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Narrative review of the efficacy and safety of the high-concentration (179mg) capsaicin patch in peripheral neuropathic pain with recommendations for clinical practice and future research

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Abstract

High-concentration capsaicin patch (HC capsaicin patch) is a locally acting treatment option for adults with peripheral neuropathic pain (pNeP) of various etiologies. Numerous clinical trials, post hoc analyses, and meta-analyses have investigated the efficacy and tolerability of the HC capsaicin patch. Despite this extensive body of research, a comprehensive narrative review covering publications on different pNeP conditions is lacking. This narrative review aims to fill the gap by analyzing 52 studies, including randomized controlled trials and real-world evidence. The results show that the HC capsaicin patch consistently provides pain relief and improves quality of life for several pNeP conditions, with increasing benefits seen with repeated treatments. It was found to be superior to placebo and comparable to standard care, regardless of the origin of the pain. Early initiation of therapy appears to improve efficacy, although patients with more prolonged pain also benefit. While the exact mechanisms of action are still unclear, there is evidence to suggest a potential benefit from nerve regeneration in some conditions. However, limited information exists regarding the alteration of treatment intervals and the variation in the size of the painful area upon re-treatment. The review also identifies variability in response rates for different types of pNeP and a lack of reliable predictors of treatment success, indicating a need for further research. In conclusion, the HC capsaicin patch is effective and well tolerated across a range of pNeP conditions, with increasing efficacy upon retreatment. It is a valuable treatment option, although more research is needed to refine its clinical use and explore its full therapeutic potential.

Keywords: High-concentration capsaicin patch (HC capsaicin patch), Peripheral neuropathic pain, Localized neuropathic pain, Topical treatment, Mode of action, Nerve regeneration, Repeated treatment, Progressive response

1. Introduction

High-concentration (179mg) capsaicin patch (HC capsaicin patch), known as capsaicin 8% topical system in the United States, provides a topical treatment option for peripheral neuropathic pain (pNeP) in adults and may be used as monotherapy or in combination with other pain medications.[18] In the European Union, it is indicated for pNeP of any cause, whereas in the United States its indication is limited to the treatment of postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (PDPN).

Current guidelines recommend the HC capsaicin patch as a second-line option for pNeP of any origin.[21,44,45,52] However,

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according to the German Society for Neurology, the HC capsaicin patch can be used as a first-line treatment for localized neuropathic pain.[52] Based on its pharmacological properties, clinical efficacy, and favourable safety/tolerability profile, the guidelines from the American Association of Clinical Endocrinology[11] and Clinical Compendia American Diabetes Association[49] also suggest it as a first-line treatment for PDPN.

Capsaicin, the active ingredient of the HC capsaicin patch, is a highly selective agonist of the transient receptor potential cation channel of the subfamily V, subtype 1 (TRPV1). Binding of capsaicin to its receptor activates the TRPV1-expressing skin nociceptors leading to temporary fiber depolarization and longer-term pain relief through reversible nerve defunctionalization. This mechanism targets TRPV1-expressing nociceptors without affecting other sensory functions like cold or touch perception.[38]

The HC capsaicin patch is applied for 30 minutes on the feet and 60 minutes on other areas, with re-treatment possible every 60 days depending on symptoms.[60] Importantly, multiple treatments may progressively increase pain relief,[9,23,42,68] and patients with insufficient pain relief after the first treatment may respond better to subsequent treatments, achieving similar improvements in pain relief, sleep quality, and overall efficacy as initial responders.[17,22] In fact, the European Medicines Agency now recommends reassessing efficacy after 3 treatments before discontinuing therapy.[60]

In patients with conditions like chemotherapy-induced peripheral neuropathy (CIPN) and PDPN, nerve biopsies have shown regeneration of intraepidermal and subepidermal nerve fibers after treatment, which seems to correlate with pain reduction.[3–5,15,54,63] Thus, it can be speculated that capsaicin relieves pain by defunctionalizing nerve fibres, followed by functional regeneration. This regeneration may restore normal sensitivity in some fibers, whereas others may regain pathological hypersensitivity (**Fig. 1**). Since its marketing authorization in 2009 (European Union and United States), a large number of clinical studies, post hoc and meta-analyses, and real-world evidence have reported on the effect of the HC capsaicin patch in various indications. This narrative review aims to provide valuable insights for daily clinical practice by summarizing the efficacy and tolerability of treatments across various pNeP conditions and by analyzing response profiles in terms of pain intensity, quality of life (QoL), size of the painful area, and length of treatment intervals.

2. Methods

For this narrative review of clinical data, we only included studies that met the following criteria:
(1) Randomized controlled trials (RCTs)
(2) Open-label trials and/or prospective observational studies
(3) Retrospective studies

Based on their objectives, designs, and methodologies, these types of studies have their specific strengths and limitations and serve a unique role in clinical research and decision making.[19,30,31] These trials were also considered in case of small numbers of patients or niche indications. Phase 1 studies (ie, healthy volunteers), case studies/reports, abstracts/posters, and articles from non-English literature were excluded. In addition, studies were excluded in case their primary end point was not either the efficacy or the tolerability of the HC capsaicin patch application (eg, focus on analgesic pretreatment and/or comedication).

The following query was used for the study search from EMBASE (conducted in October 2023):

(('capsaicin'/exp/mj OR capsaicin:ti OR qutenza:ti) AND 'transdermal drug administration'/lnk OR ('capsaicin'/exp/mj AND (tts OR tds OR 'tissue type system' OR plaster OR patch OR patches OR transcutaneous* OR percutaneous* OR transdermal* OR 'transdermal patch'/exp/mj))) AND [humans]/lim AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta-analysis]/lim) OR (('capsaicin'/exp/mj OR capsaicin:ti OR qutenza:ti) AND ('evidence based medicine'/exp OR 'postmarketing surveillance'/exp OR 'epidemiology'/exp) NOT ('gel'/exp OR 'gel' OR 'gel matrix' OR 'gelcosponge' OR 'gels' OR 'haven gel' OR 'hydraulic gel' OR 'hydrocarbon gel' OR 'hydron gel' OR 'oxygel')) OR (('capsaicin'/exp/mj OR capsaicin:ti OR qutenza:ti) AND 'transdermal patch'/exp/mj) OR (('capsaicin'/exp/mj OR capsaicin:ti OR qutenza:ti) AND ('peripheral neuropathy'/exp/mj OR 'neuropathic pain'/exp))

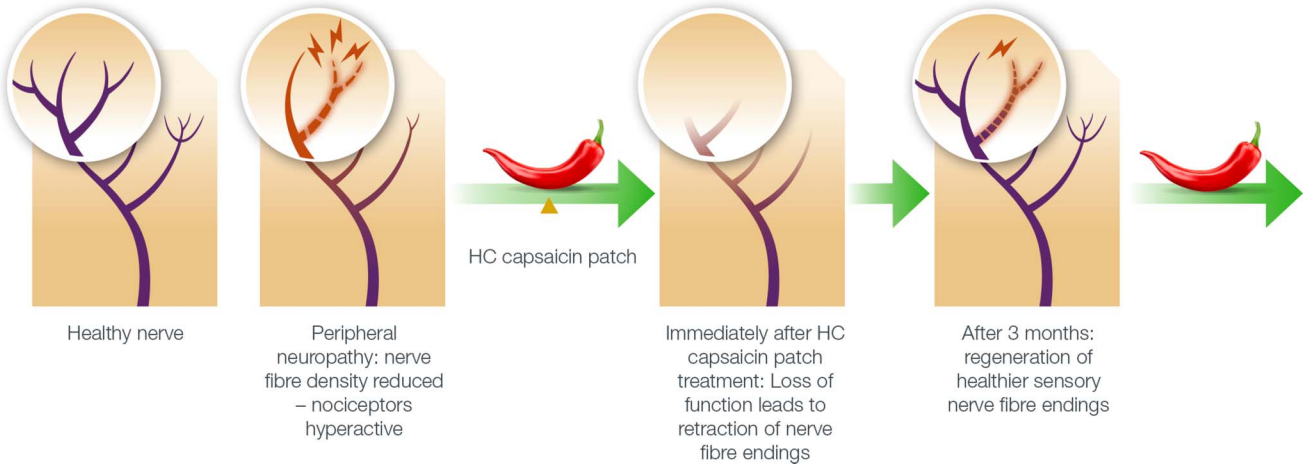

Figure 1. Model of potential disease modification by functional nerve regeneration through pruning. HC capsaicin patch–induced reversible defunctionalization of abnormal nerve fibres (indicated in red) by subsequent nerve regeneration causes an increase in nerve fibre density. This regeneration might result in restoration of normal (healthy) sensitivity in certain nerve fibres, whereas others may recover with pathological hypersensitivity, which will require retreatment. HC, high concentration.

3. Results

In total, 978 studies matched the EMBASE query. Of these, 52 studies met the predefined inclusion criteria. An overview of these studies and their main characteristics is given in **Table 1**. A more detailed compilation is provided in supplemental Table 1, http://links.lww.com/PR9/A278 (single indications) and supplemental Table 2, http://links.lww.com/PR9/A278 (multiple indications). **Figure 2** illustrates the distribution of the analyzed single and multiple treatment studies with respect to their design (post hoc or subgroup analyses of original studies were excluded from the figure to avoid double count of the same study/patients).

The most common indications analyzed in the included clinical trials were pNeP of various origins,[1,14,22,23,25,26,28,29,32,36,39–42,48,50,51,54,58,62,65,66,69,71] PHN,[6,7,34,70,72] HIV-associated neuropathy (HIV-AN),[12,13,55–57] PDPN,[4,59,67,68] postsurgical/posttraumatic nerve injury (PNI, including PSNP and PTNP),[10,46] neuropathic spine-related back pain,[8,47,73] and cancer-related neuropathic pain (CRNP), including CIPN.[3,9,17,20] Individual indications comprise nonfreezing cold injury (NFCI),[5] pelvic neuralgia and neuropathic pain associated with sickle cell disease, critical ischemia with end-stage renal disease, and hand osteoarthritis.[2,24,37,43]

For specific efficacy evaluation of the HC capsaicin patch, we considered data from RCTs (single and multiple HC capsaicin patch treatments) and long-term multiple treatment trials. **Table 2** summarizes the efficacy results based on various outcomes, including pain intensity, disease-specific QoL, overall functioning, and clinical impact of repeated treatments. NeuPSIG guidelines define responders as those with a 50% reduction in numeric pain rating scale (NPRS) scores, with a 30% reduction considered clinically significant,[27] and studies were screened accordingly. Single-treatment data comprised the indications PDPN (30% response rate: 41% of patients, 50% response rate: 22%, patient global impression of change [PGIC] improvement: 41%), PHN (30% response rate: 37–47% of patients, 50% response rate: 23–36%, PGIC improvement: 43–61%), and HIV-AN (30% response rate: 34% of patients, PGIC improvement: 67%). Patient global impression of change improvements correspond to either the percentage of patients who had improved very much, much, or slightly or the patients who had improved very much or much, as indicated in **Table 2**. Multiple treatments were carried out for HIV-AN, PHN, CRNP (including CIPN), PDPN, and pNeP of various origins (**Table 2**).

Because of variations in study design, duration, and patient numbers, no statistical analyses were performed across indications. Nevertheless, re-treatment with the HC capsaicin patch showed efficacy improvement across all pNeP conditions. Response rates and PGIC/Clinical Global Impression of Change (CGIC) scores improved consistently with multiple treatments and longer treatment duration.[9,17,23,42,51,56,58,68] A post hoc analysis of 2 long-term studies suggests that patients initially not experiencing adequate pain relief may respond positively to additional treatments, achieving outcomes comparable to those who initially responded well. These outcomes include reduced pain intensity, improved sleep quality, and other efficacy measures.[22] Similarly, data from a real-world observational retrospective study (CERCAN) focusing on CRNP and/or CIPN found that the HC capsaicin patch was more effective with early treatment initiation[17] and with multiple treatments.[9,17] Furthermore, the analgesic effect was lower after platinum salt–induced CIPN in comparison to other chemotherapies.[9]

In addition to the recorded measures of pain, patients also reported significant improvements in sleep, QoL, and sensory function[23,32,36,59] and shrinkage in the painful area after multiple treatments[23,62,65] (**Table 2**).

Further cross-study analyses of the efficacy of the HC capsaicin patch in terms of response (proportion of patients with ≥30% pain reduction) and PGIC improvements are shown in **Figures 3A and B**. Regarding analgesic response and PGIC-related improvement, the HC capsaicin patch was more effective than the control in all analyzed RCTs, with statistically significant differences in all RCTs measuring PGIC and most RCTs with respect to analgesic response (**Figs. 3A and B**). Moreover, the RCT investigating multiple treatments showed the highest response rate, with ≥30% response observed in 67% of the patients. By contrast, response rates varied between 34% and 47% in studies focusing on single treatments.[6,34,55,59,68,70] This observed impact of multiple treatments is also reflected by the number needed to treat (NNT), which ranges from 6.3 to 12.5 for single treatments as opposed to a more favourable NNT of 3.8 for multiple treatments (NNT calculated for a ≥30% pain intensity reduction). Furthermore, in the multiple treatment RCT, patients who received 7 treatments of the HC capsaicin patch showed a progressive increase in ≥30% response from 32% after the first treatment to 74% after the seventh treatment.[68] It is noteworthy that this RCT used standard of care (SOC) as a control, incorporating a range of medications, including active comparators like pregabalin or gabapentin. By contrast, single-treatment RCTs were controlled with low capsaicin (0.04%) or placebo patches.

A summary of the overall efficacy and safety of the HC capsaicin patch as reported in clinical trials (including non-RCT trials, eg, prospective open-label studies and retrospective data analyses) is provided in **Figure 4**. Across numerous studies, the HC capsaicin patch consistently demonstrated significant pain relief (as assessed by NPRS or visual analogue scale [VAS]) for diverse pNeP conditions.[2–4,6–8,10,20,23,28,29,34,36,37,39,42,47,50,54–57,59,65,67–71,73] Positive impacts on QoL and functionality (PCIG/CGIC, sleep, patient-reported outcomes [PRO]) were observed in patients with PDPN, HIV-AN, and pNeP.[2,6,9,13,17,23,29,34,36,37,39,42,46–48,50,51,56,59,67,68,70–73] In only 2 of the studies (1 study in HIV-AN and 1 study in PHN), the primary efficacy endpoints were not reached.[13,72] The effect observed in the control groups of these studies was high and could be at least partly due to the short pNeP duration (<6 months) known to be associated with higher rates of spontaneous remission. Further study data revealed noninferiority of the HC capsaicin patch to systemic medication in terms of pain intensity (in patients with pNeP and PDPN)[28,64] and superiority to systemic medication regarding tolerability (in patients with pNeP and PDPN)[1,14,28,64] and PRO (patients with pNeP).[66] Some studies have also found that the HC capsaicin patch can reduce or replace the need for systemic pain therapies,[22,36,39] which may also have a positive impact on QoL.

Repeated treatment with the HC capsaicin patch resulted in progressive response as evidenced by an improved reduction in pain (CRNP, CIPN, pNeP),[9,17,22,23,42,56,62,67,68] shrinking of the painful area (PNI, pNeP),[14,23,25,26,29,46,62,65] and increase in treatment intervals (pNeP).[42]

In addition, in indications such as CIPN, PDPN, and NFCI, HC capsaicin patch–mediated nerve defunctionalization followed by regeneration of cutaneous nociceptors has been demonstrated,

Table 1

Overview of the studies included in the review by indication.

Study (first author, y)	Indication	Study type	Total number of patients and treatments/follow-up
Postherpetic neuralgia (PHN)			
*Irving et al. Pain Med 2011;12(1):99–109	PHN	RCT	n = 416 1 treatment/12 wk
*Backonja et al. Pain Med 2010;11(4):600–608†	PHN	RCT	Blinded phase: n = 38, extension: n = 24 1 treatment/4 wk randomized/extension: 1 patch randomized + up to 3 patches/44 wk
*Webster et al. J Pain 2010;11(10):972–982	PHN	RCT	n = 299 1 treatment/12 wk
*Webster et al. BMC Neurol 2010;10:92	PHN	RCT, multicenter	n = 155 1 treatment/12 wk
*Backonja et al. Lancet Neurol 2008;7(12):1106–1112	PHN	RCT	n = 402 1 treatment/12 wk
Postsurgical and posttraumatic nerve injury (PNI)			
‡Mullins et al. Ir J Med Sci 2022;191(2):859–864†	PNI	Prospective observational, open label (OL)	n = 12 1 treatment/12 wk (up to 3 treatments in individual patients)
‡Bischoff et al. PLoS One 2014;9(10):e109144	PNI	RCT	n = 46 1 treatment/3 mo
HIV-associated neuropathy (HIV-AN)			
*Simpson et al. Clin J Pain 2014;30(2):134–142†	HIV-AN	OL extension of Simpson et al. Neurology 2008;70(24):2305–2313	n = 307 Up to 3 patches at 12 wk interval/52 wk (12 wk randomized +40 wk extension)
*Brown et al. AIDS Res Ther 2013;10(1):5	HIV-AN	Pooled analysis of 2 Phase III studies (Clifford et al. J Acquir Immune Defic Syndr 2012;59(2):126–133; Simpson et al. J Pain Symptom Manage 2008a;35(3):299–306)	n = 697 1 treatment/12 wk
*Clifford et al. J Acquir Immune Defic Syndr 2012;59(2):126–133	HIV-AN	RCT	n = 494 1 treatment/12 wk
Simpson et al. J Pain Symptom Manage 2008;35(3):299–306†	HIV-AN	OL pilot study	n = 12 1 treatment/12 wk (up to 4 treatments in individual patients)
*Simpson et al. Neurology 2008;70(24):2305–2313	HIV-AN	RCT	n = 307 1 treatment/12 wk
Painful diabetic peripheral neuropathy (PDPN)			
‡Anand et al. Front Neurol 2022;13:998904	PDPN	RCT (PDPN cohort)	n = 50 1 treatment/3 mo
*Simpson et al. J Pain 2017;18(1):42–53	PDPN	RCT	n = 369 1 treatment/12 wk
*Vinik et al. Curr Med Res Opin 2019;2:388–401†, Vinik et al. BMC Neurol 2016;16(1):251	PDPN	OL-RCT	n = 468 HC capsaicin patch: 1–7 treatments at ≥8-wk interval/52 wk
Chemotherapy-induced peripheral neuropathy (CIPN)			
Bienfait et al. Cancers (Basel) 2023;15(2)†	CIPN	Retrospective real-world data, monocenter, observational	n = 57 Mean number of HC capsaicin patch treatments per patient: 3.2 (median: 2) treatments/data collected after every patch treatment between January 2014 and December 2021
‡Anand et al. J Pain Res 2019;12:2039–2052	CIPN	OL, monocenter, longitudinal	n = 16 1 treatment/3 mo
Filipczak-Bryniarska et al. Med Oncol 2017;34(9):162	CIPN	Prospective single center	n = 18 1 treatment/12 wk
Neuropathic spine-related back pain (NBP)			
Olusanya et al. Pain Med 2023;24(1):71–78†	NBP	RCT (single-blind, crossover)	n = 11 2 treatments/24 wk
*Baron et al. Curr Med Res Opin 2017;33(8):1401–1411	NBP	Data analysis of subpopulation from QUEPP study (Maihöfner et al. Curr Med Res Opin 2013;29(6):673–683)	n = 50 1 treatment/12 wk
Zis et al. Pain Physician 2016;19(7):E1049–1053	NBP	Prospective open-label study	n = 90 1 treatment/12 wk

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Table 1 (*continued*)

Overview of the studies included in the review by indication.

Study (first author, y)	Indication	Study type	Total number of patients and treatments/follow-up
Other indications			
Mathieu et al. Joint Bone Spine 2023;90(3):105508†	Hand osteoarthritis (HOA) with neuropathic pain	Prospective multidisciplinary consultation	n = 8 1 treatment/15 d (up to 3 treatments)
Anand et al. Front Neurol 2021;12: 722875	Non-freezing cold injury (NFCI)	OL longitudinal	n = 16 1 treatment/3 mo
Glaros et al. Blood 2020;136: 36–37†	Neuropathic pain following sickle cell disease (age: 14–21 y)	OL exploratory	n = 10 3 treatments (during visits 1, 3, and 5)/7 visits at 6 wk intervals (42 wk)
Aitken et al. Pain Med 2017;18(2): 330–340	Neuropathic pain from critical ischemia with end-stage renal disease (ESRD)	Prospective observational cohort study	n = 20 1 treatment/12 wk
Levesque et al. Pain Physician 2017; 20(1):E161–E167†	Pelvic neuralgia	Prospective, observational	n = 60 Up to 3 treatments
Multiple pNeP indications			
Cancer-related neuropathic pain (CRNP)			
‡Dupoiron et al. J Pain Res 2022; 15:241–255†	CRNP, breast cancer (most frequently caused by surgery, chemotherapy, and radiotherapy)	Retrospective chart review	n = 279 Average number of HC capsaicin patch treatments: 4.1 (median 3)/retrospective (time period from January 2014–October 2020)
Others			
Santos et al. Br J Pain 2024;18(1): 42–56†	pNeP	Retrospective open-label study	n = 100 (n = 68 analyzed) 1–7 treatments (median: 2), time period: retrospective analysis
Sendel et al. Pain 2023;164(3): 534–542	pNeP	Noninterventional exploratory trial	n = 23 1 treatment/12 wk
Vieira et al. Pain Physician 2022; 25(4):E641-E647†	pNeP, PSNP, PHN, and other pNeP	Observational retrospective cohort study	n = 100 Median number of treatments: 2, with a maximum of 12 treatments per patient/ 1–3 mo after each HC capsaicin patch Treatment (from 2011 to 2019)
*§Freynhagen et al. Pain Med 2021;22(10):2324–2336†	Post-hoc analysis of STRIDE study: patients with non-diabetic neuropathic pain (Galvez et al. Clin J Pain 2017;33(10):921–931), and PACE study: patients with PDPN (Vinik et al. Curr Med Res Opin 2019;2:388–401†, Vinik et al. BMC Neurol 2016;16(1):251)	Post hoc, as-treated analysis of the prospective trials STRIDE and PACE	n = 619 STRIDE study: ≤6 treatments at 9–12 wk intervals PACE study ≤7 treatments with at least 8 wk intervals/ 52 wk follow-up
Goncalves et al. Pain Physician 2020;23(5):E541-E548	pNeP (PHN, CPSP, PTNP, complex regional pain syndrome (CRPS), HIV- associated neuropathy, lumbar neuropathic pain (LNP), trigeminal neuralgia (TN) and other neuropathies)	Retrospective observational study	n = 120 1 treatment/12 wk
*Lantéri-Minet et al. Curr Med Res Opin 2019;35(3):417–426†	Nondiabetic pNeP (mainly PTNP or PSNP)	National, longitudinal, prospective, noninterventional, OL study	n = 684 1–5 treatments at 3–4-mo interval/18 mo
‡Perrot et al. Eur J Pain 2019; 23(6):1117–1128	pNeP (mainly PSNP and PTNP, CRPS, PHN)	Prospective noninterventional multicenter stud	n = 495 (no data for n = 116 patients collected at month 3) 1 treatment with up to 4 patches/3 mo
*Hansson et al. Eur J Pain 2018; 22(5):941–950†	pNeP (because of partial nerve damage, and residual limb pain from amputations)	3 noninterventional, observational studies with identical protocols in Denmark, Norway, and Sweden	n = 412 1 or 2 treatments (interval ≥90 d)/up to 3 mo after each treatment
Tenreiro Pinto et al. Pharmacology 2018;101(5–6):290–297†	pNeP (PHN or PNI)	Retrospective study	n = 43 Number of treatments 3.7 ± 2.6/up to 7–14 d after each treatment
‡Galvez et al. Clin J Pain 2017; 33(10):921–931†	Nondiabetic pNeP (PHN, PTNP or PSNP, HIV-AN, or other pNeP)	OL single-arm safety study	n = 306 Up to 6 treatments at 9–12 wk-interval/52 wk
*Mankowski et al. BMC Neurol 2017;17(1):80†	Nondiabetic pNeP (CRNP, NBP, PNI, PHN)	Phase IV open-label, multicenter, noninterventional study	n = 429 (n = 420 treated) Up to 4 treatments at ≥90 day-interval/52 wk
‡Mainka et al. Eur J Pain 2016; 20(1):116–129	pNeP (peripheral nerve injury, polyneuropathy, postherpetic neuralgia)	Open-label study	n = 20 1 treatment/8 wk
Raber et al. Acta Neurol Belg 2015;115(3):335–343	pNeP	Prospective open-label study	n = 37 1 treatment/12 wk
Elevate			
*Haanpää et al. Eur J Pain 2016; 20(2):316–328	pNeP (PHN, PTNP, or non-diabetic painful peripheral polyneuropathy [PPP])	OL-RCT	n = 559 HC capsaicin patch: 1 treatment; pregabalin: daily/8 wk
‡§Viel et al. Pain Physician 2021; 24(6):453–463	pNeP (PHN, PTNP or non-diabetic PPP)	Database analysis of Haanpää et al. Eur J Pain 2016;20(2):316–328	n = 559 HC capsaicin patch once or pregabalin daily/8 wk

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Table 1 (*continued*)

Overview of the studies included in the review by indication.

Study (first author, y)	Indication	Study type	Total number of patients and treatments/follow-up
*§Cruccu et al. Eur J Pain 2018; 22(4):700–706	pNeP (PHN, PNI, or non-diabetic PPP)	Database analysis of a randomized, open-label, head-to-head study (Haanpää et al. Eur J Pain 2016;20(2):316–328)	n = 488 HC capsaicin patch: 1 treatment; pregabalin: daily
*§Abdulahad et al. Contemp Clin Trials Commun 2016;4: 186–191	pNeP (non-diabetic PPP, PHN, or PNI)	Database analysis of 2 non-inferiority clinical studies	n = 387 1 treatment/8 wk
‡Gustorff et al. Scand J Pain 2013;4(3):138–145	pNeP (PSNP/PTNP, PHN, and other pNeP)	Prospective, nonplacebo-controlled, observational study	n = 57 1 treatment/12 wk
QUEPP			
*Maihöfner et al. Curr Med Res Opin 2013;29(6):673–683	PHN, PSNP or PTNP, polyneuropathy, mixed pain syndromes	National, multicenter, prospective, non-interventional study	n = 1044 1 treatment/12 wk
*§Maihöfner et al. Eur J Pain 2014;18(5):671–679	Non-diabetic pNeP (73.1% of patients had a mono-NP, mainly PHN, PSNP, and PTNP)	Database analysis of Maihöfner et al. Curr Med Res Opin 2013;29(6):673–683	Subgroups of n = 1044 patients according to pain duration 1 treatment/12 wk
*§Höper et al. Curr Med Res Opin 2014;30(4):565–574	PHN, PSNP or PTNP, polyneuropathy, mixed pain syndromes	Database analysis of Maihöfner et al. Curr Med Res Opin 2013;29(6):673–683	n = 1044 1 treatment/12 wk
‡Wagner et al. Pain Med 2013; 14(8):1202–1211†	NeP (Facial NeP [severe trigeminal neuralgia in V2], polyNP, PHN, and PSNP and PTNP, radiculopathy, failed back surgery syndrome)	Retrospective analysis	n = 68 1–4 patches at 90 day-interval/8 or 12 wk follow up after first treatment (+ total time measured between treatments
*Webster et al. Diabetes Res Clin Pract 2011;93(2):187–197	Mainly PHN and painful diabetic NP	OL study	n = 117 1 treatment/12 wk
‡Simpson et al. J Pain Symptom Manage 2010;39(6): 1053–1064†	PHN and painful HIV-AN	OL study	n = 106 Up to 4 treatments (60 or 90 min) at 12 wk interval/1 y

Among others, the involvement of a pharmaceutical sponsor may induce bias, and therefore, sponsoring is specified.
* Studies conducted by pharmaceutical industry.
† Repeated HC capsaicin patch treatment trial.
‡ Investigator-initiated trials supported by a sponsor.
§ Studies represent post hoc or subgroup analyses of original studies. To avoid double evaluation of the same patients, these studies were not counted for Figure 2.

suggesting a potential for disease modification[3–5] (**Table 2**, **Fig. 4**).

Finally, tolerability of the HC capsaicin patch was generally high in the included studies. In RCTs, most reported treatment-emergent adverse events (TEAEs)/adverse events (AEs) were application-site specific (eg, burning sensation or pain, and erythema), generally mild to moderate in severity, and transient (**Table 3**). In some cases, a temporary increase in blood pressure (by an average of <8.0 mm Hg) was reported during treatment.[6,17,59] However, this seems to be a result of an increase in pain because of treatment, which may occur during and shortly after HC capsaicin patch application.[60] Overall, no relevant or sufficiently reliable differences in tolerability were observed across the study indications and with multiple treatments. In addition, repeated treatment does not increase the risk of negative effects on sensory perception, with most patients maintaining or experiencing improved sensitivity over the course of the study.[23,67] Study dropouts because of AEs were reported in 1 RCT. In this study, 2 patients (0.9%) prematurely discontinued treatment because of increased PHN pain, with both events considered treatment related.[70] An analysis of data from a direct comparison between the HC capsaicin patch and pregabalin showed a greater incidence of TEAEs with the HC capsaicin patch; however, they were of short duration and occurred for 3 days after application, whereas TEAEs with the oral agent pregabalin increased during dose titration and persisted to the end of the study. The burden of therapy was therefore considered higher with oral treatment compared with the topical treatment.[1] In a discrete choice experiment, patients' preferences regarding treatment with systemic or topical pain medication were obtained. A favourable benefit–risk profile with a low likelihood of systemic side effects, in particular, was a compelling factor for patients to opt for a treatment, as evidenced by this study conducted by Schubert et al.[53] A recent study found that 53% of

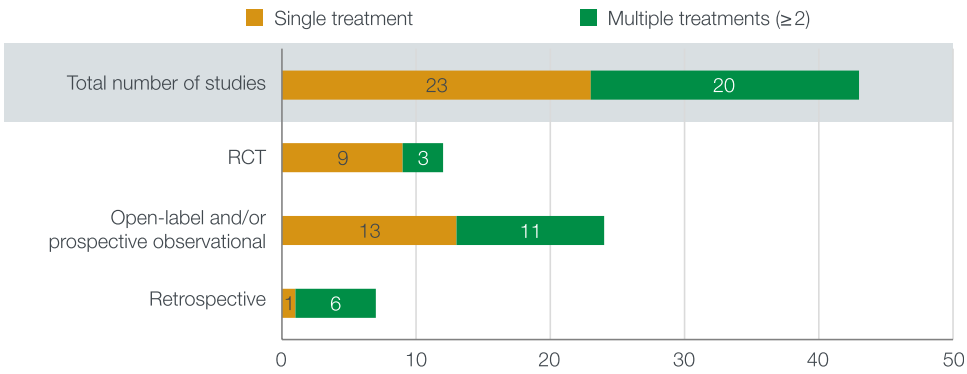

Figure 2. Key characteristics of the analyzed studies extracted from literature search (meeting the inclusion and exclusion criteria).

Table 2

Randomized controlled trials with single and multiple treatments and long-term multiple treatment trials (numbers of patients are indicated): efficacy based on the number of high-concentration capsaicin patch treatments.

Trial (indication)	No. of treatments/duration of study; number of patients per study arm	NPRS/Response (% pts)	PGIC/CGIC improvement (% pts)	Sleep/QoL
Single treatment (RCTs only)				
Anand et al. Front Neurol 2022;13:998904 (PDPN)	1 treatment, 3 mo HC capsaicin patch + SOC n = 32 SOC alone n = 18	Significant reduction of mean daily pain intensity from week 3 in PDPN patients receiving HC capsaicin patch plus SOC compared with SOC alone (mean reduction in NPRS scores from baseline to month 3: −1.97, P = 0.0001 and −0.58, P = 0.11, respectively) Correlation of pain relief after HC capsaicin patch treatment with the increase in nerve fibres (PGP9.5- and GAP43-positive IENF, P = 0.0008 and P = 0.004, respectively); no increase in nerve fibres in patients without pain relief		Significant improvement in sensation of warmth only upon HC capsaicin patch plus SOC treatment (P = 0.02); positive correlation with the improvement in the overall pain rating determined by SF-MPQ (P = 0.04)
Simpson et al. J Pain 2017; 18(1):42–53 (PDPN)	1 treatment, 12 wk HC capsaicin patch: n = 186, control† n = 183	≥30% responder rate: 41% (HC capsaicin patch) vs 32% (control)* ≥50% responder rate: 22% (HC capsaicin patch) vs 19% (control)	PGIC‡ 41% (HC capsaicin patch) vs 30% (control)	Sleep interference NRS score −34% (HC capsaicin patch) vs −25% (control)*
Irving et al. Pain Med 2011; 12(1):99–109 (PHN)	1 treatment, 12 wk HC capsaicin patch: n = 212, control n = 204	≥30% responder rate: 47% (HC capsaicin patch) vs 35% (control)* ≥50% responder rate: 29% (HC capsaicin patch) vs 20% (control)*	PGIC§ 61% (HC capsaicin patch) vs 47% (control)** CGIC§ 63% (HC capsaicin patch) vs 48% (control)**	
Webster et al. J Pain 2010a;11(10):972–982 (PHN)	1 treatment, 12 wk HC capsaicin patch: n = 222, control n = 77	≥30% responder rate: 37% (HC capsaicin patch) vs 29% (control) ≥50% responder rate: 23%–27% (HC capsaicin patch) vs 10% (control) Pooled dosage groups (30, 60 and 90 min)	PGIC§ 55% (HC capsaicin patch) vs 41% (control) CGIC§ 52% (HC capsaicin patch) vs 42% (control) Pooled dosage groups (30, 60 and 90 min)	
Webster et al. BMC Neurol 2010b;10:92 (PHN)	1 treatment, 12 wk HC capsaicin patch n = 102, control n = 53	≥30% responder rate: 45% (HC capsaicin patch) vs 45% (control) ≥50% responder rate: each 36%	PGIC‡ 43% (HC capsaicin patch) vs 30% (control) CGIC‡ 46% (HC capsaicin patch) vs 32% (control)	
Backonja et al. Lancet Neurol 2008;7(12): 1106–1112 (PHN)	1 treatment, 12 wk HC capsaicin patch n = 206, control n = 196	≥30% responder rate: 42% (HC capsaicin patch) vs 32% (control)*	PGIC§ 55% (HC capsaicin patch) vs 43% (control)*	
Simpson et al. Neurology 2008b;70(24): 2305–2313 (HIV-AN)	1 treatment, 12 wk HC capsaicin patch: n = 225, control n = 82	≥30% responder rate: 34% (HC capsaicin patch) vs 18% (control)** Pooled dosage groups (30, 60 and 90 min)	PGIC§ 67% (HC capsaicin patch) vs 31% (control)*** CGIC§ 66% (HC capsaicin patch) vs 37% (control)** Pooled dosage groups (30, 60 and 90 min)	Improvements in the Gracely Pain Scale**, SF-MPQ**, and BPI composite score in all 3 HC capsaicin patch groups
Multiple treatment studies				
Bienfait et al. Cancers (Basel) 2023;15(2) (CIPN)	3.2 treatments per patient (mean), between January 2014 and December 2021 HC capsaicin patch: n = 57		CGIC Important or complete analgesic effect: 61 treatments (43.9% patients) The analgesic effect was significantly greater For pain duration <2 y* In second vs third line* After ≥3 treatments* The analgesic effect was significantly lower After platinum-salt-induced CIPN*	

(*continued on next page*)

Table 2 (*continued*)

Randomized controlled trials with single and multiple treatments and long-term multiple treatment trials (numbers of patients are indicated): efficacy based on the number of high-concentration capsaicin patch treatments.

Trial (indication)	No. of treatments/duration of study; number of patients per study arm	NPRS/Response (% pts)	PGIC/CGIC improvement (% pts)	Sleep/QoL
Santos et al. Br J Pain 2024;18(1):42–56 (pNeP)	1–7 treatments, retrospective analysis HC capsaicin patch: n = 100	66.2% reported pain improvement after treatment with capsaicin 8% patch; all patients who underwent between 4 and 6 treatments claim improvement in pain	PGIC§ 1st treat. (n = 17): 29% 2nd treat. (n = 22): 73% 3rd treat. (n = 13): 69% 4th treat. (n = 4): 100% Highest improvement in patients with postsurgical or trauma NP	
Dupoiron et al. J Pain Res 2022;15:241–255 (CRNP)	4.1 treatments per patient (mean) HC capsaicin patch: n = 279		CGIC Important or complete analgesic effect: 82%; complete effect: 52% The analgesic effect was greater The earlier the treatment was initiated As second- or third-line treatment With ≥2 treatments in initial nonresponders	
Vieira et al. Pain Physician 2022;25(4):E641-E647 (pNeP)	2 treatments (median); maximum: 12 treatments per patient HC capsaicin patch: n = 100	≥30% responder rate 69% (from baseline to last treatment), 26% with nearly complete pain relief (NRS ≤ 1)		Absolute shrinking in the painful area (from baseline to last treatment): −29.5 cm^{2***} Absolute reduction in allodynia from baseline to last treatment: −2.5 cm^{2***}
Lantéri-Minet et al. Curr Med Res Opin 2019; 35(3):417–426 (non-diabetic pNeP)	1–5 treatments at 3–4-mo interval, 18 mo HC capsaicin patch: n = 684	Reduction in NRS 0.8 points (11%) and reduction in NPSI compared with baseline: 8.0 points (6 mo after last treatment) Success and moderate success rates increased with number of treat.: 1st treat.: 22% and 40% ≥3 treat.: 26% and 47%	PGIC§ 58% (6 mo after last treatment)	Clinically relevant improvement in health-related quality of life (EQ-5D-5L) at end of study
Vinik et al. Curr Med Res Opin 2019;2:388–401, Vinik et al. BMC Neurol 2016;16(1):251 (PDPN)	1–7 treatments at ≥8-wk interval, 52 wk HC capsaicin patch: 30 min plus SOC‖ n = 156, 60 min plus SOC‖ n = 157 SOC‖ alone n = 155	≥30% responder rate: 67% (HC capsaicin patch, 30 min) and 68% (HC capsaicin patch, 60 min) vs 41% (SOC‖) ≥50% responder rate: 45% (HC capsaicin patch, 30 min) and 48% (HC capsaicin patch, 60 min) vs 24% (SOC‖) Increase in the ≥30% responder rate in patients with 7 treatments (n = 167): 1st treat.: 32% 2nd treat.: 47% 3rd treat.: 50% 7th treat. : 74%	PGIC§ 69% (HC capsaicin patch) vs 39% (SOC‖)	Greater reduction in total BPI-DN Pain Interference and Pain Intensity Index in both HC capsaicin patch plus SOC groups vs SOC‖ alone from baseline to end of study Greater reduction in both HC capsaicin patch plus SOC groups vs SOC alone from baseline to end of study in Norfolk QoL-DN score which was even more pronounced in patients who had treatment every 2 mo
Tenreiro Pinto et al. Pharmacology 2018; 101(5–6):290–297 (pNeP)	3.7 ± 2.6 treatments, up to 7–14 d after each treatment HC capsaicin patch: n = 43	30% responder rate: 65% after last treatment compared with baseline Reduction in NRS score from baseline: −33% after the first treatment vs −40% after the last treatment*		Absolute shrinking in the painful area (from baseline to last treatment: 59.0 cm^{2**})
Galvez et al. Clin J Pain 2017;33(10):921–931 (non-diabetic pNeP)	Up to 3 patches at 12-wk interval, 52 wk HC capsaicin patch: n = 306		PGIC Very much improved or much improved: 32% by end-of-study; in patients with 4 treatments: 48% 4 wk after their fourth treatment	By end of study, 25.2% to 32.0% of patients reported improvement in a sensory modality Area of allodynia or hyperalgesia: 241.9 cm^2 (baseline) vs 219.9 cm^2 (end of study); in patients with 4 treatments: 227.4 cm^2 (baseline) vs 213.4 cm^2 (end of study) Area of spontaneous pain: 365.0 cm^2 (baseline) vs 322.7 cm^2 (end of study); in patients with 4 treatments: 310.1 cm^2 (baseline) vs 268.5 cm^2 end of study

(*continued on next page*)

Table 2 (*continued*)

Randomized controlled trials with single and multiple treatments and long-term multiple treatment trials (numbers of patients are indicated): efficacy based on the number of high-concentration capsaicin patch treatments.

Trial (indication)	No. of treatments/duration of study; number of patients per study arm	NPRS/Response (% pts)	PGIC/CGIC improvement (% pts)	Sleep/QoL
Mankowski et al. BMC Neurol 2017;17(1):80 (non-diabetic pNeP)	Up to 4 treatments at ≥90 d-interval, 52 wk HC capsaicin patch: n = 429	30% responder rate 1st treat. (n = 412): 44% 2nd treat.(n = 161): 49% 3rd treat. (n = 59): 49% 50% responder rate 1st treat. (n = 412): 26% 2nd treat. (n = 161): 30% 3rd treat. (n = 59): 31%	PGIC§ 1st treat. (n = 367): 61% 2nd treat. (n = 150): 75% 3rd treat. (n = 47): 79%	
Simpson et al. Clin J Pain 2014;30(2):134–142 [HIV-AN]	Up to 4 treatments at 12-wk interval, 52 wk HC capsaicin patch: n = 272 (open-label phase)	≥30% responder rate: 38% (from baseline to weeks 2–12 after a single treatment) ≥50% responder rate: 25% (from baseline to weeks 2–12 after a single treatment) Response rates after single treatment were comparable with those after final treatment for patients with multiple treatments	PGIC§ 1st treat. (n = 79): 59% 2nd treat. (n = 60): 62% 3rd treat. (n = 57): 68% 4th treat. (n = 30): 76% CGIC§ 1st treat.(n = 79): 61% 2nd treat. (n = 60): 58% 3rd treat. (n = 57): 70% 4th treat. (n = 30): 80%	
Simpson et al. J Pain Symptom Manage 2010; 39(6):1053–1064 (PHN and painful HIV-AN)	Up to 4 treatments at 12-wk interval, 48 wk HC capsaicin patch: n = 106		PGIC§ Week 12: 56% (PHN), 74% (HIV-AN) Week 48: 75% (PHN), 80% HIV-AN	PHN and HIV-AN patients reported improvement in all 5 categories of the BPI subject-rated questionnaire at week 48/end of study

* $P \leq 0.5$ vs control; **$P \leq 0.01$ vs control; ***$P \leq 0.001$ vs control.
† Control consisted of a low-concentration 0.04% capsaicin patch, except in case of placebo patch.
‡ Very much or much improved.
§ Very much, much, or slightly improved.
‖ Control consisted of a low-concentration 0.04% capsaicin patch, except in case of SOC; for more details see Vinik et al. Curr Med Res Opin 2019;2:388–401.
BPI, Brief Pain Inventory; CGIC, Clinical Global Impression of Change; EQ-5D, Health-related quality of life; IENF, intraepidermal nerve fiber; Norfolk QoL-DN, Norfolk quality of life for diabetic neuropathy; NPRS, numeric pain rating scale; NPSI, neuropathic pain symptom inventory; NRS, numeric rating scale; PGIC, Patient Global Impression of Change; QoL, quality of life; SF-MPQ, Short-Form McGill Pain Questionnaire; SOC, standard of care.

patients who were randomly assigned to pregabalin expressed a desire to switch to the HC capsaicin path, whereas none of the patients randomized to HC capsaicin wished to switch to pregabalin.[16]

4. Discussion

This narrative review aims at providing a comprehensive understanding of the existing literature on the efficacy and tolerability of the HC capsaicin patch in different pNeP indications. The HC capsaicin patch has a broad label for pNeP in the European Union and approval for the treatment of PHN and PDPN in the United States. As a result, most postauthorization data in indications other than PHN and PDPN are from Europe.

In this publication, we focus on the efficacy and safety data for both single and repeat treatments with the HC capsaicin patch that are relevant to clinical practice (**Table 2**, **Figs. 3 and 4**). We emphasise the importance of repeated treatment, while also highlighting areas that warrant further investigation (see research agenda below).

Because of the selection and design of the included studies (see Methods), this narrative review carries a risk of bias. Although RCTs were included for their controlled and internally valid evidence, their limited reflection of real-world scenarios may reduce the generalizability of the findings.[30] To fill data gaps and capture treatment outcomes in diverse populations and settings, prospective and retrospective observational studies using real-world data were also included.[61] However, observational studies, especially retrospective studies, are prone to selection bias and inadequate control of confounding factors. This review should be as comprehensive as possible and therefore also considers studies with small patient numbers and niche indications. Because many of these studies were open label and also lacked control/placebo arms, bias might be introduced, and no direct conclusions or recommendations were derived from these data sets. In addition, the narrative nature of the review itself—while offering the opportunity to be the most comprehensive—introduces limitations such as subjectivity, lack of systematic methodology and quality assessment, and the possibility of bias.

4.1. Common denominators for efficacy and tolerability of the HC capsaicin patch based on outcomes from clinical studies

Based on this review, the HC capsaicin patch demonstrates consistent efficacy in different pNeP conditions, although the underlying pathophysiological mechanisms are diverse and yet not fully understood. This suggests a potential role for the TRPV1 receptor in all pNeP conditions. So far, numerous clinical studies have examined the efficacy and tolerability of the HC capsaicin patch in treating pNeP of several origins. It is crucial to identify a common denominator within these data to enhance our understanding of the broad applicability of the HC capsaicin patch.

Regarding pain response, the existing data favor early initiation of treatment,[17,32,40] but even after prolonged pain duration, therapy can still be effective.[17,40] Spontaneous remission in early disease stage cannot be ruled out and might play a role in the results obtained. More reliable data are available regarding the efficacy of the HC capsaicin patch with repeated use.[9,17,22,42,51,56,62,68] Besides progressive response upon retreatment, initial nonresponders can achieve outcomes that are comparable to those observed in early responders in terms of

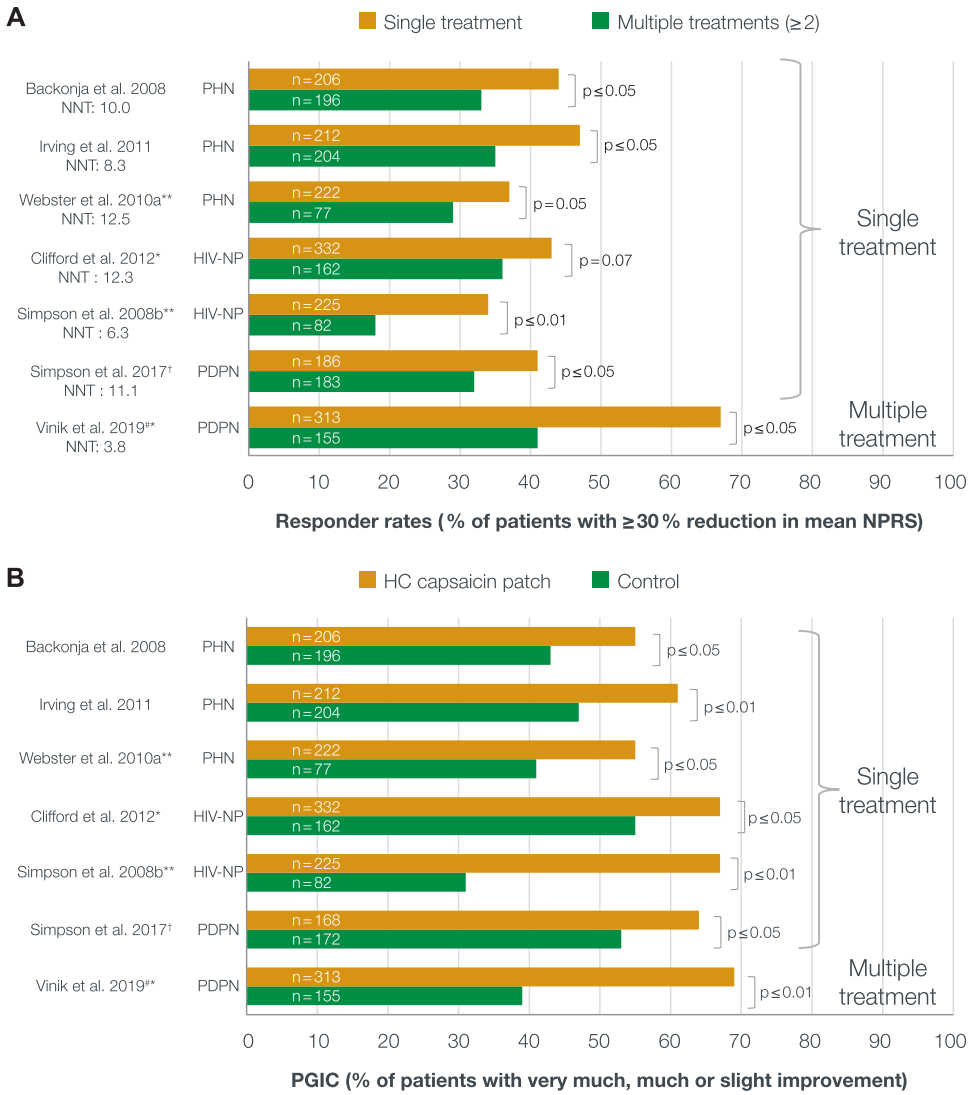

Figure 3. Efficacy of the HC Capsaicin patch. Response rates and PGIC from clinical studies. (A) ≥30% reduction in mean NPRS at week 12 after single treatment and week 52 after multiple treatments across pNeP conditions (RCTs only and response data available); modified from References 6,13,34,55,59,68,70. (B) PGIC response rates of patients with very much, much, or slight improvement at week 12[6,13,34,55,59,70] and week 52[68] after single or multiple treatment with HC capsaicin patch, respectively. Control consisted of a low-concentration 0.04% capsaicin patch, except in case of †(placebo patch) and #(SOC, standard of care; for more details see [Ref. 68]); *pooled data from 30 to 60 minutes of HC capsaicin patch treatment; **pooled data from 30, 60 and 90 minutes of HC capsaicin patch treatment. HC, high concentration; NPRS, numeric pain rating scale; PGIC, patient global impression of change; pNeP, peripheral neuropathic pain; RCT, randomized controlled trial; SOC, standard of care.

reduced pain intensity, improved QoL, and enhanced sleep quality.[22] It can be speculated that repeated treatment using the HC capsaicin patch may enhance the regenerative properties of nerve tissue, which could be the reason for the persistent and long-lasting pain relief. This is consistent with the documented nerve regenerative properties associated with HC capsaicin.[3–5] However, further research will be necessary to confirm and understand these results.

In addition to reducing pain, retreatment may lead to shrinkage of the affected area[14,23,25,26,29,46,62,65] and prolongation of the treatment intervals[42] (**Fig. 4**), which also suggests progressive response. In this context, it should also be noted that the combined NNT referring to studies described in **Figure 3A** upon single treatment was 10.1 (6.3–12.5), whereas the NNT after repetitive retreatment decreased to 3.8.[68] In **Figure 3A**, the NNTs for a ≥30% reduction in pain intensity are provided, but similar results were obtained for a ≥50% reduction as reported by Finnerup et al. The combined NNT for a ≥50% reduction in pain intensity was 10.6 (7.4–19.0) for a single treatment with the capsaicin patch compared with 3.6 (3.0–4.4) for tricyclic antidepressants, 6.4 (5.2–8.4) for the selective serotonin reuptake inhibitors duloxetine and venlafaxine, 7.7 (6.5–9.4) for pregabalin, and 7.2 (5.9–9.2) for gabapentin.[21] This suggests that the NNT may vary not only with the specific patient population and outcome being measured but also with the repetition of treatment, which is also a challenge when comparing systemic oral therapies with a topical patch formulation.

There is a strong clinical relevance to establish a responder profile, not only to motivate patients who meet the criteria but also to avoid unnecessary treatment of those suspected to be nonresponders. However, currently available clinical data are not yet sufficient to establish a reliable responder profile. So far, some indicators are available that could be used for a future responder profile after sufficient confirmation by additional studies. Besides aforementioned parameters, such as short duration of pain, these indications comprise the presence of specific neuropathic

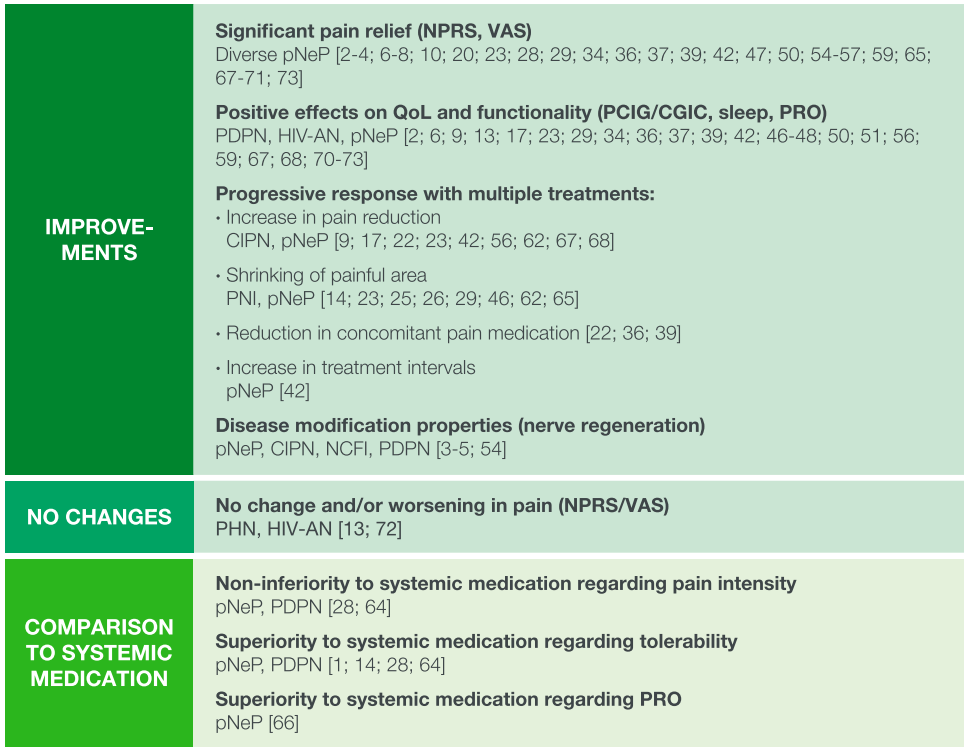

Figure 4. Summary of HC capsaicin patch efficacy and safety/tolerability data across pNeP conditions. HC, high concentration; pNeP, peripheral neuropathic pain.

symptoms, including cold and pinprick hyperalgesia,[41] burning, and pressure-evoked pain,[32] as possible predictors for response and allodynia as possible predictor for non-response.[26] Nevertheless, based on the clinical experience of the authors, burning pain upon patch application does not appear to be predictive of a treatment response. Höper et al.[32] found that the association of sensory symptoms and treatment response aids in understanding the mechanism of action of high-concentration capsaicin. However, according to the authors, it is not feasible to use sensory symptom patterns to predict treatment response to the HC capsaicin patch on an individual level.[32]

4.2. Tolerability

The tolerability profile of the HC capsaicin patch is characterized mainly by local and transient application site reactions. As a result, treatment burden is lower than with alternative oral therapies.[1]

In RCTs, the most commonly reported TEAEs were application site reactions. Other TEAEs, such as gastrointestinal complaints, were less frequent and only showed differences from the control group in individual small-scale studies (**Table 3**).

Patient preference studies suggest that patients may prefer topical treatments over oral treatments.[53] Given the benefit–risk profile of the HC capsaicin patch treatment, it would be logical to start treatment of pNeP with the HC capsaicin patch, which is rapid acting and does not impose a considerable burden of therapy, before moving on to an oral pharmacological treatment if the patch does not work.[33] Furthermore, the HC capsaicin patch is also an ideal (early) add-on therapy option for patients with neuropathic pain due to its exceptionally high safety profile.

In few studies, treatment with the HC capsaicin patch has been shown to reduce the use of concomitant neuropathic pain medications, particularly opioids and antiepileptic drugs, following both single and repeated treatments.[22,39] More recently, a retrospective chart review study evaluating the effects of repeated HC capsaicin patch treatment on concomitant pain medications reported a statistically significant decrease in the mean daily opioid dose. No significant changes were observed in the daily doses of anticonvulsants, including pregabalin and gabapentin. However, the authors noted that the observed reduction in gabapentin use, although not statistically significant, may still hold clinical relevance and pregabalin use was often maintained due to its favorable impact on sleep.[35] These findings suggest that the HC capsaicin patch may contribute to a reduction in the need for systemic medications, which are often associated with increased side effects and risks with long-term use.

4.3. Research agenda for open questions with necessity of future research/studies

A key question that remains is whether specific patient characteristics can serve as predictive indicators for the response to HC capsaicin patch therapy. So far, there is no clear answer to this question, except for the recognition that repeated treatment is beneficial for many patients, and that starting treatment early may increase its efficacy, but starting later does not rule out success. In this context, clarifying the mechanism by which the HC capsaicin patch induces nerve regeneration or modifies disease progression could be valuable. This may help to understand which patient groups respond particularly well and/or early to the therapy and for which patients success is late or unlikely. However, confirming the disease-modifying potential of the HC capsaicin patch remains crucial. This will require further research in larger cohorts and with multiple treatments, as current data remain limited by small sample sizes and the possibility of technical measurement fluctuations or spontaneous reinnervation.

Another open question concerns the potential capability of the HC capsaicin patch to improve the negative symptoms of pNeP,

Table 3

Tolerability of the high-concentration capsaicin patch in randomized controlled trials with single and multiple treatments.

Main (TE) AEs	No. of studies (References)	Pooled number of patients affected/ pooled total number of patients (%)		Comments
		HC capsaicin	Control*	
Application site reactions				• There was no indication of deterioration in sensory perception of sharp, cold, warm, or vibration stimuli[4]
Burning sensation	3[3,4,6]	47/513 (9.2%)	6/318 (1.9%)	
Pain	6[1−6]	318/1152 (27.6%)	114/796 (14.3%)	
Erythema	4[1−2,4,6]	393/705 (55.7%)	269/637 (42.2%)	• An increase in mean NPRS scores was evident during the HC capsaicin patch application; after completion of the treatment, scores declined, returning to near pre-procedure levels (+0.4) at 85 min after patch removal. By the evening of the treatment day, mean NPRS scores were decreased below baseline in both the HC capsaicin patch and control groups[2]
Pruritus	5[1−3, 5-6]	89/966 (9.2%)	29/613 (4.7%)	
Oedema/swelling	5[1−3, 5-6]	67/966 (6.9%)	15/613 (2.4%)	
Papules	5[1−3, 5-6]	53/966 (5.5%)	16/613 (2.6%)	
Gastrointestinal disorders				
Nausea	5[1−3, 5-6]	42/966 (4.3%)	16/613 (2.6%)	
Vomiting	4[1−3,5]	22/864 (2.5%)	6/560 (1.1%)	
Diarrhoea	2[3,5]	13/447 (2.9%)	6/159 (3.8%)	
Proportion of patients with (TE) AEs	6[1−6]	866/1152 (75.2%)	529/796 (66.5%)	• HC capsaicin patch did not result in detectable changes in warm, sharp, or vibratory sensation, or deep tendon reflexes[3]

* Patients in the control groups either received placebo patch[4] or low-concentration (0.04%) capsaicin patch.[1-3, 5-6] All trials analyzed a single treatment with HC capsaicin patch over a 12-week period.

[1]Backonja et al. Lancet Neurol 2008;7(12):1106–12.[6]

[2]Irving et al. Pain Med 2011;12(1):99–109.[34]

[3]Simpson et al. Neurology 2008;70(24):2305–13.[55]

[4]Simpson et al. J Pain 2017;18(1):42–53.[59]

[5]Webster et al. J Pain 2010;11(10):972–82.[70]

[6]Webster et al. BMC Neurol 2010;10:92.[72]

such as numbness, or nonprimarily painful symptoms, such as paresthesia. This could be addressed by consequent evaluation of these symptoms in trials in addition to the standard assessment of pNeP. Prior research provides context, and Anand et al.[4] first demonstrated the effect of the HC capsaicin patch on nerve regeneration in patients with nonpainful PDPN and an increase in nerve fibre density with treatment. However, the corresponding study arm included only 25 patients. Therefore, more research with greater numbers of participants would enhance the strength of these findings.

Further aspects of the HC capsaicin patch therapy could be subject of future research to personalise and target the treatment of patients with pNeP as much as possible and communicate realistic treatment goals. For instance, obtaining reliable data regarding a possible shortening of the application time in specific indications or patient groups (eg, patients who are more vulnerable to local side effects) without impact on efficacy would be important. Future research could specifically address this question by randomly assigning enough patients with pNeP conditions into shorter and longer application time groups per indication. This approach could include subgroups with cooling during treatment to evaluate the impact on the occurrence/intensity of adverse events (eg, burning sensation) in specific conditions since the origin of NeP varies and thus may also the (side) effects of therapy. In addition, it is still unclear whether cooling during the application of the HC capsaicin patch could affect its efficacy in either direction.

Although large RCTs[23,56] with the HC capsaicin patch achieved their primary end points, 2 studies—1 in HIV patients[13] and another in PHN patients[72]—did not meet efficacy end points for pain relief. The failure of these trials may be attributed to study design or other factors, such as short disease duration and frequent spontaneous remissions in the control group, rather than the underlying pain etiology. Nonetheless, this finding should be considered when designing and conducting future studies.

5. Conclusion

This narrative review of the current data on the HC capsaicin patch from clinical trials and real-world clinical practice indicates that it is generally very well tolerated and equally effective in treating pNeP of different origins, despite differences in the underlying cause. An exception to this rule may be HC capsaicin patch treatment following platinum salt–induced CIPN, which appears to be less effective, presumably depending on the specific pathophysiological mechanism. Further research is needed to fully understand this phenomenon.

Importantly, the data suggest broader treatment benefits beyond pain relief, including effects on sleep, various patient-reported outcomes, and shrinkage of the affected area.

In the absence of reliable predictors of response, other than early treatment initiation, there is substantial evidence to support continuation of treatment for at least 3 times, as reflected in the European Union product label. This ensures that even patients with inadequate pain relief after the first application of the HC capsaicin patch have the opportunity to respond to additional treatments. In addition, considering that not all patients respond initially, it would be relevant for clinical practice to also investigate predictors that could identify whether a patient will respond early or late to the treatment.

Further research could also lead to a more comprehensive understanding of the effects of HC capsaicin patch treatment on individual neuropathic symptoms associated with pNeP. Additional studies exploring the potential regenerative effects of the HC capsaicin patch might advance our knowledge of the pathophysiological mechanisms involved in pNeP and elucidate the mode of action through which HC capsaicin exerts its effects.

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