

# Neuropathic Pain in Breast Cancer: A Cohort Study in 279 Patients with a Total of 1141 High-Concentration Capsaicin Patch Applications

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## Research article

**Keywords:** breast cancer, capsaicin, chronic pain, effectiveness, peripheral neuropathic pain, safety, topical administration

**Posted Date:** July 6th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-631353/v1>

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## Abstract

**Background:** Peripheral neuropathic pain (PNP) is frequent in patients with breast cancer (BC) and BC survivors (BCSs). Data supporting the use of high-concentration (179 mg) capsaicin patches (HCCP) in PNP in oncology are limited. This observational study evaluated the effectiveness and safety of HCCP applications in BCSs/BC patients with PNP.

**Methods:** The study took place in the Anaesthesiology and Pain Medicine department of a French comprehensive cancer centre (Angers, France). For all patients treated with HCCP from 01-Jan-2014 to 18-Dec-2018 data have been collected retrospectively over this period, and for those continuing to receive HCCP after 18-Dec-2018 data collection continued prospectively until 14-Oct-2020. Treatment with HCCP was at the entire discretion of the treating pain specialists. Independent pain specialists completed the Clinical Global Impression of Change (CGIC) for each included patient based on data extracted from patient's electronic medical record completed by the treating pain specialist after each HCCP application.

**Results:** This study included 279 patients (1141 HCCP applications). Patients were on average 59.2 years old; 54.5% had received at least one medication for their PNP before entering the study. PNP was most frequently caused by surgery (62.4%) followed by chemotherapy (11.8%) and radiotherapy (6.5%). Patients received on average 4.1 repeated HCCP applications; 68.8% received HCCP as an add-on to systemic therapy and 27.9% as first-line therapy. A complete/important analgesic effect was reported at least once by 82.3% of patients; 6.0% of patients reported no effect at all. Complete/important effect was observed in 70.7% and 56.0% of applications in post-surgical PNP existing for <12 months and >10 years, and 52.7% and 52.3% of applications in chemotherapy- or radiotherapy-induced PNP respectively. HCCP application was associated with application site reactions in 54.4% of patients with burning sensation or pain (45.9%) and erythema (30.8%) being the most frequently reported. High blood pressure was reported in 7.2% and frostbite, likely due to local cooling, in 1.4% of patients.

**Conclusions:** This real-world chart review evaluating HCCP under usual practice conditions in a large cohort of patients provides important effectiveness and safety information to clinicians when considering topical options to treat PNP in BCSs/BC patients.

**Trial registration:** Not applicable

## Background

In 2020, breast cancer (BC) became the most commonly diagnosed cancer, with 2.3 million new cases, representing 11.7% of all new cancer cases. Worldwide, with 685,000 deaths, it was the fifth leading cause of cancer mortality [1]. Fortunately, advances in treatment, early diagnosis at all ages, and mammography screening programmes (especially in high-income countries) have decreased its mortality, which in 2018 was 4.1/100,000 for premenopausal and 48.9/100,000 for postmenopausal women [2]. Overall, looking at a group of countries with data available since 1950, BC mortality rates have decreased from 15–28/100,000 in 1990 to 11–17/100,000 in 2016 [3].

Although improved survival represents progress, it also means that increased numbers of patients live with the consequences of BC or its treatment, such as pain. According to a systematic review, the prevalence of pain during cancer treatment is 55.0%. In advanced, metastatic, or terminal disease, the prevalence of pain is 66.4%, and after curative treatment, it is 39.3% [4]. Breast cancer survivors (BCSs) frequently suffer from chronic pain following cancer treatment, with a prevalence of 41 to 74% according to different studies [5–9].

According to the International Association for the Study of Pain (IASP), chronic pain is defined as pain that lasts or recurs for more than 3 months. It may be nociceptive, due to the activation of nociceptors following damage to non-neuronal tissue and characterized by a sensation that is proportional to the amount of tissue damage, or neuropathic as a direct consequence of a lesion or disease affecting the somatosensory system [10]. BCSs/BC patients often experience mixed pain, a mixture of nociceptive pain and neuropathic pain of local and/or central origin. In these patients, pain is consistent with its origin that is often multifactorial and linked to the underlying cancer condition itself and its multimodal treatment, including surgery which may lead to intraoperative damage to nervous system structures and lymphedema, chemotherapy, radiotherapy, hormone therapy, and possible comorbid conditions [11, 12]. However, neuropathic pain is the most commonly reported pain type (60%), isolated or combined with other types of pain [9, 12].

Neuropathic pain is characterized by the following descriptors: numbness, pins and needles, burning, throbbing, unpredictability, shooting, scalding, and pruritus [13]. Even among patients with the same underlying cause of neuropathic pain, painful symptoms and signs may differ [14]. However, when present, neuropathic pain is usually chronic, persisting continuously or manifesting as recurrent episodes. It frequently causes major suffering and disability resulting in lower scores on health-related quality of life questionnaires (SF-36), worse sleep, and difficulty in maintaining full-time and part-time professional activity [5, 8, 15]. Recognizing the presence of neuropathic pain is important to inform pain management as it is more complex and difficult to treat than the nociceptive type and requires specific treatments targeting neuropathic mechanisms [9]. Moreover, early pain management is paramount to decrease the probability of central pain sensitisation as recommended by ESMO (European society for medical oncology), EONS (European Oncology Nursing Society), and EANO (European Association of Neuro-Oncology), although treatment options are limited [16].

Current approaches are pharmaceutical and non-pharmaceutical, including antidepressants (duloxetine, venlafaxine, amitriptyline), anticonvulsants (pregabalin), opioids (tramadol, other strong opioids), topical treatments (low-concentration menthol cream, capsaicin 179 mg patches, lidocaine 700 mg plasters), physical activity, functional training, and acupuncture [16, 17]. Unfortunately, the results of most treatment approaches, even if combined, are inconsistent and on average provide pain relief to less than half of the patients treated. Moreover, oral pharmaceutical treatments tend to have multiple side effects and contraindications, and do not treat the cause of the pain [17]. BCSs/BC patients usually prefer topical treatment to treat their PNP to avoid the adverse events associated with oral pharmaceutical treatments of pain [17] and the cumulative adverse events when oral PNP treatments are combined with cancer treatments such as aromatase inhibitors [18].

Capsaicin is a highly selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1). After cutaneous application, it activates the TRPV1-expressing cutaneous nociceptors and is followed by a desensitisation of cutaneous nociceptors that is thought to underlie the consequent pain relief. Sensations from non TRPV1-expressing cutaneous nerves are expected to remain unaltered, including the ability to detect mechanical and vibratory stimuli. Capsaicin-induced alterations in cutaneous nociceptors are reversible and it has been reported that normal function returns within weeks in healthy volunteers [19]. High-concentration (179 mg) capsaicin patches (HCCPs) offer an alternative local approach to the treatment of peripheral neuropathic pain (PNP) with efficacy comparable to oral centrally acting agents (duloxetine, pregabalin, gabapentin) but with the advantages of causing limited systemic side effects, having manageable local side effects, and addressing polypharmacy issues [20, 21]. Having shown this comparable effect and improved tolerability [22], recent guidelines have included it as a second-line option to treat PNP due to cancer and other causes [21]. However, published studies supporting its use in PNP in oncology are limited to small open-label studies [23, 24], and information on the use of HCCP in BC patients or BCSs, for whom a large unmet need exists, is largely absent from current literature.

Against this background, this real-world study evaluating the effectiveness and safety of this topical treatment option under usual practice conditions in a large sample of BCSs/BC patients with PNP provides important information to clinicians considering treatment options for these patients.

## Methods

### Study design and included patients

This was a monocentric real-world data study. It took place at the Anaesthesiology and Pain department of the comprehensive cancer centre, Institut de cancérologie de l'Ouest (ICO) in Angers, France. The Anaesthesiology and Pain department was experienced in the use of HCCPs (4-year experience at the start of the study in 2018). In this centre, HCCP was commonly used for the treatment of PNP as (i) first-line monotherapy, (ii) add-on therapy to previous neuropathic pain treatment, or (iii) add-on therapy to stop or reduce systematic treatment.

The study was observational. All patients with BC treated with HCCP for PNP at the study centre were included in the study, provided that their electronic medical file included detailed information on their treatment and follow-up. Patients could be BCSs or still receiving cancer therapy; they could be male or female and could have non-cancer-associated or cancer-associated pain. Their cancer-associated neuropathic pain could be due to chemotherapy, surgery, and/or radiotherapy or the evolution of the disease.

The study was initiated on 18-Dec-2018. It retrospectively included all patients who had been treated with HCCP at the study centre since 01-Jan-2014. Data were retrospectively obtained from 01-Jan-2014 to 18-Dec-2018. For patients continuing to receive HCCP treatment as of 18-Dec-2018, ongoing prospective data collection took place until the cut-off date of 14-Oct-2020 (last visit of the last patient).

### Study treatment

HCCP was administered at the discretion of the pain specialist responsible for the care of the patient in the outpatient unit at the study centre (treating physician). The treating physician identified the area to be treated with the patch, the number of patches to be used and the number of applications as well as the time interval between applications when applicable.

### Collected and analysed data

Each patient at the study centre has a unique electronic medical record. This file contains information on all consultations, treatments, prescriptions, and laboratory reports since the introduction of the electronic medical record in 2014. Per standard operating procedure, the treating physicians or their designated representatives complete this file at every patient visit.

In line with the study protocol, data were extracted from the electronic medical record of all included patients and transferred to the study database. This database contained: sociodemographic and medical data, and data on pain characteristics (aetiology, duration, location, intensity before and after treatment), HCCP treatment modalities (see above), previous and concomitant treatments, and potentially HCCP-related adverse events (AEs).

### Primary and secondary objectives

The main objective of this study was to assess the analgesic effect of HCCP applications in a BCS/BC patient. This analgesic effect was assessed by at least one pain specialist, who was not been responsible for the patient care at the study centre. The assessment was done by completing The Clinical Global Impression of Change (CGIC) based on information from the treating physician in the patients' electronic medical file. Five to eight pain specialists, depending on the period, reviewed the extracted data as this review took several months. Most medical files were evaluated by two pain specialists. In case of divergency in the evaluation of the analgesic effect between the two pain specialists, the most unfavourable evaluation was retained.

The analgesic effect was assessed after each application as compared to status before application according to the seven categories of the CGIC: (1) No effect; (2) Clinically observable effect without pain relief; (3) Minimal effect; (4) Mild effect; (5) Moderate effect; (6) Important effect; (7) Complete effect. Detailed information is provided in Table 1.

Table 1  
Physician impression of change evaluation

Analgesic effect	Definition
No effect	No change
Clinically observable effect but no pain relief	Reduction in pain area OR Decreased intensity of allodynia or hyperalgia
Minimal effect	2-point (NRS) or 1-category (VRS) decrease in mean pain intensity AND/OR 2-point (NRS) or 1-category (VRS) decrease in maximum pain intensity
Mild effect	2-point (NRS) or 1-category (VRS) decrease in mean pain intensity AND 2-point (NRS) or 1-category (VRS) decrease in maximum pain intensity AND Changes in one or more of the following criteria: - decrease in pain flare frequency (but at least 2/day) - decrease in sleep interference score (but at least 1 awake/night) - slight decrease in daily activities interference score - slight decrease in evoked pain reported by the patient - 50% decrease in the daily dose of at least one neuropathic pain medication - breakthrough pain analgesic dose reduction or cessation
Moderate effect	30–50% (NRS) or 2-category (VRS) decrease in mean pain intensity: OR 30–50% (NRS) or 2-category (VRS) decrease in maximum pain intensity AND Changes in one or more of the following criteria: - at least 50% decrease in pain flare frequency - no more sleep interference (or rare) - at least 50% decrease in daily activities interference score - cessation of at least one neuropathic pain medication OR at least 50% decrease in the daily dose of two neuropathic pain medications
Important effect	30–50% (NRS) or 2-category (VRS) decrease in mean pain intensity: OR 30–50% (NRS) or 2-category (VRS) decrease in maximum pain intensity AND Changes in two of the following criteria: - at least 50% decrease in pain flare frequency - no more sleep interference (or rare) - at least 50% decrease in daily activities interference score - cessation of at least one neuropathic pain medication OR at least 50% decrease in the daily dose of two neuropathic pain medications
Complete effect	No pain flares (or < 1/week max) Usual pain: absent No pain interference on sleep (or ≤ 1/week) No more neuropathic pain medication
NRS: numeric rating scale; VRS: verbal rating scale	

The primary evaluation criterion was the CGIC response per application. Other criteria were the maximum CGIC response per patient throughout the treatment period and the effect of pain aetiology (chemotherapy, radiotherapy, or surgery), pain duration, and position on treatment line (first, second, or third line) on CGIC response per application.

The safety profile of HCCP treatment in BCSs/BC patients was assessed by recording local and systemic AEs and local pain severity following each application as recorded in the electronic medical file of each patient.

## Sample size and statistical analysis

No statistical sample size calculation was performed for this study as it aimed to describe the overall cohort of BCs treated with HCCP for PNP at the study centre.

A descriptive analysis was done with categorical variables summarized by numbers and percentages, and continuous variables reported as means and standard deviations or by medians, interquartile and ranges, according to their distribution. Censored data were described using the Kaplan Meier method. Contingent on the descriptive analysis, sub-group comparisons were performed for the purpose of hypothesis generation. Statistical methods appropriate to data type and distribution were selected and included: chi-square test, or Fisher-exact test for categorical variables; one-way analysis of variance (ANOVA), Mann-Whitney or Kruskal-Wallis tests for continuous variables; cox model and log-rank test for censored data. All analyses were performed according to sub-groups defined by the intention to use HCCP (i.e., the conditions of use of HCCP at the study centre).

## Ethical considerations

The study was conducted in accordance with: the declaration of Helsinki; Public Health law (Acts No. 2004 – 806 of 9 August 2004 and 2006 – 450 of 18 April 2006); the law of modernization of our health system (No. 2016-41 of January 26, 2016); the law on Informatics, files and Freedoms (No. 78 – 17 of 6 January 1978 as amended); and general regulations on data Protection 2016/679 of 27 April 2016. The study protocol was approved by the Independent Ethics committee of the University Hospital of Angers, France, on 16-Jan-2019 and registered as n° 2019/5. A letter was sent to all patients alive at time of study initiation to inform them about the study and their rights as study participants.

## Results

### Study follow-up

From 01-Jan-2014 to 14-Feb-2020, 993 patients received at least one HCCP application at the ICO Anaesthesiology and Pain department, of which 306 were treated for or following BC (i.e., BCSs or BC patients). Among the 306 BCSs/BC patients, 279 were included in this study. Twenty-six patients were excluded from the study population as they began HCCP treatment before 01-Jan-2014 and one patient was excluded due to missing data. Overall, 1898.7 patches were used, corresponding to 1141 HCCP distinct applications (Fig. 1).

### Patients' characteristics

Of the 279 BCSs/BC patients, 277 were women (99.3%) and 2 men (0.7%). Patients were on average 59.2 (SD: 12.4) years old.

Hypertension which was reported by 66 patients (23.7%) was the most frequently reported comorbidity. Overall, 16 patients (5.7%) had bilateral BC (Table 2).

Table 2  
Patients' and HCCP treatment characteristics (N = 279)

Characteristics	N (%) or Mean (SD)
<b>Sex</b>	
Male	2 (0.7)
Female	277 (99.3)
<b>Age (years)</b>	
Mean (SD)	59.2 (12.4)
<b>Comorbidity</b>	
Hypertension	66 (23.7)
Myocardial infarction	1 (0.4)
Pulmonary embolism	6 (2.2)
Stroke	3 (1.1)
<b>Cancer Location</b>	
Breast - Bilateral	16 (5.7)
Breast - Right	129 (46.2)
Breast - Left	134 (48.0)
<b>Pain aetiology*</b>	
Pain associated with cancer therapy	
Post-surgery chronic pain syndrome	174 (62.4)
Chemotherapy induced painful neuropathy	33 (11.8)
Radiotherapy induced painful neuropathy	18 (6.5)
Non-cancer related pain	
Localized neuropathic pain	54 (19.4)
Most painful area of a diffuse neuropathic pain	20 (7.2)
<b>Duration of PNP before capsaicin use</b>	
< 1 year	115 (41.2)
1 to 5 years	107 (38.4)
> 5 years	38 (13.6)
<b>Previous pain medication</b>	
At least 1 previous (stopped before inclusion)	152 (54.5)
At least one antidepressant	54 (19.4)
At least one antiepileptic	55 (19.7)
At least one opioid	47 (16.8)
At least one other treatment	92 (33.0)
<b>Ongoing analgesic medication for neuropathic pain</b>	
At least 1 ongoing analgesic medication	202 (73.2)
<b>Purpose of the 8% capsaicin patch treatment</b>	
As add-on to a systemic medication for non-controlled pain	190 (68.8)
As first-line for non-controlled pain	77 (27.9)

CT: chemotherapy; HCCP: high-concentration (179 mg) capsaicin patches; PNP: peripheral neuropathic pain; RT: radiotherapy; SD: standard deviation

\* patients could have more than one aetiology

Characteristics	N (%) or Mean (SD)
As add-on to try to stop the systemic medication or reduce it to the minimum effective dose	9 (3.3)
<b>Treatment line for PNP</b>	
Second-line	141 (50.5)
First-line	63 (22.6)
Third-line (or more)	72 (25.8)
CT: chemotherapy; HCCP: high-concentration (179 mg) capsaicin patches; PNP: peripheral neuropathic pain; RT: radiotherapy; SD: standard deviation	
* patients could have more than one aetiology	

Medical history records indicated that 152/279 patients (54.5%) were taking a previous PNP medication which they stopped before HCCP treatment (Table 2): 55/279 patients (19.7%) had received antiepileptics, 54 (19.4%), antidepressants, and 47 (16.8%), opioids. At the time of the HCCP application, 202 patients (73.2%) concomitantly received at least one analgesic for their PNP (Table 2).

## Pain characteristics

Pain was mainly associated with cancer therapy. It was most frequently caused by surgery in 174/279 patients (62.4%). Chemotherapy and radiotherapy were less frequently the cause of pain for 33 patients (11.8%) and 18 patients (6.5%), respectively (Table 2).

More than half of the patients suffered from PNP for more than one year: 107 (38.4%) had their PNP for 1 to 5 years and 38 (13.6%) for more than 5 years (Table 2).

## Characteristics of HCCP application

Each patient had received between 1 and 21 HCCP applications, with a median of 3 patches per patient and a mean (SD) of 4.1 (3.5) patches.

Overall, 190 (68.8%) received HCCP applications as an add-on to a systemic medication for non-controlled neuropathic pain, 77 (27.9%) as monotherapy for neuropathic pain at the discretion of their treating physician, and 9 (3.3%) as add-on to try to stop the systemic medication or reduce it to the minimum effective dose (Table 2).

Patients usually received HCCP applications as second-line treatment (50.5%); however, HCCP applications were used as first-line therapy for 63/279 patients (22.6%) and as third-line or more for 72 patients (25.8%) (Table 2).

HCCP could be applied all over the body according to patient needs. The BCSS/BC patients with pain caused by surgery usually received their HCCP in axillar, breast, and/or dorsal areas, and those under chemotherapy on their hands and feet (Fig. 2).

## HCCP effectiveness

CGIC was available for 266 patients and 1008 applications. A complete or important analgesic effect was reported at least once by 219/266 patients (82.3%), and a complete effect by 138 patients (51.9%). Out of the 1008 applications, 644 applications (63.9%) and 265 (26.3%) provided complete or important and complete analgesic effect, respectively. Overall, 82/1008 applications (8.1%) resulted in no analgesic effect at all and no effect at all was reported in 16/266 patients (6.0%) (Table 3).

Table 3  
Effect of HCCP treatment on CGIC scores by patient (N = 266) or per application (N = 1008)

Analgesic effect	By patient (N = 266)	Per application (N = 1008)
	N (%)	N (%)
Complete	138 (51.9)	265 (26.3)
Important	81 (30.5)	379 (37.6)
Moderate	15 (5.6)	153 (15.2)
Mild	8 (3.0)	47 (4.7)
Minimal	8 (3.0)	53 (5.3)
Clinically observable effect without pain relief	0 (0.0)	22 (2.2)
No effect	16 (6.0)	82 (8.1)
Complete or important effect	219 (82.3)	644 (63.9)
HCCP: high-concentration (179 mg) capsaicin patches		

Irrespective of pain aetiology, pain duration, or treatment line, more than half of applications provided complete or important pain analgesic effect (Fig. 3 and Fig. 4). The proportion of HCCP patch applications providing complete or important PNP analgesic effect was higher in patients with post-surgical PNP (437/684, 63.9%) than in patients with chemotherapy- or radiotherapy-induced PNP (59/112, 52.7% and 45/86, 52.3%, respectively) (Fig. 3.a). In addition, the earlier the treatment was initiated, the more complete or important the analgesic effect was (Fig. 3.b). Finally, the proportion of HCCP patch applications providing complete or important PNP analgesic effect varied according to treatment line, the greatest analgesic effect being reported when HCCP was applied as second- or third-line treatment (Fig. 4).

Supplementary Fig. 1 presents HCCP effectiveness by patient, pain duration, and first application. After all HCCP applications, the best CGIC response per patient was consistent (from "mild effect" to "complete effect") in 91.0% of the patients (242/266) and was "minimal effect" to "no effect" in 9.0% of the patients (24/266). Among patients who did not respond to the first application (N = 39), 56.4% had at least one additional application (N = 22), and 63.6% (N = 14) of them experienced important, complete, moderate, or mild analgesic effect with these additional applications.

## Effectiveness in Post-surgical PNP (PS-PNP) Patients

CGIC was obtained for 684 applications (174 PS-PNP patients). The highest complete or important effects were observed when the application was performed within 12 months of pain occurrence. Nevertheless, important or complete effects were also observed when pain duration ranged from 1 to 10 years (Table 4). HCCP application as a first-line treatment produced complete or important effect in 59.0% of the cases. This percentage increased for second- and third-line treatments (66.6% and 63.5% of applications with complete or important effect).

Table 4

Effect of HCCP treatment in PS-PNP BCSs/BC patients on CGIC scores by pain or pain management characteristics per application (N = 684)

Characteristics	N	No effect		Clinical observable effect/ no pain relief		Minimal effect		Mild effect		Moderate effect		Important effect		Complete effect		p-value*	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)		
<b>Pain duration</b>	3 to 6 months	126	9	(7.1)	4	(3.2)	4	(3.2)	2	(1.6)	16	(12.7)	58	(46.0)	33	(26.2)	0.0655
	6 to 12 months	103	10	(9.7)	0	(0.0)	3	(2.9)	3	(2.9)	16	(15.5)	42	(40.8)	29	(28.2)	
	1 to 2 years	234	17	(7.3)	3	(1.3)	12	(5.1)	16	(6.8)	44	(18.8)	83	(35.5)	59	(25.2)	
	3 to 4 years	102	6	(5.9)	2	(2.0)	6	(5.9)	6	(5.9)	16	(15.7)	39	(38.2)	27	(26.5)	
	5 to 10 years	62	3	(4.8)	6	(9.7)	2	(3.2)	7	(11.3)	15	(24.2)	16	(25.8)	13	(21.0)	
	> 10 years	25	3	(12.0)	0	(0.0)	2	(8.0)	0	(0.0)	6	(24.0)	9	(36.0)	5	(20.0)	
<b>Treatment line</b>	First-line	200	25	(12.5)	11	(5.5)	10	(5.0)	9	(4.5)	27	(13.5)	65	(32.5)	53	(26.5)	0.0315
	Second-line	377	20	(5.3)	5	(1.3)	14	(3.7)	20	(5.3)	67	(17.8)	149	(39.5)	102	(27.1)	
	Third-line	104	6	(5.8)	1	(1.0)	5	(4.8)	6	(5.8)	20	(19.2)	39	(37.5)	27	(26.0)	
<b>Ongoing pain medication</b>	No	239	26	(10.9)	11	(4.6)	8	(3.3)	9	(3.8)	39	(16.3)	86	(36.0)	60	(25.1)	0.023
	Yes	445	25	(5.6)	6	(1.3)	22	(4.9)	26	(5.8)	75	(16.9)	168	(37.8)	123	(27.6)	
<b>At least one previous pain medication</b>	No	313	32	(10.2)	10	(3.2)	18	(5.8)	12	(3.8)	38	(12.1)	111	(35.5)	92	(29.4)	0.003
	Yes	371	19	(5.1)	7	(1.9)	12	(3.2)	23	(6.2)	76	(20.5)	143	(38.5)	91	(24.5)	
<b>Antidepressants</b>	No	559	46	(8.2)	13	(2.3)	27	(4.8)	24	(4.3)	87	(15.6)	215	(38.5)	147	(26.3)	0.0645
	Yes	125	5	(4.0)	4	(3.2)	3	(2.4)	11	(8.8)	27	(21.6)	39	(31.2)	36	(28.8)	
<b>Antiepileptics</b>	No	567	50	(8.8)	16	(2.8)	28	(4.9)	28	(4.9)	93	(16.4)	202	(35.6)	150	(26.5)	0.01
	Yes	117	1	(0.9)	1	(0.9)	2	(1.7)	7	(6.0)	21	(17.9)	52	(44.4)	33	(28.2)	
<b>Opioids</b>	No	608	44	(7.2)	17	(2.8)	26	(4.3)	31	(5.1)	99	(16.3)	223	(36.7)	168	(27.6)	0.5172
	Yes	76	7	(9.2)	0	(0.0)	4	(5.3)	4	(5.3)	15	(19.7)	31	(40.8)	15	(19.7)	

BC: Breast cancer; BCSs: Breast cancer survivors; HCCP: high-concentration (179 mg) capsaicin patches; CGIC: Clinical Global Impression of Change; PNP: peripheral neuropathic pain; PS-PNP: Post-surgical PNP.

p < 0.05 indicates that the distribution of patients within groups defined by the effect of HCCP treatment statistically significantly differed according to the considered baseline characteristic.

The percentage of HCCP applications producing complete or important analgesic response was high and clinically similar in patients with or without concomitant pain medications (65.4% vs 61.1%) or with and without previous pain medications (63.0% vs 61.1%), although the distribution of patients with or without concomitant pain medications ( $p = 0.023$ ) or with and without previous pain medications ( $p = 0.003$ ) statistically significantly differed (Table 4).

## Safety profile of HCCP

HCCP was generally well tolerated. The most common AEs were at application site (i.e., local reactions): 152/279 patients (54.4%) reported at least one local reaction following at least one of the HCCP application. These local reactions were mainly burning sensation or pain, which was reported at least once by 128/279 patients (45.9%), followed by erythema (86/279 patients, 30.8%). Frostbite due to cooling as part of the application procedure was observed in 4/279 (1.4%) patients. Other reported local reactions were 3 cases of pruritus, 1 case of plaster allergy, and 1 case of oedema. High blood pressure was reported at least once by 20/279 patients (7.2%). Other systemic AEs were rare, they included: 4 cases of headache, 1 case of reflex syncope, and 1 case of nausea.

Procedural pain at application site was rated as very intense during 52/1141 applications (4.6%), intense for 174 applications (15.2%), moderate for 247 applications (21.6%), and mild for 347 applications (30.4%); no information was collected during 321 applications (28.1%). At study centre discharge, pain at application site was rated as very intense for 37/1141 applications (3.2%), intense for 151 applications (13.2%), moderate for 134 applications (11.7%), and mild for 174 applications (15.2%); pain was absent for 97 applications (8.5%), and no information was available for 548 applications (48.0%).

## End-of-treatment and study discontinuation

Data collection was censored on 14-Oct-2020 for 90 patients (32.3%). Other patients had stopped treatment before the end of the study because they had no more pain (N = 63, 22.6%), were lost to follow-up (N = 39, 14%), died during the study (N = 39, 14%), stopped at their request (N = 22, 7.9%), or because of other reasons (N = 19, 6.8%). Finally, 7 patients stopped treatment due to lack of efficacy (2.5%). The 39 cases of death were all cancer-related; none was associated with HCCP application.

## Discussion

Persistent pain after BC treatment remains a complex clinical issue that is still poorly understood [25]. As (i) definitions of pain vary, (ii) assessment tools are inconsistently used, and (iii) methodology differs between studies, prevalence figures vary, and prevention and pain management strategies require further investigation. This chart review study of a large cohort of BCSs and BC patients (n = 279) followed at one centre where all patients from the cohort were treated by topical application of HCCP, may contribute to a better understanding of the patient population and the different types of PNP conditions occurring in this population, as well as the effectiveness and safety of the HCCP treatment.

The population in this chart review study is consistent with expectations. Firstly, less than 1% of the patients from the cohort were male, which was consistent with the literature that reports that approximately 1% of BCs are occurring in males [26]. Secondly, in line with the most commonly used intervention for the treatment of BC, the most common cause for the PNP experienced by the BCSs/BC patients from this study was surgery. Several broad classes of drugs for treating BC are currently available and their use is defined based on tumour characteristics and disease extent resulting in a recommendation for systemic chemotherapy, endocrine therapy, or HER2-directed therapy. In case of breast-conserving surgery, radiotherapy is often offered as adjunctive treatment [27]. Not surprisingly, chemotherapy- or radiotherapy-induced PNP were also observed in the cohort, and some patients experienced more than one type of PNP. The distinct cancer treatments can thus lead to the various types of PNP, all reflected in the study population. Thirdly, as the study centre was a pain centre where patients were referred to, it was not a surprise that most BCSs/BC patients had experienced PNP for over a year.

On average, BCSs/BC patients from this study had 4.1 HCCP applications (from 1 to 21 applications). Consistent with literature [28], HCCP was most often offered as a second-line treatment and as an add-on to systemic medication used for the treatment of PNP.

HCCP applications resulted in considerable effectiveness in approximately 60% of the patients (complete or important response as measured by the CGIC), irrespective of pain aetiology, duration, or treatment line.

Even though HCCP applications more often provided relief in patients with PS-PNP, complete or important analgesic effect was also reported following over 50% of applications in patients with chemotherapy- or radiotherapy-induced PNP. It is important to note that the earlier the treatment was initiated, the greater the relief. This is consistent with other real-world evidence data from a large study in Germany including several PNP indications [29].

Moreover, even though some patients did not experience sufficient pain relief with the first applications, upon repeated applications, they could experience benefit from the treatment. In other words, setting realistic expectations about treatment goals is important and may facilitate agreement between physician and patient to continue HCCP treatment even if the initial response to HCCP was deemed insufficient. This observation that repeated HCCP applications may enhance treatment benefit was in line with results from a recent *post hoc* analysis of repeated treatments with HCCP based on data from two large 52-week trials. Results showed that patients who did not experience a 30% decrease in pain scores from baseline after a first application could respond to subsequent applications [30].

The largest patient group (62.4%) had PNP resulting from surgery. Further analysis of this large patient population showed that, although patients with the shorter duration of pain experienced more relief (an observation consistent with the findings of other studies [31]), about 50% of HCCP applications provided complete or important effect in patients with PS-PNP diagnosis for 5–10 or > 10 years.

Moreover, 59% of HCCP as first-line treatment caused complete or important effect in PS-PNP patients. This information may support the use of HCCPs earlier in the treatment journey even as a first-line treatment option and is in line with current thinking about treatment algorithms for the treatment of focal neuropathic pain [32, 33]. Consideration of a first-line treatment with HCCP may be of special interest to the often poly-medicated post-surgical patients as systemic exposure to capsaicin is low and use of HCCP does not seem to lead to major drug interactions and systemic side effects often associated with oral pain treatments [34].

At the same time the effectiveness noted in this chart review study when HCCP was used as second- and third-line treatment options suggested that it could also be a useful treatment for patients who need additional treatment options when others have been exhausted. Moreover, it has been described earlier that adding HCCP treatment to existing treatment for PNP may allow for a reduction of that pre-existing treatment [35].

This study presents some limitations. Its first limitations are due to its retrospective nature, with mainly a risk of missing data. However, data collection was exhaustive, the cohort was exceptionally large (279 BCSs/BC patients and 1141 HCCP applications), and patient's electronic medical files were usually thoroughly completed by the treating physicians following each application. In addition, the evaluation of the analgesic effect was performed retrospectively. To compensate for this weakness, most medical records were evaluated by two independent pain specialists each, and in case of disagreement between them, the most unfavorable evaluation was the one reported. In total, eight different pain specialists who were not the treating physicians were involved in the independent evaluation of the medical records to ensure an impartial assessment. Its second limitation is that the study was monocentric with a potential center effect. Although this may be considered a weakness, it may have certain strengths given consistency in diagnosis, therapeutic approach and follow up of patients. Finally, the study did not allow for thorough evaluation of the impact of previous or concomitant treatments nor of the impact of the

size of the painful skin area in HCCP application responses. Prospective and comparative studies are needed to confirm the results of the present study and further evaluate HCCP treatment for this indication.

Acknowledging the limitations, it was the first time that a study evaluated a large cohort of BCSs/BC patients suffering from PNP following interventions for BC (e.g., surgery, medical oncological treatments or radiotherapy). Patient demographics matched those expected from literature and the PNP conditions observed matched expectations. Given that all patients were treated at one study centre with a similar intervention by a team of physicians specialised in pain management, consistency in method of diagnosis, delivery of therapy, and assessment was high. All of these elements contribute to the credibility of findings, and given the similarity of the findings with data already available in the literature for other PNP conditions, it is likely that the findings from this study may be extrapolated to BCSs/BC patients treated with HCCP at large.

## **Conclusion**

This study shows that HCCP represents an interesting therapeutic option for BCSs/BC patients suffering from PNP due to cancer or its treatment, as it may provide significant or complete relief. It may be a useful first line treatment option as the best response with HCCP has been observed when used early in the disease. Although best responses with HCCP are noted in patients with PNP following BC surgery, important or complete relief has also been observed in BCSs/BC patients with pain of other aetiology, in those with long-term pain, and as a second- or third-line treatment. Finally, physicians and patients need to understand that it may be useful to reapply HCCP even if initial responses are not fully meeting expectations considering its favourable risk-benefit profile and that continuous improvement is experienced with repeated applications.

## **Declarations**

### ***Ethics approval and consent to participate***

The study was conducted in accordance with: the declaration of Helsinki; Public Health law (Acts No. 2004-806 of 9 August 2004 and 2006-450 of 18 April 2006); the law of modernization of our health system (No. 2016-41 of January 26, 2016); the law on Informatics, files and Freedoms (No. 78-17 of 6 January 1978 as amended); and general regulations on data Protection 2016/679 of 27 April 2016. The study protocol was approved by the Independent Ethics committee of the University Hospital of Angers, France, on 16-Jan-2019 and registered as n° 2019/5. A letter was sent to all patients alive at time of study initiation to inform them about the study and their rights as study participants.

### ***Consent for publication***

Not applicable

### ***Availability of data and material***

The data that support the findings of this study are available from Dr Dupoirion, the corresponding author, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Dr Dupoirion, the corresponding author.

### ***Competing interests***

Dr Dupoirion, Dr Jubier-Hamon, Dr Pluchon and Dr Delorme received consultant fees from Grünenthal. The other authors declare no conflicts of interest.

### ***Funding***

This study was financially supported by Grünenthal GmbH.

### ***Authors' contributions***

DD: participated in the design of the study, participated in the study, coordinated and drafted the manuscript.

VS: participated in the design of the study, performed the statistical analysis, and drafted the manuscript.

SJH, FB, YMP, NL, VJ, TD: participated in the study, read and made comments on the manuscript.

All authors read and approved the final manuscript.

### ***Acknowledgements***

The authors want to thank Abelia Science for their help in writing the manuscript, in particular Matthieu Chanard, Fabienne Péretz, and Carolina Rojido.

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## Figures

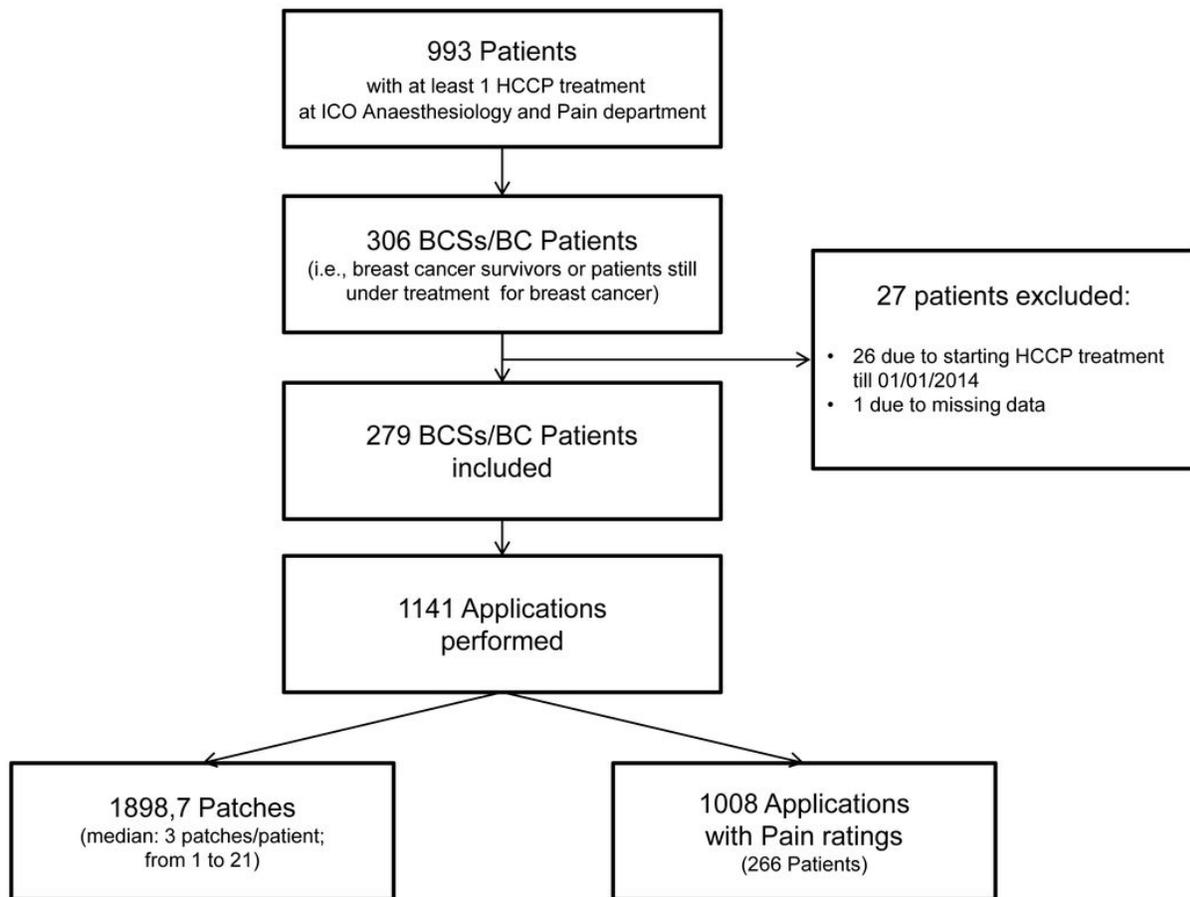


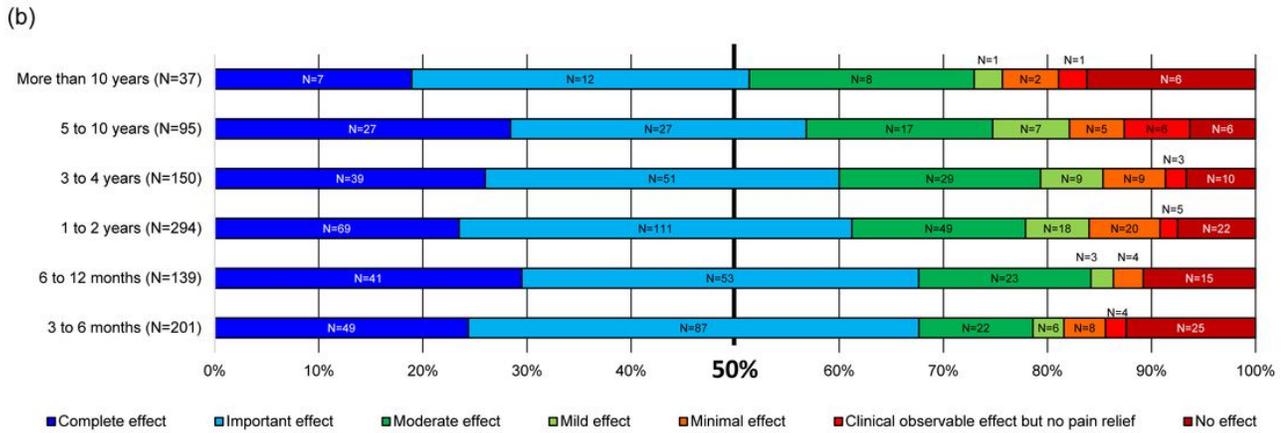
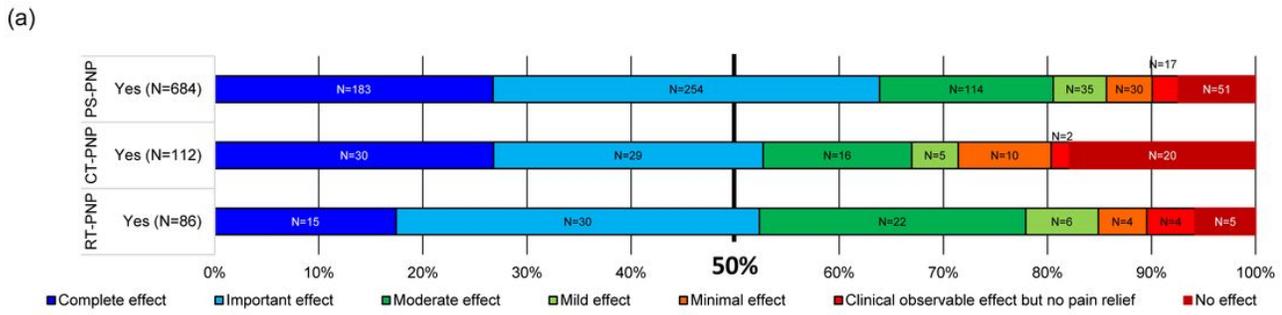
Figure 1

Flow diagram BCSs/BC: Breast cancer survivors or breast cancer patients; HCCP: high-concentration (179 mg) capsaicin patches

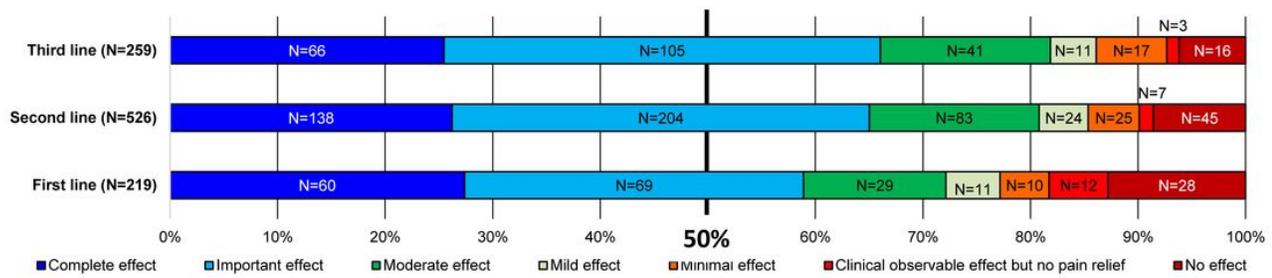
Area		Number of HCCP applications by area	Number of patients (%) with at least 1 HCCP application per area
1		185	71 (25.4)
2		404	140 (50.2)
3		472	151 (54.1)
5		14	3 (1.1)
6		11	6 (2.2)
7		36	20 (7.2)
8		64	37 (13.3)
9		103	39 (14.0)
10		84	34 (12.2)
11		5	3 (1.1)
12		30	18 (6.5)
13		57	19 (6.8)
14		56	16 (5.7)
15		63	19 (6.8)
16		125	36 (12.9)
17		76	37 (13.3)
18		85	41 (14.7)
19		93	38 (13.6)
20		98	36 (12.9)

Figure 2

Description of HCCP applications by location Note 1: One patch could be applied on several areas. For example, patches were frequently applied on area #2 and area #1, and/or area #3. Note 2: areas #1, #2, #3, and #9 are frequently associated with PS-PNP and areas #16 and #20 with CT-PNP. CT-PNP: CT-peripheral neuropathic pain; HCCP: high-concentration (179 mg) capsaicin patches; PS-PNP: Post-surgical peripheral neuropathic pain.



**Figure 3**  
 Effect of HCCP application on CGIC score (a) by PNP aetiology (b) by PNP duration Note: The number of applications is provided for each CGIC answer, and represented in percentages. HCCP: high-concentration (179 mg) capsaicin patches; CGIC: Clinical Global Impression of Change; PNP: peripheral neuropathic pain.



**Figure 4**

Effect of HCCP application on CGIC scores by treatment line HCCP: high-concentration (179 mg) capsaicin patches; CGIC: Clinical Global Impression of Change

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [BreastCancerResSuppFigure1.jpg](#)