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REVIEW ARTICLE



# Efficacy of various forms of capsaicin in the treatment of neuropathic pain – literature review

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## Abstract

**Introduction and Objective.** Pain is defined as a subjective, unpleasant sensation resulting from actual or potential tissue damage or nervous system malfunction. If left untreated or treated ineffectively, it leads to serious complications. Neuropathic pain is a particularly difficult type of pain to manage. The drugs used in its treatment include capsaicin (CP) – vanillyl amide, an antagonist of the transient receptor potential V1 (TRPV1) receptors, used for thousands of years in folk medicine and cooking.

**Review Methods.** The PubMed database was searched using the terms 'capsaicin', 'pain", and 'neuropathic', and the filters 'Clinical Trial' and 'Randomized Controlled Trial'.A total of 94 articles were identified, 27 of which were eligible for review.

**Brief description of the state of knowledge.** Capsaicin, due to its unique mechanism of action, stands out from other analgesics. Its use in everyday clinical practice has been confirmed in many clinical studies. However, there are still medical disciplines in which its usage is unexplored and should be investigated. Moreover, when taking capsaicin, clinicians should also pay attention to possible side-effects.

**Summary.** The discussed studies indicate the effectiveness of CP, used topically in the treatment of HIV-associated distal sensory polyneuropathy (HDSP), spinal cord injury, focal neuropathic pain, lumbosacral pain, post-traumatic neuropathic pain, cancer-related neuropathic pain, painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN) and phantom limb pain. Characterized by a good safety profile, CP increasingly appears in the guidelines of scientific societies, and research on its use often goes beyond the issues described.

## Key words

pain, analgesics, neuralgia, TRPV1 protein, Capsaicin.

## INTRODUCTION

Pain is a symptom that accompanies nearly all diseases involving human organism either as an effect of real or potential injury or nervous system malfunction. As a subjective complaint, it coexists not only with somatic illnesses but also with psychiatric ones. Pain can be divided, depending on its duration, into acute i.e. lasting less than three months which affects every person sooner or later, and chronic which persists longer than this period and is also very prevalent amongst people. Pain may lead to many negative consequences such as lower quality of life, decreased productivity, worsening of chronic diseases, and mental disorders like depression, anxiety state, or drug abuse [1]. Typical pain handling includes systemic administration of NSAID, opioids, and in recent times anticonvulsants and antidepressants. However, usage of these substances leads to many side effects [2–4]. Especially, among different kinds of pain, neuropathic one can be very difficult to manage. The International Association for the Study of Pain (IASP) defines it as: 'Pain caused by a lesion or disease of the somatosensory nervous system' [5].

Difficulties in the treatment of this type of pain result from many possible pathophysiological mechanisms leading to damage of the central and peripheral nervous system, which translates into different responses of patients to the drugs used. Meanwhile, the scale of the problem is large – it is estimated that up to a quarter of patients suffering from chronic pain have a neuropathic component [6]. The current recommendations for the treatment of neuropathic pain developed by the Special Interest Group on Neuropathic Pain divide the available therapeutics into three groups. First-line drugs include selective serotonin and norepinephrine reuptake inhibitors – duloxetine and venlafaxine, tricyclic antidepressants and pregabalin and gabapentin (enacarbil or extended-release form). Second-line drugs include tramadol and topical agents – patches containing 8% capsaicin (CP) or lidocaine – which can only be used to treat peripheral neuropathic pain. Third-line drugs – strong opioids and Botulinum Toxin A received a weak recommendation due to low quality of evidence and concerns with the safety of use [7]. Because of that, many alternative medications and ways of their administration are being introduced. Topical CP, mentioned previously, is one of the most prominent medications used in handling peripheral neuropathic pain. Capsaicin, first isolated in 1816 by German chemist Christian Friedrich Bucholz is a vanillyl amid [8] produced and then stored in seeds by plants from the Capsaicinum genus whose common name is pepper. Most often CP was and still is being used in gastronomy. The reason for this is its irritating activity which is perceived by human taste buds as spicy.

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The discovery in 1997 of the transient receptor potential V1 (TRPV1) whose agonist is CP, resulted in a significant increase in the scientific interest in it, which enabled its introduction into modern conventional medicine [9]. TRPV1 is the only subtype stimulated by vanilloids like CP. TRPV1 is a homotetramer consisting of six transmembrane domains, where CP binds to the region between third and fourth domain [10]. Those receptors are found on C- and A-delta fibers in the nociceptive sensory pathway whose stimulation leads to the perception of pain or burning sensation. When activated, it starts a depolarization cascade that enables the flow of sodium and calcium ions into the cell. In order to obtain an analgesic effect, the dose of CP must be high enough that, after TRPV1 activation, the concentration of Ca2+ ions increases to the level that activates calpains (Ca2+-dependent cysteine proteases) [11]. Subsequently actions lead to axonal degradation by destabilizing microtubule structure and disrupting mitochondrial function [12]. Additionally, CP causes a reduction of epidermal nerve fiber density, as well as reduces the level of hyperalgesia by acting on TRPV1+ sensory fibers that have been injured [13, 14]. Depending on the dose of topical administered CP, its effects can be divided into short and long-term ones. The short-term effect can be characterized as reversible defunctionalization (functional impairment of primary afferents without structural changes) and long–term as irreversible defunctionalization (structural ablation) [15]. The aim of this literature review is to evaluate the indications and effectiveness of CP in the treatment of neuropathic pain.

## MATERIALS AND METHODS

The PubMed database was searched for articles that investigated the use of CP in patients suffering from neuropathic pain due to various diseases. The search used the sequence: 'capsaicin', 'pain' and 'neuropathic'. Filters available on PubMed were used including type of article: 'Clinical Trial' and 'Randomized Controlled Trial', in the English language. The data collected were analyzed and categorized based on the method of CP administration and the specific diseases in which it was applied. Additionally, papers dealing with side effects and interactions of CP with other drugs were found through the PubMed database. Guidelines from societies regarding the use of CP in the treatment of pain were also collected using online sources. Studies on the alleviation of allodynia induced by CP have been rejected.

## RESULTS

A total of 94 articles were identified, of which 27 were relevant to the investigated topic and subsequently included in the review. Works that tested preparations combined with CP and other substances were rejected. Based on review papers on a similar topic, six supplementing works dealing with the effects of CP in osteoarthritis have been included. The effectiveness of different forms of CP on specific types of neuropathic pain is shown in Figure 1.

8% CP: neuropathic pain (PNP) spinal cord injury (SCI), focal neuropathic pain (FNP), lumbosacral pain (LP), post-traumatic neuropathic pain (PTNP), cancer-related neuropathic pain (CRNP), painful diabetic neuropathy

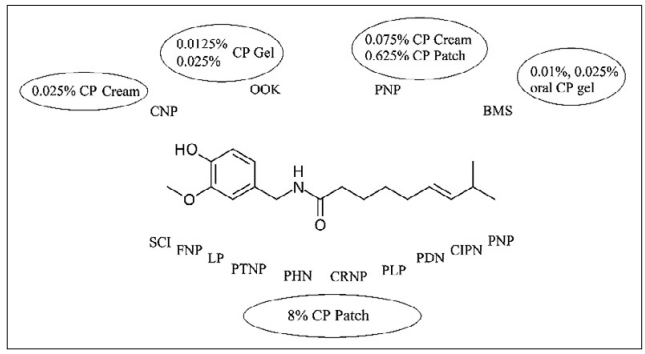


**Figure 1.** Efficacy in combating various types of neuropathic pain depending on the form of CP used

(PDN), post-herpetic neuralgia (PHN), phantom limb pain (PHLP), chemotherapy-induced peripheral neuropathy (CIPN). 0.625% CP patch and 0.075% cream: PNP. 0.01% and 0.025% oral CP gel: burning mouth syndrome (BMS). 0.0125% and 0.025% CP gel: osteoarthritis of the knee (OOK). 0.025% CP cream: chronic neuropathic pain (CNP)

The main route of CP administration is in the form of patches containing a high concentration of CP (8%, product commercial name Qutenza). Newly studied forms of CP administration include CNTX-4975 (Centrexion), which is an injectable CP for treating Morton's neuroma and pain associated with osteoarthritis of the knee, and CGS-200 (by Propella Therapeutics), a liquid form of high-concentration CP also intended for treating osteoarthritic knee pain. Both medicinal preparations have passed a double-blind phase II clinical trial [16–18]. The positive effects of CP as an analgesic are proven by numerous clinical trials (including randomized trials), which constitute the basis for including CP in daily practice as well as further research in the field of pain treatment. 8% topical CP patch is effective in the treatment of peripheral neuropathic pain (PNP) spinal cord injury, focal neuropathic pain, lumbosacral pain, post-traumatic neuropathic pain, cancer-related neuropathic pain, painful diabetic *neuropathy* (PDN), post-herpetic neuralgia (PHN), phantom limb pain [19–25].

Application of the CP 8% cutaneous patch resulted in significant relief of PNP in both HIV positive (HIV-p) and HIV negative (HIV-n) patients. Statistically significant differences were demonstrated in the reduction of the mean Numerical Rating Scale (NRS) score with the best effect after 2–4 weeks. In HIV-p patients NRS scores before therapy, at 2–4 weeks and at 12 week were respectively 8, 3 and 4. In HIV-n group NRS scores before therapy, at 2–4 weeks and at 12 week were respectively 9, 4 and 5,5. The evaluation of the painDETECT score (a self-reported assessment of neuropathic pain qualities [26]) yielded that 48.6 % of patients experienced a decrease in pain [27]. A study conducted on 1,044 patients suffering from PNP as a result of various diseases also used the painDETECT questionnaire. Based on the questionnaire results, application of 8% CP patch had a significant effect on all sensory symptoms recorded (burning, prickling, allodynia, pain attacks, numbness, thermal hyperalgesia, pressure-evoked pain) [28]. Among the same group of patients, it was also shown that after applying 8% topical CP, the greatest benefit was achieved by patients whose pain duration was shorter than 6 months, and regardless of the specificity of the patient group, a decrease in the level of pain measured using NRS was demonstrated

**Table 1.** Characteristics of individual studies included in the analysis

| Author and year | Typ of study | Form of administration | Type of pain/ilness | Results |
|---|---|---|---|---|
| Stevens et al. 2019 | Phase II multicentre double-blind study | Intraarticular injection of placebo, capsaicin 0.5 mg, or capsaicin 1.0 mg | Chronic moderate-to-severe osteoarthritis (OA) associated knee pain | At 12 week for 0.5 mg Capsaicin and 12 week and 24 weeks decrease for 1.0mg Capsaicin in comparison to placebo in Daily Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain with walking score. |
| Billard et al. 2019 | Multicentre, randomized, double-blind, parallel group study | Administration of topical capsaicin 1% , or capsaicin 5% or vehicle | OA – associated knee pain | At day 35, CGS-200-5, but not CGS-200-1, met the primary OA – associated knee pain WOMAC efficacy endpoint compared to vehicle. |
| Cambell et al. 2016 | Randomized, double-blind, placebo-controlled, single dose, parallel-group study | Injection of single 0.1 mg dose of capsaicin or placebo into the region of the neuroma | Morton's neuroma | At weeks 1 and 4, decrease in pain was significantly greater in the subjects treated with capsaicin. |
| Olusanya et al. 2023 | Randomized single-blind crossover study | Capsaicin 8% patch or 0.025% capsaicin patch | Neuropathic pain after spinal cord injury | At weeks 2 and 4 significant pain reduction of capsaicin 8% in VAS and MPI-SCI compared to capsaicin 0.025%. |
| Haanpää et al. 2016 | Multicentre, open-label, randomized, non-inferiority study. | Capsaicin 8% patch or an optimized dose of oral pregabalin | Peripheral neuropathic pain | The capsaicin 8% patch was non-inferior to pregabalin in reaching a significant mean decrease in NPRS (Numeric Pain Rating Scale) score from baseline to week 8. |
| Zis et al. 2016 | Prospective, open-label study. | Capsaicin 8% patch | Lumbosacral pain. | Statistically significant reduction of the VAS (Visual analog scale) score between baseline and week 2, week 2 and 8 and between weeks 8 and 12. |
| Mankowski et al. 2017 | Phase IV, multi-centre, open-label, non-interventional study. | Capsaicin 8% patch | Peripheral neuropathic pain | Reduction in mean NPRS score from baseline throughout weeks 2,8,12 and 52. |
| Musharraf et al. 2017 | Randomized controlled study. | Capsaicin 0.075% cream or turpentine oil. | Diabetes associated peripheral neuropathic pain. | Significantly similar to turpentine oil reduction of pain in VAS scale after 3 months treatment. |
| Irving et al. 2012 | Four separate randomized controlled studies | Capsaicin 8% patch or 0.04% capsaicin patch (control) | Postherpetic neuralgia | Between weeks 2 - 8, study group patients reported greater reductions in NPRS scores compared with control. |
| Privitera et al. 2017 | Open-label, longitudinal study. | Capsaicin 8% patch. | Chronic amputation stump and phantom limb pain. | At 4 weeks significant reduction in NRPS score in spontaneous amputation stump pain, phantom limb pain, and evoked stump pain. |
| Raber et al. 2015 | Case series | Capsaicin 8% patch | Peripheral neuropathic pain | A significant reduction of NRS during 12 weeks, with a maximum between 2 - 4 weeks post administration. |
| Maihöfner et al. 2014 | Multi-centre, prospective, non-interventional study. | Capsaicin 8% patch | Peripheral neuropathic pain | A significant reduction of NRS score between 1-12 weeks. The shorter the duration of pain the greater reduction of it. |
| Sendel et al. 2023 | Non-interventional, exploratory study. | Capsaicin 8% patch | Peripheral neuropathic pain | Significant reduction in NRS score with a maximum at 4 weeks |
| Filipczak – Bryniarska et al. 2017 | Case series | Capsaicin 8% patch | Chemotherapy associated neuropathic pain. | Significant reduction in NRS score after 8 days and 12 weeks. |
| Kulkantrakorn et al. 2013 | Randomized, double-blind, crossover, study. | Capsaicin 0.025% gel or placebo. | Diabetes associated neuropathic pain. | No significant improvement in NRS score with capsaicin gel, compared with placebo. |
| Kulkantrakorn et al. 2019 | Randomized, double-blind, crossover, placebo-controlled study. | Capsaicin 0.075% lotion or placebo. | Diabetes associated neuropathic pain. | No significant improvement among all pain scales used with capsaicin lotion compared with placebo. |
| McCleane 2000 | Randomized, double-blind, placebo-controlled study | Capsaicin 0.025% cream, 3.3% doxepine hydrochloride cream, combination of both or placebo. | Peripheral neuropathic pain. | Significantly reduction of VAS score by doxepin, capsaicin and doxepin/capsaicin to a similar extent, compared to placebo. |
| Persson et al. 2020 | Randomized, open label study | Capsaicin 0.025% cream or 5% ibuprofen gel. | OA - associated knee pain | Significantly reduction of VAS score by ibuprofen and capsaicin. |
| Kosuwon et al. 2010 | Randomized, double blinded, cross-over, controlled study | Capsaicin 0.0125% gel or placebo. | OA - associated knee pain | Significantly reduction of VAS and WOMAC score after 4 weeks compared to placebo. |
| Moon et al. 2017 | Phase II, randomized, semi-double blind, placebo-controlled study. | Capsaicin 1.25% patch, capsaicin 0.625% patch or capsaicin 0.075% cream. | Peripheral neuropathic pain | Statistically significant reduction in NRS score after 6-weeks treatment with 0.625% capsaicin patch and 0.075% capsaicin cream. |
| Jørgensen et al. 2017 | Randomized double-blind cross-over study. | Capsaicin 0.01% oral gel or capsaicin 0.025% oral gel. | Burning mouth syndrome. | Statistically significant and similar reduction in VAS score after 6 weeks treatment with 0.01% and 0.025% capsaicin oral gel. |

(Mean reduction -24,7%) [29]. The latest reports indicate the effectiveness of highly concentrated CP in reducing the intensity of PNP along with the regeneration of nerve fibers, which is reflected in vasodilation [30]. In a single-centre study examining the effect of 8% CP on chemotherapy-induced (oxaliplatin) peripheral *neuropathy*, the average values in the NRS decreased from 7.45 to 0.2 among 18 patients treated with CP. However, it should be noted that patients with lower sensitivity to neurotoxic agents achieved slightly better results [31].

Over the years, attempts have been made to use CP in the form of a gel or cream to treat neuropathic pain. In a 20 weeks long double-blind, crossover, randomized, single-centre trial patients with PDN who received 0.025% gel did not benefit from the intervention regardless of the pain scale used [32] It is worthy to mention that an attempt to use 0.075% CP lotion in the treatment of neuropathic pain was made as a part of a randomized, double-blinded, crossover placebo controlled trial. However, after 8 weeks of therapy there was no significant difference between the research group and the control group [33]. In another study, in which 0.025% CP cream was used among 33 patients suffering from chronic neuropathic pain, a significant improvement was obtained in the form of a decrease in the Visual Analogue Scale (VAS) for overall pain and shooting pain (respectively 1,12 and 0,75 reduction from baseline) after 4 weeks of treatment [34].

The effectiveness of CP in the form of a gel with concentrations of 0.0125% and 0.025% among patients with pain associated with osteoarthritis of the knee was demonstrated by a reduction in the values of the NRS (0.025% CP gel), VAS, and Western Ontario and McMaster Universities Index of Osteoarthritis (0.0125% CP gel). The effectiveness of CP gel at 0.0125% and 0.025% concentrations among patients with osteoarthritis was demonstrated by a reduction in the NRS (0.025% CP gel), VAS, and The Western Ontario and McMaster Universities Arthritis Index (0.0125% CP gel) scores. It is worth mentioning that the study with 0.025% CP gel was conducted on 22 patients, of which the preparation was used in only 9 patients, while the study assessing the effects of 0.0125% CP gel was conducted on a total of 100 patients in a cross-over study (4 weeks of treatment and 1 week wash-out period) [35, 36]. In a study comparing the effectiveness of CP in the form of 0.075% cream, 0.625% (50 μg/cm2) and 1.25% patch (100 μg/cm2) 6 weeks after application of the drug, significant effectiveness in reducing PNP measured by NRS was demonstrated for 0.075% cream and 0.625% patch (intension to treat analyses). At the same time, there were no statistically significant reductions in pain scores for the 1.25% CP [37]. In turn, the use of 0.01% and 0.025% oral CP gel may bring benefits in the treatment of pain in patients with burning mouth syndrome, as indicated by a randomized double-blind cross-over study, in which a significant decrease in the VAS score (mean reduction – 1.4) 14 days after applying the gel [38].

## DISCUSSION

The CP 8% topical system is officially recommended as a first-line drug for treating PDN according to 2022 guidelines from the American Association of Clinical Endocrinology [39] and Clinical Compendia American Diabetes Association [40]. Additionally, the American College of Rheumatology/Arthritis Foundation guidelines recommend the use of CP for the treatment of knee osteoarthritis but discourage the use of CP for the treatment of hand osteoarthritis, because of the absence of direct evidence to support its efficacy [41]. The Polish Diabetes Association guidelines have recommended topical CP as second-line treatment in symptomatic neuropathic pain in somatic PDN [42].

CP is not free from adverse effects, especially when administered topically. The most common side effects, regardless of the route of administration, include a burning sensation, itching, dryness, swelling, redness, and soreness at the site of administration. Less frequently, but still observed are muscle pain, chills, nasopharyngitis, sinusitis, bronchitis, and cough. Nevertheless, most effects may disappear during treatment. Several studies indicate that treatment with the CP 8% topical system could lead to temporary increases in blood pressure that may be linked to the pain experienced at the application site. Therefore, blood pressure should be monitored periodically during and after the use of CP 8% topical system. The CP 8% topical system, despite causing some discomfort at the site of application, is generally well tolerated and has no identified drug interactions or contraindications [43, 44].

## CONCLUSIONS

As in separate reviews and meta-analyses, we were able to note progress in the clinical use of CP and attempts to create new forms of it. Despite the long history of using CP as an analgesic, there are still medical disciplines in which its usage is unexplored and should be investigated. Continuous research and evaluation of the effectiveness of drugs used to treat neuropathic pain are extremely important due to the complexity of the mechanisms of its development and the scale of the problem. Topical CP is a well-studied and effective drug in the treatment of peripheral neuropathic pain. Characterized by a good safety profile, CP increasingly appears in the guidelines of scientific societies, and research on its use often goes beyond the issues described. The coming years should bring further evidence of the usefulness of this substance in the treatment of pain, as well as potentially completely new possibilities for its use.

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