PainWeek

Clinical Update: Utilizing Topical Analgesics for Diabetic Peripheral Neuropathy

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Title & Affiliation

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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

PainWeek 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

PainWeek Yoo 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

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

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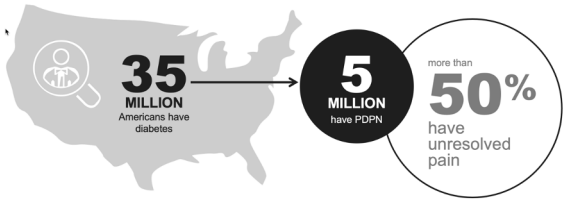
More than 50% of Patients with PDPN Have Unresolved Pain[1-4]



Neuropathic pain is often misdiagnosed or underdiagnosed, and can remain untreated over months or years[5]

PDPN: Painful Diabetic Peripheral Neuropathy.
1. Iqbal Z, et al. *Clin Ther.* 2018;40,(6):828-850. 2. International Diabetes Federation. IDF diabetes atlas, ninth edition. 2019. 3. Gore M, et al. *J Pain Symptl Manag.* 2005;30(4):374-385. 4. Gore M, et al. *J Pain.* 2006;7(12):892-900. 5. Mick G, et al. *Curr Med Res Opin.* 2014;30(7):1357-1366.

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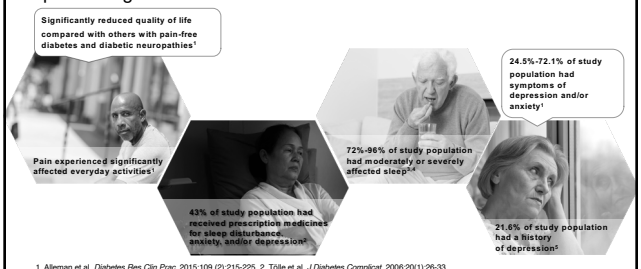
Humanistic Burden of DPN Has Been Shown in Epidemiological Studies



1. Alleman et al. *Diabetes Res Clin Prac.* 2015;109 (2):215-225. 2. Tölle et al. *J Diabetes Complicat.* 2006;20(1):26-33.
3. Thomas et al. *Diabetologia.* 2012;55(Suppl 1):S181. 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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There Is a Need to Improve PDPN Treatment

When treating patients with PDPN, it is important to consider:

Leading drugs prescribed as first-line are often associated with[3,4]:

- Inadequate therapeutic response
- Long titration periods
- Drug-drug interactions
- Potential for addiction, abuse, and withdrawal

PDPN: Painful Diabetic Peripheral Neuropathy.
1. Gore M. et al. *J Pain.* 2006;7(12):892-900. 2. Obando AO. et al. *Clin Therapeu.* 2012;34(3):605-613. 3. Alarcón U, et al. *Drugs.* 2020;80(4):363-384. 4. Ellis JJ. BMC Health Serv Res. 2015;15:159.

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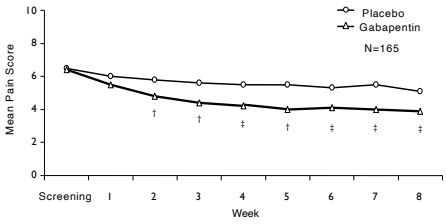
Gabapentin in the Treatment of Painful Diabetic Neuropathy*



*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

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

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Clinical Syndromes and Anticonvulsant Use

- Migraine
  - Topiramate
  - Divalproex sodium
- Postherpetic neuralgia
  - Gabapentin
  - Pregabalin
- Diabetic neuropathy
  - Carbamazepine
  - Phenytoin
  - Gabapentin
  - Lamotrigine
  - Lacosamide
  - Pregabalin
- Spinal cord injury
  - Pregabalin
- HIV-associated neuropathy
  - Lamotrigine
- Trigeminal neuralgia
  - Carbamazepine
  - Lamotrigine
  - Oxcarbazepine
- Fibromyalgia
  - Pregabalin
- Central poststroke pain
  - Lamotrigine

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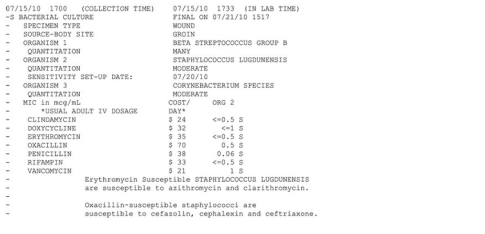
Treating Neuropathic Pain Associated with DPN Is Not Equivalent to Treating an Infection



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07/15/10  1700   (COLLECTION TIME)    07/15/10  1733  (IN LAB TIME)
-S BACTERIAL CULTURE                  FINAL ON 07/21/10 1517
-   SPECIMEN TYPE                     WOUND
-   SOURCE-BODY SITE                  GROIN
-   ORGANISM 1                        BETA STREPTOCOCCUS GROUP B
-    QUANTITATION                     MANY
-   ORGANISM 2                        STAPHYLOCOCCUS LUGDUNENSIS
-    QUANTITATION                     MODERATE
-    SENSITIVITY SET-UP DATE:         07/20/10
-  ORGANISM 3                        CORYNEBACTERIUM SPECIES
-    QUANTITATION                     MODERATE
-   MIC in mcg/mL                    COST/     ORG 2
-      *USUAL 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
-    RIFAMPIN                        $ 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, cephalexin 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

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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

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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

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Ca^{2+} 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

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FDA-Approved Intrathecal Analgesics with Different Mechanisms

Morphine	Ziconotide
▪ μ-opioid receptor agonist ▪ Most serious adverse event are respiratory depression –Risk increased with other agents that depress the central nervous system (eg, benzodiazepines)	▪ N-type Ca^{2+} channel blocker ▪ Most serious adverse events are neurocognitive –Confusion, dizziness, hallucinations, etc –Urinary retention also can lead to treatment discontinuation

PainWeek Coffey et al. *Anesthesiology.* 2009;111(4):881-891. Deer et al. *Neuromodulation.* 2012;15(5):436-466. Prager et al. *Neuromodulation.* 2014;17(4):354-372. Webster 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

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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

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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

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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

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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

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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

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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

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Bannister 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

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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

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Gudin et al. *Postgrad Med.* 2020 Jan;132(1): 28-36.
Bannister et al. *Annu Rev Pharmacol Toxicol.* 2020.60:257-274.

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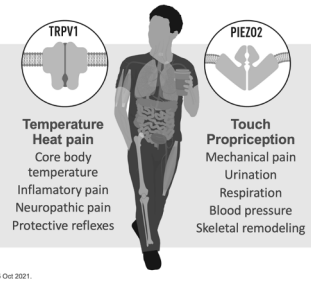
New targets to treat pain and disease

- Discovered how heat, cold, and touch trigger our nervous system
- Important for many physiological functions and implicated in chronic conditions.
- Developing new treatments targeting these ion channels to treat diseases.



Temperature
Heat pain
Core body temperature
Inflamatory pain
Neuropathic pain
Protective reflexes

Touch
Propriception
Mechanical pain
Urination
Respiration
Blood pressure
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: A Highly Selective Agonist for TRPV11

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 transient receptor potential vanilloid-1 (TRPV1) channel
- Capsaicin activates the cell membrane receptor TRPV1, which causes an influx of Ca^{2+} and Na+ into nociceptors (sensory receptors for painful stimuli) within the epidermis[2]
- Continuous TRPV1 activation can lead to defunctionalization and recession of the nociceptors from the epidermis[2,3]

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® (capsaicin) 8% topical system Prescribing Information. August 2021. 2. Anand et al. *Br J Anaesth*. 2011;107(4):490-502. 3. Blair. *Drugs*. 2018;78(14):1489-1500. 4. Burness 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

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

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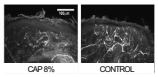
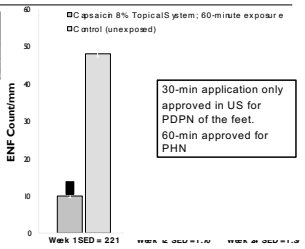
8%Topical Capsaicin Reduces Epidermal Nerve Fiber (ENF) Density in Healthy Volunteers

1 week after application:

- Significant reduction in ENF density vs control[1,2]
- Increase in tactile thresholds[3]
- Decrease in sharp mechanical pain[3]



ENF reduction (80%)



30-min application only approved in US for PDPN of the feet. 60-min approved for PHN

*$P<.05$ relative to control.
CAP, capsaicin; ENF, Epidermal Nerve Fiber; SED, standard error.
1. Nolano et al. *Pain*. 1999;81(1-2):135-145. 2. Malmberg et al. *Pain*. 2004;111(3):360-367.
3. Kennedy et al. *J Pain*. 2010;11(6):579-587.

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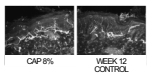
8% Topical Capsaicin Reduces ENF Density in Healthy Volunteers

1 week after application:

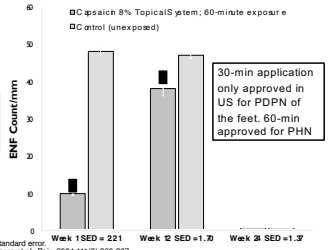
- Significant reduction in ENF density vs control[1,2]
- Increase in tactile thresholds[3]
- Decrease in sharp mechanical pain[3]

12 weeks after application:

- Evidence of ENF regeneration[3]



Partial ENF regeneration



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8% Topical Capsaicin Reduces ENF Density in Healthy Volunteers

1 week after application:

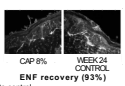
- Significant reduction in ENF density vs control[1,2]
- Increase in tactile thresholds[3]
- Decrease in sharp mechanical pain[3]

12 weeks after application:

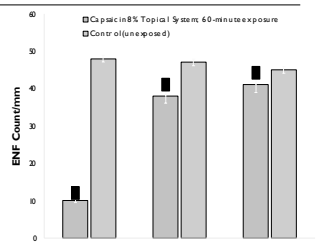
- Evidence of ENF regeneration[3]

24 weeks after application:

- Nearly full (93%) recovery of ENF[3]



ENF recovery (93%)



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Clinical Evidence of Safety and Efficacy of 8% Topical Capsaicin for Patients with PDPN

PHASE 3 TRIAL: STEP	PHASE 3 TRIAL: PACE	META ANALYSIS: VAN NOOTEN
Phase III PDPN 8% topical capsaicin vs placebo 12-week follow-up[1]	Phase III Safety Study PDPN 8% topical capsaicin with SoC vs SoC only 52-week follow-up[2,3]	Meta-analysis PDPN 25 randomized controlled trials, 8% topical capsaicin and SoC oral agents[4]

PDPN: painful diabetic peripheral neuropathy; SoC: standard of care.
1. Simpson et al. *J Pain*. 2017;18(1):42-53. 2. Vinik et al. *BMC Neur*. 2016;16(1):251-265. 3. Vinik et al. *JCMRO*. 2019;2(12):388-401.
4. van Nooten et al. *Clin Ther*. 2017,39(4);787-822.

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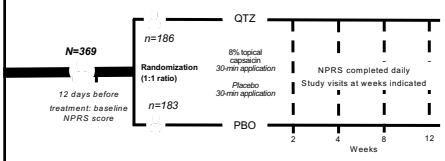
STEP Study Design

Phase III, randomized, double-blind trial; 8% topical capsaicin vs PBO; one 30-min application to feet only; 12-week follow-up



*(all patients could use opioid rescue medication up to 5 days after; no topical pain medications)**

Primary endpoint
Percentage change in NPRS as assessed over the previous 24 hours, according to question 5 of the BPI-DN from baseline to mean score over weeks 2-8

Secondary endpoints
- NPRS average daily pain score
- Response rates (30% and 50%)
- Change in sleep interference
- Time to treatment response
- PGIC
- EQ-5D

*Use of any oral, transdermal, or parenteral opioids, or topical pain medications including nonsteroidal anti-inflammatory drugs, menthol, methyl salicylate, local anesthetics, or capsaicin products on or near the affected areas where study drug was to be applied, was not permitted. Placebo refers to patch without capsaicin.
BPI-DN: Brief Pain Inventory – Diabetic Neuropathy; EQ-5D: EuroQol 5-dimensions questionnaire; NPRS: Numeric Pain Rating Scale; PDPN: painful diabetic peripheral neuropathy; PBO: placebo; PGIC: Patient Global Impression of Change; QTZ: QUTENZA.
Simpson et al. *J Pain*. 2017;18(1):42-53.

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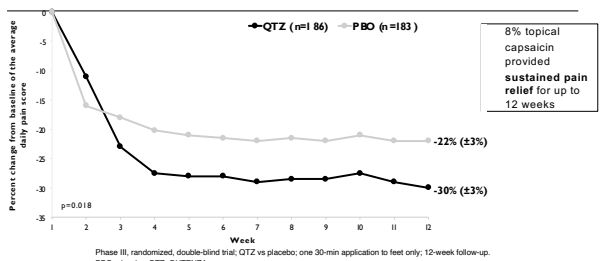
8% Topical Capsaicin Resulted in Greater Average Pain Reduction vs Placebo from Baseline to Week 12



8% topical capsaicin provided **sustained pain relief** for up to 12 weeks

Phase III, randomized, double-blind trial; QTZ vs placebo; one 30-min application to feet only; 12-week follow-up.
PBO: placebo; QTZ: QUTENZA
Simpson et al. *J Pain*. 2017;18(1):42-53.

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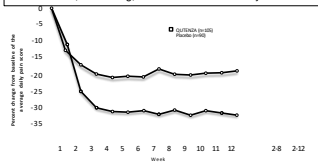
In a post-hoc analysis, when used alone, 8% topical capsaicin reduced the NPRS score over 12 weeks of treatment

Post-hoc analysis of efficacy **among participants NOT taking concomitant systemic medications** at the start of, and during, the 12 weeks of the study*



- This post-hoc analysis excluded patients taking concomitant medications for neuropathic pain associated with DPN.
- Those medications included anticonvulsants and non-SSRI antidepressants.
- Patients may have been taking other medications for pain associated with DPN

Limitation: This is a post-hoc analysis that is considered exploratory; therefore, the results require cautious interpretation and could represent chance findings.

Average change from baseline to between weeks 2-12 was -31% for QUTENZA vs 20% for placebo; the least-squares mean difference (QUTENZA – placebo) was -9.5%
*Baseline and last observation carried forward.

Simpson, D.M. et al. 2017.

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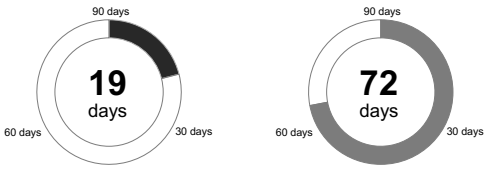
Patients Achieved ≥30% Pain Reduction More Quickly with 8% Topical Capsaicin vs Placebo

50% of patients achieving at least a 30% reduction in average daily pain after:



8% topical capsaicin **group**
(95% CI for median, 12.0-37.0)

PBO group
(95% CI for median, 19.0-NC)

CI: confidence interval; NC: not calculable; PBO: placebo; QTZ: QUTENZA.
Simpson et al. *J Pain*. 2017;18(1):42-53.

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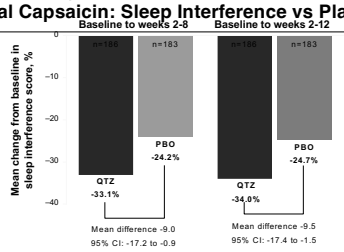
Additional Quality of Life Data
8% Topical Capsaicin: Sleep Interference vs Placebo



Limitation: Sleep interference was a secondary endpoint that was not powered for statistical analysis and should be considered descriptive only. Therefore, the results require cautious interpretation and could represent chance findings.

Results from the STEP Study (secondary endpoint)
CI: confidence interval; QoL: quality of life; QTZ: QUTENZA; PBO: placebo.
Simpson et al. *J Pain*. 2016;18(1):42-53.

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8% Topical Capsaicin Dosing

PACE Study[1,2]

- 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 Treating PDPN Patients[3]

- 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. Vinik et al. *BMC Neurol.* 2016(1);16:251-265. 2. Vinik et al. *JCMRO.* 2019;2(12);388-401. 3. QUTENZA® (capsaicin) 8% topical system Prescribing Information. August 2021.

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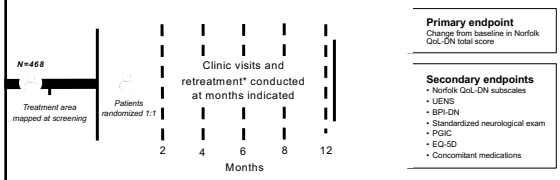
PACE Study Design[1,2]

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



Primary endpoint
Change from baseline in Norfolk QoL-DN total score

Secondary endpoints
- Norfolk QoL-DN subscales
- UENS
- BPI-DN
- Standardized neurological exam
- PGIC
- EQ-5D
- Concomitant medications

*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: Utah Early Neuropathy Scale.
1. Vinik et al. *BMC Neurol.* 2016(1);16:251-265. 2. Vinik et al. *JCMRO.* 2019;2(12);388-401.

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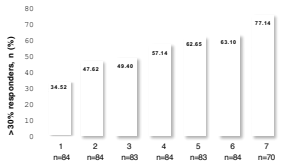
Response Rates with Repeated Applications in a 52-Week, Open-label Safety Study

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 DPN 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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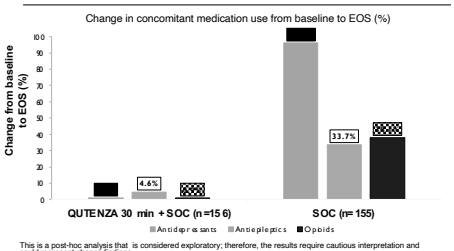
Post-Hoc Analysis on Concomitant PDPN Medication Use by 8% Topical Capsaicin + SOC vs SOC



This is a post-hoc analysis that is considered exploratory; therefore, the results require cautious interpretation and could represent chance findings.

- Patients in the QUTENZA 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
- Patients were allowed to take appropriate measures for pain during the QUTENZA application (analgesic medication and/or cooling pack)

* 8% Topical Capsaicin **is not approved for every 8 weeks.**
*** 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.**

EOS: end of study; PDPN: painful diabetic peripheral neuropathy; SoC: standard of care.
Vinik. *JCMRO.* 2019;2(12);388-401.

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The Most Common Adverse Reactions Were Related to the 8% Topical Capsaicin Application Site[1,2]

ARs occurring in ≥5% of patients in any treatment group

n (%)	QTZ 30 min + SOC (n=156)
≥1 AR	104 (66.7)
Application site reactions	60 (38.5)
Application site pain	44 (28.2)
Burning sensation	14 (9.0)
Application site erythema	12 (7.7)
Pain in extremity	6 (3.8)
AR leading to permanent discontinuation	7 (4.5)
Drug-related AR	62 (39.7)

Drug-related ARs leading to permanent discontinuation

QTZ 30 min + SOC (n=156)

Over 52 weeks, QTZ for 30 min was generally well tolerated

AR; adverse reaction; QTZ; QUTENZA.
1. QUTENZA® (capsaicin) 8% topical system Prescribing Information. August 2021. 2. Vinik et al. *BMC Neurol.* 2016(1);16:251-265.

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PACE Conclusions[1,2]

8% topical capsaicin + SOC was well tolerated and was not associated with any negative functional or neurological safety consequences[1]

8% topical capsaicin + SOC was not associated with deterioration in quality of life, PGIC, or patient satisfaction with treatment compared with SOC alone[2]

PGIC: patient global impression of change; SOC: standard of care.
1. Vinik et al. *BMC Neurol.* 2016;16(1):251-265. 2. Vinik 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.

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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

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