MANAGEMENT PERSPECTIVE

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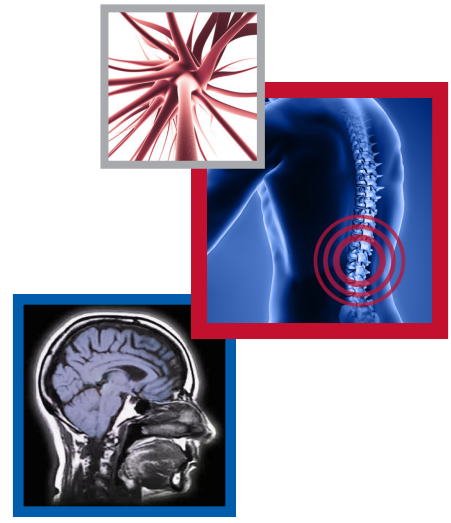
Capsaicin 8% patch for peripheral neuropathic pain: review of treatment best practice from 'real-world' clinical experience



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Practice Points

- The capsaicin 8% patch is licensed in the EU for the treatment of peripheral neuropathic pain (NP) in nondiabetic adults either alone or in combination with other medicinal products for pain. It is designed to directly target the source of peripheral NP and can provide pain relief for up to 3 months with a single application. Real-world observations have shown that the capsaicin 8% patch is effective in a range of conditions including postherpetic neuralgia, HIV-associated neuropathy and cancer-related NP.
- The capsaicin 8% patch is an important addition to the treatment options for patients with NP. Observations from real-life use of the product, particularly on how to optimize application of the patch and manage patients appropriately, will help to maximize its therapeutic potential.
- Patients treated with the capsaicin 8% patch are often able to reduce their intake of concomitant pain medications.
- In the authors' experience, there has been no observed loss in the effect on pain reduction in patients who have been treated with the capsaicin 8% patch for a second time, and there has been no reduction in the level of tolerability to treatment with the patch.
- Although it is recommended in the product prescribing information, local anesthetic pretreatment may not always be necessary; observations made by healthcare professionals suggest that tolerability to the capsaicin 8% patch is similar regardless of whether the patient received pretreatment.
- Cooling measures used directly after the application procedure are the most practical and beneficial method of reducing any application site discomfort. Only a minority of patients require pharmaceutical analgesia during and/or after patch application.
- Transient, clinically important increases in blood pressure owing to treatment-related discomfort are very rare; we have not experienced problems with hypertension or extreme fluctuations in any patients treated with the capsaicin 8% patch.

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SUMMARY The capsaicin 8% patch is licensed in Europe for the treatment of peripheral neuropathic pain in nondiabetic adults. In controlled trials it provided pain relief for up to 3 months with a single 30- or 60-min application. In this article, a group of pain specialists from Germany and the UK share their considerable experience of real-world use of the capsaicin 8% patch. This experience comes from treating >200 patients with a variety of neuropathic pain etiologies including postherpetic neuralgia, peripheral neuropathy and cancer-related neuropathy. These patients, a slight majority of whom were female, had experienced neuropathic pain for varied lengths of time (3 months to >15 years) and the majority were receiving concomitant medications for their pain at the time of capsaicin 8% patch treatment. Observations by the group suggest that patients with positive symptoms might respond best to therapy. To optimize response to treatment, the group reports that it is important to achieve good adhesion of the patch to the skin. The experience of the group is that the capsaicin 8% patch is a tolerable treatment and local anesthetic pretreatment may not always be required. Cooling measures used after treatments were found to be the most practical and beneficial means of relieving any treatment-related discomfort. The group observed that transient, clinically important increases in blood pressure owing to treatment-related discomfort are very rare and they have seen no correlation between treatment-related discomfort or erythema and response to treatment. In the real-life clinical setting, response to capsaicin 8% patch treatment may be higher than observed in the clinical trial program. Response to retreatment also appears to be equal to that of the first treatment, even in patients treated for the fifth time. It was also observed that patients receiving capsaicin 8% patch treatment are often able to reduce their intake of concomitant pain medications. Observations from real-life use of the capsaicin 8% patch will help to maximize its therapeutic potential.

Neuropathic pain

Neuropathic pain (NP) has been defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [1]. Common treatments for NP conditions include tricyclic antidepressants, anticonvulsants, opioids and topical creams as well as patches [2,3]. However, such treatments can have limited efficacy: topical creams can have a cumbersome treatment regimen requiring constant reapplication [4], while available oral treatments may be associated with systemic side effects such as dizziness, somnolence and nausea [3,5]. Moreover, multidrug therapy is often required for patients to achieve any meaningful pain reduction [6], resulting in an increased side-effect burden and a more complicated treatment regimen.

The capsaicin 8% patch

A capsaicin 8% patch was licensed in the EU in 2009 for the treatment of peripheral NP (PNP) in nondiabetic adults either alone or in combination with other medicinal products for pain. The treatment is designed to directly target the source of PNP and in controlled clinical trials has been shown to provide pain relief for up to 3 months with a single application [7–10]. The active ingredient of the patch – capsaicin – is the primary pungent constituent of hot chilli peppers and is a selective agonist of TRPV1 channels, which are highly expressed on nociceptors [11,12]. When used therapeutically, the initial excitation of TRPV1 channels with capsaicin-containing preparations causes the generation of action potentials and a burning sensation [13]. However, constant overstimulation of the nociceptors results in reversible reduction in epidermal nerve fiber density and defunctionalization of the nociceptors, leading to a reduction in NP [14].

The broad indication for the capsaicin 8% patch encompasses many PNP conditions including radiculopathy, peripheral neuropathy, polyneuropathy, postherpetic neuralgia (PHN) and postsurgical NP. It can also be used to treat patients with cancer-related NP caused by chemotherapy, radiotherapy or tumor infiltration. The capsaicin 8% patch can be used on most parts of the body including the torso, limbs, hands and feet. However, treatment of the face, above the hairline of the scalp and/or in proximity to mucous membranes is not recommended in the product's prescribing information owing to the risk of contamination of sensitive areas [101].

In clinical use, the capsaicin 8% patch must be applied by a healthcare professional (HCP) and it is recommended that HCPs who are planning

to undertake the procedure are trained to ensure correct patch application and to optimize the efficacy and tolerability of the procedure. The application procedure comprises several straightforward steps: identification of the painful area, pretreatment with a topical anesthetic, application of the capsaicin 8% patch (for 30 min if treating the feet or for 60 min for treatment of all other areas) and cleansing the area to remove any residual capsaicin [15,101].

The experienced user group

As with all procedures that employ a relatively new agent, routine use of the product in daily clinical practice can provide a wealth of useful information regarding best practice for product application, patient management and response to therapy. A group of pain specialist physicians and nurses from Germany and the UK have accumulated considerable knowledge on the use of the capsaicin 8% patch through real-world clinical experience of the patch since its introduction. This experienced user group consists of regular users of the capsaicin 8% patch: two pain specialists from the Medizinisches Zentrum Städte Region Aachen in Germany (TW and AR-D), one pain specialist from the Centre for Pain Management and Palliative Care in Wiesbaden, Germany (K-UK), a Lead Pain Nurse Specialist from the Christie NHS Foundation Trust in Manchester in the UK (JE) and a Research Sister from the Portsmouth Hospitals NHS Trust in the UK (AS). These HCPs have extensive experience of treatment and retreatment of patients with the capsaicin 8% patch and have treated >200 patients between them **(Table 1)**.

For each patient, the treating HCP carried out a detailed individual assessment of the NP and previous therapies prior to treatment with the capsaicin 8% patch and documented patients' outcomes during the follow-up period. The methods used to measure response to treatment varied between clinics. Changes in pain were measured by patient-reported pain scores using the commonly utilized 11-point Numerical Pain Rating Scale, Verbal Numerical Rating Scale or Visual Analog Scale [16]. Some patients were asked to keep a pain diary, others were asked to rate their pain during pretreatment, treatment and follow-up visits (or follow-up telephone calls). In addition, change in area of pain from baseline was measured as an assessment of response and patients self-reported changes in quality of life using questionnaires. No physical testing was carried out to determine changes in epidermal nerve fiber density.

Overall, there was a slightly higher proportion of female patients compared with male patients; the mean age was approximately 60 years (range: 21–88 years). The duration of PNP varied greatly among patients, ranging from 3 months to over 15 years. The majority of patients were taking other NP medications, such as opioids, antidepressants or anticonvulsants, at the time of receiving capsaicin 8% patch treatment. Among the indications treated, PHN or peripheral neuropathy were the most common. In patients with cancer, the most common cause of NP was chemotherapy-induced neuropathy.

Here, this experienced user group share their experience and recommendations for treatment best practice and highlight issues that should be considered when planning treatment with the capsaicin 8% patch to ensure patients get the most from therapy.

Observations of the experienced user group

■ Potential predictors of response to treatment with the capsaicin 8% patch

The response that an individual patient with NP has to any form of treatment is known to be unpredictable, largely owing to the complexity of the condition. NP can result from a variety of nerve-damaging stimuli that may be independent of the patient's specific condition. Therefore, patients with the same condition may respond differently to the same therapy, while patients with different underlying conditions may respond in a similar way to each other. This has led some investigators to suggest that it may be better to analyze NP according to the signs and symptoms of the pathophysiologic mechanism of the pain rather than the patient's condition [17,18]. However, it has not yet been possible to identify the phenotype of responders to any type of NP therapy.

To date, there has been no systematic study of the capsaicin 8% patch to determine which patients are most likely to respond to therapy and which symptoms of NP are most likely to respond. However, real-world experience from the collected observations of this user group suggests that there are certain signs and symptoms that appear to be positive or negative indicators for treatment success with this therapy **(Box 1)**. In many cases the authors have found that patients with positive symptoms, such as paresthesia and

Table 1. Patients treated by the experienced user group.

Healthcare professional	Patients treated with the capsaicin 8% patch (n)	Treatments (including retreatments) with the capsaicin 8% patch (n)
Till Wagner and Andrea Roth-Daniek	116	189
Angela Sell	>50[†]	>50[†]
Janice England	40	56
Kai-Uwe Kern	84	121

[†]The majority of these patients were treated as part of the live training program.

hyperalgesia, are more likely to respond to the treatment than those who do not have such symptoms.

Positive outcomes with the capsaicin 8% patch have also been observed by the user group when treating patients who have a definite diagnosis of NP or a single NP condition; these patients commonly achieved a reduction in pain levels following treatment with the patch. By contrast, those patients who have a complex pain situation generally benefit less from treatment.

It has been noted by the user group that good dialog and interaction between the patient and the treating HCP are important in helping to ensure that the patient is fully informed, has a positive attitude to therapy and remains fully engaged during and after the treatment procedure.

■ Requirement for topical anesthesia before patch application

Patients treated with the capsaicin 8% patch may experience a burning sensation during application. Pretreatment of the area with a topical anesthetic, such as lidocaine cream or EMLA® cream, is recommended in the product prescribing information in an attempt to reduce any discomfort [101].

Lidocaine and prilocaine (the other component of EMLA) are both amide-type anesthetics that inhibit sodium ion channels and the ion influx that is required for action potential generation. This reduces pain responses through the prevention of nerve impulse transmission [102,103]. However, it has long been known that TRPV1 receptors and sodium channels act independently at peripheral nerve terminals and therefore TRPV1 can induce axonal depolarization and defunctionalization even in the presence of sodium channel blockade [19,20]. Clinical evidence is mixed as to what degree the discomfort associated with capsaicin treatment might be reduced with lidocaine or other topical anesthetics [13,19].

When pretreating patients before application of the capsaicin 8% patch, the authors generally use lidocaine or EMLA for 60 min. The authors have observed that following pretreatment with topical anesthetic, the onset of capsaicin-induced discomfort (but not the first detection of any sensation) occurs approximately 30–40 min after patch application on most sites of the body. However, when treating the feet, the authors have observed that the onset of treatment-related discomfort is usually delayed, often until the evening of the treatment day. In certain cases where topical anesthetic cream was not used, for example, because of a patient's allergy to lidocaine, discomfort owing to capsaicin also occurred approximately 30 min after patch application. These observations led the authors to question whether anesthetic pretreatment is necessary or useful.

To investigate this further, the authors have attempted retreatment of a small number of patients with the capsaicin 8% patch without any pretreatment anesthetic. These patients had received pretreatment with local anesthetic before their first capsaicin 8% patch application, but they received no pretreatment anesthetic before the second application. All patients receiving capsaicin 8% patch retreatment for 60 min reported that the experience appeared to be the same as their first treatment, with no perceived difference in the level of discomfort they experienced during the two treatments. Patients also reported that both the first and subsequent treatments with the capsaicin 8% patch were tolerable, using appropriate and comparable post-treatment analgesic measures.

The authors have also treated a number of patients with their first capsaicin 8% patch without any topical pretreatment anesthetic. All of these treatments were successful, and observations of the patients have suggested that tolerability of the capsaicin 8% patch is similar under both conditions. One author observed that 32 patients receiving anesthetic

pretreatment experienced similar levels of discomfort to a separate group of 26 patients who received no pretreatment before application of the capsaicin 8% patch [21].

Many of the patients receiving capsaicin 8% patch treatment without topical anesthetic pretreatment received no analgesic medication, including no prophylactic medications, other than cooling measures after treatment. Some patients received intravenous nonsteroidal anti-inflammatory analgesics; in a very few cases, patients were treated with intravenous opioids [21,22]. However, all patients completed ≥90% of the intended patch application duration.

Aside from the issue of whether anesthetic pretreatment is necessary from the perspective of reducing discomfort, there are also practical advantages to not using it. In the authors' experience, an oily topical anesthetic cream, such as EMLA, can be difficult to remove and EMLA can also make the skin on the feet become particularly cold and damp, making patch adhesion difficult. Additionally, the authors have observed that application of the cream can aggravate PNP in patients with allodynia; therefore, these patients may prefer not to be pretreated with the anesthetic cream. It is also worth noting that the total duration of the capsaicin 8% patch treatment procedure can be substantially reduced if the pretreatment step is removed.

These experiences have led the authors to debate the utility of pretreatment analgesia. While the prescribing information recommends that users of the capsaicin 8% patch should pretreat their patients with topical anesthetic [101], the authors' accumulated evidence suggests that this may not be necessary. The authors recommend that HCPs who are first-time users of the capsaicin 8% patch should pretreat patients with lidocaine or EMLA cream, but with further experience, HCPs may wish to re-evaluate whether pretreatment is necessary. In the case of retreatment with the capsaicin 8% patch, one option may be to offer the patient the choice – if they had a good experience with their first treatment, they may not want to receive a pretreatment anesthetic. It is notable that a trial has recently been initiated investigating the use of an oral analgesic (tramadol) as an alternative pretreatment to topical anesthetic prior to capsaicin 8% patch application [104]. The results of this trial are likely to be a useful addition to discussion of this topic.

Application procedure

It is important to follow the correct procedure for application of the capsaicin 8% patch in order to optimize the efficacy and tolerability of the treatment. However, the procedure is easy to get used to and straightforward to carry out. The authors follow the application procedure as described previously and as detailed in the product prescribing information [15,101]. During the authors' initial treatments with the capsaicin 8% patch, they found that full and close contact of the patch with the skin was not always achieved, particularly when treating the feet, and this appeared to correlate with a mixed or poor response to treatment. Thus, one of the most important techniques the authors have learned through real-life use of the capsaicin 8% patch has been to ensure good adhesion of the patch to the skin. Wrapping the patch onto the treatment area using bandages or cling film, or using sand bags or the patient's own body weight to press the patch against the skin, have all been observed to help enhance the response to treatment with the patch. Similarly, using a hairdryer to warm and dry the body – particularly the feet – before patch application also enhances the response because the capsaicin 8% patch adheres better to dry and warm skin.

Treatment of the face, above the hairline of the scalp, and/or in proximity to mucous membranes is not recommended in the capsaicin 8% patch prescribing information owing to the potential risk of contamination of sensitive mucous areas [101]. However, the authors have used the capsaicin 8% patch to successfully treat an area of

Box 1. Potential positive and negative indicators for treatment success with the capsaicin 8% patch.

Positive

- Definite diagnosis of NP
- Tingling
- Positive symptoms (e.g., paresthesia and hyperalgesia)
- A single NP condition

Negative

- A complex pain situation and, in particular, one that includes a psychologic component
- Any inflamed treatment area
- 'Cut-of-a-knife' sensations
- Small-fiber neuropathy†

†In the authors' experience, small-fiber neuropathy may only be a negative indicator for treatment success if the treating healthcare professional is inexperienced. Therefore, they do not recommend treating patients with small-fiber neuropathy if it is the healthcare professional's first time using the capsaicin 8% patch.
NP: Neuropathic pain.

NP on the face in three patients: one patient with PHN at the trigeminal nerve (V1) and two patients with severe trigeminal neuralgia in V2. No extra measures were taken to protect the eyes in these cases, but all patients were pretreated with topical anesthetic and had no untoward symptoms during or after treatment. Therefore, while extra care is needed if the capsaicin 8% patch is brought into close proximity to the eyes, the authors' experience suggests that it can be used by practiced users to successfully treat NP on the face.

■ Erythema & application-site discomfort

Another observation the authors have made during the application procedure is that although the majority of patients experience redness and some burning at the site of application, redness and/or application-site discomfort do not always occur during treatment with the capsaicin 8% patch. This observation is supported by data from the clinical trial program: 193 out of 205 patients (94%) with PHN who were treated with the patch experienced erythema, while 114 out of 205 patients (56%) reported application-site discomfort [10]. It is worth noting that erythema can be difficult to observe in some cases, for example when treating patients with dark skin or when treating the hands or, particularly, the soles of the feet. Indeed, the authors have observed that erythema does not appear to occur on the soles of the feet but occasionally mild erythema occurs on the dorsum. This is perhaps not surprising as data from a long-term safety study of the capsaicin 8% patch in patients with PHN and HIV-associated distal sensory polyneuropathy (HIV-DSP) have demonstrated that the incidence of application-site erythema was lower in patients with HIV-DSP compared with PHN [23]. There also appears to be considerable interpatient variability in the timing of erythema and application-site discomfort after capsaicin 8% patch treatment. In some cases, patients do not experience application-site discomfort during treatment, but may experience a burning sensation for up to 1 week post-treatment.

The mechanism of this interpatient variability in erythema and application-site discomfort after capsaicin treatment is not yet clear. TRPV1 activation and excitation of C-fibers following capsaicin application cause the release of neuropeptides from a subpopulation of C-fiber terminals. Vasoactive neuropeptides, which are mediators of the neurogenic inflammatory response, include substance P (SP) and CGRP, which are involved in the formation of erythema or flare [24,25]. It is possible that the nociceptors of some patients are depleted of SP or CGRP, and they would therefore be unable to cause vasodilation and erythema following capsaicin treatment (without losing the therapeutic benefit of nociceptor defunctionalization). It is known that depletion of SP can occur at nerve terminals, with capsaicin reducing SP levels in skin nerve terminals and prior capsaicin treatment diminishing components of neurogenic inflammation, such as erythema [26,27]. Furthermore, the recovery of SP levels may be slower than that of C-fiber signaling functions following capsaicin treatment [27]. These effects can be long lasting; studies in healthy volunteers have demonstrated that it can take up to 20 days for a normal flare response to occur following repeated applications of capsaicin 1% [26]. It is also possible that some patients may have fewer neuropeptide-expressing peripheral nociceptors and therefore release smaller quantities of SP or CGRP when treated with capsaicin. However, as depletion of SP does not account for capsaicin-mediated pain relief [14], the authors' experience of an absence of a correlation between application-site discomfort and erythema may not be surprising. Furthermore, to date the authors have not observed any correlation between lack of erythema and response to capsaicin 8% patch treatment.

■ Management of treatment-related discomfort & tolerability of treatment

In general, the authors have found that treatment with the capsaicin 8% patch is tolerable. Separate analyses of 58 patients from the clinic in Wiesbaden and 68 patients from Aachen have shown that 100% of patients completed the intended duration of patch application [21,22]. It was also observed that by 6 h after the initiation of capsaicin 8% patch treatment, any increase in pain scores owing to application of the patch had returned to pretreatment baseline levels [21]. Similar observations were made during the clinical trial program. Here, an integrated analysis of 1696 patients demonstrated that ≥98% of patients completed ≥90% of the intended treatment duration [28] and transient increases in pain that occurred during treatment returned to baseline levels by the evening of the treatment day in patients with

PHN and by the evening of day 2 in patients with HIV-DSP [28].

Through experience of using the capsaicin 8% patch, the authors have found that cooling measures used immediately after the application procedure to be the most practical and beneficial method of reducing any discomfort caused by treatment. However, cooling during the application procedure is to be avoided if possible. TRPV1 channels are heat activated, normally opening at approximately 43°C, but capsaicin reduces this threshold so they can be activated at temperatures of approximately 37°C [13]. There is therefore speculation that lowering the temperature of the skin may alter the treatment effect on TRPV1 channels and/or change the kinetics of capsaicin movement into the skin, although this has not been scientifically tested. Thus, cooling should not be used pre-emptively at the start of the patch application; however, chilled cool packs may be used in response to intolerable patch-related discomfort at the end of the procedure if this would ensure that the patient completes the full application duration. To avoid causing damage to the skin, frozen cool packs should never be used.

Any discomfort during treatment generally arises approximately 30 min after the start of the application procedure. Oral opioid analgesics require approximately 30 min to achieve a significant pain decrease; therefore, if opioid analgesia is needed during treatment then this should ideally be administered intravenously. Although oral analgesics could be administered prophylactically at the beginning or just before patch application, the authors' experience to date has shown that very few patients require opioid analgesics during treatment. The authors therefore do not advocate prophylactic analgesic treatment; they only recommend that patients continue with any regular use of analgesic medication. Indeed, in many cases, patients will not require any pain management at all during or after treatment, with distraction alone being sufficient. Based on their experience, the authors do not feel that any kind of invasive regional anesthesia or sedation is necessary.

In some patients, the burning sensation that can occur on application of the patch does not occur during treatment or immediately after. The authors' observations suggest that there is potential for a delayed or prolonged burning sensation after treatment, especially when treating peripheral areas, for example the feet or fingers. Some patients treated on the feet experience tingling at application of the patch, with the burning sensation starting within an hour of treatment and increasing in intensity over the following 12 h. In some patients the burning sensation lasts for 48 h and in others for up to 7 days. This difference in duration of treatment-related discomfort between treatment sites has been observed previously in the integrated analysis of tolerability data from the capsaicin 8% patch clinical trial program [28]. The data demonstrated that mean pain scores decreased to baseline pretreatment levels by the evening of the treatment day in patients with PHN who were treated on the torso. However, in patients with HIV-DSP or painful diabetic neuropathy who were treated on the feet, pain scores did not return to baseline levels until the evening of day 2 after treatment [28]. These variations may be owing to differences in the thickness of the skin between body sites [28].

Patients should be advised that cooling measures can also be effective for relieving treatment-related discomfort at home. Cooling can be in the form of cool packs, cold floor tiles (for the feet) or tepid water. Patients can also take over-the-counter pain medications, such as acetaminophen (paracetamol) or ibuprofen, to relieve any treatment-related discomfort at home. If patients feel it is necessary, oral opioids can also be taken to relieve discomfort; however, in the authors' experience, few patients required this level of analgesia and, in some cases, patients who have taken opioids at home have reported little or no benefit. Using this approach, the authors found that no patients subsequently made contact with the clinic after the treatment owing to 'intolerable pain'.

Blood pressure monitoring

Transient increases in blood pressure may occur during and after treatment as a result of treatment-related discomfort, and the product prescribing information recommends that HCPs should monitor the blood pressure of patients that they treat with the capsaicin 8% patch [101]. However, from their experience, the authors feel that once confidence in the application procedure has been gained, monitoring of blood pressure is not normally necessary unless the patient has heart disease, is hypertensive or has a high heart rate. As a group, the authors have not experienced problems with hypertension in any patients and have seen no extreme fluctuations compared with baseline measurements. Indeed,

they have observed that repeated monitoring of patients during application of the capsaicin 8% patch may result in the patient focusing on any treatment-related discomfort. In some cases, particularly with younger and healthy patients who are less likely to experience hypertension, it may be beneficial not to monitor blood pressure during treatment, although blood pressure should be checked before and afterwards. In cases where blood pressure is not monitored during treatment, the authors advise that a HCP is present with the patient for the duration of treatment.

Reducing concomitant NP medications & patient follow-up

Patients who experience pain reduction with the capsaicin 8% patch may be keen to reduce their concomitant NP medications. This is often the case even if the patient is still in some pain, as patients often wish to reduce the side effects of systemic medications. All of the authors have treated patients who were able to reduce their concomitant medications following treatment with the capsaicin patch. At the clinic in Aachen, patients treated with the capsaicin 8% patch have exhibited a 54% reduction in the mean number of concomitant medications after treatment compared with baseline [29]. It is important to note, however, that concomitant medications should only be reduced following consultation between the patient and their prescribing HCP.

Within this user group, the extent of patient follow-up has varied between individual HCPs; however, from experience, the authors recommend that new users of the capsaicin 8% patch should follow-up with their patients regularly, for example on days 2, 8 and 15 after treatment, to ensure there have been no issues with the treatment or treatment-related discomfort. More experienced users may be comfortable with reducing the frequency of follow-up. It may be beneficial to provide patients with a telephone number that they can call at any time if they have concerns about treatment-related discomfort or want to request another appointment if their NP returns. A study in healthy volunteers has shown that epidermal nerve fiber density is reduced by approximately 80% by 7 days after treatment with the capsaicin 8% patch [30]. Therefore, one could expect that any response to treatment would have manifested by this time, and in accordance with this, the authors have only observed a small number of patients with an onset of pain reduction later than 7 days after treatment.

Retreatment with the capsaicin 8% patch

As a group, the authors have retreated over 50 patients with the capsaicin 8% patch, some of whom have been retreated more than once. In the authors' experience, the retreatment response appears to be equal to that of the first treatment; they have observed no loss in response to treatment with the capsaicin 8% patch when treating patients for a second, third or even a fifth time. The authors have also observed no reduction in the level of tolerability to treatment in these patients. These observations are not surprising when compared with observations from clinical studies of the capsaicin 8% patch. A study of patients with PHN demonstrated that pain reduction can be maintained over 1 year with up to three repeated applications of the capsaicin 8% patch, with no loss in efficacy after each treatment [7]. Tolerability to repeated treatments was also maintained in patients from the clinical trial program [7,23,28]. The integrated tolerability study demonstrated that the maximum change in pain score did not increase after repeated treatments and that the proportion of patients completing ≥90% of the intended treatment duration did not decrease with up to four treatments with the capsaicin 8% patch [28].

Normally retreatment with the capsaicin 8% patch is not undertaken until the NP has returned, and it is recommended in the product prescribing information that at least 12 weeks should have elapsed since the last treatment [101]. The authors have seen patients who have not needed retreatment until 14–16 weeks after the first application and some who have not requested retreatment until 8 months after initial treatment. One author has also observed a patient who is still pain-free 10 months after their first treatment with the capsaicin 8% patch. However, in a number of cases the authors have carried out retreatments 9 or 10 weeks after the first treatment owing to a return of the patient's pain. The authors do not feel it is appropriate to wait until a patient's pain level has returned to baseline levels before retreating, therefore they recommend carrying out further treatment when the pain returns to two-thirds of the baseline level, or when the patient requests it, if clinically appropriate.

In addition to being preferable for the patient, there is also the possibility that treating a patient before their pain returns to baseline levels could result in an overall 'wind-down' of pain [31]. One of the putative mechanisms behind NP is a phenomenon called central sensitization or 'wind-up', which results from repeated stimulation of peripheral C-fibers leading to a progressive increase in the activity of dorsal horn cells involved in transmitting sensory signals within the CNS [32]. This hyperexcitability of the CNS causes normally innocuous stimuli to produce pain responses owing to the abnormal processing of these stimuli within the CNS [105]. It is possible to block 'wind-up' by reducing the release of primary afferent transmitters from peripheral C-fibers or through conversion of the amplified response into a steady response [32,33]. Therefore, the defunctionalization of nociceptors caused by capsaicin and the consequent reduction in C-fiber signaling may abolish or reduce 'wind-up'. Indeed, the authors have seen some preliminary evidence of 'wind-down' in a few of their patients, with pain returning following retreatment but each time tending towards a reduced baseline level and/or a smaller painful area [31]. Retreating patients before their pain fully returns, as a preventative measure, may reduce 'wind-up' or prevent it from returning and so mitigate one of the causes of the NP.

■ Real-life experience with capsaicin 8% patch treatment compared with clinical trial observations

As discussed previously, it is important to note that the capsaicin 8% patch is indicated for the treatment of a wide variety of NP conditions. However, during the clinical trial program, the capsaicin 8% patch was tested only in patients with PHN, HIV-DSP or painful diabetic neuropathy. The authors' real-life experience has shown that the capsaicin patch is also effective at reducing pain in a range of other NP conditions including polyneuropathy and cancer-related NP. They have also used the capsaicin 8% patch to successfully treat sites of the body other than those treated during the clinical trials program, for example, the head and face.

Overall, the response rate to the capsaicin 8% patch appears to be greater in the real-life setting compared with the published clinical trial data. At the clinic in Aachen, 67% of patients with PHN and 70% of patients overall responded (exhibited ≥30% decrease in pain levels) to treatment with the capsaicin 8% patch [22] compared with 42 or 46% of patients with PHN in two separate studies [9,10] and 34% of patients with HIV-DSP [8]. In a further trial of patients with HIV-DSP, 38% of patients treated for 30 min with the capsaicin 8% patch exhibited a ≥30% decrease in pain levels, although this was not significantly different from the proportion of patients treated with a control patch achieving a ≥30% decrease in pain levels [34].

The authors also found that there was less of a need to use additional pain medication for treatment-related discomfort in the real-life setting than there appeared to be in the clinical trials, where over half of all patients used oral opioid analgesics (oxycodone or hydrocodone) on post-treatment days 0–5 [28]. In the authors' experience, <10% of patients required additional opioid medication during treatment. Furthermore, patients who have taken their normal breakthrough analgesia, such as instant-release opioids, at home after treatment have reported them to be of little or no benefit. It is possible that this difference between clinical trials and the real-life setting occurs because medication for treatment-associated discomfort was provided to all patients for the days immediately following capsaicin 8% patch treatment in the clinical trials.

Conclusion & future perspective

The authors – a group of HCPs experienced in the use of the capsaicin 8% patch – have found that patients with a variety of NP etiologies respond to treatment and that it is well tolerated. Through repeated use of the patch, the authors have discovered techniques that they find enhance the response to treatment, such as bandaging the patch to the skin to increase adhesion, and have observed that pretreatment with topical anesthetic may not be, in their opinion, necessary or useful. The authors have found that local cooling after treatment is the most beneficial technique for alleviating any discomfort associated with capsaicin 8% patch treatment. The authors also observed that treatment with the capsaicin 8% patch often enables concomitant medications for NP to be reduced or discontinued.

The capsaicin 8% patch is an important addition to the treatment options for patients with NP. Although the capsaicin 8% patch has been

shown to be effective in clinical trials, in Europe it has been approved for a far wider range of indications than those studied in these trials. Accordingly, the authors have found that the capsaicin 8% patch can be effective for treating a variety of NP conditions and body sites, many of which have not been investigated in clinical trials. Notably, the authors have not found the capsaicin 8% patch to be associated with any serious adverse events in the >200 patients they have treated. The experience and knowledge that the authors have gained from their use of the capsaicin 8% patch have provided valuable insight into maximizing its treatment potential and identifying treatment best practice.

One of the major differences between the capsaicin 8% patch treatment and other medications for NP is that the application procedure has to be carried out by an HCP in a clinic or treatment room. While this has time implications and therefore could potentially be seen as a burden by patients, in the authors' experience it is not generally viewed in this way. Many patients are motivated to receive a new treatment that may provide much-needed pain relief. In other cases, patients feel that the relief provided by the capsaicin 8% patch more than outweighs any possible inconvenience of the treatment, particularly when the effect lasts for several weeks. In addition, capsaicin 8% patch treatment does not add any additional pill burden to patients and is not associated with potential drug interactions. Indeed, if patients are able to reduce their other NP medications following capsaicin 8% patch treatment, this will actually reduce the patient's pill burden. The main concern that HCPs may have about the office-based capsaicin 8% patch application procedure is that it will be difficult to find time to treat all patients who require it, especially if patient numbers are increasing. However, overall the authors have found that the time spent with patients receiving capsaicin 8% treatment is similar to the time spent with patients receiving systemic medications. While application of the patch itself takes time, there are fewer follow-up visits by the patient and less time is spent processing repeat prescriptions and counseling patients when a new treatment is required. Furthermore, as the capsaicin 8% patch application procedure is an in-office procedure carried out by an HCP, treatment is not associated with adherence issues. The authors feel that the benefits of the capsaicin 8% patch treatment outweigh any burden associated with it being an in-office procedure.

It is important that HCPs continue to gather and share information about the capsaicin 8% patch treatment. As clinical experience with the capsaicin 8% patch accumulates, more knowledge will be gained on a number of important aspects. For example, the need for pretreatment with topical anesthetic before applying the capsaicin 8% patch is a subject of much discussion, not least because the pretreatment substantially increases the overall treatment time for the capsaicin 8% patch, which has implications for both patients and HCPs. Data from an ongoing trial investigating different pretreatment regimens [104], together with increasing amounts of real-world evidence, will be important to gain a definite consensus on the necessity and/or optimal type of pretreatment. It will also be both important and interesting to be able to identify patients who are likely to be responders to capsaicin 8% patch treatment, as this will reduce the number of unnecessary treatments and will help to manage the patient expectations.

The authors have also noted that there may be the possibility of reducing concomitant pain medications in patients who are treated with the capsaicin 8% patch. It will be crucial to quantify any reductions and to evaluate this from both a patient's perspective and an economic perspective. Patients may benefit from a reduction in unwanted systemic side effects associated with concomitant medications, which could have a positive effect on their quality of life; a reduction in concomitant medications would also be associated with a decrease in healthcare expenditure. As more HCPs gain real-world experience, more evidence will become available about these issues.

Over time, more evidence will also become available with regard to retreatment with the capsaicin 8% patch, which will be important to further demonstrate its efficacy when used repeatedly. This will be key to further assessment of the long-term safety of the capsaicin 8% patch, which is currently being investigated in a clinical trial setting [106].

It is the opinion of the authors that as more experience is gained in the use of the capsaicin 8% patch to treat NP, it is likely that treatment practice will change and by learning from accumulated experience and following treatment best practice, use of the capsaicin 8% patch is likely to benefit many patients who experience NP.

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