



**Clinical Update:  
Utilizing Topical Analgesics for  
Diabetic Peripheral Neuropathy**

Charles E. Argoff, MD

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**Learning Objectives**

- Describe the pathogenesis and the epidemiology surrounding diabetic peripheral neuropathy (DPN)
- Summarize the clinical presentation of DPN
- Define painful diabetic neuropathy (PDN)
- Identify the unmet needs and daily occupational impact this disease state has on patients' lives
- Review nonopioid topical treatment options available for DPN, along with their safety, efficacy, and benefit



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### Clinical Presentation of DPN

- Diabetic peripheral neuropathy is a common complication of both type 1 and 2 diabetes and is the leading cause of lower limb amputation
- DPN can put an individual at risk for injuries to feet and toes and lead to development of ulcers, wounds, and chronic infections in the feet

www.hopkinsmedicine.org/health/conditions-and-diseases/diabetes/diabetic-neuropathy-nerve-problems.



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### Signs and Symptoms of DPN

- Paresthesias such as tingling, burning, or prickling
- Numbing pain of the hands, feet, and legs
- Muscles in hands and feet tend to feel weaker
- Extreme sensitivity to touch
- Insensitivity to pain or temperature changes
- Loss of balance or coordination
- Difficulty walking on uneven surfaces

www.hopkinsmedicine.org/health/conditions-and-diseases/diabetes/diabetic-neuropathy-nerve-problems.



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### Painful Diabetic Neuropathy (PDN)

- Painful diabetic neuropathy is a phenotype of DPN that affects up to 1/3 of the diabetic population
- PDN can cause significant reductions in quality of life and increased anxiety and depression, sleep impairment, and greater gait variability
- PDN is more common in patients with type 2 diabetes than in patients with type 1 diabetes
- Pain is usually bilateral and occurs in the lower extremities; upper extremities may be affected in some cases

Yoon et al. J Diabetes Metab. 2013;Suppl 10:005. doi:10.4172/2155-6156.S10-005.



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### PDN (Continued)

- Pain tends to be worse at night and when patient is stressed and fatigued
- Pain is usually described as hot, burning, electric, jolts, sharp, tingling, and pins and needles
- It is believed that increased levels of advanced glycation end products (AGE) and protein kinase C (PKC) due to prolonged hyperglycemia are thought to be involved in peripheral nerve damage

**PainWeek** Yoon et al. J Diabetes Metab. 2013;Suppl 10:005. doi:10.4172/2155-6156.S10-005.

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### Facts & Stats

Neuropathic pain is often underdiagnosed or undiagnosed and can be left untreated for years, forcing patients to live with chronic pain<sup>5</sup>

35 million Americans have diabetes

5 million have PDPN

More than 50% have unresolved pain

More than 50% of patients with PDPN have unresolved pain<sup>1-4</sup>

**PainWeek** PDPN: painful diabetic peripheral neuropathy. 1. Iqbal et al. Clin Ther. 2016;40(6):859-850. 2. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. 2019. 3. Gore et al. J Pain Symptom Manag. 2005;30(4):374-380. 4. Gore et al. J Pain. 2006;7(12):892-900. 5. Mick et al. Curr Med Res Opin. 2014;30(7):1357-1366.

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### Epidemiological Studies Show the Humanistic Burden of DPN



- Pain impacts the QOL and daily activities for many patients with PDPN<sup>1</sup>
- 43% of those studied received prescription medications for sleep disturbances, anxiety and/or depression.<sup>2</sup> Up to 96% had moderately or severely affected sleep.<sup>3,4</sup>
- Almost 22% of the study population had a history of depression<sup>5</sup>

**PainWeek** Allerman et al. Diabetes Res Clin Pract. 2015;109(2):215-225. 2. Tolle et al. Diabetes Complicat. 2008;20(1):26-33. 3. Thomas et al. Diabetologia. 2012;55(Suppl 1):S11881. 4. Baron et al. Pain. 2009;146(1):34-40. 5. Hall et al. Pain. 2006;122(1-2):156-162.

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### PDPN Treatment Needs to Improve

- Considerations when treating PDPN:
  - Comorbidities<sup>1</sup>
  - Polypharmacy<sup>1</sup>
  - Compliance/medication adherence<sup>2</sup>
  - Tolerability<sup>2</sup>
- First line options for DPN are often associated with<sup>3,4</sup>:
  - Inadequate therapeutic or clinical response
  - Long titration periods
  - Kinetic reactions
  - Drug-drug interactions
  - The potential of abuse, withdrawal, dependency



1. Gore et al. *J Pain*. 2006;7(12):992-999. 2. Chazardo et al. *Clin Therapeut*. 2012;34(3):605-613.  
 3. Alam et al. *Drugs*. 2002;64(4):363-384. 4. Ellis. *BMC Health Serv Res*. 2015;15:119.

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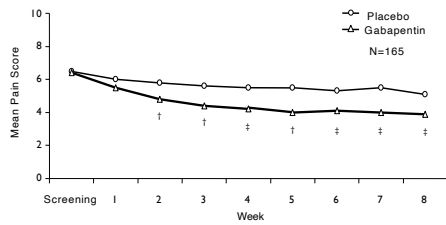
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### Gabapentin in the Treatment of Painful Diabetic Neuropathy\*



\*Not approved by FDA for this use  
 † P < 0.01; ‡ P < 0.05



Adapted from Backonja et al. *JAMA*. 1998;280(21):1831-1836.

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### Evidence-Based Medicine

▪ Evidence-based medicine (EBM) has been defined as "the conscientious, explicit and judicious use of current best evidence in **making decisions about the care of individual patients**"

Sackett. *BMJ*. 1996;312:71-72.

▪ Evidence-based medicine: The judicious use of the best current available scientific research in making decisions about the care of patients. Evidence-based medicine (EBM) is intended to **integrate clinical expertise** with the research evidence and patient value



www.medterms.com/script/main/art.asp?articlekey=33300.

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**What do we mean by mechanism-based?**

- Mechanism of underlying disease associated with neuropathic pain (NeP)?
- Mechanism of NeP associated with a particular disease?
- Mechanism of pharmacological agent used to treat NeP?
- Can these be coordinated/matched?



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**Drug Mechanisms of Action**

- Gabapentinoids
- Ketamine
- TCA/SNRI
- Opioids and opioids with NRI
- Sodium channel blockers
- Cannabinoids
- Botulinum toxin
- Capsaicin



Barricaster et al. Annu Rev Pharmacol Toxicol. 2020.60:257-274.

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**Clinical Syndromes and Anticonvulsant Use**

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|---|---|
| <ul style="list-style-type: none"> <li>▪ Migraine           <ul style="list-style-type: none"> <li>- Topiramate</li> <li>- Divalproex sodium</li> </ul> </li> <li>▪ Postherpetic neuralgia           <ul style="list-style-type: none"> <li>- Gabapentin</li> <li>- Pregabalin</li> </ul> </li> <li>▪ Diabetic neuropathy           <ul style="list-style-type: none"> <li>- Carbamazepine</li> <li>- Phenytoin</li> <li>- Gabapentin</li> <li>- Lamotrigine</li> <li>- Lacosamide</li> <li>- Pregabalin</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>▪ Spinal cord injury           <ul style="list-style-type: none"> <li>- Pregabalin</li> </ul> </li> <li>▪ HIV-associated neuropathy           <ul style="list-style-type: none"> <li>- Lamotrigine</li> </ul> </li> <li>▪ Trigeminal neuralgia           <ul style="list-style-type: none"> <li>- Carbamazepine</li> <li>- Lamotrigine</li> <li>- Oxcarbazepine</li> </ul> </li> <li>▪ Fibromyalgia           <ul style="list-style-type: none"> <li>- Pregabalin</li> </ul> </li> <li>▪ Central poststroke pain           <ul style="list-style-type: none"> <li>- Lamotrigine</li> </ul> </li> </ul> |
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### Treating Neuropathic Pain Associated with DPN Is Not Equivalent to Treating an Infection

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07/15/10 1700 (COLLECTION TIME) 07/15/10 1733 (IN LAB TIME)
-# BACTERIAL CULTURE          FUNG ON 07/15/10 1517
- SPECIMEN TYPE              MURID
- SOURCE-BODY SITE           SWAB
- ORGANISM 1                 META STREPTOCOCCUS GROUP B
- QUANTIFICATION             MANY
- ORGANISM 2                 STAPHYLOCOCCUS LUGDUNENSIS
- QUANTIFICATION             MODERATE
- SENSITIVITY SET-UP DATE:   07/20/10
- ORGANISM 3                 CORYNEBACTERIUM SPECIES
- QUANTIFICATION             MODERATE
- MIC in mcg/ml             COST7  ORG 2
- NORMAL ADULT IV DOSAGE    DAY#
- CLINDAMYCIN                $ 24  <=0.5 S
- DOXYCYCLINE                $ 32  <=1 S
- ERYTHROMYCIN               $ 35  <=0.5 S
- OXACILLIN                  $ 70  <=0.5 S
- PENICILLIN                 $ 38  0.06 S
- STEPHENIN                  $ 33  <=0.5 S
- VANCOMYCIN                 $ 21  1 S
Erythromycin Susceptible STAPHYLOCOCCUS LUGDUNENSIS
are susceptible to azithromycin and clarithromycin.
Oxacillin-susceptible staphylococci are
susceptible to cefazolin, cephalixin and ceftriaxone.
    
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### Current Pharmacotherapy of Neuropathic Pain Associated with DPN

- TCA or SNRI antidepressant agents
- Na+ blocker anticonvulsants
- Ca2+ modulating anticonvulsants
- Tramadol
- Opioids
- TRPV1 topical agents
- Local anesthetic topical agents
- Botulinum toxin



Barrister et al. Annu Rev Pharmacol Toxicol. 2020;60:257-274.

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### TCA Antidepressant Agents

- Numerous studies have demonstrated the benefit of TCA agents (amitriptyline, nortriptyline) for NeP
- NNT ranges from 3-4.4
- The evidence is rated as strong and these are considered first line agents
- Common side effects include somnolence, constipation, dry mouth



Barrister et al. Annu Rev Pharmacol Toxicol. 2020;60:257-274.

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### SNRI Antidepressant Agents

- Multiple studies demonstrate the analgesic benefit in NeP
- NNT ranges from 5.2-8.4
- The evidence is rated as strong
- Nausea is a common side effect especially for duloxetine

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol*. 2020;60:257-274.

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### Ca<sup>2+</sup> Modulating Anticonvulsants

- Multiple studies demonstrate the analgesic benefit of these agents for NeP
- Pregabalin is considered a first line agent with NNT ranging from 6.5-9.4
- Gabapentin is considered a first line agent with NNT ranging from 5.9-9.1
- Side effects include somnolence, dizziness and weight gain
- Recent labeling changes point out the enhanced risk of respiratory depression when used with opioids

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol*. 2020;60:257-274.

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### FDA-Approved Intrathecal Analgesics with Different Mechanisms

Morphine	Ziconotide
<ul style="list-style-type: none"> <li>▪ <math>\mu</math>-opioid receptor agonist</li> <li>▪ Most serious adverse event are respiratory depression               <ul style="list-style-type: none"> <li>– Risk increased with other agents that depress the central nervous system (eg, benzodiazepines)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▪ N-type Ca<sup>2+</sup> channel blocker</li> <li>▪ Most serious adverse events are neurocognitive               <ul style="list-style-type: none"> <li>– Confusion, dizziness, hallucinations, etc</li> <li>– Urinary retention also can lead to treatment discontinuation</li> </ul> </li> </ul>

**PainWeek** Colley et al. *Anesthesiology*. 2009;111(4):881-891. Over et al. *Neuromodulation*. 2012;15(6):436-466. Page et al. *Neuromodulation*. 2014;17(4):354-372. Weisler et al. *J Pain Symptom Manage*. 2009;37(3):363-372.

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### Opioids

- Opioids have demonstrated benefit in multiple neuropathic pain conditions including neuropathic pain associated with diabetic peripheral neuropathy
- NNT ranges from 3.4-5.8
- Tapentadol ER is specifically FDA approved for neuropathic pain associated with diabetic peripheral neuropathy when an around the clock opioid is considered appropriate
- The evidence for their benefit is considered weak and opioids are considered third line agents
- Side effects include constipation, nausea, emesis, pruritus

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol*. 2020;60:257-274.

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### Tramadol

- The evidence for the use of tramadol in NeP is weak
- NNT ranges from 3.6-6.7
- Tramadol is considered a second line agent for NeP
- Tramadol has tricyclic like activity and its metabolite has weak mu receptor activity
- Side effects include nausea, constipation, dizziness, and dry mouth

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol*. 2020;60:257-274.

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### Botulinum Toxin

- Multiple animal studies and/or evaluations of known pain models in healthy subjects, have demonstrated that botulinum toxin (specifically onabotulinum toxin A) may result in analgesia independent of its effect on muscle
- Multiple single center RTC have evaluated the long term efficacy of subcutaneous or intradermal injections (50-200 units) in PHN, painful diabetic neuropathy of neuropathic pain following traumatic nerve injury
- A multicenter double-blind RTC has evaluated the effect of 2 subcutaneous treatments of onabotulinum toxin A, 12 weeks apart in 66 patients with PHN. Post-traumatic neuropathy or painful polyneuropathy- treatment resulted in improved average pain intensity compared to placebo and the second injection provided greater benefit- allodynia and paroxysmal pain was specifically helped
- The NNT ranges from 1.5-2.4
- Adverse events include local pain

**PainWeek** Bouhassira et al. *Pain*. 2018;159(2018):576-582.

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### Gabapentinoids

- Central sensitization may be lessened by medications that act on calcium channels
- Pregabalin and gabapentin are used commonly for NeP- their exact mechanism is still unknown
- Gabapentin can act directly on the spinal cord to suppress nociception and have supraspinal mechanisms as well
- The anti-allodynic effects of these drugs requires the presence of the alpha 2 delta agonist 1 subunit of the voltage-gated calcium channels

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol* 2020.60:257-274.

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### Ketamine

- Ketamine may attenuate central sensitization via NMDA receptor antagonism
- Ketamine has been helpful for some people with PDN and CRPS but has not been shown to be as helpful in PHN
- The role of metabotropic glutamate receptor ligands and glutamate transporters as targets for the treatment of NeP is under active investigation

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol* 2020.60:257-274.

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### TCA/SNRIs

- Medications that act as reuptake inhibitors of norepinephrine and serotonin are believed to modulate descending control systems
- Medications that act on both norepinephrine and serotonin work better than those which act on serotonin only
- A few studies have suggested that TCAs may also have NMDA antagonist properties as well as act as a sodium channel blocker

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol* 2020.60:257-274.

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### Cannabinoids

- These agents act on CB1 and CB2 receptors
- These receptors are located on neuronal as well as other tissues with the PNS and CNS
- Only modest analgesic effects have been noted through activation of these targets
- It remains unclear whether these agents are effective in NeP

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol* 2020;60:257-274.

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### Botulinum Toxin

- Known benefit in chronic migraine
- Botulinum toxin DOES NOT only inhibit the release of acetylcholine
- In migraine, the effect is believed to be via a block of peripheral CGRP release
- However, no effect on peripheral CGRP levels has been seen in NeP

**PainWeek** Barrister et al. *Annu Rev Pharmacol Toxicol* 2020;60:257-274.

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### Sodium Channel Blockers

- Sodium channel blocking drugs including lidocaine and other local anesthetics likely act on peripheral pain generating mechanisms
- Damaged peripheral nerves are known to demonstrate altered sodium channel function; this may be the basis for using lidocaine, carbamazepine as well as oxcarbazepine
- Multiple studies and guidelines have recommended the use of a topical lidocaine patch system for the management of neuropathic pain associated with diabetic peripheral neuropathy

**PainWeek** Quin et al. *Postgrad Med* 2020; Jan;132(1): 28-36.  
Barrister et al. *Annu Rev Pharmacol Toxicol* 2020;60:257-274.

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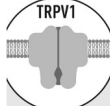
### Novel Targets for Treating Pain and Disease

Discover how heat, cold, and touch trigger our nervous system

Implications in chronic conditions

Important for many physiological functions


Targeting specific ion channels when developing novel drug treatments



**TRPV1**

**Temperature Heat Pain**

- Core body temperature
- Inflammatory pain
- Neuropathic pain
- Protective reflexes



**PIEZO2**

**Touch Proprioception**

- Mechanical pain
- Blood pressure
- Urination
- Respiration
- Skeletal remodeling

The Nobel Prize in Physiology or Medicine 2021. NobelPrize.org. Nobel Prize Outreach AB. 2021. Fri. 15 Oct 2021. <https://www.nobelprize.org/prizes/medicine/2021/summary>

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### Capsaicin: Highly Selective Agonist for TRPV1

Capsaicin is a highly selective agonist for the transient receptor potential vanilloid-1 receptor (TRPV1) found on nociceptive nerve fibers in the skin

**What is capsaicin? 1-5**

- Potent and highly selective agonist (or activator) for the TRPV1 channel
- Capsaicin activates the cell membrane receptor TRPV1, which causes an influx of Ca<sup>2+</sup> and Na<sup>+</sup> into nociceptors (sensory receptors for painful stimuli) within the epidermis<sup>2</sup>
- Continuous TRPV1 activation can lead to defunctionalization and recession of the nociceptors from the epidermis<sup>2,3</sup>

**What is TRPV1? 2-5**

- Transmembrane receptor-ion channel complex distributed throughout the CNS and PNS
- Preferentially expressed on sensory (nociceptive) nerve fibers – mainly C and Aδ fibers
- Important in pain perception – provides integrated responses to heat, acidic conditions, and endogenous inflammatory substances
- Detects harmful stimuli and conveys this information to CNS

CNS, central nervous system; PNS, peripheral nervous system.

1. QUTENZA<sup>®</sup> (capsaicin) 8% topical system. Prescribing Information. August 2021. 2. Anand et al. *Br J Anaesth*. 2011;107(4):490-502.

3. Blair. *Drugs*. 2019;79(14):1489-1500. 4. Buresse et al. *Drugs*. 2016;76(1):123-134.

5. Moran et al. *Br J Pharmacol*. 2018;175(12):2185-2203.

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### Topical Capsaicin

- The 8% capsaicin patch may be considered for peripheral neuropathic pain
- It is now FDA approved for PHN and neuropathic pain associated with diabetic peripheral neuropathy
- The NNT ranges from 7.4-18.8 BUT recent studies suggest patients who do not benefit from initial application may benefit from repeated application
- Side effects include local pain and erythema

Barnister et al. *Annu Rev Pharmacol Toxicol*. 2020;60:257-274.

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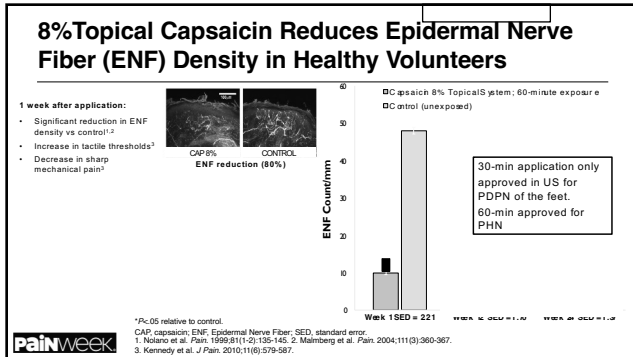
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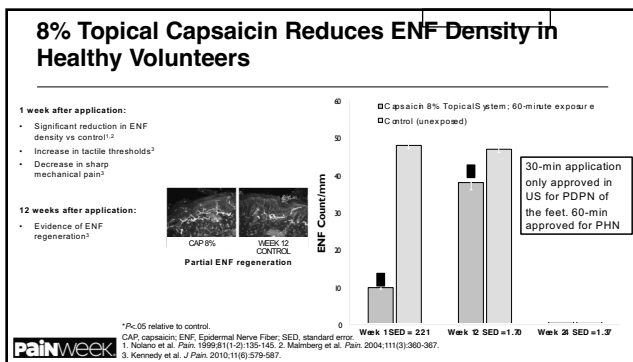
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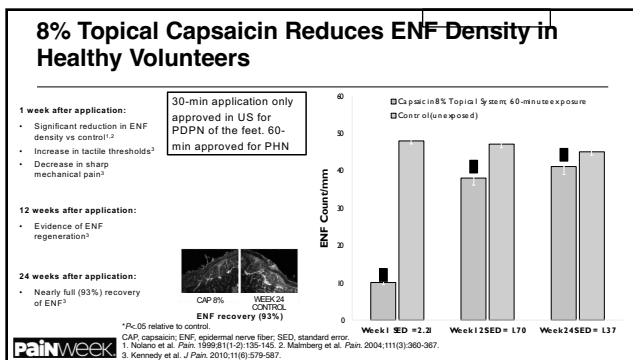
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### 8% Topical Capsaicin Dosing

PACE Study <sup>1,2</sup>	For Treating PDPN Patients <sup>3</sup>
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- 8% topical capsaicin was administered for 30 minutes in one treatment arm
- Patients in the 8% topical capsaicin arm could receive repeated treatments, at the investigator's discretion, no more than every 8 weeks\*, up to a total of 7 treatments over the 52 weeks of the study

- For PDPN, apply to up 4 topical systems for 30 minutes on feet
- Repeat every 3 months or as warranted by the return of the pain (not more frequently than every 3 months)

\*Treatment with 8% topical capsaicin may be repeated every three months (not more frequently than every three months) and is approved for a 30-minute treatment for patients with PDPN of the feet.

1. Vink et al. BMC Neurol 2016(1):16251-265. 2. Vink et al. JCMRO 2019;2(12):388-401. 3. QUTENZA® (capsaicin) 8% topical system Prescribing Information, August 2021.



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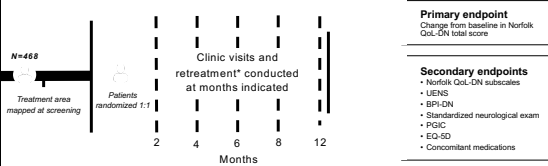
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### PACE Study Design<sup>1,2</sup>

Phase III, open-label, long-term safety study – QTZ + SOC vs SOC alone; 52-week follow-up



\*1-7 treatments with 8-week intervals. SOC was optimized for each patient at the discretion of each investigator and was assessed at clinic visits and on days 1 to 5 post-treatment, by completion of a rescue pain medication diary.  
BPI-DN: Brief Pain Inventory – Diabetic Neuropathy; EQ-5D: EuroQol 5-dimensions questionnaire; PDPN: painful diabetic peripheral neuropathy; PGIC: Patient Global Impression of Change; QoL-DN: Quality of Life Questionnaire – Diabetic Neuropathy; QTZ: QUTENZA; SOC: standard of care; UENS: Ulm Early Neuropathy Scale.  
1. Vink et al. BMC Neurol 2016(1):16251-265. 2. Vink et al. JCMRO 2019;2(12):388-401.



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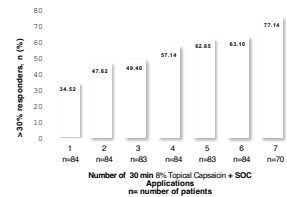
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### Response Rates with Repeated Applications in a 52-Week, Open-label Safety Study

Treatment with 8% topical capsaicin may be repeated every 3 months (not more frequently than every 3 months) and is approved for a 30-minute treatment for patients with PDPN of the feet.



- Patients in the 8% topical capsaicin arm could receive repeated treatments, at the investigator's discretion, no more than every 8 weeks, up to a total of 7 treatments over the 52 weeks of the study
- SOC medications were antidepressants, antiepileptics, and/or opioids were optimized for each patient in each study arm, at the investigator's discretion

Limitations: These results must be interpreted with caution. The open-label study was not designed for efficacy and may be confounded by evaluator bias, and results could represent chance findings. Furthermore, all patients who received QUTENZA also received a standard of care (SOC) treatment (including antidepressants, antiepileptics, and/or opioids) at the investigator's discretion.



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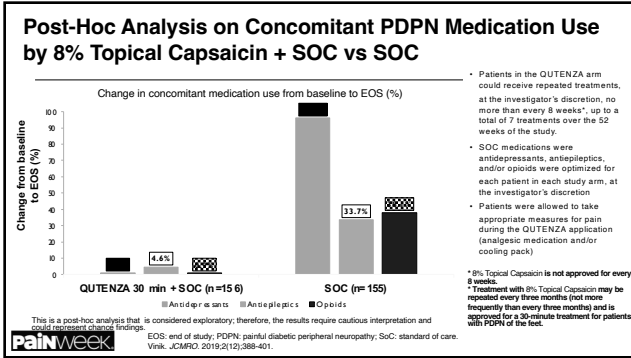
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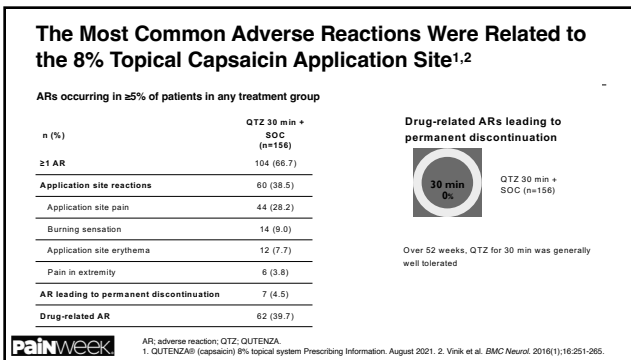
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### PACE Conclusions<sup>1,2</sup>

<p>8% topical capsaicin + SOC was well tolerated and was not associated with any negative functional or neurological safety consequences<sup>1</sup></p>	<p>8% topical capsaicin + SOC was not associated with deterioration in quality of life, PGIC, or patient satisfaction with treatment compared with SOC alone<sup>2</sup></p>
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PGIC: patient global impression of change; SOC: standard of care.  
1. Vink et al. BMC Neurol. 2018;18(1):251-265. 2. Vink et al. JCMRO 2019;2(12):388-401.

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### Tolerability Outcomes

#### Clinical meta-analysis

- Oral agents (pregabalin, gabapentin, and duloxetine) were associated with risk of somnolence, dizziness, and discontinuation because of adverse events compared with placebo
- The most common adverse reactions with 8% topical capsaicin are application site reactions (burning sensation, pain in extremity, application site pain)

**PainWeek** van Nooten et al. Clin Ther. 2017;39(4):787-822.

49

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### Conclusions

- Mechanism based pharmacological therapy for neuropathic pain associated with diabetic peripheral neuropathy is in development
- Future clinical trials should incorporate strategies to identify pain mechanisms with treatment mechanisms in an individual with neuropathic pain associated with diabetic peripheral neuropathy
- Topical therapies for the management of neuropathic pain associated with diabetic peripheral neuropathy have emerged as useful either alone or in combination with other agents

**PainWeek**

50

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