

High-Dose Capsaicin for the Treatment of Neuropathic Pain: What We Know and What We Need to Know

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ABSTRACT

Neuropathic pain is a frequent and disabling condition with diverse underlying etiologies and is often difficult to treat. Systemic drug treatment is often limited in efficacy. Furthermore, adverse effects may be a limiting factor when trying to reach the necessary dose. Analgesics that can be applied topically have the potential to largely overcome this problem. They may be of particular advantage in localized neuropathic pain syndromes such as postherpetic neuralgia or small fiber neuropathy. Capsaicin, the pungent component of chili peppers, is a natural ligand of the transient receptor potential vanilloid 1 channel and has long been used as topically applicable cream with concentrations of 0.025 to 0.075%. In 2009, a high-concentration transdermal capsaicin 8% patch (Qutenza®; Acorda Therapeutics, Inc., Ardsley, NY, USA;

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Astellas Pharma Europe Ltd., Chertsey, Surrey, UK) was introduced for the treatment of peripheral neuropathic pain syndromes other than of diabetic origin in adults. It has since been widely used in diverse neuropathic pain disorders. In this review article, we summarize current knowledge on Qutenza, its advantages and problems, and expose unmet needs.

Keywords: Analgesia; Capsaicin; Neuropathic pain; Qutenza; Transient receptor potential vanilloid 1 (TRPV1)

NEUROPATHIC PAIN

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system [1] and affects an estimated 8% of the general population [2], leading to severe impairment and reduction of health-related quality of life. The peripheral nervous system is more frequently the source of neuropathic pain rather than the central nervous system. Examples for peripheral neuropathic pain syndromes include postherpetic neuralgia (PHN), painful diabetic neuropathy, human

immunodeficiency virus (HIV)-associated neuropathy, or chemotherapy-induced neuropathic pain. Phantom limb pain after amputation is considered to have a peripheral and central component. Spinal cord injury pain or pain due to cerebral infarction would be examples for centrally induced neuropathic pain conditions. Peripheral neuropathic pain is mostly localized in the area supplied by the affected nerves and is reported to be of burning, stabbing, or electrifying character. Additional symptoms are plus symptoms such as hyperalgesia (i.e., increased pain upon application of painful stimulus), allodynia (i.e., pain upon application of painless stimulus), painless paresthesias, or painful dysesthesias, and minus symptoms that include hypoesthesia and hypoalgesia [3]. While neuropathic pain and additional symptoms initially may be of episodic character, in the majority of cases pain becomes permanent and chronic in the long term.

The causes of neuropathic pain are diverse. From the clinical point of view, trauma, hemorrhage, ischemia, inflammation, or metabolic alterations are some examples of how the central and the peripheral parts of the somatosensory nervous system can be impaired. However, this small and selective list of possibilities already implies that the pathophysiological mechanisms underlying neuropathic pain are manifold. These mechanisms are still incompletely understood despite intensive research.

Pathological ion channel activity is of particular importance when discussing neuropathic pain pathophysiology. Different subgroups of ion channels are critically involved in neuropathic pain development via ectopic discharges and sensitization. The family of voltage-gated sodium channels (NaV) is an outstanding example since the discovery of

mutations in the gene of Nav1.7 as the molecular basis of erythromelalgia first opened the avenue of genetic pain research [4]. Another family of voltage-gated ion channels that has a crucial role in neuropathic pain is the transient receptor potential (TRP) family. The TRP channels regulate action potential firing frequencies by gating neuronal transmembrane ion influx and modulate the sensitivity of afferent somatosensory neurons [5]. Another factor inducing and maintaining neuropathic pain is the dysfunctional effect and imbalance of algescic and analgesic mediators like cytokines or chemokines during neuro-immune interactions in the peripheral and central nervous system [6]. NaV as well as TRP channels are modulated by these mediators [7, 8].

So far, the best studied member of the TRP is the transient receptor potential vanilloid 1 (TRPV1) channel [9]. This non-selective cation channel is highly expressed on thinly myelinated A-delta fibers and unmyelinated C fibers (nociceptors) and is in particular permeable to calcium ions. TRPV1 activation typically leads to burning pain sensation and heat hyperalgesia [9]. Numerous TRPV1 activators are known to date that include high temperatures (>42 °C), acidic pH, and the pungent ingredient of hot chili peppers, capsaicin, which is a natural ligand of TRPV1 and makes this channel a delicate candidate for pain research.

CURRENT PHARMACOLOGICAL TREATMENTS OF NEUROPATHIC PAIN AND UNMET NEEDS

Treatment of neuropathic pain follows national [10, 11] and international guidelines [12, 13] that broadly overlap with regard to recommendations. In most guidelines, first-line therapy is the use of oral drugs such as

tricyclic antidepressants (e.g., amitriptyline), anticonvulsants including calcium channel blockers (e.g., gabapentin, pregabalin), and selective serotonin and noradrenalin reuptake inhibitors (e.g., duloxetine). In the case of localized pain, topical lidocaine can be applied as well as capsaicin cream or patch. If patients do not respond or have mixed pain (i.e., neuropathic pain plus nociceptive pain) the use of opioids can be considered [10].

Oral medication is used by the majority of patients suffering from neuropathic pain; however, only one-third of these patients seem to achieve satisfying pain relief [14]. Thus, the main problem with oral drugs is the lack of efficacy in a large proportion of patients even after intake of a sufficient dosage, changing to alternative drugs, and when used in combination. In addition, the occurrence of systemic side effects such as weight gain, xerostomia, dizziness, nausea, or cognitive impairment hampers acceptance. The fact that oral medication also needs individual titration and regular intake on a daily basis is an additional limitation reducing flexibility in life, especially for young patients. Drug–drug interactions may also constrain the already limited treatment options, especially in elderly patients with comorbidities. In this context, drug dosage needs to be adapted if renal or hepatic impairment is present. The effect of oral analgesic drugs also starts late; for some drugs an intake period of 6–8 weeks at the maximum dose is needed before drug efficacy can be judged. In localized neuropathic pain states, topically applicable lidocaine and ketamine, as well as low-dose capsaicin cream (0.025–0.075%), are in use. However, these require regular administration and also bear less hazardous but inconvenient disadvantages (e.g., potential contamination of hands during application or clothes afterwards).

Thus, despite a major effort to improve and facilitate oral analgesics there are still several challenges to be taken to meet the needs of patients with neuropathic pain syndromes [15]. One key obstacle is the lack of knowledge on the precise mechanisms that underlie the different types of neuropathic pain and that drugs are chosen mostly with regard to neuropathic pain in general without differentiation. Neuropathic pain, in general, covers many diverse entities that are of such a different pathophysiological background that a “one-drug-good-for-all” approach is condemned to failure. A second problem is that currently available analgesic pharmaceuticals are not exclusively selective for one target. Unselective drug choice (i.e., treating neuropathic pain in general) and molecularly relative unselective drugs (i.e., binding to different targets) are the major reasons that lower drug efficacy and tolerability. Therefore, the transdermal capsaicin 8% patch Qutenza[®] (Acorda Therapeutics, Inc., Ardsley, NY, USA; Astellas Pharma Europe Ltd., Chertsey, Surrey, UK) has been an important addition to the treatment options in neuropathic pain conditions [16].

HIGH-DOSE CAPSAICIN

Mechanism of Action

Transient receptor potential vanilloid 1 is selectively expressed in nociceptors. The distal endings of cutaneous nociceptors are present in the epidermis and are thus accessible to local treatment. The high-concentration transdermal 8% capsaicin patch Qutenza releases capsaicin into the skin, which can then act on TRPV1 receptors on the nociceptor terminals. This leads to an initial over-excitation of these nerve fibers, which is perceived as burning pain by patients. After this initial excitation,

the axons are believed to be “defunctionalized”, that is, to be less sensitive to external stimuli and also to cease any spontaneous activity that may have been present. Morphologically, intraepidermal nerve fiber endings disappear after capsaicin application, which can be assessed using immunohistochemistry and the panaxonal marker protein gene product (PGP) 9.5 which is routinely used to visualize intraepidermal nerve fibers [17]. In the case of Qutenza, these nerve fiber endings recover after 24 weeks, at least in healthy volunteers [18]. Investigations in patients with pain states treated with capsaicin have not been performed so far. Thus, several questions remain, such as a potential correlation between fiber density and pain intensity and the phenotype of the regenerating fibers with regard to their channel repertoire. Also, whether this disappearance and recovery of immunostaining for PGP 9.5 reflects true degeneration and regeneration or repressed production of the antigen detected in the immunofluorescence, is as yet unknown. Another potential mechanism is based on the interaction of TRPV1 with β -tubulin. TRPV1 activation leads to a microtubule disassembly *in vitro* by direct action and supported by the axonal calcium ion overload via excessive ion influx [19]. Whether Qutenza has a similar effect *in vivo* remains to be proven.

One apparent paradox is that neuropathic pain states are usually associated with a loss of intraepidermal nociceptor terminals [20, 21]. If these target fibers are gone, where would a TRPV1 agonist bind? The most favored hypothesis in this context is that the remaining nociceptors become hyperactive and hypersensitive on the basis of alterations in TRPV1 channel activity and expression. There is evidence for an increase in TRPV1 channel quantity on inflamed nociceptors [22]

and also for the sensitization of these nociceptors by local algescic inflammatory mediators and growth factors [23, 24].

There are several other unsolved questions. It is unclear why some patients do respond to Qutenza treatment and others do not. If Qutenza leads to nociceptor defunctionalization or degeneration, then all patients suffering from peripheral neuropathic pain should experience pain relief. Here, diversity of neuropathic pain pathophysiology and mechanisms is important. Obviously, TRPV1-mediated pain is not responsible for all neuropathic pain states. This is also underscored by the fact that some patients develop a skin flush upon patch application which can be associated with severe additional burning patch-pain for days to weeks and some do not. Interestingly, the development of such a patch-pain does not predict treatment response [41]. No data are available about how deep capsaicin from the Qutenza patch penetrates the different skin layers and how much capsaicin reaches the nociceptors. Skin penetration studies with Qutenza are ongoing, as with other novel formulations [25]. It is also not known whether capsaicin acts on peripheral nerve TRPV1 channels only or if an action, for example, on keratinocyte TRPV1 channels, also plays at least a modulatory role [26]. The pharmacokinetics of capsaicin in the skin are still under investigation (J. Wohlrab, personal communication, January 2014).

Dose and Administration, and Benefits of Localized Rather Than Systemic Analgesia

The application of the transdermal capsaicin 8% patch Qutenza containing 179 mg capsaicin needs to be performed at a medical center as special precautions are needed [27]. First, the

area that needs to be treated has to be determined and marked by the treating physician or the applying nurse. Afterwards, the skin is cleaned and lidocaine gel may be applied to reduce patch-induced pain; alternatively, patients may take oral analgesics (e.g., tramadol) prior to Qutenza application (see below). Thereafter, the Qutenza patch is placed on the affected region for 30 min if the feet are treated or for 60 min for any of the other approved body regions. After this time, the patch is removed and the affected skin area is cleansed. The effect of the Qutenza patch starts within days and analgesia can be achieved for at least 12 weeks. After this time treatment can be repeated.

The major advantages of the localized treatment are that potential systemic side effects of Qutenza, comprising hypertension, first-degree atrioventricular block, coughing, or nausea, occur very rarely. Side effects that are usually associated with the intake of analgesics like cognitive impairment or drowsiness are absent. This is of particular relevance for young patients who work and drive cars. For elderly patients who also need to take other drugs, the local application of transdermal Qutenza is an advantage since no drug–drug interactions will occur.

Clinical Trial Data That Led to its Launch, Including the Recent EC Approval for Expanded Treatment Options

In 2009, the European Medicines Agency approved the use of Qutenza for the treatment of peripheral neuropathic pain other than of diabetic origin in adults as a monotherapy or in combination with other analgesic drugs [28]. The approval was based on data from randomized, double-blind, placebo controlled studies in patients with PHN [29–32] and

painful HIV-associated neuropathy [33, 34] on the efficacy and safety of transdermal 8% capsaicin versus a control patch with low-dose capsaicin (0.04%).

In one multicenter, randomized-controlled trial (RCT), 206 patients with PHN were treated with transdermal 8% capsaicin and 42% of them reported a $\geq 30\%$ reduction in pain intensity versus 32% in patients treated with the placebo patch [29]. Similar results were reported by others after application of the 8% capsaicin patch in 194 patients [31]. In another RCT, 32 patients with PHN were randomized to be treated with transdermal 8% capsaicin; a decrease in pain intensity ratings of approximately 30% in the verum group compared to the control group was reported [30]. The treatment of 200 patients with PHN with 8% capsaicin patch led to a reduction of the mean percentage of pain ratings that was greater than in the placebo group [32]. In 225 patients with painful HIV-associated neuropathy, transdermal 8% capsaicin led to a reduction in pain ratings in 23% of patients on verum versus 11% of patients on placebo [34]. In another study this effect could not be confirmed [33]. Taken together one study [33] out of six was negative on the primary outcome with the capsaicin 8% patch, while in the other five studies more patients reported a positive effect when treated with the high-concentration patch compared to the low concentrated patch, as also stated in a recent Cochrane review [35]. Table 1 summarizes the major characteristics of the reported studies [29–34].

Particularly when comparing data of the verum (high-dose) and control (low-dose) patch in the reported studies, it is apparent that a low-dose capsaicin patch may also have a notable analgesic effect. In the majority of the studies summarized in Table 1 the difference in analgesic efficacy between the high and the

Table 1 Details of studies assessing transdermal capsaicin 8% patch (Qutenza) in patients with neuropathic pain syndromes

References	Study design	Diagnosis	N verum/N placebo	Treatment	Outcome	Percentage of adverse events	
[29]	Multicenter, double-blind, randomized, controlled	Postherpetic neuralgia	206/196	One 60-min application of 640 µg/cm ² capsaicin 8% patch	One 60-min application of 3.2 µg/cm ² capsaicin 0.04% patch	Verum: ≥30% reduction in pain intensity of 42% in verum versus 32% in control group Mean change in numeric pain rating scale score: -29.6% in verum versus -19.9% in control group	Verum: 99% control: 88%; any adverse event
[31]	Multicenter, double-blind, randomized, controlled (conformational study)	Postherpetic neuralgia	194/186	One 60-min application of 640 µg/cm ² capsaicin 8% patch	One 60-min application of 3.2 µg/cm ² capsaicin 0.04% patch	≥30% reduction in pain intensity of 46% in verum versus 34% in control group 32.0% mean reduction from baseline in pain in verum versus 24.4% in control group	Verum: 98% control: 87%; any adverse event
[30]	Randomized, double-blind, controlled study (with open-label extension)	Postherpetic neuralgia	32/12 Open-label extension: 15/7	One 60-min application of 640 µg/cm ² capsaicin 8% patch	One 60-min application of 3.2 µg/cm ² capsaicin 0.04% patch	Mean change in numeric pain rating scale score: -32.7% in verum versus -4.4% in control group	Verum: 42% control: 17%; any adverse event
[32]	Multicenter, double-blind, randomized, controlled (dose finding)	Postherpetic neuralgia	200/73	One 30, 60 or 90-min application of 640 µg/cm ² capsaicin 8% patch	One 30, 60 or 90-min application of 3.2 µg/cm ² capsaicin 0.04% patch	Mean percent reductions in numeric pain ratings from baseline were 26.5% in total verum versus 17.3% in the pooled control group 60-min treatment with mean percent reduction in average pain scores of 28%	Verum: 59% control: 56%; ≥1 adverse event

Table 1 continued

References	Study design	Diagnosis	N verum/N placebo	Treatment	Outcome	Percentage of adverse events
[34]	Multicenter, double-blind, randomized, controlled	Painful HIV-associated neuropathy	225/82	One 30, 60 or 90-min application of 640 µg/cm ² capsaicin patch	One 30, 60 or 90-min application of 3.2 µg/cm ² capsaicin patch	Verum: 72%, control: 55%; any adverse event
					≥30% reduction in pain intensity of 33% in verum versus 18% in control group Reduction in pain ratings in 23% of patients on verum versus 11% of patients on control Mean pain reductions in 30-, 60- and 90-min groups: 27.7, 15.9, and 24.7%	
[33]	Double-blind, randomized, controlled	Painful HIV-associated neuropathy	332/162	One 30 or 60-min application of 640 µg/cm ² capsaicin patch	One 30 or 60-min application of 3.2 µg/cm ² capsaicin patch	Verum: 93%, control: 83%; ≥1 adverse event
					Pain reduction not different between total groups (−29.5% verum versus −24.5% control) Pain reduction not different between 30-min groups (−26.2% verum versus −19.1% control) Pain reduction not different between 60-min groups (−32.8% verum versus −30% control)	

HIV human immunodeficiency virus

low-dose patch was less than 15%. Side effects were reported inhomogeneously in the respective studies, however, while high-dose capsaicin caused a higher percentage of adverse events, the control patch also led to similar results.

In 2013, an expanded pre-treatment procedure was approved by the European Commission based on the results of a study investigating 122 patients who received either the already approved topical lidocaine pre-treatment before Qutenza application or tramadol tablets [36]. Both pre-treatment regimes proved to be equally effective and can now be used in clinical practice.

HOW QUTENZA FITS INTO TREATMENT REGIMENS IN THE REAL WORLD

In clinical practice, patients with neuropathic pain conditions are treated with oral pharmacological drugs as first-line therapy as recommended by national and international guidelines. However, not all patients treated with oral analgesic drugs experience pain relief to a satisfying extent. The consequence is that drug dosage is increased. If this measure also fails to reduce pain, the medication is changed to a drug from a different group, as detailed above, or combination pharmacotherapy is installed. During this mostly exhausting phase of trial and error, the outcome may be biased by decreasing patient compliance. The experience of ineffective drugs with unpleasant adverse effects reduces the motivation of the patient and sometimes may also lead to catastrophizing. The inconvenience of obligatory daily drug intake is in particular difficult to accept for young and active patients. In this situation, Qutenza may be an alternative for the treating

physician and the patient. The novel application and the fact that treatment is episodic are attractive features that are very well accepted by the patients. Qutenza can then be used as monotherapy or in combination with oral analgesic drugs that may, however, be reduced in dosage. This is a good addition to the overall small palette of possibilities for non-interventional pharmaceutical analgesic treatment in neuropathic pain conditions.

Current Experience

Several studies have been published after the approval of Qutenza assessing the efficacy and safety in patients with PHN and HIV-associated painful neuropathy. A meta-analysis including 1,120 patients with PHN and 338 with HIV-associated neuropathy favored Qutenza over the low-dose capsaicin patch when assessing the number of patients with 30% pain reduction as primary outcome [37]. In these trials, overall 44% of the PHN and 41% of the HIV-associated neuropathy patients had a 30% response. Complete pain relief 2–12 weeks after treatment was reported in 11% of patients with PHN and 7% of patients with HIV-associated neuropathy [38]. It took a mean time of 3.4 days for PHN patients and of 6.5 days for HIV-neuropathy patients to respond. The mean duration of response after the first Qutenza treatment was 5 months [38]. In the largest non-interventional study so far, QUEPP (Qutenza—safety and effectiveness in peripheral neuropathic pain), the effect of a single Qutenza application was assessed over a period of 3 months in 1,044 patients with neuropathic pain other than of diabetic origin [39]. The authors reported that 43% of patients had 30% pain relief and 24% experienced 50% pain relief. Also, pain intensity and the frequency of pain attacks declined and

additional intake of analgesic drugs was reduced. In this study [39], pre-treatment pain duration was negatively correlated to the effectiveness of Qutenza; however, there have been conflicting data depending on pain etiology [31, 40, 41].

Another question is how to determine who are responders and who are non-responders of Qutenza treatment. Efforts have been made to identify predictors of a positive Qutenza response. A post hoc analysis of the clinical trial data showed that efficacy of lidocaine pretreatment and a high pretreatment pain score variability were important predictors [42]. In a multi-center open study with multivariate analysis, time of disease was a major predictor, with a history of pain of less than 6 months being a positive predictor for a response to Qutenza [41]. In this context, effective lidocaine pretreatment and a higher pre-treatment pain score variability were found as potential predictors of good treatment response: older age and longer duration of pre-treatment pain were predictors for poorer outcome after Qutenza treatment [41, 42]. One critical aspect, however, is that a high efficacy of the control patch (0.04%) was also reported [33, 37, 42].

Qutenza is mostly well tolerated. The major side effects are at site erythema, burning pain, and itch upon patch application that may last for days to weeks [35]. Currently no predictors are known for who will develop patch-pain. Also, no correlation exists so far with regard to patch-pain and analgesic effect of Qutenza.

SUMMARY AND OUTLOOK

Neuropathic pain is a major challenge due to chronification and low treatment response. The non-interventional pharmacological treatment options used so far are effective only in subgroups of patients and are mostly afflicted

with intolerable side effects. Topically applicable substances are of need, especially in focal neuropathic pain conditions. Qutenza is therefore a valuable addition to the palette of analgesic options against neuropathic pain in adults. The application is easy and mostly well tolerated and leads to pain relief in a subset of patients.

The aim is to further improve and facilitate the Qutenza application so that, for example, it might be applied by the patients themselves. A further reduction in local side effects would be desirable. Further studies are underway to investigate the efficacy and safety of Qutenza in other peripheral neuropathic pain states including those related to diabetes. There are no studies about pain relief by Qutenza in children. Although no data are available on the prevalence of neuropathic pain in children, being able to use Qutenza in pediatric patients with localized neuropathic pain might be a worthwhile goal with regard to the general reluctance to give systemic analgesics in child pain management. Data on potential biomarkers that can be used as potential predictors of treatment response would be useful for effective patient selection and to avoid unnecessary treatment of pre-defined non-responders. This may be achieved by research focusing on the molecular mechanisms of the interaction of transdermal capsaicin with cutaneous cells and nerve fibers.

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Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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