



Diabetic Foot

2023

November 30 – December 2

Gaylord Texan Resort &
Convention Center
Dallas, Texas

GDUDIABETICFOOT.COM



Patient-Centric Advancements for Painful and Non-Painful Diabetic Neuropathy

Supported by an educational grant from Averitas Pharma

Michael J. King, DPM, FACFAS

Upperline Health
Nashville, TN

Jason Snyder, DPM, FACFAS

Professional Podiatry Services of New York
New York, NY

Disclosures

- **Michael J. King, DPM, FACFAS**
Speakers Bureau: Averitas
- **Jason Snyder, DPM, FACFAS**
Consultant, Speakers Bureau: Acumed, Integra LifeSciences, Medtronic,
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Learning Objectives

- Review the prevalence and impact of painful diabetic neuropathy
- Review the landscape of technologies for management of painful and non-painful diabetic neuropathy
- Assess the clinical evidence for the use of capsaicin 8% patch application for pain relief and restoration of function via nerve fiber regeneration
- Correlate the loss of sensory nerve fibers or their protective function as major contributors to the development, recurrence, or nonhealing of diabetic ulcers

Diabetic Nerve Pain: Disease State, Epidemiology, and Treatment Challenges

The Diabetes Population Is Growing

2019

2030

The rate of painful DPN may continue to rise

28.7

MILLION

Americans have diagnosed diabetes

5.6

MILLION

have painful DPN

2.5

MILLION

have unresolved DPN pain with other first line therapies

39.7

MILLION

Americans projected to have diagnosed diabetes

10

MILLION

Americans projected to have painful DPN

DPN = diabetic peripheral neuropathy.

Iqbal Z, et al. *Clin Ther*. 2018;40,(6):828-850. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. 2019. Gore M, et al. *J Pain Symptom Manage*. 2005;30(4):374-385. Gore M, et al. *J Pain*. 2006;7(12):892-900. Backonja M, et al. *Lancet Neurol*. 2008;7:1106-1112 [published correction *Lancet Neurol*. 2009;8(1):31]. Rowley WR, et al. *Popul Health Manag*. 2017;20(1):6-12. Centers for Disease Control and Prevention. Accessed Nov. 16, 2023. [cdc.gov/diabetes/data/statistics-report/index.html](https://www.cdc.gov/diabetes/data/statistics-report/index.html). Lin J, et al. *Popul Health Metrics*. 2018;16(9):1-9. Pop-Busui R, et al. American Diabetes Association. Updated Feb. 2022. [ncbi.nlm.nih.gov/books/NBK580224](https://www.ncbi.nlm.nih.gov/books/NBK580224).

At What Point Does a Painful DPN Diagnosis Become Clear?

Symptoms of painful DPN can be difficult to describe, which makes it challenging to diagnose

- Reduced ability to work or perform daily activities
- Reduced quality of life
- Poor sleep
- Depressed mood
- Anxiety
- Morbidity

“

I would rather sit all day and do nothing because of the pain.

“

I gained weight because I stopped all physical activities.

“

Socks are uncomfortable. No matter the size, they feel tight and leave indentations.

“

I haven't seen my friends in months. I'm not able to leave home because my feet hurt so badly.

*Quotes are paraphrases of comments made by actual DPN patients

Alleman C, et al. *Diabetes Res Clin Pract.* 2015;109(2):215-225. Hall GC, et al. *Pain.* 2006;122(1-2):156-162. Tölle T, et al. *J Diabetes Complications.* 2006;20(1):26-33. Hicks CW. *Curr Diab Rep.* 2019;19(10):86. Thomas L, et al. *Diabetologia.* 2012;55(Suppl 1):S1181. Baron R, et al. *Pain.* 2009;146(1):34-40. Kiyani M, et al. *Neurol Clin Pract.* 2020;10:47-57.

DPN Is a Well-known Complication of Diabetes And the Most Common of All Neuropathic Pain

Patients with DPN suffer from nerve damage that results in sensory changes, which can be painful as the disease progresses.

- In painful DPN, there are alterations in neural signaling pathways, particularly those involving **C and A-delta fibers**, which are nociceptive fibers responsible for transmitting sensations associated with pain
- **TRPV1 receptors** located on C and A-delta fibers are normally activated in response to heat, control neuronal excitability, and relay pain signals from the periphery to the central nervous system
- In chronic pain states, **TRPV1 receptors are upregulated** on C and A-delta fibers which results in increased neuronal excitability and pain perception



NOBEL PRIZE 2021

CNS = central nervous system; TRPV1 = Transient receptor potential vanilloid 1.

Yang H, et al. *Front Endocrinol* (Lausanne). 2020;10:929. Feldman EL, et al. *Nat Rev Dis Primers*. 2019;5(1):42. Colloca L, et al. *Nat Rev Dis Primers*. 2017;3:17002.

Schreiber AK, et al. *World J Diabetes*. 2015;6(3). Aslam A, et al. *Pain Res Treat*. 2014;2014:412041.

Management of Painful and Non-Painful Diabetic Peripheral Neuropathy

Treatments of DPN

- Neuropathy treatments if painful

- Medications

- Vitamin B complex
- Gabapentin
- Duloxetine
- Pregabalin
- Tapentadol ER
- Capsaicin for foot DPN only

- Surgical

- Peripheral nerve release
- Spinal cord stimulation (SCS)

- Neuropathy treatments if NOT painful

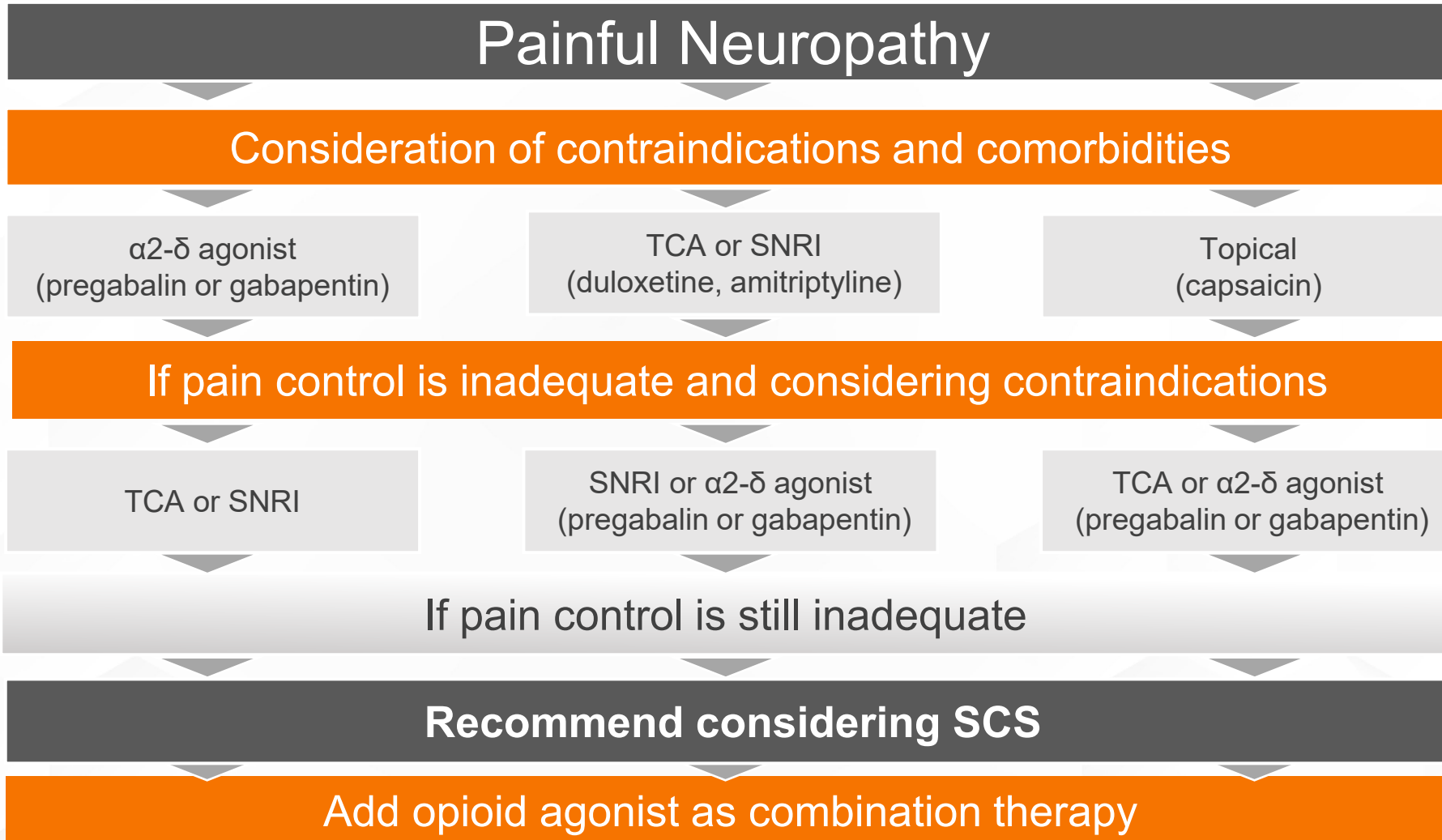
- Medications

- Vitamin B complex
- Tight glycemic control
- Capsaicin for foot DPN only

- Podiatric

- Shoe gear
- Wound care
- Reconstruction

DPN Treatment Algorithm



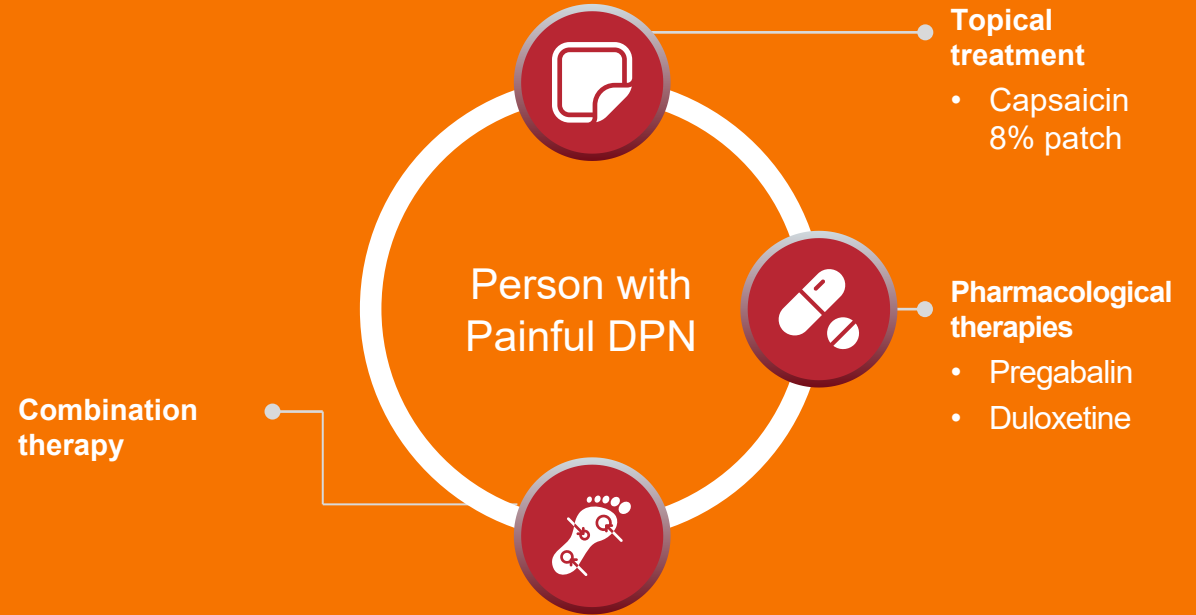
Up to
50%
of patients discontinue
initial treatment within
3 months

Clinical Evidence for the Use of High-Concentration Capsaicin

The Complexity of Painful DPN Demands a Personalized Treatment Plan

American Diabetes Association Clinical Compendium

American Association Clinical Endocrinology Guideline



Opioids are discouraged by both societies

Visual adapted from Fig. 8 included in the 2022 American Diabetes Association clinical compendium.

Pop-Busui R, et al. *Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy*. Arlington (VA): American Diabetes Association; February 2022. Blonde L, et al. *Endocr Pract*. 2022;28(10):923-1049.

High-Concentration Capsaicin 8% Topical To Treat Painful DPN of the Feet



Treatment Flexibility

- Can be used alone or in combination
- No known drug-drug interactions



Low Risk for Systemic Side Effects

- Localized
- Non-systemic
- Non-opioid
- No contraindications



Low Discontinuation Rates

- 1% of patients discontinued in clinical studies due to an adverse event



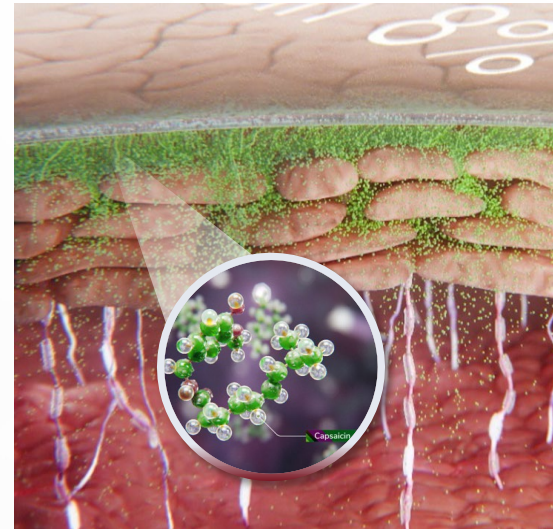
4 Treatments per Year

- 4 treatments per year may deliver significant and sustained pain relief

High-Concentration Capsaicin 8% Topical: Technology and Mechanism of Action

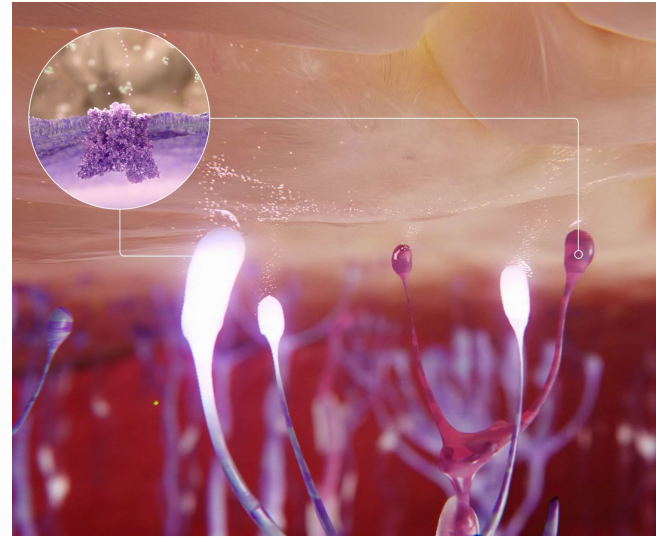
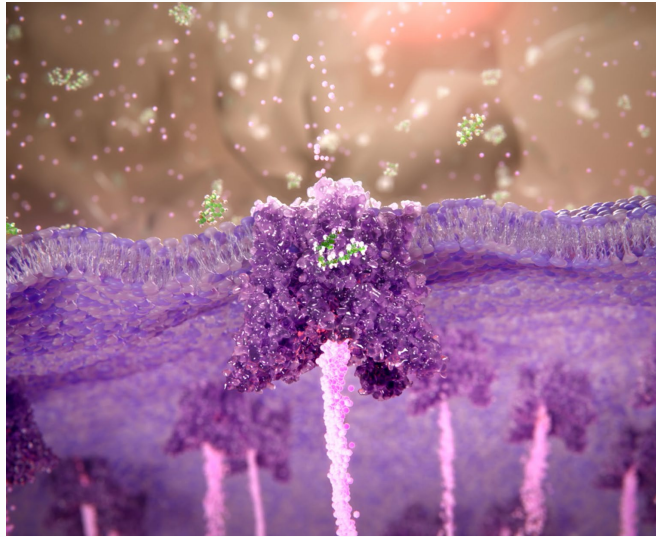
Forced Diffusion of High-Concentration Capsaicin Directly to the Site of Pain

- Matrix technology delivers high-concentration (8%) capsaicin in 30 minutes
- Even at high concentrations, capsaicin is unable to effectively penetrate the skin without matrix technology
- The matrix technology creates a **forced diffusion**, which drives high-concentration capsaicin through the epidermal layers directly to TRPV1 receptors



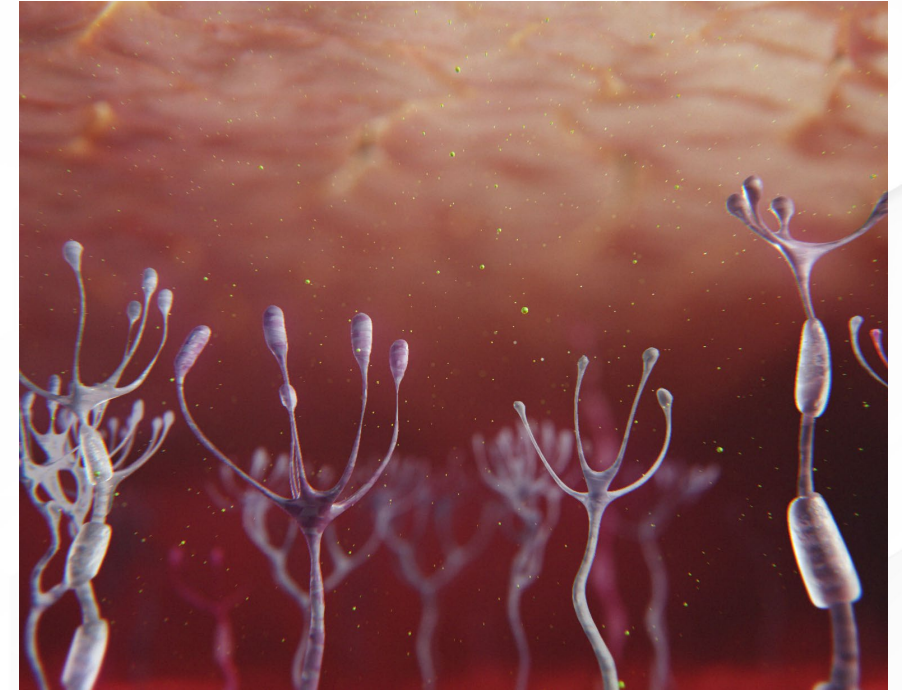
Capsaicin Targets the TRPV1 Receptors Involved in Pain Signaling

- Capsaicin is a highly-selective agonist for TRPV1 receptors
- **Nociceptive** (C and A-delta) fibers expressing TRPV1 receptors are responsible for sending pain signals to the brain
- **Upon entering the epidermal layers, high-concentration capsaicin binds to and activates the TRPV1 receptors**



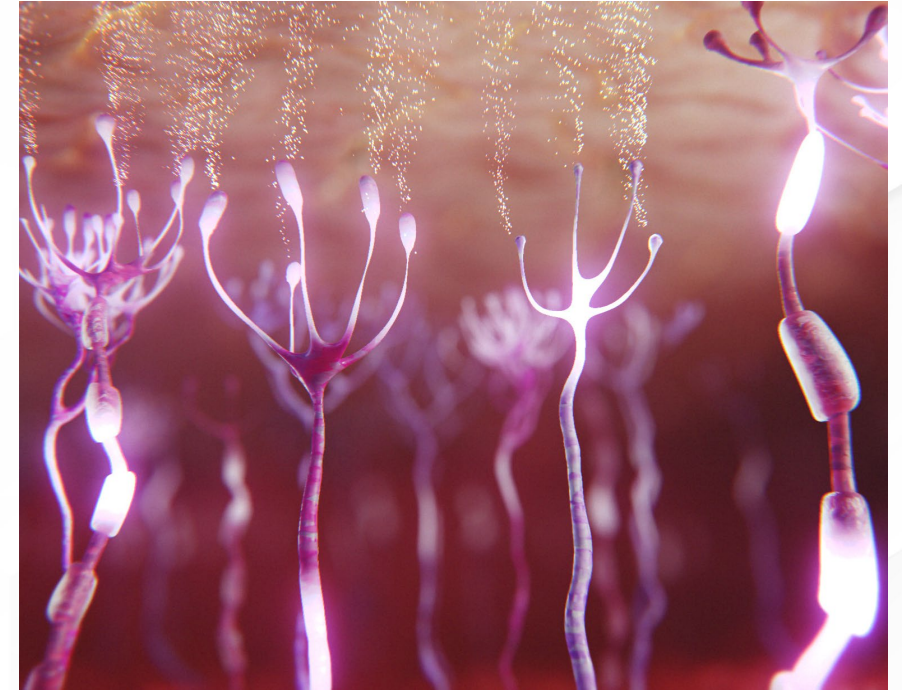
High-Concentration Capsaicin Initiates a Chemical Cascade That Results in a Reversible Ablation of TRPV1 Expressing Fibers

- Initially, high-concentration capsaicin increases TRPV1 receptor activity, which **desensitizes** the nociceptive fibers
- A **chemical cascade** is triggered that is driven by multiple mechanisms and is associated with marked increase of **intracellular calcium**
- This leads to a **reversible ablation** of TRPV1-expressing nociceptive fibers, rendering them **defunctionalized** and incapable of sending pain signals to the brain



Over Time, Ablated TRPV1-Expressing Fibers Regenerate and Reinnervate, Which May Result in the Return of Pain

- Diabetes and painful DPN of the feet are chronic and often progressive conditions
- As the nociceptive fibers **regenerate and reinnervate** the epidermal layers, some may become hyperactive again, resulting in the return of pain
- **Ongoing treatments every 3 months** may help control the symptoms of painful DPN of the feet



Effect on Epidermal Nerve Fiber Density

Capsaicin 8% topical system in healthy volunteers

1 week after use: significant reduction in ENF density versus unexposed skin sites⁵ and placebo⁶
Increase in tactile thresholds⁵.
Decrease in sharp mechanical pain⁶.

12 weeks after use: evidence of ENF regeneration⁵

24 weeks after use: nearly full (93%) recovery of ENF⁵

ENF, epidermal nerve fibers.

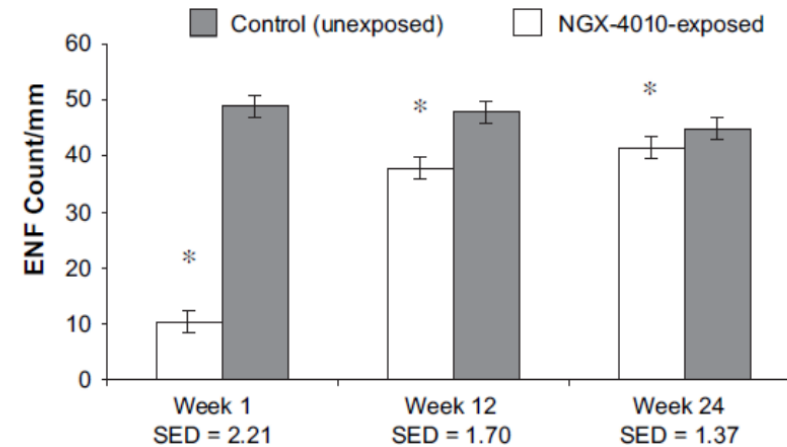


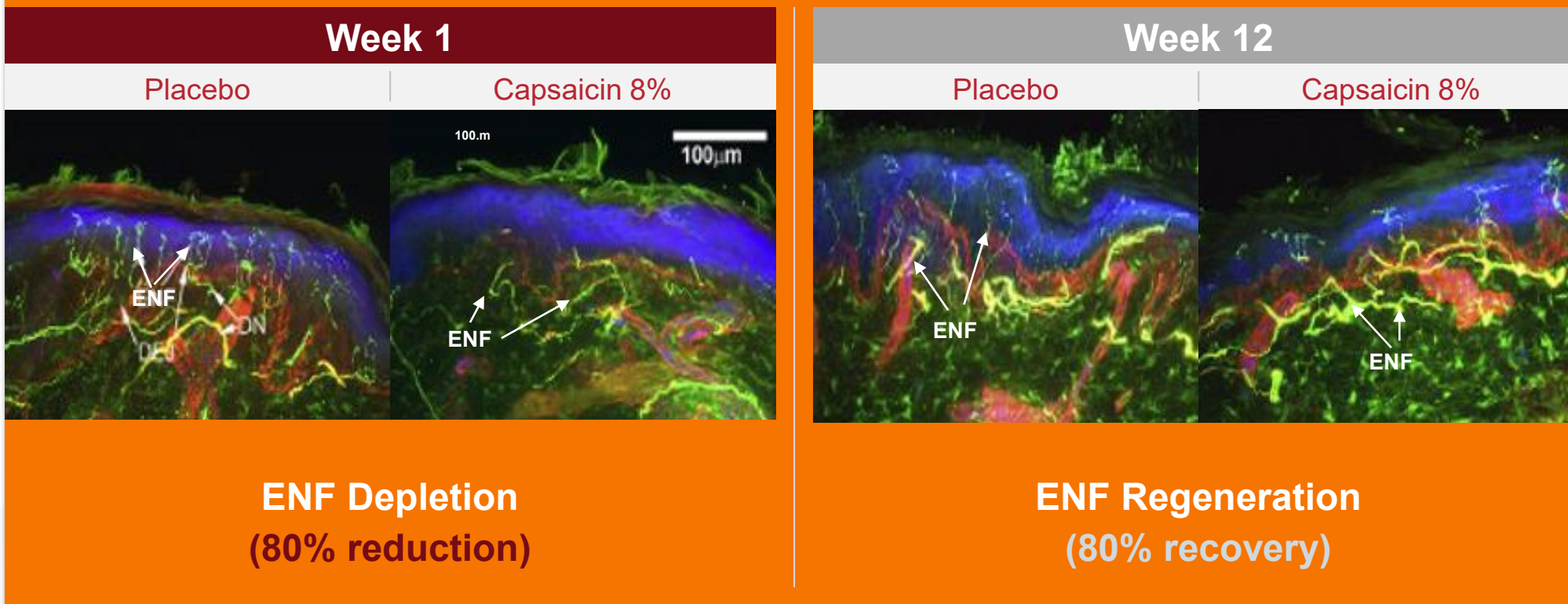
Figure 4. Mean reductions in epidermal nerve fiber (ENF) density at 1, 12 and 24 weeks after a single NGX-4010 patch application. Number of subjects is 36 for weeks 1 and 12, and 35 for week 24. Values represent least square means and error bars indicate standard errors of the means. *indicates $P < .05$ relative to control. SED = Standard error of difference between NGX-4010 and Control.

Reduction of Epidermal Nerve Fiber (ENF) After Single High-Concentration Capsaicin Application

High-concentration capsaicin reversibly induces ablation of TRPV1-expressing nerve terminals – a major contributor to its analgesic effect

Study in Healthy Volunteers

Scale bar=100um



Immunostaining Color Key

- Epidermal Nerve Fibers
- Basement membrane at the dermal-epidermal junction and around blood vessels
- Epidermis

ENF = epidermal nerve fiber.

Nolano M, et al. *Pain*. 1999;81(1-2):135-145. Malmberg AB, et al. *Pain*. 2004;111(3):360-367. Kennedy WR, et al. *J Pain*. 2010;11(6):579-587.

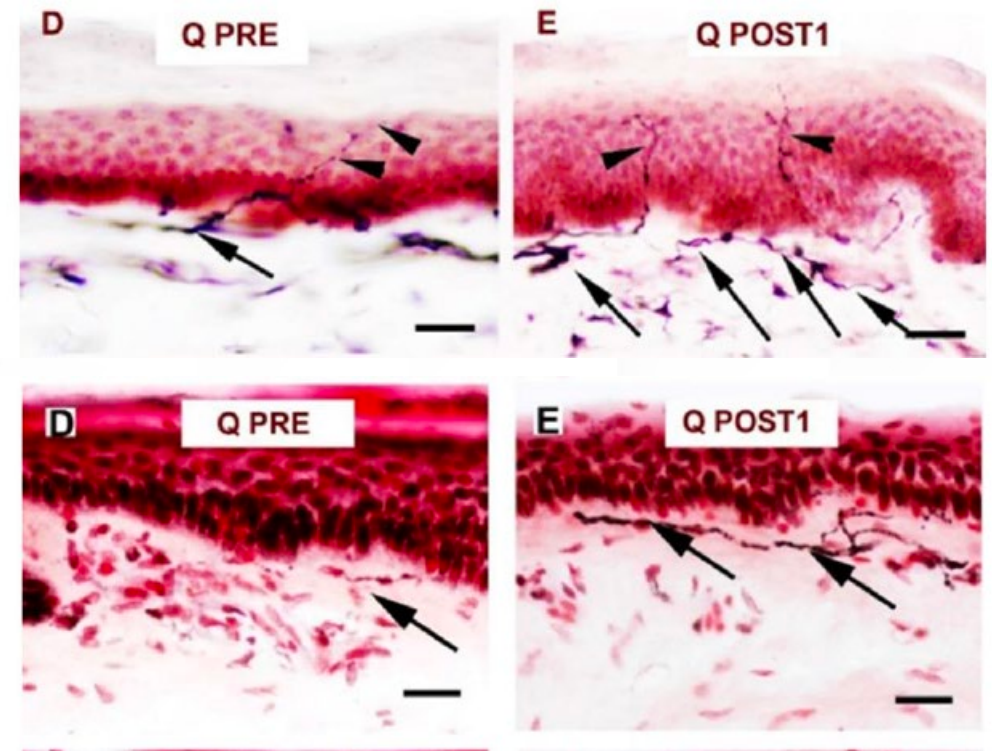
Reduction of ENF After Single High-Concentration Capsaicin Application in Painful DPN of the Feet

Reversible ablation of TRPV1-expressing nerve fibers has also been observed in patients with painful DPN who received capsaicin 8%

Randomized, Controlled Study in Patients with Painful DPN High-Concentration Capsaicin+SoC (n=32) vs SoC Alone (n=18)

- Patients with painful DPN were randomly allocated to receive either 30-min capsaicin 8% patch application to both feet up to the distal calf while continuing to take medication as part of their SoC (PDPN capsaicin 8% + SoC group; n=32, n=25 completers at 3 mos) or receive SoC alone (PDPN SoC alone group; n=18, n=12 completers at 3 mos)
- Density of intra-epidermal nerve fibers (IENF) with PGP9.5 (marker of intraepidermal peripheral nerve fibers) was increased at 3 mos in PDPN capsaicin 8% + SoC ($p=0.0002$)
- Increased sub-epidermal nerve fibers (SENF) were observed with GAP43 (marker of regenerating nerve fibers) only in capsaicin 8% + SoC ($p=0.003$)
- In contrast, IENF and SENF were decreased in the SoC alone group after 3 mos, in comparison with baseline biopsies

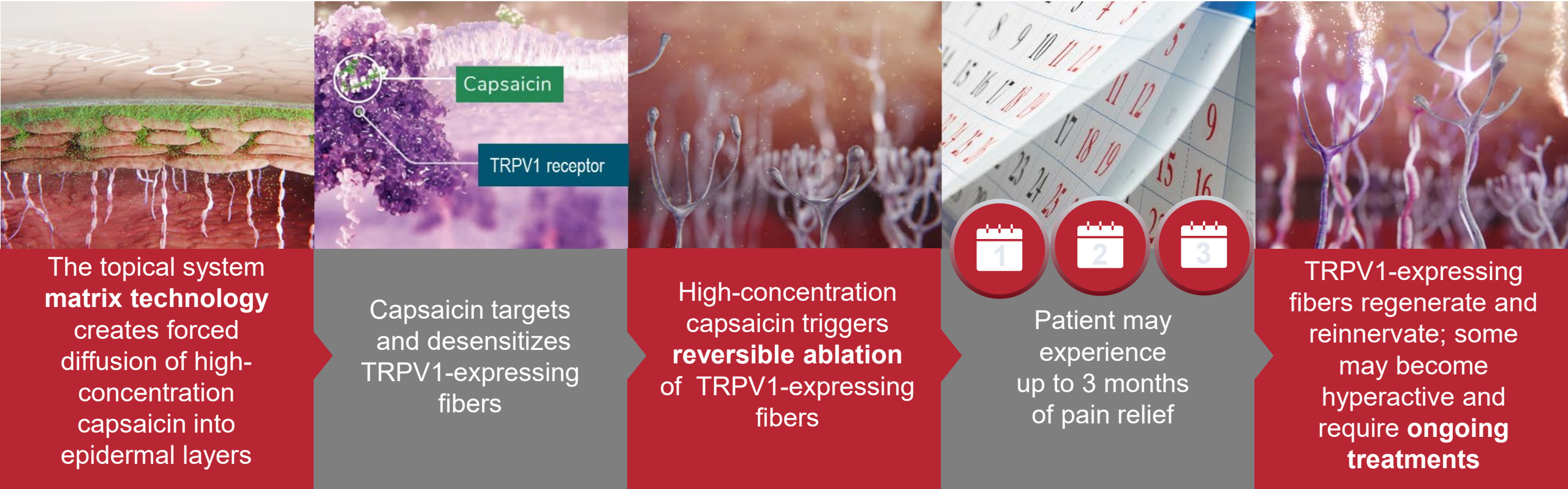
Pre-treatment vs 3 mos Post-treatment With High-Concentration Capsaicin + SoC



Takeaway...

A key finding was that sub-epidermal nerve fibers assessed with GAP43, a selective marker of regenerating nerve fibers, were significantly higher 3 months after treatment. In contrast, these nerve fibers decreased in the PDPN SOC alone group after 3 months. The investigators concluded that repeated applications of high-concentration capsaicin may progressively enhance this regenerative process toward normalization.

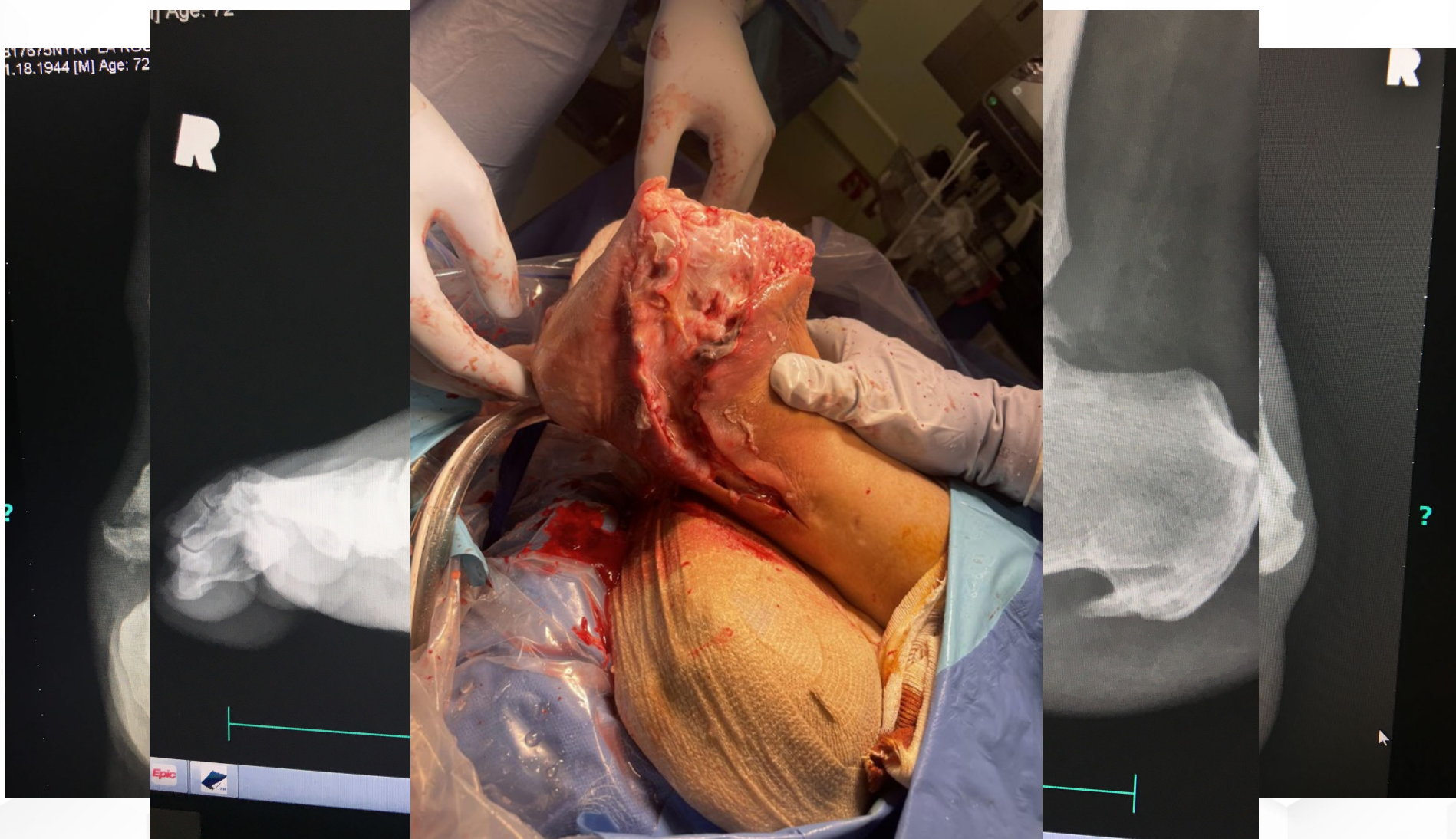
Ongoing Treatment Cycles with High-Concentration Capsaicin Can Effectively Treat DPN of the Feet



Why Bother?



Too Late



Prevention Works!

- Diabetic shoes/inserts
- Team approach
- High-quality foot care
- Product usage
- Medications
- Diligence



Thank you!