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PERIPHERAL NEUROPATHY®

Welcome!

FPN Webinar:

Demystifying Diabetic Peripheral Neuropathy *with Rodica Pop-Busui, MD, PhD*

Wednesday, September 7, 2022

Sponsored by:  **AveritasPharma**™

We will begin our presentation shortly.



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Moderator:



Lindsay Colbert
Executive Director
the Foundation for Peripheral Neuropathy

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Before We Begin



This presentation is being recorded. The recording link will be emailed to you so you can view it again later.



Submit your questions anytime via the Questions Box. We will try to answer them during this webinar.



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Presenter:



Rodica Pop-Busui, MD, PhD
Michigan Medicine

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Demystifying Diabetic Peripheral Neuropathy

Rodica Pop-Busui MD, PhD

Larry D. Soderquist Professor of Diabetes

Director Clinical Research, Caswell Diabetes Institute

Vice Chair Clinical Research

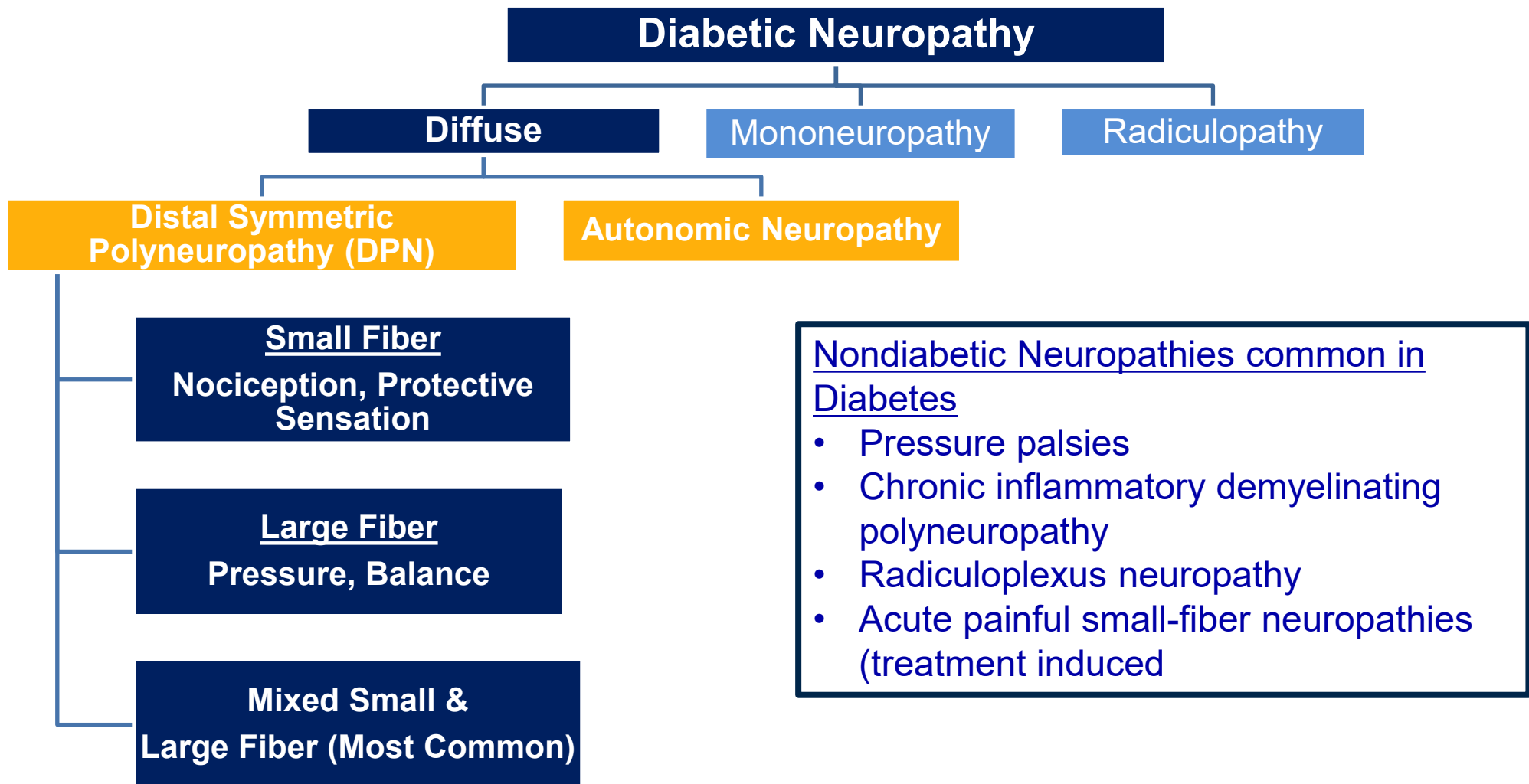
University of Michigan, Ann Arbor, MI

President-Elect American Diabetes Association

OUTLINE

- **Summarize various clinical forms of diabetic neuropathies and examine current epidemiology trends**
- **Review sensitive and cost-effective diagnostic steps for diabetic peripheral neuropathy.**
- **Discuss management options**

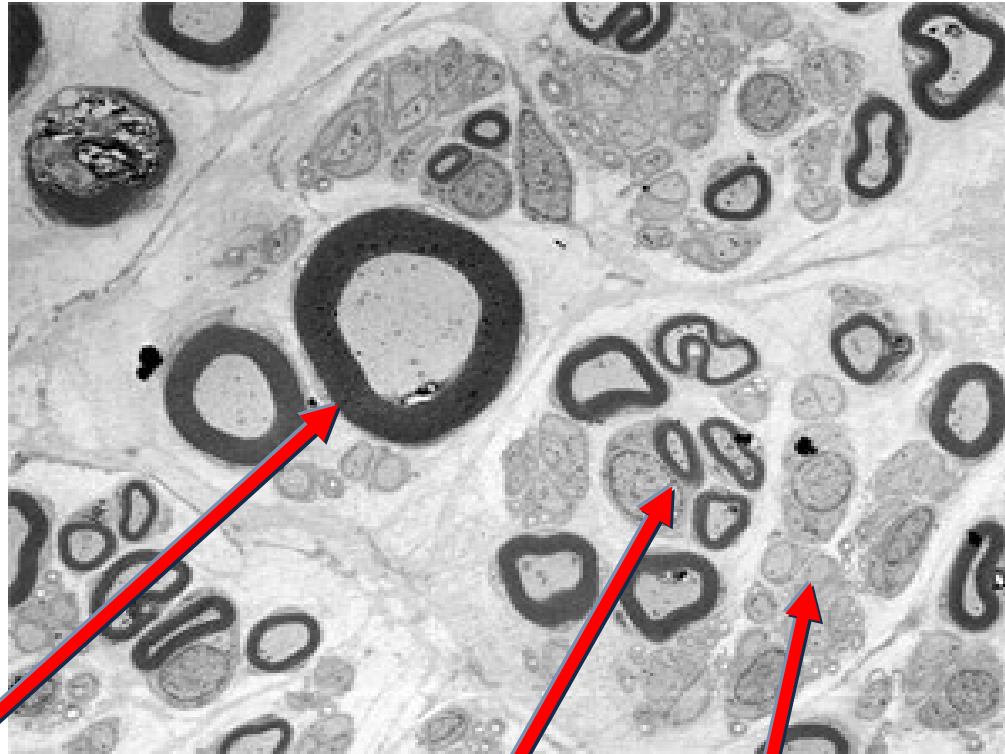
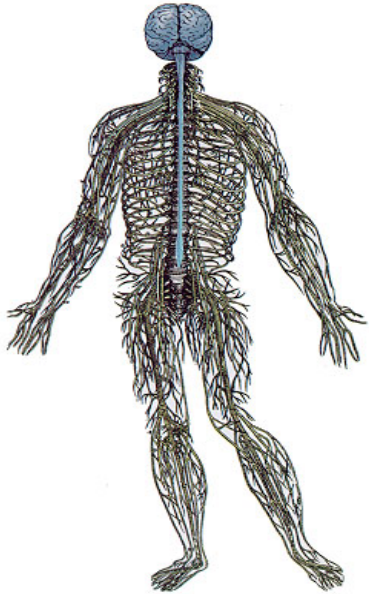
Diabetic Neuropathies-Broad Spectrum



Nondiabetic Neuropathies common in Diabetes

- Pressure palsies
- Chronic inflammatory demyelinating polyneuropathy
- Radiculoplexus neuropathy
- Acute painful small-fiber neuropathies (treatment induced)

The Peripheral Nervous System is Complex

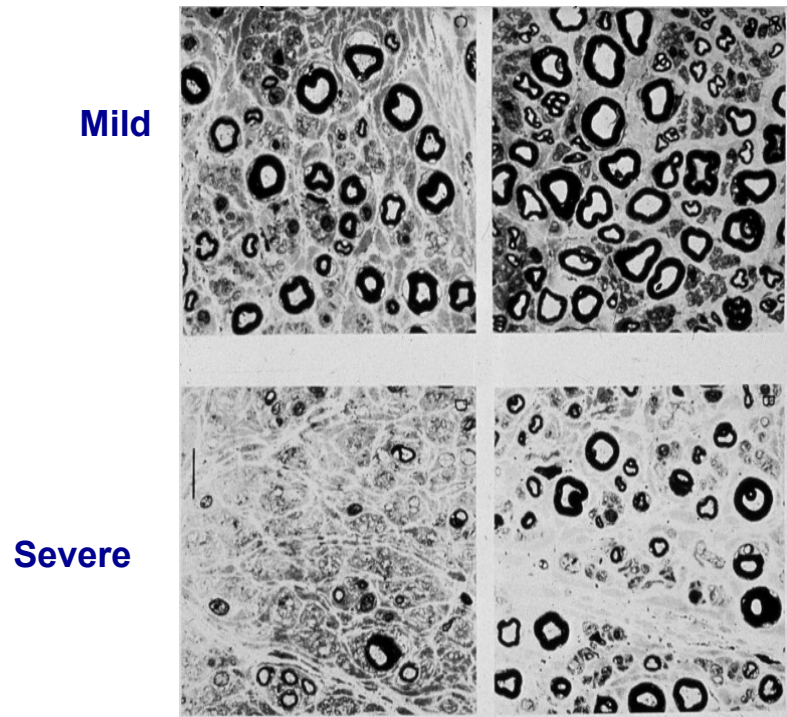


**Large myelinated
fiber**

**Small myelinated
fiber**

**Unmyelinated
fibers**

Diabetic Peripheral Neuropathy (DPN)



Normal

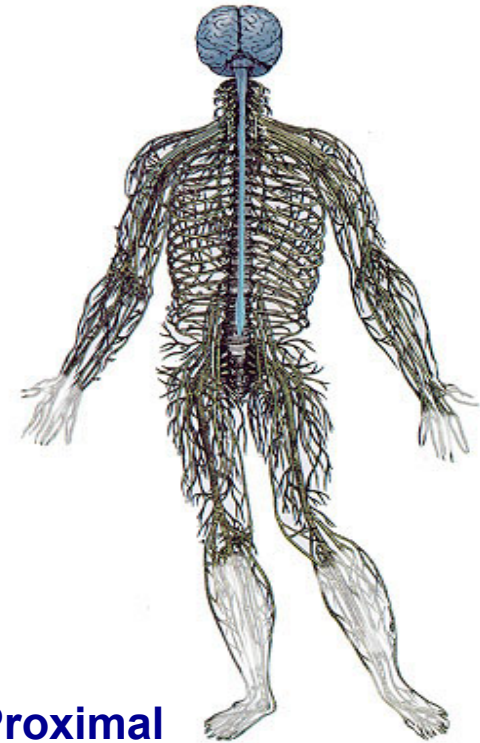
Small Fibers



Large Fibers

Moderate

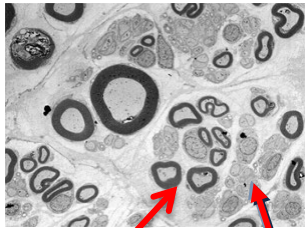
Distal → **Proximal**



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Evaluation of Small Fibers- Painful DPN



Small Myelinated Unmyelinated
fibers

Nerve Function

- Nociception (pain and temperature)
- Protective sensations

History

- Burning **Pain**
- Lancing
- Electric shocks
- Stabbing
- Hyperalgesia
- Allodynia

Exam Techniques

- Thermal discrimination (hot/cold)
- Pinprick sensation



Evaluation of Large Myelinated Fibers in Clinical Care



Large Myelinated
Fibers

Nerve Function

- Pressure
- Balance

History

- Numbness
- Tingling
- Poor balance



Exam Techniques

- Vibration perception
- Proprioception
- Ankle reflexes
- 10 gm monofilament

Diagnosis of DPN in Clinical Care

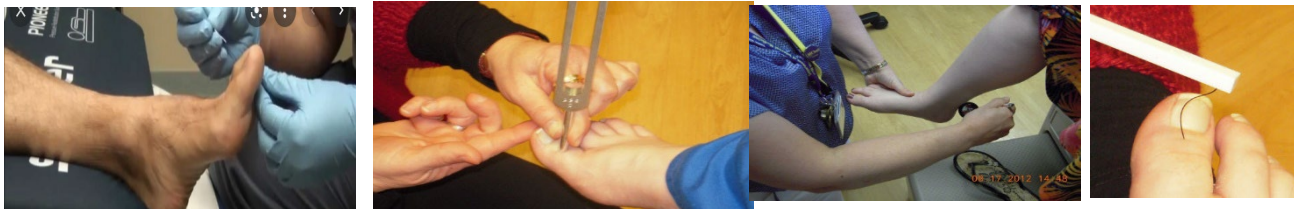
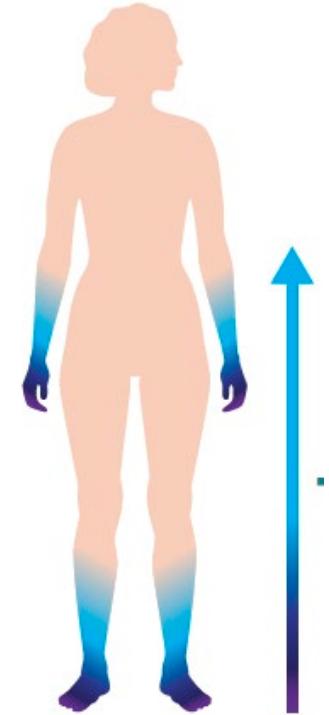


Pop-Busui, Boulton, et al, *Diabetes Care* 2017; 40: 136-154



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Diagnosis of DPN Clinical Care and Research



Combining at Least 2 Examinations is Recommended!

Screening Instruments DPN

	Michigan Neuropathy Screening Instrument (MNSI) Index	Toronto Clinical Neuropathy Score (TCNS)	Neuropathy Disability Score (NDS)
Symptoms	15 items Self-administered	6 item symptom score	None
Exam	Inspection Vibration testing Ankle Reflexes	<u>Reflex score</u> (knee, ankle) <u>Sensory test score</u> (pinprick, temperature, light touch, vibration and position sense)	<u>Sensation</u> (vibration, temperature, pin-prick) <u>Ankle Reflexes</u>
Scoring	≥4 symptoms >2 clinical	6-8: Mild neuropathy 9-11: Mod neuropathy ≥12: Severe neuropathy	0-2: Mild neuropathy 6-8: Mod neuropathy 9-10: Severe



Diabetes Care 1994; 17(11):1281-89.
Diabet Med 2012; 29(7):937-44.

Diabetes Care 2002; 25(11):2048-52.
Diabetologia 1993;36:150-4.



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Diabetic Neuropathy Differential

Metabolic Disease

- Thyroid
- Renal

Systemic Disease

- Vasculitis
- Paraproteinemia
- Amyloidosis

Infectious Disease

- HIV
- Hepatitis B
- Lyme disease

Inflammatory Disease

- Chronic inflammatory demyelinating polyradiculoneuropathy

Nutrition

- Vitamin B12 deficiency
- Pyridoxine
- Thiamine
- Tocopherol

Industrial Agents

- Acrylamide
- Organophosphorous agents

Drugs

- Alcohol
- Amiodarone
- Chemotherapy

Heavy Metals

- Arsenic
- Mercury

Heredity/Genetics



DPN- Clinical Pearls

People with diabetes may present with other forms of peripheral neuropathies that may be treatable by specific measures!

A timely referral to a neurologist may be needed only in atypical cases involving:

- **Asymmetrical distribution of symptoms and clinical signs**
- **Weakness predominance**
- **Rapid onset and rapid progression of signs such as severe weakness**

Painful DPN and DPN Quality of Life

Pain



Neuropathic Pain
Douleur Neuropatique-4 (DN4)
Short Form McGill Pain (SF-MPQ-2)
VAS
painDETECT

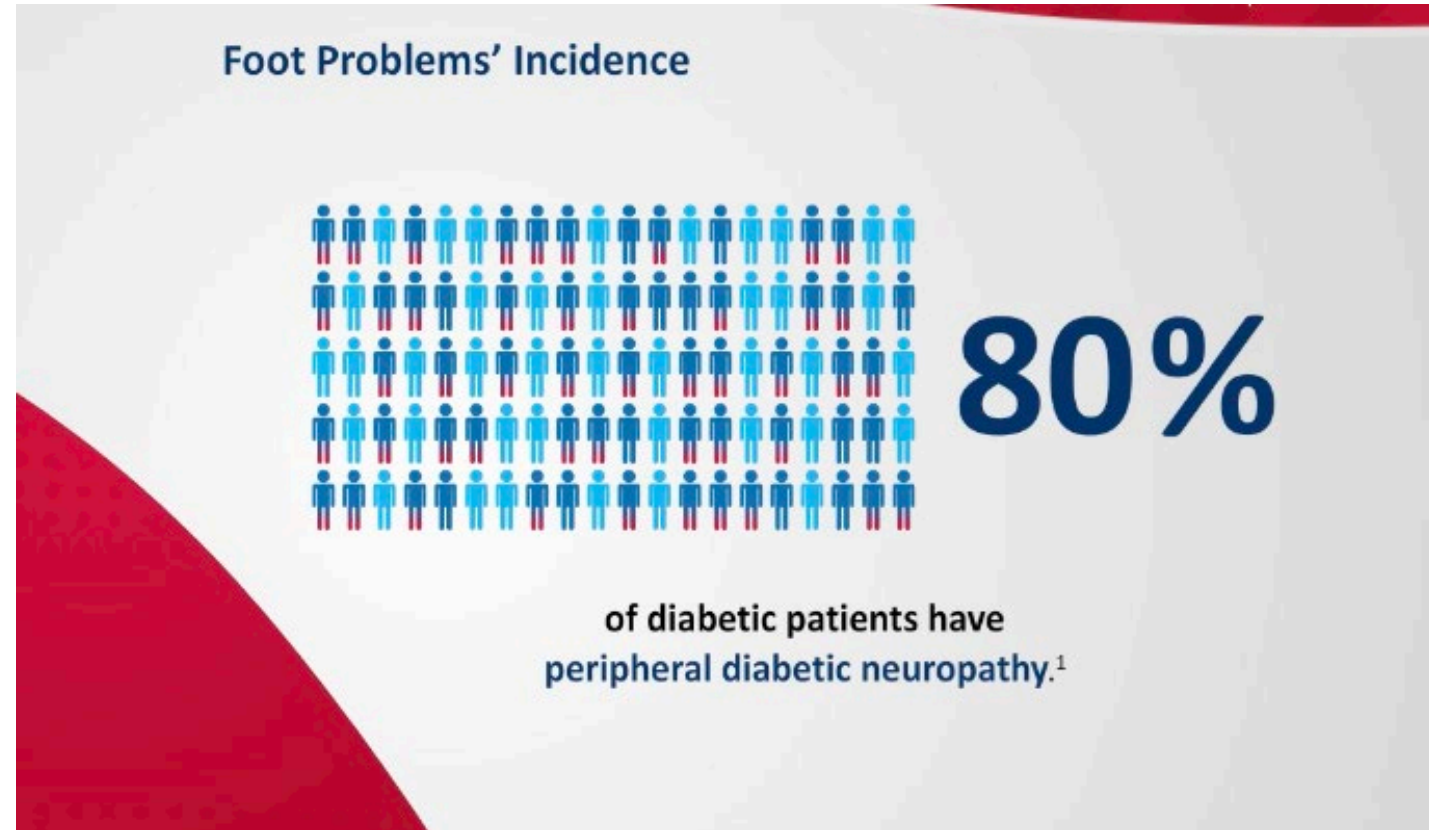
Patient reported outcomes

DN Quality of life
Neuropathy NeuroQOL
Norfolk



Advanced DPN Complications

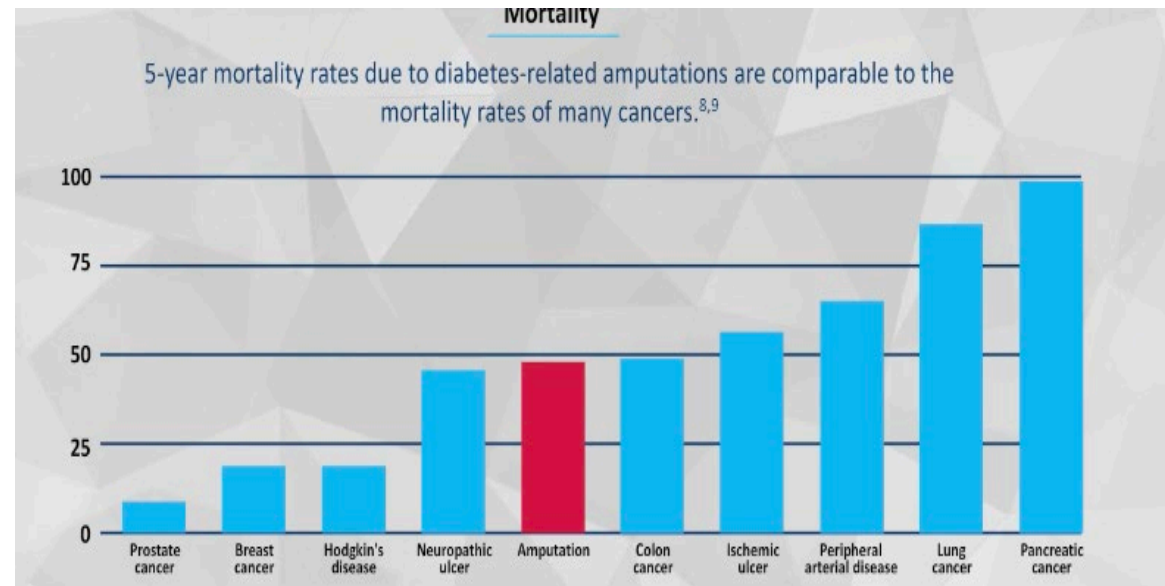
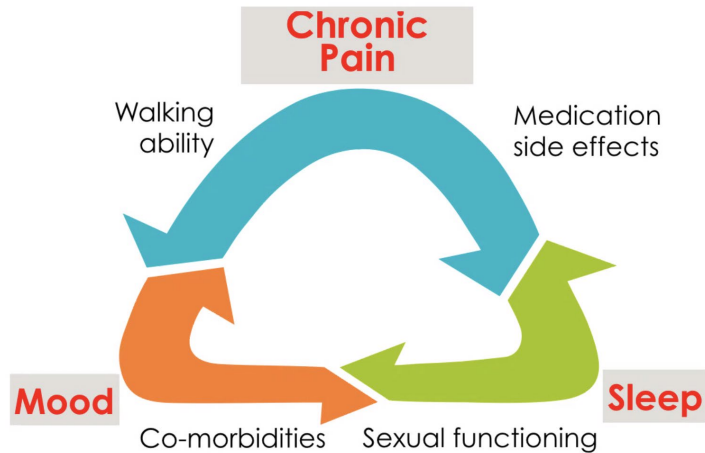
Diabetic foot ulcers



DPN - Impact

Loss of sensation, loss of balance, falls, loss of daily function, pain, ulcers, amputations, death

**Painful diabetic neuropathy:
a disabling problem for many patients**

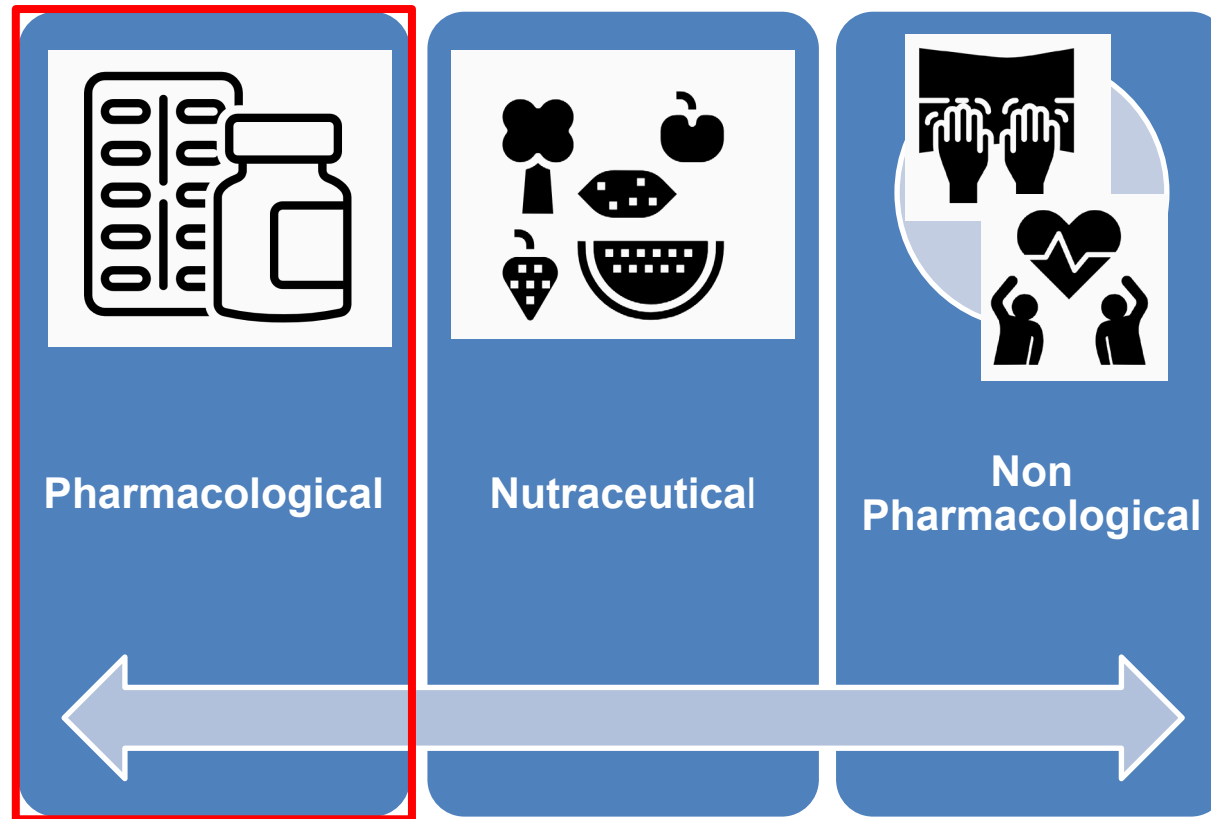


Armstrong et al, IWJ 2007

OUTLINE

- Summarize various clinical forms of diabetic neuropathies and examine current epidemiology trends
- Review sensitive and cost-effective diagnostic steps for peripheral diabetic neuropathy.
- **Discuss management options**

Painful DPN Therapeutic Approaches



Pharmacological Approach Painful DPN

Drug	Drug Class	Dose		Number Needed to Treat*
		Initial	Effective	
Pregabalin**	Anticonvulsant	25-75 mg, 1-3x daily	300-600 mg/day	3.3-7.7
Duloxetine**	Antidepressant	20-30 mg/day	60-120 mg/day	3.8-11
Gabapentin	Anticonvulsant	100-300 mg, 1-3x daily	1800-3600 mg/day	3.3-7.2
Amitriptyline/Tricyclics	Antidepressant	10-25 mg daily	25-100 mg/day	2.1-4.2

***Based on 30-50% improvement in symptoms**

****FDA approved for DPN treatment**

Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM)

130 participants with painful DPN

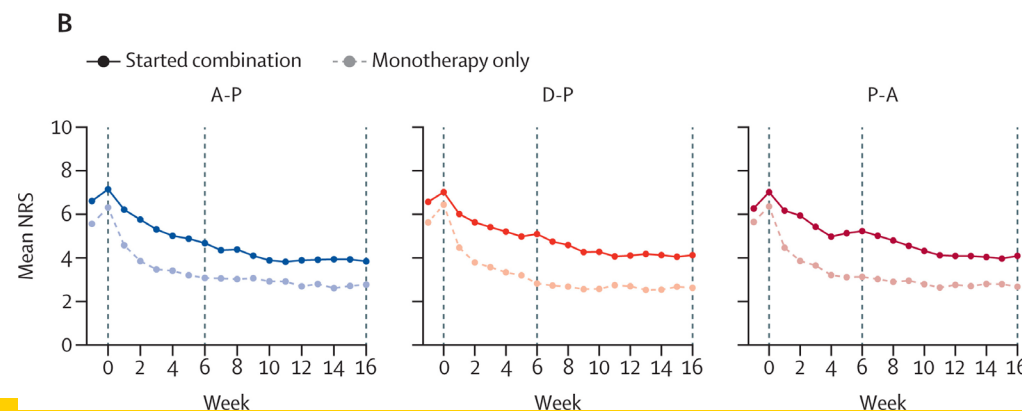
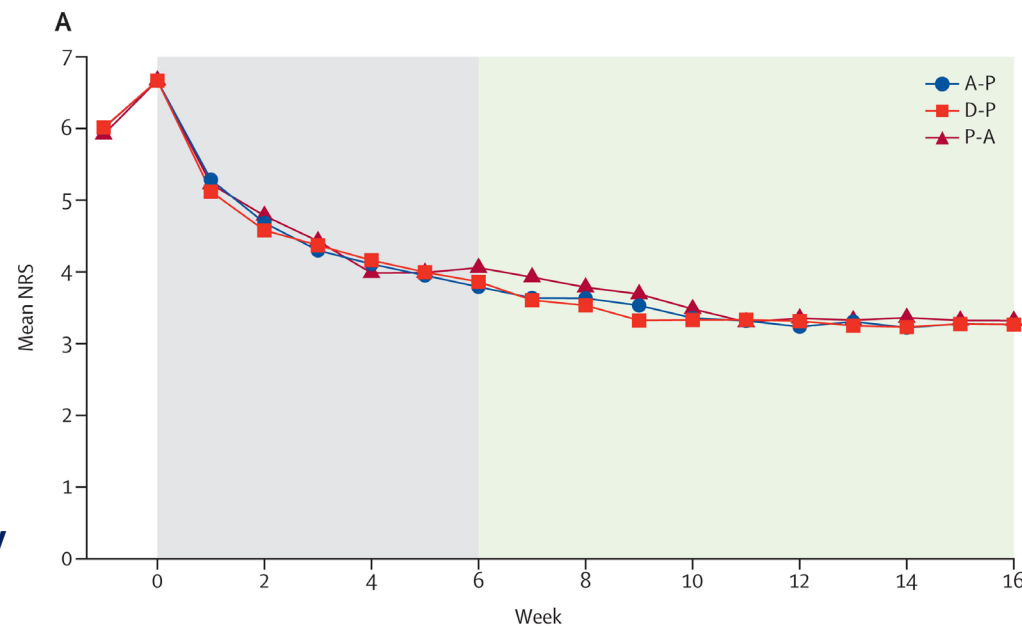
↓
Monotherapy for 6 weeks

Nonresponders:

Responders (NRS<3)

- A-P=amitriptyline + pregabalin.
 - D-P=duloxetine + pregabalin.
 - P-A=pregabalin + amitriptyline.
- Continued monotherapy

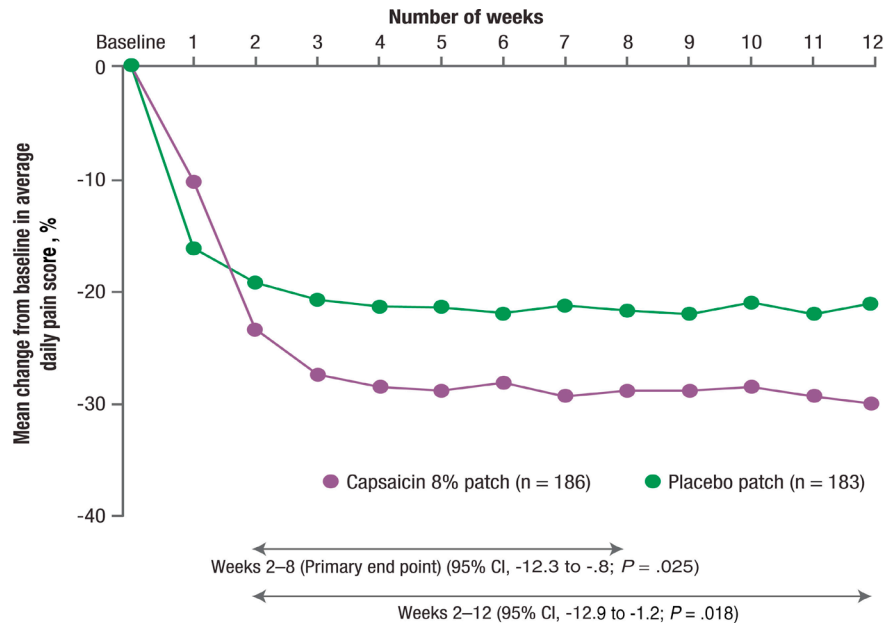
75 mg/day amitriptyline
120 mg/day duloxetine
600 mg/day pregabalin



Pharmacological Approach - Limitations

- **All trials short duration- most 12 or max 16 weeks**
- **Large drop-out rates**
- **Limiting side effects**
 - **Dizziness**
 - **Sedation- drowsiness**
 - **Fatigue**
 - **Dry mouth**
 - **Nausea**
 - **Balance problems/falls**

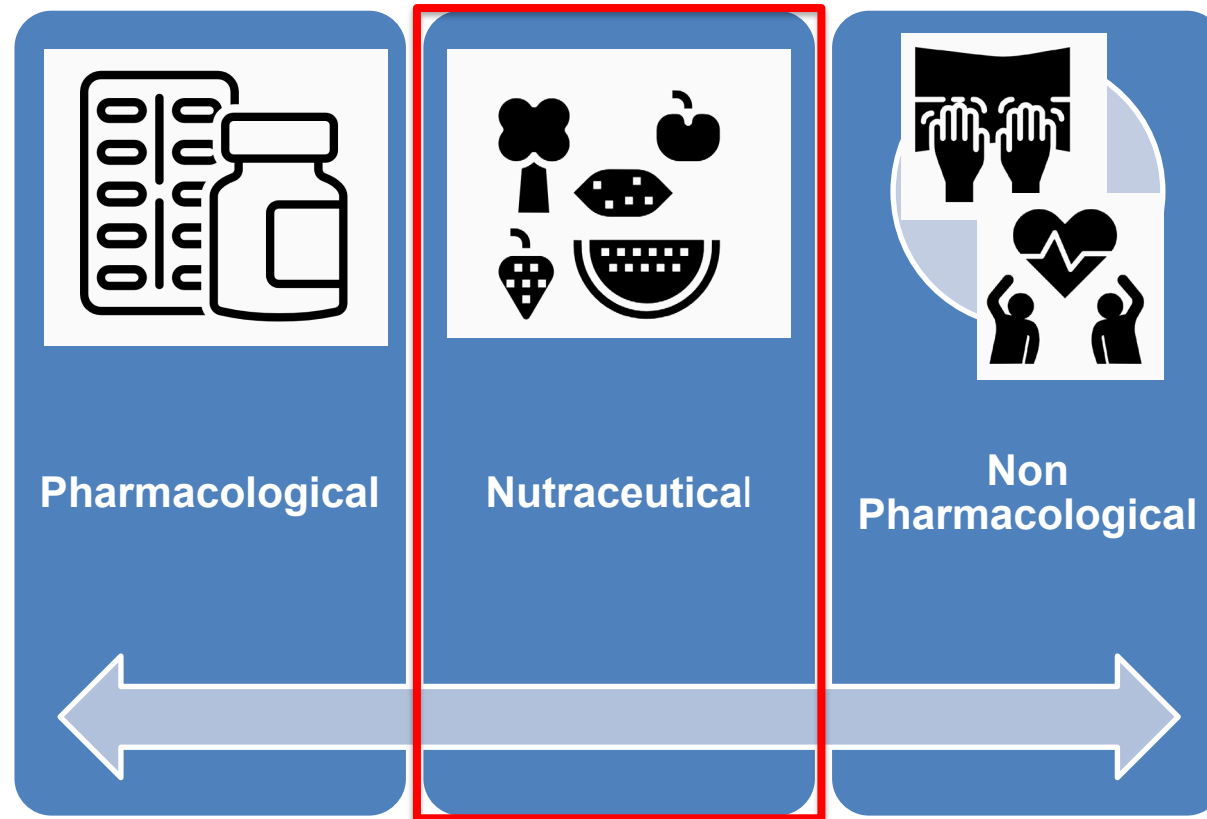
Topical Options Painful DPN: Capsaicin 8% Patch - FDA Approved



Mean difference: -6.6 (95% CI, -12.3, - 8) $p=0.025$

Weekly 95% CI	N/A	-10.4, 2.3	-13.1, -0.4	-13.5, -0.8	-13.6, -1.0	-12.6, 0.0	-14.4, -1.8	-13.5, -0.8	13.2, -0.6	-13.9, -1.2	-13.7, -1.1	-15.3, -2.7
Weekly P value	N/A	.208	.036	.027	.024	.051	.012	.026	.032	.020	.022	.005
Number of patients												
Capsaicin	186	186	186	186	186	186	186	186	186	186	186	186
Placebo	183	183	183	183	183	183	183	183	183	183	183	183

Painful DPN Therapeutic Approaches

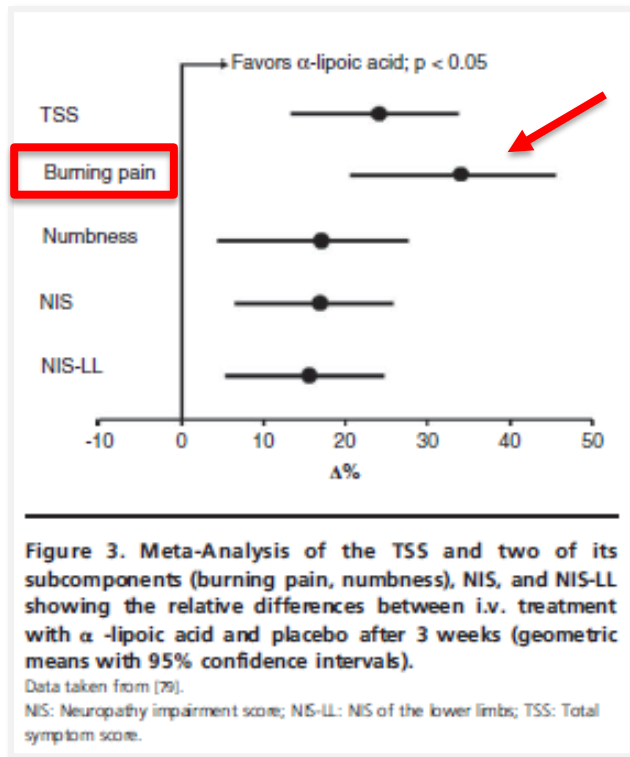


Nutraceuticals for Neuropathic Pain

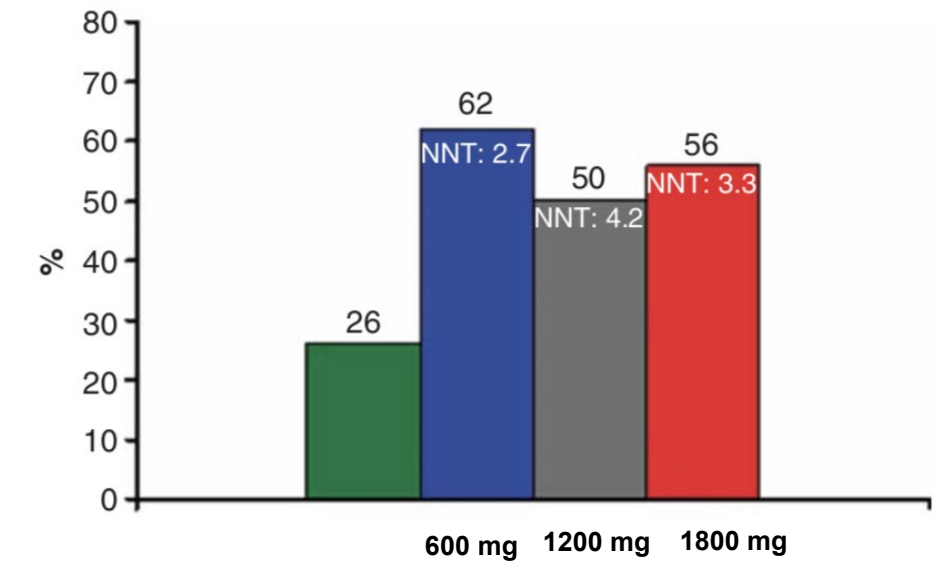
Nutraceutical	Study (ref.)	T1D/T2D ⁿ	Daily dose (mg)	Duration	Effects	Adverse events
Benfotiamine	BENDIP	16/117	300/600/placebo	6 weeks	Symptoms+ (PP) Signs--	None
	BEDIP	8/32	400/placebo	3 weeks	Symptoms/signs+ Pain+	None
Vitamin B12	Didangelos et al.	0/90	1/placebo	1 year	Symptoms+, Signs-- Pain+, VPT+ NCS+	None
Vitamin D	Karonova et al.	0/67	40000 IU/5000 IU per week	24 weeks	Pain+ Symptoms+ Signs+	None
Vitamin E	VENUS	300*	400/placebo	1 year	Symptoms-- Lancinating pain (+)	None
Acetyl-L-carnitine	Sima et al.	1257*	3000/placebo	1 year	Pain+ VPT+ NCS--	None
γ-Linolenic acid (GLA)	Keen et al.	57/51	480/placebo	1 year	NCS+ Signs+	None
	Won et al.	0/100	320 GLA/600 ALA	12 weeks	Symptoms, pain non-inferior [#]	None
Magnesium	de Leeuw et al.	110/0	300/no supplement	5 years	DPN stage+ ^{\$} NCS+	GI symptoms

Nutraceuticals and Neuropathic Pain -ALA

ALA- metanalysis



Diabet Med 2004;21:114-21



NNT for 50% reduction in the total symptom score after 5 weeks

Expert Opin. Pharmacother. (2014) 15(18)

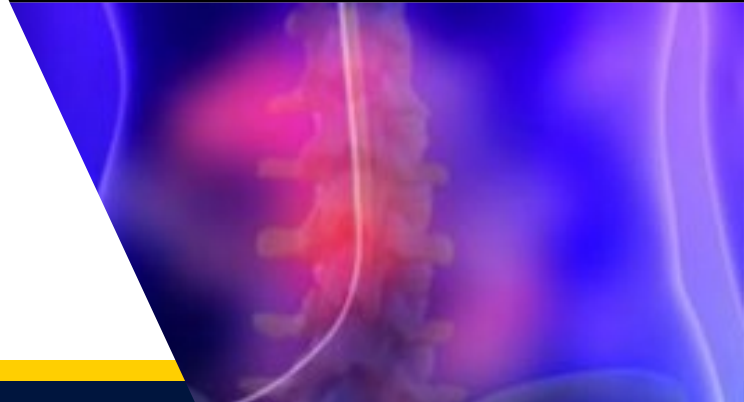
Non-Pharmacological Approaches

Non Pharmacological Approaches

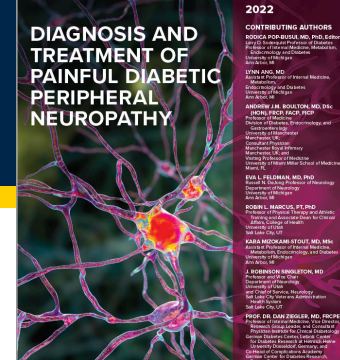
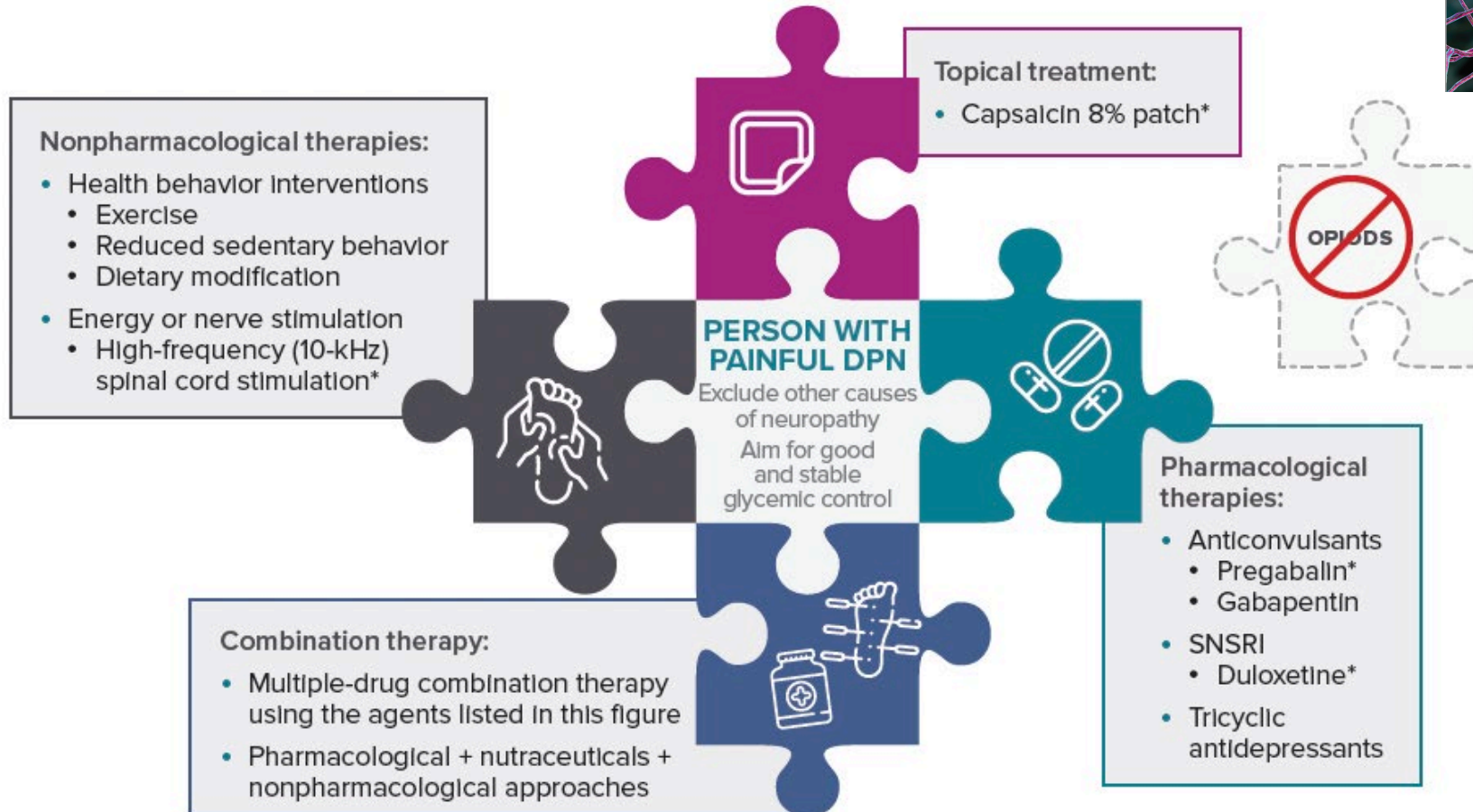
Dietary Modifications

Exercise/Physical Activity

Electromagnetic Stimulation



Algorithm for Treatment of DPN



Pop-Busui et al Diagnosis and treatment of painful peripheral neuropathy; ADA Clinical Compendia Series, 2022.



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Thank you !



All Research Participants!





The **Speak For Your Feet contest** launched in May 2022 to help people who experience PDPN know that they are not alone.

The contest will collect and identify a **winning mnemonic** to encourage people experiencing PDPN to **discuss symptoms**, **receive important healthcare reminders**, and **call patients with PDPN to action** to work with their HCPs to identify potential treatment solutions to speak for their feet!

Already, **over 100 mnemonics have been submitted**, like this one:

SHOES:

Stinging pain and electric shocks

Hard to walk or balance

Overnight pain making sleep difficult

Explain symptoms to your doctor

Seek treatment options

There is still time to submit and win! The contest doesn't end until October 1st and the **winner will receive a \$1,000 gift card** or other prizes!

To submit your entry, **scan the QR code** or visit **[nervepainandme.com/contest!](https://nervepainandme.com/contest/)**





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Questions?

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Can we help with anything else? Call 847-883-9942 or email info@tffpn.org. You may also mail inquiries and donations to *the* Foundation *for* Peripheral Neuropathy at 485 E. Half Day Road, Suite 350, Buffalo Grove, Illinois 60089.

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