

ORIGINAL ARTICLE

Treatment of peripheral neuropathic pain by topical capsaicin: Impact of pre-existing pain in the QUEPP-study

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Conflicts of interest

The author Christian Maihöfner has received honoraria as consultant for Astellas, Bionorica and Mundipharma, and has participated in speakers bureaus of Allergan, Astellas, Grunenthal, Janssen and Pfizer. University Hospital Erlangen received financial support from Astellas Pharma to fund the investigation. The author Marie-Luise Heskamp was a salaried employee of Astellas Pharma at the time of the study.

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Abstract

Background: This study evaluates the impact of the duration of pre-existing peripheral neuropathic pain on the therapeutic response to the capsaicin 8% cutaneous patch.

Methods: The non-interventional QUEPP (QUTENZA – safety and effectiveness in peripheral neuropathic pain) study evaluated the effectiveness of Qutenza™ in 1044 non-diabetic patients with peripheral neuropathic pain, who received a single application. Follow-up visits were scheduled at weeks 1–2, 4, 8 and 12. A pre-defined co-analysis of changes in average pain intensity was performed based on the duration of pre-existing pain.

Results: In patients with pre-existing pain for <6 months, the mean relative change of the numeric pain rating scale score on days 7–14 to week 12 versus baseline was –36.6% [4.6 standard error of the mean (SEM); *n* = 105], –25.1% (1.9 SEM; *n* = 311) in patients with pain duration of 6 months to 2 years, –22.3% (1.6 SEM; *n* = 391) in patients with pain for >2–10 years, and –19.2% (2.6 SEM; *n* = 99) in patients with pain for >10 years. Thirty percent and 50% responder rates were 61.7% and 39.3% in patients with pre-existing pain for <6 months, 42.3% and 23.3% in patients with pain for 6 months to 2 years, 40.9% and 21.6% in patients with pain for >2–10 years, and 32.3% and 14.1% in patients with pain for >10 years.

Conclusions: The highest treatment response to the capsaicin 8% cutaneous patch 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.

1. Introduction

Causal treatment of peripheral neuropathic pain often fails and can lead to difficulties in treating chronic pain and to long-term disability (Hughes, 2002; Novak et al., 2009). The most common causes of non-diabetic sensory neuropathies are traumatic nerve injury and herpes zoster infection (Marchettini et al., 2006). Nearly every surgery can elicit a rather therapy-resistant post-operative pain (Deumens et al., 2013), and transformation from acute to chronic pain is a frequent post-surgical complication (Gerbershagen,

2013). Following recovery from an acute herpes zoster infection, long-lasting neuropathic pain occurs in about 5% of patients (Portenoy et al., 1986; Ultsch et al., 2012).

In neuropathic pain, the nervous system itself is injured (von Hehn et al., 2012). Pain can occur spontaneously; its threshold may fall dramatically, such that innocuous stimuli produce pain; and the duration and the amplitude of its response to noxious stimuli are amplified (Nickel et al., 2012). Because of structural neural changes, pain can become persistent. Chronic neuropathic pain, once manifested, should be

What's already known about this topic?

- There are conflicting data on the relevance of early intervention on the treatment response in patients with peripheral neuropathic pain.

What does this study add?

- The results of this study show that the response to topical treatment with the capsaicin 8% cutaneous patch significantly depends on the duration of pre-existing pain. Data indicate that an early treatment with 8% capsaicin leads to higher response.

regarded as an autonomous disease state of the nervous system (von Hehn et al., 2012).

These pathophysiological changes are frequently accompanied and enhanced by psychological factors that promote the transition from acute to chronic pain (Turk et al., 2010). Especially, chronic stress in daily life, work dissatisfaction, depression and pain-related cognitions, and coping behaviour are important contributors to the development of chronic pain (Hasenbring et al., 2001; Frettlöh et al., 2009).

Neuroimaging studies have shown that chronic nociceptive input from the periphery or from lesions within the central nervous system may result in cortical reorganization and changes in large-scale neuronal network connectivity (Seifert and Maihöfner, 2011). These structural brain changes indicate that an aberrantly functioning endogenous pain modulating system may play a role in chronic pain (Burgmer et al., 2012). Once manifested, chronic neuropathic pain rarely improves spontaneously, and treatment is challenging (Woolf, 2011).

To avoid these maladaptive pathophysiological and psychological changes, pain experts commonly agree that treatment of neuropathic pain should start early (Dickinson et al., 2010). However, only limited data addressing this issue are in public domain. There are various internationally accepted guidelines with evidence-based recommendations for the pharmacological management of neuropathic pain, but none of them gives an evidence-based recommendation regarding the adequate time point for specific interventions, such as the topical treatment with the capsaicin patch (O'Connor and Dworkin, 2009; National Institute for Health and Care Excellence, 2010). Therefore, the objective of this co-analysis was to investigate whether the duration of pre-existing peripheral neuropathic pain can predict treatment outcome.

The non-interventional QUEPP (**Q**UTENZA – safety and effectiveness in peripheral neuropathic pain) study collected data on safety and analgesic effectiveness of the capsaicin 8% cutaneous patch in a large cohort of non-diabetic patients who were treated for various aetiologies of peripheral neuropathic pain. The results of this study have been published elsewhere (Maihöfner and Heskamp, 2013). Based on a single dose, the high number of patients ($n = 1044$, effectiveness population) and good data quality allowed the authors to perform a reasonable analysis (Wang et al., 2007; Moye, 2012) to achieve the objective.

2. Materials and methods

2.1 Study design and visits

This was a national (Germany), multi-centre, prospective, non-interventional study conducted in accordance with the German Drug Law (§ 67,6 AMG). Ethics committee approval was obtained from the Friedrich-Alexander-University, Erlangen-Nuremberg (Ref. No. 4458). Notification was made to the Competent Authority (BfArM) and the German Statutory Health Insurance, and the study was registered in the public database of the Research-based Pharmaceutical Companies (VfA) in Germany (VfA, 2010).

The study took place between 15 March 2011 (first patient in) and 29 March 2012 (last patient out). One hundred and twelve office-based and 49 hospital-based pain physicians participated in the study. All patients received a single treatment with up to four capsaicin 8% cutaneous patches and were observed over a follow-up period of 12 weeks. Treatment was to be applied in accordance with the recommendations of the approved Qutenza™ SmPC (Summary of Product Characteristics, Astellas Pharma GmbH, Munich, Germany, February 2011). Patients were eligible for inclusion if they were at least 18 years old, suffering from peripheral neuropathic pain and had given their written informed consent for participation in the study.

Patients had to be excluded if they had diabetes mellitus, known intolerance to capsaicin or other ingredients of the cutaneous patch or if the neuropathic pain was localized in the head region.

Patients were treated by a single application with up to four capsaicin 8% cutaneous patches. Patches were applied by a physician or by a nurse under the supervision of a physician.

The patches with an original size of 14 × 20 cm had to be cut to the appropriate size to cover the most painful skin area. The skin had to be intact and dry before application. The patch was to be applied for 30 min to the feet and 60 min to other parts of the body. After removal of the patch, the skin was carefully cleaned with the provided cleansing gel.

Following the treatment, regular visits were conducted via telephone call at 7–14 days, 4 weeks and 8 weeks. Patients

returned to the study centres for the final visit 12 weeks after the patch application.

2.2 Effectiveness parameters

According to the definition of Cochrane-Glossar (2013), the term 'effectiveness' covers routine conditions, whereas in clinical studies, the term 'efficacy' covers ideal conditions. The effectiveness parameters for the analysis assessing the potential effect of the duration of pre-existing peripheral neuropathic pain on the treatment response to the capsaicin 8% cutaneous patch were as follows:

2.2.1 Pain intensity

Average pain intensity during the past 24 h was measured at each visit using an 11-point numeric pain rating scale (NPRS) ranging from 0 = no pain to 10 = worst imaginable pain.

2.2.2 Thirty percent and 50% responder rates

Responder rates were calculated for reduction of the arithmetic mean of the NPRS score at all visits between days 7–14 and week 12 versus baseline of at least 30% and 50%, respectively.

2.2.3 Quality of life (QoL) parameters

The short form-12 (SF-12) questionnaire for the assessment of QoL parameters over the last 4 weeks was completed at baseline and at the end of the observation period (Gandek et al., 1998). Physical and mental summary scale scores were calculated.

2.2.4 Co-medication for neuropathic pain

The requirement for concomitant medication to treat neuropathic pain was assessed at all visits, and the ratio of patients receiving co-medication was calculated for each subgroup.

2.3 Safety parameters

Adverse events (AEs) were either spontaneously reported by patients or their occurrence was queried at each visit throughout the observation period. AEs and serious AEs were classified according to good clinical practice standards. The causal relationship of an AE to the capsaicin 8% cutaneous patch was assessed by the investigator according to the guideline of the German Medicines Agency BfArM (Stammschulte et al., 2010). They were defined as adverse drug reactions (ADRs) if a causal relationship to study medication was possible or probably/likely. For each subgroup, the ratio of patients with ADRs that occurred during the 12-week observation period following patch application was calculated.

3. Statistical methods

3.1 Sample size, data management and analysis

It was expected that inclusion of 1000 patients would suffice to obtain 800 complete data sets.

Data were recorded using paper documentation forms. Incoming documentation forms were checked for completeness of essential parameters and data consistency. All analyses were conducted by Factum GmbH, Offenbach, Germany. Free text entries were coded according to the World Health Organization Drug Dictionary 2010 Enhanced (medicines) and MedDRA 15.0 (AEs and ADRs).

3.2 Data analysis

Descriptive analysis was performed for all data. Retrospectively collected data were excluded from the effectiveness analysis, but were included for assessment of AEs, improper use and off-label use. Biometrical analysis followed a statistical analysis plan that was implemented prior to database closure. Arithmetic mean, median, standard deviation (SD), standard error of the mean (SEM), interquartile, minimum and maximum were used for the description of continuous data. For categorical data, absolute and relative frequency were calculated.

Due to the non-confirmatory study design, imputation of missing data, e.g., 'last value-carried forward', was not performed and the actual number of evaluated patients is always referred to in this manuscript.

For the analysis according to the duration of pre-existing peripheral neuropathic pain, all patients were collated to one of four categorical subgroups: pain duration for <6 months; pain duration for 6 months to 2 years; pain duration for >2–10 years; pain duration for >10 years.

Following a single application of the capsaicin 8% patch, maximum analgesic effectiveness is expected to be reached after 2–8 weeks. Thereafter, effectiveness decreases gradually, with partial effectiveness remaining in the majority of patients at week 12. Therefore, the mean relative change over the period between days 7–14 and week 12 after patch application versus baseline was calculated for each subgroup, together with the respective 30% and 50% response rates. Descriptive *p*-values were calculated for differences between groups. If not described otherwise, paired *t*-test was used.

Table 1 Baseline characteristics of the subgroups of duration of pre-existing peripheral neuropathic pain.

Pain duration	<i>n</i>	Women (%)	Mean No. of patches		Mean baseline NPRS score (SEM)	Patients with NP co-medication (%)
			(\pm SD)	Mean age, years (\pm SD)		
<6 months	107	57.9	1.4 (0.9)	62.8 (15.1)	6.2 (0.2)	73.8
6 months–2 years	317	50.8	1.4 (0.9)	61.5 (14.9)	6.2 (0.1)	73.8
>2–10 years	399	52.6	1.4 (0.9)	60.7 (13.9)	6.4 (0.1)	74.7
>10 years	99	36.4	1.5 (0.9)	60.3 (13.2)	6.1 (0.2)	75.8
No data	122	50.8	1.2 (0.8)	61.3 (15.3)	–	–

NP, neuropathic pain; NPRS, numeric pain rating scale 0–10; SEM, standard error of the mean; SD, standard deviation.

4. Results

4.1 Baseline data

4.1.1 Disposition of patients

A total of 1063 patients receiving a single treatment of the capsaicin 8% cutaneous patch were evaluated for safety parameters (safety population). An effectiveness evaluation was available from 1044 patients, 531 (50.9%) of which were female and 509 (48.8%) were male (missing information for 4 patients, 0.4%).

4.1.2 Demographic data and neuropathic pain at baseline

The mean age was 61.2 ± 14.4 (mean \pm SD) years; there was no significant difference between females (61.0 ± 15.0) and males (61.4 ± 13.8). Four hundred and forty-two (42.4%) patients were above 65 years of age.

Mean body weight at baseline was 78.8 ± 16.6 (SD) kg. Mean systolic and diastolic arterial blood pressure was 133.5 ± 16.2 and 80.6 ± 9.9 (SD) mmHg, respectively.

Documented diagnoses showed neuropathic pain in 96.9% ($n = 1012$) of patients and peripheral neuropathic pain in 96.6% ($n = 1008$) of patients. At least one type of peripheral mononeuropathy (multiple entries possible) was present in 73.1% of patients ($n = 763$). Most frequent mononeuropathies were postherpetic neuralgia (PHN, 31.9%; $n = 333$), post-surgical neuralgia (22.8%; $n = 238$) and post-traumatic neuropathy (12.4%; $n = 129$) caused by accidents or other injuries.

Polyneuropathy of various aetiologies [chemotherapy-induced 1.9% ($n = 20$); alcohol-induced 1.2% ($n = 12$); HIV-associated 2.9% ($n = 30$); tumour-associated 0.5% ($n = 5$); chronic inflammatory demyelinating polyneuritis 0.8% ($n = 8$); and not specified 8.0% ($n = 84$)] occurred in 14.3% ($n = 149$) of all cases (multiple entries were possible). Mixed pain with a

peripheral neuropathic and a nociceptive pain component was recorded for 16.6% ($n = 173$) of patients, with radiculopathy (8.5%; $n = 89$) and complex regional pain syndrome (5.1%; $n = 53$) being the most frequent subgroups. Other neuropathies and pain of non-specified origin were quoted in 3.8% of patients ($n = 44$). The mean duration of pre-existing pain was 4.4 ± 6.0 (SD) years. Mean pain intensity at baseline was 6.3 ± 1.8 (SD).

The demographic parameters of the subgroups according to the duration of pre-existing pain are summarized in Table 1. All subgroups were comparable regarding sex, age, pain intensity at baseline, number of patches applied and co-medication for neuropathic pain.

4.2 Treatment results

4.2.1 Application of the capsaicin 8% cutaneous patch

The mean number of applied capsaicin 8% cutaneous patches at visit 1 was 1.4 ± 0.9 (SD) per patient. Up to one complete patch was used in the majority of patients ($n = 636$). Patches were applied to the following body areas (multiple areas were possible): foot/feet (25.2%; $n = 263$), thoracic region (24.5%; $n = 256$), leg/legs (18.7%; $n = 195$), hand/hands (10.6%; $n = 111$), lumbar region (10.3%; $n = 108$), arm/arms (7.9%; $n = 82$), shoulder (6.1%; $n = 64$) and cervical region (2.87; $n = 30$). Other or non-specified body regions were treated in 7.6% of patients ($n = 79$), thereof 24 (2.3%) received applications to the head.

4.3 Effectiveness parameters

4.3.1 Pain intensity (NPRS scores)

Changes in mean NPRS scores over time for the individual subgroups are shown in Fig. 1. The mean changes of pain intensity between 7–14 days and 12

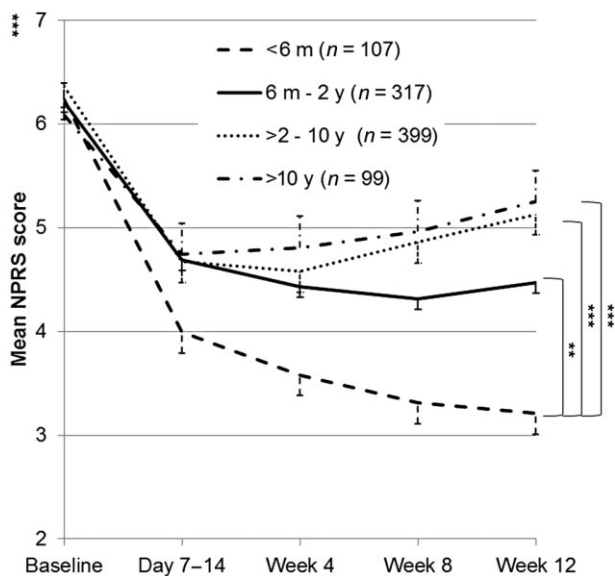


Figure 1 Time course of mean pain intensities in the subgroups of duration of pre-existing peripheral neuropathic pain (m, months; y, years, NPRS, numeric pain rating scale 0–10; ** $p \leq 0.01$; *** $p \leq 0.001$, single t-test).

weeks versus baseline according to the duration of pre-existing neuropathic pain are summarized in Table 2. All four subgroups had a significant mean pain reduction compared with baseline. 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 SEM; $p \leq 0.001$) 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; $p \leq 0.001$) and

Table 2 Relative change (%) of mean pain intensity [numeric pain rating scale (NPRS) score] during days 7–14 to week 12 versus baseline for subgroups of duration of pre-existing peripheral neuropathic pain (patients with baseline NPRS score = 0 were excluded from this evaluation).

Pain duration	Change from baseline		
	Mean (%)	SEM	n
<6 months	-36.6	4.6	105
6 months–2 years	-25.1	1.9	311
>2–10 years	-22.3	1.6	391
>10 years	-19.2	2.6	99
No data	-25.9	2.9	119
Total	-24.7	1.1	1025

SEM, standard error of the mean.

Table 3 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.

Pain duration	Responder rates (% patients)	
	$\geq 30\%$	$\geq 50\%$
<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

* $p < 0.001$ 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).

19.2% improvement. The mean NPRS score for patients with pre-existing pain for less than 6 months did not increase again within the observation period, whereas a rise in mean NPRS scores was noted in the other subgroups.

Within the subgroup of patients with less than 6 months of pain, the possibility of an over-representation of PHN patients was tested. In this group, 58 patients were diagnosed with PHN and 47 patients had any other peripheral neuropathic pain syndrome. In patients with PHN for less than 6 months, the mean change of the NPRS score was -2.94 (SEM 0.36) compared to -2.37 (SEM 0.34) in patients with any other pain syndrome for less than 6 months. There was no statistically significant difference between both subgroups ($p = 0.253$).

4.3.2 Responder rates

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 ($p \leq 0.001$; chi-square test) (Table 3). Compared with 30% and 50% responder rates of 61.7% and 39.3% observed in the group of patients with less than 6 months of pain, corresponding responder rates were 32.3% and 14.1% in the subgroup with pain duration of more than 10 years.

Also, the rate of patients with a mean reduction of the mean pain intensity of at least 2 points measured with the NPRS 0–10 was significantly higher in patients with short pain duration as compared to patients with pre-existing pain for more than 6 months. With 25.3%, the respective rate of patients with a pain history of more than 10 years was less than half of that of patients with pain duration of less than 6 months (56.1%).

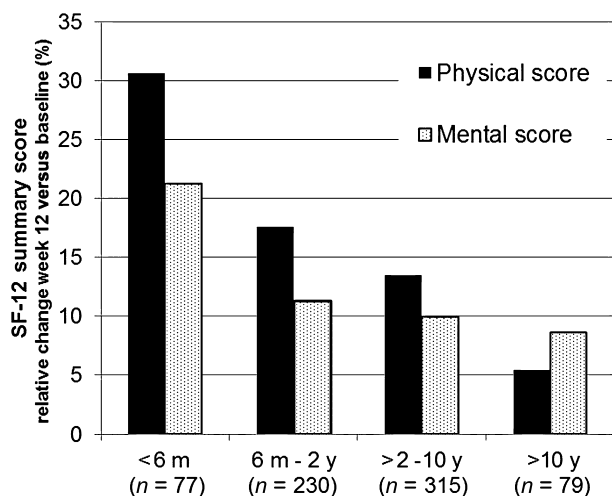


Figure 2 Mean relative changes (%) of short form-12 (SF-12) physical and mental summary scale scores between week 12 and baseline in subgroups of duration of pre-existing pain (m, months; y, years).

4.3.3 QoL parameters

The duration of pre-existing neuropathic pain had a significant impact on the mean change of the physical and mental summary scale score following the treatment with capsaicin 8% cutaneous patches (Fig. 2). At final visit after 12 weeks, the relative improvement of the physical summary scale score was 30.6% (4.7 SEM) in patients with pre-existing pain for <6 months, and 17.6% (2.4 SEM), 13.5% (1.7 SEM) and 5.4% (2.7 SEM) in patients with pre-existing pain for 6 months to 2 years, >2–10 years and more than 10 years, respectively. The relative improvement of the mental summary scale score was 21.3% (4.1 SEM) in patients with pre-existing pain for <6 months, and 11.3% (2.1 SEM), 10.0% (1.7 SEM) and 8.6% (2.7 SEM) in patients with pre-existing pain for 6 months to 2 years, >2–10 years and more than 10 years, respectively.

4.3.4 Co-medication for neuropathic pain

The percentage of patients requiring co-medication for their neuropathic pain over time is shown in Fig. 3. Whereas this percentage was similar in all subgroups at baseline, discontinuation of concomitant medication was reported for 28% (pain duration up to 6 months), 13.9% (pain for 6 months to 2 years), 6.8% (pain for >2–10 years) and 2% (pre-existing pain for more than 10 years) of patients at the end of the observation period.

4.4 Safety parameters

The overall rate of patients with ADRs was 10.0%. In patients with pre-existing pain for <6 months, the ADR rate was 11.1%. The respective rates were 11.2%, 9.4% and 11.7% in patients with pre-existing pain for 6 months to 2 years, >2–10 years and >10 years. There were no significant differences between these subgroups. The most frequent ADRs in all subgroups were pain and erythema at the application site.

5. Discussion

Treatment with a single application of the capsaicin 8% cutaneous patch leads to a significant improvement of pain intensity and QoL parameters in all subgroups studied.

The results of the co-analysis indicate an inverse correlation of the effectiveness of treatment with the duration of pre-existing peripheral neuropathic pain in the studied patient population. Patients with pre-existing pain of less than 6 months seem to benefit to an even greater extent from treatment than those with a longer history of pain. In the subgroup of patients with a history of prior pain of up to 6 months, high $\geq 30\%$ and $\geq 50\%$ responder rates of 61.7% and 39.3%, respectively, were observed, which were accompanied by an improvement in the QoL scores. The $\geq 30\%$ responder rates decreased to 42.3% and 40.8% for

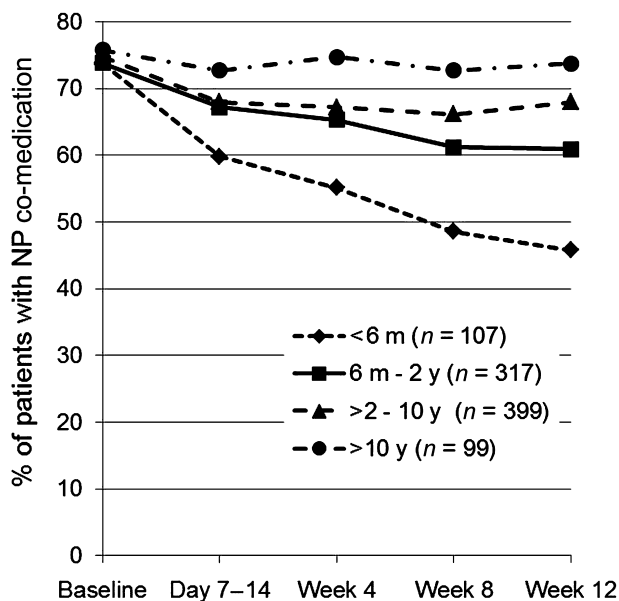


Figure 3 Percentage of patients with co-medication for neuropathic pain in the subgroups of pre-existing duration of pain (m, months; y, years; NP, neuropathic pain).

patients with pre-existing pain duration of >6 months up to 2 years and of >2 years up to 10 years, respectively, and to 32.3% for patients with a pain history of more than 10 years. Although further investigations are warranted, these preliminary findings suggest that early initiation of treatment should be considered. This is further supported by the observed changes in mean NPRS and reduction of concomitant medication for neuropathic pain over time for the individual subgroups. The mean NPRS score for patients with prior pain of <6 months did not rise again within the observation period, whereas an increase in mean NPRS scores was observed in other subgroups.

A well-known clinical phenomenon is the comparably good prognosis of early PHN. However, the positive results in the <6 months group cannot be explained by an over-representation of PHN patients.

Concomitant medication administered for the treatment of neuropathic pain at baseline could be discontinued in one of three patients with prior pain of <6 months during the course of the study. This may lead to an improvement in patient safety and reduced costs for health care providers.

Information regarding the response to early treatment (less than 6 months) of neuropathic pain with the capsaicin 8% patch has up to now been lacking in public domain, although a potential impact of prior pain duration has been considered in earlier studies.

Backonja et al. (2011) performed an integrated data analysis from four multi-centre, randomized, double-blind, 12-week controlled capsaicin 8% cutaneous patch trials in PHN. The primary endpoint was the mean percentage change in NPRS scores (average pain for the past 24 h, daily recordings) from baseline to weeks 2–8. The observed differences for patients with PHN duration of <2.1 and ≥ 2.1 years were similar to 33.1% and 29.6%, respectively. Within the current study investigating multiple aetiologies of neuropathic pain, the relative change (%) of mean pain intensity (NPRS score) during day 7–14 to week 12 versus baseline was –25.1% for a pain duration of 6 months to 2 years and –22.3% for prior pain of >2–10 years. The corresponding change for patients with a history of less than 6 months of pain was –36.6%.

Recently, Brown et al. reported data from an integrated analysis of two phase III, controlled trials investigating the capsaicin 8% cutaneous patch for the treatment of painful HIV-associated distal sensory polyneuropathy. An analysis based on duration of pain of <5.1 and ≥ 5.1 years revealed a numerically lower (–23.1% vs. –30.7%) mean percentage change in NPRS score from baseline to weeks 2–12 in patients with a shorter history of pain (Brown et al., 2013).

These findings seem to be in contrast with the results from the current study. Different baseline characteristics may account for the observations made.

A literature search to retrieve information of the potential impact of pain duration on treatment outcome for other neuropathic pain medications did not yield any results.

Time-to-treat has however been addressed in general. A task force established by the Canadian Pain Society in December 2005 conducted a systematic literature review to assess the relationship between waiting times, health status and health outcomes for patients awaiting chronic pain treatment (Lynch et al., 2008). A significant deterioration in psychological well-being and health-related QoL was observed during the 6-month waiting time between referral and treatment of chronic pain. The task force therefore concluded that delays of ≥ 6 months to initiate treatment for chronic pain are medically unacceptable. It was further stated that additional investigations are required to assess the onset of deterioration relative to the occurrence of pain and the potential impact of waiting time on treatment outcome.

The herein reported data may provide a supporting argument for early initiation of therapy.

As baseline demographic and clinical characteristics, including NPRS and SF-12 scores, were comparable for the four subgroups of the current analysis, it seems unlikely that parameters other than prior duration of pain contributed to the observed treatment response. Events that occur in the early stage after onset of pain need to be considered. Thus, it cannot be excluded that ongoing spontaneous healing processes may have added to the better treatment outcome in patients with prior pain of less than 6 months. Further, pathophysiological and psychological processes that drive the chronification process of peripheral neuropathic pain may still be reversible with adequate intervention during this period.

Treatment success based on stages of chronification has been retrospectively investigated by Huppe et al. (2011) in a large cohort of patients ($n = 1461$) using the Mainz pain staging system (MPSS). Main diagnosis of pain were headache ($n = 164$), neuropathic pain ($n = 338$), back pain ($n = 689$), and muscle, joint and bone pain ($n = 270$). Chronification stage I, II and III was established for 13.8%, 44.7% and 41.5% of patients, respectively. Intensity of pain, psychological disability and patient global impression of success were outcome measures. Significant improvement was noted for these measures regardless of the MPSS stage. Although reduction in pain intensity was most pronounced in patients with low pain chronification,

the effect size of change was stronger than 0.80 for patients with the highest MPSS stage (III). These findings suggest that the influence of the chronification process may be limited. However, although the general mechanisms of chronification may be similar in various types of neuropathic pain, pathophysiological, psychological and clinical variables need to be considered when comparing the results. In addition, Huppe et al. evaluated data, irrespective of the treatment applied, whereas the current study focuses on topical treatment using the capsaicin 8% cutaneous patch.

Although it is intriguing to assume that early initiation of treatment for peripheral neuropathic pain may result in additional patient benefit, the limitation of the current investigation is the lack of a control arm. The non-interventional design of the study had been chosen to capture data from daily clinical routine. Although the co-analysis was planned prior to database closure, the observation that patients with a history of peripheral neuropathic pain of less than 6 months showed a better treatment response compared to those with a longer duration of pain was somewhat unexpected.

The observation period of 3 months limits the long-term interpretation of this study. It cannot be taken for granted that the patients who had a good response after one application would have the same response after the next application. Further controlled studies are necessary to confirm the efficacy of the capsaicin 8% cutaneous patch treatment based on the duration of pre-existing pain.

6. Conclusions

Treatment outcome with the capsaicin 8% cutaneous patch depends on the duration of pre-existing peripheral neuropathic pain. It was observed that patients with a history of peripheral neuropathic pain of less than 6 months showed a better treatment response compared with those with a longer duration of pain.

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Author contributions

Prof. Dr. Christian Maihöfner was the principal investigator of this non-interventional study and made substantial con-

tributions to the conception and study design as well as to data analysis and the clinical and scientific interpretation of data. He critically reviewed and revised the manuscript for medical and scientific content and granted approval for the final manuscript.

Dr. Marie-Luise Heskamp, an employee of the study sponsor, was responsible for conception and study design, including statistical analysis of data as well as interpretation of results. She provided the framework for the manuscript and critically reviewed and revised medical and scientific content. She approved the final manuscript.

The authors jointly discussed study results and manuscripts.

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