PAINWEEK®

Treatment Options for Painful Diabetic Neuropathy: A Review of the Latest Clinical Evidence

Neel Mehta, MD

Erika Petersen, MD

Disclosure

Dr. Mehta

- Grant/Research Support: Nevro
- Honoraria: Nevro

Dr. Petersen

- Consultant/Independent Contractor: Abbott/St. Jude Medical, Medtronic Neuromodulation, Nevro
- Grant/Research Support: Nevro, Neuros Medical, ReNeuron, and Medtronic Neuromodulation
- Advisory Board: SynerFuse
- Stock Shareholder: SynerFuse

Learning Objectives

- Describe the mechanism of painful diabetic neuropathy
- Cite accepted protocol for treatment
- Compare emerging studies for novel treatment

Classification of Diabetic Neuropathies (75%)

- DSPN
  - Primarily small-fiber neuropathy
  - Primarily large-fiber neuropathy
  - Mixed small- and large-fiber neuropathy (most common)
- Autonomic
  - Cardiovascular
  - Reduced HRV
  - Resting tachycardia
  - Orthostatic hypotension
  - Sudden death (malignant arrhythmia)
- Gastrointestinal
  - Diabetic gastroparesis (gastropathy)
  - Diabetic enteropathy (diarrhea)
  - Colonic hypomotility (constipation)
- Urogenital
  - Diabetic cystopathy (neurogenic bladder)
  - Erectile dysfunction
  - Female sexual dysfunction

Classification of Diabetic Neuropathies (cont)

- Sudomotor dysfunction
  - Distal hypohydrosis/anhidrosis,
  - Gustatory sweating
- Hypoglycemia unawareness
- Abnormal pupillary function
- Mononeuropathy (mononeuritis multiplex) (atypical forms)
  - Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal)
  - Mononeuritis multiplex (if confluent may resemble polyneuropathy)
- C. Radiculopathy or polyradiculopathy (atypical forms)
  - Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy)
  - Thoracic radiculopathy
- Nondiabetic neuropathies common in diabetes
  - Pressure palsies
  - Chronic inflammatory demyelinating polyneuropathy
  - Radiculoplexus neuropathy
  - Acute painful small-fiber neuropathies (treatment-induced)

ADA position statement on diabetic neuropathy, Pop-Busui et al. Diabetes Care 2017

Definition of DSPN

Table 2—Symptoms and signs of DSPN

	Large myelinated nerve fibers	Small myelinated nerve fibers
Function	Pressure, balance	Nociception, protective sensation
Symptoms§	Numbness, tingling, poor balance	Pain: burning, electric shocks, stabbing
Examination (clinically diagnostic)**	Ankle reflexes: reduced/absent Vibration perception: reduced/absent 10-g monofilament: reduced/absent Proprioception: reduced/absent	Thermal (cold/hot) discrimination: reduced/absent** Pinprick sensation: reduced/absent**

§To document the presence of symptoms for diagnosis; **Documented in symmetrical, distal to proximal pattern.

- Diagnosis of exclusion
- Present in at least 20% of people with DM-1 after 20 years of disease duration
- May be present in at least 10%–15% of newly diagnosed patients with DM-2, and up to 50% after 10 years of disease duration

ADA position statement on diabetic neuropathy, Pop-Busui et al. Diabetes Care 2017

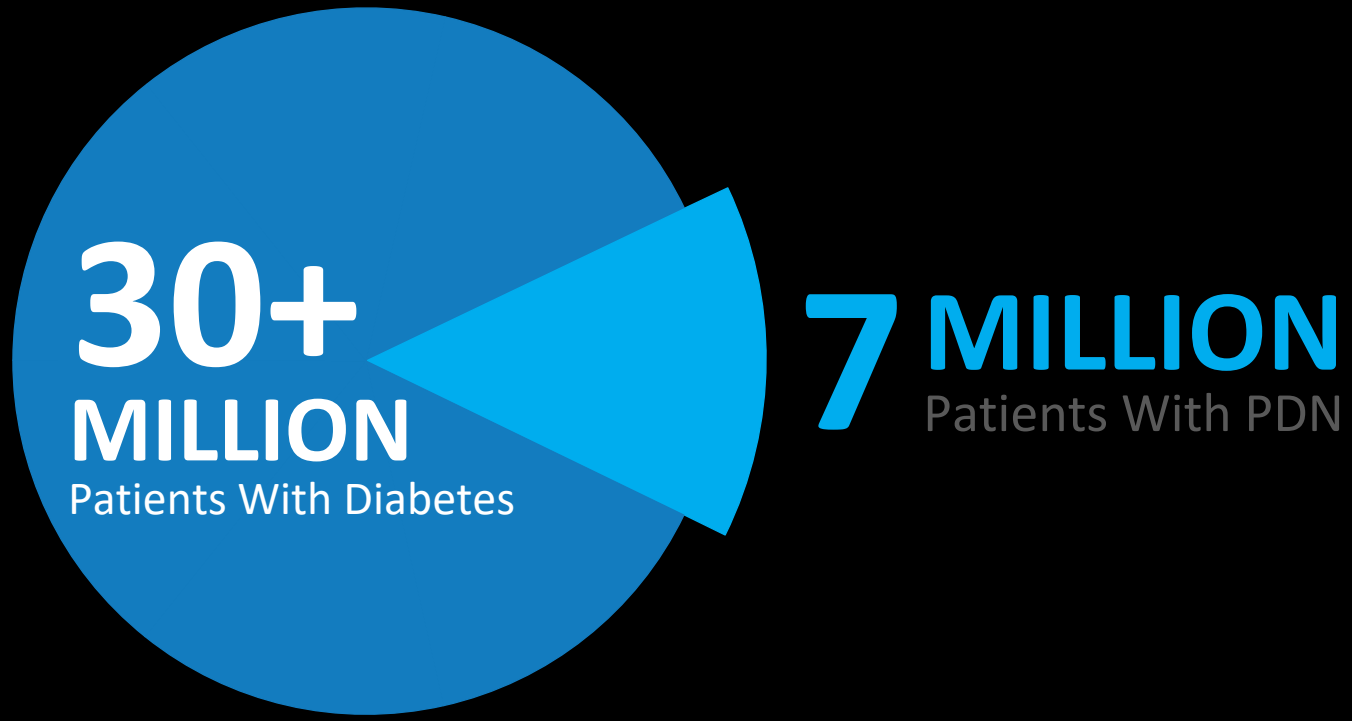
Disease Prevalence & Cost

Diabetes is a National Epidemic

- 34.2 million people with diabetes = 10.5% of the population
- Another 88 million people with prediabetes (more than 1 in 3 adults)
- Costs: $327 billion
  - Direct medical costs = $237 billion
  - Indirect costs = $90 billion

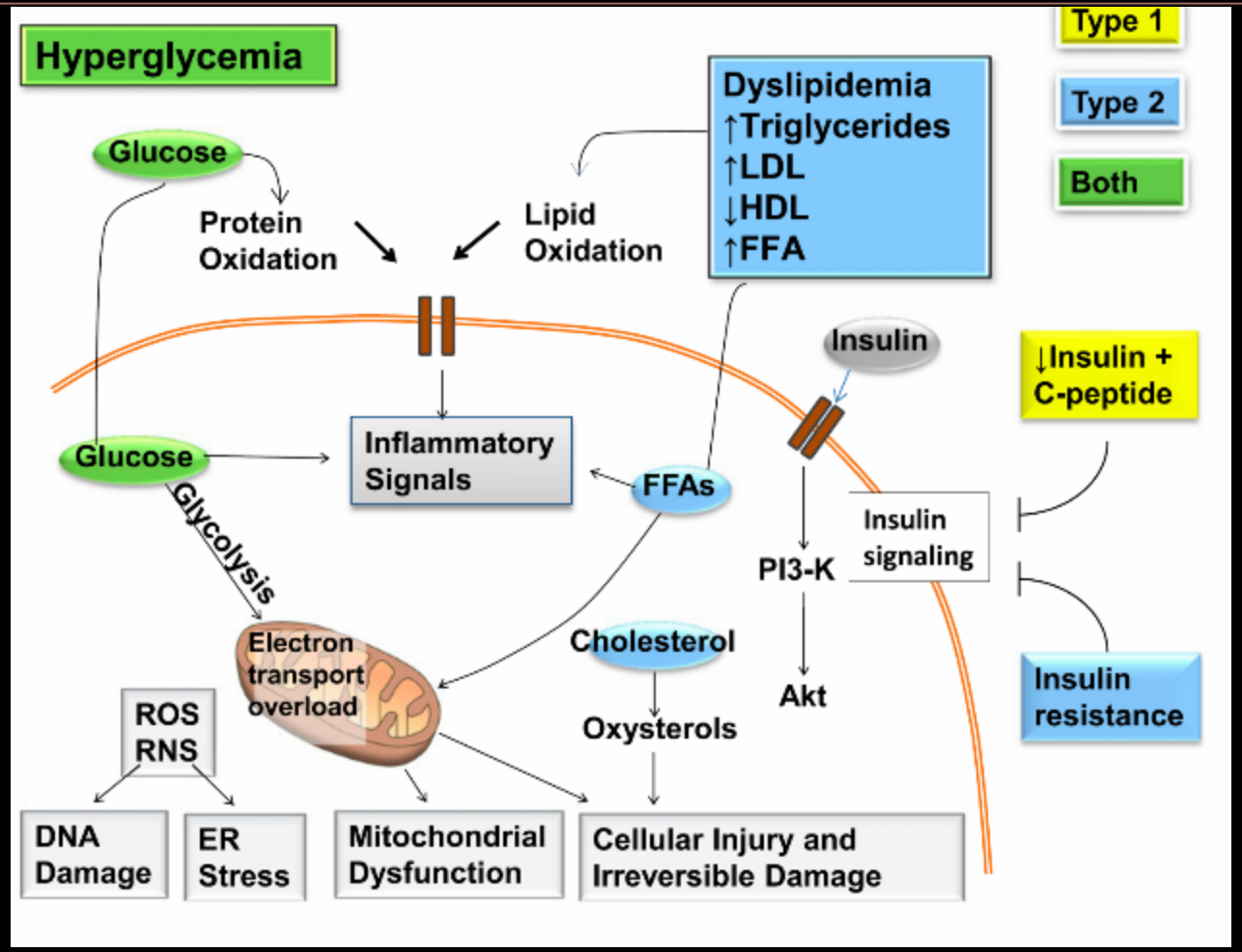
Painful Diabetic Neuropathy is Common

- 20% to 26% of those with diabetes have PDN



CDC National Diabetes Statistics Report, 2020; Davies M et al. Diabetes Care 2006; Schmader KE. Clin J Pain 2002

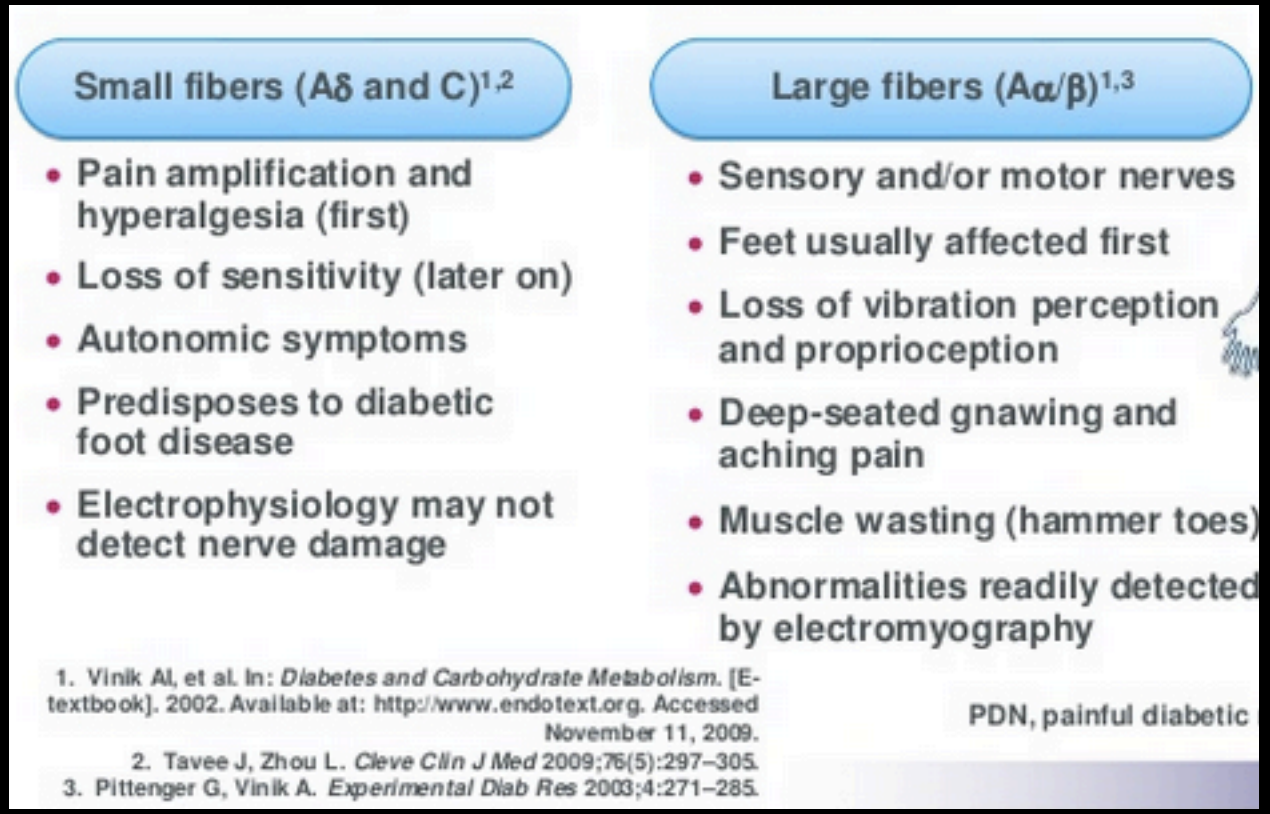
Mechanisms of Diabetic Neuropathy



ADA position statement on diabetic neuropathy, Pop-Busui et al. Diabetes

Symptomatology

- Symptoms vary according to the class of sensory fibers involved
- The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesias

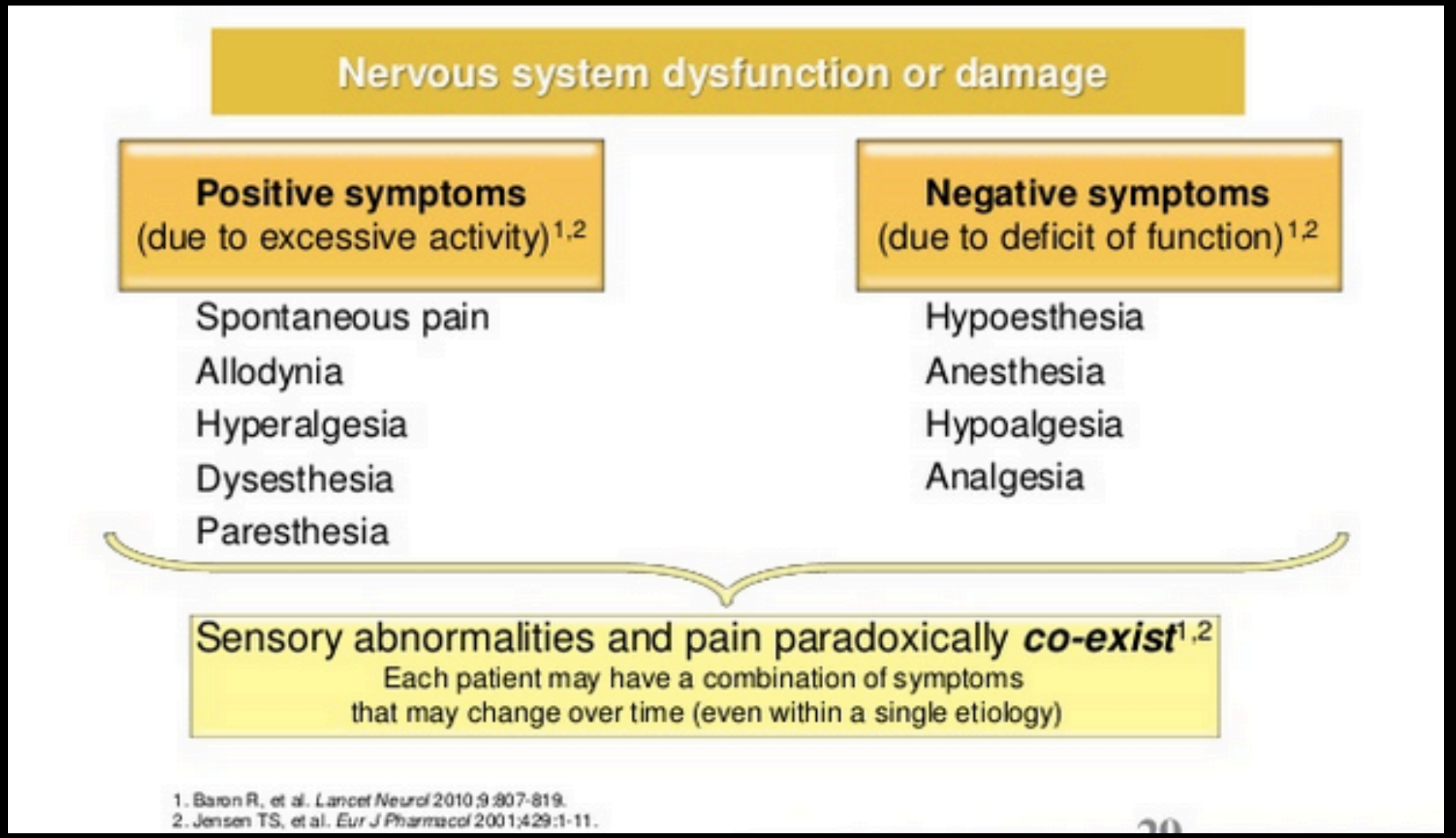


Risk Factors

- Distal symmetric polyneuropathy (DSPN) has been associated with:
  - Glycemia
  - Height
  - Smoking
  - Blood pressure
  - Weight
  - Lipids

Impact of Neuropathic Pain

- It may lead to interference with daily activities, disability, psychosocial impairment, and reduced health-related quality of life
- The direct and indirect economic burden associated with neuropathic pain is substantial



1. Baron R, et al. *Lancet Neurol* 2010;9:807-819.
2. Jensen TS, et al. *Eur J Pharmacol* 2001;429:1-11.

- Pain may significantly **interfere with a patient's ability to exercise or walk**[1]
  - Walking has been shown to improve HbA_{1C} in patients with diabetes regardless of change in body mass[2,3]
- Pain often intensifies at night and may significantly **interfere with sleep**[4]
  - Sleep debt has been shown to have a negative impact on metabolic and endocrine control[5-7]
- Pain is significantly correlated with **depression** in diabetic patients[8]

PDN, painful diabetic neuropathy; HbA_{1C}, glycated hemoglobin

1. Novak P, et al. *J Rehabil Med* 2004;36:249–252.
2. Boule NG, et al. *JAMA* 2001;286:1218–1227.
3. American Diabetes Association. *Diabetes Care* 2011;34(Suppl1):S11–S61.
4. Quattrini C, et al. *Diabetes Metab Res Rev* 2003;19:S2–S8.
5. Zelman DC, et al. *Clin J Pain* 2006;22:681–685.
6. Spiegel K, et al. *Lancet* 1999;354:1435–1339.
7. Åkerstedt T, Nilsson PM. *J Intern Med* 2003;254:6–12.
8. Raval A, et al. *Indian J Med Res* 2010;132:195-200.

Therapies

- Pathogenetic therapies: “There is a lack of treatment options that effectively target the natural history of DSPN.”

- Glucose control: “No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions.”

Therapies

Pain management:

- Consider either pregabalin or duloxetine as the initial approach
- Gabapentin may also be used as an effective initial approach, taking into account patients' socioeconomic status, comorbidities, and potential drug interactions
- Tricyclic antidepressants should be used with caution given the higher risk of serious side effects
- The use of opioids, including tapentadol or tramadol, is not recommended as first- or second-line agents

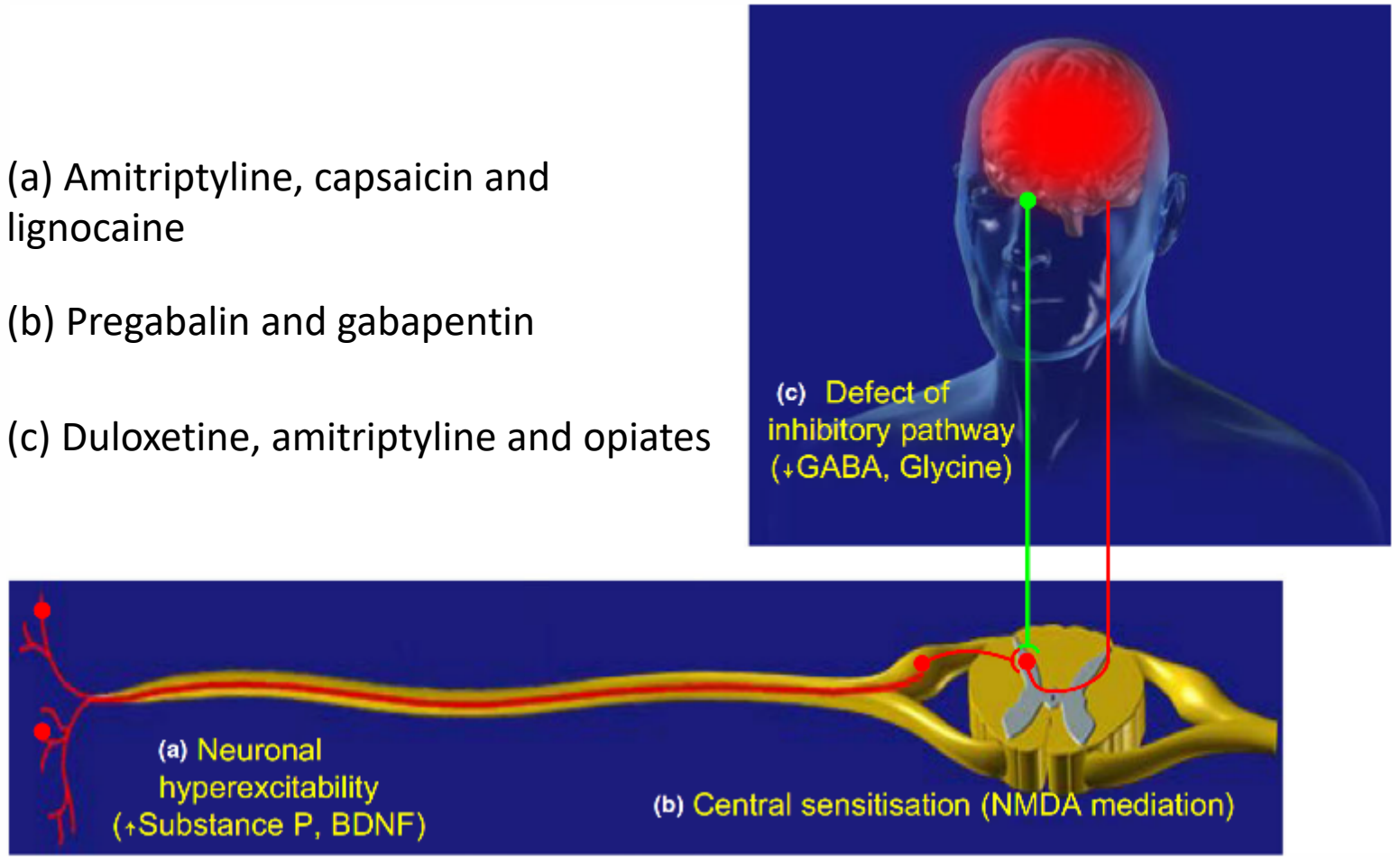
ADA position statement on diabetic neuropathy, Pop-Busui et al. Diabetes Care 2017

Level of Action of Commonly Used Treatments

(a) Amitriptyline, capsaicin and lignocaine

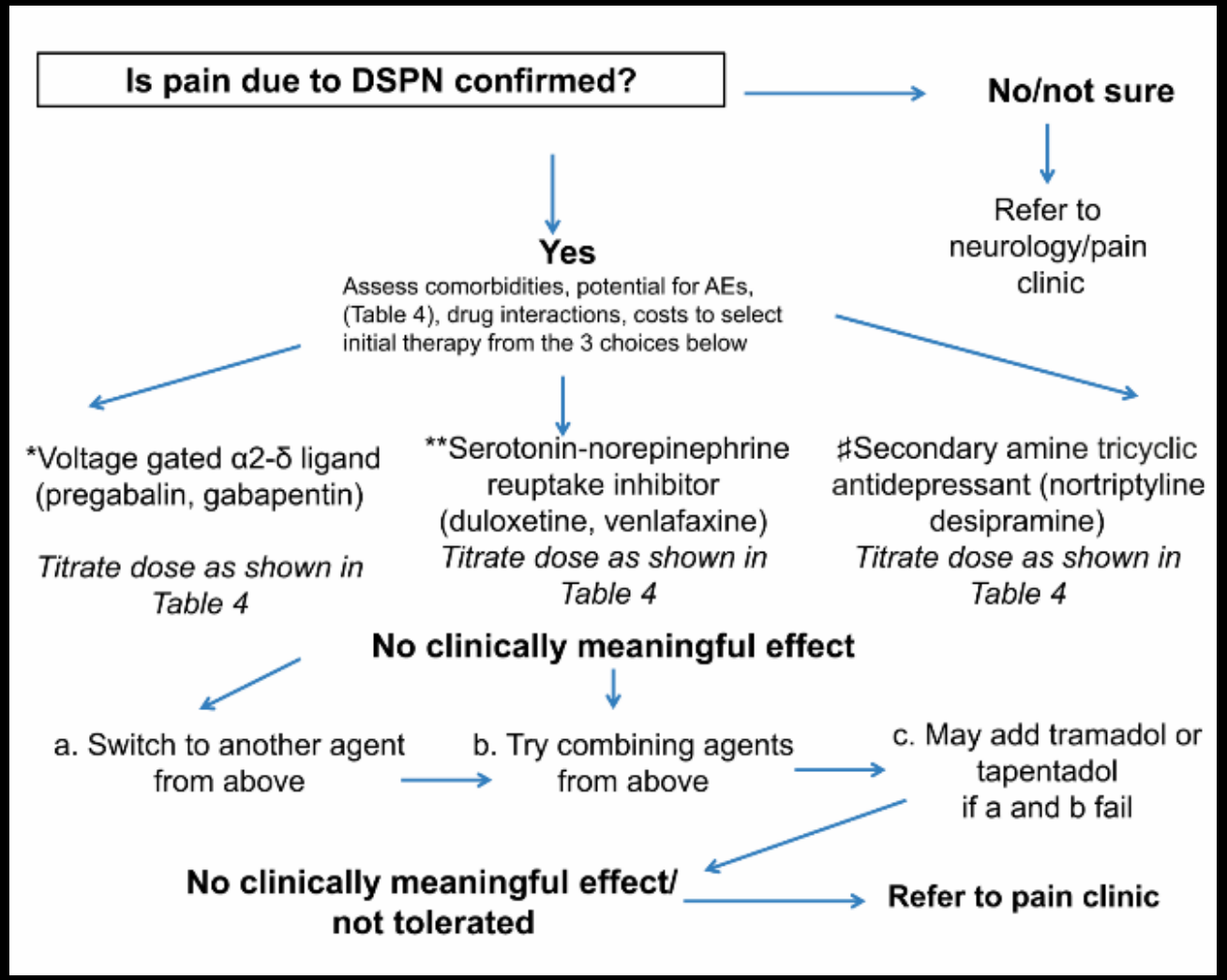
(b) Pregabalin and gabapentin

(c) Duloxetine, amitriptyline and opiates



Coppini et al. Diabetic Medicine 2016

Algorithm for Management of Distal Symmetric Polyneuropathy (DSPN)



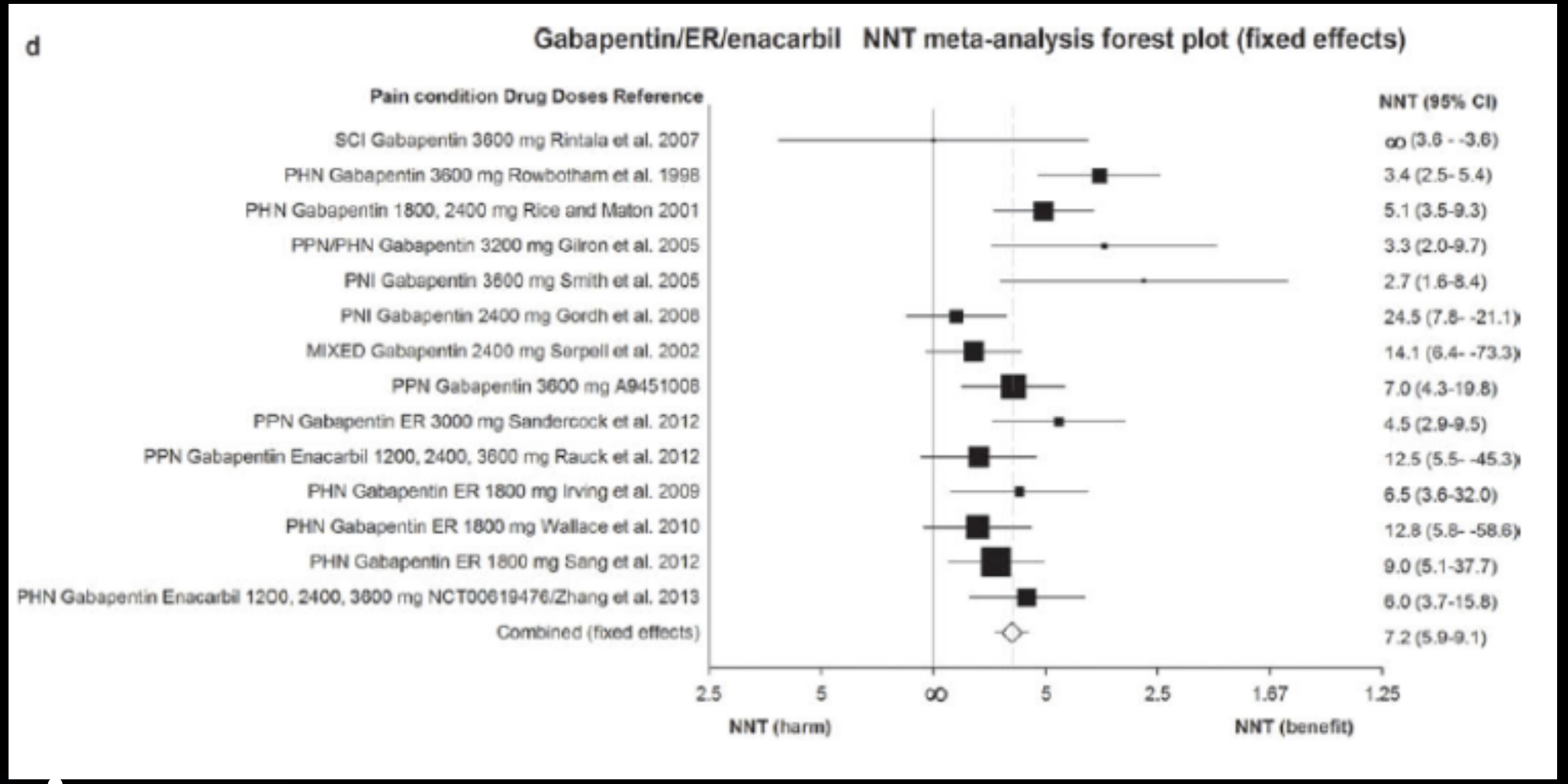
ADA position statement on diabetic neuropathy, Pop-Busui et al. Diabetes Care 2017

Recommendations from the Neuropathic Pain Special Interest Group (NeuPSIG)

GRADE classification	Drugs	Daily dosages and dose regime	Recommendations
STRONG FOR	Gapabentin Gabapentin ER/enacarbil Pregabalin SNRIs duloxetine/venlafaxine TCAs	1200–3600 mg TID 1200–3600 mg BID 300–600 mg BID 60–120 mg QD (duloxetine);150–225 mg QD (venlafaxine ER) 25–150 mg qd or BID	First-line First-line First-line First-line First-line [1]
WEAK FOR	Capsaicin 8% patches Lidocaine patches Tramadol BTX- A (SC) Strong opioids	1–4 patches to the painful area for 30–60 min every 3 months 1–3 patches to the painful area for up to 12 hours 200–400 mg BID (tramadol ER) or TID 50–200 units to the painful area every 3 months Individual titration	Second-line (PNP) [2] Second-line (PNP) Second-line Third-line ; specialist use (PNP) Third line[3]
INCONCLUSIVE	Combination therapy Capsaicin cream Carbamazepine Clonidine topical Lacosamide Lamotrigine NMDA antagonists Oxcarbazepine SSRI antidepressants Tapentadol Topiramate Zonisamide		
WEAK AGAINST	Cannabinoids Valproate		
STRONG AGAINST	Levetiracetam Mexiletine		

Finnerup et al. Lancet Neurol. 2016

Meta-analysis: Gabapentin

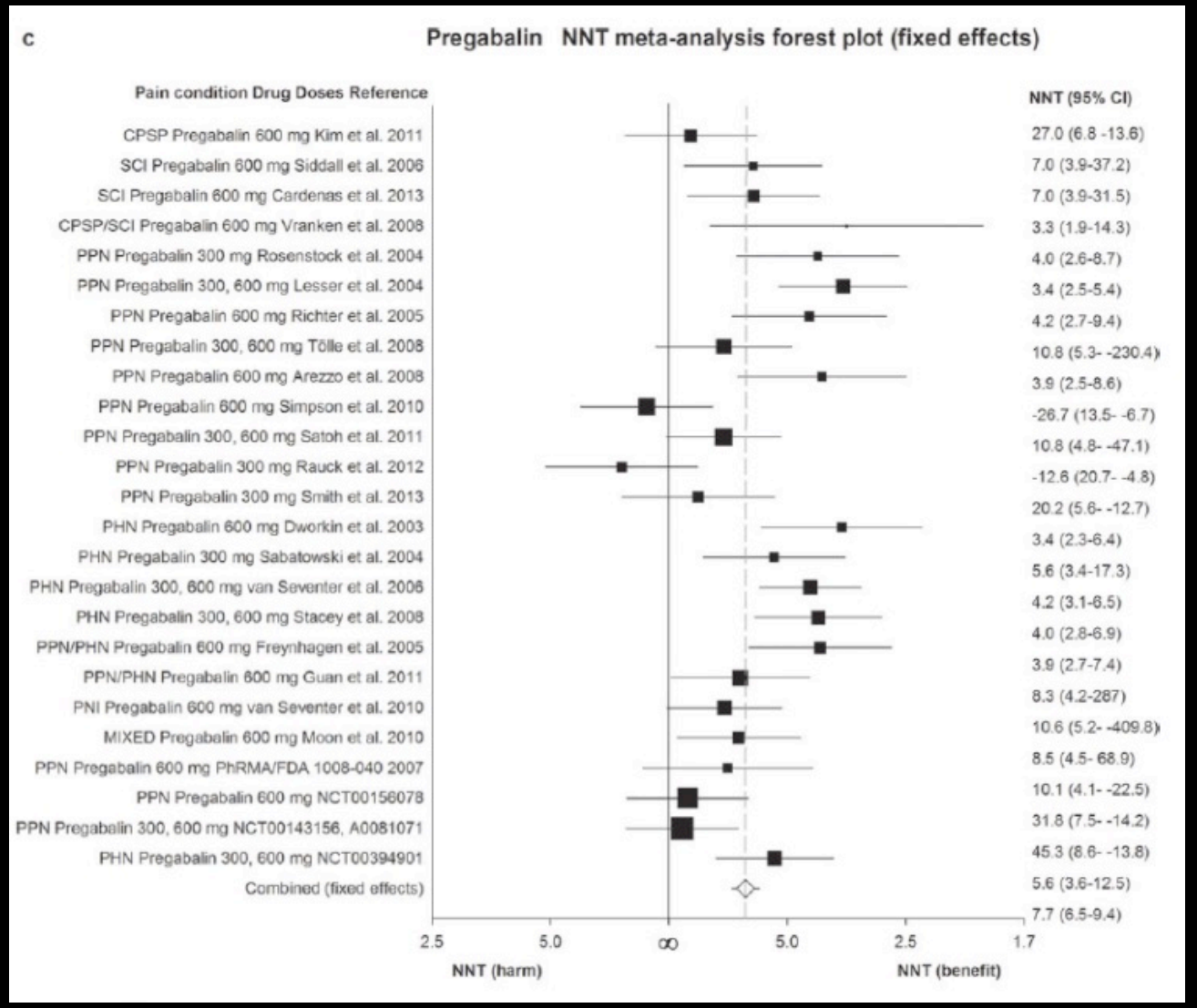


NNT: 7.2
NNH: 31.9

PainWeek

Finnerup et al. Lancet Neurol. 2016

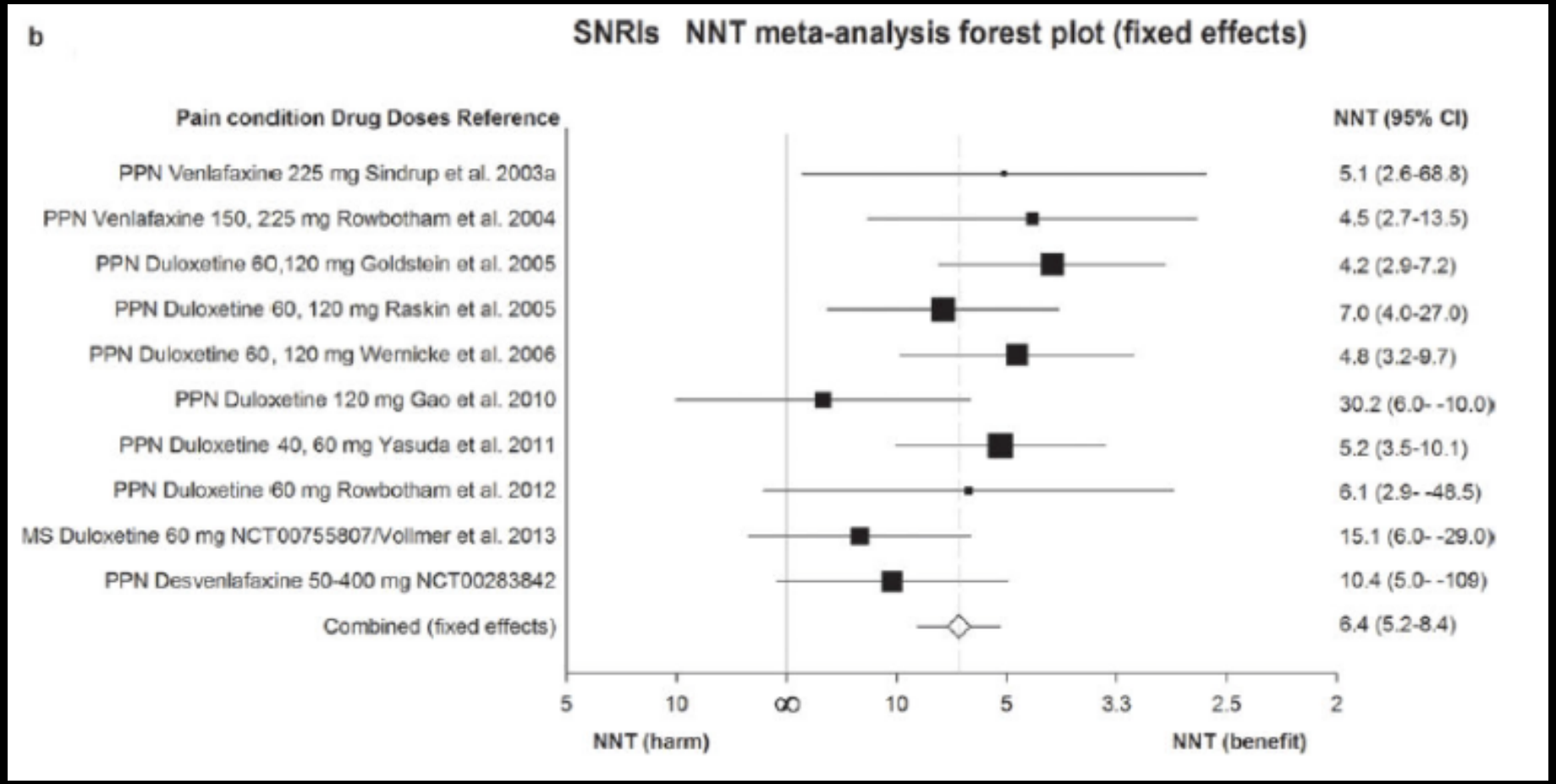
Meta-analysis: Pregabalin



NNT: 7.7
NNH: 13.9

Finnerup et al. Lancet Neurol. 2016

Meta-analysis: SNRIs

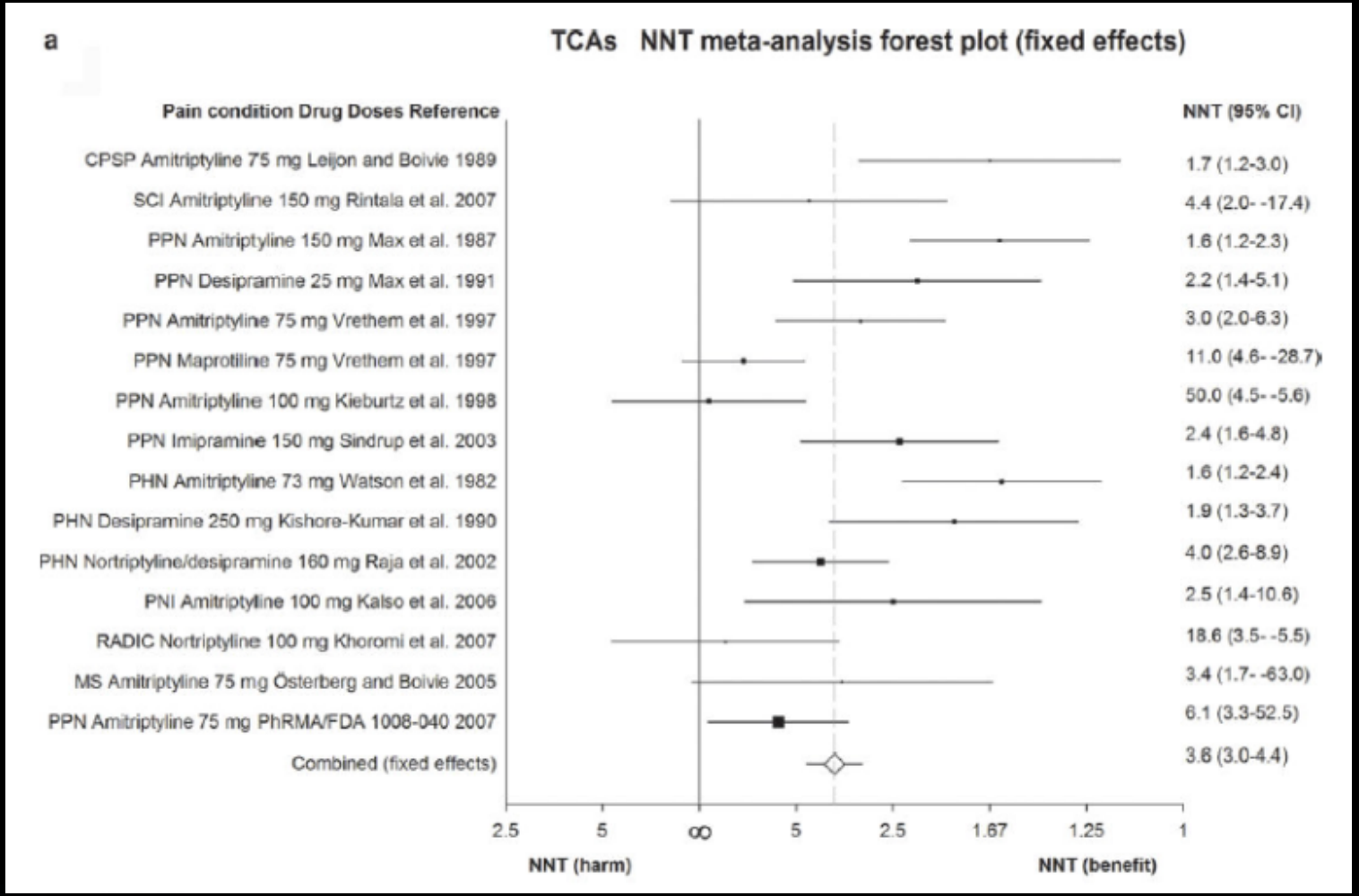


NNT: 6.4
NNH: 11.8

PAINWEEK

Finnerup et al. Lancet Neurol. 2016

Meta-analysis: TCAs



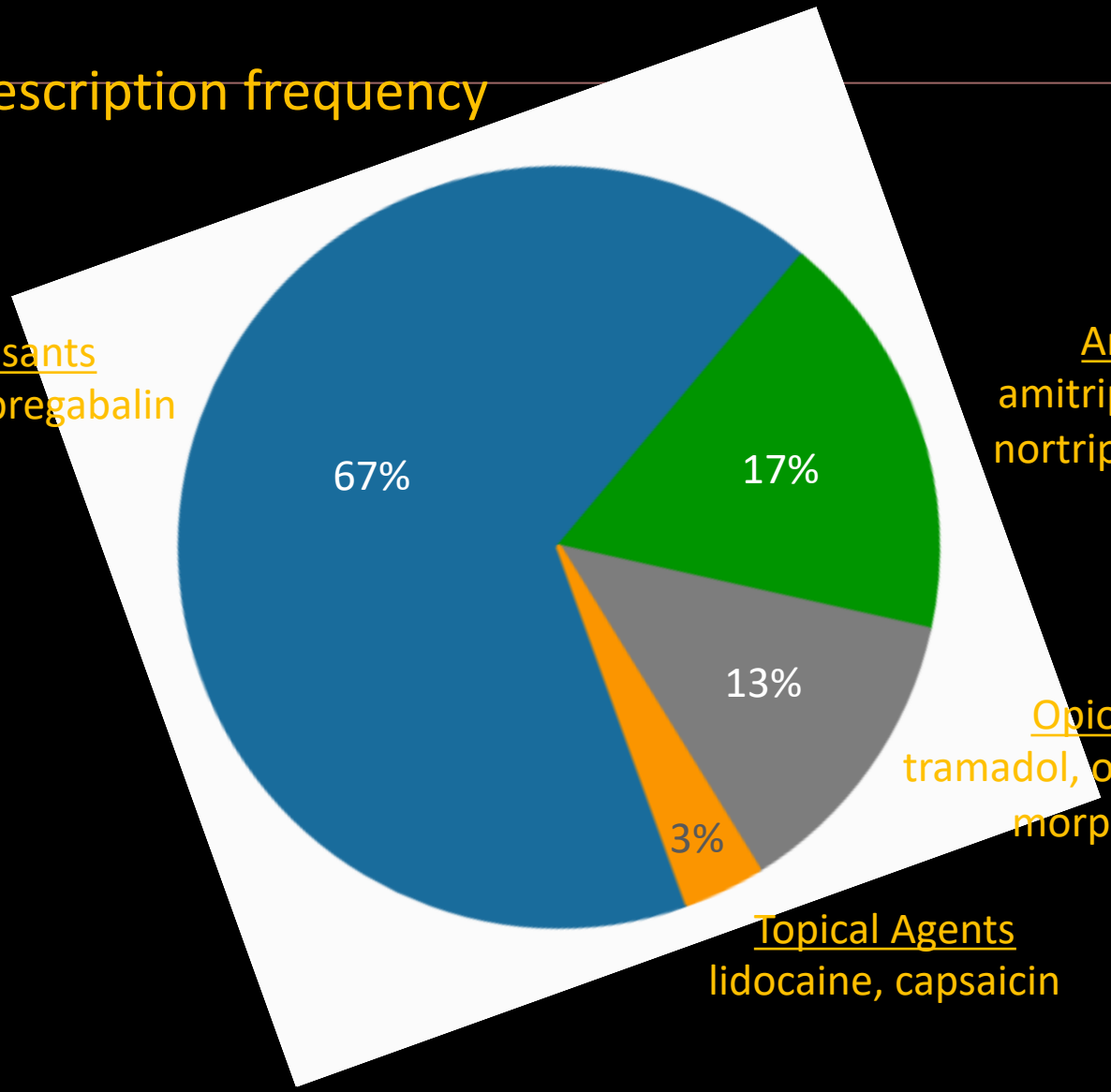
NNT: 3.6
NNH: 13.4

PainWeek

Finnerup et al. Lancet Neurol. 2016

Current Treatments for PDN

- Relative prescription frequency



Anticonvulsants
gabapentin & pregabalin

Antidepressants
amitriptyline, duloxetine, nortriptyline, venlafaxine, desipramine

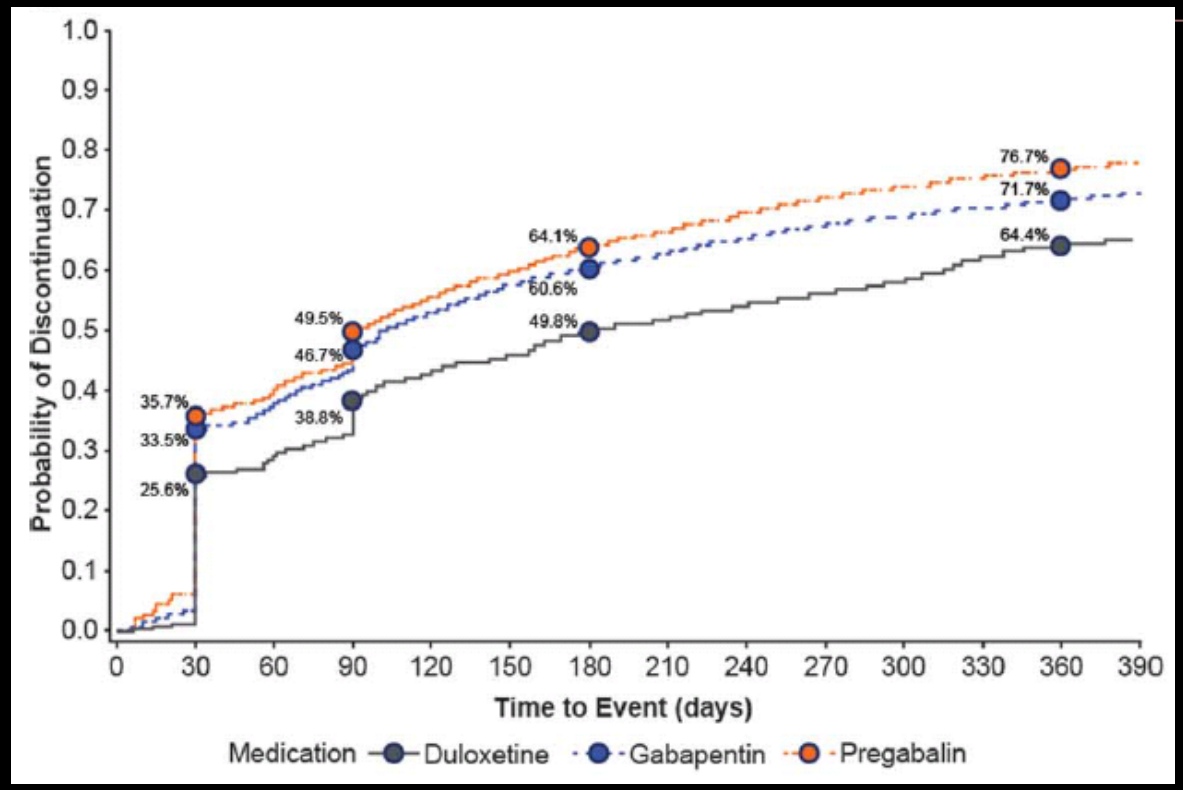
Opioids
tramadol, oxycodone, morphine

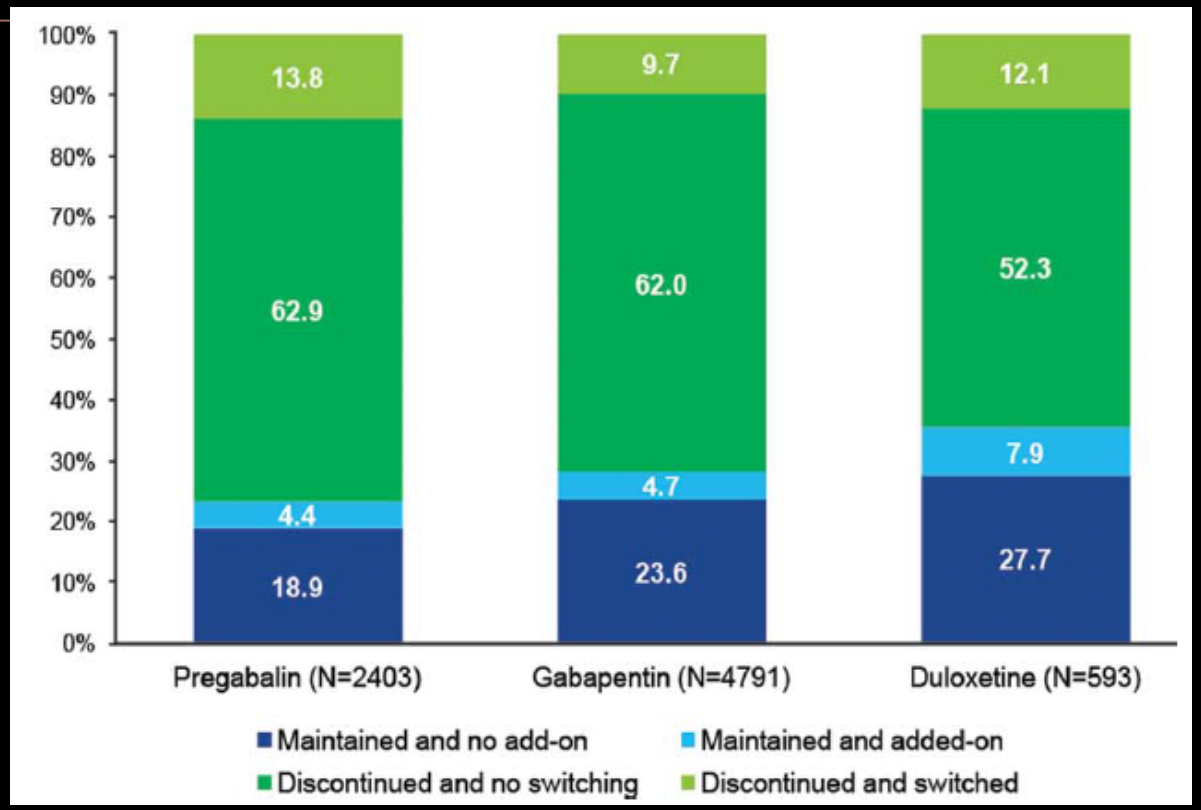
Topical Agents
lidocaine, capsaicin

PainWeek

Yang M *et al*. *Pain Medicine* 2015

Current Treatments for PDN





- Most patients D/C medications 6-12 months from initiating due to inefficacy and/or side effects
- Most patients do not switch to a different medication

PainWeek®

Yang M *et al*. *Pain Medicine* 2015

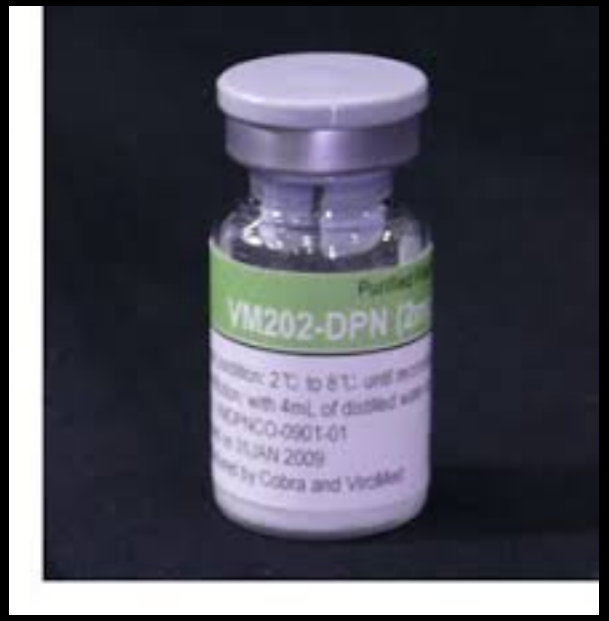
Unmet Needs for PDN Patients

- Current treatment options leave many PDN patients with insufficient pain relief
- Medications for neuropathic pain can have significant side effects
- Spinal cord stimulation may result in better pain relief

VM 202-DPN

- Gene therapy, VM202 is a plasmid product that encodes for the human hepatocyte growth factor (HGF).
- Due to its dual neurotrophic and angiogenic properties, the drug is believed to alleviate pain caused by diabetic neuropathy.
- Pain relieving and regenerative properties hypothesized

VM202-DPN Studies



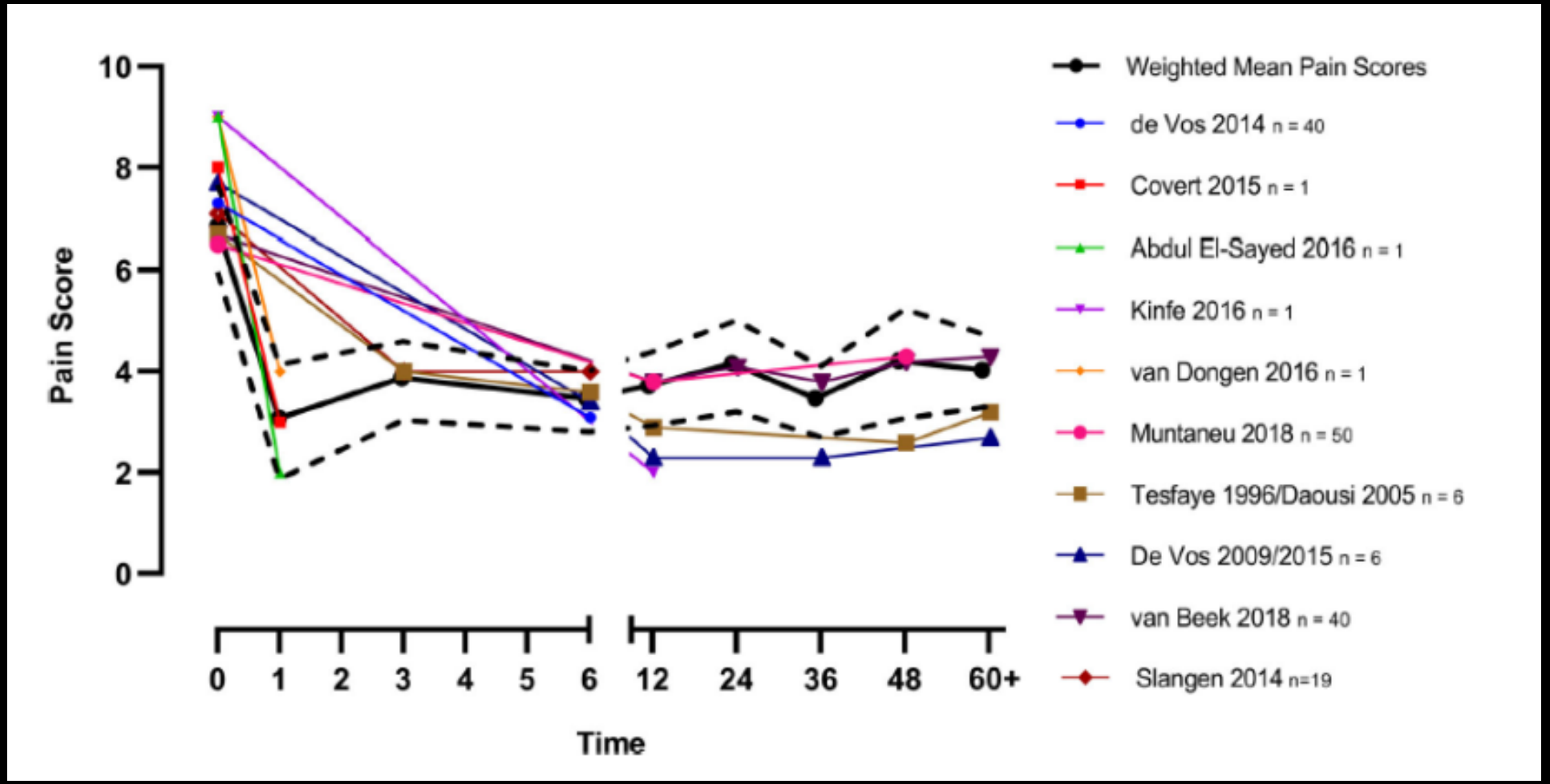
- Initial Phase 3 clinical trial (DPN 3-1, N=500 subjects, 9 months) did not meet its primary efficacy endpoint
- Double-blind placebo-controlled 3-month extension study (DPN 3-1B, a subset of N=101 subjects) met its primary endpoint (12 months long-term safety) and key secondary endpoint (analgesic efficacy at Day 365).

Spinal Cord Stimulation

- Safe, effective treatment for chronic pain in use 50 years
- Minimally invasive, reversible procedure
- Traditional low frequency SCS:
  - Pulse rate ~40-60 Hz
  - Requires induction of paresthesias overlapping painful area
- High frequency SCS at 10 kHz
  - Pulse rate 10,000 Hz
  - Paresthesia-independent
  - Superior to LF-SCS for back and leg pain based on 2 yr RCT data1

[1]Kapural et al. Neurosurgery 2016

Spinal Cord Stimulation for PDN



Erika Petersen, MD, FAANS, FACS
Professor
Director of Functional & Restorative Neurosurgery and Neuromodulation
Department of Neurosurgery
University of Arkansas for Medical Sciences

Neuromodulation for Treatment of Painful Diabetic Neuropathy: A Multicenter, Randomized, Controlled Trial

Disclosures

Consulting, speaking fees:	Medtronic, Neuros Medical, Nevro, Abbott
Stock options:	SynerFuse
Research funding:	Medtronic, Neuros Medical, ReNeuron, Nevro

This study is funded by Nevro and registered on ClinicalTrials.gov:
SENZA-PDN (NCT03228420)

Methods

- Painful diabetic neuropathy (PDN) in patients with symptoms refractory to conservative treatments
- Spinal cord stimulation (SCS): established, non-pharmacological, reversible therapy for pain that delivers energy to the spinal cord through small wires in the back
- HbA1c < 10%, BMI < 45
- 18 US centers randomized 216 subjects 1:1
- Independent Medical Monitors reviewed all subjects
- Treatments: Conventional medical management (CMM) alone

  vs.

  10 kHz SCS (Senza SCS System) + CMM
- 3-month follow-up assessing
  - Pain
  - Quality of life
  - Neurological function
    - Including diabetic foot exam w/ Semmes-Weinstein 10g monofilament and 40g pinprick tests

Mekhail et al. *Trials* 2020

Baseline Characteristics

	CMM n = 103	10 kHz SCS + CMM n = 113
Age in years, mean (SD)	60.8 (9.9)	60.7 (11.4)
Male, n (%)	66 (64%)	70 (62%)
Race		
White, n (%)	85 (82.5%)	87 (77.0%)
Black or African American, n (%)	13 (12.6%)	18 (15.9%)
Other, n (%)	5 (4.9%)	8 (7.1%)
Diabetes		
Type 1, n (%)	3 (3%)	8 (7%)
Type 2, n (%)	100 (97%)	105 (93%)
Duration in years		
Diabetes, mean (SD)	12.2 (8.5)	12.9 (8.5)
Peripheral neuropathy, mean (SD)	7.1 (5.1)	7.4 (5.7)
HbA1c, mean (SD)	7.4% (1.2%)	7.3% (1.1%)
< 7.0%, n (%)	40 (39%)	46 (41%)
≥ 7.0%, n (%)	63 (61%)	67 (59%)
BMI, mean (SD)	33.9 (5.2)	33.6 (5.4)

Safety

Study-Related Adverse Events	CMM n = 103	10 kHz SCS + CMM n = 113
Total, n (# of subjects, %)	None reported	16 (14, 12.4%)
Rated as Serious*	-	1 (1, 0.9%)
By type of event:		
Wound dehiscence	-	2 (2, 1.8%)
Infection	-	2 (2, 1.8%)
Incision or IPG discomfort	-	2 (2, 1.8%)
Irritation from surgical dressings	-	2 (2, 1.8%)
Impaired healing	-	1 (1, 0.9%)
Lead migration	-	1 (1, 0.9%)
Radiculopathy	-	1 (1, 0.9%)
Uncomfortable stimulation	-	1 (1, 0.9%)
Gastroesophageal reflux	-	1 (1, 0.9%)
Myalgia	-	1 (1, 0.9%)
Arthralgia	-	1 (1, 0.9%)
Hyporeflexia	-	1 (1, 0.9%)

***Outcome of the SAE:** Infection resulted in device explant

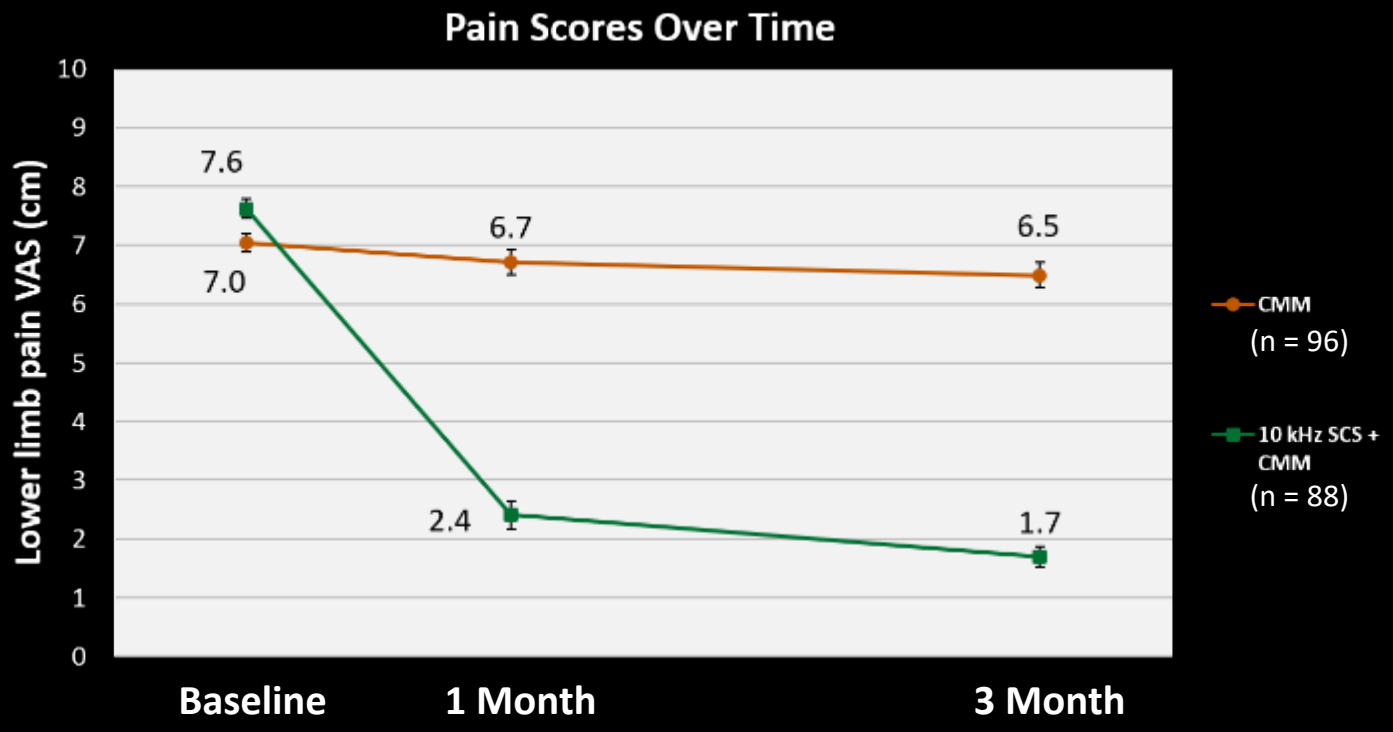
Reported SCS infection rates:

- 2.45% (Hoelzer et al. 2017)
- 2.5% (PDN RCT, de Vos et al. 2014)
- 3.4% (Kumar et al. 2006)
- 4.5% (Mekhail et al. 2011)
- 4.5% (PDN RCT, Slangen et al. 2014)
- 8.9% (Diabetes cohort, Mekhail et al. 2011)

Primary Endpoint Analysis & Pain Relief

Primary Endpoint: compare responders at 3 months (≥ 50% pain relief) without a worsening neurological deficit from baseline in the intent-to-treat population

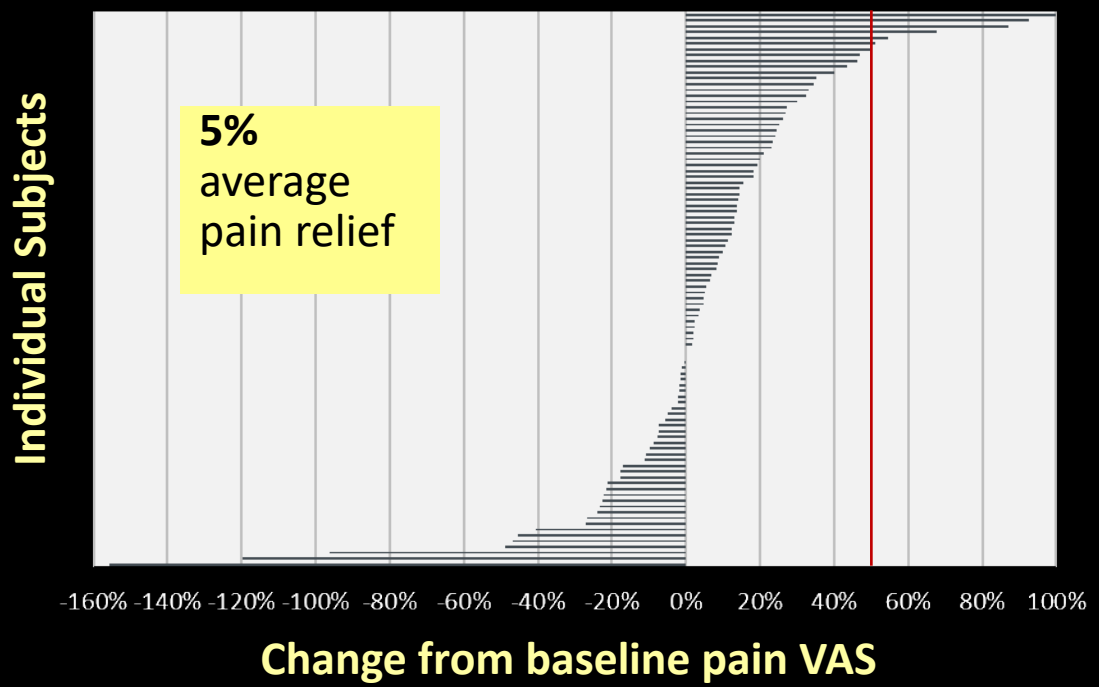
	CMM n = 94	10 kHz SCS + CMM n = 95	
Met primary endpoint, n (%)	5 (5.3%)	75 (78.9%)	$p < 0.001$



Individual Pain Relief at 3 Months

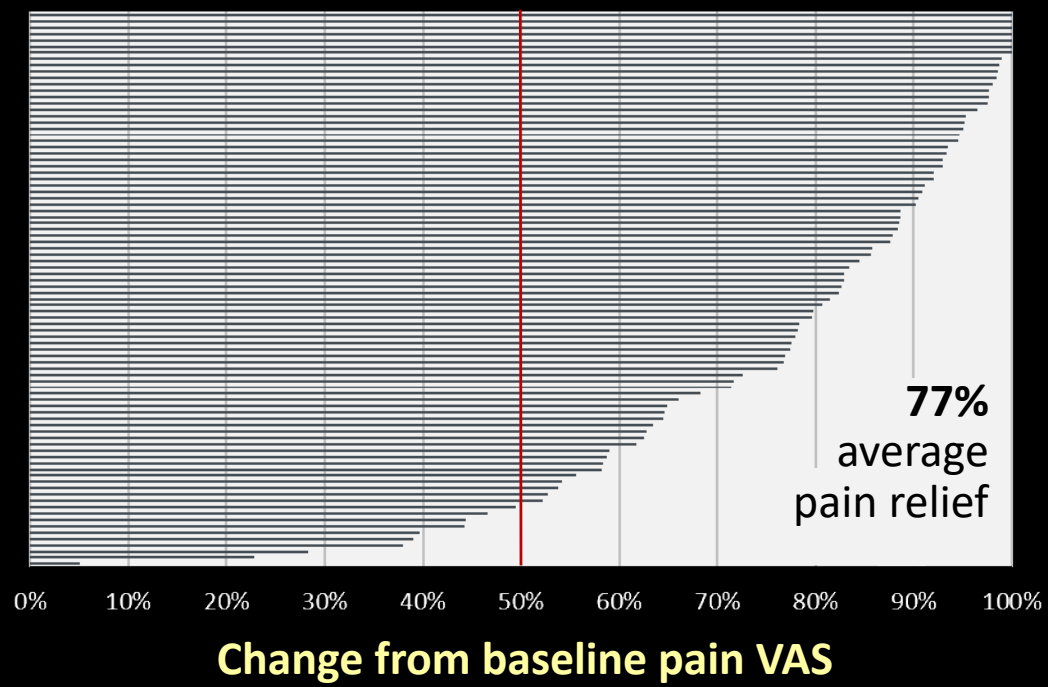
CMM

7% responders (n = 7/96)



10 kHz SCS + CMM

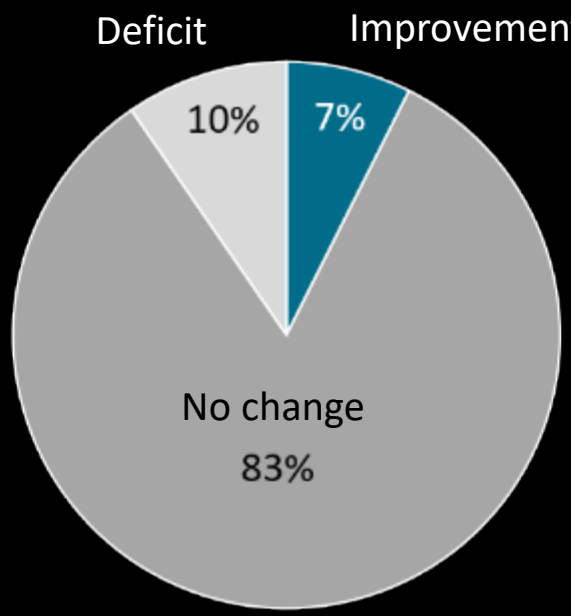
89% responders (n = 78/88)



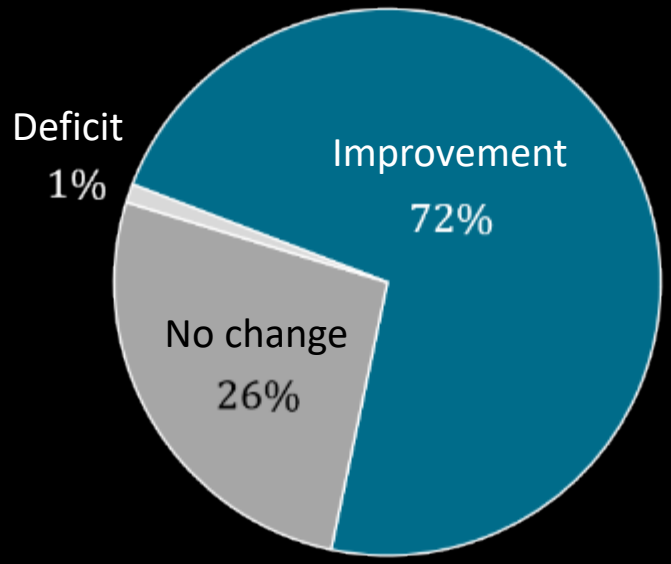
Sensory Assessments at 3 Months

Investigator assessed sensory changes compared to baseline

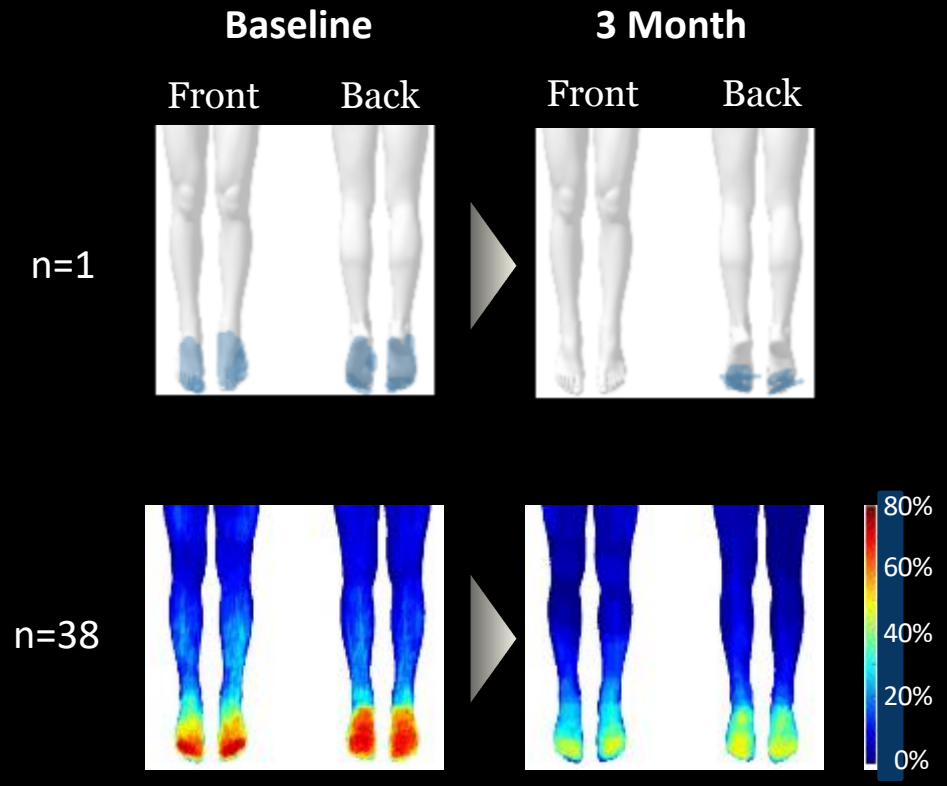
CMM
(n = 94)



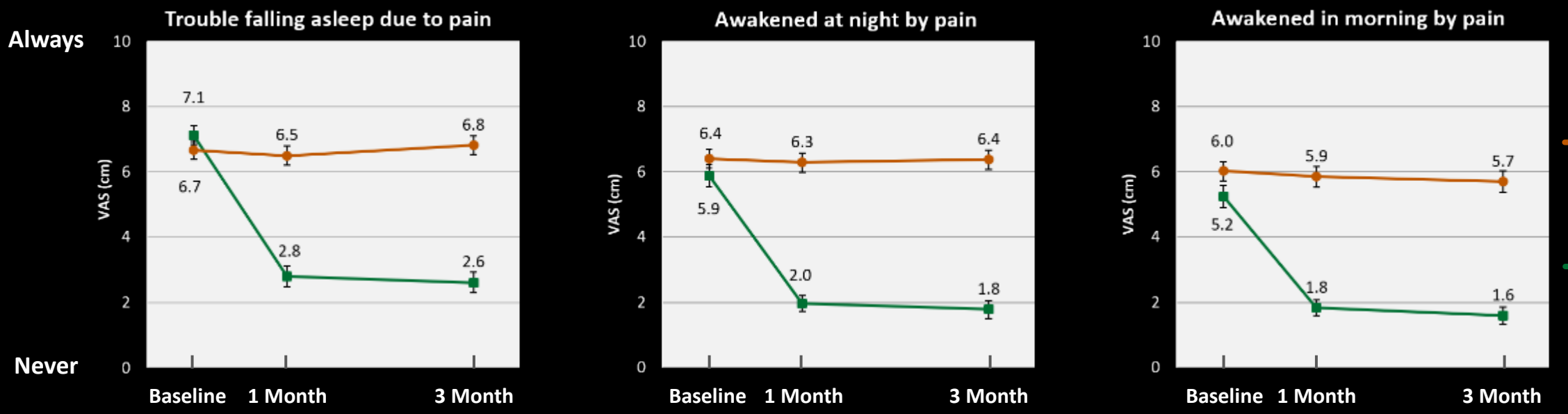
10 kHz SCS + CMM
(n = 87)



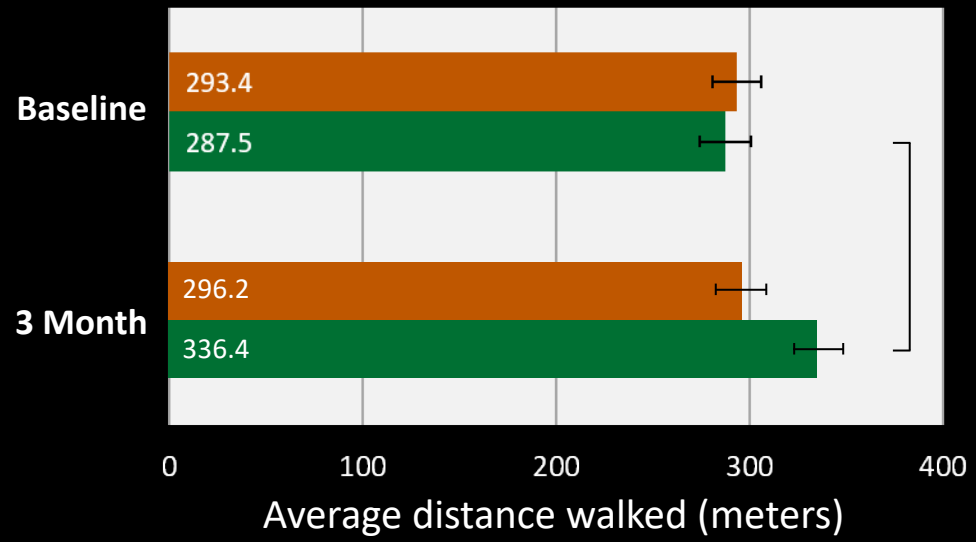
Numbness diagrams drawn by SCS patients



Quality of Life Improvements: Sleep & Activity



6-Minute Walk Test

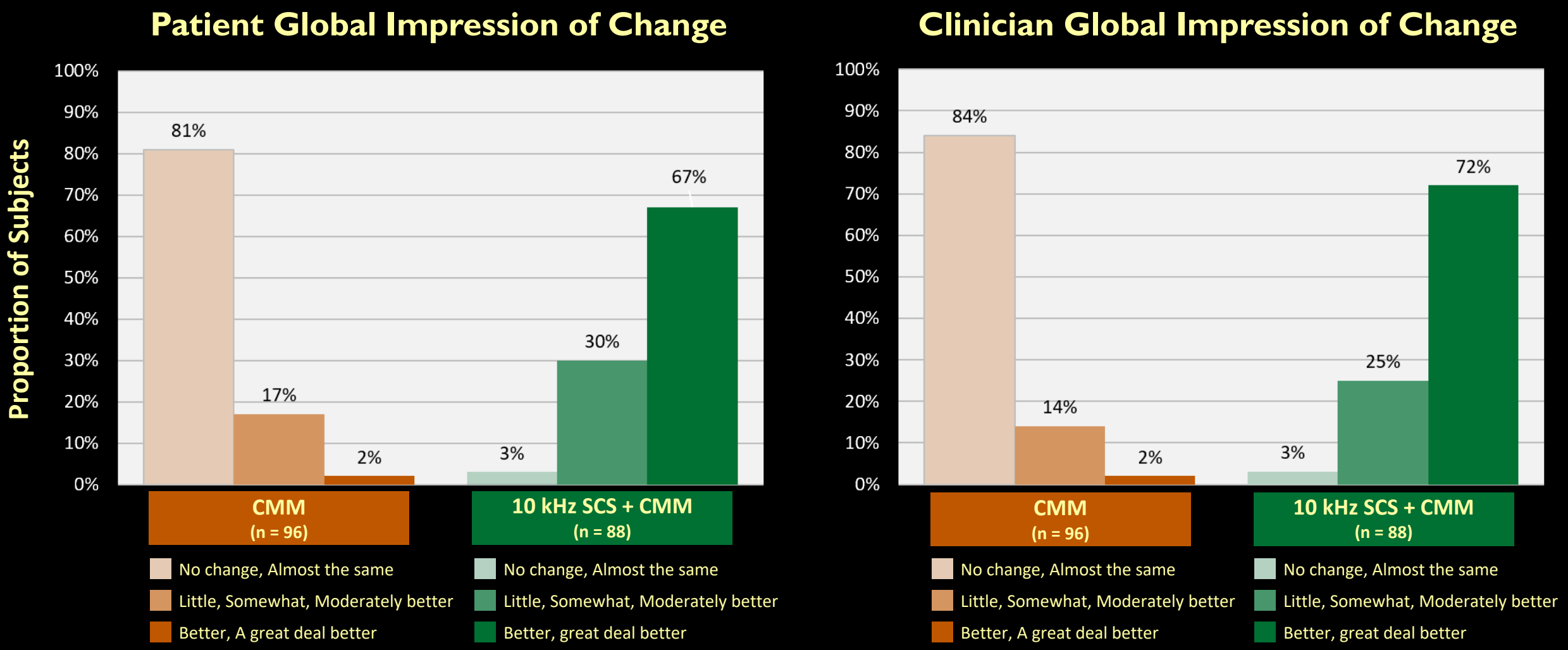


+49 m
17% increase

CMM
(n = 93)

10 kHz SCS + CMM
(n = 86)

Quality of Life Improvements: Impression of Change



Conclusions

- **Study primary endpoint met** - A large proportion of subjects benefited from 10 kHz SCS
- 10 kHz SCS is a safe and effective treatment for PDN patients with symptoms refractory to CMM
- Sensory improvements observed in many patients with 10 kHz SCS
- Improvements seen in function & quality of life measures
- Study follow-up will continue for 24 months total with evaluation of health economics and pain medication usage

SENZA-PDN Investigators


Kas Amirdelfan


Matthew Bennett


Rick Bundschu


Gassan Chaiban


Paul Chang


Heejung Choi


Michael Creamer


David DiBenedetto


Yashar Eshraghi


Vincent Galan


Gennady Gekht


Johnathan Goree


Maged Guirguis


Nathan Harrison


Nandan Lad


Neel Mehta


Ali Nairizi


Denis Patterson


Christopher Paul


Dawood Sayed


Jim Scowcroft


Khalid Sethi


Shawn Sills


Thomas Stauss


Kostandinos Tsoulfas


Judith White


Tyson Wickboldt


Paul Wu


Jijun Xu


Cong Yu

References

- Rodica Pop-Busui, Andrew J.M. Boulton, Eva L. Feldman, Vera Bril, Roy Freeman, Rayaz A. Malik, Jay M. Sosenko, Dan Ziegler. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* Jan 2017, 40 (1) 136-154.
- CDC National Diabetes Statistics Report, https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.Pdf 2020
- Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*. 2006;29(7):1518-1522.
- Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain*. 2002;18(6):350-354.
- Coppini , D. Enigma of painful diabetic neuropathy: can we use the basic science, research outcomes and real-world data to help improve patient care and outcomes? *Diabet. Med.* 2016. 33, 1477– 1482.
- Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173.
- Yang M, Qian C, Liu Y. Suboptimal Treatment of Diabetic Peripheral Neuropathic Pain in the United States. *Pain Med*. 2015;16(11):2075-2083.
- Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. *Neurosurgery*. 2016;79(5):667-677.
- Raghu ALB, Parker T, Aziz TZ, et al. Invasive Electrical Neuromodulation for the Treatment of Painful Diabetic Neuropathy: Systematic Review and Meta-Analysis [published online ahead of print, 2020 Jun 26]. *Neuromodulation*. 2020;10.1111/ner.13216.
- Mekhail NA, Argoff CE, Taylor RS, et al. High-frequency spinal cord stimulation at 10 kHz for the treatment of painful diabetic neuropathy: design of a multicenter, randomized controlled trial (SENZA-PDN). *Trials*. 2020;21(1):87. Published 2020 Jan 15