Northern Treatment Advisory Group

Qutenza® capsaicin cutaneous patch for neuropathic pain

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Summary

- Qutenza is a cutaneous patch containing capsaicin 8%, considered to be a high concentration capsaicin preparation. It is licensed for treatment of peripheral neuropathic pain in adults. Capsaicin is thought to be useful for the treatment of pain due to stimulation and desensitisation of pain receptors in the skin.
- One open-label randomised trial found that capsaicin 8% and oral pregabalin provide comparable pain relief, but that the onset of analgesia may be faster with capsaicin. The study was short (8 weeks) and therefore provides no data on how treatments compare in the long term.
- Meta-analyses have assessed the efficacy of capsaicin 8% patches compared to capsaicin 0.04% patches. This comparator causes local skin reactions such as erythema and pain, but does not provide long term pain relief. It was chosen to prevent unintentional unblinding.
- Capsaicin 8% was more likely than control to be associated with improvements in pain scores. However, the differences were small and may not be clinically important. In addition the studies were short, with endpoints assessed 8-12 weeks after treatment. The response to treatment in the control group was also highly variable, and several trials found no significant difference between Qutenza and control.
- In patients with post-herpetic neuralgia, Qutenza was associated with a quicker onset of pain relief than control. In patients with HIV-associated neuropathy, there was an initial increase in pain scores with Qutenza which resulted in a relatively slower onset of pain relief than in the control arm. Most patients had no offset of pain relief during the 12 weeks of the study, irrespective of treatment arm or diagnosis.
- A systematic review and indirect comparison of drugs for neuropathic pain found that the number of people needed to treat (NNT) to obtain a treatment response was higher with Qutenza than pregabalin, gabapentin, tricyclic antidepressants or SNRIs.
- There are no major safety concerns related to Qutenza use. The majority of reported adverse effects are minor or moderate, and tend to be application site reactions such as pain and erythema. These can be treated with analgesia and local cooling, and are transient. Systemic adverse effects are not common with Qutenza (incidence of 0-1.1%).
- Qutenza costs £210 per patch. It is licensed for use once every 90 days, but in practice is likely to be used less often. A cost-effectiveness model found Qutenza to be more cost effective than pregabalin for treatment of neuropathic pain. However the model made several assumptions that may not reflect usual clinical practice. Costs for pregabalin are likely to change in the near future pending the outcome of an ongoing court case regarding a patent for Lyrica®.

Introduction and background

Neuropathic pain is defined as any pain caused by a lesion or disease of the somatosensory nervous system. Peripheral neuropathic pain specifically is caused by lesions or diseases of the peripheral somatosensory nervous system. Neuropathic pain is therefore very diverse in its origins, presentation and causes, and can be challenging to treat. Symptoms vary, but pain is typically described as shooting, stabbing, electric, burning, tingling, tight, numb, prickling or itching. Pain may be intermittent or constant, and may or may not have an obvious cause. The prevalence is difficult to determine, but has been estimated at 6-8% of the general population. The following estimates have been made for patients with specific conditions:

- Painful diabetic neuropathy – 16-26% of people with diabetes
- Post-herpetic neuralgia (PHN) – 8-19% of people with herpes zoster
- Chronic pain after surgery – 10-50% after many common surgeries, e.g. 30-50% after amputation.

Pharmacological options for treatment include antidepressants, antiepileptics, topical treatments and opioid analgesics. However, response to therapy is often inadequate; only 40-60% of people experience partial pain relief. Referral to a specialist pain service may often be necessary.[1,2]

Capsaicin is the substance in chilli peppers which makes them hot. It acts as an agonist of a receptor known as TRPV1, which is a type of nociceptor (pain receptor) that appears to sense noxious heat stimuli. This suggests a mechanism by which capsaicin exposure can be perceived as both hot and painful. Persistent stimulation of TRPV1 receptors, for example by application of high strength capsaicin formulations, is hypothesised to lead to desensitisation and may therefore have analgesic effects.[3,4]

Qutenza® (Astellas Pharma) is a cutaneous capsaicin patch which has been available in the UK since July 2010.[5] It is licensed for treatment of peripheral neuropathic pain in adults, either alone or in combination with other medicinal products for pain. Qutenza contains capsaicin 8%, which equates to 179 mg capsaicin per 14 cm x 20 cm (280 cm^2) patch. This is considered a high strength formulation; the other licensed medicinal products in the UK are capsaicin 0.075% (Axsain® cream, licensed for neuropathic pain) or capsaicin 0.025% (Zacin® cream, licensed for osteoarthritis).[6-8]

Qutenza was reviewed by NETAG in 2011. It was not recommended for use at that time on the basis that it was not considered cost-effective.[9] This document will review the new evidence for effectiveness and cost-effectiveness which has been published in the interim.

Guidance and related advice

NICE guidance on pharmacological management of neuropathic pain in primary care was updated in 2013. Initial treatment for neuropathic pain should be with one of amitriptyline (off-label), duloxetine, gabapentin or pregabalin. If the first choice is not tolerated or is not effective, one of the remaining three drugs should be offered. Consideration may be given to switching again if a third choice is also ineffective. Capsaicin cream may be considered for people with localised pain who wish to avoid

or cannot tolerate systemic treatments. There are no other topical treatments recommended. Topical lidocaine was recommended in a previous version of the guidance, but was removed in 2013 due to a lack of good quality evidence. Patients with persistent pain after exhausting these options should be referred to secondary care. Other drugs, including capsaicin patches, should not be initiated in primary care unless advised by a specialist.[1,2]

NICE has not produced a technology appraisal of Qutenza, or any other specific advice specific to capsaicin patches. The Scottish Medicines Consortium (SMC) reviewed Qutenza in 2011 and recommended it for restricted use. The restriction specified that Qutenza should only be used in non-diabetic patients with PHN who have not achieved adequate pain relief from, or who have not tolerated, conventional first and second-line treatments. Treatment should be under the supervision of a specialist in pain management.[10] This recommendation was updated in 2014, when the restriction to patients with PHN was removed. Instead, the updated advice stated that Qutenza should be restricted to use in non-diabetic patients with peripheral neuropathic pain who have not achieved adequate pain relief from, or have not tolerated, conventional first and second line treatments.[11]

In February 2016 the SMC published a final statement of advice, stating that Qutenza was not recommended for treatment of peripheral neuropathic pain in diabetic adults.[12] The treatment was not recommended on the grounds that the holder of the marketing authorisation did not make a submission regarding this indication.

Clinical efficacy

One randomised controlled trial, plus several systematic reviews and meta-analyses, have been published since NETAG reviewed this topic in 2011. Pain was generally assessed using a numeric rating scale which assigns scores ranging from 0 (no pain) to 10 (worst pain imaginable). There are no published trials in patients with diabetic peripheral neuropathy.

Direct comparison: capsaicin vs. pregabalin

The randomised open-label ELEVATE trial, which compared capsaicin 8% patches with pregabalin, was published in 2016. Patients (n=568) were adults aged 18 to 80 with definite or probable peripheral neuropathic pain due to PHN, post-traumatic nerve injury, or non-diabetic peripheral polyneuropathy and were required to have average pain scores ≥4 on at least 4 consecutive days. Patients were naïve to capsaicin 8%, and were either naïve to pregabalin and gabapentin or were judged to have had inadequate treatment with pregabalin or gabapentin.[13]

Reasons for exclusion included other causes of neuropathic pain (including complex regional pain syndrome), pain located only on the face, scalp or in proximity to mucus membranes, severe loss of heat sensation in the painful area, daily pain score of 10 for ≥4 days during screening, and history of diabetes mellitus, cardiovascular disease (including poorly controlled hypertension) or renal impairment. Background medications for neuropathic pain were required to be stable for at least 4 weeks prior to baseline, and opioid dose could not exceed morphine 200 mg/day or equivalent. Patients were not eligible for inclusion if they received

tapentadol or intravenous opioids in the 7 days preceding the baseline visit, chemotherapy in the preceding 3 months, or any investigational agent within 30 days. Patients were excluded if they had an active or chronic substance abuse problem.

Patients were randomised 1:1 to receive capsaicin 8% patch or pregabalin titrated to response. Pregabalin was started at 75 mg daily, increased by 75 mg every 3-4 days up to a maximum of 600 mg daily in divided doses. One down-titration was permitted by week 4. Topical anaesthetic was used prior to capsaicin patch application and short-acting analgesia was available for up to 5 days following application, if required.

The primary endpoint was proportion of patients with ≥30% reduction in pain after 8 weeks, as measured on a numeric pain rating scale. The primary analysis was conducted in the full analysis set, which comprised all patients who were randomised and started treatment. The safety analysis set comprised all patients who received study drug. Baseline observation carried forward (BOCF) was used to account for missing data, which is a conservative approach.

The mean number of capsaicin patches used per treatment was 1.4, and over 50% of participants received only one patch. The mean dose of pregabalin was 183 mg daily in the first 2 weeks, 364 mg daily between weeks 4 and 8, and 344 mg daily in week 8. The mean pain score at baseline was similar in both groups (6.5 vs. 6.7 for capsaicin and pregabalin respectively).

The proportion of patients achieving ≥30% reduction in pain at week 8 was similar in the capsaicin and pregabalin arms (55.7% vs. 54.5%, treatment difference 1.2%, OR 1.03, 95% CI 0.71 to 1.50). There was no difference between groups in the proportion of patients achieving an optimal therapeutic effect. The median time to onset of pain relief was defined as the time point at which 50% of patients had a 30% reduction in pain scores for 3 consecutive days. This was significantly shorter with capsaicin (7.5 days vs. 36 days, HR 1.68, 95% CI 1.35 to 2.08, p<0.0001), and was supported by a larger mean reduction in pain scores in the capsaicin arm up to week 3. However, over the total study duration of 8 weeks mean reductions in pain scores were not significantly different between groups.

Meta-analyses of efficacy

A Cochrane review was published in 2013, incorporating study-level data from six published randomised controlled trials of high strength (8%) topical capsaicin for neuropathic pain.[14] Trials were included if they had a double-blind design and enrolled adults with neuropathic pain of at least moderate intensity. All patients had neuropathic pain caused by either PHN or HIV-associated neuropathy (HIV-AN). The review protocol specified that studies comparing topical capsaicin 8% to placebo or active comparator were eligible for inclusion. However in practice, all trials which met the entry criteria used capsaicin 0.04% as a comparator. Capsaicin 0.04% causes a local burning sensation and erythema at the application site similar to capsaicin 8%, but not long-term pain relief. It was chosen as a control in these trials to prevent accidental unblinding due to application site reactions.

All studies allowed other concomitant pain relief, but transdermal analgesics were discontinued at least one week before starting study treatment. The total dose of other analgesics was ≤60 mg morphine/day or equivalent. The number of

participants ranged from 150 to 500 per trial and totalled 2,073, of whom 1,272 had PHN and 801 had HIV-AN. Trials were all 12 weeks in length, and assessed efficacy at 8 or 12 weeks after capsaicin application.

The primary outcome was clinical improvement, which was defined as ≥50% improvement in pain scores, or equivalent measures such as a global assessment of treatment of at least "very good", or a categorical pain assessment of "none" or "slight". Qutenza was associated with better outcomes than control (table 1). Confidence intervals approached 1.0 in several cases, implying that the true difference between Qutenza and control may be small.

Table 1. Outcomes from Cochrane review of capsaicin 8%

Control	Outcome measure	Time	Risk ratio (95% CI)	NNT
Post-herpetic neuralgia	Much or very much improved	8 weeks	1.42 (1.10 to 1.84)	8.8
		12 weeks	1.55 (1.20 to 1.99)	7.0
	≥50% pain intensity reduction	Weeks 2-8	1.44 (1.12 to 1.86)	12
		Weeks 2-12	1.3 (1.0 to 1.7)	11
HIV-associated neuropathy	Much or very much improved	12 weeks	2.8 (1.4 to 5.6)	5.8
	≥30% pain intensity reduction	Weeks 2-12	1.4 (1.1 to 1.7)	11

A second meta-analysis was published by Mou et al in 2013.[15] It included patient-level data from all six of the studies covered by the Cochrane review, plus one small (n=44) phase 2 trial in patients with PHN. This trial lasted 28 days and had a 48 week extension. This meta-analysis reported that use of concomitant analgesia was common, with opioids the most frequently used (52-33% of patients) followed by anticonvulsants (47-36%) and NSAIDs (25-31%).

Both Qutenza and control (capsaicin 0.04%) were associated with a decrease in pain intensity between weeks 2 and 12 (30.7% vs. 22.7%). The difference between the two groups was statistically significant (8%, 95% CI 4.6 to 11.5, p<0.001), but unlikely to be considered clinically important. The treatment difference was slightly larger in patients with HIV-AN (11.3%, 95% CI 3.6 to 19.0) than for PHN (7.9%, 95% CI 4.0 to 11.8). The proportion of patients with ≥30% decrease in pain intensity was higher with Qutenza than control (44% vs. 34%), as was the proportion of patients with ≥50% decrease in pain (28% vs. 22%).

The effect of Qutenza was relatively consistent between trials, with a 24-37% decrease in pain reported. However, the response to the control capsaicin 0.04% was highly variable, ranging from 4-33%. As a result only four of the seven trials found Qutenza to be statistically superior to the control patch, and in one case the response to Qutenza was numerically smaller than the response to control (24.2% vs. 28.2%, treatment difference -4.0%, 95% CI -19.8 to 11.7, p=0.61). The placebo response in these trials therefore appears to be very variable, and may be large.

Treatment effect onset and duration

Mou et al published another meta-analysis in 2014, in this case assessing the onset and duration of pain relief associated with capsaicin.[16] Data from the same seven trials were included, plus a 40 week open-label extension of a single 12 week trial in patients with HIV-AN. As would be expected this analysis found that the proportion of patients with a ≥30% change in pain intensity was as described above, but added that the relative risk of this outcome was 1.27 (95% CI 1.13 to 1.43), which is comparable to the findings of the Cochrane review.

In PHN patients the mean pain score was 5.7 in both treatment arms prior to patch application. One day after patch application, pain scores decreased to 4.0 in the Qutenza arm (-29.8%) and 4.2 in the control arm (-26.3%). Scores remained below the baseline value in both groups throughout the first 2 weeks of treatment. The mean time to onset of treatment response was shorter in the Qutenza arm (3.4 vs. 4.7 days, p=0.044).

In HIV-AN patients pain decreased from a mean 5.9 at baseline to 4.7 after 3 days of treatment, and scores remained in the range of 4.5-4.7 for the first 2 weeks of treatment. Pain initially increased in the Qutenza arm, from 6.0 at baseline to 6.8 after 1 day, but was below baseline at day 3 and reached 4.4 on day 14. Pain scores were higher in the Qutenza arm than with placebo for the first 8 days following treatment. The initial increase in pain with Qutenza meant that the mean time to onset of response was longer with Qutenza than placebo (6.5 vs. 3.8 days, p value not reported).

Most patients did not have offset of treatment effect during the 12 week studies, irrespective of treatment arm or diagnosis. In the 40 week open-label extension study 42.5% of patients with a treatment response (30% improvement in baseline pain scores) maintained the response until the end of treatment without any additional treatments. The mean duration of response was 157 ±125 days with Qutenza; this outcome was not assessable for the control patch.

The rate of complete treatment response (freedom from pain) was low in both groups, but higher with Qutenza (9% vs. 6%). This effect was greater with PHN (11% vs. 6%) than HIV-AN (7% vs. 6%).

Indirect comparison with other therapies

A systematic review assessed 229 double-blind RCTs of patients with neuropathic pain. All included studies were of parallel group or crossover design, and enrolled at least 10 patients per arm. Primary outcomes were measures of neuropathic pain intensity; studies which assessed a composite of paraesthesia and pain, or paraesthesia alone, were excluded. The drugs involved included tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), other antidepressants, pregabalin, gabapentin, other antiepileptics, tramadol, opioids, cannabinoids, lidocaine 5% patch, capsaicin 8% patch and cream, and others.[17]

The mean quality score of the included trials was 4.1 on the Oxford Quality Scale, which rates quality out of 5. There was some evidence of publication bias, and the authors stated that the effect size for capsaicin 8% patches may become clinically non-significant if studies with no effect were published.

Outcomes were reported in terms of number needed to treat (NNT) to obtain 50% pain intensity reduction. Where necessary, 30% pain intensity reduction or moderate pain relief was used. The NNT was higher for capsaicin 8% patches (10.6) than for any other treatment assessed (see table 2). The authors noted that the evidence relating to capsaicin was of high quality.

Table 2: Outcomes from systematic review of neuropathic pain treatments

Drug/class	NNT	95% confidence interval
Tricyclic antidepressants	3.6	3 to 4.4
SNRIs	6.4	5.2 to 8.4
Pregabalin	7.7	6.5 to 9.4
Gabapentin*	7.2	5.9 to 9.1
Tramadol	4.7	3.6 to 6.7
Strong opioids	4.3	3.4 to 5.8
Capsaicin 8% patch	10.6	7.4 to 19
Botulinum toxin type A	1.85	1.5 to 2.4

*includes gabapentin encarbil and extended release preparations

Safety

The Cochrane review found reporting of adverse events (AEs) to be inconsistent and incomplete. Most AEs were mild to moderate, and were transient. The most common events were application site reactions, but rates varied since some trials counted erythema and pain on the day of application as pain scores, not AEs. These trials were designated as Group 2; Group 1 counted all application site reactions as AEs. Reaction site AEs were more common with capsaicin 8% than with control in Group 1, but not in group 2 (see table 3). Systemic AEs (e.g. GI events, hypotension, dizziness, headache) were rare, and with no apparent difference between capsaicin 8% and control groups. Similarly, there was no significant difference in the rate of serious AEs. There was no difference in the rate of withdrawals due to AEs.[14]

Table 3: risk of skin adverse events[14]

Control	Group 1		Group 2	
	Relative risk (95% CI)	NNH	Relative risk (95% CI)	NNH
Erythema	1.4 (1.3 to 1.5)	5.9	No sig difference	-
Pain	2.3 (2.0 to 2.6)	2.4	1.9 (0.99 to 3.5)	-
Papules	3.6 (1.9 to 6.9)	23	1.6 (0.59 to 4.2)	-
Pruritus	2.0 (0.98 to 4.0)	-	1.6 (0.98 to 2.5)	-
Oedema	3.0 (1.4 to 6.2)	38	1.3 (0.75 to 2.4)	-

NNH: number needed to harm

Mou et al did not discuss safety outcomes in their first meta-analysis. The second analysis reports outcomes on effect of capsaicin 8% on sensory function, but no other safety outcomes. Sensation was assessed in terms of responses to different

stimuli: a light brush, pin prick, vibration and warmth. The analysis found that the proportion of patients with sensory loss or increased sensation was not significantly different between groups at the last study visit. However, the proportion of patients with normal sensory responses was consistently higher in the control group (light brish 41.0% vs. 38.2%, pin prick 42.2% vs. 38.2%, vibration 53.9% vs. 46.8%, warmth 56.7% vs. 53.0%). This suggests that capsaicin 8% may alter sensory function, but with no consistent pattern as to increased or decreased sensation.[15,16]

Capsaicin vs. pregabalin

The proportion of patients with treatment-emergent AEs was higher with capsaicin than pregabalin (74.5% vs. 63.9%), as was the proportion of patients with drug-related treatment-emergent AEs (61.3% vs. 54.5%). Most AEs were mild or moderate in severity, and only three were considered severe (one application site burn with capsaicin, one event each of cardiac failure and swollen tongue with pregabalin). AEs leading to discontinuation were only reported in the pregabalin arm (n=24, 8.5%).

Patients in the pregabalin arm largely reported reaction site reactions such as pain and erythema, while rates of dizziness, somnolence, nausea, peripheral oedema and weight gain were all more common with pregabalin. Systemic effects were less common in the Qutenza arm (0-1.1%) and more common with pregabalin (2.5-18.4%).

Dosage and administration

Qutenza is a single-use patch, and should be applied to the most painful areas of skin. Up to four patches may be used in one application but they should be cut to match the size and shape of the treatment area.

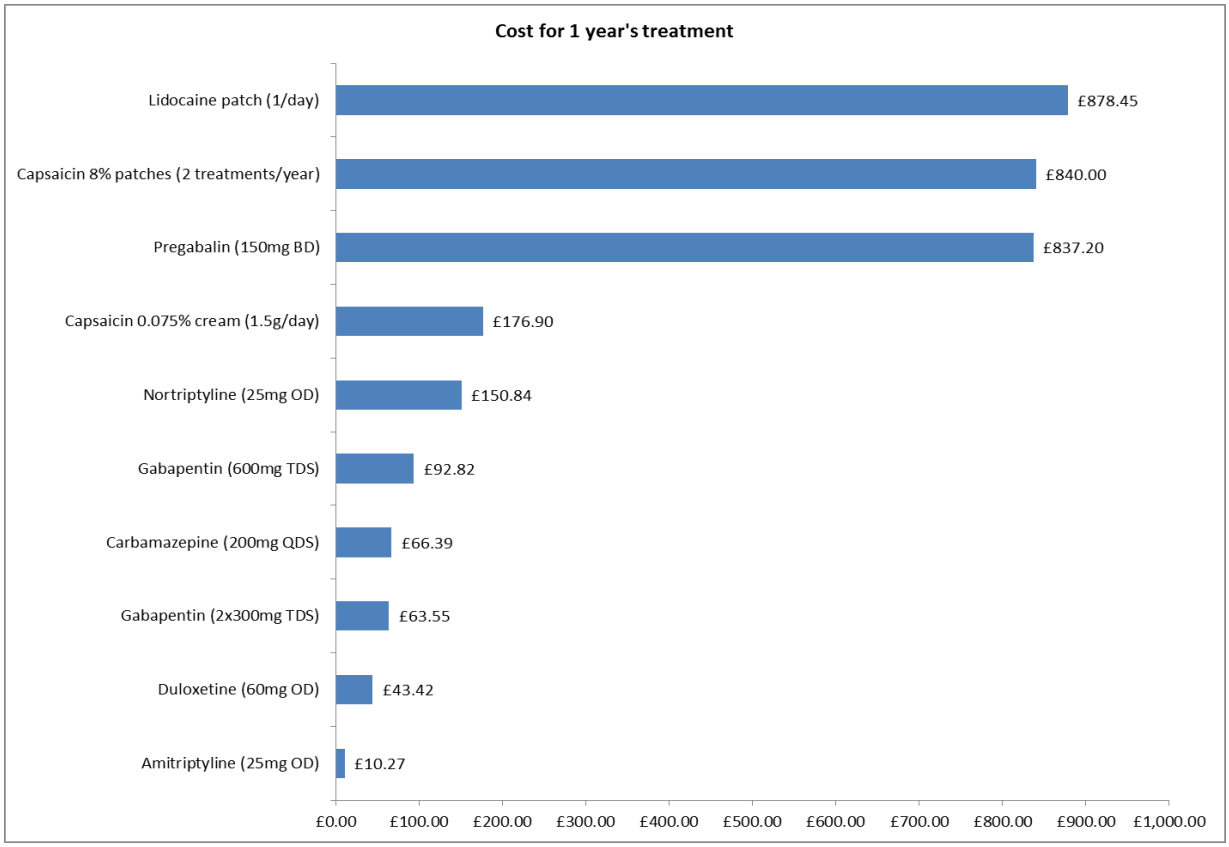
Patches must be applied by a health professional, who should wear nitrile gloves and consider also using a mask and protective glasses to prevent unintended exposure to capsaicin. Patches should be left in place for 30 minutes (feet) or 60 minutes (other areas). Consideration may be given to pre-treating the patient with oral analgesics or topical anaesthetics to reduce discomfort during the capsaicin application, but this is no longer a requirement for licensed use.

After patch removal the treatment area should be cleaned using the supplied cleansing gel, and then with soap and water. Acute pain during or after application can be treated with local cooling or oral analgesics. Treatment may be repeated after 90 days, if required.[6] An interim analysis of an observational trial currently underway in Europe found that the mean time to retreatment is 179 days.[18]

Cost analysis

The NHS list price for Qutenza is £210 per 280 cm^2 patch. Pregabalin is currently a Drug Tariff category C product, costing £1.15 per capsule (all strengths).[19] Generic pregabalin currently varies in cost from £1.15 per capsule (matching Lyrica) to £0.69 per capsule (40% cheaper), depending on brand.[20]

Generics pregabalin capsules are currently only licensed for use in epilepsy and generalised anxiety disorder. A second-use patent is in place for pregabalin which means that only Lyrica can be prescribed for treatment of neuropathic pain. The patent was found to be invalid by the High Court in 2015, and this judgement was upheld by the Court of Appeal in October 2016. Pfizer intends to appeal the latest decision but is currently working with NHS England to update the advice on use of pregabalin in the NHS. Current NHS England advice is that generic pregabalin cannot currently be prescribed for neuropathic pain. The second-use patent expires in June 2017. The cost of using pregabalin to treat neuropathic pain may therefore change in the near future.[21-24]



NB: costs are for comparison only and do not imply therapeutic equivalence. Cost for capsaicin 8% patches assumes 1 treatment every 180 days, requiring 2 patches per treatment.

Cost-effectiveness

A cost-effectiveness analysis was published in 2016, comparing Qutenza with oral pregabalin in the Scottish NHS. The study assumed an average of 1.38 patches was required per treatment. It was assumed that all responders would be retreated, after a mean interval of 179 days. This interval were taken from an interim analysis of a non-interventional study conducted in Europe, published only in abstract form.[18]

The costs for Qutenza included 30 minutes of nurse time and one pair of nitrile gloves, but not topical or oral analgesia. Follow up with a GP or specialist for adverse effects was assumed to cost £0 for Qutenza patients and £14 for pregabalin patients. Cost of routine monitoring was not included, since this was considered to have equal cost in both groups. Health utility scores were derived from the

ELEVATE study of capsaicin vs. pregabalin, discussed above. Adverse events were not included in the model, although the health utility scores used may have been impacted by health-related quality of life.

The model found that Qutenza dominated pregabalin, costing £11 less over 2 years and providing a gain of 0.049 quality-adjusted life years (QALYs). Including topical anaesthetic prior to Qutenza application in the model resulted in increased cost (£79 more than pregabalin over 2 years) and made no difference in QALYs gained.

Table 4: summary of assumptions from cost-effectiveness model

	Qutenza	Pregabalin	Difference
Probability of response	55.7%	54.5%	-
Discontinuation due to ADRs	0	8.5%	-
Time to response onset	7.5 days	36 days	-
Cost per treatment	£349.99	-	-
Drug cost per year	-	£839.50	-
Total cost per 2 years* (base case)	£1,197	£1,207	-£11
QALYs gained per patient	1.360	1.310	0.049

* Includes cost of last line therapy and GP/pain specialist visits.

It should be noted that this model will be sensitive to the cost of pregabalin. Discounting the total cost of pregabalin by 40% in line with the current cheapest generic) results in an estimated cost per QALY of £6,848 for Qutenza.

Several sensitivity analyses were performed, with the following outcomes:

- Decreasing the retreatment interval from 179 to 117 days – ICER £7,951
- Increasing required band 6 nurse time from 30 minutes to 1 hour – ICER approx. £3,000
- Increasing mean patches per treatment from 1.38 to 1.51 – ICER approx. £1000

The model found that increasing the mean number of patches per treatment from 1.38 to 1.51 resulted in increased costs. This implies that the base case assumes that 100% of every patch will be used to treat patients, or in other words that one patch may be shared between two or more patients. This may not be practical or possible in clinical practice, and would need to be subject to careful risk assessment. Assuming that two full Qutenza patches will be dispensed to treat each patient at each visit is therefore likely to increase costs significantly, from £349.99 to £479.56 per treatment. The impact of this increase on the ICER is not clear.

Author's declaration: The author has no relevant interests to declare.

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