Capsaicin 8% Patch Versus Oral Neuropathic Pain Medications for the Treatment of Painful Diabetic Peripheral Neuropathy: A Systematic Literature Review and Network Meta-analysis

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ABSTRACT

Purpose: A network meta-analysis (NMA) was performed, aiming to assess the relative efficacy and tolerability of the capsaicin 179-mg (8% weight for weight) cutaneous patch (capsaicin 8% patch) compared with oral, centrally acting agents (ie, pregabalin, gabapentin, duloxetine, amitriptyline) in patients with painful diabetic peripheral neuropathy (PDPN).

Methods: A systematic search of EMBASE/MEDLINE, Cochrane Library, and the National Health Service Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects was conducted to identify all randomized controlled trials. Data from eligible studies according to predefined inclusion and exclusion criteria were extracted, and analyses were based on aggregate-level data. Efficacy outcomes were the proportions of patients with ≥30% and ≥50% reductions in pain, and tolerability outcomes were somnolence, dizziness, nausea, diarrhea, constipation, headache, fatigue, insomnia, and rate of discontinuation due to adverse events (AEs). Data were analyzed by using a Bayesian NMA. Fixed and random effects models were estimated. Relative treatment effect was presented as odds ratios (ORs) with 95% CIs. Sources of heterogeneity were assessed.

Findings: The NMA included 25 randomized controlled trials. For ≥30% pain reduction, the capsaicin 8% patch was significantly more effective than placebo (OR, 2.28 [95% CI, 1.19–4.03]), exhibited a numerical advantage compared with pregabalin (OR, 1.83 [95% CI, 0.91–3.34]) and gabapentin (OR, 1.66 [95% CI, 0.74–3.23]), and had similar efficacy compared with duloxetine (OR, 0.99 [95% CI, 0.5–1.79]). The evidence available was not sufficient to assess the relative efficacy of amitriptyline. In the NMA for tolerability, the capsaicin 8% patch was only included for headache because the incidence was 0% for the other outcomes. Oral, centrally acting agents had a significantly elevated risk compared with placebo for somnolence (pregabalin, gabapentin, duloxetine, and amitriptyline), dizziness (pregabalin, gabapentin, duloxetine, and amitriptyline), nausea (duloxetine), diarrhea (duloxetine), fatigue (duloxetine), and discontinuation because of AEs (pregabalin, gabapentin, and duloxetine). Compared with pregabalin and gabapentin, duloxetine had a significantly lower risk of dizziness but a significantly higher risk of nausea.

Implications: This NMA suggests that the efficacy observed with the capsaicin 8% patch is similar to that observed with oral agents (ie, pregabalin, duloxetine, gabapentin) in patients with PDPN. The oral agents were associated with a significantly elevated risk of somnolence, dizziness, fatigue, and discontinuation because of AEs compared with placebo. The capsaicin 8% patch was as effective as oral centrally acting agents in these patients with PDPN but

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Key words: capsaicin patch, duloxetine, gabapentin, network meta-analysis, painful diabetic peripheral neuropathy, pregabalin.

INTRODUCTION

Neuropathies are a common long-term complication of diabetes. They are characterized by the progressive loss of nerve fibers and can affect the somatic peripheral and autonomic nervous systems.[1] Painful diabetic neuropathy occurs in 10% to 20% of patients with diabetes and in 40% to 50% of those with diabetic neuropathies.[2] Symptoms, which include electrical or stabbing sensations, paresthesias, hyperesthesias, burning pain, and deep aching pain,[3] adversely affect health-related quality of life and functioning[4] and can lead to sleep problems, anxiety, and depression.[5]

In the United Kingdom, annual health care costs related to painful diabetic peripheral neuropathy (PDPN) range from an estimated £1612 to £3217 per patient depending on the level of pain severity (2005 costs).[6] In addition, PDPN is associated with productivity losses and disruptions to employment status, driven primarily by impairment while working (presenteeism). In the United Kingdom, the estimated mean annual total cost of lost productivity associated with PDPN is €12,438 per patient (2008 costs).[7]

PDPN is a challenging condition to treat. Evidence-based treatment guidelines principally recommend oral, centrally acting pharmacologic agents (including anticonvulsant drugs, tricyclic antidepressant agents, and serotonin-noradrenaline reuptake inhibitors) for the treatment of neuropathic pain, including PDPN. The specific agents recommended and the strength of the recommendations, however, vary between guidelines.[8–11] Localized and topical treatments are also recognized treatment options, although supporting evidence for their use in patients with PDPN remains limited.[8]

The capsaicin 179 mg (8% weight for weight) cutaneous patch (capsaicin 8% patch)* is a localized treatment that provides effective durable pain relief from a single application in patients with peripheral neuropathic pain.[12–14] In nondiabetic adults, direct comparison has shown the capsaicin 8% patch to be noninferior to pregabalin in the control of neuropathic pain but with a faster onset of analgesia and considerably fewer systemic side effects.[15]

Results from 2 randomized controlled Phase III trials (STEP [A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of QUTENZA™ in Subjects with Painful Diabetic Peripheral Neuropathy][16] and PACE [A Randomized, Controlled, Long-Term Safety Study Evaluating the Effect of Repeated Applications of QUTENZA™ plus Standard of Care Versus Standard of Care Alone in Patients with Painful Diabetic Peripheral Neuropathy][17]) evaluating the capsaicin 8% patch in patients with PDPN have recently been reported. STEP was a 12-week, double-blind, placebo-controlled trial evaluating the efficacy and safety of a single application of the capsaicin 8% patch in 369 patients with PDPN. It found a greater mean reduction in average daily pain score from baseline at weeks 2 to 8 with the capsaicin 8% patch versus placebo (–27.4% vs –20.9%; $P = 0.025$).[16] PACE, a 52-week multicenter randomized study, assessed the longer term safety of repeated applications of the capsaicin 8% patch as add-on therapy to individualized standard of care versus standardof care alone in 468 patients with PDPN. These data formed part of a successful regulatory submission and label variation for the capsaicin 8% patch in Europe to remove the exclusion of patients with diabetes.[18]

Currently, there is no direct clinical evidence comparing the efficacy and tolerability of the capsaicin 8% patch with other pharmacologic agents in patients with PDPN, and it is impractical to conduct randomized active-controlled comparisons for all of the available treatment options. In the absence of direct comparative data, network meta-analyses (NMA) provide a method of estimating differences between competing interventions by integrating data from available trials.[19] NMA combine effect sizes from all possible pairwise comparisons (direct and indirect) to provide an estimate of relative effectiveness. To better understand the efficacy and tolerability of the capsaicin 8% patch compared with oral agents in patients with PDPN, a systematic literature review and NMA were performed.

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