 on damaged fibers or fibers involved in pain generation. The expression of TRPV1 might be different among patients with the same form of localized PNP and an accurate clinical evaluation of their presence is a prerequisite for a fully successful therapy. Indeed, 'defunctionalization' of small afferent fibers localized in the area of skin application is the key pharmacodynamic property of capsaicin 8% patch. This is a long-lasting phenomenon that allows the drug to produce analgesic effects well beyond its removal. This aspect along with the fact that this is a topical therapy with no systemic adverse drug reactions, make capsaicin 8% patch an ideal approach to promote patient adherence to therapy.

It must be pointed out that the efficacy of capsaicin 8% patch requires access to its target and so will be dependent on the peripheral expression of TRPV1 receptors in a pain patient. Therefore, testing of thermal sensibility (hot/cold) should be performed before application. Pain at application is a good predictive factor, since it can be attributed to the presence of TRPV1 receptors in the application zone.

In any case, a reduction in the painful area is observed after the first application, while reduction of pain intensity is observed after 2–8 weeks of the application [1]. The efficacy of capsaicin 8% is greatest if the pain generator is superficial in the affected tissue (approximately 1–1.5 cm), such as in the case of PHN, DPN, painful post-surgical scars (e.g., thoracic/abdominal surgery, orthopedic surgery, hernia removal) or ischemic pain. Advantages of capsaicin 8% patch treatment include its excellent efficacy – which is associated with a reduction of painful area – and systemic tolerability, which make it a suitable therapy in elderly patients, and ease of use. It is particularly suitable for patients with burning pain and allodynia due to peripheral and consequent central sensitization. Other potentially suitable patients include those with contraindication to systemic treatment (e.g., patients on working duties and long-driving requirements), oncological patients – given the lack of interactions with oncological therapies – and patients with chemotherapy-induced neuropathy.

The ability of capsaicin 8% patch in reducing the intensity and area of pain in patients with localized NP whilst avoiding central and systemic side-effects is a great advantage over oral agents. Moreover, given the high patients' preference for capsaicin and because of the unique pharmacodynamics properties of this drug, capsaicin 8% patch is also suitable for combination therapy, in which synergistic effects can be obtained only by combining drugs with different and complimentary mechanisms of action. Moreover, it can be given as a short course of treatment, with the possibility to repeat as needed. Proper evaluation of the area to be treated (measurement, testing of skin integrity, assessment of thermal sensitivity), as well as proper training of healthcare professionals involved is essential.

In conclusion, topical capsaicin 8% patch has the potential to represent a first-choice treatment for localized PNP, given its peculiar pharmacodynamic properties and its good efficacy/safety ratio.

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