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SUMMARY WITH CRITICAL APPRAISAL

Capsaicin for Acute or Chronic Non-Cancer Pain: A Review of Clinical Effectiveness, Safety, and Cost-Effectiveness

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Abbreviations

DPN	diabetic peripheral neuropathy
ICER	incremental cost-effectiveness ratio
NP	neuropathic pain
NPRS	numeric pain rating scale
OA	osteoarthritis
PHN	post-herpetic neuralgia
PNI	post-traumatic nerve injury
PNP	peripheral neuropathic pain
POM_{WP}	pain on movement for worst procedure
QALY	quality adjusted life year
TCA	tricyclic antidepressant
TRPV1	transient receptor potential vanilloid 1 receptor
VAS	visual analog scale

Context and Policy Issues

Pain is a common experience. Generally, acute pain is defined as lasting less than three months, and chronic pain is defined as pain lasting three months or longer.[1] Acute pain includes pain from sprains, strains, and tendonitis; and muscle aches. Chronic pain includes pain associated with osteoarthritis (OA), neuropathic pain (NP), and back pain.[1] According to the Canadian Community Health Survey of individuals during the period 2007 to 2008, the prevalence of chronic pain in adults over the age of 18 years was 18.9% in Canada, and ranged between 16% and 22% for the different provinces.[2] Pain is associated with reduced quality of life, absenteeism from work, and substantial healthcare costs.[1]

There are several treatment options for managing pain; both pharmacological and non-pharmacological options. A variety of pharmacological options such as non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetics, tricyclic antidepressants, and capsaicin have been used for pain management.[1,3] Capsaicin, which is found in chili peppers, has been used as a topical agent to relieve pain.[4] It is a transient receptor potential vanilloid 1 receptor (TRPV1) agonist; it binds to nociceptors (sensory receptors responsible for sending signals that cause the perception of pain) in the skin, specifically to the TRVP1 receptor. This binding initially results in depolarization, initiation of action potential, and pain signal transmission to the spinal cord, and subsequently causes desensitization of the sensory axons and inhibition of pain transmission.[4-6] There are various formulations for capsaicin: cream, gel, lotion and patch.[5] It is available as low concentration (e.g., 0.025%, 0.075%, and 0.25%) and high concentration (e.g., 8%) product.[4-6] Several capsaicin products are available over-the-counter in Canada. According to a report dated 2018, capsaicin is available in Canada as a cream (0.025%, 0.05%, and 0.075%), gel (0.025%), and patch (0.025%), as well as in creams, gels, or lotions (0.025% or 0.035%) in

combination with other active ingredients.[7] There appears to be some uncertainty regarding the therapeutic efficacy of capsaicin for the management of pain.[8]

A recent CADTH rapid response report,[9] presented a summary and critical appraisal of evidence-based guidelines regarding capsaicin products for the treatment of acute and chronic non-cancer pain. There was variability in the recommendations for use of capsaicin for the management of pain due to OA. Two guidelines recommended the use of capsaicin (8%) patch as second line therapy for NP. The purpose of this report is to review the clinical effectiveness, safety and cost-effectiveness of capsaicin products for the treatment of acute and chronic non-cancer pain.

Research Questions

1. What is the clinical effectiveness of over-the-counter capsaicin products for the treatment of acute and chronic non-cancer pain?
2. What is the safety of over-the-counter capsaicin products for the treatment of acute and chronic non-cancer pain?
3. What is the cost-effectiveness of over-the-counter capsaicin products for the treatment of acute and chronic non-cancer pain?

Key Findings

The eight relevant publications identified comprised two systematic reviews with network meta-analysis (NMA), four randomized controlled trials (RCTs) and two economic evaluations.

Six publications reported on clinical efficacy (related to pain relief) of capsaicin compared to other drugs. Four publications reported on neuropathic pain (peripheral neuropathic pain [PNP] or painful diabetic neuropathy [DPN]); these comprised one systematic review with network analysis (NMA) (with comparators: pregabalin, gabapentin, and duloxetine) and three non-inferiority randomized controlled trials (with comparators: pregabalin, amitriptyline, or clonidine; one each). For neuropathic pain, similar or non-inferior efficacy was reported for capsaicin (8%) patch compared to oral drugs (pregabalin, gabapentin, and duloxetine), and capsaicin (0.75%) cream compared to topical drugs (amitriptyline and clonidine). One systematic review with NMA involving patients with pain due to osteoarthritis, reported similar efficacy with capsaicin (0.0125% or 0.025%) compared to topical non-steroidal anti-inflammatory drugs. One randomized controlled trial involving patients with acute back and neck pain suggested greater efficacy with capsaicin (0.075%) compared with diclofenac, statistical significance was not reported.

Four publications reported on safety outcomes (related to adverse events). These comprised one systematic review with NMA and three RCTs (two being non-inferiority trials). Capsaicin was associated with dermatological complications (application site pain, erythema, itching, and burning sensation) whereas pregabalin, gabapentin, and duloxetine were associated with somnolence, dizziness, and nausea. There was no statistically significant difference in headache events with capsaicin compared to pregabalin, gabapentin, or duloxetine. Itching was greater with capsaicin compared to amitriptyline or clonidine; statistical significance was not reported.

One cost utility analysis showed that for patients with PNP, the probability of capsaicin (8%) patch being cost-effective versus optimized dose pregabalin was 97%, at a willingness to pay threshold of £20,000 per QALY. Another cost utility analysis showed that for patients with post-herpetic neuropathy (PHN), treatment with capsaicin (8%) patch versus oral agents (tricyclic antidepressant [TCA], gabapentin, pregabalin, or duloxetine) was cost-effective at a willingness to pay threshold of US$50,000 to US$100,000.

Findings need to be interpreted with caution considering the limitations, such as limited quantity of evidence, variable quality of evidence, limited number of head-to-head trials comparing capsaicin with other agents, concerns related to reliability of findings from indirect comparisons, unclear long term effects, and potential biases; and for economic evaluations, findings are dependent on the assumptions on which the evaluations were based.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search was used for both this report and a previous related report[9]. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were capsaicin or capsaicin and safety. Search filters were applied to limit retrieval by publication type as follows: Question 1 - health technology assessments, systematic reviews, meta-analyses, or network meta-analyses; Question 2 - randomized controlled trials, controlled clinical trials, any other type of clinical trial or safety data; Question 3 - economic studies. Where possible, retrieval was limited to the human population. The search was limited to English language documents published between January 1, 2015 and May 19, 2020 for Questions 1 and 2. For Question 3 the search was limited to English language documents published between January 1, 2010 and May 19, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (18 years and older) with acute or chronic non-cancer pain (e.g., backache, lumbago, strains, sprains, pain of tendons and ligaments, neuropathic pain [e.g. diabetic neuropathy, post-herpetic neuralgia], osteoarthritis, rheumatoid arthritis, pruritic disorders [e.g., pruritic psoriasis, peripheral neuropathic itching disorders, intractable idiopathic pruritus ani])
Intervention	Topical capsaicin (e.g., cream, gel, lotion, or patch), as a single product formulation
Comparator	Other pharmacological treatments: • topical diclofenac, • tricyclic antidepressants (e.g., amitriptyline)

	• serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) • oral nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac) • oral acetaminophen • oral opiate agonists (e.g., codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium, oxycodone, oxymorphone, remifentanil, sufentanil, tapentadol, tramadol) • antiepileptic (e.g. topiramate) • gabapentinoids (e.g., gabapentin, pregabalin) • botulinum toxin • cortisone injections • topical anesthetics (e.g., lidocaine, xylocaine)
Outcomes	Q1: Clinical effectiveness (e.g., therapeutic response in signs and symptoms, pain relief, functional status) Q2: Safety (e.g., morbidity, mortality, adverse drug reaction, misuse, abuse) Q3: Cost-effectiveness (e.g., cost per quality adjusted life years, cost per patient adverse event avoided, cost per clinical outcome)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies (for safety only), and economic evaluations.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015 for Q1 and Q2, or prior to 2010 for Q3. Systematic reviews, which lacked details of the included primary studies, were excluded, if the primary study reports were identified by the literature search and could be used instead.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[10] for systematic reviews, the "Questionnaire to assess the relevance and credibility of a network meta-analysis"[11] for network meta-analyses, the Downs and Black checklist[12] for randomized and non-randomized studies, and the Drummond checklist[13] for economic evaluations. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 445 citations were identified in the literature search. Following screening of titles and abstracts, 416 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 29 potentially

relevant articles, 21 publications were excluded for various reasons, and eight publications met the inclusion criteria and were included in this report. These comprised two systematic reviews,[14,15] four randomized controlled trials (RCTs),[16-19] and two economic evaluations.[20,21] Appendix 1 presents the PRISMA[22] flowchart of the study selection.

Summary of Study Characteristics

The study characteristics are summarized below. Additional details regarding the characteristics of included publications are provided in Appendix 2, Table 2 (systematic reviews), Table 3 (RCTs), and Table 4 (economic evaluations).

Study Design

The two included systematic reviews[14,15] included network meta-analysis (NMA). One systematic review[14] included 28 RCTs published between 1991 and 2017, and another systematic review included 25 RCTs published between 1987 and 2017. In both systematic reviews[14,15] the network structure was presented; in one NMA[14] both frequentist and Bayesian approaches were used and in the second NMA[15] a Bayesian approach was used.

The four included primary studies[16-19] were RCTs. One RCT[16] was a double-blind trial, two RCTs[18,19] were double-blind non-inferiority trials, and one RCT[17] was an open-label non-inferiority trial.

Two relevant economic evaluations[20,21] were identified. One economic evaluation[20] was a cost utility analysis using a decision tree model, and the second economic evaluation[21] used was a cost utility analysis using a Markov model. For one economic evaluation[20] the perspective was that of the National Health Services and Personal and Social Services of Scotland, UK; and the time horizon was two years; and data sources included clinical data from published literature and the files of the Industry, and cost data from the British National Formulary and Scottish Medicines Consortium. In this economic evaluation, it was assumed that patients with initial response continued to respond, all patients who responded to capsaicin were retreated, and no additional costs were incurred to manage adverse events. For the second economic evaluation[21] the perspective was that of the payer (managed care organization); and the time horizon was one year; and data sources included clinical data from published literature, and cost data from drug store data or the industry. In this economic evaluation it was assumed that nortriptyline represented the TCA class, for capsaicin the next administration was linear and divided equally over the monthly cycle, and 30% change in pain was taken as the efficacy endpoint. Sensitivity analyses were conducted in both economic evaluations.[20,21]

Country of Origin

The two systematic reviews[14,15] were from the UK [14] and the Netherlands.[15]

The first author of one RCT[16] was from Germany, and the study was conducted in Germany and Russia. The first author of the second RCT[17] was from Finland and the study was conducted in several European countries and the UK. The first author of remaining two RCTs[18,19] were from Iran and the studies were conducted in Iran.

The two economic evaluations,[20,21] were from the UK,[20] and the USA.[21]

Patient Population

One systematic review[14] included 28 RCTs with a total of 6,957 patients with pain due to OA; in the included RCTs, the mean age ranged between 49 years and 69 years; proportion of females ranged between 45% and 100%; duration of OA was not reported. The second systematic review[15] included 25 RCTs with a total of 999 patients with painful diabetic peripheral neuropathy (DPN); in the included RCTs the mean age varied between 53 years and 71 years, the proportion of females were not reported, and the mean duration of painful DPN, when reported, ranged between 0.8 to 5.7 years across 14 RCTs and was not reported in 11 RCTs.

One RCT[16] involved 446 patients with acute back and neck pain, mean age was 43.7 years, proportion of females was 59.2%, and time of onset of pain was 10 days. The second RCT[17] involved 559 patients with peripheral neuropathic pain (PNP) (includes postherpetic neuralgia [PHN], post-traumatic nerve injury [PNI], non-diabetic painful peripheral polyneuropathy), mean age was 55.9 years, proportion of females was 59.2%, and duration of pain was 2 years. The third RCT[18] involved 102 patients with DPN, mean age was 56.7 years, proportion of females was 67.7%, and duration of pain was 19 years. The fourth RCT[19] involved 139 patients with DPN, mean age was 57 years, proportion of females was 72.6%, and 17.3 years.

One economic[20] evaluation involved patients with peripheral neuropathic pain (PNP). The second economic evaluation[21] involved patients with postherpetic neuropathy (PHN).

Interventions and Comparators

One systematic review[14] compared capsaicin (0.025% or 0.0125%) cream with topical non-steroidal anti-inflammatory drugs (NSAIDs) using NMA involving RCTs comparing NSAIDs with placebo, and five RCTs comparing capsaicin cream (0.0125% or 0.025%) with placebo. The second systematic review[15] compared capsaicin (8%) patch with oral neuropathic pain medication (duloxetine, gabapentin, pregabalin, and amitriptyline), using NMA involving RCTs comparing duloxetine, gabapentin, pregabalin, and amitriptyline, with placebo or amongst each other, and one RCT comparing capsaicin (8%) with placebo.

One RCT[16] compared capsaicin (0.075%) gel with diclofenac (2%) gel. The second RCT[17] compared capsaicin (8%) patch with optimized dose pregabalin. The third RCT[18] compared capsaicin (0.75%) cream with amitriptyline (2%) cream. The fourth RCT[19] compared capsaicin (0.75%) cream with clonidine (0.1%) gel.

One economic evaluation[20] compared capsaicin (8%) patch with optimized dose pregabalin. The second economic evaluation[21] compared capsaicin (8%) patch with tricylic antidepressants (TCAs), pregabalin, gabapentin, duloxetine, and lidocaine.

Outcomes

Outcomes reported included change in pain,[14-19] and adverse events.[15-19] In one systematic review[14] change in pain was measured using various scales and was expressed as effect size. The second systematic review[15] reported on proportion of responders (≥ 30% reduction in pain scores and ≥ 50% reduction in pain scores, assessed using the 11-point numeric rating scale; scale details were not presented). One RCT reported on change in pain in terms of pain on movement for worst procedure (POM_{WP}); measured with a visual analogue scale (VAS) ranging from 0 to 10 centimeters, and decrease in POM_{WP} indicates less pain.[16] The second RCT reported on the proportion of responders (≥ 30% reduction in

pain scores, assessed using the numeric pain rating scale; scale details were not presented).[17] The third and fourth RCTs reported on proportion of responders (≥ 50% reduction in pain, assessed using a VAS with scores from 0 to 10; higher scores indicating greater pain).[18,19] In the two systematic reviews[14,15] the study duration of the included studies varied between one week and 12 weeks in one systematic eview[14] and between four weeks and 14 weeks in another systematic review.[15] In the included RCTs[16-19] the treatment duration varied between 5 days and 12 weeks.

The two included economic evaluations,[20,21] reported on incremental cost-effectiveness ratio (ICER) expressed as cost per quality of life year gained (QALY).

Summary of Critical Appraisal

An overview of the critical appraisal of the included publications is summarized below. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 5 (systematic reviews), Table 6 (RCTs), and Table 7 (economic evaluations).

In the two included systematic reviews,[14,15] the objective was stated, a comprehensive literature search was conducted, and the article selection was described (i.e., number of articles selected and flow chart of selection provided) but it was unclear if article selection was done in duplicate. In one systematic review[14] the data extraction and quality assessment were done in duplicate, and studies were judged by the systematic review authors to have considerable risk of bias. In another systematic review[15] data extraction was done by one reviewer and checked by another reviewer, and quality assessment was done by one reviewer and the studies were judged to be of variable quality. One systematic review[14] did not appear to have investigated publication bias, and in one systematic review[15] investigation of publication had been planned, but could not be done due to few studies. In both systematic reviews conflicts of interest were declared and one or more authors were associated with industry, hence the potential for bias cannot be ruled out.

Both systematic reviews[14,15] conducted NMA. In one systematic review,[14] both frequentist and Bayesian approaches were used; a random effects model was used; and effect size and uncertainty (associated confidence intervals and credible intervals) of the estimate were reported. There was difference in the populations with respect to the type of OA among the studies included in the NMA. The majority of NSAID studies involved patients with knee OA, whereas the capsaicin studies involved patients with hand, elbow, wrist, shoulder, hip, knee, and ankle OA. This difference in population could impact results of the indirect comparison in the NMA. The direction of impact is unclear. In the second systematic review[15] a Bayesian approach was used; effect size and uncertainty (credible intervals) of the estimate was reported. The fixed effects models were used, as goodness-of-fit was similar or better for fixed effects models compared to random effects models. The authors mentioned that impact of effect modifiers was assessed. In case of heterogeneity identified in terms of factors such as drug dose, efficacy definitions, and treatment duration, analyses were conducted excluding heterogeneous studies or conducting scenario analyses. However, these results were not presented. The authors also mentioned that it was not possible to control for many other factors such as patient inclusion criteria, and concomitant medications used. Reliability of the NMA findings is unclear.

In the four included RCTs[16-19] the objective, and inclusion and exclusion criteria were stated, patient characteristics, interventions and outcomes were described. In three RCTs, randomization method was described and appeared to be appropriate. Three RCTs[16,18,19]

were mentioned to be double-blinded, and in one RCT[17] there was no blinding, hence possibility of detection bias and performance bias cannot be ruled out. In one RCT[16] the withdrawals were few, but in three RCTs[17-19] withdrawals were high and varied between capsaicin and the comparator groups. In one RCT[17] withdrawals (reasons not reported) were 2.1% with capsaicin and 14.8% with pregabalin. In the second RCT[18] withdrawals due to adverse events were 43.4% with capsaicin and 37.3% with amitriptyline. In the third RCT,[19] withdrawals due to adverse events were 42.9% with capsaicin and 23.1% with clonidine, hence there is potential for attrition bias. In two RCTs [18,19] conflicts of interest were not declared, and in two RCTs,[16,17] the authors had association with industry, hence the potential for bias cannot be ruled out.

In the two included economic evaluations[20,21], the objective, strategies compared, perspective taken, time horizon, sources for clinical and cost data were stated. Time horizons were between one and two years, hence outcome in the long term would not be captured. The sources of clinical and cost data used seemed appropriate. The models used were described, and assumptions were reported and appeared to be reasonable. Sensitivity analyses were conducted by varying different model parameters to ensure the validity of the model. Incremental analyses were reported. Conclusions were consistent with the results reported. Conflicts of interest of the authors were declared and some of the authors had association with or were employed by the industry hence potential for bias cannot be ruled out.

Summary of Findings

The main findings are summarized below. Details of the main study findings and authors' conclusions are presented in Appendix 4, Table 8 (systematic reviews) Table 9 (RCTs), and Table 10 (economic evaluations).

Clinical effectiveness of capsaicin for treating various pain conditions

Peripheral neuropathic pain (PNP)

One RCT[17] involving patients with PNP (includes PHN, PNI, non-diabetic painful peripheral polyneuropathy) reported that capsaicin (8%) patch was non-inferior to optimized dose pregabalin with respect to the proportion of treatment responders (assessed using a non-inferiority margin of a change of -8.5% for the proportion of responders). Treatment duration was eight weeks.

Diabetic peripheral neuropathy (DPN)

One systematic review[15] with NMA, reported odds ratios and 95% credible intervals and reported on pain relief (in terms of proportions of patients having ≥ 30% reduction in pain and ≥ 50% reduction in pain, assessed using a 11-point numerical rating scale, with higher values indicating greater pain). This systematic review showed (based on indirect comparison) that for patients with painful DPN, treatments with capsaicin (8%) and oral agents (duloxetine, gabapentin, or pregabalin) were similar in terms of pain relief (i.e., in terms of proportions of patients having ≥ 30% reduction in pain), as demonstrated by the 95% credible interval (0.91 to 3.34) for capsaicin compared to pregabalin; (0.74 to 3.23) for capsaicin compared to gabapentin, and (0.50 to 1.79) for capsaicin compared to duloxetine. Also, this systematic review showed (based on indirect comparison) that for patients with painful DPN, treatments with capsaicin (8%) and oral agents (duloxetine, gabapentin, or pregabalin) were similar in terms of pain relief (i.e., in terms of proportion of patients having ≥ 50% reduction in pain) as demonstrated by the 95% credible interval (0.55 to 2.40) for

capsaicin compared to pregabalin; (0.39 to 2.00) for capsaicin compared to gabapentin; and (0.40 to 1.71) for capsaicin compared to duloxetine. Treatment duration varied between four to 13 weeks.

One RCT[18] reported that for patients with painful DPN, there was no statistically significant difference between capsaicin (0.75%) cream and amitriptyline (2%) cream (P = 0.545) in terms of proportion of treatment responders (having ≥ 50% reduction in pain, using VAS scores). Treatment duration was 12 weeks

One RCT[19] reported that for patients with painful DPN, the proportion of treatment responders (having ≥ 50% reduction in pain, using VAS scores) was 40.6% with capsaicin (0.75%) cream and 57.1% with clonidine (0.1%) gel, P = 0.051. The authors reported a non-inferiority limit of 25%, i.e., "the upper limit of a 95% two-sided confidence interval would exclude a difference in favor of the standard group of more than 25%. [p. 3 of 11]"[19]). The graphical representation of VAS scores over the treatment duration of 12 weeks were presented and it was reported that that there was no statistically significant difference between the capsaicin and clonidine treatments (P = 0.931); the slopes of VAS decline were not statistically significantly different between the two treatments, P = 0.189.

Osteoarthritis (OA)

One systematic review[14] with NMA, showed (based on indirect comparison) that for patients with pain due to OA, treatments with topical capsaicin (0.25% or 0.125%) and topical NSAIDs were similar in terms of pain relief, as demonstrated by the credible interval (-0.28 to 0.35) for the difference in effect. Treatment duration varied between one to 12 weeks.

Back and neck pain

One RCT[16] involving patients with acute back and neck pain showed that numerically, decrease in POM_{WP} from baseline was greater for capsaicin than for diclofenac, statistical significance was not reported. Treatment duration was five days.

Safety of capsaicin for treating various pain conditions

Peripheral neuropathic pain (PNP)

One RCT[17] involving patients with PNP (includes PHN, PNI, non-diabetic painful peripheral polyneuropathy) reported that capsaicin (8%) patch was associated with treatment emergent adverse events (TEAEs) such as application site pain, erythema, and burning sensation, whereas optimized dose pregabalin was associated with TEAEs such as nausea, dizziness, and somnolence.

Diabetic peripheral neuropathy (DPN)

One systematic review[15] with NMA, involving patients with painful DPN, reported odds ratios and 95% credible intervals for tolerance of treatment (in terms of adverse event: headache) for patients with painful DPN. It reported credible intervals 0.01 to 1.33 for pregabalin compared to capsaicin (8%) patch, 0.01 to 1.96 for gabapentin compared with capsaicin (8%) patch, and 0.01 to 3.05 for duloxetine compared with capsaicin (8%) patch, indicating similar tolerability of capsaicin (8%) patch compared with pregabalin, gabapentin and duloxetine.

One RCT[18] involving patients with painful DPN showed that the proportion of patients with adverse events was greater with capsaicin (0.75%) cream compared with amitriptyline (2%); 56.9% in the capsaicin group, 29.9% in the amitriptyline group, P = 0.001. In the

capsaicin group, proportions of patients with itching, blister formation, and erythema were 20%, 8.5%, and 5.7% respectively. In the amitriptyline group, proportion of patients with dryness and itching were 8.8% and 4.4% respectively.

One RCT[19] involving patients with painful DPN, showed that the proportions of patients with dermatological complications were 58% with capsaicin, and 5.7% with clonidine, P = 0.001.

Back and neck pain

One RCT[16] involving patients with acute back and neck pain reported that the proportion of patients experiencing adverse events such as application site pain, infection and infestation, and skin and subcutaneous tissue disorder were numerically higher with capsaicin (0.075%) gel than with diclofenac (2%) gel. Also, the proportion of patients experiencing nervous system disorders were numerically higher with diclofenac compared with capsaicin.

Cost-Effectiveness of capsaicin for treating various pain conditions

Peripheral neuropathic pain (PNP)

One economic evaluation[20] investigated cost-effectiveness of capsaicin (8%) patch versus dose optimized pregabalin in non-diabetic patients with PNP from the perspective of the National Health Service and Personal and Social Services in Scotland, UK. The ICER (incremental cost per incremental QALY gained) indicated that capsaicin dominated pregabalin, i.e., capsaicin was more effective with lower cost. One-way sensitivity analysis showed on varying different parameters (such as time to retreatment with capsaicin, grade 6 nurse time, and number of capsaicin patches per treatment) capsaicin either dominated or was cost-effective (i.e., ICER was less than the willingness to pay threshold of £20,000 per QALY). The ICER was most sensitive to variations in the time to retreatment with the capsaicin patch; at the low value (117 days), the ICER increased to £7,951 per QALY, whereas at the high value (241 days), the capsaicin patch was the dominant treatment strategy. The cost-effectiveness acceptability curve showed that the probability of capsaicin being cost-effective versus pregabalin was 97%, at a willingness to pay threshold of £20,000 per QALY.

One economic evaluation[21] investigated cost-effectiveness of capsaicin (8%) patch versus lidocaine (5%) patch, or oral agents (TCA, gabapentin, pregabalin, or duloxetine) for treating patients with PHN, from a payer perspective. ICER for capsaicin compared to TCAs was approximately US$60,000; and compared to duloxetine, gabapentin, or pregabalin was less than US$40,000. Capsaicin was considered cost-effective compared to TCAs, duloxetine, gabapentin and pregabalin at a willingness to pay threshold of US$50,000 per QALY gained to US$100,000 per QALY gained. Sensitivity analysis showed that the ICER (incremental cost per incremental QALY gained) was most sensitive to the retreatment time. If the capsaicin patch retreatment interval was increased to 14.5 weeks, the ICER for capsaicin compared to the oral agents (TCAs, duloxetine, gabapentin, and pregabalin) was less than US$51,000 per QALY gained. If the capsaicin patch retreatment interval was increased to 17.7 weeks, the ICER for capsaicin compared to the oral agents (TCAs, duloxetine, gabapentin, and pregabalin) was less than US$44,000 per QALY gained.

Limitations

The evidence is limited in quantity. In the systematic reviews, the studies included in the NMA were of low quality or variable quality, furthermore in one systematic review, for

capsaicin only one study of limited size was included, hence reliability of the findings is uncertain. Head-to-head studies comparing capsaicin with other pharmacological medications were lacking Comparison across studies was difficult as populations, types of capsaicin used, and comparator treatments varied. The studies in the systematic reviews, as well as the selected RCTs were of short duration (5 days to 14 weeks), hence long-term effects are not known. In one non-inferiority RCT, the non-inferiority margin was not reported and in one non-inferiority RCT, the non-inferiority margin was substantial and furthermore the rationale for choosing such a margin was not presented.

Most of the studies were funded by industry, and many of the study authors were associated with or employed by the industry; potential for bias cannot be ruled out.

Generalizability of the findings to the Canadian context is unclear as the studies were conducted in various countries. Furthermore, according to a 2018 report,[7] topical capsaicin is not approved by Health Canada for indications such as OA, PHN, DPN, and pruritic disorders. Also, one systematic review,[15] one primary study,[17] and the two economic evaluations were on capsaicin (8%) patch, a product that is not available in Canada.[7]

Findings need to be interpreted with caution considering the limitations, such as evidence of limited quantity, lack of head-to-head trials, potential biases; and for economic evaluations, findings are dependent on the assumptions on which the evaluations were based.

Conclusions and Implications for Decision or Policy Making

The eight relevant publications identified comprised two systematic reviews,[14,15] with NMA, four RCTs,[16-19] and two economic evaluations.[20,21] The majority of these studies were on neuropathic pain.

Six publications[14-19] reported on clinical effectiveness outcomes. One RCT[17] showed that for patients with PNP, treatment with capsaicin (8%) patch was non-inferior to pregabalin, in terms of the proportion of treatment responders. Three publications[15,18,19] reported on painful DPN. One systematic review[15] with NMA, suggested that for patients with painful DPN and based on indirect evidence, treatment with capsaicin (8%) patch was similar to oral agents: pregabalin, gabapentin and duloxetine, in terms of pain relief. One RCT[18] showed that for patients with painful DPN, there was no statistically significant difference between treatment with capsaicin (0.75%) cream and amitriptyline (2%) cream, in terms of the proportion of treatment responders. One RCT[19] showed that for patients with painful DPN, there was no statistically significant difference between capsaicin (0.75%) and clonidine (0.1%) gel, in terms of proportion of treatment responders. One systematic review[14] with NMA, suggested that for patients with pain due to OA and based on indirect evidence, treatments with topical capsaicin (0.025% or 0.0125%) and topical NSAIDs were similar in terms of pain relief. One RCT[16] involving patients with acute back and neck pain showed that capsaicin (0.075%) produced a greater decrease in the pain outcome (POM_{WP}) from baseline value compared with diclofenac (2%), statistical significance was not reported.

Four publications[15,17-19] reported on safety outcomes. One RCT[17] involving patients with PNP (includes PHN, PNI, non-diabetic painful peripheral polyneuropathy) reported that capsaicin (8%) patch was associated with adverse events such as application site pain, erythema, and burning sensation, whereas optimized dose pregabalin was associated with adverse events such as nausea, dizziness, and somnolence. One systematic review with NMA, suggested that for patients with painful DPN, tolerance was similar for capsaicin (8%)

patch, pregabalin, gabapentin and duloxetine. One RCT[18] involving patients with painful DPN showed that the proportion of patients with adverse events was greater with capsaicin (0.75%) cream than with amitriptyline (2%) cream. One RCT[19] involving patients with painful DPN, showed that the proportion of patients with dermatological complications were statistically significantly higher with capsaicin (0.75%) compared with clonidine (0.1%) gel. One RCT[16] involving patients with acute back and neck pain, reported that the proportion of patients experiencing dermatological adverse events was numerically higher with capsaicin (0.075%) gel compared with diclofenac (2%) gel.

One cost utility analysis[20] showed that for patients with PNP, the probability of capsaicin (8%) patch being cost-effective versus optimized dose pregabalin was 97%, at a willingness to pay threshold of £20,000 per QALY. Another cost utility analysis[21] showed that for patients with PHN, treatment with capsaicin (8%) patch versus oral agents (TCA, gabapentin, pregabalin, or duloxetine) was cost-effective at a willingness to pay threshold of US$50,000 to US$100,000. Similar cost-effectiveness ratios for the capsaicin (8%) patch and lidocaine (5%) patch were reported.

One economic evaluation[23] did not meet are inclusion criteria as the comparison did not meet inclusion criteria for this current report. It may provide some useful insights, so is discussed here. It was a cost-effectiveness analysis conducted in Germany and investigating prior and post capsaicin use, in patients with brachioradial pruritis and notalgia paraesthetica. It found that after introduction of capsaicin (8%) patch, there was reduced pruritis and improved quality of life, and the overall cost (cost to the health insurer and cost to the patient) was similar. Study authors mentioned that investigating cost-effectiveness over the long term is necessary.

Findings need to be interpreted with caution considering the limitations, such as evidence of limited quantity and variable quality, lack of head-to-head trials, reliability concerns regarding the findings from indirect comparisons, unclear long-term effects, and potential biases.

Further studies are needed to investigate long term effects, various pain conditions, and direct evidence of capsaicin versus alternative pharmacological treatment options for pain, to have a better understanding of the role of capsaicin for management of pain.

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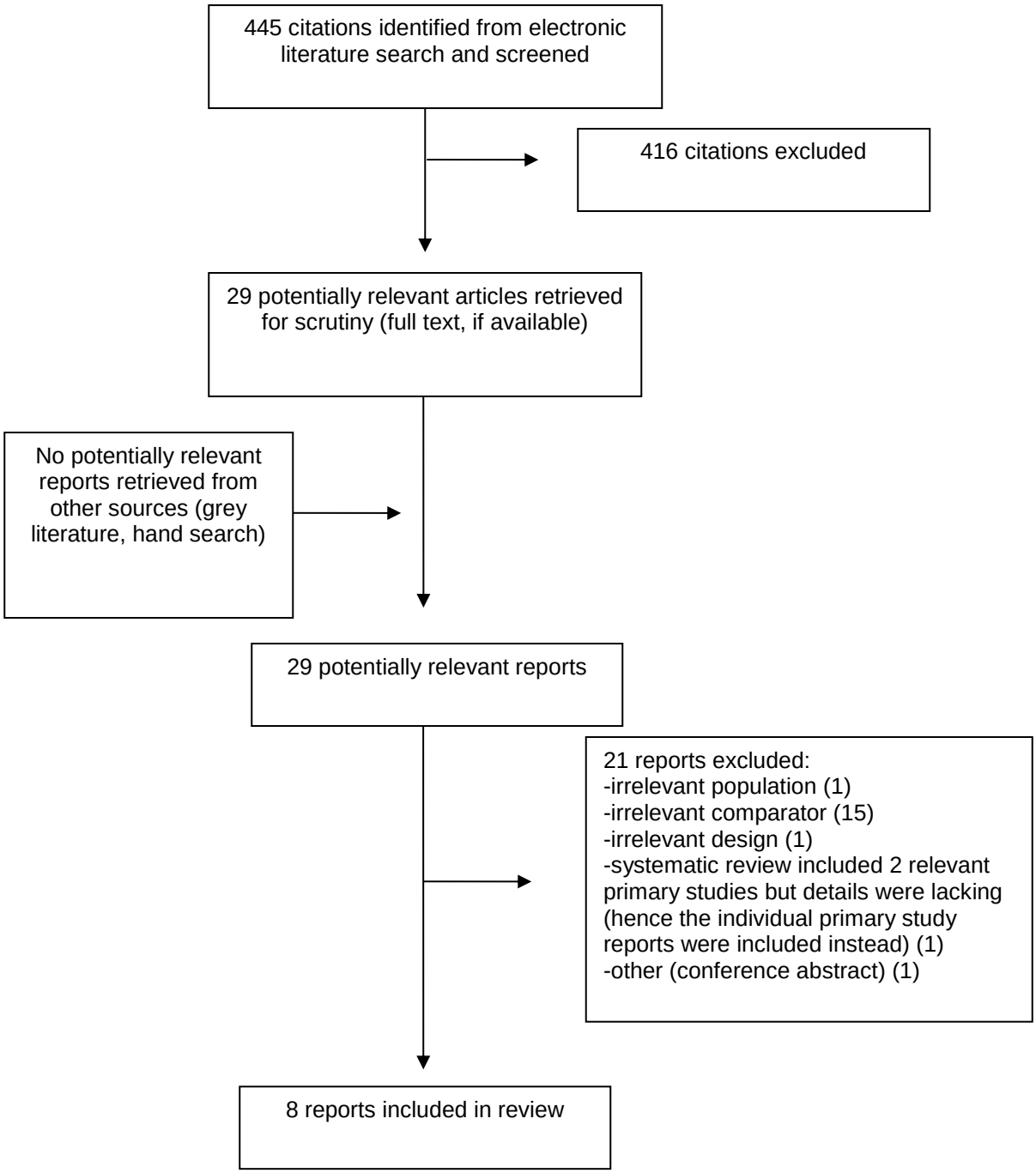
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Network Meta-Analyses

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Persson, 2018,[14] UK. Funding: Grant from Arthritis Research, UK. The funders had no role in this project.	Systematic review with NMA (frequentist and Bayesian approach) included 28 placebo-controlled RCTs (23 RCTs on NSAIDs versus placebo [published between 1993 and 2017]; and 5 RCTs on capsaicin versus placebo [published between 1991 and 2010]). Inclusion criteria: RCTs comparing any NSAIDs or capsaicin to placebo in patients with OA, study duration at least 1 week, and reporting pain outcomes. Exclusion criteria: Spinal pain was excluded because of difficulty in differentiating between OA pain and back pain secondary to other etiologies.	Patients with OA N = 6957 (of these 415 patients were in the 5 RCTs on capsaicin; and 6542 patients in the 23 RCTs on NSAIDs) Mean age (years): 60 to 67 (in NSAIDs RCTs); 49 to 69 (in capsaicin RCTs) % Female: 52% to 100% (in NSAIDs RCTs); 45% to 100% (in capsaicin RCTs). Mean duration of OA = not reported Baseline pain levels: not reported	Topical NSAIDS versus topical capsaicin. Topical NSAIDs: 2.29% ketoprofen gel; 1% and 2% diclofenac sodium gel; 1.5% diclofenac sodium solution; 1.16% diclofenac diethylamine; 180 mg diclofenac hydroxyethyl pyrrolidine patch; 180 mg diclofenac epolamine patch; 5%,and 10% ibuprofen cream; 0.1%, 0.3%, and 1% eltenac gel; 10, 20, 40 mg S-flurbiprofen patch. Capsaicin cream: 0.025% (4 RCTs); 0.0125% (1RCT)	Pain (Assessment tools used in each individual study was not reported. However, it was reported that in case of a study using multiple assessment tools then for data extraction the hierarchy below was followed. (1) visual analogue scale (VAS) global pain score; (2) categorical global pain score; (3) pain during activity, such as walking; (4) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale or pain subscale of other disease-specific composite tools; (5) Short Form-36 (SF-36) bodily pain subscale; (6) Health Assessment Questionnaire (HAQ) pain subscale, McGill pain questionnaire; (7) tenderness; (8) physician's assessment of pain. Study duration (range): 1 to 12 weeks (in RCTs on NSAIDs); 3 to 4 weeks (in RCTs on capsaicin)
Van Nooten, 2017,[15] The Netherlands. Funded by industry	Systematic review with NMA (Bayesian approach) included 25 studies (24 RCTs on pregabalin, gabapentin, amitriptyline, or duloxetine versus placebo [majority] or each other [published	Adult patients with painful DPN Number of patients in the 26 RCTs ranged between 25 and 804 (195 patients in the 1 RCT on capsaicin).	Intervention: Capsaicin (8%) patch Comparators: pregabalin, gabapentin, duloxetine, and amitriptyline (Placebo controlled trial of these agents were	Pain (≥30% reduction in pain, ≥50% reduction in pain, in terms of scores based on a 11-point numerical rating scale). Tolerability (considering somnolence, dizziness,

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	between 1987 and 2014]; and 1 RCT on capsaicin versus placebo [published in 2017]) Inclusion criteria: RCTs (duration ≥ 4 weeks, and sample size ≥ 10) on adults with painful DPN Exclusion criteria: Interventions other than capsaicin, pregabalin, gabapentin, duloxetine, and amitriptyline; neuropathic pain other than painful DPN; and non-English articles	% Female: not reported Mean duration of painful DPN (range) (years): ranged between 0.8 to 5.7 (14 RCTs) and not reported (12 RCTs) Mean pain score (using 11-point NRS): 3.2 to 6.7 (20 RCTs), and not reported (6 RCTs)	also included in the NMA)	fatigue, nausea, headache, constipation, diarrhea, and discontinuation due to AE) Study duration: 4 to 13 weeks

DPN = diabetic peripheral neuropathy; NMA = network meta-analysis; NRS = numerical rating scale; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; RCT = randomized controlled trial;

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Predel, 2020,[16] Germany The study was sponsored by several industries and the authors were employed by these industries or had received financial support from them.	RCT: double-blind, multinational, multicenter (18 centers in Germany and Russia). This RCT had four treatment arms (diclofenac + capsaicin), capsaicin, diclofenac, and placebo. Only the two treatment arms (i.e., capsaicin versus diclofenac) relevant for this current report will be considered.	Adult patients with acute back or neck pain for at least 24 h, but less than 21 days, diagnosed as POM ≥ 5.0 cm (using VAS [range 0 to 10 cm]) for at least one POM procedure out of five standardized procedures. Patients were excluded if they had experienced ≥3 episodes of back or neck pain in the previous 6 months, had surgery due to	Capsaicin (0.075%) gel versus diclofenac (2%) gel. Applied twice daily with a 12-hour gap (which could be shortened or extended by 4 hours) If required rescue medication (paracetamol) was provided.	Change in POM. Adverse effects. Treatment applied each day for 5 days. Final assessment was done on the 6th day.

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		back or neck pain in the previous 12 months, or experienced trauma or strains of the back or neck muscles, or had received pharmacological or non-pharmacological treatment 3 days prior to the first visit. N = 446 (223 in capsaicin (C) group and 223 in diclofenac (D) group. Age (mean ± SD) (years): 43.2 ±15.42 in C group and 44.0 ± 15.96 in D group. % Female: 57.4 in C group and 61.0 in D group. Time since onset of pain (mean ± SD) (days): 9.9 ± 4.97 in C group, and 9.6 ± 5.11 in D group.		
Haanpää, (ELEVATE study) 2016,[17] Finland Funding: Funded by industry. The authors had association with or were employed by the industry.	RCT: open-label, multinational, multicenter non-inferiority trial. The non-inferiority margin was a change of -8.5% for the proportion of responders based on a systematic FDA review. Study was conducted in several European countries and UK	Adult patients with probable or definite PNP. PNP included PHN (pain persisting for at least 6 months since shingles vesicle crusting), PNI (minimum of 3 months) or non-diabetic painful PNP (minimum of 3 months); pain score NPRS ≥ 4 over 4 consecutive days. Exclusion: Individuals with severe loss of heat sensation in the painful area	Capsaicin (8%) patch versus optimized dose pregabalin. During the pregabalin titration period, the initial dose of 75 mg/day was increased by 75 mg every 3 to 4 days, up to the highest tolerated dose or 600 mg/day	Change in pain (using NPRS). Adverse events. Treatment duration: 8 weeks. Outcomes were reported at end-point (i.e. at 8 weeks). Mean change in NPRS scores from baseline, at weeks 1 to 8 were reported graphically.

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		indicative of C-fibre denervation; a daily pain score of 10 on the NPRS for ≥4 days during the screening period; past or current history of diabetes mellitus; unstable or poorly controlled hypertension or a recent history of a cardiovascular event, and pregnant women. N = 559 (282 in capsaicin [C] group, 277 in pregabalin [P] group). Age (mean ± SD) (years): 55.4 ± 14.0 in C group, 56.3 ± 13.5 in P group. % Female: 56.4% in C group, 56.0% in in P group. Duration of neuropathic pain (years): 2.58 ± 4.3 in C group, 2.12 ± 2.9 in P group		
Kiani, 2015,[18] Iran. Funding: Grant from the Hamedan University of Medical Sciences	RCT: double blind non-inferiority trial. The non-inferiority margin was not stated.	Adult patients with type 2 diabetes with painful DPN, having chronic daily pain for > 3 months and VAS score ≥4. Exclusion: Patients with diabetes > 1 year duration, opium or alcohol use, other causes of neuropathy, hepatic or renal failure, clinically significant cardiovascular disease, A1C ≥ 9%, ulcer or infection of foot and	Capsaicin (0.75%) cream versus amitriptyline (2%) cream. The creams were applied below the ankle on the feet three times daily	Change in pain (using VAS). Adverse events. Treatment duration: 12 weeks VAS scores at baseline, week 4, week 8, and week 12 were presented graphically.

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		hypersensitivity to pepper, and pregnant or lactating women were excluded. N = 102 (51 in capsaicin (C) group and 51 in amitriptyline (A) group. Age (mean ± SD) (years): 55.4 ± 10.6 in C group, 57.5 ±10.8 in A group. % Female: 68.6 in C group, 66.7 in A group. Pain duration: 19.02 ± 18.3 in C group,18.9 ± 15.3 in A group.		
Kiani, 2015,[19] Iran. Funding: Grant from the Hamedan University of Medical Sciences. Both drugs were provided free from the respective industries.	RCT: double blind, non-inferiority trial. The non-inferiority limit was 25%.	Adult patients with type 2 diabetes with painful DPN, having chronic daily pain for > 3 months and VAS score ≥4. Exclusion: Patients with diabetes > 1 year duration, opium or alcohol use, other causes of neuropathy, hepatic or renal failure, clinically significant cardiovascular disease, A1C ≥ 9%, ulcer or infection of foot and hypersensitivity to pepper, and pregnant or lactating women were excluded. N = 139 (70 in capsaicin (C) group and 69 in clonidine (CL) group.	Capsaicin (0.75%) cream versus clonidine (0.1%) gel	Change in pain (using VAS). Adverse events. Treatment duration: 12 weeks VAS scores at baseline, week 4, week 8, and week 12 were presented graphically.

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Age (mean ± SD) (years): 56.49 ± 10.25 in C group, 56.88 ± 9.54 in CL group. % Female: 71 in C group, 74.3 in CL group. Pain duration: 18.04 ± 16.57 in C group, 21.17 ± 30 in CL group.		

A = amitriptyline; A1C = glycated hemoglobin; C = capsaicin; CL = clonidine; D = diclofenac; DPN = diabetic peripheral neuropathy; NPRS = numeric pain rating scale; PHN = postherpetic neuralgia; PNI = post-traumatic nerve injury; PNP = peripheral neuropathic pain; POM = pain on movement; RCT = randomized controlled trial; VAS = visual analog scale

Table 4: Characteristics of Included Economic Evaluations

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Mankowski, 2016,[20] UK The study was funded by industry and many of the authors were employed by them.	Cost-utility analysis. Time horizon: 2 years Perspective: National Health Services (Scotland, UK)	Non-diabetic patients with PNP, who were pregabalin naïve and who had not achieved adequate pain relief or had not tolerated first- or second line treatment (amitriptyline and gabapentin)	Capsaicin (8%) patch versus oral pregabalin. Pregabalin dose of 150 mg/day (started as 2 capsules of 75 mg) titrated to an optimal dose (maximum 600 mg/day)	A cost-utility model using a decision tree approach. Patients treated with capsaicin or pregabalin who did not respond or did not tolerate the drugs were assumed to be given last line treatment (duloxetine) Results presented as ICER expressed as incremental cost per	Efficacy data were taken from the ELEVATE study: RCT (non-inferiority trial) comparing capsaicin (8%) with pregabalin. Uitility data were from the files of the Industry that funded the study. Cost data were obtained mainly from BNF, and SMC	Responders were assumed to have a linear increase in utility from baseline. Patients with initial response continued to respond. All patients who responded to capsaicin were retreated. No additional costs were incurred to manage adverse events. Patients failing to respond to last-line therapy were

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
				quality adjusted life year One-way sensitivity analysis and probabilistic sensitivity analysis were conducted. Monte Carlo (10,000) simulations were performed and results were presented as cost-effectiveness plane and cost-effective acceptability curve		assumed to continue to incur the cost of therapy regardless of response status. A grade 6 nurse (higher qualification than base level) was needed to apply capsaicin.
Armstrong, 2011,[21] USA The was funded by industry. All authors had association with the industry (4 authors were consultants and 1 author was an employee)	Cost utility analysis Time horizon: 1 year Perspective: payer perspective, managed-care organization	Patients with PHN	Capsaicin (8%) patch versus current treatments (TCA [nortriptyline], topical lidocaine patch, duloxetine, gabapentin, and pregabalin)	Markov model was constructed based on monthly cycles over a year and included dose titrations and management of adverse events. Individual variables for cost, utility, and treatment probabilities were stochastic, based on their respective distributions.	Clinical data from trials identified in the literature; no head to head trials were identified. Cost data from drugstore.com except cost of capsaicin was from the manufacturer. Utility data was from publications; utility data of capsaicin was from the product label	For capsaicin the next administration was assumed to be linear and divided equally over the monthly cycle. 30% change in pain was taken as the efficacy end-point (which is considered to be a clinically meaningful change).

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
				Results presented as ICER expressed as incremental cost per quality adjusted life year. Sensitivity analysis conducted		

BNF = British National Formulary; ICER = incremental cost-effectiveness ratio; PHN = postherpetic neuralgia; PNP = peripheral neuropathic pain; RCT = randomized controlled trial; SMC = Scottish Medicines Consortium; TCA = tricyclic antidepressant;

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Network Meta-Analyses Using AMSTAR 2[10] and the ISPOR Questionnaire[11]

Strengths	Limitations
Persson, 2018,[14] UK	
• The objective was clearly stated • Multiple databases (Medline, Embase, CINHAL, Allied and Complimentary Medicine database, Cochrane library, and Web of Sciences) were searched up to June 2015, and subsequently updated on January 2018. Also, reference list of include studies were searched. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Data extraction was done independently by two reviewers • Quality assessment was done independently by two reviewers using the Cochrane risk of bias tool, and the studies were judged to have considerable risk of bias. • Characteristics of the studies were described. • The systematic review included NMA. • The network structure was presented • Network meta-analysis was conducted, both frequentist and Bayesian approaches were used; effect size and uncertainty (associated confidence intervals and credible intervals) of the estimate were reported. • The Bayesian NMA was conducted using MCMC simulations. Non-informative prior distributions were set, and normal likelihood distributions were assumed. There was convergence within 10,000 simulations and the model was deemed to be appropriate. • The authors' conclusion appears to be fair	• A list of excluded studies was not provided • Unclear if article selection was done in duplicate • Publication bias does not appear to have been explored • For NMA the network diagram was presented; the number of studies in each comparison arm was reported. It was an open loop (not a connected network), as comparisons between NSAIDs and placebo; and capsaicin and placebo were available, but not between NSAIDs and capsaicin. Hence, it was not possible to check if the results of direct and indirect comparison were consistent. • The majority of NSAID studies involved patients with knee OA, whereas the capsaicin studies involved patients with hand, elbow, wrist, shoulder, hip, knee, and ankle OA. This difference in population could impact results of the indirect comparison in the NMA. The direction of impact is unclear. • It was mentioned that individual study results (Hedge's effect size and corresponding standard error) were calculated but results were not reported. • Heterogeneity among the studies was not reported. Impact of effect modifiers was not assessed. • Two authors had no conflicts of interest but three authors received fees from industry, hence potential for bias cannot be ruled out
Van Nooten, 2017,[15] The Netherlands	
• The objective was clearly stated • Multiple databases (Medline, Embase, Cochrane Library, DARE, and clinical trials register) were searched up to February, 2014 (there appears to be some discrepancy in this date stated in the publication, as a study published in 2017 was included) Publications prior to 1950 were excluded. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Data extraction was done by one reviewer and quality control was conducted by a second reviewer. • Quality assessment was conducted by one reviewer according to the NICE guideline. The quality of the studies was variable. • The systematic review included NMA. The NMA was conducted based on the NICE and ISPOR guidelines • The network structure was presented	• Unclear if article selection was done in duplicate • A list of excluded studies was not provided • Investigation of publication bias was planned but could not be done due to few (<10) studies for each pairwise comparison. • The authors mentioned that studies with treatment duration ≤ 8 weeks were not considered in the NMA for efficacy, in order to create a homogeneous evidence network, as the magnitude of treatment effect decreased in studies with longer duration compared to those with shorter duration. Also, studies that did not report efficacy outcomes that could be expressed in terms of the 11-point numerical rating scale were excluded. However, the network structure actually used for the efficacy NMA was not presented. NMA results were reported as Odds ratio (95% CI), but the acronym CI was not explained; as a Bayesian approach was used it was assumed that CI was the credible interval. • The authors mentioned that impact of effect modifiers was assessed. In case of heterogeneity identified in terms of

Strengths	Limitations
• NMA was conducted using a Bayesian approach, The model fit was assessed using the deviance information criterion. • Fixed effects model was used. For efficacy outcomes fixed effects model was used as goodness-of-fit was similar for fixed effects and random effects models. For tolerability outcomes, fixed effects model was used as goodness-of-fit was slightly better for the fixed effect model compared with the random effects model. • Posterior densities for the unknown model parameters in the NMA were estimated using MCMC simulations. • The authors' conclusion appears to be fair	factors such as drug dose, efficacy definitions, and treatment duration, analyses were conducted by excluding heterogeneous studies or conducting scenario analyses. However, these results were not presented. • Scenario analysis to assess the impact of effect modifiers was conducted but results were not presented. • The study was funded by industry and some of the authors were employed by the industry. Though it was mentioned that the authors had no other conflicts of interest regarding the contents of the report, the potential for bias cannot be ruled out.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MCMC = Markov chain Monte Carlo; NICE = National Institute of Health and Care excellence; NMA = network meta-analysis; .

Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[12]

Strengths	Limitations
Predel, 2020,[16] Germany	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized study but method of randomization was not described study • Double blinded (it was stated that the patients were blinded, but it was not explicitly stated if the assessor/ investigator was blinded) • Sample size calculation was conducted, and the appropriate number of patients were recruited. • Discontinuation and associated reasons were reported; 3.1% in the capsaicin group and 1.8% in the diclofenac group. • Restricted maximum likelihood based repeated measures approach was used and results for full analysis set (FAS) was reported. • Conflicts of interest were declared	• P values or confidence intervals were not reported for the comparison between capsaicin and diclofenac., as the intent of the study was to compare capsaicin, diclofenac or placebo with the combination of capsaicin and diclofenac for these comparisons p values were presented. • The study was sponsored by several industries and the authors were employed them or had received financial support from them; potential for bias cannot be ruled out.
Haanpää, 2016,[17] Finland	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized study. Randomization was done centrally using an interactive voice response system • Non-inferiority trial and the non-inferiority margin was reported; it was based on a systematic FDA review of pregabalin.	• No blinding • The study was funded by industry and the authors were associated with or employed by the industry, hence potential for bias cannot be ruled out

Strengths	Limitations
• Sample size calculation was conducted. It was not explicitly mentioned if the appropriate sample size was achieved. • Discontinuation was reported but reasons were not stated. Discontinuations were 2.12% and 14.8% with capsaicin and pregabalin, respectively. • Both full set analysis and per protocol analysis were conducted. • Conflicts of interest were declared	
Kiani, 2015,[18] Iran	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized study. Randomization was done using permuted block design. • Double-blind study, however, it was not specifically mentioned if patient and assessor/investigator were blinded. • Discontinuations were high in both groups: 43.1% in the capsaicin group, and 37.3% in the amitriptyline group, discontinuation was due to adverse events. • ITT analysis was conducted. Imputations were done for missing data using multiple imputations by regression method.	• Sample size calculations does not appear to have been conducted • The study was described as a non-inferiority trial but no non-inferiority margin was defined. • There was no mention of conflicts of interest.
Kiani, 2015,[19] Iran	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized study. Randomization was done using permuted block design. • Double-blind study, however, it was not specifically mentioned if patient and assessor/investigator were blinded. • Sample size calculations were conducted and the appropriate number of patients was recruited. However, the rationale of using a non-inferiority limit of 25% was not explained. • Discontinuations were: 42.85% in the capsaicin group, and 23.1% in the clonidine group, discontinuation was due to adverse events. • ITT analysis was conducted. Imputations were done for missing data using multiple imputations by regression method.	• There was no mention of conflicts of interest. • The study was funded by a University grant. The drugs for the study were provided free by the manufacturers.

ITT = intent-to-treat analysis

Table 7: Strengths and Limitations of Economic Evaluations Using the Drummond Checklist[13]

Strengths	Limitations
Mankowski, 2016,[20] UK.	
• Objectives were stated. • Strategies compared were stated. • Time horizon (2 years) and perspective were stated. • Clinical data sources were stated (data from a head-to-head trial was available). • Cost data source were stated • Discounting rate (3.5%) was stated. • Model description was presented • Incremental analysis was reported. • One-way sensitivity analysis and probabilistic sensitivity analysis were conducted	• The study was funded by industry and some of the authors were employed there.
Armstrong, 2011,[21] USA	
• Objectives were stated. • The strategies compared were stated. • Time horizon (1 year) and perspective were stated. • Clinical data sources were stated (clinical trials identified from the literature). • Cost data source were stated (mostly from drugstore.com) • Discounting was not applicable as the time horizon was one year • Model description was presented • Incremental analysis was reported. • Sensitivity analysis was conducted	• Direct data from head to head trials were not available • The study was funded by industry and the authors were associated with or employed by the industry.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews and Network Meta-Analyses

<table>
<tr><th>Main study findings</th><th>Authors' conclusion</th></tr>
<tr><td colspan="2">Persson, 2018,[14] UK</td></tr>
<tr><td>Comparison of treatments with capsaicin (0.025%, 0.0125%), NSAIDs and placebo for patients with OA. Results from NMA using frequentist and Bayesian approach
Results (ES [CI], frequentist; and ES [CrI], Bayesian) for direct and indirect comparisons, considering all trials (trials: 23 for NSAIDs, and 5 for capsaicin).
Topical NSAIDs vs placebo (direct): ES (CI) = 0.30 (0.19 to 0.41), and ES (CrI) = and 0.30 0.19 to 0.43.
Capsaicin vs placebo (direct): ES (CI) = 0.27 (-0.01 to 0.54), ES (CrI) = 0.27 (-0.02 to 0.56).
(Topical NSAIDs vs Capsaicin (indirect): ES (CI) = 0.04 (-0.26 to 0.33), ES (CrI) = 0.04 (-0.28 to 0.35).

Results (ES [CI], frequentist; and ES [CrI], Bayesian) for direct and indirect comparisons, considering only trials with drug used as licensed (trials: 13 for NSAIDs, and 4 for capsaicin).
Topical NSAIDs vs placebo (direct): ES (CI) = 0.32 (0.24 to 0.39), and ES (CrI) = 0.32 (0.24 to 0.42).
Capsaicin vs placebo (direct): ES (CI) = 0.41 (0.17 to 0.64), ES (CrI) = 0.41 (0.16 to 0.66).
Topical NSAIDs vs Capsaicin (indirect): ES (CI) = -0.09 (-0.34 to 0.16), ES (CrI) = -0.09 (-0.35 to 0.18).

Note: Licensed refers to licensed according to the British National Formulary.</td><td>"In conclusion, current evidence indicates that topical NSAIDs and capsaicin offer similar levels of pain relief in OA. Larger and better conducted RCTs, particularly for capsaicin, are required to confirm this. However, it is unknown whether individuals with different pain phenotypes respond differently to these two commonly used topical analgesics. Further work on phenotypic features of OA pain and their response to these two drugs is warranted. (p. 1579)"[14]</td></tr>
<tr><td colspan="2">Van Nooten, 2017,[15] The Netherlands</td></tr>
<tr><td>NMA findings for adult patients with painful DPN (the network included capsaicin (8%) patch, pregabalin, duloxetine, gabapentin, amitriptyline, and placebo).
(The amitriptyline studies were not considered in the NMA for efficacy, because the pain scale used could not be converted to a 11-point scale or the study duration was ≤ 8 weeks. For the purpose of homogeneity, studies with ≤ 8 weeks were excluded as the magnitude of treatment effect decreased in studies with longer duration compared to those with shorter duration.)

Efficacy: ≥ 30% pain relief
<table>
<tr><th>Intervention</th><th>Comparator</th><th>OR (95% CrI)</th></tr>
<tr><td rowspan="4">Capsaicin (8%) patch</td><td>Placebo</td><td>2.28 (1.19 to 4.03)</td></tr>
<tr><td>Pregabalin</td><td>1.83 (0.91 to 3.34)</td></tr>
<tr><td>Gabapentin</td><td>1.66 (0.74 to 3.23)</td></tr>
<tr><td>Duloxetine</td><td>0.99 (0.50 to 1.79)</td></tr>
<tr><td colspan="3">It was reported that scenario analysis (excluding 3 studies with different end-point definitions) found no major difference compared to base-case analysis.</td></tr>
</table>
Efficacy: ≥ 50% pain relief
<table>
<tr><th>Intervention</th><th>Comparator</th><th>OR (95% CrI)</th></tr>
<tr><td rowspan="4">Capsaicin (8%) patch</td><td>Placebo</td><td>1.77 (0.84 to 3.37)</td></tr>
<tr><td>Pregabalin</td><td>1.21 (0.55 to 2.40)</td></tr>
<tr><td>Gabapentin</td><td>0.94 (0.39 to 2.00)</td></tr>
<tr><td>Duloxetine</td><td>0.88 (0.40 to 1.71)</td></tr>
</table></td><td>"This NMA suggests that pain relief with the capsaicin 8% patch is similar to that observed with pregabalin, duloxetine, and gabapentin in patients with PDPN. These oral agents were associated with a significantly elevated risk of somnolence, dizziness, and discontinuation because of adverse events compared with placebo; none of these events was reported in association with the capsaicin 8% patch. Localized treatment with the capsaicin 8% patch had similar efficacy but offered tolerability benefits in terms of systemic adverse events compared with NICE-recommended oral agents in patients with PDPN. (p. 800)[15]</td></tr>
</table>

Main study findings	Authors' conclusion
It was reported that scenario analysis considering different doses of pregabalin (≤ 150 mg/d and ≥ 300mg/d) and duloxetine(≤ 20 mg/d and ≥40 mg/d), as well as exclusion of studies with different end-point definitions, found no major differences compared with the base case analysis. *Tolerability (considering adverse effect: headache)* Intervention / Comparator / OR (95% CrI): Capsaicin (8%) patch / Placebo / 31.34 (0.58 to 134.74). Pregabalin / Capsaicin (8%) patch / 0.33 (0.01 to 1.33) Gabapentin / Capsaicin (8%) patch / 0.42 (0.01 to 1.96) Duloxetine / Capsaicin (8%) patch / 0.64 (0.01 to 3.05) *Tolerability (considering of other adverse effects somnolence, dizziness, fatigue, nausea, constipation, diarrhea, and discontinuation due to AE).* These adverse effects were not reported for capsaicin. These adverse effects were reported for pregabalin, duloxetine, gabapentin, and amitriptyline and results were variable.	

CI = confidence interval; CrI = credible interval; ES = effect size;

Table 9: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Predel, 2020,[16] Germany	
Comparison capsaicin (0.075%) versus diclofenac for treating adult patients with acute back or neck pain. *Change in POM_{WP} (cm) from baseline at day 2, 1 hour after application* Intervention / Baseline value, mean ± SD / Adjusted change from baseline, mean ± SE: Capsaicin / 7.22 ± 1.16 / -3.26 ± 0.16 Diclofenac / 7.28 ± 1.27 / -2.33 ± 0.16 Negative value indicates decrease in POM_{WP}, i.e., better health. Restricted maximum likelihood based repeated measures approach was used. The model included treatment, country, application site, time, treatment by time interaction, baseline POM_{WP} and baseline POM_{WP} by time interaction. *Adverse effects* Adverse effect / Patients (%) reporting adverse effects: Capsaicin / Diclofenac: All adverse effects / 26.5 / 12.1 Some examples of the types of adverse effects encountered: Gastrointestinal disorder / 1.3 / 0.4 Application site pain / 4.5 / 0.0 Infection and infestation / 5.4 / 2.2 Headache / 2.2 / 2.7 Skin and subcutaneous tissue disorder / 5.8 / 1.3 Nervous system disorders / 2.2 / 3.6	"Capsaicin alone and the combination therapy diclofenac + capsaicin were superior to placebo and to diclofenac alone, but the combination provided no additional pain relief when compared with capsaicin alone in analyses of change in POM_{WP} between baseline and evening of day 2, POM_{WP} over 72 and 120 h and for all other key efficacy endpoints. (p. 293)" [16]

<table>
<tr><th>Main study findings</th><th>Authors' conclusion</th></tr>
<tr><td>Tolerability
Capsaicin treatment was considered good or very good by 77.1% of patients and 81.6% of investigators.
Diclofenac treatment was considered good or very good by 91.9 % of patients and 92.8% of investigators</td><td></td></tr>
<tr><td colspan="2">Haanpää, 2016,[17] Finland</td></tr>
<tr><td>Comparison of capsaicin (8%) versus pregabalin for treating adult patients with PNP (includes PHN, PNI, non-diabetic painful peripheral polyneuropathy)

Treatment responders (≥30% reduction in pain score [using NPRS] from baseline):
<table>
<tr><th rowspan="2">Intervention</th><th rowspan="2">Number of patients</th><th rowspan="2">Percentage of responders</th><th colspan="2">Effect size (%)</th></tr>
<tr><th>MD (95% CI)</th><th>OR (95% CI)</th></tr>
<tr><td>Capsaicin</td><td>282</td><td>55.7%</td><td rowspan="2">1.2 (-7.1 to 9.4)</td><td rowspan="2">1.034 (0.715 to 1.496)</td></tr>
<tr><td>Pregabalin</td><td>277</td><td>54.5%</td></tr>
</table>
Treatment responders (≥30% reduction in pain score) by subgroups
<table>
<tr><th>Subgroup</th><th>Intervention</th><th>Number of patients</th><th>Percentage of responders</th><th>Effect size (%): MD (95% CI)</th></tr>
<tr><td rowspan="2">PHN</td><td>Capsaicin</td><td>63</td><td>71.4</td><td rowspan="2">-5.3 (-20.1 to 9.5)</td></tr>
<tr><td>Pregabalin</td><td>73</td><td>76.7</td></tr>
<tr><td rowspan="2">PNI</td><td>Capsaicin</td><td>146</td><td>53.4</td><td rowspan="2">12.5 (1.0 to 24.1)</td></tr>
<tr><td>Pregabalin</td><td>137</td><td>40.9</td></tr>
<tr><td rowspan="2">Non-diabetic peripheral polyneuropathy</td><td>Capsaicin</td><td>73</td><td>46.6</td><td rowspan="2">-11.6 (-28.1 to 4.0)</td></tr>
<tr><td>Pregabalin</td><td>67</td><td>58.2</td></tr>
</table>
Time to onset of pain relief
<table>
<tr><th>Intervention</th><th>Median time to pain relief (95% CI)</th><th>Hazard ratio (95% CI)</th></tr>
<tr><td>Capsaicin</td><td>7.5 (6.0 to 10.0)</td><td rowspan="2">1.68 (1.35 to 2.08), favoring capsaicin</td></tr>
<tr><td>Pregabalin</td><td>36.0 (22.0 to 56.0)</td></tr>
</table>
Treatment satisfaction
Proportion of patients willing to carry on treatment at week 8, was 78.4% in the capsaicin group compared to 66.4% in the pregabalin group; MD (95% CI): 12.0% (4.6% to 19.3%), favoring capsaicin.

Adverse events (proportion of patients with drug related TEAE [>5%])
All adverse events: 61.3% with capsaicin, 54.5% with pregabalin
Application site pain: 23.0% with capsaicin, 0.0% with pregabalin
Erythema; 20.9% with capsaicin, 0.4% with pregabalin
Burning sensation; 15.6% with capsaicin, 0.0% with pregabalin
Application site erythema; 8.9% with capsaicin, 0.0% with pregabalin
Pain; 5.3% with capsaicin, 0.7% with pregabalin
Headache: 1.1% with capsaicin, 9.4% with pregabalin
Nausea: 0.4% with capsaicin, 10.8% with pregabalin
Dizziness: 0.0% with capsaicin, 18.4% with pregabalin
Somnolence: 0.0% with capsaicin, 15.5% with pregabalin</td><td>"The capsaicin 8% patch was non-inferior to an optimized dose of pregabalin in relieving pain in patients with PNP over 8 weeks. The capsaicin patch offered a faster onset of pain relief and an overall higher level of satisfaction versus pregabalin. The majority of TEAEs were mild or moderate in severity and, for the capsaicin patch, were largely application related. In contrast, pregabalin was associated with largely systemic TEAEs. TEAEs leading to permanent discontinuation of the study drug were reported only for pregabalin. (p. 326 to 327)"[17]</td></tr>
</table>

Main study findings	Authors' conclusion
Weight increase: 0.0% with capsaicin, 6.1% with pregabalin Vertigo: 0.0% with capsaicin, 5.1% with pregabalin	
Kiani, 2015,[18] Iran	
Comparison of capsaicin (0.75%) cream versus amitriptyline for treating adult patients with DPN. *Treatment responders (≥50%reduction in pain score [using VAS] from baseline):* 43.1% in the capsaicin group, and 37.3% in the amitriptyline group, P = 0.545. *Adverse events* Adverse events were greater with capsaicin. Proportion of patients with adverse events: 56.9% in the capsaicin group, 29.9% in the amitriptyline group, P = 0.001. In the capsaicin group, proportion of patients with itching, blister formation, and erythema were 20%, 8.5%, and 5.7% respectively In the amitriptyline group, proportion of patients with dryness and itching were 8.8% and 4.4% respectively. *Compliance:* During treatment, 43.1% discontinued in the capsaicin group, and 31.3% discontinued in the amitriptyline group, P = 0.219 *Note:* It was reported that logistic regression analysis showed that there was no relationship between patient's basic characteristics and response to treatment, however no data were presented.	"In sum, this study demonstrates that amitriptyline is effective in managing diabetic neuropathic pain similar to capsaicin cream with less side effects and better patient compliance. Treatment with topical amitriptyline was safe and without significant side effects associated with systemic therapies. Further studies are required to confirm the efficacy and safety of topical amitriptyline as a treatment of PDN." (p. 1267)"[18]
Kiani, 2015,[19] Iran	
Comparison of capsaicin (0.75%) cream versus clonidine (0.1%) gel for treating adult patients with DPN. *Treatment responders (≥50%reduction in pain score [using VAS] from baseline):* 40.6% in the capsaicin group, and 57.1% in the clonidine group, P = 0.051. (The non-inferiority limit was considered as 25%, the reason for this choice was not presented.) The graphical representation of VAS scores over the treatment duration of 12 weeks were presented and it was reported that the slopes of VAS decline were not statistically significantly different between the capsaicin and clonidine groups, P = 0.189. *Adverse events* Dermatological complications were more common in the clonidine group. The proportion of patients with dermatological complications were 58% with capsaicin, and 5.7% with clonidine, P = 0.001. In the capsaicin group, proportion of patients with itching, blister formation, and erythema were 45.5%, 13.6%, and 9.1% respectively In the clonidine group, proportion of patients with dryness and itching were 4.2% and 1.4% respectively. *Compliance:* During treatment, 43.5% discontinued in the capsaicin group, and 22.9% discontinued in the clonidine group.	"In general, in our study clonidine was well tolerated and safe during this 12-week study. There were more discontinuations due to adverse events in the capsaicin treatment group than in the clonidine treatment group. This study compared the efficacy of clonidine gel with capsaicin cream, a FDA approved drug, but prolonged therapy and evaluation for a longer duration than the 12 weeks can better evaluate the benefits of this drug. More studies are required to better evaluate the efficacy and safety of this topical compound for relieving pain in DPN. (p. 5 of 11).[19]

Main study findings	Authors' conclusion
Visual analog scale (VAS): scores from 0 to 10, with higher scores indicating greater pain.[18,19]	

CI = confidence interval; DPN = diabetic peripheral neuropathy; FDA = Food and Drug Administration (USA); MD = mean difference; NPRS = numeric pain rating scale; OR = odds ratio; PDN = painful diabetic neuropathy; PHN = post herpetic neuralgia; PNI = post traumatic nerve injury; PNP = peripheral neuropathic pain; POM_{WP} = pain on movement for the worst procedure; SD = standard deviation; SE = standard error; TEAE = treatment emergent adverse effect; VAS = visual analog scale

Table 10: Summary of Findings of Included Economic Evaluations

Main study findings	Authors' conclusion
Mankowski, 2016,[20] UK.	
Cost-effectiveness of capsaicin 8% patch versus dose optimized pregabalin in non-diabetic patients with PNP from the perspective of the National Health Service and Personal and Social Services in Scotland, UK. *Base-case analysis (2 year time horizon)* Cost per patient treated was £1,197 and £1,207 for capsaicin and pregabalin, respectively; **d**ifference in cost per patient treated = -£11. (The cost included costs of the drug, last-line therapy, and GP or pain specialist visits.) QALYs per patient treated was 1.36 and 1.31 for capsaicin and pregabalin, respectively; difference in QALY = 0.049 ICER: Capsaicin dominated pregabalin, i.e., capsaicin is more effective with lower cost. *One-way sensitivity analyses (2 year time horizon)* For base case: time to retreatment with capsaicin = 179 days; units of grade 6 nurse needed = 0.5; and units of capsaicin patch needed = 1.38 One-way sensitivity analysis showed on varying different parameters capsaicin either dominated or was cost-effective (i.e., ICER was less than the willingness to pay threshold of £20,000 per QALY). The ICER was most sensitive to variations in the time to retreatment with the capsaicin; at the low value (117 days), the ICER increased to £7,951 per QALY, whereas at the high value (241 days), the capsaicin patch was the dominant treatment strategy. Other variables for which capsaicin patch was cost-effective rather than dominant were: for grade 6 nurse time at high value i.e. 1 unit, ICER was £2,941 per QALY; number of capsaicin patches per treatment (high value of 1.51 units, ICER was £1,188 per QALY); *Probabilistic sensitivity analysis (2 year time horizon)* The probabilistic analysis showed that varying inputs to the model had limited impact on the results. The cost-effectiveness plane showed that the mean incremental cost and the mean incremental QALY gained were respectively £22.50 and 0.052 for capsaicin compared with pregabalin. The cost-effectiveness acceptability curve showed that the probability of capsaicin being cost-effective versus pregabalin was 97%, at a willingness to pay threshold of £20,000 per QALY.	"This economic analysis suggest that capsaicin 8% patch is a cost-effective treatment option compared with pregabalin for patients with PNP who have not tolerated or have not achieved adequate pain relief from conventional first- and second-line treatments from the perspective of the NHS and Personal and Social Services in Scotland. (p. 14 of 16)"[20]
Armstrong, 2011,[21] USA	
Cost-effectiveness of capsaicin 8% patch versus lidocaine patch, or oral agents(TCA, gabapentin, pregabalin, or duloxetine) for treating patients with PHN, from a payer perspective (managed care organization)	"This cost-effectiveness analysis demonstrates the importance of including a clinically meaningful efficacy endpoint, along with

Main study findings	Authors' conclusion

Effectiveness and cost
Effectiveness rates of capsaicin was not significantly different compared to lidocaine, but both capsaicin and lidocaine had significantly greater effectiveness rates compared with TCAs, duloxetine, gabapentin or pregabalin. Treatment costs over one year indicated that TCAs were the least costly and significantly less compared to the other agents. There were no significant differences in treatment costs between duloxetine, gabapentin and pregabalin. Capsaicin and lidocaine were the most costly and there were no significant differences in treatment costs between them.

Cost effectiveness ratio

Intervention	Cost effectiveness ratio (cost per QALY), mean (95% CI)
Capsaicin	8762 (7653 to 9871)
Lidocaine	8277 (6699 to 9847)
TCA	3131 (2374 to 3888)
Duloxetine	4464 (3851 to 5077
Gabapentin	4153 (3451 to 4855)
Pregabalin	5078 (4365 to 5791)

Cost effectiveness ratio: sensitivity analysis (varying time of retreatment with capsaicin)

Capsaicin retreatment interval	Cost effectiveness ratio (cost [US$] per QALY), mean (95% CI)
Every 12 weeks (base case)	8762 (7653 to 9871)
Every 14.5 weeks	7903 (6923 to 8883)
Every 17.7 weeks	7141 (6261 to 8021)

ICER for capsaicin

Comparator	Mean ICER (incremental cost [US$] per QALY gained) with respect to comparator
TCA	Approximately 60, 000
Duloxetine, gabapentin, or pregabalin	Less than 40,000

Capsaicin was considered cost-effective compared to TCAs, duloxetine, gabapentin and pregabalin at a willingness to pay threshold of $50,000 per QALY gained to US$100,000 per QALY gained.
There was considerable overlap in values between capsaicin and lidocaine, i.e., there was no significant difference in cost effectiveness between these two agents

ICER: Sensitivity analysis
If the capsaicin patch retreatment interval was increased to 14.5 weeks, the ICER for capsaicin compared to the oral agents (TCAs, duloxetine, gabapentin, and pregabalin) was less than US$51,000 per QALY gained.
If the capsaicin patch retreatment interval was increased to 17.7 weeks, the ICER for capsaicin compared to the oral agents (TCAs, duloxetine, gabapentin, and pregabalin) was less than US$44,000 per QALY gained.

titration and adverse event management in order to more closely reflect the real world impact of PHN treatments. The effectiveness results demonstrated that 8% capsaicin patch and topical lidocaine patch had the highest effectiveness rates. The ICER analysis found broad overlap between the two types of patches and that the cost effectiveness of the 8% capsaicin patch occurred within an accepted cost per QALY gained threshold compared to all oral products. (p. 946)"[21]

BRP = brachioradial pruritis; DLQI: Dermatological Life Quality Index; ICER = incremental cost effectiveness ratio; MCID = minimum clinically important difference; NPT = notalgia paraesthetica; NRS: numerical rating scale; PHN = postherpetic neuropathy; PNP = peripheral neuropathic pain; QALY = quality adjusted life year; TCA = tricyclic antidepressant; VAS: visual analogue scale: VRS: verbal rating scale.