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ORIGINAL ARTICLE

Capsaicin 8 % as a cutaneous patch (Qutenza^{TM}): analgesic effect on patients with peripheral neuropathic pain

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Abstract Evaluation of the analgesic effect after a single application of the capsaicin 8 % cutaneous patch (Qutenza^{TM}) in 37 patients suffering from painful, distal symmetric polyneuropathy (PNP) for an average of 5 years. Patients ranged from 40 to 78 years of age and 22 subjects were HIV-positive. Patients were observed 4 weeks prior to 12 weeks post administration. An evaluation of the therapeutic effect of capsaicin 8 % as a dermal patch in terms of pain reduction, change of sleeping behavior and social activities was performed and statistical analysis of data was conducted using non-parametric methods. Patients were selected according to clinical criteria. Numerical rating scale (NRS 0–10) was used to inquire pain intensity and a pain score was calculated using the painDETECT© questionnaire Freynhagen R (Curr Med Res Opin 22:1911–1920, [2006]). A significant reduction of pain was achieved for up to 12 weeks, with a maximum after 2–4 weeks post administration. After patient education and before application of capsaicin patch, a significant reduction of three levels on the NRS was observed. Symptoms of painful PNP decreased over the period of investigation and 8 patients reported a reduction of systemic pain medication. In patients with an HIV infection, a significant extension of sleep was achieved for 2, 4 and 8 weeks after application. Thus, the application of the capsaicin 8 % patch resulted in a significant relief of neuropathic pain, a prolongation of sleep, a reduction of oral pain medication and a resumption of social activities.

Keywords Capsaicin 8 % patch · Reduction of pain · Peripheral neuropathic pain

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Introduction

Neuropathic pain is defined as pain due to injury or disease affecting the somatosensory system [23]. It can be caused by a disorder of the central or the peripheral nervous system. Peripheral neuropathic pain is perceived in the epidermal nociceptors and transmitted via A-δ und C-fibers to the central nervous system.

Capsaicin 8 % dermal patch (Qutenza^{TM}) is a new option for the treatment of localized neuropathic pain, e.g. PNP as post herpetic neuralgia (PHN) or as HIV-associated neuropathy (HIV-AN). In randomized, controlled, clinical trials relevant pain relief for up to 12 weeks after a single application was achieved for about one third of patients [22]. A meta-analysis of seven randomized, double-blind, controlled trials testing the capsaicin 8 % patch (Qutenza^{TM}) [18] proved a significant reduction in pain for a period of 5 months. Other studies reported median response of 22 weeks and in 14 % of patients a response for over 40 weeks after a single application was achieved [17].

Capsaicin, an alkaloid extracted from the chili pepper, is a selective agonist to the TRPV1-receptor (transient

receptor potential vanilloid 1), a nonselective, heat activated cation channel. Prolonged activation of this channel causes a vast depletion of presynaptic neuropeptides, leading to transient effects such as erythema, pruritus and burning sensation on the application site. An influx of calcium into the neurons is induced [5], leading to a reversible loss of function of the distal nociceptive fibers. Additionally, topically applied capsaicin causes dysfunctioning of the upregulated TRPV1-receptors located in the nervous endings of the skin and reduces the density of epidermal nerve fibers for up to 60 % after one single, maximum 60 min application [10, 12, 16].

The advantage of locally applied capsaicin consists in its minimal systemic drug levels [1], a very low side effect profile and hence an easy combination with conventional systemic pain medication [6, 14, 25]. It is particularly suitable for patients with an HIV infection in combination with combined Antiretroviral Therapy (cART) [22] and for elder, multimorbid and polymedicated patients.

Methods

Data of 37 patients (7 ♀, 30 ♂) with distal symmetric, non-diabetic polyneuropathy were analyzed. All patients agreed to an anonymous scientific evaluation. For further demographic data see Table 1.

Patients were selected according to clinical criteria such as pain status, loss of reflexes and characteristic PNP symptoms, for example allodynia, paraesthesia, hyper- and hypalgesia, numbness of the affected area and reduced sensitivity to temperature. A clinical-neurological examination was conducted before initiating the treatment. In 22 patients, the distal symmetric PNP was associated with HIV infection, in 2 patients with chronic inflammatory demyelinating polyneuropathy (CIDP), in 1 patient with chemotherapy; in 12 patients the cause remained unknown despite extensive diagnostics; 27 of 37 patients have been receiving oral pain medication for over 3 years.

Patients were interviewed 4 weeks before treatment, 1 day before treatment and on the day of intervention to investigate current pain intensity (NRS 0–10), sleep duration and additional oral drug medication for the treatment of the neuropathic pain. A pain score was calculated using the painDETECT©-questionnaire [8]. Patients were contacted 2, 4 and 8 weeks post administration in order to inquire current pain intensity, sleep duration and changes in pain medication. Follow-up was completed 12 weeks after treatment by adding information about the progression of the PNP symptoms, restriction in social activities due to the disease and the current pain score was calculated. In addition, an evaluation of the treatment from patients' perspective, its impact on their quality of life and the pain status compared to baseline was requested.

Table 1 Demographic data ($n = 37$)

		Number of cases (n)
Sex (male:female)	30:7 (HIV positive: 20:2)	
Mean age (years)	56.46 ± 11.96 (range 40–78)	
HIV (positive:negative)	22:15	
HIV-RNA < 37 c/ml		21
CD4+/μL	568.45 (±320.15)	
Etiopathogenesis of the PNP	HIV-associated	22
	Chronic inflammation (CIDP)	2
	Chemotherapy-induced	1
	Unknown origin	12
Treated area	Hands	3
	Feet	23
	Legs (except feet)	5
	Face	1
	Feet and legs	3
	Hands and feet	1
	Hands, feet and legs	1
PNP for (years)	4.68 (range 2–13)	
Pain medication (number of patients)		27
Pain medication (substances)	Amitriptyline (75–225 mg)	3
	Gabapentin (900–4800 mg)	12
	Pregabalin (150–900 mg)	15
	Duloxetine (30–120 mg)	12
	Mirtazapine (30 mg)	1
	Opipramol (150 mg)	1
	NSAID	7
	Opioids (Fentanyl patch 50 μg/h, tilidine)	4
Changes in oral pain medication during investigation	Dose reduced	8
	Dose increased	4
	No change	8

The painDETECT© -pain score is a highly sensitive and specific screening tool developed in 2006 in cooperation with the German Research Network on Neuropathic Pain (DFNS) to differentiate burning and tingling sensation, pain due to light touch, electrifying pain attacks, temperature associated pain, numbness and intense sensitivity of

the affected area. It consists in 7 questions; 0–5 points may be awarded for each answer. A maximal value of 35 points can be calculated. When using the painDETECT questionnaire for screening purposes, Freynhagen et al. considered cut-off scores ≤12 (a neuropathic component is unlikely, <15 %) and ≥19 (a neuropathic component is likely, >90 %) to be most appropriate. To detect a neuropathic pain component, its sensitivity and specificity were 85 and 80 %, respectively, compared to clinical diagnosis [8]. However, when used in patients suffering from other musculoskeletal disorders (e.g. fibromyalgia), values for sensitivity (79 %) and specificity (53 %) differ and hence the questionnaire may not be suitable for screening [9].

Capsaicin 8 % dermal patch (Qutenza™) is a silicon-based adhesive conceived for single use. The patch is applied under medical supervision on the previously determined painful area for a maximum of 30 min (treatment of the feet) or 60 min (treatment of other areas). After completion, residual capsaicin is removed with a cleansing gel and the area is thoroughly washed with water and soap. Up to four of the 14 × 20 cm sized patches can be used simultaneously on intact, non-irritated and dry skin. An elastic bandage should be used to optimize the contact between skin and patch during application and thus guarantee a complete penetration to the skin. Treatment with the capsaicin patch (Qutenza™) can be repeated every 90 days [7].

Statistical analyses were performed using Microsoft Office Excel 2007 for Windows® (United States) and IBM SPSS®Statistics 21 for Windows (IBM Corporation, Somers, NY, USA). Due to the small sample size and the failure to ensure the assumption of normal distribution of continuous variables, non-parametric methods were applied: Friedman test for the analysis of variance, Wilcoxon test for paired samples and Mann–Whitney *U* test for independent samples. As numeric value for continuous variables we used median, minimum and maximum, for categorical variables we used absolute and relative frequencies. Inferential statistics are intended to be exploratory (hypotheses generating), not confirmatory, and are interpreted accordingly. Results with a p value of <0.05 were considered to be statistically significant.

Results

Demographic data of the patients are reported in Table 1.

As Table 2 shows, the neuropathic pain was continuously reduced after treatment with the capsaicin patch for up to 4 weeks after application. After the 8th week, a new pain increase was observed. There was a significant reduction in NRS scores from 9.0 (4 weeks prior to the application of the patch) to 4.0 (2 weeks after application).

Table 2 Intensity of NRS during course of investigation

	Median reduction compared to baseline	p value	Median/ mean ± SD
4 weeks before therapy (baseline)			9.0 8.35 ± 1.80
24 h before therapy	3.0	<0.01	6.0 5.73 ± 1.90
Day of intervention (before therapy)	3.0	<0.01	5.0 4.89 ± 2.58
2 weeks after therapy	5.0	<0.01	4.0 4.42 ± 2.76
4 weeks after therapy	5.0	<0.01	4.0 4.39 ± 2.60
8 weeks after therapy	4.0	<0.01	4.0 4.68 ± 2.63
8th–12th week after therapy	1.0	<0.01	7.0 6.78 ± 2.82
12 weeks after therapy	3.0	<0.05	5.0 5.16 ± 2.30

Subsequently, an increase to 7.0 followed in week 8–12, which dropped to 5.0 after 12 weeks. There was a clear reduction in pain intensity of 3.0 levels (min 0, max 5, $p < 0.01$) in the last 24 h before treatment of and a reduction of 3.0 levels (min 0, max 10, $p < 0.01$) on the admission day compared to 4 weeks prior to treatment. This corresponds to a reduction of pain intensity in anticipation of therapy. Figure 1 shows the intensities of pain throughout the observation time.

The analyses indicate that men and women as well as HIV-positive and HIV-negative patients show different pain behavior. Hence, these groups were analyzed separately.

Table 3 shows the intensities of NRS for HIV-positive ($n = 22$) and HIV-negative ($n = 15$) patients. HIV-positive patients displayed an initial value of 8.0 4 weeks before therapy. The lowest values were reached after 2 weeks with 3.0 (min 0, max 9, $p < 0.01$) and 4 weeks after treatment with 3.0 (min 1, max 7, $p < 0.01$). 12 weeks after therapy, the pain intensity increased to 4.0 (min 1, max 9, $p < 0.01$). Additionally, a significant reduction of pain scores was observed in anticipation of the therapy. HIV-negative patients showed an initial value of 9.0. The lowest values were reached after 2 weeks with 4.0 (min 2, max 10, $p < 0.01$). 12 weeks after the application, the intensity increased up to 5.5 (min 2, max 9, $p < 0.01$). Figure 2 shows the intensities of pain for HIV-positive and HIV-negative patients during the course of observation.

Table 4 shows the intensities of NRS for male ($n = 30$) and female ($n = 7$) patients. In male subjects, a statistically significant reduction of pain ($p < 0.01$) was achieved at all observation times compared to baseline. Male patients

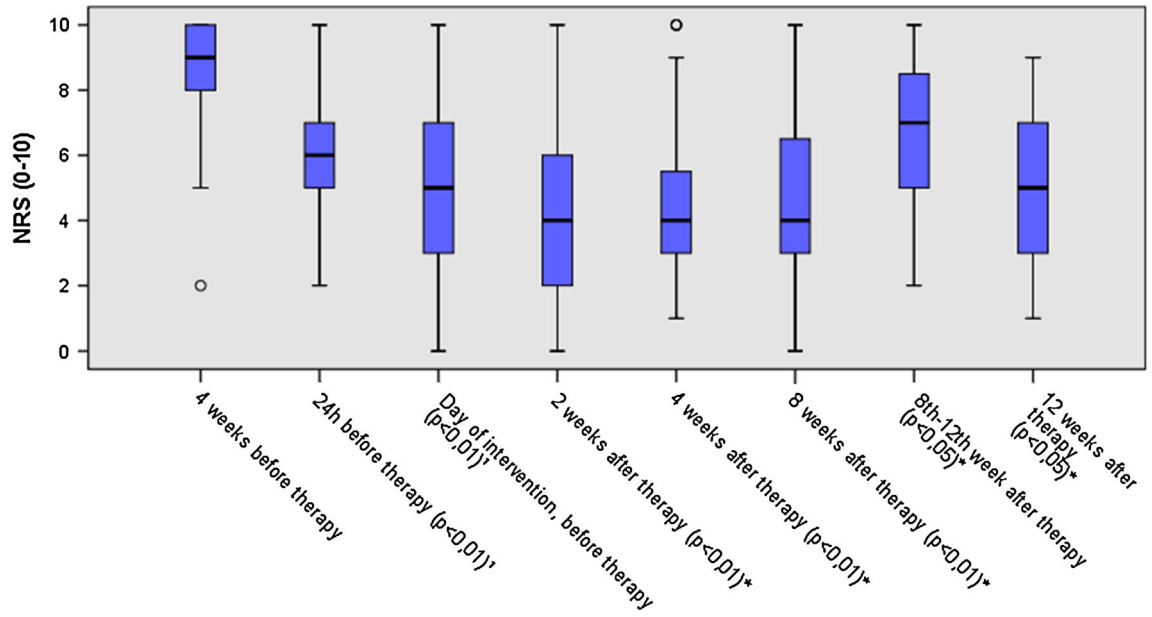

Fig. 1 NRS over the course of investigation. The intensity of neuropathic pain was continuously reduced after treatment with the capsaicin patch for up to 4 weeks after application. NRS scores dropped from a median of 9.0 (4 weeks prior to the application of the patch) to 4.0 (2 and 4 weeks after application). Subsequently, an increase to 7.0 followed in week 8–12, which dropped to 5.0 (12 weeks post application). [1]NRS compared to 4 weeks before treatment; *NRS compared to 24 h before treatment

Table 3 Intensity of NRS for HIV-positive/negative patients

	4 weeks before therapy	24 h before therapy	2 weeks after therapy	4 weeks after therapy	12 weeks after therapy
HIV positive					
Median	8.0	6.0	3.0	3.0	4.0
p value		<0.01	<0.01	<0.01	<0.01
HIV negative					
Median	9.0	6.0	4.0	4.5	5.5
p value		<0.01	<0.01	<0.01	<0.01

showed a median output value of 8.5 (4 weeks before therapy). The lowest values were reached 4 weeks after treatment with 3.0 (min 1, max 10, $p < 0.01$). In week 8–12 an increase up to 7.0 (min 2, max 10, $p < 0.01$) was observed. 12 weeks after therapy, pain intensities decreased to 5.0 (min 1, max 9, $p < 0.01$). Female patients showed an initial median value of 9.0. The lowest NRS scores were reached 2 weeks after therapy with 5.5 (min 2, max 10, $p < 0.26$). In week 8–12, an increase to 8.0 (min 4, max 10, $p < 0.13$) was observed; after 12 weeks, the value dropped back to 6.5 (min 2, max 9, $p < 0.04$). Additionally, a statistically significant reduction in pain was achieved in the last 24 h before treatment [7.0 (min 3, max 10), $p < 0.04$)] and on the day of intervention, before administration of the capsaicin patch [6.0 (Min 2, Max 10), $p < 0.04$)]. This corresponds to a pain relief in anticipation of the therapy. Figure 3 shows the intensities of pain for male and female patients during the course of observation.

The evaluation of the painDETECT scores yielded the following results: 48.6 % of patients experienced a decrease in pain score (Maximum decrease: 11 points, 31.4 %). In 18.9 % of patients the score increased during the course of observation (Maximum increase: 9 points, 25.7 %) and in 18.9 % of patients no change occurred. The statistical analysis revealed a highly significant reduction ($p < 0.01$) of the score 12 weeks after treatment [median = 14.0 (min 5, max 30)] compared to baseline [median = 17.0 (min 7, max 30)]. The group-specific analysis of data revealed a statistically significant reduction ($p < 0.03$) 12 weeks after treatment [median = 13.5 (min 5, max 24)] compared to baseline [median = 16.0 (min 7, max 26)] for patients with HIV-associated PNP ($n = 22$). In addition, a significant reduction ($p < 0.02$) of the score 12 weeks after treatment [median = 13.5 (min 5, max 29)] compared to baseline [median = 16.0 (min 7, max 26)] was obtained for male subjects ($n = 30$). The 8 % capsaicin patch was able to relieve patients' pain and, according to anamnesis and clinical-neurological examinations, clearly reduced symptoms such as paraesthesia, allodynia, and the increased sensitivity to temperature and touch.

Table 5 shows the sleep duration per night for HIV-positive ($n = 22$) and HIV-negative ($n = 15$) patients. For HIV-positive patients, a highly significant prolongation of sleep was achieved 2 weeks ($p < 0.01$), 4 weeks ($p < 0.01$) and 8 weeks ($p < 0.03$) after treatment

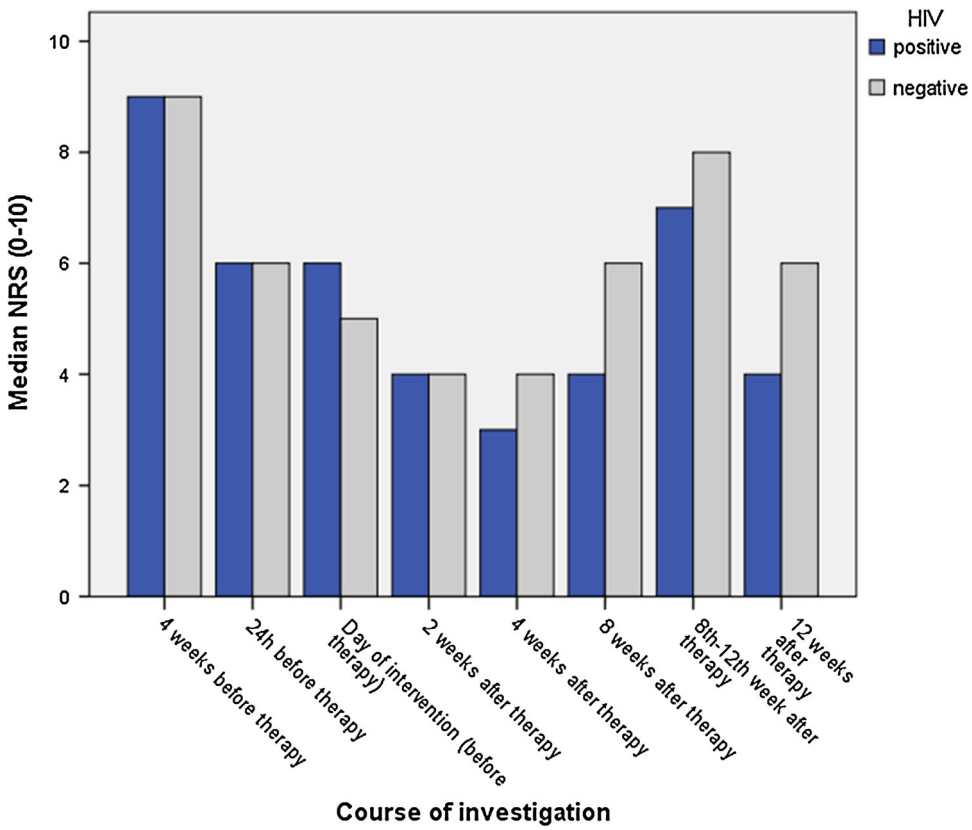

Fig. 2 NRS for HIV-positive/negative patients. Numerical rating scale (NRS) of pain intensities for HIV-positive/negative patients over the course of investigation: HIV-positive patients displayed an initial median value of 8.0 (4 weeks before therapy). The lowest values were reached after 2 weeks with 3.0, and 4 weeks after treatment with 3.0. HIV-negative patients showed an initial median value of 9.0. The lowest values were reached after 2 weeks with a median score of 4.0

Table 4 Intensity of NRS for male/female patients

	24 h before therapy	2 weeks after therapy	4 weeks after therapy	8th–12th week after therapy	12 weeks after therapy
Male					
Median	6.0	4.0	3.0	7.0	5.0
p value	<0.01	<0.01	<0.01	<0.01	<0.01
Female					
Median	7.0	5.5	6.5	8.0	6.5
p value	<0.04	<0.26	<0.26	<0.13	<0.04

compared to baseline. The average hours of sleep increased from 6.00 ± 1.41 h (before treatment) to a maximum of 6.44 ± 1.20 h after 2 weeks. 12 weeks after treatment it dropped to 6.39 ± 0.92 h. For HIV-negative patients, a prolongation of sleep from 6.87 ± 1.54 h (before treatment) to a maximum of 7.38 ± 1.04 h after 4 weeks was achieved. 12 weeks after treatment, the values were stable at 7.38 ± 1.12 h per night. Figure 4 shows the sleep duration for HIV-positive and HIV-negative patients throughout the period of observation.

When asked, how often patients felt restricted in their social activities because of the pain, a great improvement was noticed for female subjects (28.6 % responded with "always" before the treatment, whereas 0 % 12 weeks after treatment) and in HIV-positive, male subjects (21.1 % responded with "mostly" before the treatment, whereas 5.9 % 12 weeks after treatment).

As part of the termination visit, 12 weeks after therapy, patients were asked to evaluate the treatment, eventual changes in their quality of life and the pain condition compared to baseline. A total of 62.2 % of patients reported an improvement in the pain condition trough the treatment and 77.4 % of patients would agree to repeat the therapy at any time; 8 out of 27 patients, who initially received further oral pain medication, were able to reduce the dose during the follow-up examinations.

General discussion

These results illustrate, that a single application of the high-dose, 8 % capsaicin patch (Qutenza^{TM}) was able to achieve a severe reduction of neuropathic pain over a period of 12 weeks, with a maximum pain relief after 2–4 weeks. After the patient education and prior to the application of the capsaicin patch, a statistically significant reduction in pain ($p < 0.01$) of three levels on the numerical rating scale (NRS) compared to baseline was achieved. Symptoms of the painful PNP, such as paraesthesia, allodynia as well as the increased sensitivity to temperature

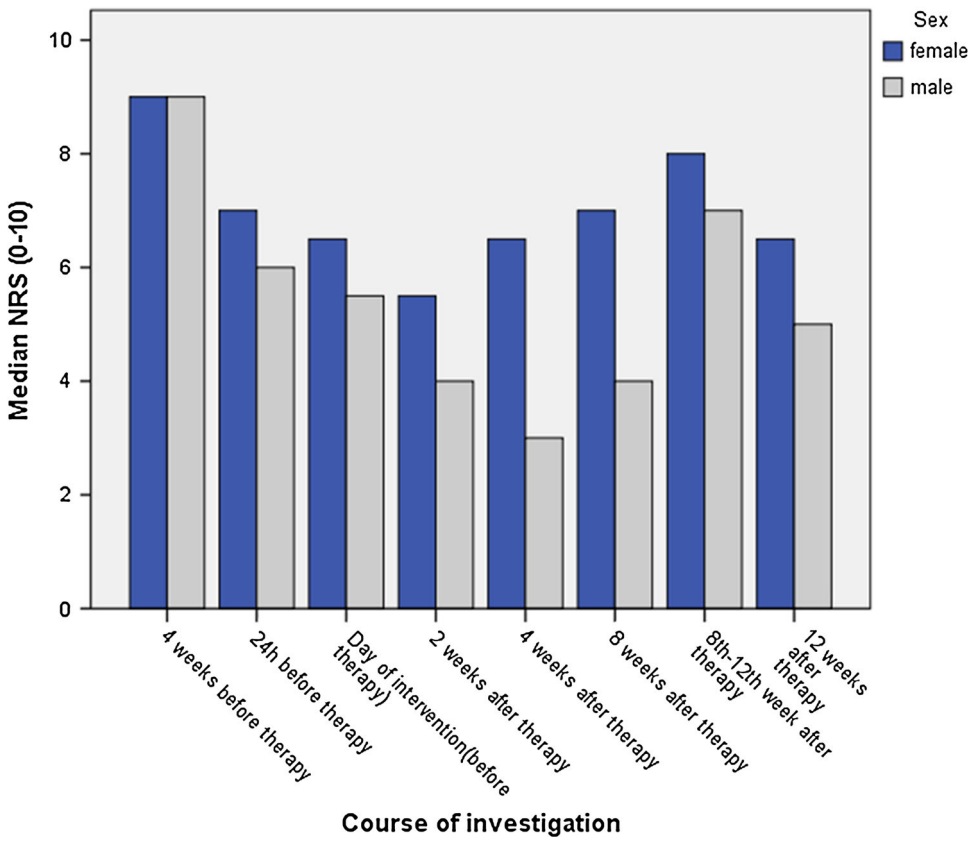

Fig. 3 NRS for male/female patients. Pain intensities for male/female patients over the course of investigation: Male patients showed a median output value of 8.5 (4 weeks before therapy). The lowest values were reached 4 weeks after treatment with a median score of 3.0. Female patients showed an initial median value of 9.0. The lowest scores were reached 2 weeks after therapy with a median score of 5.5

Table 5 Duration of night sleep (h) for HIV-positive/negative patients

	Baseline	2 weeks after therapy	4 weeks after therapy	8 weeks after therapy	12 weeks after therapy
HIV positive					
Mean (h)	6.00 ± 1.41	6.44 ± 1.20	6.41 ± 1.12	6.33 ± 1.09	6.39 ± 0.92
p value		<0.01	<0.01	<0.03	<0.08
HIV negative					
Mean (h)	6.87 ± 1.54	7.15 ± 1.35	7.38 ± 1.04	7.08 ± 1.26	7.38 ± 1.12
p value		<0.88	<0.30	<0.82	<0.30

and touch, decreased over the course of investigation. Eight patients reported a reduction of systemic pain medication after treatment. Four weeks prior to the application, 32.4 % of patients reported a pain intensity of 10 points, and 86.0 % a value of ≥7 points on the NRS. Twelve weeks after treatment, none of the patients reached a value of 10 points and only 29.7 % showed a value of ≥7 points on the NRS.

For male patients, the gender-specific analysis of data revealed a significant decrease of pain ($p < 0.01$) throughout all observation points compared to baseline, with a maximum after 2 weeks. Female patients, however, exhibited higher initial values and less pain reduction was achieved through the application of the capsaicin patch. Values were significant 24 h prior to therapy, on the day of intervention and 12 weeks after treatment, with a maximum pain reduction after 4 weeks. Differences in the response to the therapy might be due to the small number of female subjects ($n = 7$).

The separate analysis of HIV-positive and HIV-negative patients showed in both groups a median reduction of five levels on the NRS after a single application of the 8 % capsaicin patch. Compared to HIV-negative patients, HIV-positive subjects reported lower output-values; a greater pain relief was obtained and, 12 weeks after application, intensities of pain were lower than for HIV-negative patients.

The sleep duration per night was prolonged throughout the observation. In the long-term study, HIV-positive patients slept significantly longer at all observation points

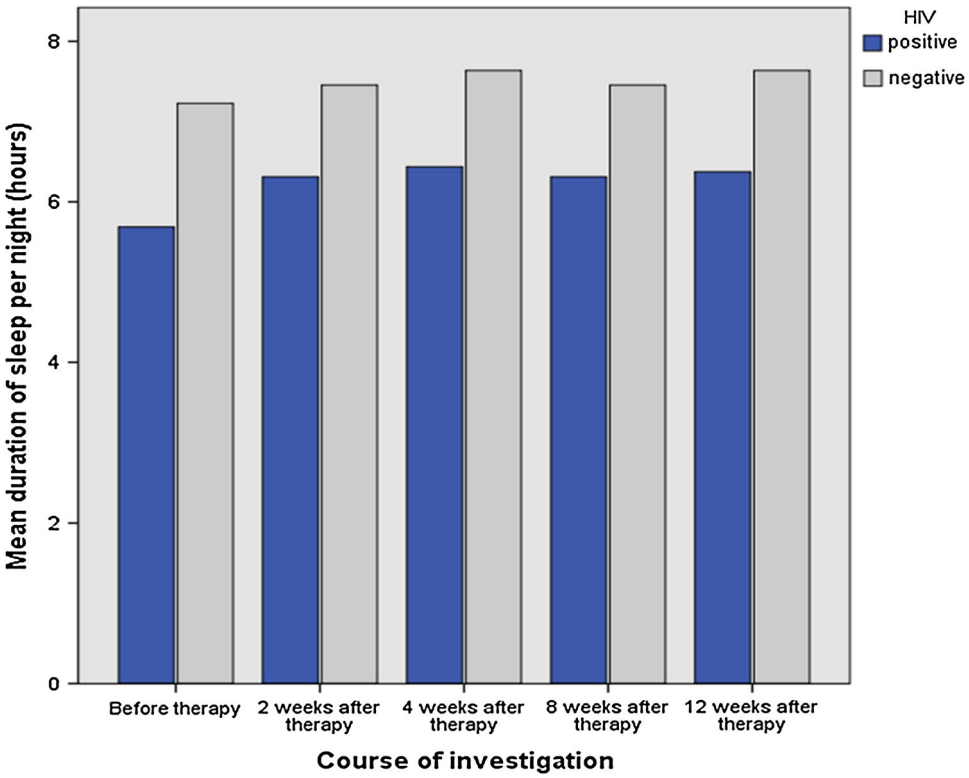

Fig. 4 Sleep duration for HIV-positive/negative patients. Mean sleep duration per night (h) for HIV-positive/negative patients over the course of investigation: for HIV-positive patients, a highly significant prolongation of sleep was achieved 2 weeks ($p < 0.01$), 4 weeks ($p < 0.01$) and 8 weeks ($p < 0.03$) after treatment compared to baseline

compared to baseline; a maximum was achieved 2 weeks after therapy. For HIV-negative patients, a continuous increase of sleep, with a maximum after 4 weeks, was observed.

It is highly informative, that a reduction in NRS occurred in anticipation of the therapy. The analysis showed a statistically significant reduction in pain in the last 24 h before treatment and on the day of intervention (before treatment) compared to baseline. This effect was analogously described in a randomized trial on the effect of acupuncture in patients with migraine [15]. There was a significant increase in days without headache after patients were placed on a waiting list. This impact on patients' ailment was described as the general effect caused by participating in a study (Hawthorne effect). Latest investigations on placebo effects in neuropathic pain patients revealed that expectations and emotional feelings contribute to placebo-induced pain relief [21] and activate the pain-modulating system [24]. The sole announcement of a treatment or a treatment contract combined with positive treatment expectancy can substantially enhance the therapeutic effect. The neurobiological correlate of this subjective impact, i.e. an alternation in neuronal activity in the corresponding brain region, was visualized using functional magnetic resonance imaging [4].

The increase of pain intensity, 8 weeks after therapy, is explained by the gradual sprouting of epidermal nerve fibers in the treated area as well as the continuous regression of the capsaicin-induced depolarization of the distal nociceptive fibers [12]. The result is a consecutive return of pain perception. Considering the growth behavior of peripheral nerve endings, further research should clarify, whether, under neurophysiologic aspects, a sooner repetition of the capsaicin application is recommendable.

It was shown, that the 8 % capsaicin patch (Qutenza^{TM}) achieved a statistically significant reduction of the pain scores 12 weeks after treatment compared to baseline. Thus, the application lead to a pain decrease and further reduced symptoms of the painful PNP, such as paraesthesia, allodynia, and the increased sensitivity to temperature and touch. This effect was especially noticeable for male ($p < 0.02$) and HIV-positive patients ($p < 0.03$).

Similar to the results of this trial, regarding the influence of the application on patients' social activity, quality of life and additional systemic pain medication, a recent study on patients' satisfaction ($n = 21$) demonstrated that 3 months after administration of the 8 % capsaicin patch a general pain reduction of 32.7 % was achieved. 47 % of patients witnessed a positive effect on their sleeping behavior, mood, and everyday activities. 35 % of patients were able to reduce additional oral pain medication during the course of observation [27].

Therapy with capsaicin 8 % as a cutaneous patch (Qutenza^{TM}) has been approved in the US for the treatment of neuropathic pain as a result of post herpetic neuralgia (PHN) and in the EU, since 2009, for the treatment of

peripheral neuropathic pain (except for diabetes-induced neuropathic pain) [7, 20]. For HIV-associated neuropathy (HIV-AN), the 8 % capsaicin patch currently represents the only admitted treatment option, which, according to recent studies, can achieve a significant reduction of pain (>30 %) over several months after a single application [19]; thus it was included in the guidelines of the German Neurological Society (DGN) in September 2012. Meanwhile, the 8 % capsaicin dermal patch takes part in the first-line therapy for the treatment of neuropathic pain in patients with HIV infection.

There are very heterogeneous study results in terms of response and duration of the effect of the capsaicin treatment. Recent investigation showed, that the 8 % capsaicin patch is to be considered clearly superior to the low-dose 0.04 % patch for the treatment of PHN and HIV-AN, for a period of 2–12 weeks after therapy [19]. Similar to our observations, a strong initial pain decrease was noticed from week 2–8 post administration, followed by an important increase in pain intensity [11, 26]. In a meta-analysis of seven randomized, double-blind, controlled capsaicin 8 % (Qutenza^{TM}) trials with 1,313 patients with PHN and 801 patients with HIV-AN [18], a significant pain reduction for an average duration of 5 months after a single application was observed. Other studies achieved a median response over 22 weeks; in 14 % of patients a response over 40 weeks after a single application was recorded [17].

High-dose capsaicin leads to an initial release of neuropeptides on the application site, causing transient local effects such as burning sensation, pruritus, and erythema. In order to minimize this temporary discomfort for the patients, the manufacturer recommends a pre-treatment of the skin with a local anesthetic (e.g. lidocaine cream). Latest studies proved, that a pre-treatment causes no significant benefit regarding safety and efficacy of the capsaicin application [13, 22], thus, according to the new guidelines (April 2013), pre-treatment is considered obsolete.

To distinguish responders from non-responders and to optimize response rates, a pre-therapeutic, systematic testing and profiling of the patients using pin prick, thermal threshold and mechanical allodynia is recommended. Additionally, repetitive application of the patch appears to enhance the therapeutic effect. It is important to guarantee a sufficient contact between patch and skin throughout the entire application process, to ensure an even and complete penetration into the skin. An incomplete absorption of the capsaicin is a common reason for reduced response to treatment [22].

A trial exploring the cost-efficiency of the treatment of PHN [2] showed that topically applied 8 % capsaicin is significantly more effective than oral agents, such as tricyclic antidepressants, Duloxetine, Gabapentin, Pregabalin, and that the costs for the capsaicin patches are not higher than those for conventional lidocaine patches.

For study purposes, capsaicin is successfully applied in other painful conditions, such as postoperative neuropathic pain, scar pain and peripheral neuropathy. For the treatment of tumor-associated neuropathic pain, a 90 % pain reduction was achieved in 71 % of patients [3].

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References

1. Anand P, Bley K (2011) Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8 % patch. Br J Anaesth 107(4):490–502
2. Armstrong EP, Malone DC, Mc Carberg B, CJ Panarites (2011) Pham SV Cost-effectiveness analysis of a new 8 % capsaicin patch compared to existing therapies for postherpetic neuralgia. Curr Med Res Opin 27(5):939–950
3. Bhaskar A, England J, Lowe J (2012) Management of neuropathic pain (NP) using the capsaicin 8 % patch in patients with cancer. Presented at the European association for palliative care, NorwayPoster 465
4. Bingel U, Wanigasekera V, Wiech K, Mhuircheartaigh R, Lee MC, Ploner M, Tracey I (2011) The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med 3(70):70ra14
5. Chung M-K, Güler A, Caterina M (2008) TRPV1 shows dynamic ionic selectivity during agonist stimulation. Nat Neurosci 11:555–564
6. Derry S, Lloyd R, Moore RA, McQuay HJ (2009) Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database, Syst Rev 4:CD007393
7. European Medicines Agency (2013) Summary of product characteristics: Qutenza 179 mg cutaneous patch. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000909/WC500040453.pdf. Accessed July 2013
8. Freynhagen R, Baron R, Gockel U, Tölle TR (2006) painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 22(10):1911–1920
9. Gauffin J, Hankama T, Kautiainen H, Hannonen P, Haanpää M (2013) Neuropathic pain and use of PainDETECT in patients with fibromyalgia: a cohort study. BMC Neurol 13:21. doi:10.1186/1471-2377-13-21
10. Holzer P (2008) The pharmacological challenge to tame the transient receptor potential vanilloid-1 (TRPV1) nocisensor. Br J Pharmacol 155(8):1145–1162
11. Jones VM, Moore KA (2011) Peterson DM Capsaicin 8 % topical patch (Qutenza)-a review of the evidence. J Pain Palliat Care Pharmacother 25(1):32–41
12. Kennedy WR, Vanhove GF, Lu SP, Tobias J, Bley KR, Walk D et al (2010) A randomized, controlled, open-label study of the

long-term effects of NGX-4010, a high-concentration capsaicin patch, on epidermal nerve fiber density and sensory function in healthy volunteers. J Pain 11(6):579–587
13. Kern KU, Nowack W, Poole C (2014) Treatment of neuropathic pain with the capsaicin 8 % patch: is pretreatment with lidocaine necessary? Pain Pract 14(2):E42–E50
14. Lambert DG (2009) Capsaicin receptor antagonists: a promising new addition to the pain clinic. Br J Anaesth 102(2):153–155
15. Linde K, Streng A, Jürgens S, Hoppe A, Brinkhaus B, Witt C et al (2005) Acupuncture for patients with migraine: a randomized controlled trial. JAMA 293(17):2118–2125
16. Malmberg AB, Mizisin AP, Calcutt NA, von Stein T, Robbins WR, Bley KR (2004) Reduced heat sensitivity and epidermal nerve fiber immunostaining following single applications of a high-concentration capsaicin patch. Pain 111:360–367
17. MCCormack PL (2010) Review capsaicin dermal patch, in non-diabetic peripheral neuropathic pain. Drugs 70(14):1831–1842
18. Mou J, Paillard F, Turnbull B, Trudeau J, Stoker M, Katz NP (2014) Qutenza (capsaicin) 8 % patch onset and duration of response and effects of multiple treatments in neuropathic pain patients. Clin J Pain 30(4):286–294
19. Mou J, Paillard F, Turnbull B, Trudeau J, Stoker M, Katz NP (2013) Efficacy of Qutenza® (capsaicin) 8 % patch for neuropathic pain: a meta-analysis of the Qutenza clinical trials database. Pain 154(9):1632–1639
20. NeurogesX (2009) Qutenza® (capsaicin) 8 % patch [prescribing information] NeurogesX, San Mateo, CA, http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=aab4f0b9-5b08-4ed7-b85b-93dcee5c50ad
21. Petersen GL, Finnerup NB, Grosen K, Pilegaard HK, Tracey I, Benedetti F, Price DD, Jensen TS, Vase L (2014) Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. Pain. pii: S0304-3959(14)00459-X
22. Treede RD, Wagner T, Kern KU, Husstedt IW, Arendt G, Birklein F et al (2013) Mechanism- and experience-based strategies to optimize treatment response to the capsaicin 8 % cutaneous patch in patients with localized neuropathic pain. Curr Med Res Opin 29(5):527–538
23. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW et al (2008) Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 29(70):1630–1635
24. Vase L, Petersen GL, Lund K (2014) Placebo effects in idiopathic and neuropathic pain conditions. Handb Exp Pharmacol 225:121–136
25. Wallace M, Pappagallo M (2011) Qutenza®: a capsaicin 8 % patch for the management of postherpetic neuralgia. Expert Rev Neurother 11:15–27
26. Webster LR, Malan TP, Tuchman MM, Mollen MD, Tobias JK, Vanhove GF (2010) A multicenter, randomized, double-blind, controlled dose finding study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. J Pain 11(10):972–982
27. Weekes G, O'Brien J, Murphy K, Keavney J, Pollard V (2013) Qutenza patch-our early experience. Ir Med J 106(3):89–90