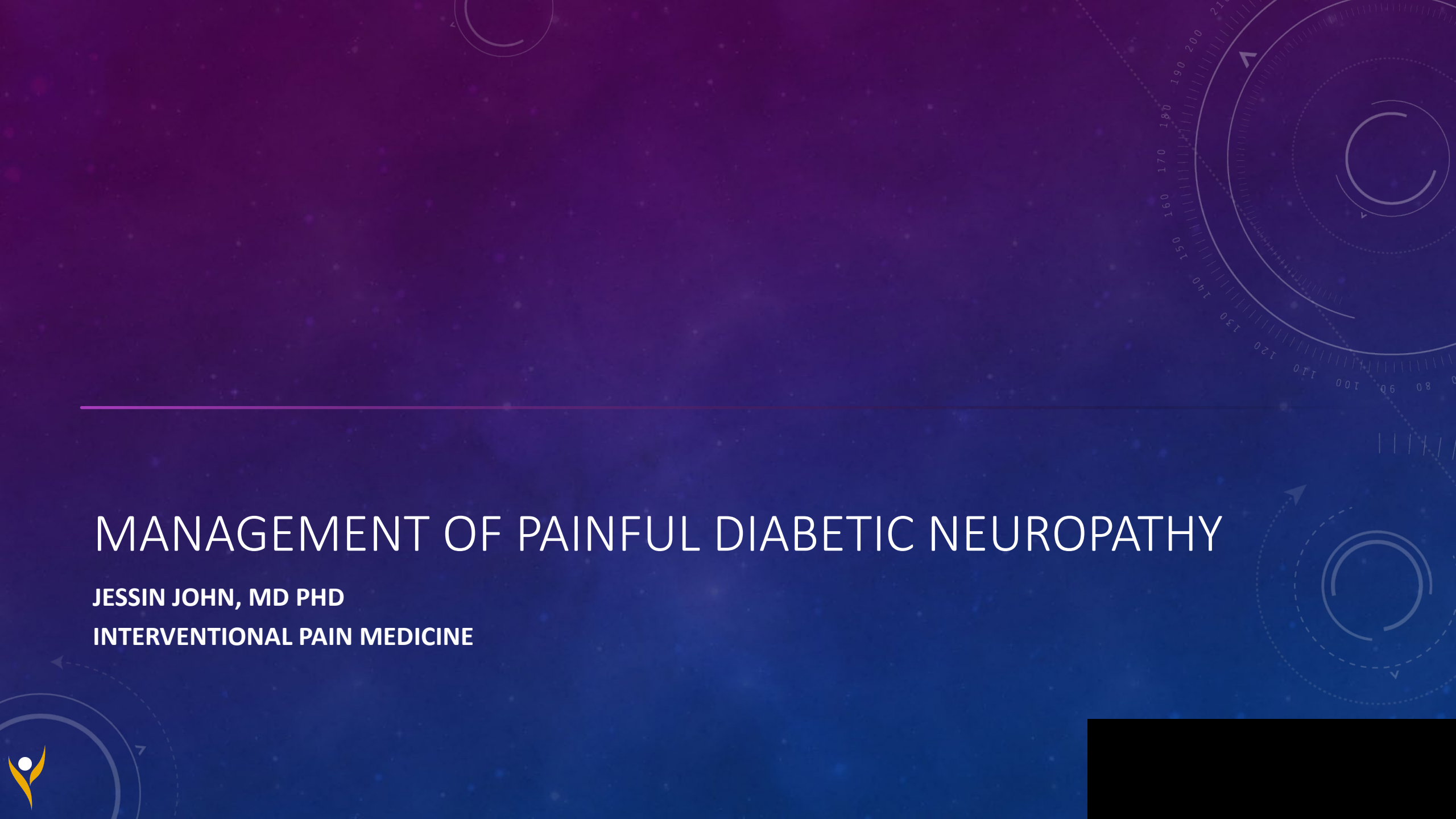




MANAGEMENT OF PAINFUL DIABETIC NEUROPATHY

JESSIN JOHN, MD PHD

INTERVENTIONAL PAIN MEDICINE



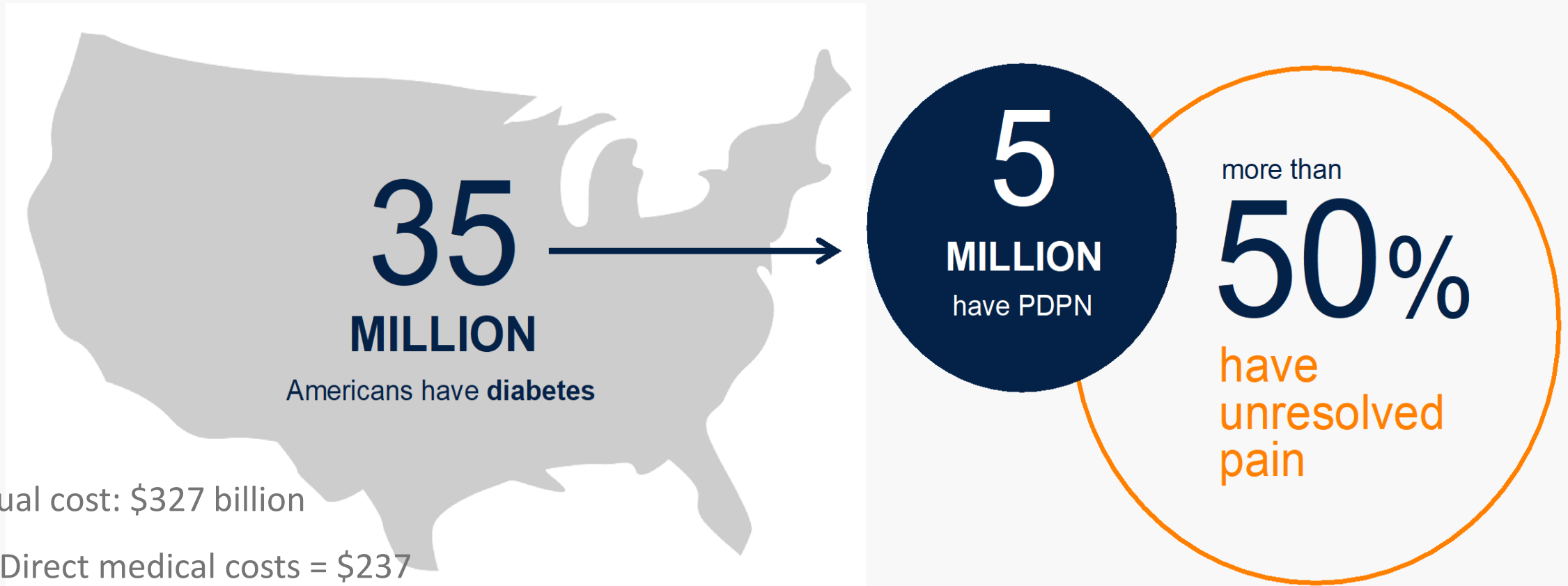
DISCLOSURES

Research

- Nevro (ongoing painful diabetic neuropathy sensory study)
- No financial incentive



35 million Americans have diabetes, 5 million have PDPN, and more than 50% of patients with PDPN have unresolved pain with first-line pain therapies¹⁻⁴



- Annual cost: \$327 billion

- Direct medical costs = \$237 billion

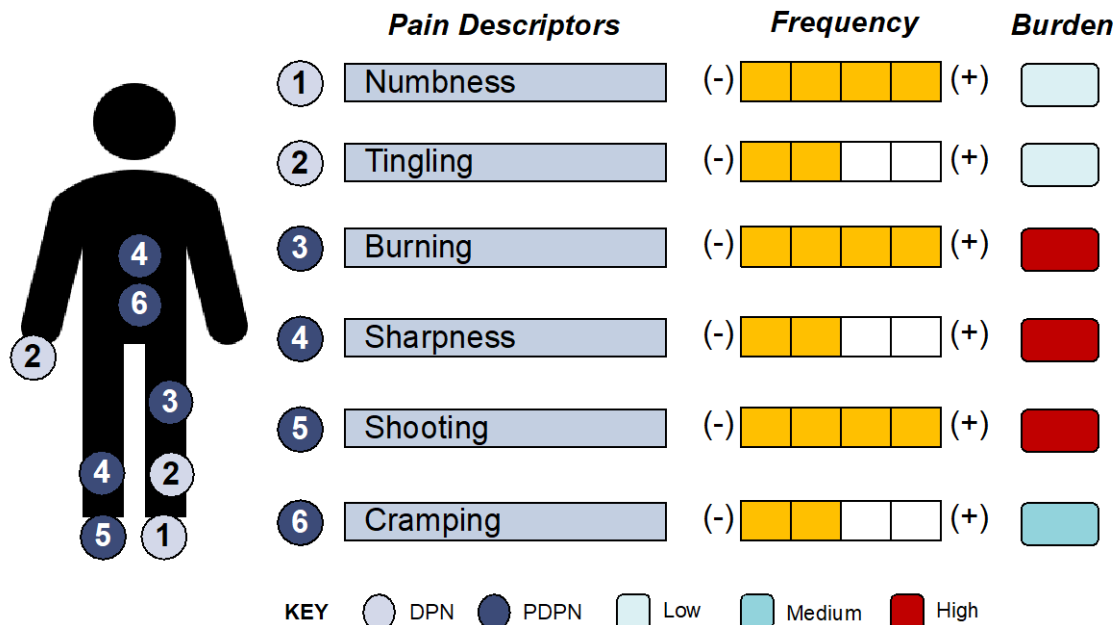
- Indirect costs = \$90 billion

Unresolved PDPN can result in higher opioid use, loss of employment, and higher healthcare resource use such as surgical interventions^{1,5-7}

DPN Is A Significant Clinical Problem: Pain Is A Debilitating Feature Of DPN Resulting In Significant Morbidity¹

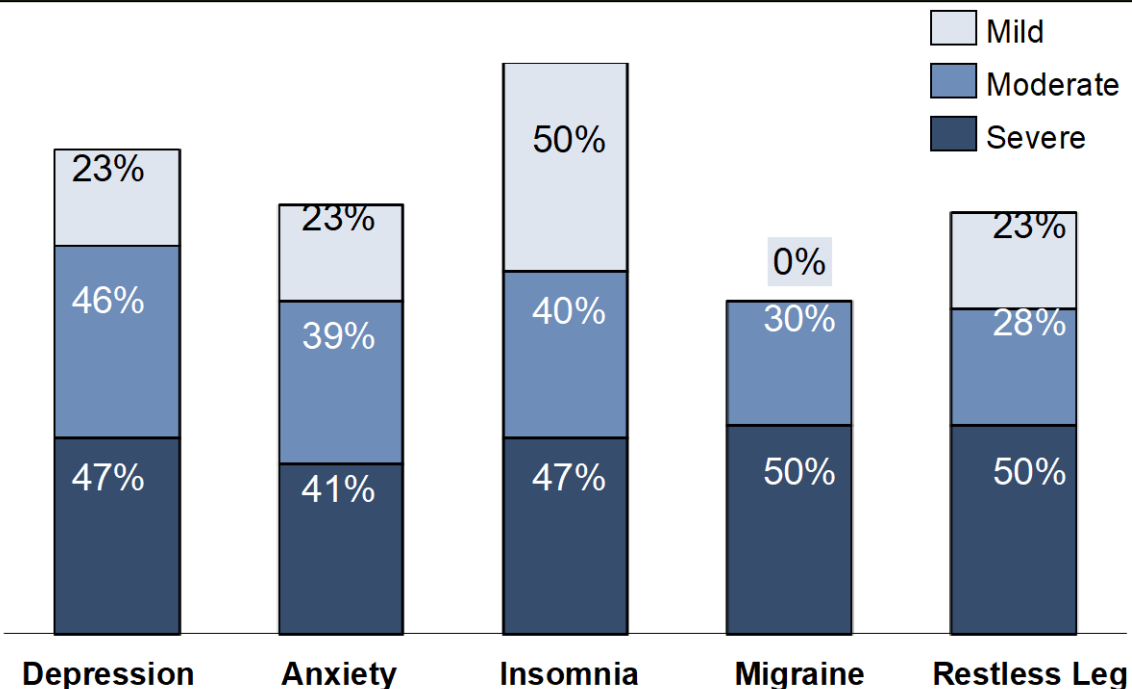
Painful DPN (PDPN) can be severe, chronic, & disabling, leading to substantial limitations, particularly with increasing severity

Clinical Presentation¹



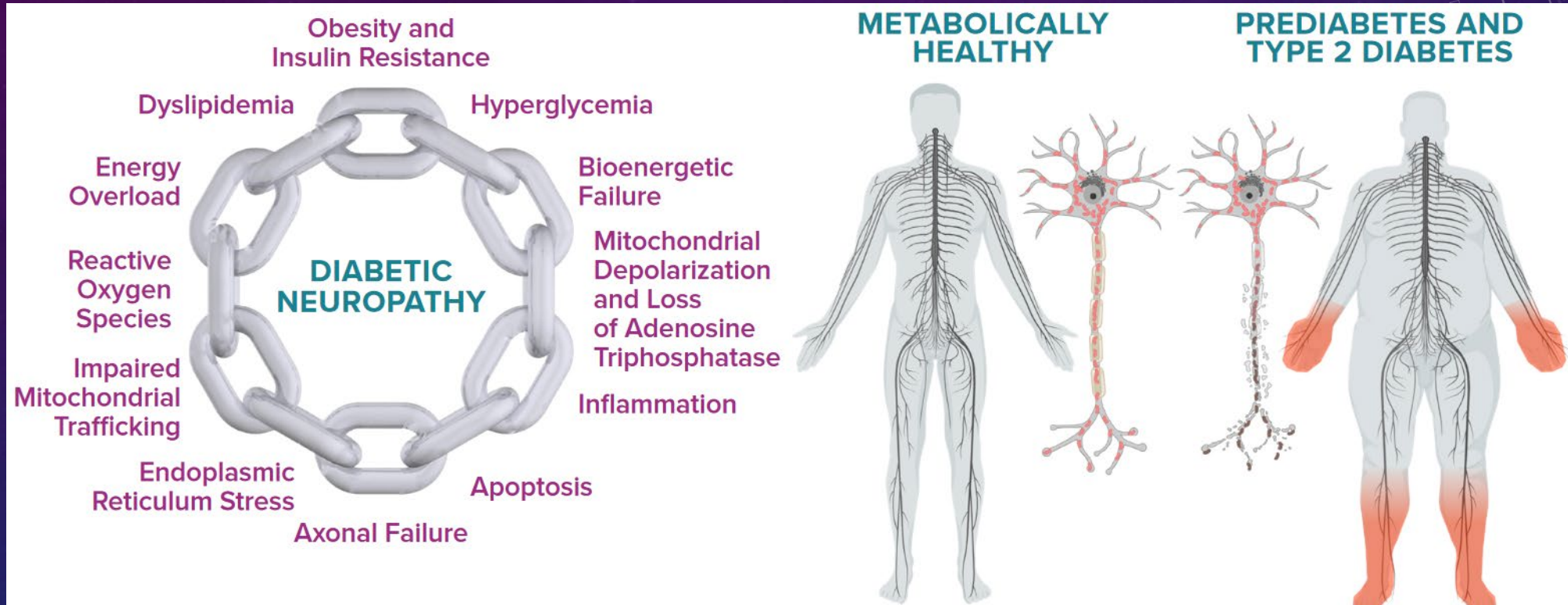
- Patients often use descriptors for their pain during diagnosis^{3,4}
- The classic presentation of PDPN is pain or tingling in the feet that can be described as “burning” or “shooting”^{3,4}

PDPN Is Associated With Additional Comorbidities^{2,5}

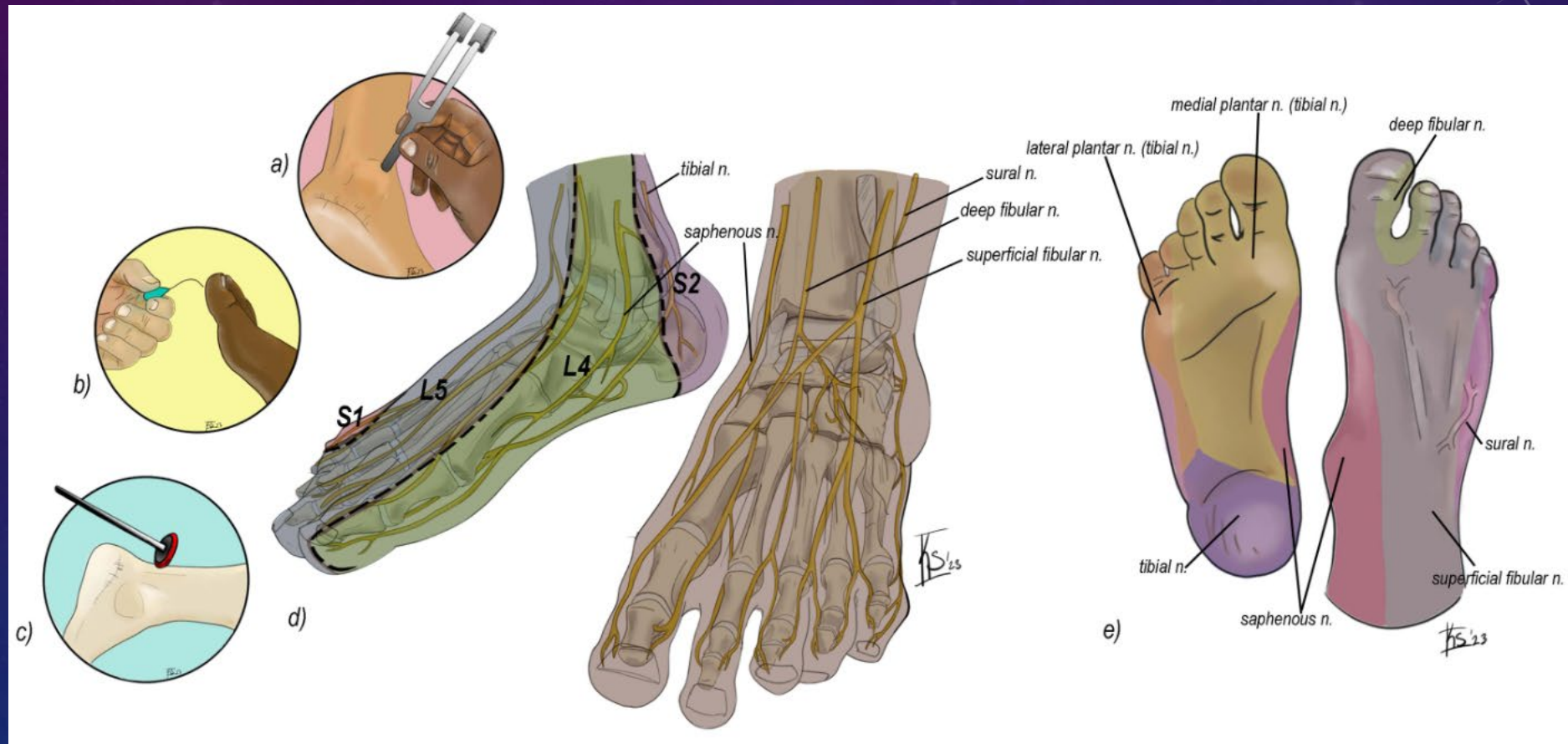


Sources: 1 Colloca, L. et al. 2017; 2 Sadosky, A. et al. 2013; 3 Eichholz, M. et al. 2017; 4 Jensen, T.S. et al 2006; 5 Schadina, S. & Toth, C. 2013

PATHOPHYSIOLOGY OF PDPN



IT ALL STARTS WITH HISTORY AND PHYSICAL



PDPN...FORMING A DIAGNOSIS

- Primarily a clinical diagnosis
 - intermittent or continuous symptoms of pain described as burning, stabbing, tingling, numb, hot, cold or itching in a distal-to-proximal 'glove-and-stockings' distribution, usually beginning in the feet.
 - The pain is typically symmetrical and worsens at night. Abnormal sensory perception
- Quantitative Sensory Testing and Intra-epidural Skin Biopsies
- Rule out other potential causes (vitamin deficiencies, lumbar pathology, etc)



PHARMACOLOGICAL TREATMENT MOA/NNT

Drug	NNT	AAN [2011]	NICE [2013]	EFNS [2010]	NeuPSIG IASP [2010]	Mechanism of action
<i>TCAs</i>				First line		Inhibit reuptake of noradrenaline and serotonin
Amitriptyline	1.3	Second line	First line		First line	
Desipramine	2.6					
Imipramine	2.2					
<i>SNRIs</i>		Second line		First line	First line	Inhibit reuptake of noradrenaline and serotonin augmenting descending inhibitory pathways
Duloxetine	6.0		First line			
Venlafaxine	3.1					
<i>GABA analogues</i>				First line	First line	
Gabapentin	5.8		First line			Bind to voltage-gated calcium channels and reduces the synaptic release of several neurotransmitters
Pregabalin	5.0	First line	First line			
<i>Opioids</i>		Second line		Second line	Second line	
Tramadol	3.8		Second line			μ -opioid receptor agonist
<i>Topical</i>						
Capsaicin (0.075% cream)	6.6					Depletion of the neurotransmitter substance P from primary afferent neurones and loss if IENFD

AAN, American Academy of Neurology; EFNS, European Federation of Neurological Societies; IENFD, intraepidermal nerve fibre density; NeuPSIG IASP, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; NICE, National Institute for Health and Care Excellence.

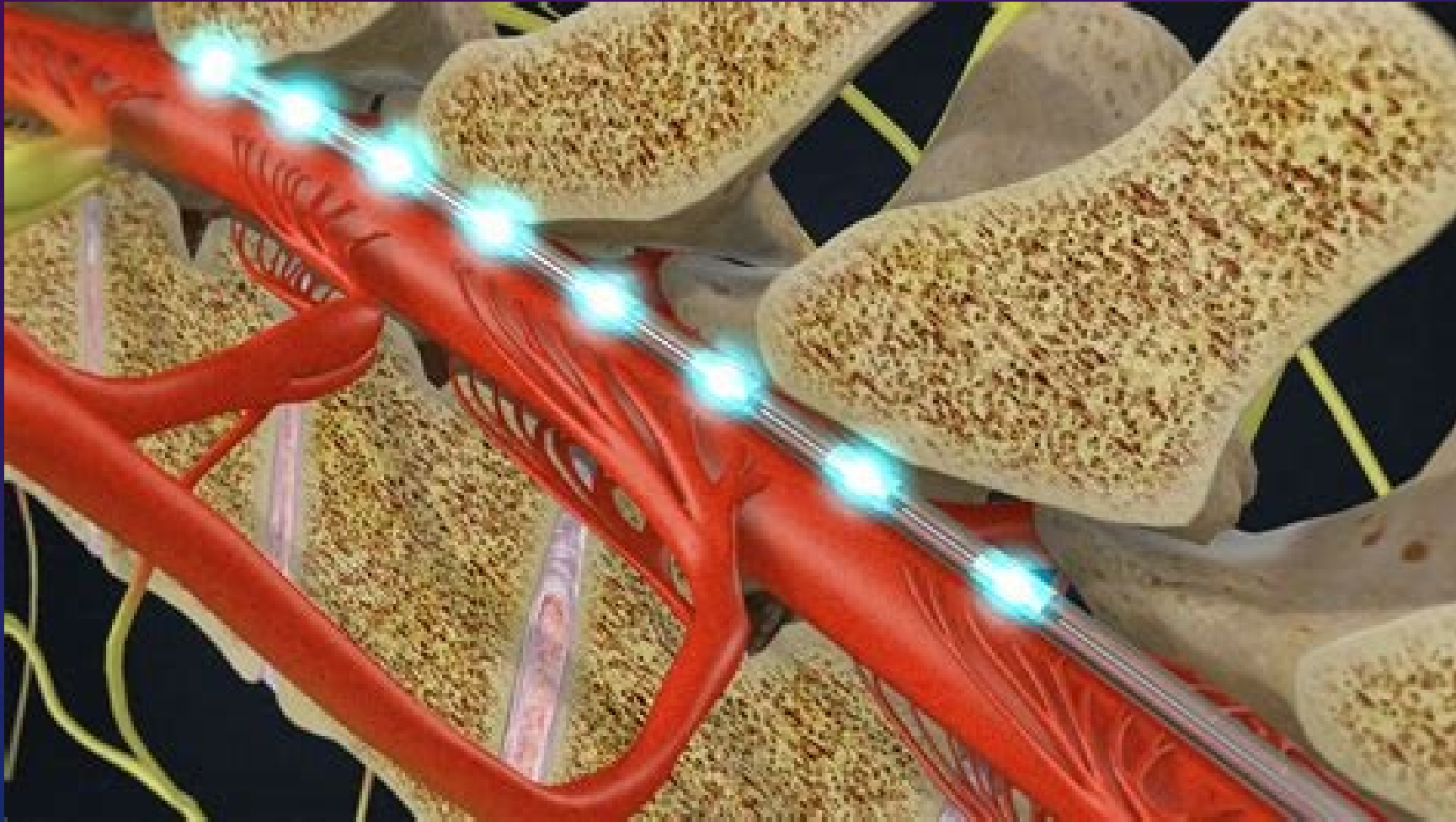
[Hollingshead *et al.* 2006; Saarto and Wiffen, 2007; Derry *et al.* 2009; Lunn *et al.* 2009; Moore *et al.* 2009a, 2011; Attal *et al.* 2010; Dworkin *et al.* 2010; Bril *et al.* 2011; Spallone, 2012].

PHARMACOLOGICAL TREATMENT LANDSCAPE

Class	Agent	Starting dosage	Titration	Maximum dosage	Major side effects	Precautions
Secondary amine TCAs	Nortriptyline*	25 mg at bedtime	Increase by 25 mg daily every 3-7 days, as tolerated, until pain relief	150 mg daily; If blood level of active drug and its metabolite is 100 mg/mL, continue titration with caution	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol
	Desipramine*					
SSNRIs	Duloxetine	30 mg once daily	Increase to 60 mg once daily after 1 week	60 mg twice daily	Nausea	Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol
	Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg each week, as tolerated until pain relief	225 mg daily	Nausea	Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation
Calcium channel $\alpha 2\text{-}\delta$ ligands	Gabapentin*	100-300 mg at bedtime or 100-300 mg 3 times daily	Increase by 100-300 mg 3 times daily every 1-7 days, as tolerated, until pain relief	3,600 mg daily (1,200 mg 3 times daily); reduce if impaired renal function	Sedation, dizziness, peripheral edema	Renal insufficiency
	Pregabalin*	50 mg 3 times daily or 75 mg twice daily	Increase to 300 mg daily after 3-7 days, then by 150 mg/day every 3-7 days, as tolerated, until pain relief	600 mg daily (200 mg 3 times daily or 300 mg twice daily); reduce if impaired renal function	Sedation, dizziness, peripheral edema	Renal insufficiency
	Topical lidocaine 5% lidocaine patch	Maximum of 3 patches daily for a maximum of 12 hr	None needed	Maximum of 3 patches daily for a maximum of 12-18 hr	Local erythema, rash	None
Opioid agonists**	Morphine, oxycodone, methadone, levorphanol*	10-15 mg morphine every 4 hr or as needed (equianalgesic dosages should be used for other opioid analgesics)	After 1-2 week convert total daily dosage to long-acting opioid analgesic and continue short acting medication as needed	No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (e.g., 120-180 mg morphine daily, equianalgesic dosages should be used for other opioid analgesics)	Nausea/vomiting, constipation, drowsiness, dizziness	History of substance abuse, suicide risk, driving impairment during treatment initiation
	Tramadol***	50 mg once or twice daily	Increase by 50-100 mg daily in divided doses every 3-7 days, as tolerated, until pain relief	400 mg daily (100 mg 4 times daily); In patients aged >75 years, 300 mg daily	Nausea/vomiting, constipation, drowsiness, dizziness, seizures	History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SSNRI, or TCA

Sources: 1 Adapted from O'Connor et al, 2009

SPINAL CORD STIMULATION



IT ALL STARTED WITH THE FISH...

- Ancient romans and the torpedo fish for gout
- TENS Unit (Electreat) in 1919 by Charles Kent
- 1965 Gate control Theory
- 1967 Shealy
- 1968 Medtronic SCS
- 1980s Multi-Lead Arrays and lithium IPGs



SHOOTING ELECTRICITY IN, FORCES THE PAIN OUT

Electreat
Mechanical Pain Relieves Pain
No Charges. Free Trial Demonstration

1. How to Start
Muscle Building, Lung Development, Improves Circulation

2. Sponge (+) Relieves Pain
Headache, Earache, Toothache, Neuralgia, Neuritis, Soreness

3. Sponge (-) Roller (+)
Tonsillitis, Catarrh, Asthma, Goitre, Voice, Throat

4. Roller (+)
Pleurisy, Chest Pains, Reducing, Making Lethesome

5. Roller (+)
Breaks Up Congestion, Lumbago and Backache

6. Sponge and Roller
Regulating Internal Organs, Stomach, Indigestion, Bowels, Constipation

7. Spinal Treatment
Tonic, Up Current, Debility, Nervousness, Liver, Kidneys, Spine

8. Electric Hand Massage
The Touch That Soothes—Electricity and Personal Magnetism

9. Concentrated Application
Rheumatism, Stiff Joints, Breaking Up Chronic Conditions

10. Sponge (-) Stimulates
Electric Bath, Poor Circulation, Tired Feet, Improving Dry Chapped Skin

11. Scalp Brush
Falling Hair, Dandruff, Itchy Scalp, Brain Stimulation, Restfulness

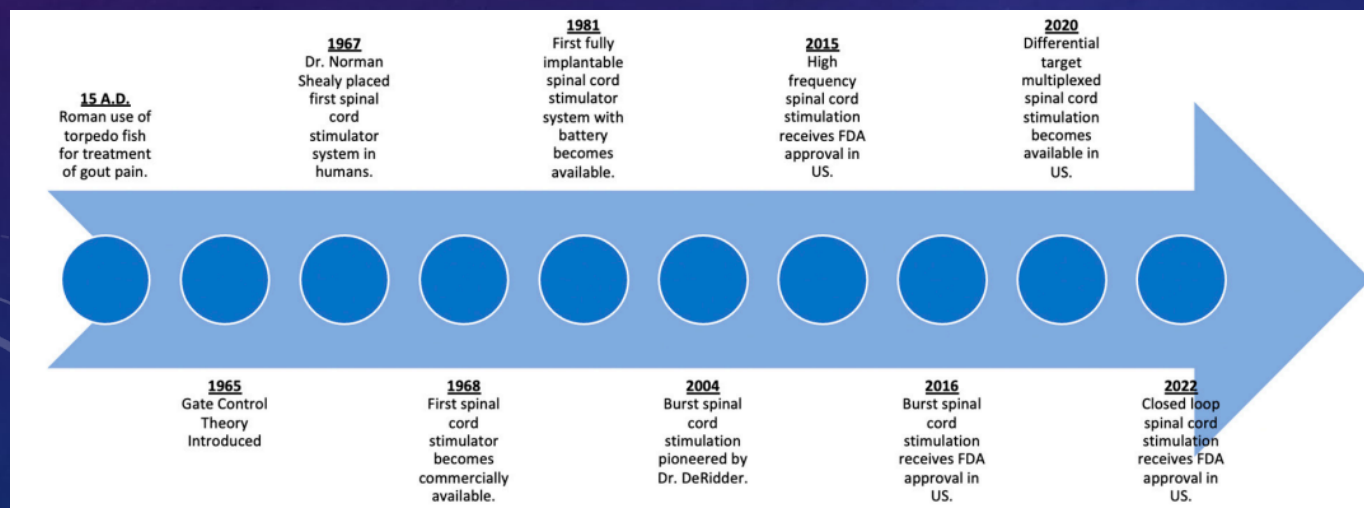
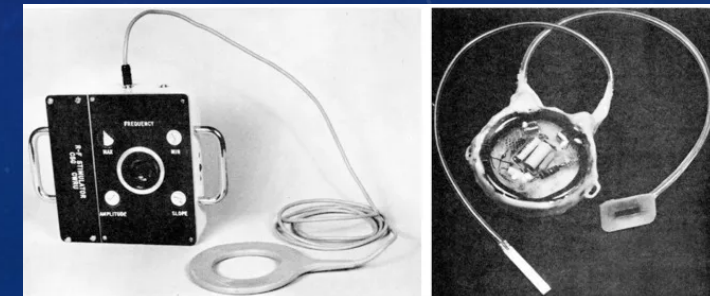
12. Beautifying Hair
Enlivens the Hair, Enriches the Color, Stimulates Luxuriant Growth

Free Trial Demonstration
If you are suffering in your city, or any of your friends, relatives, or neighbors, of any kind, or any of the ailments named on opposite side in our testimonials, telephone us at once and our Demonstrator will call at your home and show how quickly Electreat will give you relief.

Free Trial Demonstration
No Charges. Free Trial Demonstration

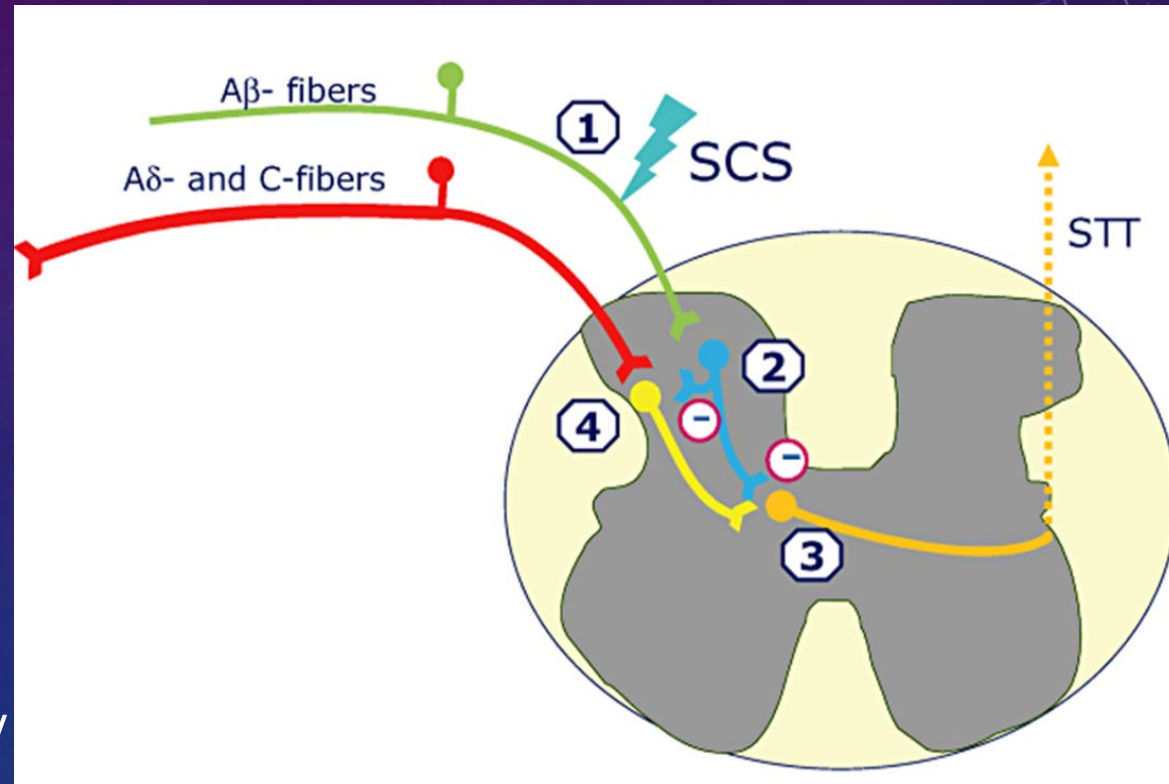
MRS. MARION PARKER
For Free Demonstration Write or Phone
Box 817 So. Boulder, Ark. 3
PHONE 3-3502 TULSA, OKLA.

ELECTREAT MECHANICAL HEART GIVES NEW LIFE TO YOUR VEINS AND RELIEVES YOUR PAINS



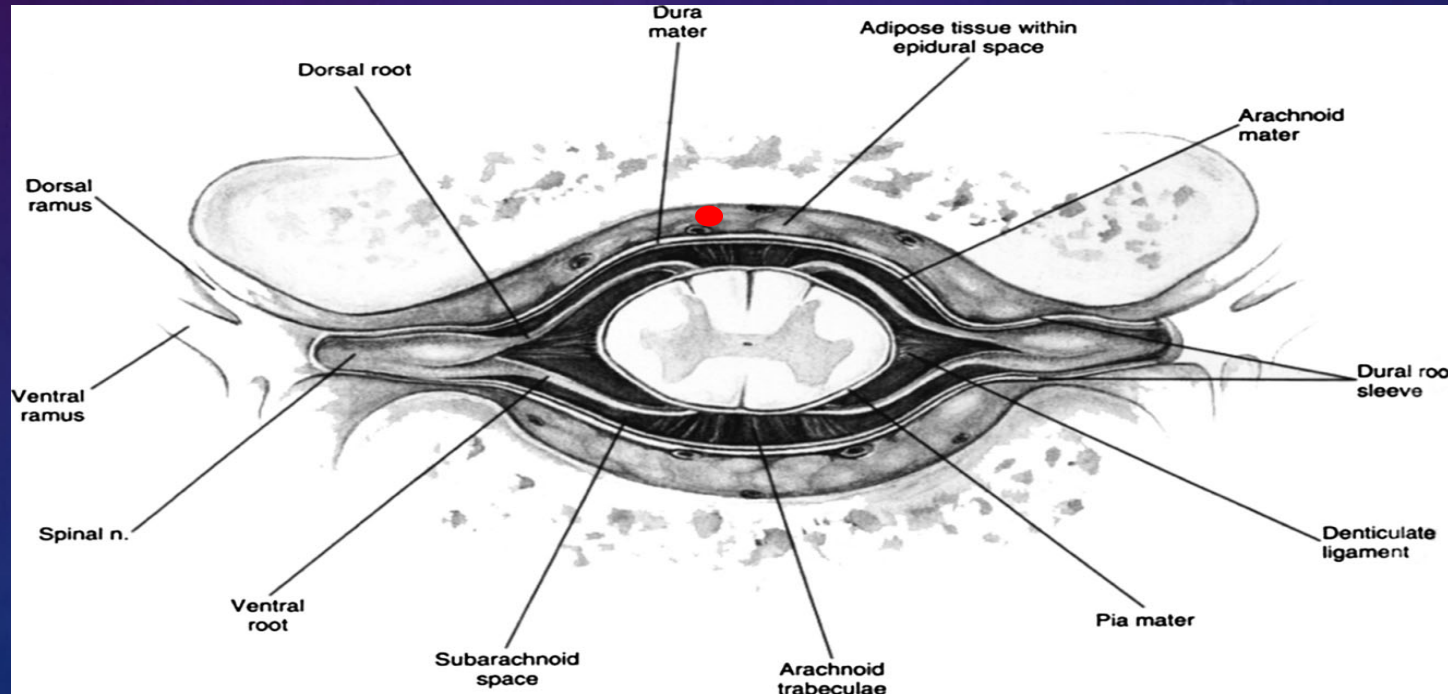
GATE THEORY

- In the dorsal horn (where pain signals relay), there is a '**gate**' that opens and closes to allow pain signals up to the brain.
- C and A delta fibers are small pain fibers. When their signals get to the brain, you feel pain
- A beta fibers are larger fibers that carry non painful signals (vibration, light touch, etc)
- When A beta fibers are stimulated, they 'close the gate', and signals from the smaller pain fibers cannot get up to the brain



SCS: MECHANISMS OF ACTION

- One of the main ways we believe SCS works is by utilizing this gate theory. SCS stimulates these A-beta fibers in the dorsal horn, so instead of patients feeling pain they feel a tingling/vibration sensation instead.

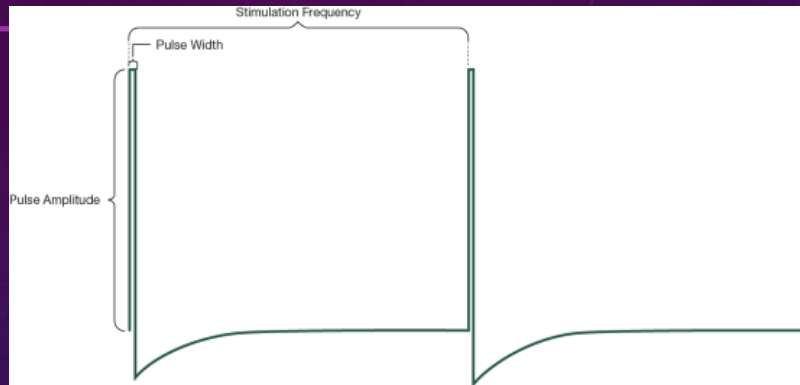
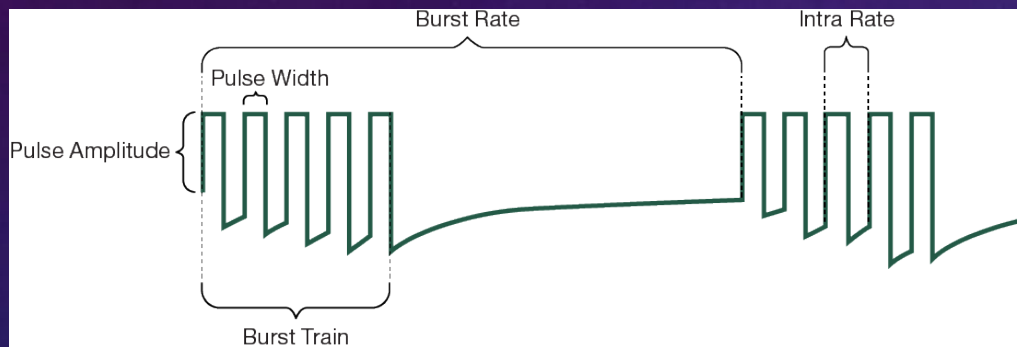
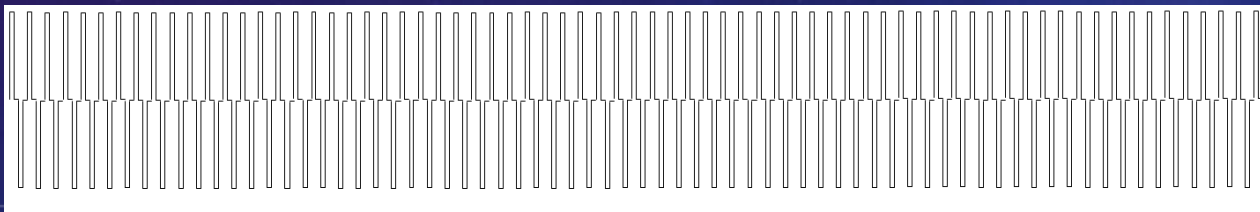


SCS: MECHANISMS OF ACTION

- Releases certain neurotransmitters that cause **vasodilation**- helpful for angina, PVD and CRPS
- Increases levels of **GABA**... in patients with allodynia (CRPS), GABA levels are decreased in the CSF
- **Blocks sympathetic outflow**. For some CRPS patients, abnormal activity of the SNS is responsible for a lot of their symptoms, and SCS can help significantly with temperature and skin color changes as well as with pain.



SPINAL CORD STIMULATION WAVEFORMS



Traditional Tonic

- Relatively low energy
- Recharge every 1-2 weeks

Burst Stimulation

- Parameters within traditional ranges
- Low-moderate energy
- Average recharge similar to tonic
- Device provides both tonic & burst¹
- Same projected device life as traditional tonic¹

High Frequency Stimulation

- Parameters outside the traditional ranges
- Highest energy, daily recharge
- Device only provides tonic stimulation at programmable frequencies (up to 10,000hz)²
- Reduced projected device life compared to traditional tonic



Device	Target	MOA	Indications	Notes
HF	Dorsal horn	HF/10 kHz stimulation waveforms (200–10 kHz)	Back pain, leg pain, and peripheral diabetic neuropathy	Paresthesia-free
Glial modulation	Glial cells throughout spinal cord	Differential target multiplexed programming—varied high- and low-rate signals	LBP and leg pain	Variable
Surround inhibition therapy	Dorsal column	Activation of A β -axons in dorsal columns to inhibit WDR	Leg, back, and overall pain	Paresthesia-independent
Dorsal horn modulation	Dorsal horn	Anatomic targeting of dorsal horn with constant 200 Hz, 200 μ s signals. 10 kHz is paresthesia-free	Back, limb, and generalized pain	Paresthesia-independent
Active and passive burst neuromodulation	Dorsal horn	Cumulative charge of five 1000- μ s spikes	Back, limb, and generalized pain	Paresthesia-independent
Multiphase	Not defined	HF energy dispersion	Back and limb pain	Paresthesia-independent
DRG stimulation	DRG	Stimulation of sensory afferent neurons	CRPS, PSPS, peripheral nerve damage, pain after vascular stenting, and post-surgical neuropathic pain	
ECAPs	Dorsal column	A β -fibers in the dorsal columns	Back and leg pain	Closed loop system



SENZA PDN Randomized Controlled Trial (RCT)

To determine whether high frequency 10-kHz Therapy improves outcomes for patients with refractory PDN.

- 216 subjects with diabetes
- ≥ 5 on pain VAS
- $A1c \leq 10\%$
- $BMI < 45$
- 18 US centers randomized 216 subjects 1:1
- Crossover at 6 months with 24-month follow-up (93% of those eligible crossed over from CMM)

Treatments

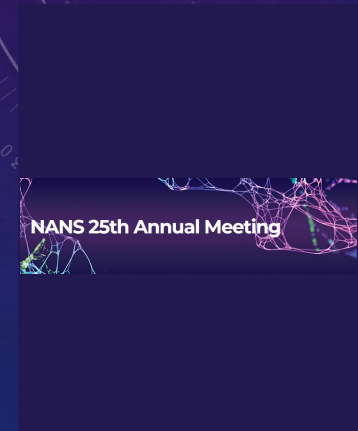
- CMM vs. 10 kHz Therapy (Nevro Corp.) + CMM.



6-month¹
JAMA Neurology
Apr 2021



12-month²
Diabetes Care
Nov 2021



18-month³
Presented at NANS
Jan 2022

1. Petersen E. et al. Effect of high frequency (10-kHz) spinal cord stimulation in patients with painful diabetic neuropathy: a randomized clinical trial. JAMA Neurology Apr 2021
2. Petersen E. et. al. Durability of high-frequency 10 kHz spinal cord stimulation for patients with painful diabetic neuropathy refractory to conventional treatments. Diabetes Care, Nov 2021.
3. Petersen E. et. al. Durability of 10 kHz spinal cord stimulation for painful diabetic neuropathy: 18-month results. NANS, Jan 2022.



Identifying the patient: Inclusion criteria and baseline characteristics

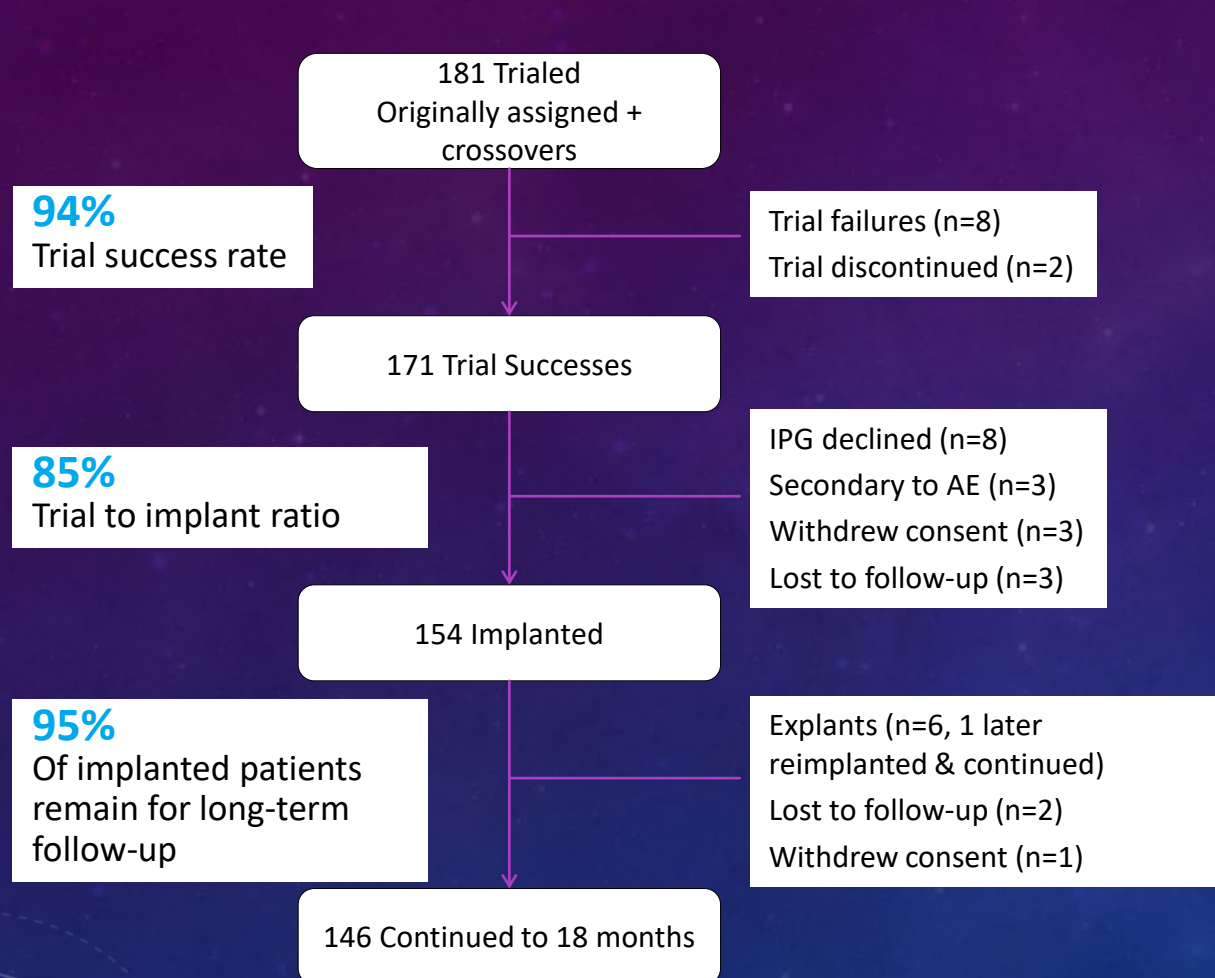
SENZA-PDN RCT Inclusion criteria:

- PDN diagnosis with symptoms for 12 months or more
- Refractory to 2 or more pharmacologic treatments (gabapentin or pregabalin and at least 1 other class of analgesic)
- Lower limb pain intensity of 5 cm or more on a 10-cm visual analogue scale (VAS)
- Appropriate surgical candidate

Baseline Characteristics	N = 100	N = 118	Standardized Difference*
Age in years, mean (SD)	60.8 (9.9)	60.7 (11.4)	0.01
Male, n (%)	66 (64%)	70 (62%)	0.04
Race			
White, n (%)	85 (82.5%)	87 (77.0%)	0.14
Black or African American, n (%)	13 (12.6%)	18 (15.9%)	
Native Hawaiian or other Pacific Islander, n (%)	1 (1.0%)	3 (2.7%)	
American Indian or Alaska Native, n (%)	0 (0.0%)	2 (1.8%)	
Asian, n (%)	1 (1.0%)	1 (0.9%)	
Other, n (%)	3 (2.9%)	2 (1.8%)	
Diabetes			
Type 1, n (%)	3 (3%)	8 (7%)	0.19
Type 2, n (%)	100 (97%)	105 (93%)	
Duration in years			
Diabetes, mean (SD)	12.2 (8.5)	12.9 (8.5)	0.09
Peripheral neuropathy, mean (SD)	7.1 (5.1)	7.4 (5.7)	0.06
Lower limb pain VAS in cm, mean (SD)	7.1 (1.6)	7.5 (1.6)	0.22
< 7.5 cm, n (%)	57 (55%)	54 (48%)	0.15
≥ 7.5 cm, n (%)	46 (45%)	59 (52%)	
HbA1c, mean (SD)	7.4% (1.2%)	7.3% (1.1%)	0.11
< 7.0%, n (%)	40 (39%)	46 (41%)	0.04
≥ 7.0%, n (%)	63 (61%)	67 (59%)	
BMI, mean (SD)	33.9 (5.2)	33.6 (5.4)	0.06



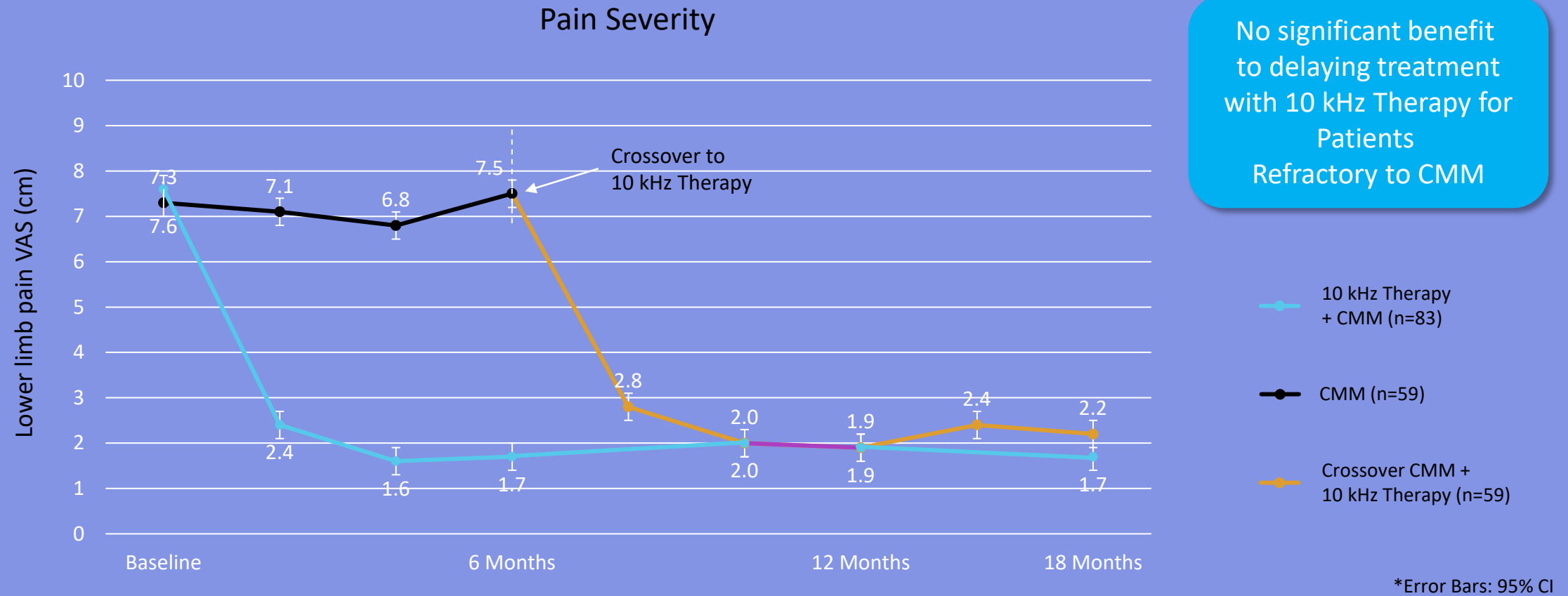
SENZA PDN RCT Subject Disposition: 10 kHz SCS



Safety
No stimulation-related neurological deficits
No explants for loss of efficacy
8 procedure-related infections (5.2%) 3 resolved with antibiotics 5 required explant (3.2%, 1 patient reimplanted)
1 explant as a precaution for an unrelated infection
3 IPG revisions (1.9%)
1 IPG replacement (0.6%)
1 lead revision (0.6%)

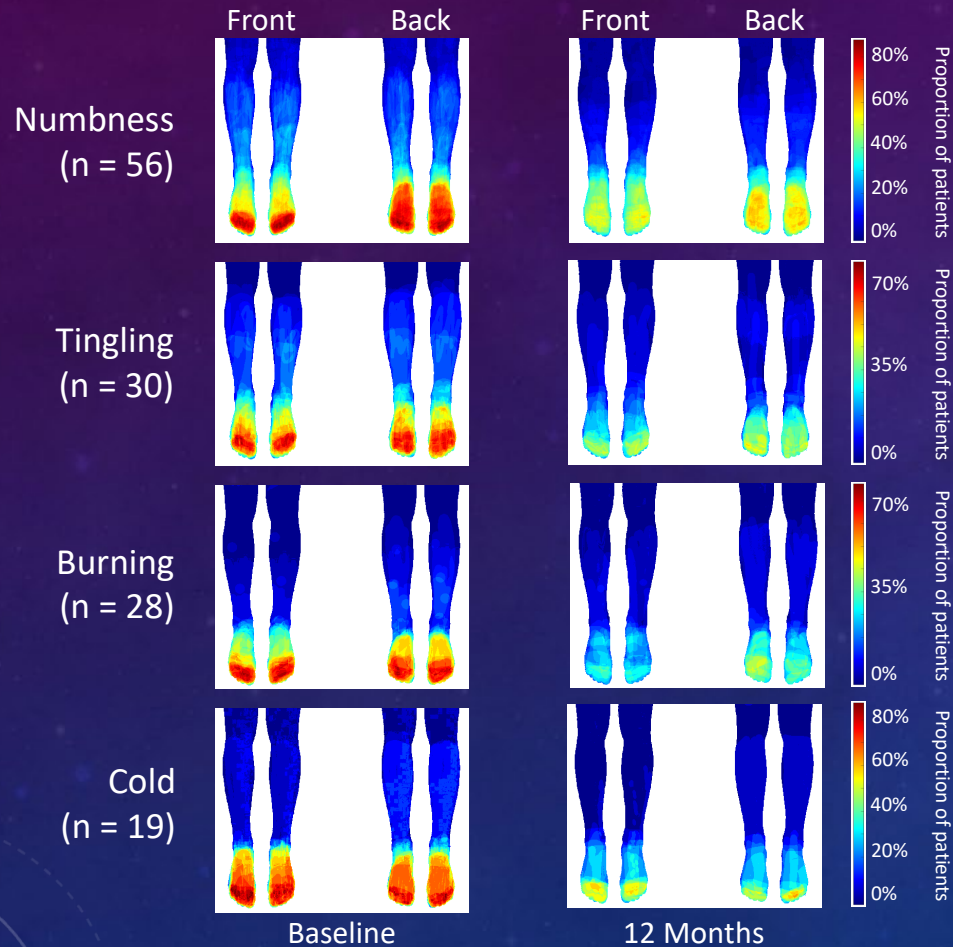


SENZA PDN RCT | Pain Relief over 18-Months

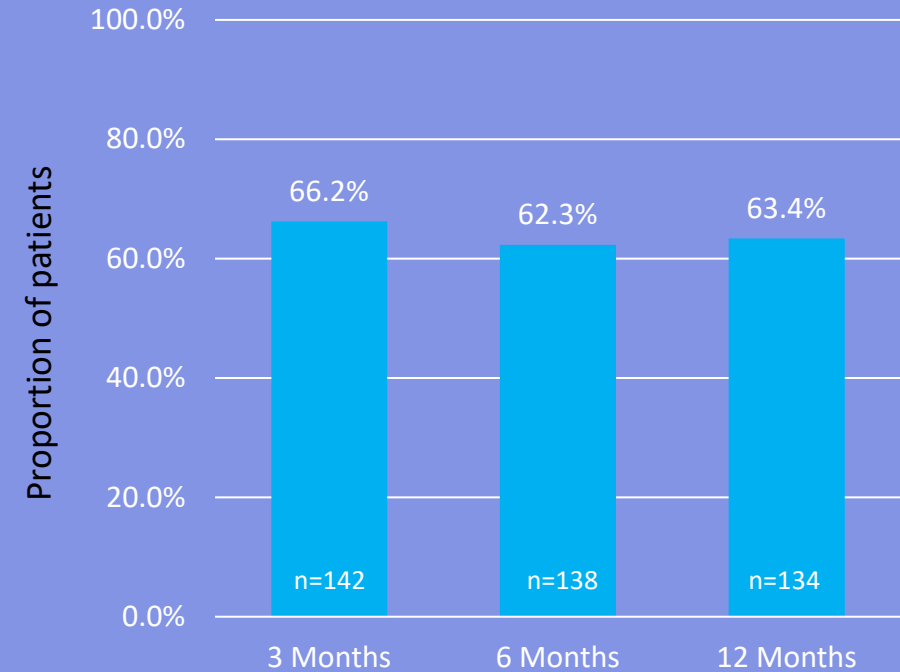


SENZA PDN RCT | Neurological Improvement with 10 kHz SCS

Patient-reported reductions in dysesthesias



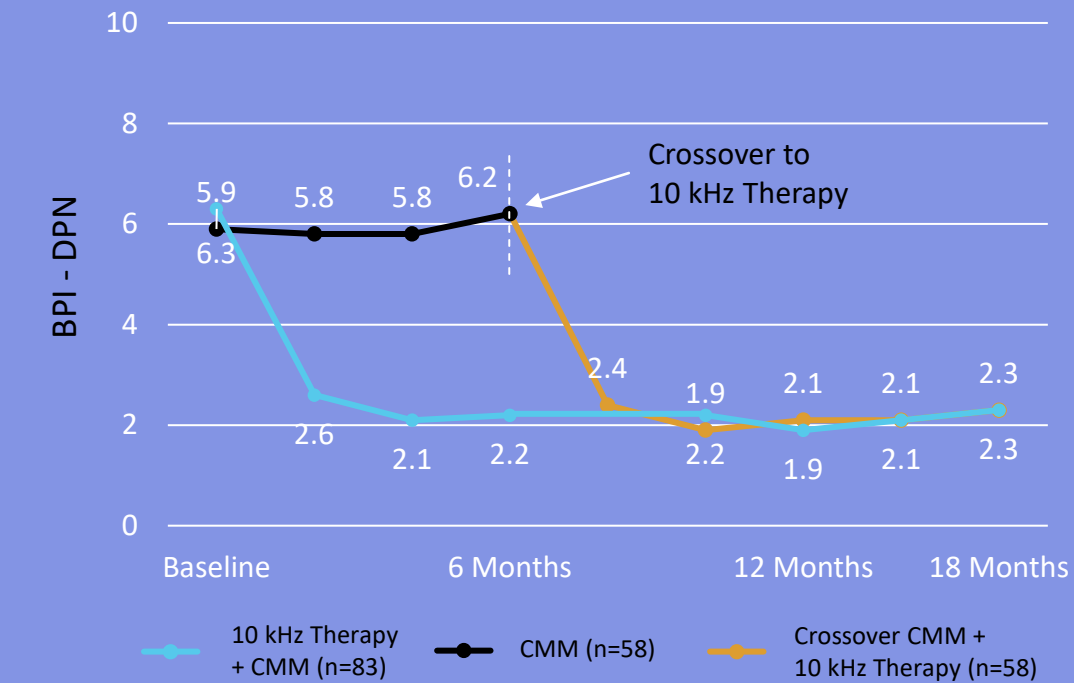
Did the investigator note improvement compared to baseline in motor, sensory, or reflex function, without deterioration in any category?



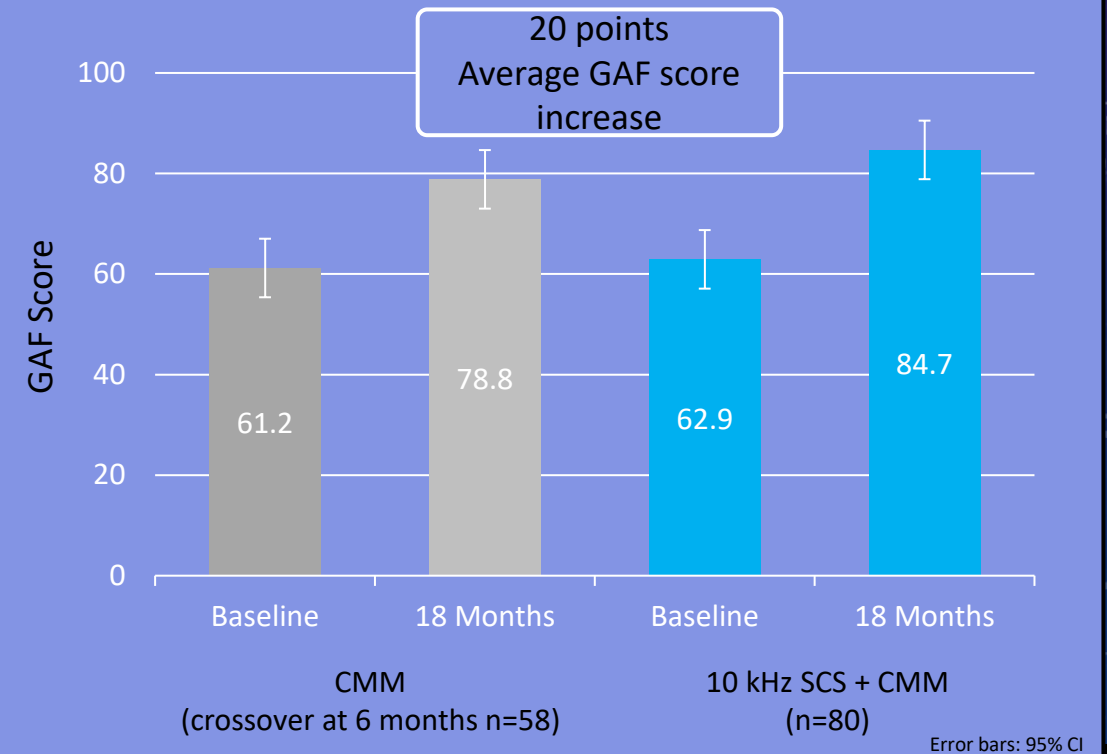
SENZA PDN RCT | Quality of Life Improvements

Patients reported an average 61% reduction in sleep disturbances due to pain

Pain Interference with Mood and Daily Activities



Global Assessment of Functioning



SENZA PDN RCT | Other Observed Endpoints

6-month: Other observed endpoints reported

Opioid reduction

- Decreased or eliminated: 23% of 10 kHz Therapy subjects vs 8% of CMM subjects
- Increased: 2% of 10 kHz Therapy subjects vs 11% of CMM subjects

Reduced hospital & ED visits

- Over 6 months, there were 7 fewer visits per 100 patients in the 10 kHz SCS group
 - 1.35 visits/CMM subject vs 1.27 visits/10 kHz SCS subject

18-month: Other observed endpoints reported

Significant improvement in overall health-related quality of life

- Sleep disturbance due to pain markedly improved by 61% with 10 kHz Therapy.
- Subjects experienced substantial, durable pain relief over 18-months



SCS – FDA Labeling including PDN specific additions

Indications for Use	<ul style="list-style-type: none">• The Senza[®], Senza II[™] and Senza Omnia[™] neuromodulation systems are indicated as aids in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain, and leg pain.• The Senza[®], Senza II[™] and Senza Omnia[™] neuromodulation systems, when programmed to include a frequency of 10 kHz, are indicated as aids in the management of chronic intractable pain of the lower limbs, including unilateral or bilateral pain, associated with diabetic neuropathy.
Contraindications	<p>The Senza, Senza II, and Senza Omnia Systems should not be used for those patients who:</p> <ul style="list-style-type: none">• Are poor surgical candidates, including those with poor glycemic control in whom the safety of the device has not yet been characterized, i.e. HbA1C >10%.• Fail to receive effective pain relief during trial stimulation.• Are unable to operate the SCS system.
Warnings	<p>Patients with diabetes:</p> <p>This device was only studied in patients with HbA1C up to 10%. In general, patients with diabetes have a higher risk of surgical complications, especially those who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure. Appropriate patient selection, pre-operative risk assessment, and reasonable optimization of glycemic control are recommended.</p>



CAPSAICIN 8% PATCH



CAPSAICIN: HIGHLY SELECTIVE AGONIST FOR TRPV1

What is capsaicin?

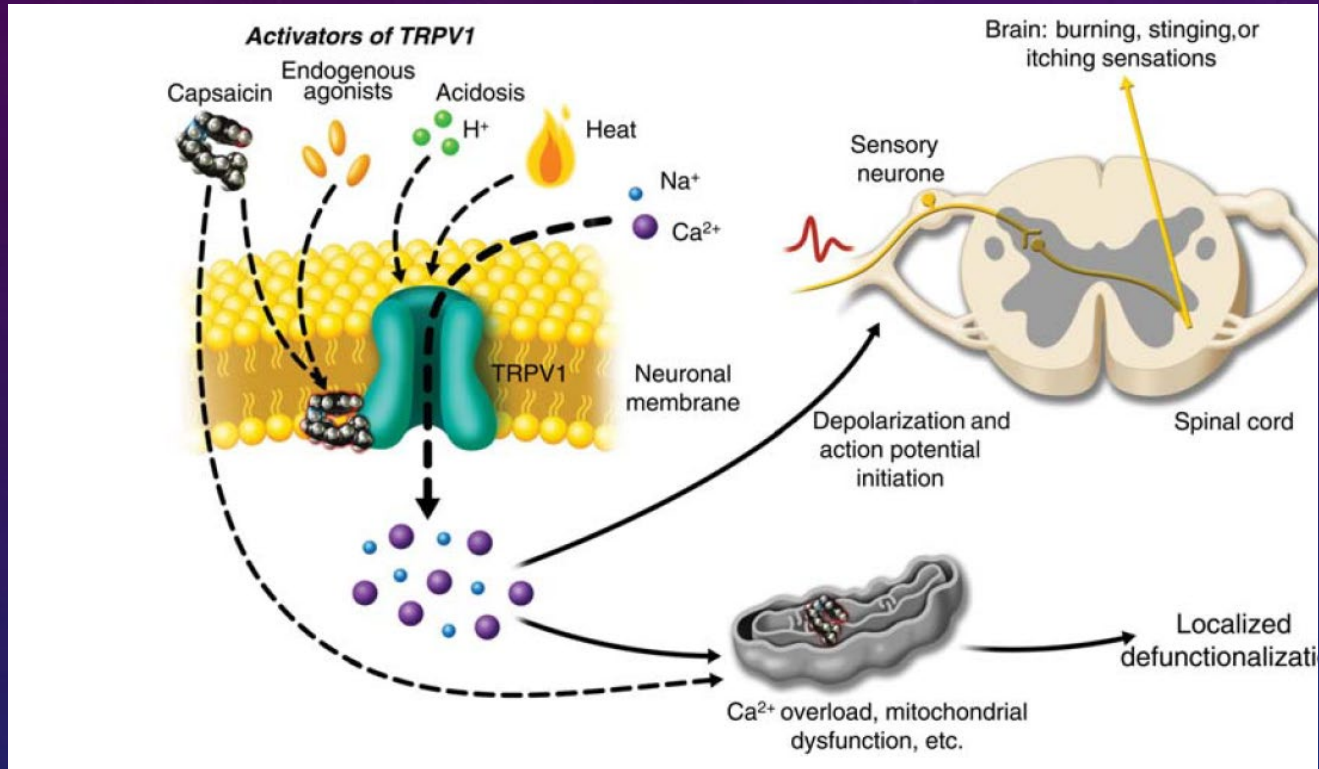
- Potent and highly selective agonist (or activator) for the transient receptor potential vanilloid-1 receptor (TRPV1)
- Capsaicin activates the cell membrane receptor TRPV1, which causes an influx of Ca^{2+} and Na^{+} into nociceptors (sensory receptors for painful stimuli) within the epidermis
- Continuous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

What is TRPV1?

- Transmembrane receptor-ion channel complex distributed throughout the CNS and PNS
- Preferentially expressed on sensory (nociceptive) nerve fibers – mainly C and $\text{A}\delta$ 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.



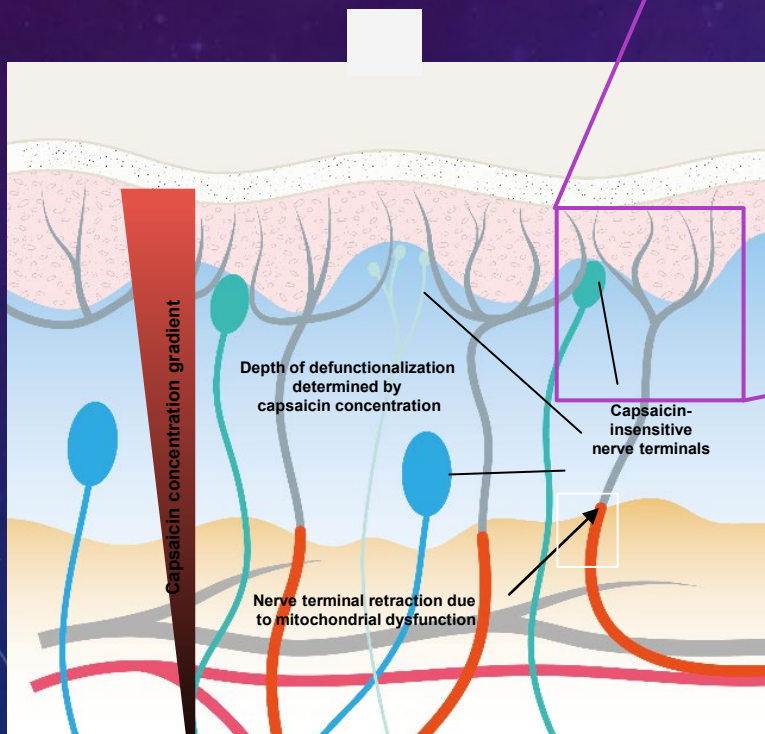
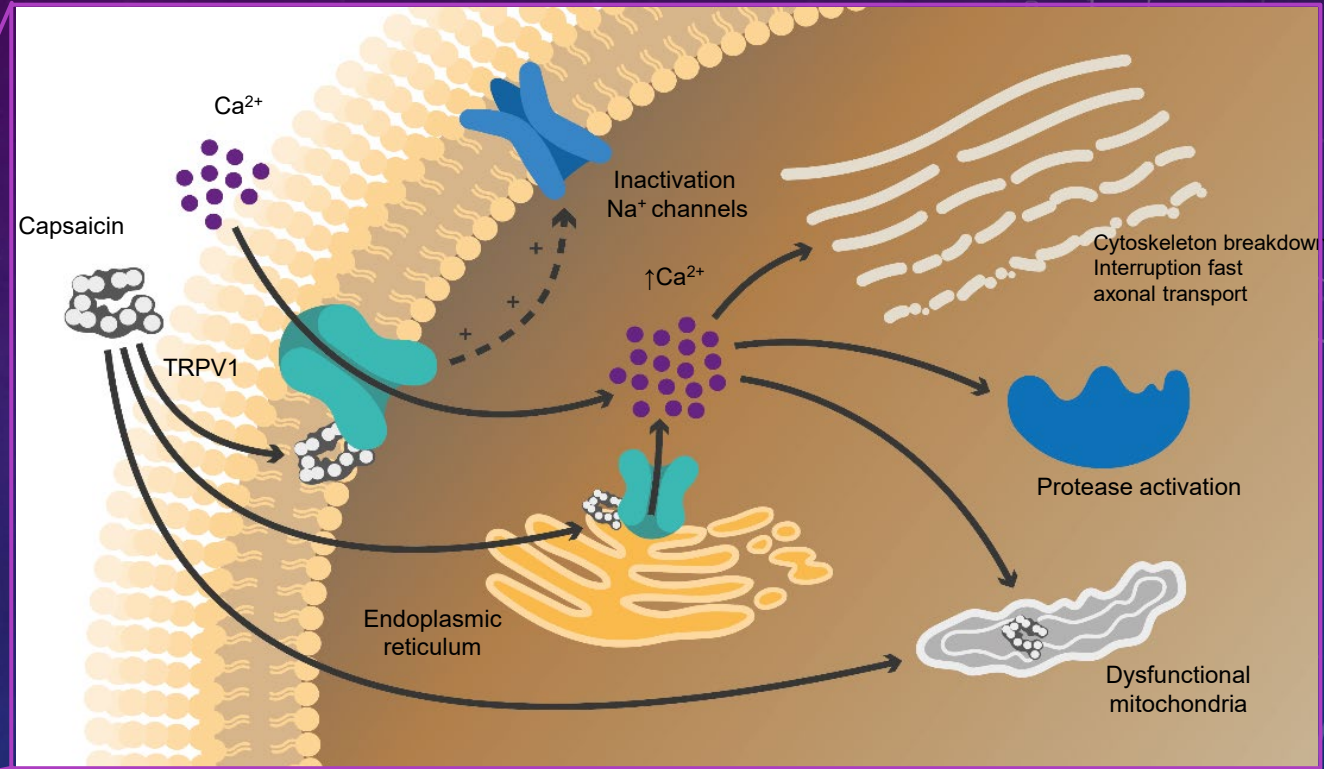
CAPSAICIN MECHANISM OF ACTION



- Activation of TRPV1 by capsaicin results in sensory neuronal depolarization, and can induce local sensitization to activation by heat, acidosis, and endogenous agonists.
- Topical exposure to capsaicin leads to the sensations of heat, burning, stinging, or itching.
- High concentrations of capsaicin or repeated applications can produce a persistent local effect on cutaneous nociceptors, which is best described as defunctionalization and constituted by reduced spontaneous activity and a loss of responsiveness to a wide range of sensory stimuli.

MITOCHONDRIAL DYSFUNCTION IS KEY CONTRIBUTOR

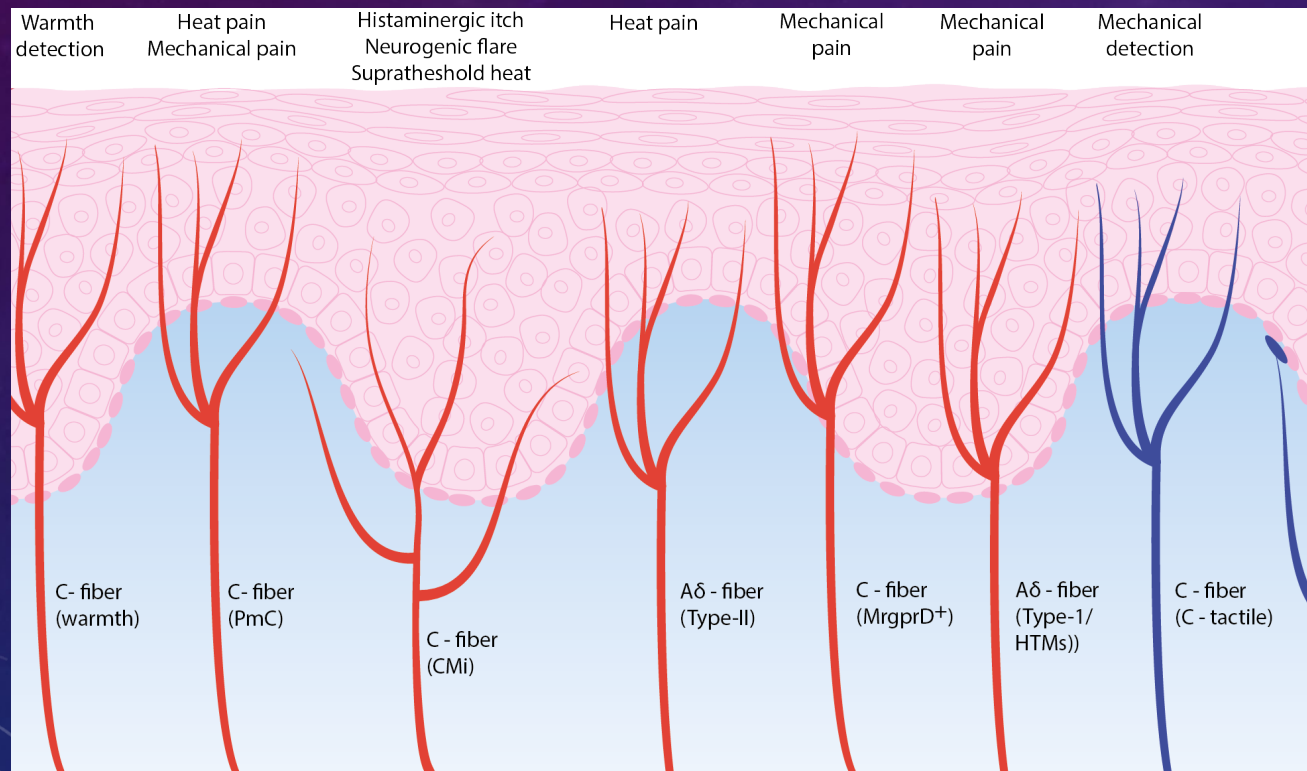
Multiple mechanisms underlie
capsaicin-induced
defunctionalization²



Anand P *et al.* 2011. *Br J Anaesth* 107:490–502.

Premkumar LS *et al.* 2008. *Curr Neuropharmacol* 6(2): 151–163

DEFUNCTIONALIZATION OF AFFERENT FIBER SUBPOPULATIONS

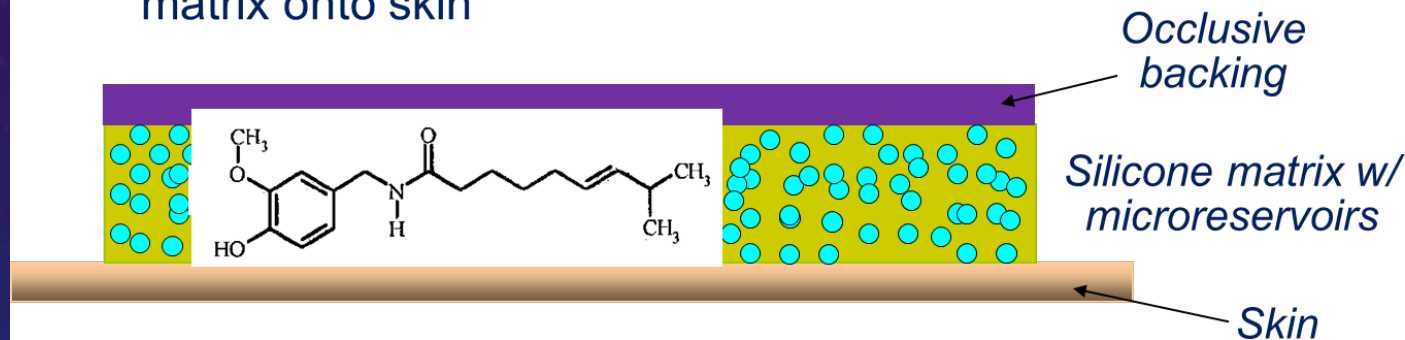


- Schematic model of primary afferent fiber subpopulations thought to be robustly defunctionalized by the 8% capsaicin treatment (shown in red). Not all fiber subpopulations have been included (e.g. tactile)

CAPSAICIN 8% TOPICAL SYSTEM

- indicated in adults for the treatment of neuropathic pain associated with postherpetic neuralgia (PHN) and for neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet.

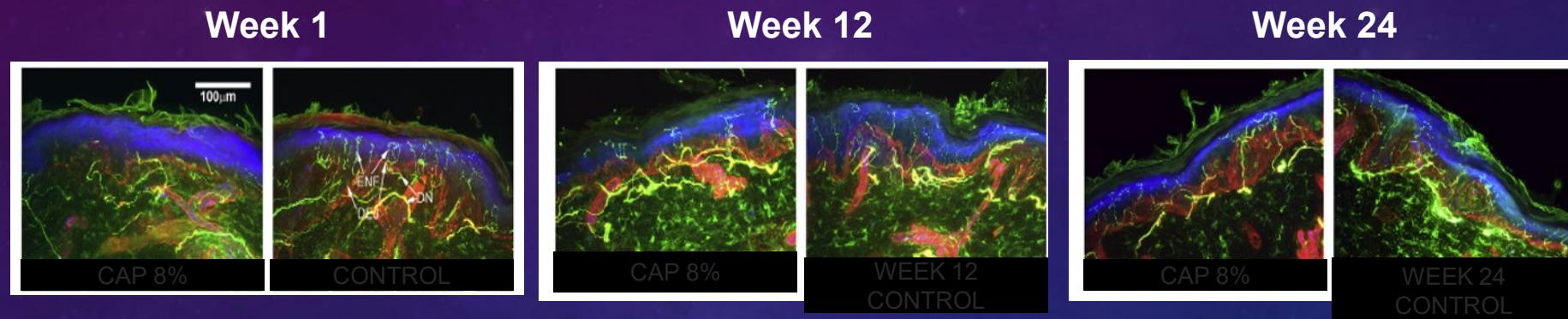
- Capsaicin fully solubilized in Transcutol (DGME)
- Capsaicin and DGME diffuse through silicone adhesive matrix onto skin



- Occlusion potentiates delivery and limits contamination
- Capsaicin released: $\sim 2.5\%$ of $640 \mu\text{g}/\text{cm}^2$, or $\sim 16 \mu\text{g}/\text{cm}^2/\text{hr}$
- Capsaicin absorbed: $\sim 1.1\%$, or $7 \mu\text{g}/\text{cm}^2$ skin

REVERSIBLE REDUCTION OF NERVE FIBERS DENSITY

Visualization of the reduction of epidermal nerve fibers (ENF) following single capsaicin 8% application to the thighs of healthy volunteers:



ENF reduction (80%)

Partial ENF regeneration

ENF recovery (93%)

Scale bar = 100 μm.

Immunostaining at time point indicated:

ENF and dermal nerves = **yellow** or **green**

Basement membrane at the dermal-epidermal junction and around blood vessels = **red**

Epidermis = **blue**

CAPSAICIN 8% TOPICAL SYSTEM HAS AMASSED CLINICAL EVIDENCE TO SUPPORT ITS SAFETY AND EFFICACY TO PATIENTS WITH PDPN

PHASE 3 TRIAL:

STEP

Phase III, PDPN
Capsaicin 8% topical system
vs Placebo
12-week follow-up¹

PHASE 3 TRIAL:

PACE

Phase III, PDPN
Capsaicin 8% topical system
with SoC vs SoC only
52-week follow-up^{2,3}

META ANALYSIS:

VAN NOOTEN

Meta Analysis, PDPN
25 randomized controlled trials,
Capsaicin 8% topical system and SoC
oral agents⁴

- ² Vinik, A.I. et al. 2019; ⁴ van Nooten et al. 2017;; ³ Vinik et al. 2016 ¹. Simpson, D.M. et al. 2017

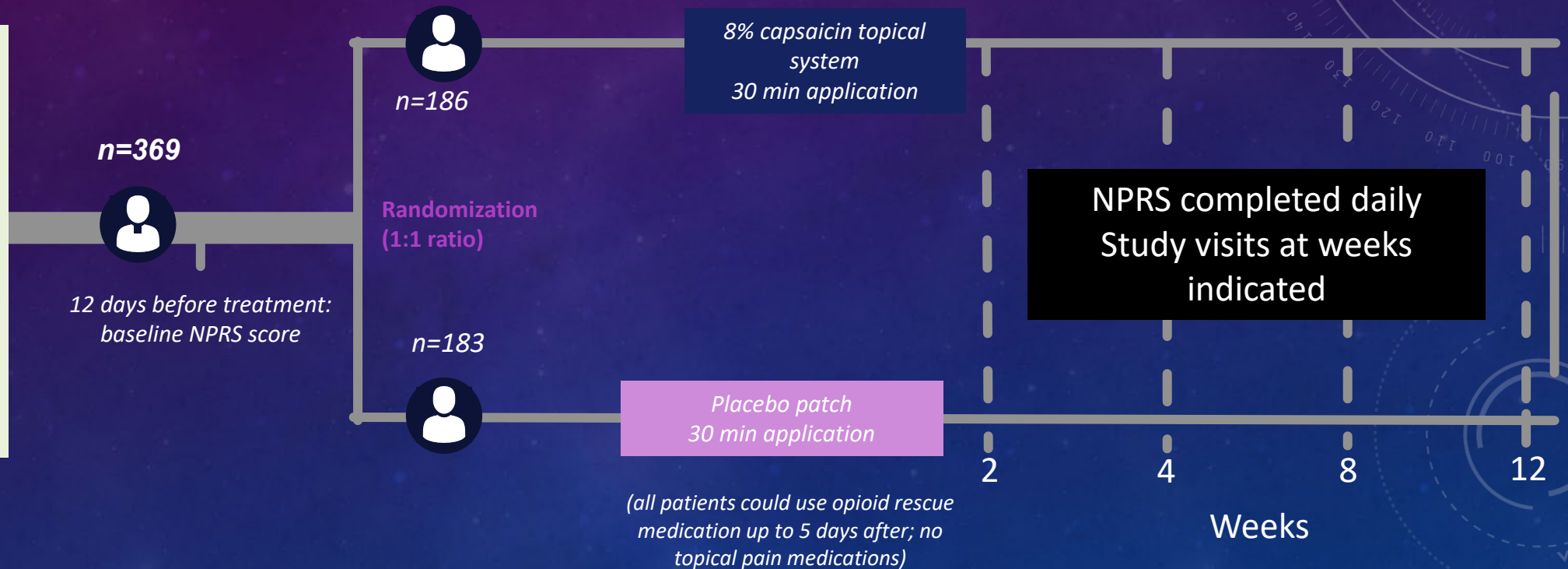


STEP

In this Phase 3 study, 369 DPN patients were randomized 1:1 to receive either a Capsaicin 8% topical system or placebo 30-min. patch application to painful areas of the feet, with daily NPRS reports and other evaluations over for 12 weeks: areas of the feet

Key inclusion criteria:

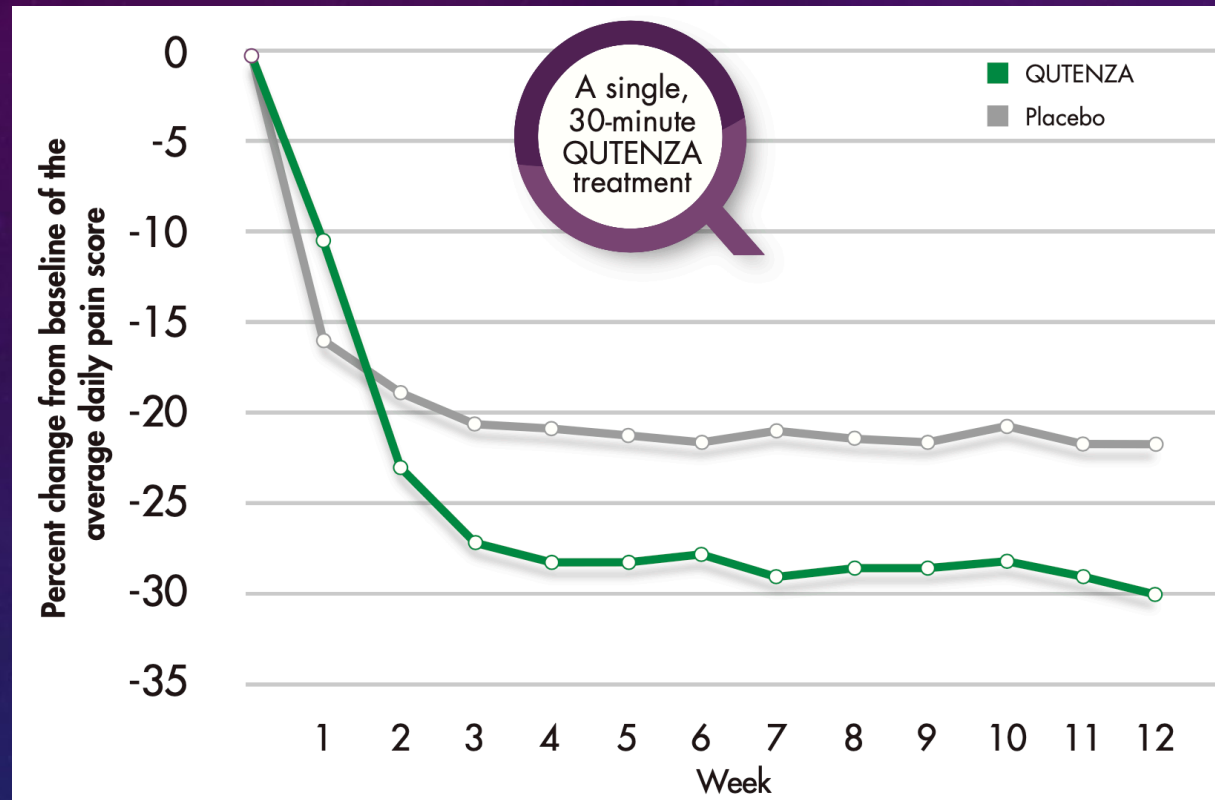
- Aged ≥ 18 years with a diagnosis of DPN for at least 1 year
- HbA1c $\leq 11\%$ at screening and 3–6 months
- Stable doses of pain medication >4 weeks before screening*
- Average NPRS score over the last 24 hours of ≥ 4 during the screening period



NPRS, numeric pain rating scale; PGIC, Patient Global Impression of Change; EQ-5D, EuroQol 5-dimensions questionnaire; BPI-DN, Brief Pain Inventory – Diabetic Neuropathy

Simpson DM *et al.* J Pain. 2017;18:42–53.

Pain relief that has a fast onset of action and is durable for up to 3 months



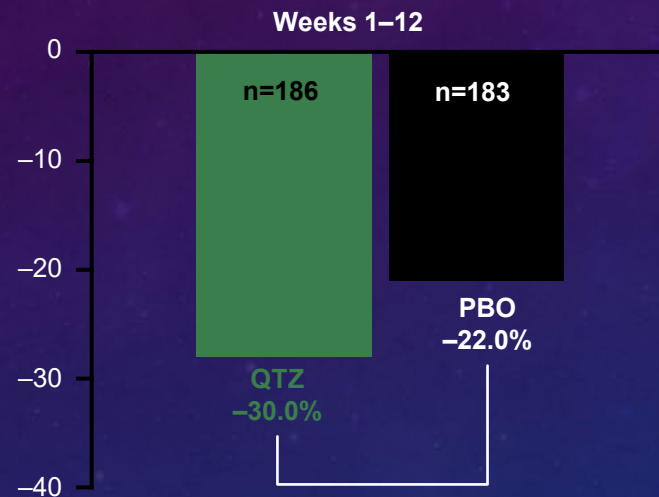
One application of Capsaicin 8% topical system provided a durable reduction in pain from weeks 2 - 12¹

The median time to onset of pain relief for Capsaicin 8% topical system is faster than for treatments commonly prescribed in PDPN, for example pregabalin has a 36-day onset of pain relief^{1,2}

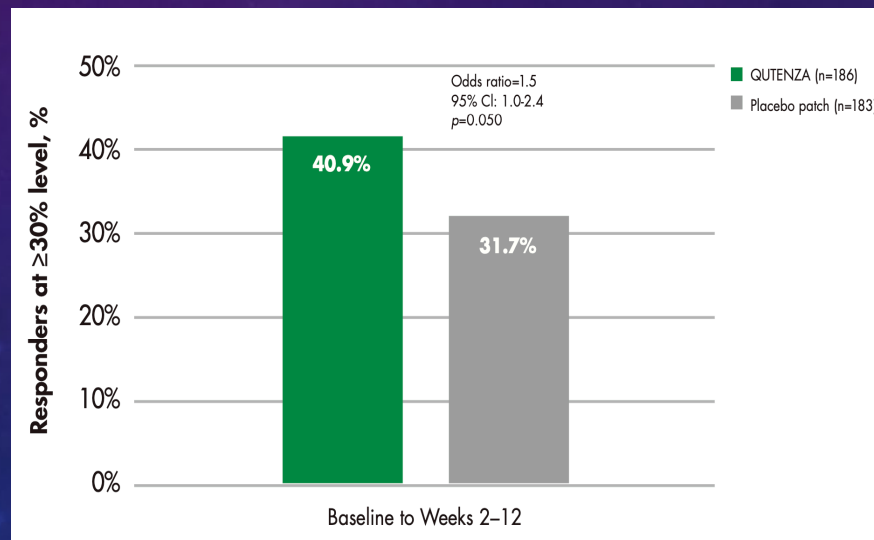
Sources: 1 Simpson, D.M. et al. 2017; 2 Haanpää M. et al. 2016

Reduction in pain

Mean percentage change from baseline in average daily pain score throughout the study¹



Proportion of patients achieving $\geq 30\%$ reduction in pain from baseline¹



There was a statistically significant reduction in average daily pain in the Capsaicin 8% topical system group versus the placebo topical system group¹

Capsaicin 8% topical system delivered fast pain relief, as early as week 2¹

Capsaicin 8% topical system provided prolonged pain relief up to week 12¹

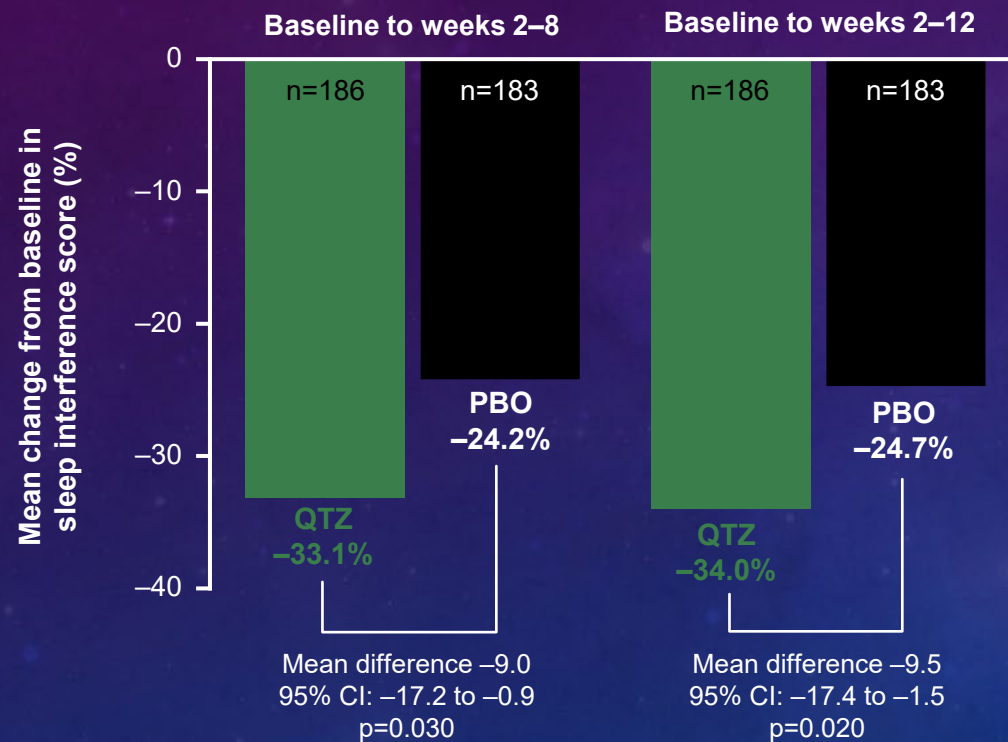
19 days in the Capsaicin 8% topical system group (95% CI for median, 12.0–37.0)

72 days in the placebo group (95% CI for median, 19.0–not calculable)

Sources: 1 Simpson, D.M. et al. 2017

Improvements in sleep

Findings from STEP: Change in sleep interference score, Capsaicin 8% topical system vs. placebo (PBO); One 30-minute application to feet; 12-week follow-up¹



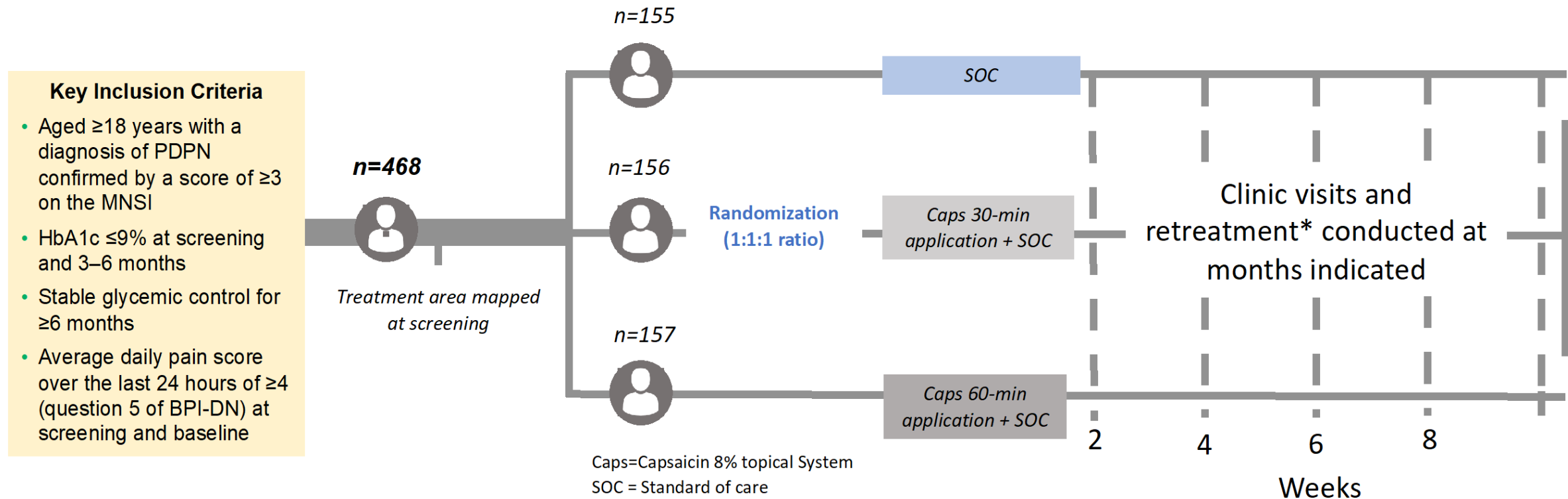
- A reduction in sleep interference score was observed with Capsaicin 8% topical system vs PBO
- Capsaicin 8% topical system provides a holistic benefit to patients, including relief of pain and associated Quality of Life (QoL) reducing symptoms such as poor sleep quality

PACE Study Design

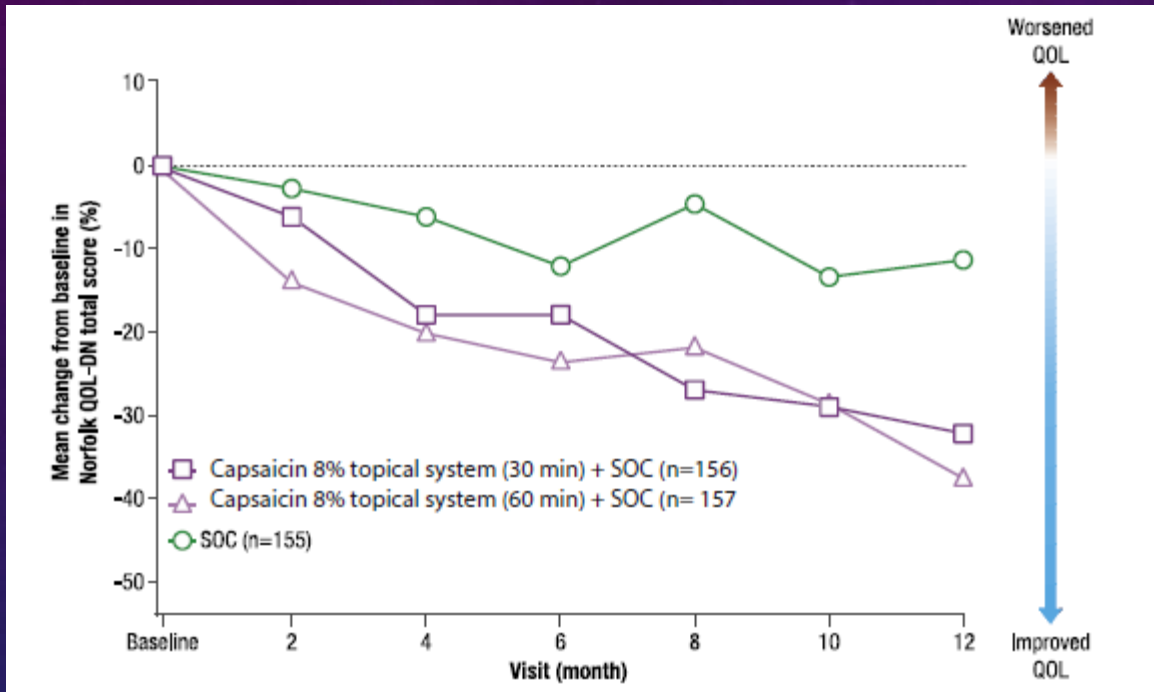
Phase III, open-label, long-term safety study –

Capsaicin 8% topical system (30- or 60 minute repeated applications* to feet only) + SOC vs SOC alone; 52-week follow-up

The primary objective was the evaluation of safety, in particular with regard to effects on sensory function in diabetic patients



Mean Percentage Change in Norfolk QOL-DN total score from baseline



- Patients treated with Capsaicin experienced no deterioration in mean Norfolk QOL-DN total score from baseline to end of study

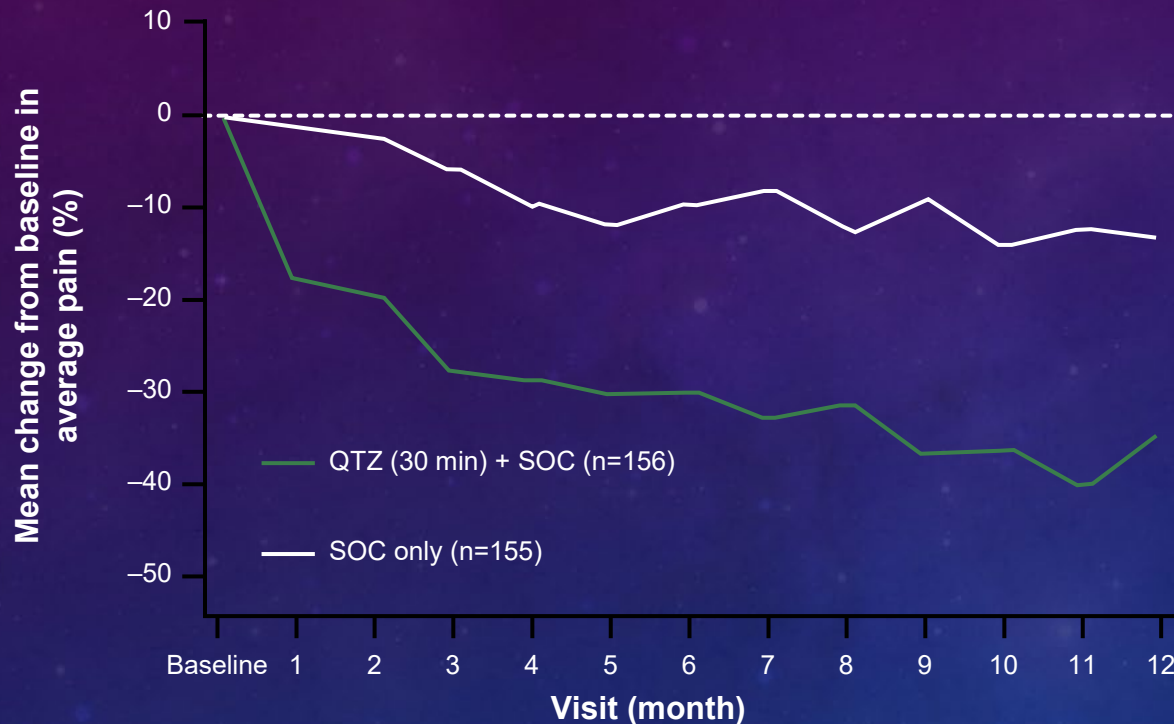
Similar improvements were observed across Norfolk subscale scores:1,2

- Small fiber
- Symptoms
- Autonomic
- Physical function
- Activities of daily living

Mean percentage change in Norfolk QOL-DN total score from baseline during the study (SAS)
In patients who received a capsaicin treatment at Month 12 and had an end of study visit at Month 14, mean [SD] change in Norfolk total score by Month 14 was: 30 min, -36.1% [51.6] (n = 79); 60 min, -40.2% [39.4] (n = 76). SAS safety analysis set, SOC standard of care

52-week study pain relief

Reduction in pain intensity over 12 months in PACE study
(mean pain, 24 hours)¹



*1–7 treatments with ≥8-week intervals.

Capsaicin 8% topical system is applied q3 months and maintains its pain-relieving effects for up to one year, with some patients experiencing improved pain relief upon repeated treatments¹

Capsaicin 8% topical system delivered a mean response rate of 67.3% amongst the 156-patient study population over 52-weeks¹

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 an SoC treatment (including antidepressants, antiepileptics, and/or opioids) at the investigator's discretion.

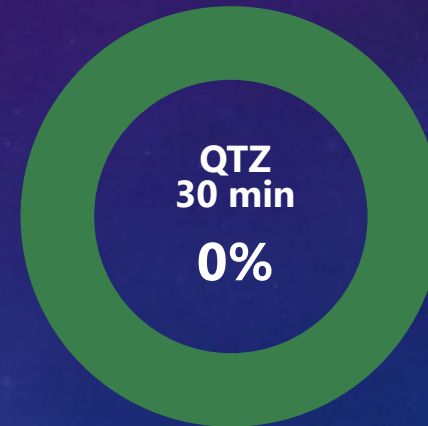
Sources: 1 van Nooten et al. 2017; 2 Vinik, A.I. et al. 2016

Tolerability

TEAEs occurring in $\geq 5\%$ of patients in treatment group, 52-week PACE clinical study²

n (%)	QTZ 30 min (n=156)
≥ 1 TEAE	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%)
TEAE leading to permanent discontinuation	7 (4.5%)
Drug-related TEAE	62 (39.75%)

Drug-related TEAEs leading to permanent discontinuation²



Capsaicin 8% topical system 30 min (n=156)

Clinical evidence suggests that the effectiveness of Capsaicin 8% topical system is accompanied by a favorable tolerability profile with 0% drug-related TEAEs leading to permanent discontinuation, in clinical studies^{1,2}

Sources: **1** van Nooten et al. 2017; **2** Vinik, A.I. et al. 2016

Reduce the patient need for requiring additional medications to manage PDPN

Usage of concomitant medications at baseline and end of 52-week clinical trial¹

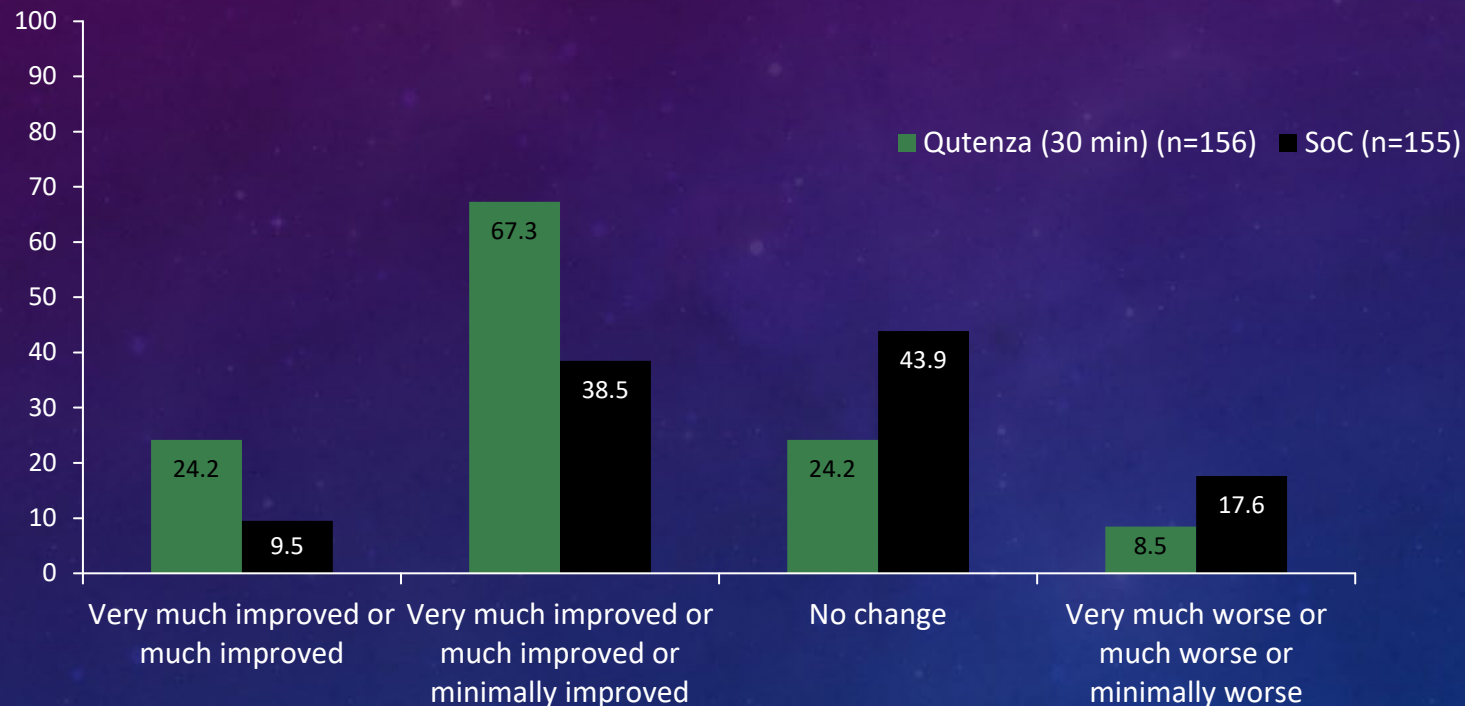
n, (%)	Capsaicin 8% topical system (30 min) + SoC	SoC
Baseline	n = 156	n = 155
Antidepressants	17 (10.9%)	12 (7.7%)
Antiepileptic drugs	44 (28.2%)	50 (32.3%)
Opioids	17 (10.9%)	13 (8.4%)
End of Study	n = 146	n = 146
Antidepressants	16 (11.0%)	22 (15.1%)
Antiepileptic drugs	43 (29.5%)	63 (43.2%)
Opioids	16 (11.0%)	17 (11.6%)

Clinical evidence suggests that Capsaicin 8% topical system usage may reduce use of opioids in PDPN pain management¹

Sources: 1 Vinik, A.I. et al. 2016

EQ-5D utility index

Patient global impression of change, 52-week clinical study¹



Patient experience is positively associated with clinical effectiveness and patient safety¹

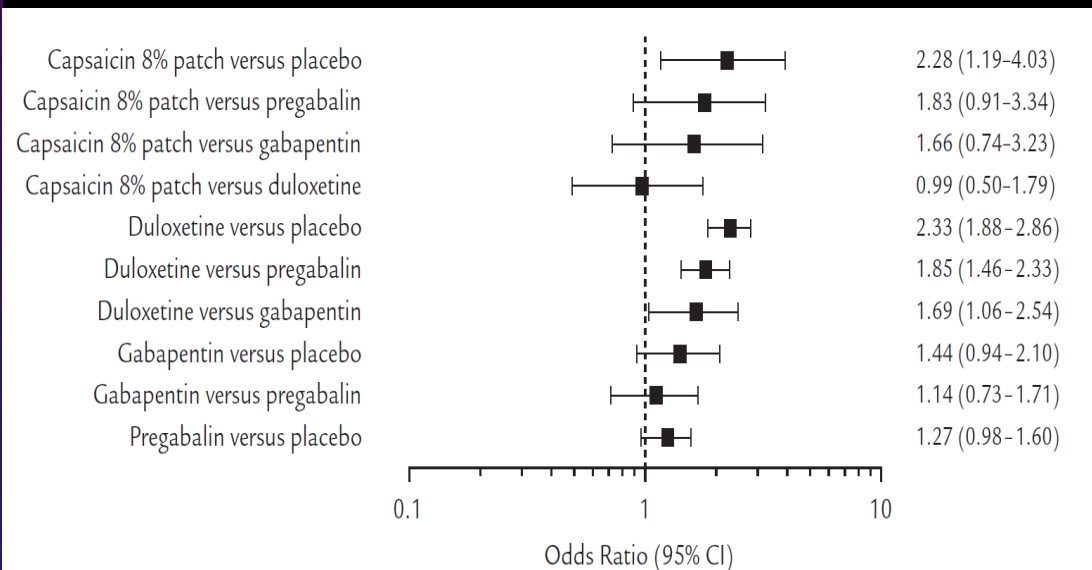
Findings from the PACE study illustrate the improvement in EQ-5D utility index with Capsaicin 8% topical system use versus SoC¹

Limitation: These results must be interpreted with caution. This was an open-label study and may be confounded by evaluator bias; results could represent chance findings.

Sources: 1 Vinik, A.I. et al. 2016

PDPN Meta-Analysis shows favorable efficacy and safety of Capsaicin 8% topical system vs. first line oral agents

At least 30% pain relief



Sources: 1 van Nooten et al. 2017

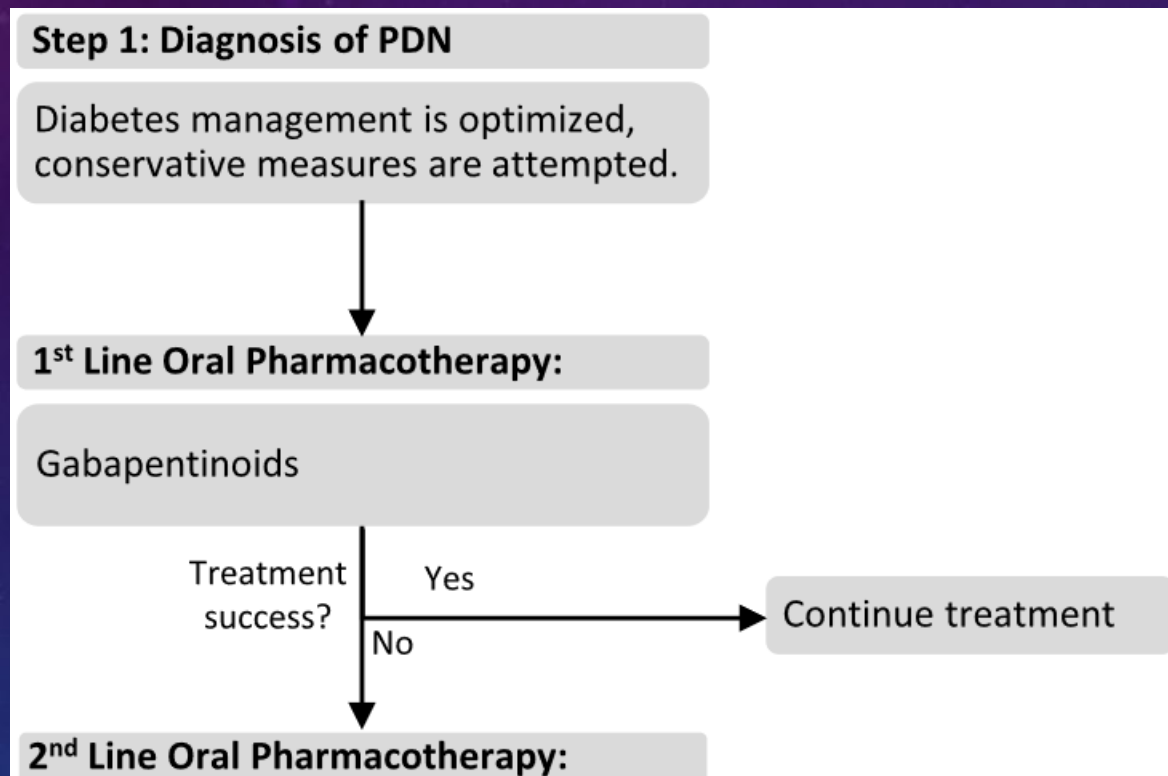
Tolerability of PDPN treatments¹

Tolerability outcomes	Capsaicin 8% topical system	Pregabalin	Gabapentin	Duloxetine
Somnolence	~0%	40.2%	48.1%	6.1%
Dizziness	~0%	35.0%	36.3%	74.7%
Nausea	~0%	65.5%	42.1%	0.4%
Headache	10.6%	83.3%	60.4%	28.8%
Fatigue	~0%	61.4%	22.3%	29.1%
Constipation	~0%	41.1%	49.9%	86.9%
Diarrhea	~0%	67.9%	60.1%	2.8%
Discontinuation due to adverse events	~0%	46.2%	34.3%	19.5%

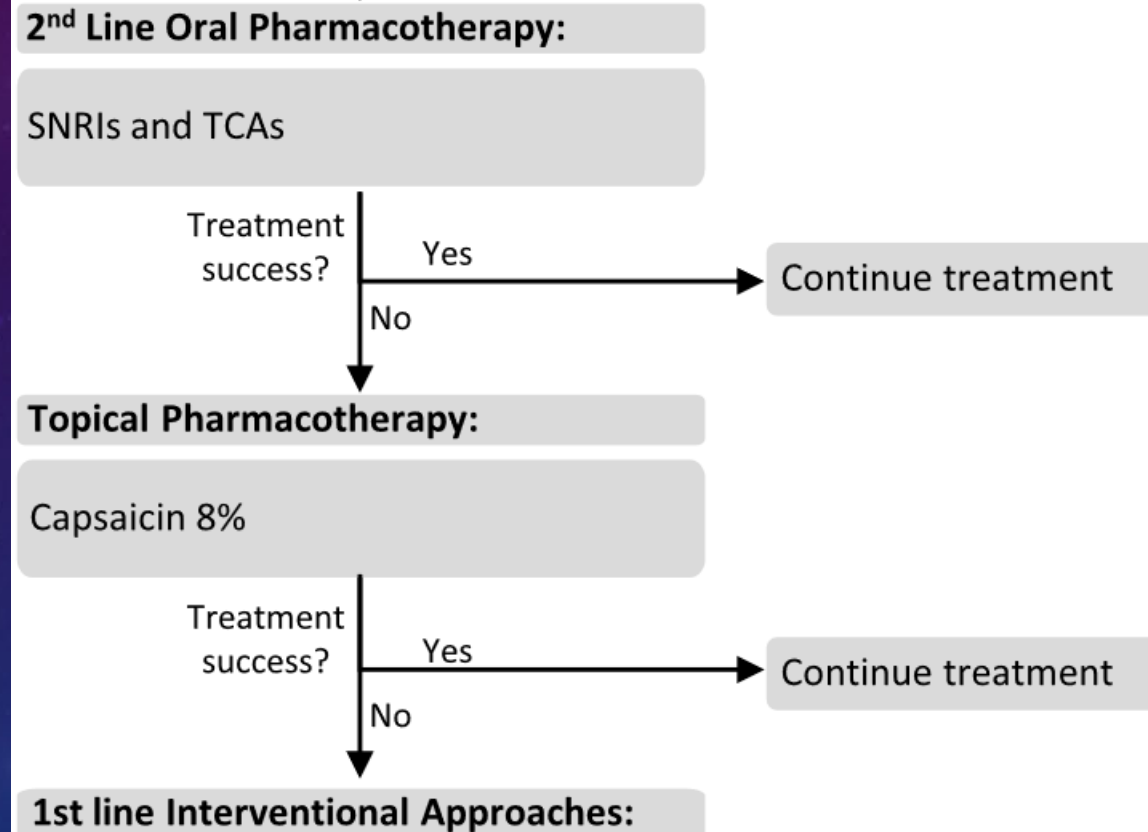
Meta-analysis of clinical studies versus SoC options found that Capsaicin 8% topical system was associated with similar pain relief to other commonly prescribed PDPN treatments¹

Limitation: This meta-analysis is an indirect comparison between available treatments for the same indication and should be considered descriptive only. Therefore, the results require cautious interpretation and could represent chance findings.

ASPN PROPOSED TREATMENT ALGORITHM



ASPN PROPOSED TREATMENT ALGORITHM



ASPN PROPOSED TREATMENT ALGORITHM

1st line Interventional Approaches:

Spinal cord stimulation trial

Treatment
success
(50% pain
relief)?

Yes

Permanent implant
SCS

No

2nd Line Interventional and Non-invasive Approaches:

Trial for DRG-S, PNS, intrathecal pump,
or mPNS

Treatment
success
(50% pain
relief)?

Yes

Permanent implant
DRG-S, PNS,
Intrathecal pump,
repeat mPNS

No

3rd Line Treatments:

ASPN PROPOSED TREATMENT ALGORITHM

3rd Line Treatments:

Oral pharmacotherapy (Na⁺ blocker, SNRI/opioid), ketamine/lidocaine infusions, Botox, neurolysis/RFA, opioid agonists



FUTURE DIRECTIONS

- SCS waveforms continue to improve which could improve efficacy for management of PDPN
- HF10 Sensory Study (in progress)
- QuTenza (Reversing PDPN and NPDPN)
- Acupuncture for PDPN
- Virtual Reality/Mindfulness for PDPN



IN SUMMARY

- Management of Painful Diabetic Peripheral Neuropathy starts with identification and diagnosis
- Non-Opioid medication management remains a first-line treatment strategy
- Alternative, evidence-based therapies do exist, including spinal cord stimulation and capsaicin patch
- Future directions include some restoration of sensation



THANK YOU

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