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Capsaicin 8% Patch for Alternative Therapy of Painful Diabetic Peripheral Neuropathy

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Abstract

Diabetes is one of the most common health problems due to its high incidence and complications. One of the complications associated with diabetes is painful diabetic peripheral neuropathy (PDPN). The capsaicin 8% patch is a localized pain treatment that provides effective pain relief from a single application in patients with peripheral neuropathic pain. The aim of this review is to discuss the effect of capsaicin patch 8% in patients with painful diabetic peripheral neuropathy. The search strategy was conducted in PubMed and modified for other databases. The search was limited to English-language reports. The keywords used were "capsaicin", "capsaicin patch", "painful diabetic peripheral neuropathy", and "pain management". The inclusion criteria used were randomized controlled trials (RCTs), clinical trials or another interventional analysis with full text in English with publications less than the last 10 years. The exclusion criteria used were a review, systematic review, or meta-analysis, studies that were not conducted in humans and non-full text in English with publications over the last 10 years. Results: There are 2 full-text that meet inclusion criteria. From articles related to studies that have been conducted, the use of capsaicin 8% patch can reduce pain, improve nerve function and quality of life in PDPN patients. The use of capsaicin 8% patch has the advantage to pain relief for patients with painful diabetic peripheral neuropathy.

Keywords: Alternative therapy, Capsaicin 8% Patch, Diabetes complications, Pain Relief, Painful Diabetic Peripheral Neuropathy, topical drugs

Abstrak

[Capsaicin 8% Patch untuk Terapi Alternatif Neuropati Perifer Diabetik yang Menyakitkan]

Diabetes merupakan salah satu permasalahan kesehatan karena insidensi yang tinggi dan komplikasinya. Salah satu komplikasi terkait diabetes adalah nyeri neuropati diabetikum perifer/painful diabetic peripheral neuropathy (PDPN). Capsaicin 8% patch merupakan pengobatan nyeri yang terlokalisir yang menyediakan pereda nyeri pada pasien dengan nyeri neuropati perifer. Tujuan dari tinjauan ini adalah untuk membahas efek capsaicin patch 8% pada pasien dengan nyeri neuropati perifer diabetikum. Pencarian literatur dilakukan dengan menggunakan mesin pencari PubMed dan sumber data terkait lainnya. Pencarian terbatas pada studi berbahasa Inggris. Kata kunci yang digunakan antara lain "capsaicin", "capsaicin patch", "painful diabetic peripheral neuropathy", dan "pain management". Kriteria inklusi yang digunakan antara lain studi berupa randomized controlled trials (RCTs), clinical trials atau studi intervensi lainnya dengan full text berbahasa Inggris dengan publikasi kurang dari 10 tahun. Kriteria eksklusi yang digunakan adalah studi berupa tinjauan, tinjauan sistematis, atau meta-analisis, studi tidak dilakukan pada manusia, bukan full text berbahasa Inggris dengan riwayat publikasi lebih dari 10 tahun. Terdapat dua studi yang memenuhi kriteria inklusi. Dari artikel studi yang telah dilakukan, penggunaan capsaicin 8% patch dapat menurunkan nyeri, memperbaiki fungsi saraf dan kualitas hidup pasien dengan nyeri neuropati perifer diabetikum. Penggunaan capsaicin 8% patch memiliki keuntungan pereda nyeri untuk pasien nyeri neuropati perifer diabetikum.

Kata kunci: capsaicin 8% patch, komplikasi diabetes, nyeri neuropati perifer diabetikum, obat topikal, pereda nyeri, terapi alternatif

INTRODUCTION

Diabetes is one of the most common health problems due to its high incidence and complications.¹ The prevalence of diabetes patients has reached 476 million

worldwide, with 462 million of them being T2DM patients or the equivalent of 6.28% of the world's population.^{2,3} By 2025, diabetes is projected to increase to 570.9 million with an increase in the death rate from

diabetes reaching 1.59 million each year.³ The prevalence of diabetes-related complications reached 18.8% microvascular complications and 12.7% macrovascular complications.⁴

One of the common complications associated with diabetes is painful diabetic peripheral neuropathy (PDPN).⁵ PDPN is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" which is characterized by burning or stabbing pain, tingling, hyperesthesia, or an electric shock-like sensation. PDPN can result in decreased quality of life for diabetic patients and increase diabetes-related care costs.⁶ PDPN symptoms can appear after 10 years of diagnosis and 20% of diabetic patients are diagnosed with PDPN at the same time as the diagnosis of diabetes.⁷ Although several studies have shown the effect of glucose control on neurological pain-related complications in diabetic patients, its effectiveness is unclear because some studies have shown the opposite result.⁸

Topical treatment is an alternative management of PDPN.⁹ One of the topical drugs that can be used as a topical treatment for PDPN is capsaicin, a natural alkaloid that often found in chillies.^{9,10} Currently, there are two capsaicin dosage measures for topical drugs, namely low dose (0.075%) and high dose (8%).⁹ The capsaicin 179 mg (8% weight for weight) cutaneous patch (capsaicin 8% patch) is a localized pain treatment that provides effective pain relief from a single application in patients with peripheral neuropathic pain with faster analgesics and fewer side effects versus oral analgesic therapy.¹¹

Capsaicin 8% patch has been widely used to help relieve pain syndrome although results were inconsistent.¹² Several studies have shown that the effect of the capsaicin 8% patch can reduce pain intensity with the same effectiveness as orally systemic pain relief (eg pregabalin, gabapentin) with fewer systemic side effects (drowsiness, vomiting, fatigue).¹³ However,

there are still few studies related to the use of capsaicin 8% patch so that its effectiveness is still limited to a small population. The aim of this review was to understand the effect of using the capsaicin 8% patch for pain relief in PDPN patients.

METHOD

Search strategy

The systemic literature review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline. The search strategy was with search engine PubMed and modified for other databases (Google Scholar, Science Direct) from Augustus-October 2020. The search was limited to English-language reports and published less than 10 years. The keywords used were "capsaicin", "capsaicin patch", "painful diabetic peripheral neuropathy", and "pain management".

Study selection

The following title and abstract keyword search terms were used in all databases, with limitations to humans. The inclusion criteria used were randomized controlled trials (RCTs), clinical trials or other interventional study with full text in English with publications less than the last 10 years. The study was considered eligible when using patients who had been diagnosed with PDPN. There were no restrictions placed on duration, intensity, or setting of intervention (i.e., inpatient and outpatient). The exclusion criteria used were a review, systematic review, or meta-analysis with non-full text in English. The studies that were conducted not in human and not in patient who had been diagnosed with PDPN also excluded. The study selection process began with general keyword (from title and abstract) searching in the databases and reference lists of appropriate studies. From those titles and abstracts that appeared relevant, a more thorough abstract review was conducted and all eligible full-text articles were included in this paper.

Data extraction and assessment of studies

The author extracted and collated all details of the data items and study characteristics from all articles. Data extraction table including, if available, sample size, country, mean of age, duration of PDPN, history of pain medication before study, type and duration of study, type of intervention, primary and secondary outcome, and any adverse event that reported. All data from extraction then were input into table.

RESULT

Study selection

Based on the flowchart that describes the identification, screening, exclusion, eligibility, and selection processes as shown in Figure 1, 315 studies were identified in the search system with 256 of them excluded because based on the title and abstract review, it was identified that the studies carried out were not in English, the study was systematic reviews or reviews or meta-analysis, case studies and not full text. Of the 59 articles that passed the screening process, a full review was carried out and excluded 57 articles with most of the studies conducted not on PDPN patients and carried out in test animals or in vitro studies.

Study characteristic

Characteristics of patients and description of interventions are shown in Table 1 and 2. The studies were limited to the United States and Europe (country specification not specified) with sample sizes ranging from 155 to 186 people in adults (ranging in age from 59.1 to 63.9 years). The study sample had diagnosed PDPN ranging from 4.1 to 5.8 years with most of the use of analgesic drugs to treat PDPN. The study reported the racial composition of the sample which was predominantly Caucasian (71.0-99.4%). The population sample had levels of HbA1C \geq 6.5% and body mass index (BMI) \geq 30 kg / m². All studies performed using the Capsaicin 8% patch (Qutenza; Acorda Therapeutics, Inc, Ardsley, NY; obtained

from Astellas Pharma Europe BV, Leiden, The Netherlands). One study compared an intervention with a placebo patch for 30 minutes and another with a standard care and a difference in duration of 30 minutes and 60 minutes.

Outcome measures

All studies reported primary outcome and secondary outcome showed in Table 3. The outcomes were measured from baseline until the end of study. Outcome measures include daily pain score, treatment satisfaction, quality of life, sensory perception and reflex testing, adverse sign, and other pain medication during the study.

Primary outcome

Simpson *et al* showed that intervention group had significant reduction in average daily pain score of the Numeric Pain Rating Scale (NPRS) from 2-8 weeks (-27.4% vs -20.9%; 95% CI, -12.3 to -0.8; P = 0.025) and 2-12 weeks (-28.0% vs -21.0%; 95% CI, -12.9 to -1.2; P = 0.018) after intervention.¹⁴ Vinik *et al* showed there were reduction of mean change of Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) from baseline (estimated mean difference versus SOC alone; 90% CI for difference) of patients which treated with 30 minute use capsaicin 8% patch and standard of care (SOC) -27.6% (-20.9%; 95% CI, -31.7 to -10.1), treated with 60 minute use capsaicin 8% patch and SOC -32.8% (-26.1; 95% CI, -36.8 to -15.4), and SOC alone -6.7%.¹⁵ The reduction of QOL-DN score was associated with improved function of sensory nerve and quality of life.

Secondary outcome

Simpson *et al* showed that intervention group had significant modest improvements in sleep interference scores (from NPRS) from baseline to between weeks 2 through 8 (P = 0.03) and weeks 2 through 12 (P = 0.02). This study also showed patient satisfaction of therapy and life (from Patient Global Impression of Change and Self-Assessment of Treatment II question-

naire) but not significant change in health-related quality of life (no significance difference from EuroQoL).

Vinik *et al* showed there were reduction of mean change of Utah Early Neuropathy Scale (UENS) from baseline (estimated mean difference versus SOC alone; 90% CI for difference) of patients which treated with 30 minute use capsaicin 8% patch and SOC -2.1 (-0.9; 95% CI, -1.8 to 0.1), treated with 60 minute use capsaicin 8% patch and SOC -3.0 (-1.7; 95% CI, -2.7 to -0.8), and SOC alone -1.2.

For sensory perception and reflex testing result, all studies reported no negative results at baseline and the end of the study. Simpson *et al* showed there was increase report from patient to 'normal' sensation and reduce the report of 'painful' sensation. Vinik *et al* also showed there was improvement of sensory perception in intervention group with greatest change in 60-min capsaicin 8% patch group.

All study also reported there were other pain medications during this study (62.8-76.3%) in both of groups. The most common pain medication used is analgesics agents (50.6-57.5%), followed with antiepileptic drugs (34.6-47.1%), anti-inflammatory/antirheumatic drugs (18.6-30.6%), topical joint/muscular pain products (18.1-30.1%), and psycholeptics drugs (14.0-25.8%). One study also reported the use of stomatological preparations (11.5-14.0%), psychoanaleptics (3.8-13.5%), and ophthalmologicals (9.6-12.7%).

There were also adverse event reported from all studies which all adverse events were more reported in intervention group (from 46.8-69.4%) than in control group (33.9-48.4%). Adverse events are including burning sensation in patch site in skin, pain in extremities, application site pain, and application site erythema. No one participant has drug-related problems that caused dropout or death.

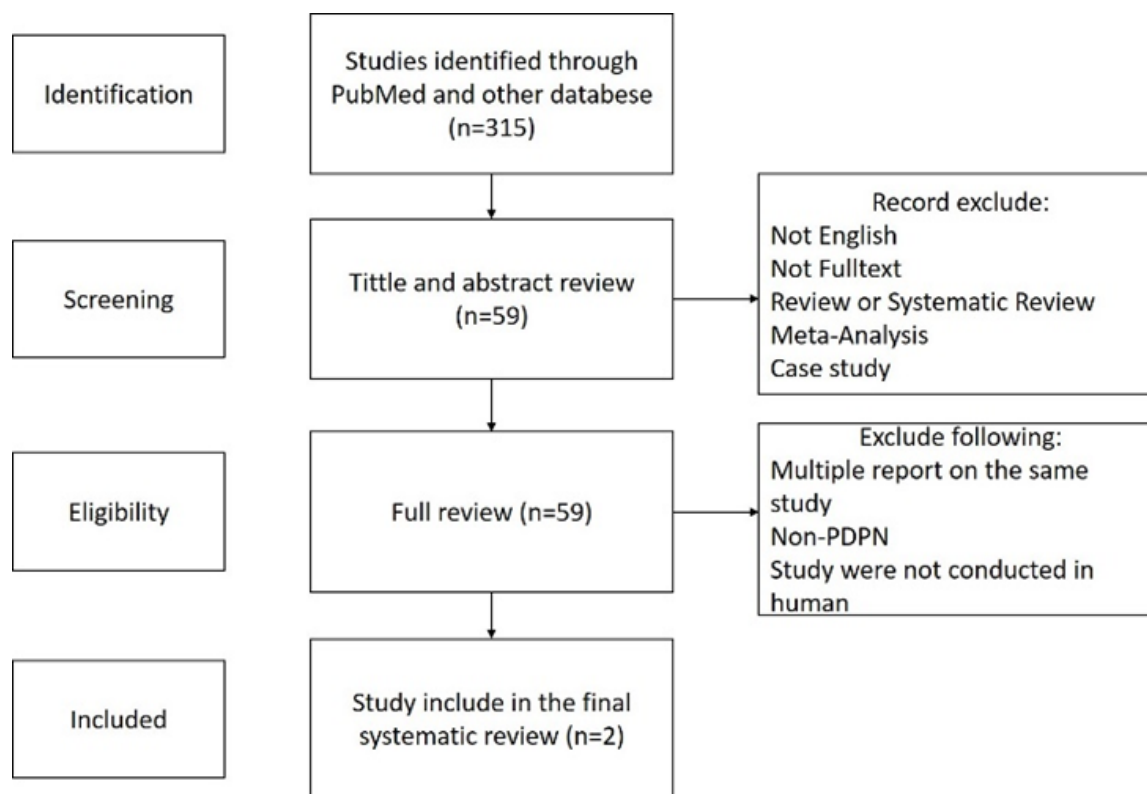


Figure 1. Flowchart of article screening and eligibility

Table 1. Characteristic of included studies.

Study (Reference number)	Country	Participants (Sex, n(%))		Age (Mean±SD)		Duration PDPN, years		Pain medication before study (n, (%))	
		Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Simpson <i>et al</i> (14)	US	183 (101) (55.2%) male and 82 (44.8%) female)	186 (114) (61.3%) male and 72 (38.7%) female)	62.0 (10.8)	63.9 (10.6)	5.7 (4.0)	5.8 (4.0)	101 (55.2%) use analgesics agents, 82 (44.8%) anti-epileptic drugs, 41 (22.4%) anti-inflammatory/antirheumatic drugs, 45 (24.6%) topical joint/muscular pain products	90 (48.4%) use analgesics agents, 71 (38.2%) anti-epileptic drugs, 46 (24.7%) anti-inflammatory/antirheumatic drugs, 46 (24.7%) topical joint/muscular pain products
Vinik <i>et al</i> (15)	Europe	155 (71) (45.8%) male and 84 (54.2%) female)	156 (74) (47.4%) male and 82 (52.6%) female) for use capsaicin patch 8% in 30 minutes and 157 (79) (50.3%) male and 78 (49.7%) female) for use capsaicin patch 8% in 60 minutes	59.1 (10.3)	60.9 (10.9) in group of participant with capsaicin patch 8% for 30 minutes and 61.0 (10.3) in group of participant with capsaicin patch 8% for 60 minutes	4.4 (3.6)	4.1 (3.7) in group of participant with capsaicin patch 8% in 30 minutes and 4.4 (3.9) in group of participant with capsaicin patch 8% in 60 minutes	79 (51%) use pain medication with 59 (38.1%) use analgesics agents, 52 (33.3%) anti-epileptic drugs, 24 (15.5%) psycholeptics drugs, 17 (11.0%) anti-inflammatory/antirheumatic drugs, 15 (9.7%) topical joint/muscular pain products	70 (44.9%) in group of participant with capsaicin patch 8% for 30 minutes and 71 (45.2) in group of participant with capsaicin patch 8% for 60 minutes use pain medication with 56 (35.9%) and 54 (34.4%) use analgesics agents, 44 (28.2%) and 49 (31.2%) anti-epileptic drugs, 22 (14.1%) and 19 (12.1%) psycholeptics drugs, 14 (9.0%) and 12 (7.6%) anti-inflammatory/antirheumatic drugs, 14 (9.0%) and 11 (7.0) topical joint/muscular pain products

Table 2. Characteristic intervention of the included studies

Study (Reference number)	Type of study	Type of Intervention (dosage)		Duration of study	Pain medication during study (N,%)	
		Control	Intervention		Control	Intervention
Simpson <i>et al</i> (14)	Randomized controlled trial	Placebo patch	Capsaicin patch 8% (30 minutes)	12 weeks	142 (76.3%) with 107 (57.5%) use analgesic agents, 72 (38.7%) anti-inflammatory/antirheumatic drugs, 56 (30.1%) topical joint/muscular pain products	131 (71.6%) with 105 (57.4%) use analgesic agents, 82 (44.8%) antiepileptic, 40 (21.9%) anti-inflammatory/antirheumatic drugs, 43 (23.5%) topical joint/muscular pain products
Vinik <i>et al</i> (15)	Randomized controlled trial	Standard of care	Standard care+Capsaicin 8% patch (30 and 60 minutes)	52 weeks	107 (69.0%) use pain medication with 81 (52.3%) use analgesics agents, 73 (47.1%) antiepileptic drugs, 29 (18.1%) topical joint/muscular pain products, 30 (19.4%) anti-inflammatory/antirheumatic drugs, 40 (25.8%) psycholeptics drugs, 18 (11.6%) stomatological preparations, 21 (13.5%) psychoanaesthetics, and ophthalmologicals	98 (62.8%) in group of participant with capsaicin patch 8% for 30 minutes and 105 (66.9%) in group of participant with capsaicin patch 8% for 60 minutes use pain medication with 79 (50.6%) and 84 (53.5%) use analgesics agents, 54 (34.6%) and 57 (36.3%) antiepileptic drugs, 30 (19.2%) and 35 (22.3%) topical joint/muscular pain products, 29 (18.6%) and 35 (22.3%) anti-inflammatory/antirheumatic drugs, 24 (15.4%) and 22 (14.0%) psycholeptics drugs, 18 (11.5%) and 22 (14.0%) stomatological preparations, 16 (10.3%) and 6 (3.8%) psychoanaesthetics, and 15 (9.6%) and 20 (12.7%) ophthalmologicals.

Table 3. Outcome measure and result of the included studies

Study (Reference number)	Duration of study	Objective outcome		Result		Adverse event
		Primary outcome	Secondary outcome	Primary outcome	Secondary outcome	
Simpson <i>et al</i> (14)	12 weeks	Daily pain score from The Numeric Pain Rating Scale (NPRS) according to the Brief Pain Inventory (BPI)-Diabetic Neuropathy (BPI-DN).	Sleep interfere from NPRS, Patient Global Impression of Change, the Self-Assessment of Treatment II questionnaire for treatment satisfaction, EuroQol	↓ Average daily pain score from 2-8 weeks in intervention group	Intervention group has modest improvement of sleep interfere, more patient being "very much improvement" and "much improvement" from Patient Global Impression of Change, improvement of pain and life aspects from Self-Assessment of Treatment II questionnaire but no notable difference in EuroQol	There is more adverse event in intervention group (N=87 (46.8%)) than control group (N=62 (33.9%)) including burning sensation in patch site in skin, pain in extremities, and application site pain.
Vinik <i>et al</i> (15)	52 weeks	Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN)	Utah Early Neuropathy Scale (UENS), sensory perception and reflex testing	↓ QOL-DN	↓ UENS and more improvement of sensory perception in 60 minute-capsaicin 8% patch	There is more adverse event in intervention group (N=105 (67.3%)) in 30-minutes capsaicin 8% patch group and N=109 (69.4%) in 60-minutes capsaicin 8% patch group than control group (N=75 (48.4%)) including application site pain and application site erythema

DISCUSSION

This review focuses on assessing the effectiveness of using the capsaicin 8% patch for pain relief in PDPN patients. Although there have been several studies comparing the use of capsaicin 8% patch to relieve pain in PDPN patients with the comparison with other pain medication, studies that focus on the effectiveness of using the capsaicin 8% patch are still not many.¹³ Although the outcome measurement performed for each study were different, all studies showed the effect of capsaicin 8% patch to reduce the effect of pain in PDPN patients.^{14,15}

Subjective measures of the quantity of pain and impact on patients are key to pain management, although current assessments lack reliability and risk of bias due to the subject's ability to perceive pain differently.¹⁶ The use of the NPRS as the primary outcome has been widely used to assess the mean pain score during 24 hours of treatment.^{11,17} Although pain assessment is subjective, the use of pain scores is useful for screening non-specialists to identify pain and response to treatment used.¹⁸ Measurement of the mean daily pain value of PDPN patients with the capsaicin 8% patch showed that the effect of intervention with the capsaicin 8% patch had an effect on relieving pain felt by the patient.

Measuring the quantity of pain can also be done to determine the effect of pain on the patient's quality of life.¹⁹ Pain in PDPN patients is characterized by chronic pain which in the long term can influence the quality of life of diabetic patients.²⁰ Therefore, assessment of patient-related outcomes (PROs) is needed to evaluate health services and medical treatment decisions needed for pain management in PDPN patients.²¹ Choosing a good treatment by doctors can help PDPN patients reduce the burden of disease and thus improve the patient's quality of life.²² For both studies, the capsaicin 8% patch was used for both the short term (12 weeks) and the long term (52 weeks).^{14,15}

The use of capsaicin substances can also improve nerve function and reduce

pain in neuropathic pain.²³ Chronic pain that occurs in PDPN is mediated by activation of the transient receptor potential vanilloid subtype 1 (TRPV1), a Ca²⁺ - permeable ion channel, which is expressed on C and A δ nociceptive sensory nerves.^{24,25} TRPV1 is a capsaicin receptor that works to de-functionalize nerve fibers through influx Ca²⁺ overload, causing mitochondrial dysfunction as well as reducing nerve fiber function.¹² In several studies, the effect of capsaicin at high doses showed better analgesic effects than low doses (8% vs 0.025% and 0.075%).²⁶ Although the pathophysiology of PDPN is still unclear, this existing study shows that capsaicin can help improve nerve function in PDPN patients.²⁷

This review has several limitations. First, a literature search that focused on studies reported in English, limited other studies that were not in English. Although this condition is prone to bias in literature searches, most studies regarding the use of capsaicin 8% patch in PDPN patients were conducted in English-speaking populations and published reports in English. Therefore, this review does not include studies published in other languages.

In addition, outcome measures used subjective assessments, namely assessments based on the level of pain felt by the patient. As previously discussed, the pain assessment for each person is different, making it difficult to validate the level of pain felt by the patient. The assessment of pain status influenced the pain management prescribed to the patient, in which the patient was also given pain medication throughout the study, thereby influencing the assessment of the level of pain that the patient felt.²⁸ The assessment of pain by the patient also influences the patient's perception of the quality of life-related to health, so it becomes a focus regarding the choice of patient therapy.^{29,30}

Another limitation is the limited literature search in the last 10 years, where the limitation of the search relates to the use of capsaicin 8% patch which was approved by the Food and Drug Association (FDA) in 2009 for use as a long-term pain reliever in

cases of post-herpetic neuralgia (PHN).³¹ Restrictions on the literature search were undertaken aimed at reducing the risk of damage and insecurity from drugs which may increase the risk of adverse side effects. However, restricting the literature search regarding the risk of damage and insecurity of the study carried out can risk positive bias because researchers want to report positive effects of their study that lead to misinformation consequences among researchers, physicians and policymakers.³² In this review, the authors minimized the risk of bias by including all adverse events reported in the study.

CONCLUSION

The use of capsaicin patch 8% can be a pain reliever and improve the quality of life in PDPN patients. Further studies in a wider population are needed to assess the effectiveness and safety of using the 8% capsaicin patch as a pain reliever and its effect on improving nerve for PDPN patients.

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