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Predictors of Treatment Response to Capsaicin Patch

Ancor Serrano Afonso

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Abstract

Neuropathic pain is a very difficult to treat chronic condition. One of the most promising treatments developed in recent years is the capsaicin 8% patch. But given the high cost of treatment, the patch should be applied only to those most likely to benefit from improvement. There have been several studies that have tried to look for predictors of treatment response. Three of them found correlation with pain and response to treatment. The predictors found were: baseline pain scores, variability of pain prior to treatment, pain response for lidocaine pretreatment, and time with preexisting pain. Four studies found that sensory abnormalities used for prediction of response to treatment seems to be useful as well. Though the correct sensory sensations are not clear there seems to be a tendency for the burning or heat-pain sensations and the pressure-pain sensations to be taken into account. From this findings, it seems that patients with exclusively peripheral damage and with no central plastic changes are the most suitable for treatment. There must be some more research to be done, where a combination of the predictors already found could give a very high predictability of treatment response, lowering de NNT to almost 1.
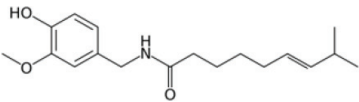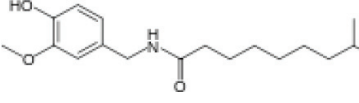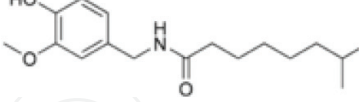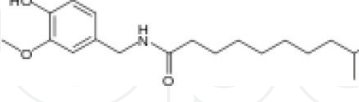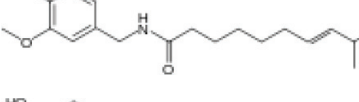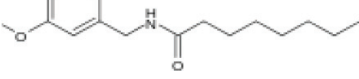
Keywords: capsaicin patch, QST, QTT, sensory symptoms, response to treatment, pain scores

1. Introduction

Neuropathic pain (NP) is a very difficult to treat chronic condition [1]. Additionally, managing NP involves selecting the appropriate treatment for each patient, since not all patients respond to the same treatments. Currently, there is little to no information regarding the prognostic factors associated with positive treatment outcomes for clinicians who treat patients with NP to decide which is the better course of action with each patient. One of the most promising treatments developed in recent years is the capsaicin 8% patch (CP8%) (QutenzaTM) [2] which delivers capsaicin into the skin providing up to 12 weeks of relief with a single topical patch

application [3–5]. CP8% delivers up to 179 mg of capsaicin to the skin in a pharmacokinetic linear administration. Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the most frequently found capsaicinoid, and a well-known exogenous activator of transient receptor potential vanilloid 1 (TRPV1) [6]. Other capsaicinoids have been described [7]. See **Table 1** for the other capsaicinoids. Especial interest may be given to Nonivamide, also called pelargonic acid vanillylamide (PAVA), which is used as the active ingredient in most pepper spray. Even though, the most studied has been capsaicin, being the active component of CP8%. Capsaicin, up to date, is the only capsaicinoid used for clinical treatment in humans.

Capsaicin in CP8% works by directly targeting the TRPV1 receptor (present in C-fibers and in some Aδ-fibers) The largest group of nociceptors found in the skin is the family of channels of the transient receptor potential [8]. There are four different molecules (TRPV1, TRPV2, TRPV3 and TRPV4) that respond to different degrees of temperature increase, ranging from the perception of heat all the way up to harmful levels [9–11]. TRPV1 is a non-selective, ligand-dependent cationic channel that can be activated by a series of exogenous and endogenous physical and chemical stimuli, [12, 13], allowing the passage of different monovalent or divalent cations [14, 15], such as sodium and calcium. This triggers the release of various peptides, causing the transmission of nociceptive information to the brain, which is interpreted

Common name	Chemical name	Chemical structure	Freq.	Heat units
Capsaicin	*8-methyl-N-vanillyl-6-nonenamide*		69	16
Dihydrocapsaicin	*N-(4-Hydroxy-3-methoxybenzyl)-8-methylnonanamide*		22	15
Nordihydrocapsaicin	*N-(4-Hydroxy-3-methoxybenzyl)-7-methyloctanamide*		7	9.1
Homodihydrocapsaicin	*N-(4-Hydroxy-3-methoxybenzyl)-9-methyldecanamide*		1	8.6
Homocapsaicin	*(6E)-N-(4-Hydroxy-3-methoxybenzyl)-8-methyldec-6-enamide*		1	8.6
Nonivamide	*N-[(4-Hydroxy-3-methoxyphenyl)methyl]nonanamide*		*	9.2

Freq. stands for percentage (%) of the capsaicinoid found in nature.
*Nonivamide can be found in less frequency, but is mostly synthetically manufactured. Heat Units stands for the pungency, which is measured with the Scoville scale. Numbers for the Heat Units are in millions.

Table 1. Description of most common capsaicinoids.

as a burning pain or an itch. Its pain relief effect is believed to be due to the activation of small diameter afferent nerve fibers and specialized dorsal root ganglia neurons after high dose application of capsaicin, resulting in the defunctionalization of the nociceptor nerve fibers. After defunctionalization, patients perceive a decrease in pain [16–18], which is frequently referred to as "desensitization". This desensitization allows the use of capsaicin as an analgesic [19]. Long term treatment have been studied along several prospective cohort studies [20–22] CP8% treatment have been studied up to 52 weeks of follow-up, with repeated patch application. In these studies no sensory changes in the skin was found after repeated treatment. Also, skin biopsy reports in these studies showed that intraepidermal nerve fiber density change was only temporary. Adverse effects reported were all topical and localized to the site of application. All of them were temporal and reversed to normal after some time.

The European Medical Agency (EMA) has recommended that CP8% be applied by a doctor, or other healthcare professional under the supervision of a doctor. Treatment is to be done for no more than 60 minutes, as the pharmacodynamic studies showed no increase in benefit [23]. This recommendation limits treatment options and also makes treatment more expensive. In addition, the indirect costs of personnel and other materials must be added to the direct cost of CP8% [24]. While many patients with peripheral NP (PeNP) respond positively to treatment with the capsaicin 8% patch, others do not. Given the aforementioned high cost of treatment and adding to it that the number-needed-to-treat (NNT) for CP8% is high [25], the patch should be applied only to those most likely to benefit from improvement. At present, there are no reliable predictors of response to treatment with capsaicin for analgesia. There have been several studies that have tried to look for predictors of treatment response [26–31]. In this chapter we are going to comment on them trying to give more light into this issue.

2. Pain as a predictor of response to treatment

Three studies have found correlation with pain and response to treatment [26–28]. Although, the correlation is not the same, and the quality of pain investigated was different too. The predictors found were: baseline pain scores, variability of pain prior to treatment, pain response for lidocaine pretreatment, and time with preexisting pain.

One investigated data from 4 double-blind, randomized controlled trials (RCT) [26]. All trials were done on the efficacy of the capsaicin 8% patch versus capsaicin 0.04% patch in patients suffering from post-herpetic neuralgia (PHN). For the purpose of analyzing old data in this new study, the investigators used a Bateman function for a non-linear mixed effect. For such extent they used a longitudinal model. The overall number of patients was 1248. Treatment outcomes, or responders was to be identified at week 12. So it is a meta-analysis with revised data from different studies.

The procedure resulted in five distinct response populations:

- Subgroup 1. worsening of pain during treatment (i.e., pain increases)
- Subgroup 2. no response to treatment

- Subgroup 3. (partial or full) analgesic response with return to pretreatment pain levels within 12 weeks

- Subgroup 4. partial analgesic response at week 1 that remained constant during the study period

- Subgroup 5. ongoing decline in pain rating during the 12 weeks.

Analyzing the treatment outcomes in this groups and the data extracted from them, some predictors could be found.

1. Pain scores following lidocaine pretreatment over the skin on numeric pain rating scale (NPRS) score predicted the efficacy of the capsaicin 8% patch. In contrast, when pain scores were elevated after lidocaine pretreatment (NPRS = 10), the probability of capsaicin 8% treatment success decreased. High variability in pain rating scores could be due to a more recent development of chronic pain status.

2. The variability of pain reporting in the 14 days prior to treatment also had a significant impact on treatment efficacy. When variability was high, the probability of full response to treatment was almost 80%. Possibly the low variability NRPSs are an indication of a rigid and fully manifested long-term chronic pain process with severe central plastic changes unresponsive to therapy. Although not as potential predictors as the above, it was also found that concomitant opioid use and high baseline pain scores reduce the probability of a full analgesic response.

Maihöfner et al. [27] studied A total of 1063 patients receiving a single treatment of the CP8% were evaluated. The highest treatment response to the CP8% was observed in patients with a history of pre-existing peripheral neuropathic pain of less than 6 months, suggesting that early initiation of topical treatment might be indicated. Responder rates of 30 and 50% in patients with pain duration of <6 months were significantly higher than in patients with pain duration of 6 months to 2 years, >2–10 years or > 10 years (p ≤ 0.001; chi-square test) (**Table 2**).

Patients with a pain history of less than 6 months had the highest pain reduction with an average of −2.7 points (n = 105; 0.3 standard error of the mean (SEM); p ≤ 0.001) and improvement of 36.6% (4.6 SEM). This difference was significantly higher compared to patients with pre-existing pain for more than 6 months. Patients with a pain history of more than 10 years experienced the lowest absolute and relative change of pain intensity, with a mean value of −1.2 points (n = 99; 0.2 SEM; p ≤ 0.001) and 19.2% improvement. Thus, Patients with preexisting pain of less than 6 months seem to benefit to an even greater extent from treatment than those with a longer history of pain.

Katz et al. [28] conducted meta-analyses out of 6 completed randomized and controlled Qutenza studies evaluating the capsaicin patch efficacy, and used individual data patient data from capsaicin patch–treated patients only to identify which types of patients have the greatest response to capsaicin patch treatment. Logistic regression was used to identify predictors of response and Complete Response, and subgroups of patients who respond best to the capsaicin patch. The potential predictors of response selected were the baseline patient characteristics that can easily be measured by physicians during office visits and for which data were

	Responder rates (% patients)	
Pain duration	>30%	>50%
<6 months	61.7*	39.3**
6 months-2 years	42.3	23.3***
>2-10 years	40.8	21.6
>10 years	32.3	14.1
No data	41.8	24.6
Total	42.7	23.6

From Maihöfner et al. [27].
*p < 0.001 versus 6 months-2 years, >2–10 years, >10 years (chi-square test).
**p < 0.001 versus 6 months-2 years, >2–10 years, >10 years (chi-square test).
***p = 0.042 versus >10 years (chi-square test).

Table 2. Responder rates: Pain relief of at least 30 and 50% at day 7–14 to week 12 versus baseline for subgroups of duration of pre-existing peripheral neuropathic pain.

collected in the trials. This is another meta-analysis with data obtained from different studies done before. Treatment outcomes and response rate was to be compared to week 12. Baseline characteristics with X2 P-value ≤0.15 were considered as potential predictors of the respective efficacy outcomes.

Characteristics associated with the highest chance of responding to the capsaicin patch were, for PHN, baseline pain intensity score (BPIS) ≤ 4, McGill Pain Questionnaire (MPQ) sensory score ≤ 22, absence of allodynia, and presence of hypoesthesia; for human immunodeficiency virus associated neuropathy (HIV-AN), they were female sex and BPIS ≤ 4.

• Absence of allodynia on examination was associated with better outcome in the PHN-Sustained Response group;

• Absence of allodynia and presence of hypoesthesia on examination, and absence of allodynia and presence of hypoesthesia on the Neurological/Sensory Assessment (NSA; a questionnaire), was associated with better outcome in the PHN Complete Response group;

• MPQ sensory scores were associated with better outcome for PHN patients;

• Better physical and mental health (SF-36) was associated with better outcome across disease and efficacy response categories;

• Female sex and absence of use of concomitant analgesics were associated with better outcome in HIV-AN patients;

• Higher body mass index (BMI) was associated with better outcome in PHN patients;

• Decreased sensation on the baseline sensory examination was associated with better outcome in PHN patients.

They found that baseline pain intensity was a consistent predictor of response. Patients with a Mean baseline pain intensity ≤4 had a significantly better response than when they reported >7. But they also found that sensory symptoms could be useful for response to treatment too.

3. Sensory symptoms and response to treatment

As stated above, Katz et al. found not only predictability with pain scores. They also found sensory abnormalities which, at baseline visit, could be useful predictors. Patients without allodynia and with hypoesthesia, on both the physical examination and the NSA, had better outcomes. This seems to be a robust finding as it is consistent across clinical examination and patient self-report methods of capturing these phenomena.

Another study evaluated sensory neuropathic abnormalities (painDETECT questionnaire), collected from a multi-center, prospective, non-interventional study 1044 patients [29]. Treatment outcomes or response rate was to be compared to week 12. In this paper, only weak associations were found: Short disease duration predicted an improved treatment effect. High painDETECT score, presence of burning and pressure-evoked pain were weak predictors of treatment response.

Patients with a positive painDETECT score showed an average overall pain reduction of 24% following treatment, whereas patients with a negative score had a mean reduction of 13%. At single symptom level a weak association was found between burning and pressure-evoked pain at baseline and response. However, for the majority of symptoms the extent was greater in patients with a short duration of pain (**Table 3**).

Thermal hyperalgesia is difficult to interpret, which could be due to the fact that the painDETECT questionnaire does not distinguish between cold and heat-evoked pain. Since the burning quality (data on heat-evoked pain) is frequently associated with the presence of

Pain duration	<6 m [57]	6 m–2 y [166]	>2 y–10 y [225]	>10 y [54]
Symptoms				
Burning	43.1 (5.6)	23.4 (3.5)	15.9 (2.6)	12.1 (10.8)
Prickling	21.6 (8.3)	21.9 (3.7)	12.9 (3.4)	18.6 (5.0)
Allodynia	36.9 (6.8)	20.9 (4.0)	18.9 (3.6)	8.5 (4.5)
Pain attacks	35.9 (7.4)	23.5 (4.4)	15.3 (3.5)	10.6 (5.3)
Thermal hyperalgesia	24.1 (10.8)	24.9 (4.6)	20.5 (4.1)	15.7 (6.9)
Numbness	35.9 (6.5)	15.7 (3.5)	16.2 (3.6)	5.2 (9.7)
Pressure-evoked pain	30.7 (10.2)	18.1 (4.2)	11.9 (3.8)	12.2 (6.1)

Modified from Hoeper et al. [29] Pain duration. m = months. y = years. In brackets, [] number of patients in each subgroup with different duration of preexisting pain. Reduction in symptom intensity. Numbers are % of reduction and in parenthesis () the standard error of the mean is shown.

Table 3. Reduction in sensory symptom intensity depending on duration of preexisting pain.

TRPV1 receptors on nociceptors, this association is in line with the proposed mechanism of action of capsaicin.

The previous two studies found sensory profiles in clinical examination or in self-reported questionnaires. Two attempts have been made to find predictability for capsaicin treatment response with quantitative sensory profiles. Given that capsaicin affects unmyelinated or, slightly myelinated fibers, and studies have shown that the CP8% patch involves heat sensation [7], a retrospective study of clinical records was performed to see if that quantitative thermal testing (QTT) could be a potential predictor of treatment response [30]. The QTT profiles at the target localized PeNP (PeLNP) area were compared to the corresponding QTT profile at the contralateral area. There were no baseline differences between responders and nonresponders in terms of gender, age, Douleur Neuropathique 4 scores, etiological diagnosis (PHN, chronic post-surgical pain, chronic post-traumatic pain, complex regional pain syndrome) or NPRS scores. QTT could not be compared to already published normalized data due to slight simple heterogeneity, which made subgroup analysis impossible. Heterogeneity was due to the following: concomitant medication, pain localization, and time elapsed from injury to treatment. Thus, QTT was compared between the treatment area and the asymptomatic contralateral healthy area, used as a control. Differences between the values in the target and control areas were considered not significant when there was a crossover between mean results ($\pm$1.96SD) for the measurement on both areas; when this occurred, the painful area was considered to present normal thermal sensations.

Two distinct groups were identified (**Figure 1**):

- Homogenous profile group: defined as either the presence of significant differences in the same direction (both high or both low) in warm sensation threshold (WST) and heat pain
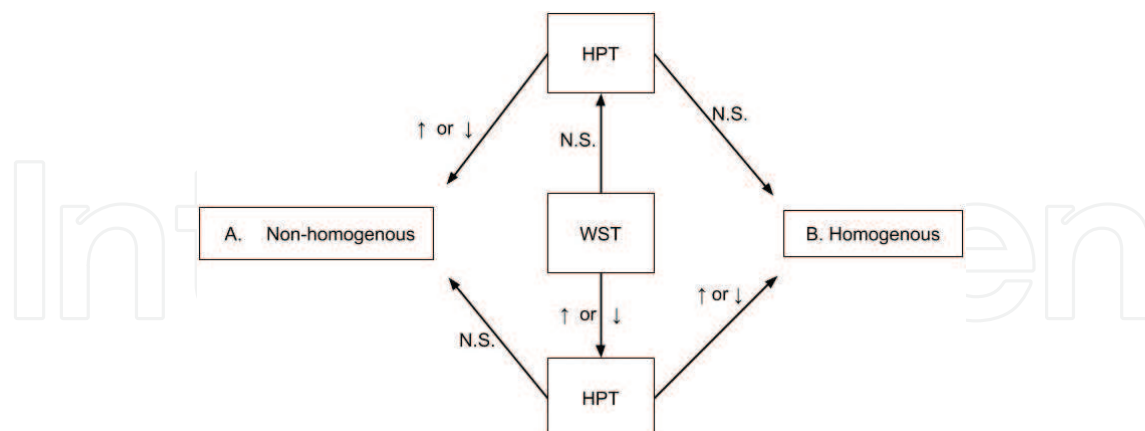

Figure 1. QTT profile flow diagram. From Serrano et al. [27] QTT profile groups identified after matching responder and non-responders to treatment with capsaicin patch. WST: Warm sensation threshold. HPT: Heat pain threshold. N.S. Stands for no significant difference between pain site and asymptomatic contralateral area for the thermal test. ↑ stands for a significantly higher result for the thermal test on the painful area versus the asymptomatic contralateral area. ↓ stands for a significantly lower result for the thermal test on the painful area versus the asymptomatic contralateral area. For the arrow coming from the HPT box to the homogenous box, the painful area was significantly higher when WST was significantly higher or significantly lower when WST was significantly lower than the asymptomatic contralateral area, being both QTT test in the same direction.

threshold (HPT) values between the PeLNP region and the asymptomatic contralateral area; or no significant difference in these measures (both the treatment and control sites normal).

- Non-homogenous group: defined as the presence of significant differences between the PeLNP area and the contralateral site in only one (either WST or HPT) measure but not the other.

For instance, a significantly differently low HPT (i.e., heat hyperalgesia) with no significant difference in WST was considered non-homogeneous. By contrast, if the WST was also significantly different between the control and treatment areas, then the QTT profile was considered homogenous.

Most patients (27/31, 87.1%) with a homogenous profile were non-responders. By contrast, more than half of the patients (13/24, 54.2%) with a nonhomogeneous profile were responders (p = 0.0028). The clinical effects of CP8% were better in patients with non-homogenous QTT profiles. These patients showed a significantly higher response rate than patients with homogenous QTT profiles. It appears that patients who show a non-homogenous profile in terms of WST and HPT values are significantly more likely to respond to capsaicin treatment, probably due to the presence of incomplete nerve damage. This nociceptors are giving imbalanced inputs to second order neurons. So, patients with this non-homogeneous profile seem to have purely peripheral pain, with no central plastic changes. Treating them with CP8% could have removed such imbalance through desensitization, giving pain relief. By contrast, an homogeneous QTT profile is to be expected in patients with either no peripheral damage at all, with peripheral nociceptors working properly; or either in patients with complete peripheral nerve damage. When there is no peripheral nerve damage there should be no differences to be expected in WST/HPT values between painful and contralateral asymptomatic area. And when there is complete damage, the loss of peripheral nociceptors should give differences in both warm and heat pain sensations between both areas. Being this the neurophysiological reasoning for patients with an homogeneous profile to have Little or no clinical improvement.

Another study [31] used quantitative sensory testing (QST) to determine whether any patient characteristics can predict response to treatment with the capsaicin 8% patch where a total of 57 patients were treated. Responders to treatment were defined as those with ≥30% reduction in pain score at Day 7/10 post-treatment compared with baseline. They identified potential differences in the sensory profiles—particularly the pressure pain threshold and degree of allodynia—of patients with PeNP who responded to CP8% and those who did not. The authors found similar QTT profiles at baseline for both responders and nonresponders. There was no difference in temperature perception or heat and cold thresholds, and did not identify warm hyperaesthesia or heat hyperalgesia in responders.

Responders showed a trend towards a reduction in warm perception and also appeared to show normalization of the pinprick hyperalgesia at some stimulus levels. They also had a significant reduction in the size of the painful area at Day 28. (**Table 4**). At baseline the PNeP area in responders was found to have a significantly lower pressure pain threshold compared with the control area.

Stimulus (units)	Non-responders			Responders		
	n	PNeP site	Control area	n	PNeP site	Control area
MPT (mN)	12	32.2 (14.0–92.9)	34.3 (21.2–46.9)	9	58.7 (22.5–134.5)	90.5 (41.9–115.4)
PPT (kPa)	6	380 (250–500)	510 (300–630)	7	320 (290–800)	480 (410–1000)*
PS (mN)	14			9		
8		3.4 (1.3–13.3)	1.5 (.0–3.5)		4.6 (.0–10.4)	1.2 8.0–4.4)
16		5.2 (.0–15.4)	1.6 (.4–7.0)		6.6 (1.8–11.7)	2.3 (.0–6.3)**
32		14.5 (1.9–21.3)	3.5 (1.3–12.5)[1]		10.0 (1.5–17.5)	4.0 (1.1–9.1)**
64		10.0 (2.9–35.0)	5.0 (2.8–21.5)		12.0 (1.3–26.7)	7.9 (3.9–11.9)
128		16.3 (3.0–36.3)	8.9 (2.9–23.0)		10.0 (3.6–25.0)	10.0 (7.2–19.8)
256		32.5 (4.7–48.8)	11.0 (3.2–28.8)		16.6 (7.1–31.0)	12.1 (9.1–25.4)
512		38.5 (5.8–71.3)	14.0 (5.1–44.8)		19.4 89.9–38.8)	20.0 (11.5–43.0)

Modified from Gustorff et al. [31] PNeP, peripheral neuropathic pain. MPT = Mechanical pain threshold. PPT = Pressure pain threshold. PS = pinprick stimuli, in a stimulus–response function, using a numerical pain rating scale (0–100). For non-responders and responders, numbers represent the median, with the interquartile range in parenthesis (). When comparing PNeP site vs. control area: * $p < 0.01$, ** $p < 0.05$, [1] $p = 0.51$.

Table 4. Sensory thresholds in PNeP sites compared with control areas at baseline, for non-responders and responders to capsaicin 8% patch treatment, as determined by quantitative sensory testing (QST).

Non-responders had approximately three times greater degree of allodynia at baseline compared with responders. At baseline in non-responders, there was a trend towards greater sensitivity to painful pinprick stimuli at most intensities (8–512 mN) in areas of PNeP compared with control areas (**Table 4**). Non-responders appeared to display a generally higher mechanical pain sensitivity in the painful area than in the control area and three times higher allodynia than in responders.

4. Overall, predictors and limitations

From the published studies so far, several predictors have been already been found to be useful in clinical practice. But comparing published studies is not possible due to methodological differences (**Table 5**). However, from them, it can be hypothesized that patients characteristics are important for treatment response, and a careful selection will be more efficient in cost-effectiveness.

Pain have been found to be a good predictor of response. Both, high variability and less than 6 months of preexisting pain suggest the importance of treating patients when no central plastic changes are organized. Other predictors as lidocaine pretreatment response or low basal pain rating have do not have a certain neurophysiological assumption. There is even some contradiction within high variability in pain scores previous to treatment and low

	N	Study type	Timeline	NP type	Response definition	Control	Predictor
Martini [26]	1248	DB re-analyses	retrospective	PHN	Week 12 subgroups	Capsaicin 0.04%	1) Pain scores after lidocaine 2) Pain scores variability
Hoeper [29]	1044	Cohort	prospective	PeNP (excluding DM or head)	Week 12	None	painDETECT sensory symptoms
Gustorf [31]	57	Cohort	prospective	PeNP	Day 7–10	None	QST: PPT/PS
Katz [28]	1299	DB re-analyses	Retrospective	PHN HIV-AN	Week 12	Capsaicin 0.04%	1) Baseline pain score 2) allodynia hypoesthesia
Maihöfner [27]	1063	Cohort	Prospective	PeNP (excluding DM or head)	Days 7–14 Week 12	None	Time with preexisting pain
Serrano [30]	55	Cohort	Retrospective	PeLNP	Week 6 Week 12	None	QTT profile

Description of main variables of the different studies published with predictors of response to capsaicin patch.
N = number of patients in study. NP = Neuropathic Pain. DB = Data Base, PHN = Postherpetic Neuralgia. PeNP = Peripheral Neuropathic Pain. DM = Diabetes Mellitus. QST = Quantitative Sensory Testing. PPT = Pressure Pain Threshold. PS = Pinprick Stimulation. HIV-AN = Human Immunodeficiency Virus Associated Neuralgia. PeLNP = Peripheral Localized Neuropathic Pain. QTT = Quantitative Thermal Test.

Table 5. Published studies characteristics with predictors for response to capsaicin patch.

baseline pain score. Both are meta-analyses done with several RCT, where one only was done with PHN patients. The time with preexisting pain was found within a cohort prospective study, where any kind of PeNP was included, except for DM or pain in the head.

Sensory abnormalities used for prediction of response to treatment seems to be useful as well. Though the correct sensory sensations are not clear. Whereas burning and pressure evoked-pain symptoms where potential predictors in painDETECT questionnaire in a cohort study, These findings support the hypothesis developed by Malmberg et al. [17], who argued that the foremost psychophysical manifestation of topical capsaicin treatment is a reduced sensitivity to heat stimuli. This is the expression of an elevated-warmth detection threshold, corresponding to a loss of cutaneous sensory nerve fibers. QTT homogeneity profiles between WST and HPT was found to be useful. But, thermal sensations could not be found when applying QST in another cohort. However, response definition was not the same in neither of the studies. Also, it has to be taken into account that QST/QTT is time consuming. This is a big limitation for the number of patients to be studied with. This can be seen in **Table 5** where the QST studies have a big difference in number of patients, where both studies had a relatively small number of patients, which precluded the use of subgroup analysis, compared with the other studies.

From the predictors that have been found it already seems that patients with exclusively peripheral damage and with no central plastic changes are the most suitable for treatment. Patients with a partial loss of cutaneous nerve fibers or receptors are more likely to respond to

treatment. By contrast, when severe nerve damage or normal cutaneous sensations are present, responsive to capsaicin treatment is not so good. This difference may be due to incomplete nerve damage in these patients, leading to an imbalance in the sensitive inputs to second order neurons from peripheral receptors, and to the presence of ectopic discharges on nerve endings. If so, pain in these patients may be purely peripheral, with no additional central sensitizaion (CS) mechanisms. Capsaicin application in these patients could eliminate the factor resulting in dysaesthesia when they activate the remaining TRPV1 receptors, desensitizing the nerve terminals of nociceptors by destroying the remaining axons and nociceptors. Pain in non-responders could be due to CS mechanisms, with inputs multiplied at the DH, that is, the origin of the pain in these patients is probably less peripheral and more central. For this reason, the capsaicin is less effective in providing pain relief. Nevertheless, these findings need to be confirmed in a prospective controlled blinded study, preferably with a large sample to enable subgroup analysis to better identify the different pain scores found since far, and the QTT profile of responders.

5. Conclusion

Although there are no clear predictors for response to treatment with capsaicin patch, several attempts have been made. It is clear that there is a relationship between pain scores and response to treatment. The most probable patients to benefit from capsaicin patch treatment should be the ones with less than 6 month to 1 year of preexisting pain and high variability with pain scores, thus with a recent chronic pain problem, where no central sensitization has developed, or yet organized. It also seems clear that sensory symptoms can be useful to predict treatment response. But here there must be some more research to be done, as the number of patients under investigation is low, and studies have found different sensory abnormalities. Studies could not be compared as the methods were different too. Even though, there seems to be a tendency for the burning-heat sensations and the pressure sensations to be useful as predictors of treatment response. Also, a combination of the 4 mentioned above (recent chronic pain development with high variability in pain scores previous to treatment and with burning/heat-pain and/or pressure-pain sensory symptoms) could give a very high predict-ability of treatment response, lowering de NNT to almost 1.

Acknowledgements

Conflict of interest

Nomenclature

BMI	body mass index
BPIS	baseline pain intensity score
CP8%	capsaicin patch
CS	central sensitizaion
EMA	European Medical Agency
HIV-AN	human immunodeficiency virus associated neuropathy
HPT	heat pain threshold
MPQ	McGill pain questionnaire
NNT	number needed to treat
NP	neuropathic pain
NPRS	numeric pain rating scale
NSA	neurological/sensory assessment
PeNP	peripheral neuropathic pain
PeLNP	localized PeNP
PHN	post-herpetic neuralgia
QTT	quantitative thermal testing
QST	quantitative sensory testing
RCT	randomized controlled trials
SEM	standard error of the mean
TRPV1	transient receptor potential vanilloid 1
WST	warm sensation threshold

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