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# Welcome!

*FPN Webinar:*

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

Wednesday, September 7, 2022

Sponsored by:  **Averitas**Pharma™

***We will begin our presentation shortly.***



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**Moderator:**



**Lindsay Colbert**  
*Executive Director*  
*the Foundation for Peripheral Neuropathy*

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***Presenter:***



**Rodica Pop-Busui, MD, PhD**  
*Michigan Medicine*

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# Demystifying Diabetic Peripheral Neuropathy

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Larry D. Soderquist Professor of Diabetes

Director Clinical Research, Caswell Diabetes Institute

Vice Chair Clinical Research

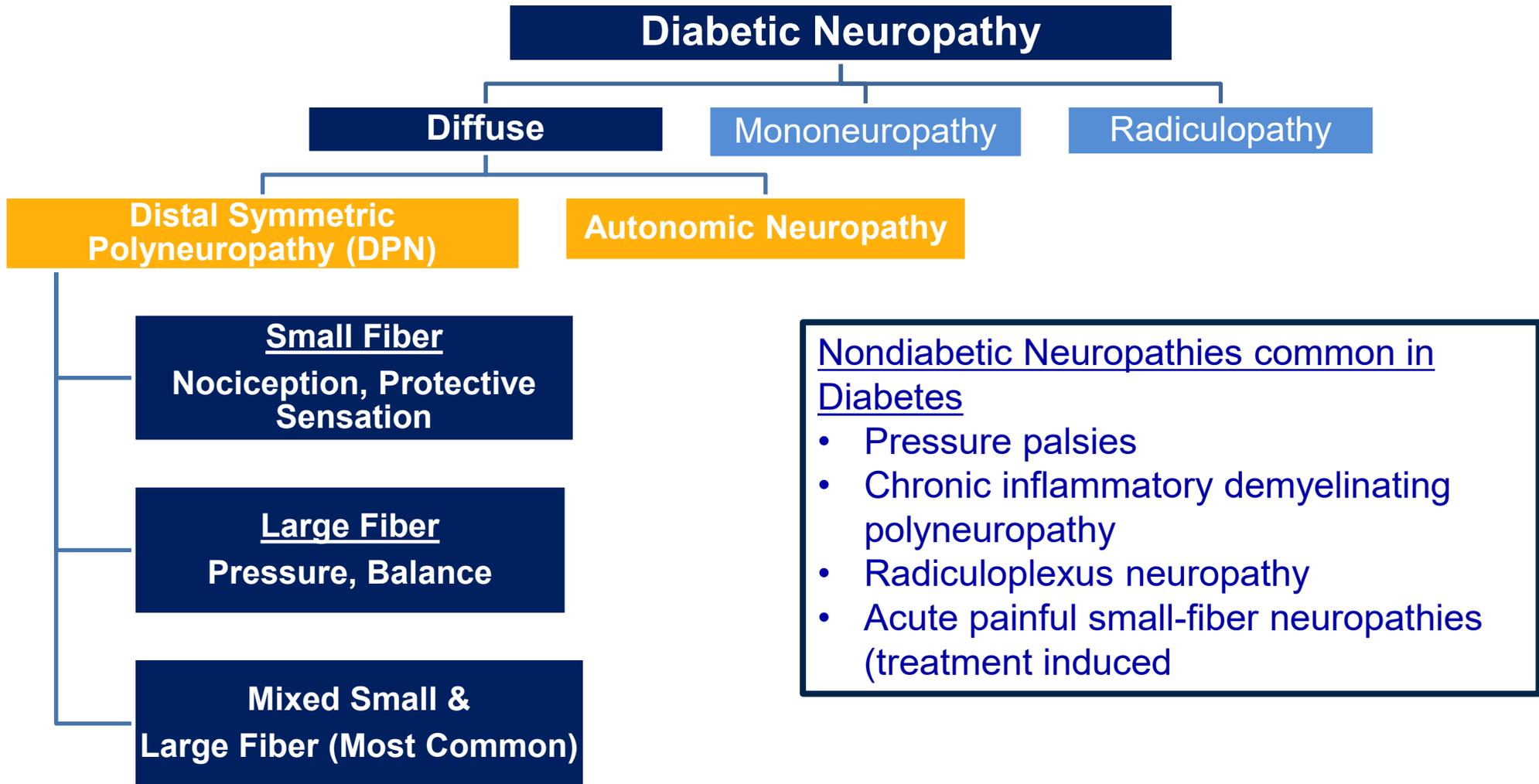
University of Michigan, Ann Arbor, MI

**President-Elect American Diabetes Association**

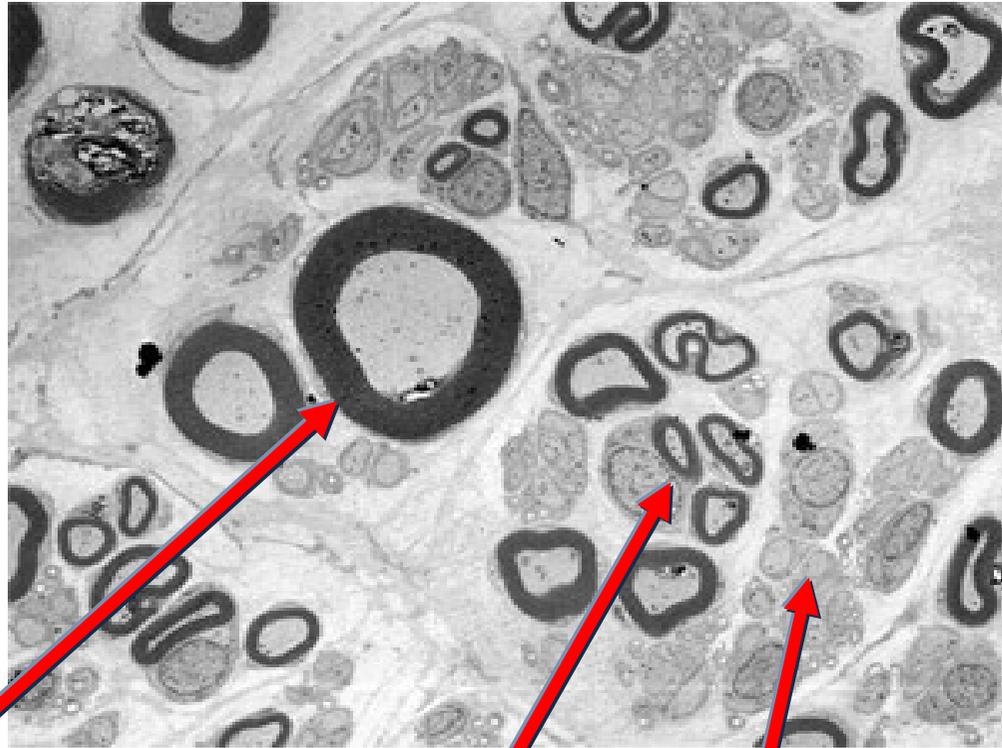
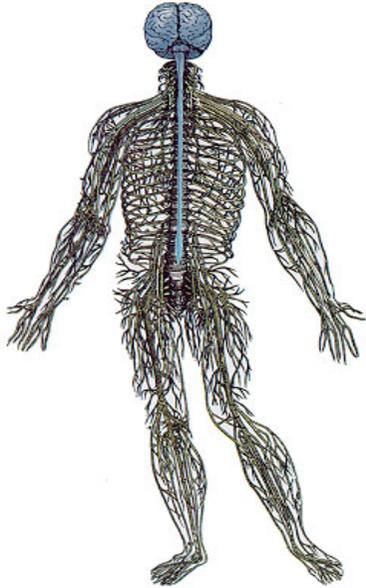
# OUTLINE

- **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



# The Peripheral Nervous System is Complex

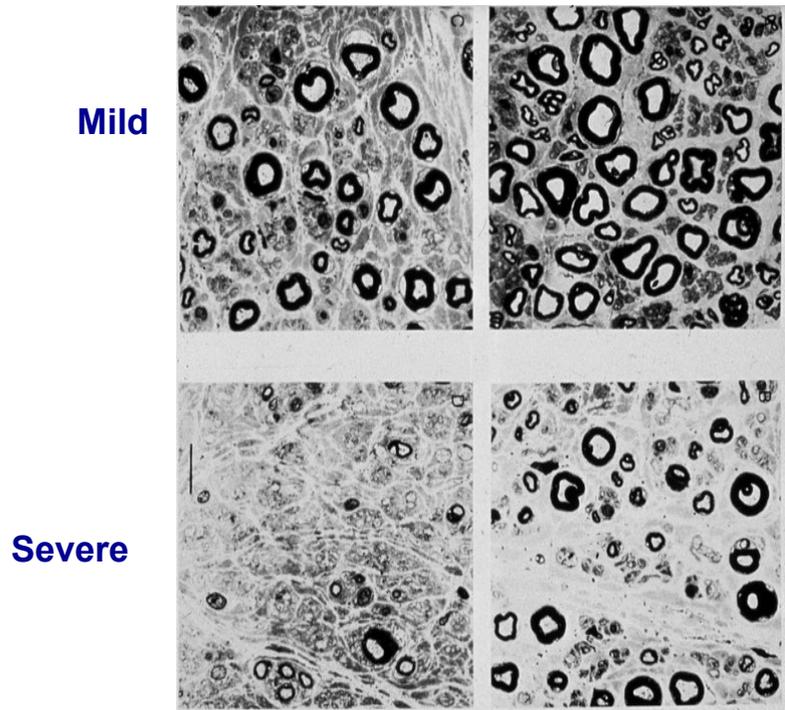


**Large myelinated  
fiber**

**Small myelinated  
fiber**

**Unmyelinated  
fibers**

# Diabetic Peripheral Neuropathy (DPN)



Normal

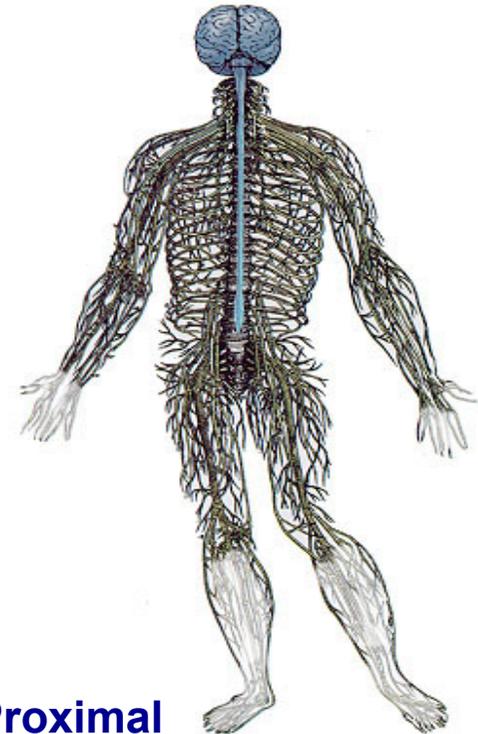
Small Fibers



Large Fibers

Moderate

Distal → Proximal



# OUTLINE

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# Evaluation of Small Fibers- Painful DPN



Small Myelinated      Unmyelinated  
fibers

## Nerve Function

- Nociception (pain and temperature)
- Protective sensations

## History

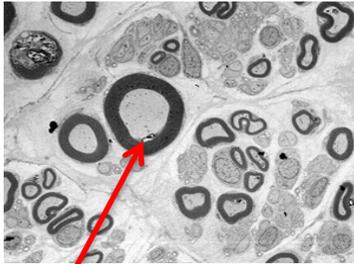
- Burning **Pain**
- Lancing
- Electric shocks
- Stabbing
- Hyperalgesia
- Allodynia

## 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

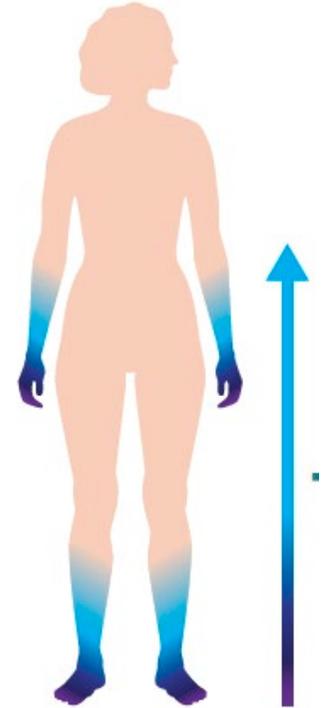


Pop-Busui, Boulton, et al, *Diabetes Care* 2017; 40: 136-154



MICHIGAN MEDICINE  
UNIVERSITY OF MICHIGAN

# 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)
<b>Symptoms</b>	15 items Self-administered	6 item symptom score	None
<b>Exam</b>	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>
<b>Scoring</b>	≥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.

# 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

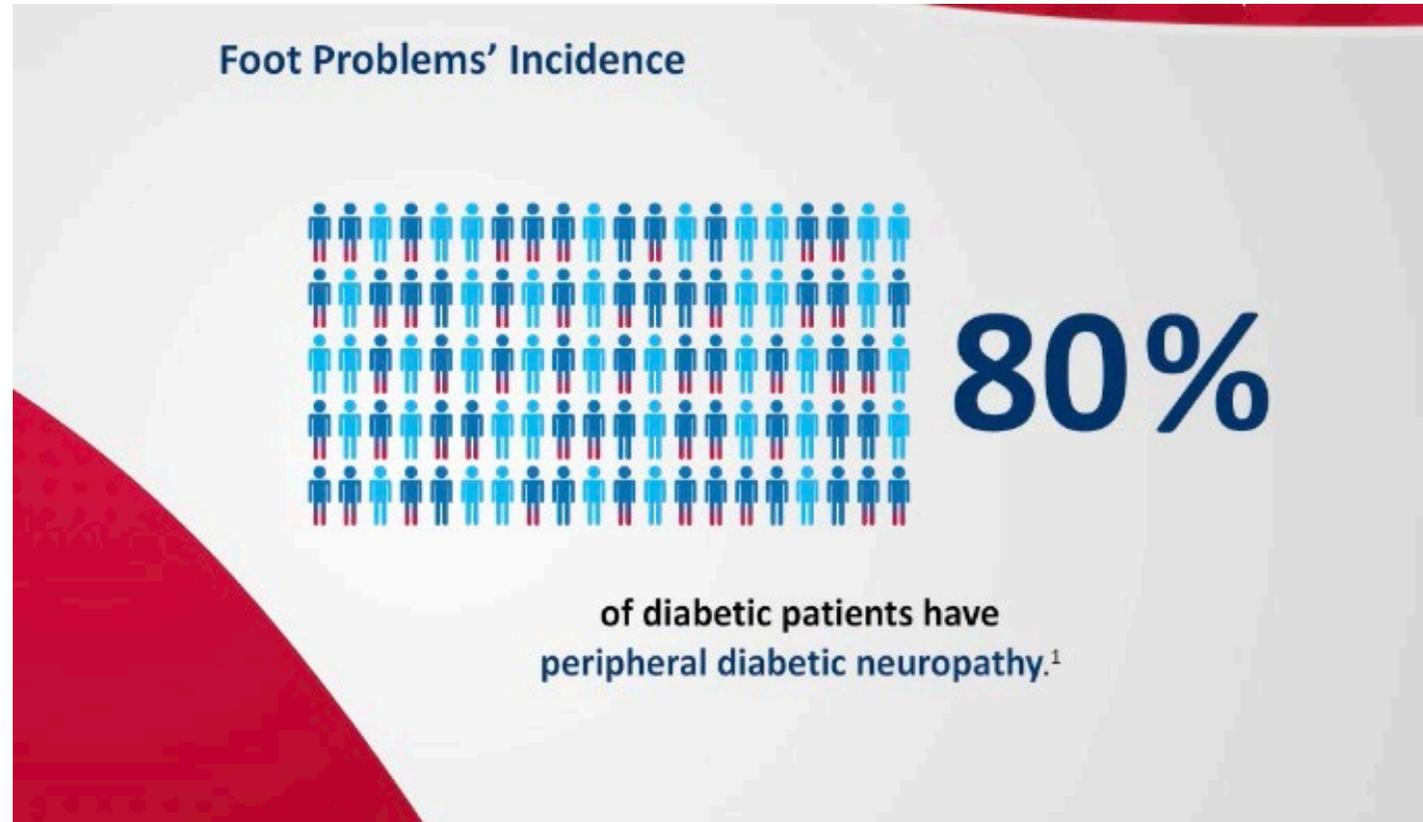
## Patient reported outcomes

DN Quality of life
Neuropathy NeuroQOL
Norfolk



# Advanced DPN Complications

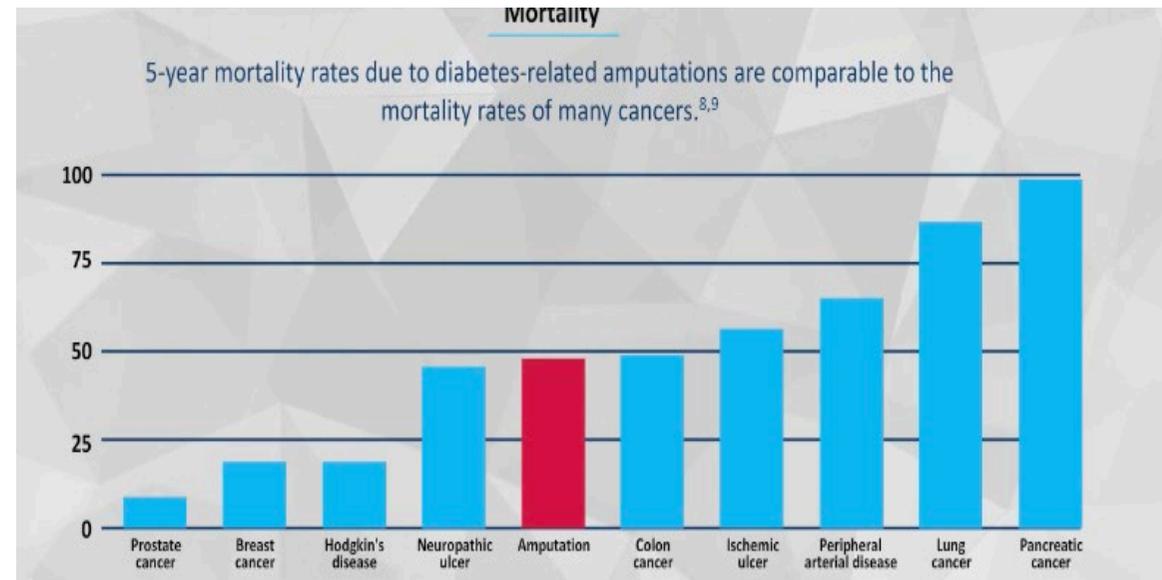
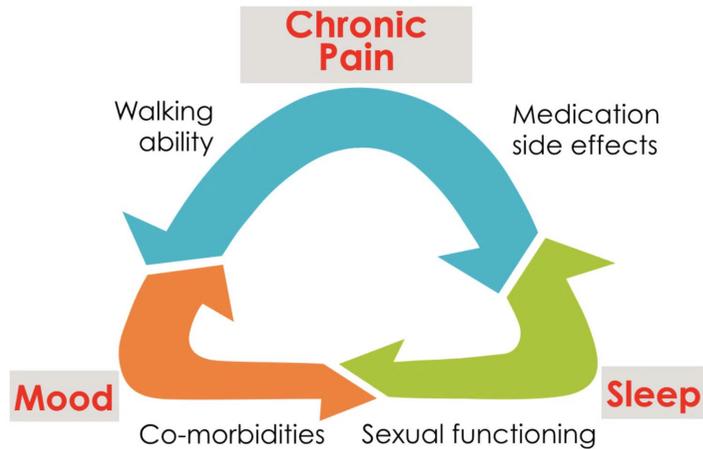
## Diabetic foot ulcers



# 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**

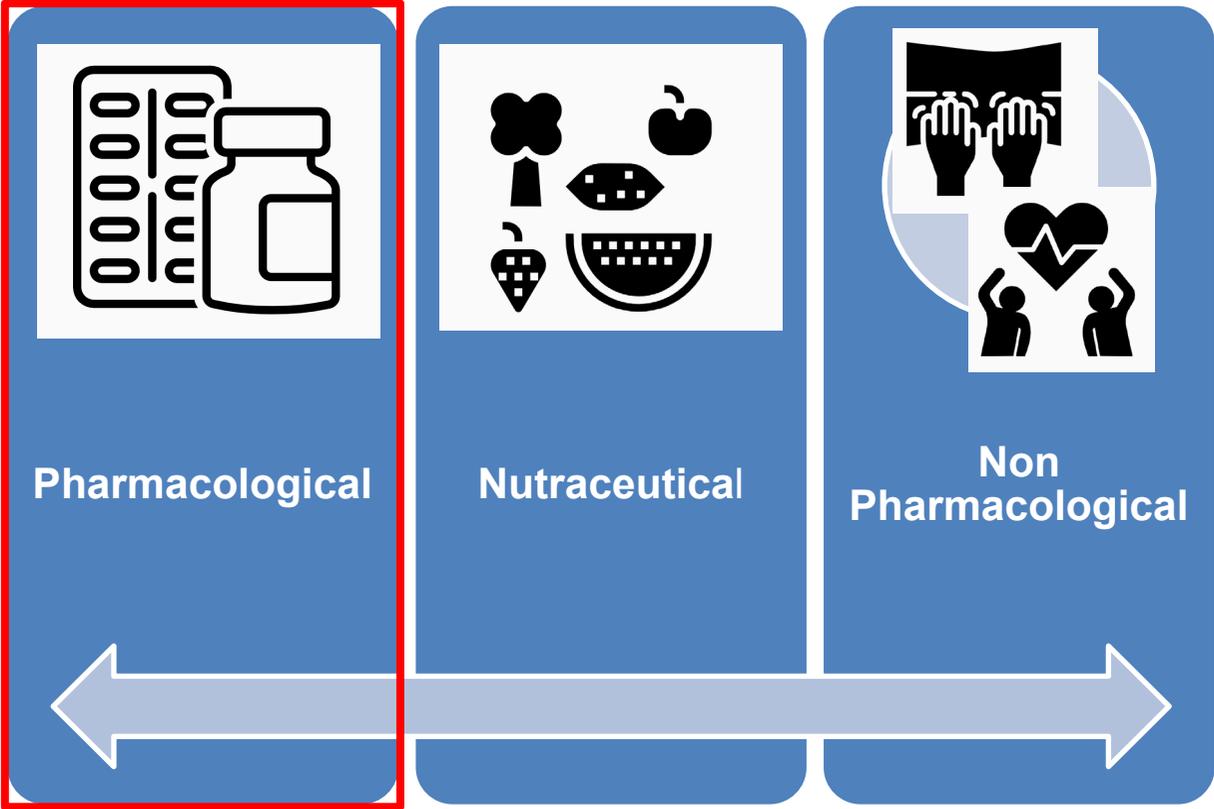


*Armstrong et al, IWJ 2007*

# 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

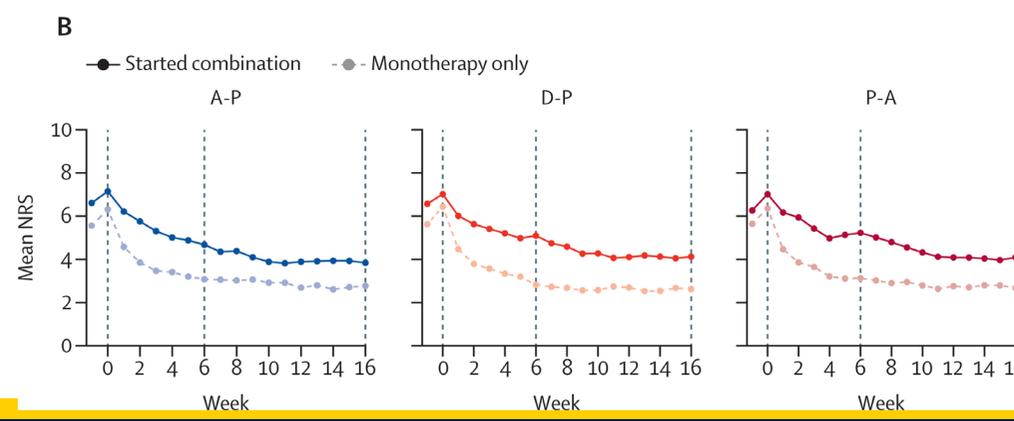
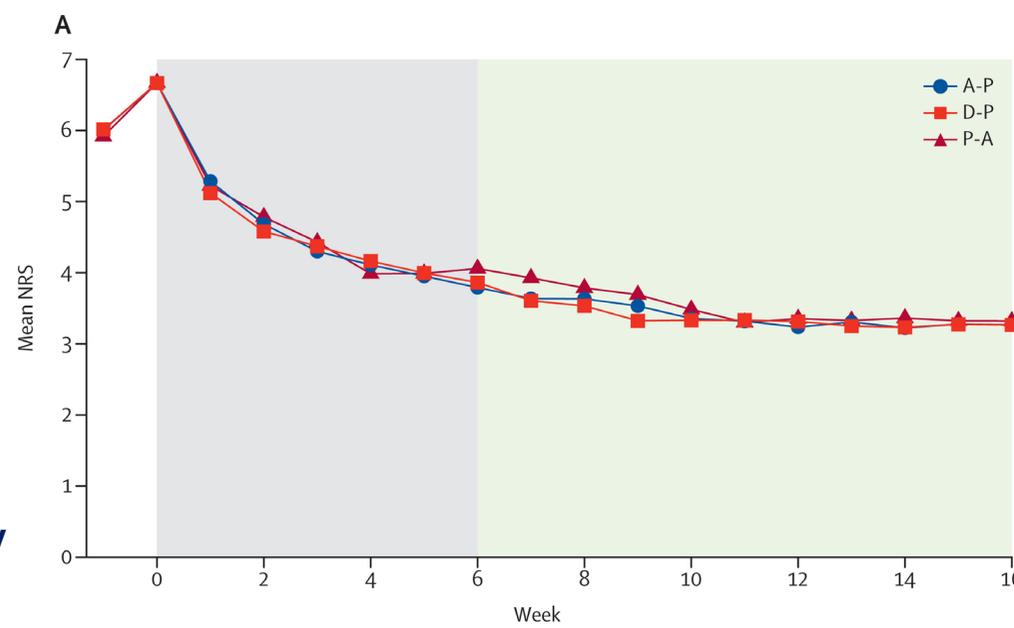
↙  
Nonresponders:

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

↘  
Responders (NRS<3)

- Continued monotherapy

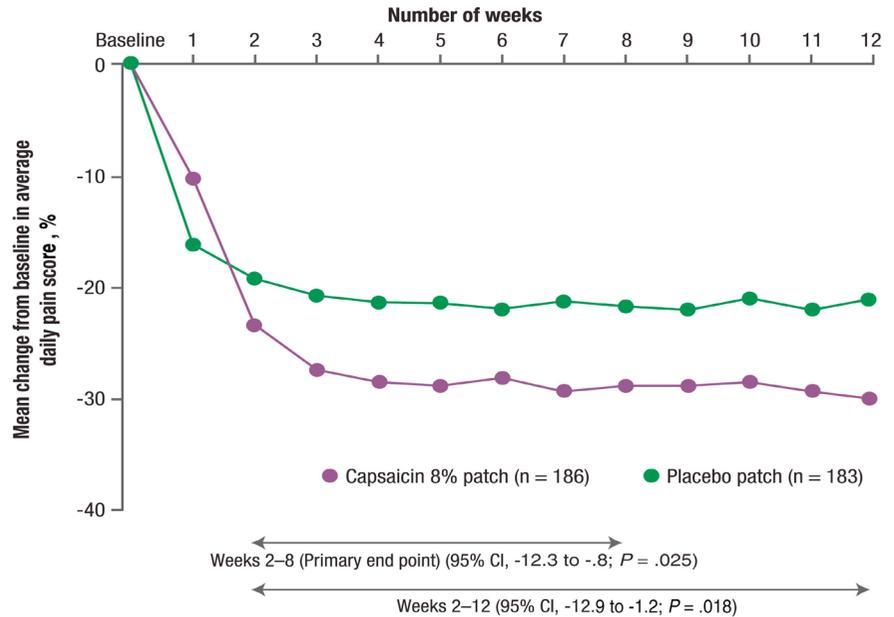
75 mg/day amitriptyline  
120 mg/day duloxetine  
600 mg/day pregabalin



# 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**

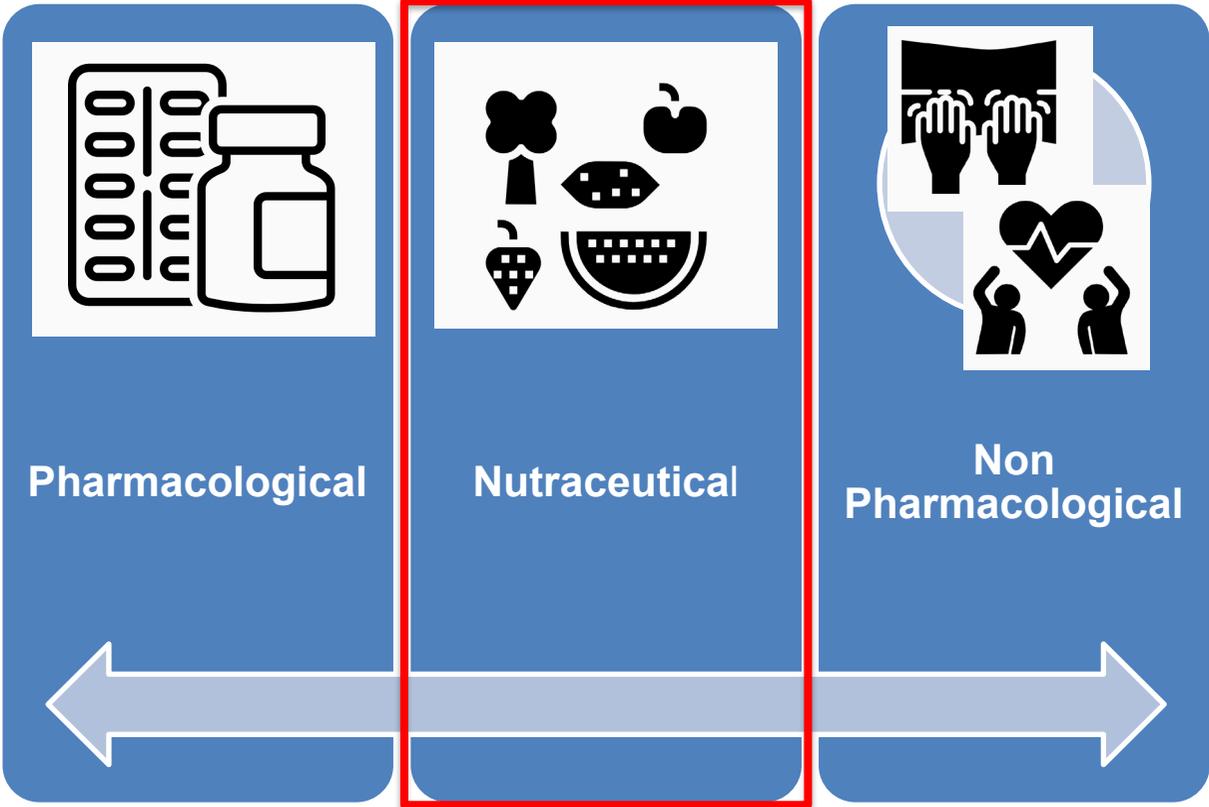
# Topical Options Painful DPN: Capsaicin 8% Patch - FDA Approved



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

	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
<b>Weekly 95% CI</b>	N/A	-10.4, 2.3	-13.1, -4	-13.5, -8	-13.6, -1.0	-12.6, .0	-14.4, -1.8	-13.5, -8	13.2, -6	-13.9, -1.2	-13.7, -1.1	-15.3, -2.7	
<b>Weekly P value</b>	N/A	.208	.036	.027	.024	.051	.012	.026	.032	.020	.022	.005	
<b>Number of patients</b>													
Capsaicin	186	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	183

# Painful DPN Therapeutic Approaches

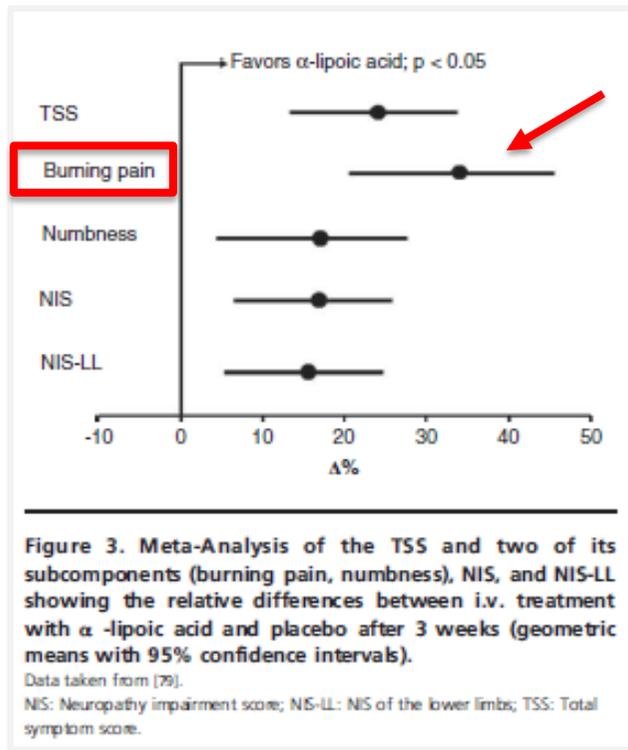


# Nutraceuticals for Neuropathic Pain

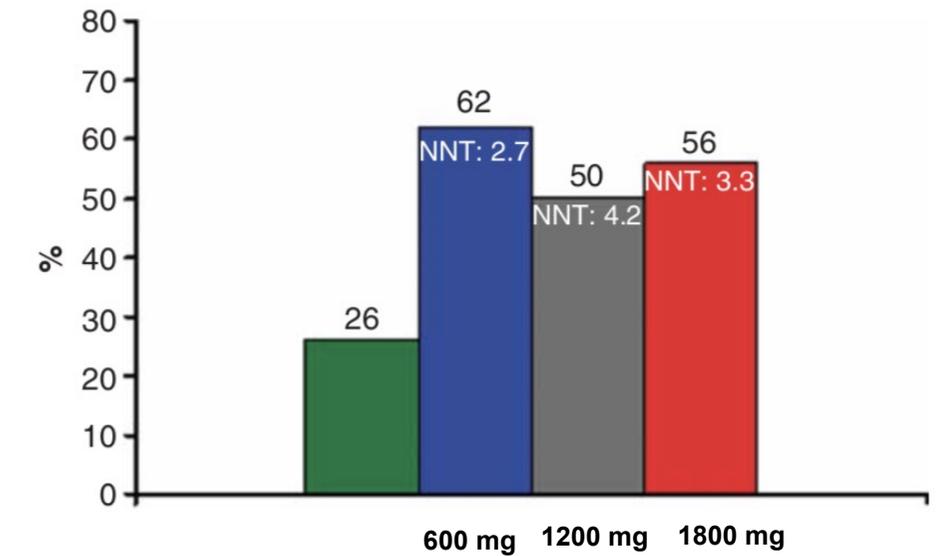
Nutraceutical	Study (ref.)	T1D/T2D <sup>n</sup>	Daily dose (mg)	Duration	Effects	Adverse events
Benfotiamine	BENDIP	16/117	300/600/placebo	6 weeks	Symptoms+ (PP) Signs--	None
	BEDIP	8/32	400/placebo	3 weeks	Symptoms/signs+ Pain+	None
Vitamin B12	Didangelos et al.	0/90	1/placebo	1 year	Symptoms+, Signs--, 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 <sup>#</sup>	None
Magnesium	de Leeuw et al.	110/0	300/no supplement	5 years	DPN stage+ <sup>\$</sup> 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

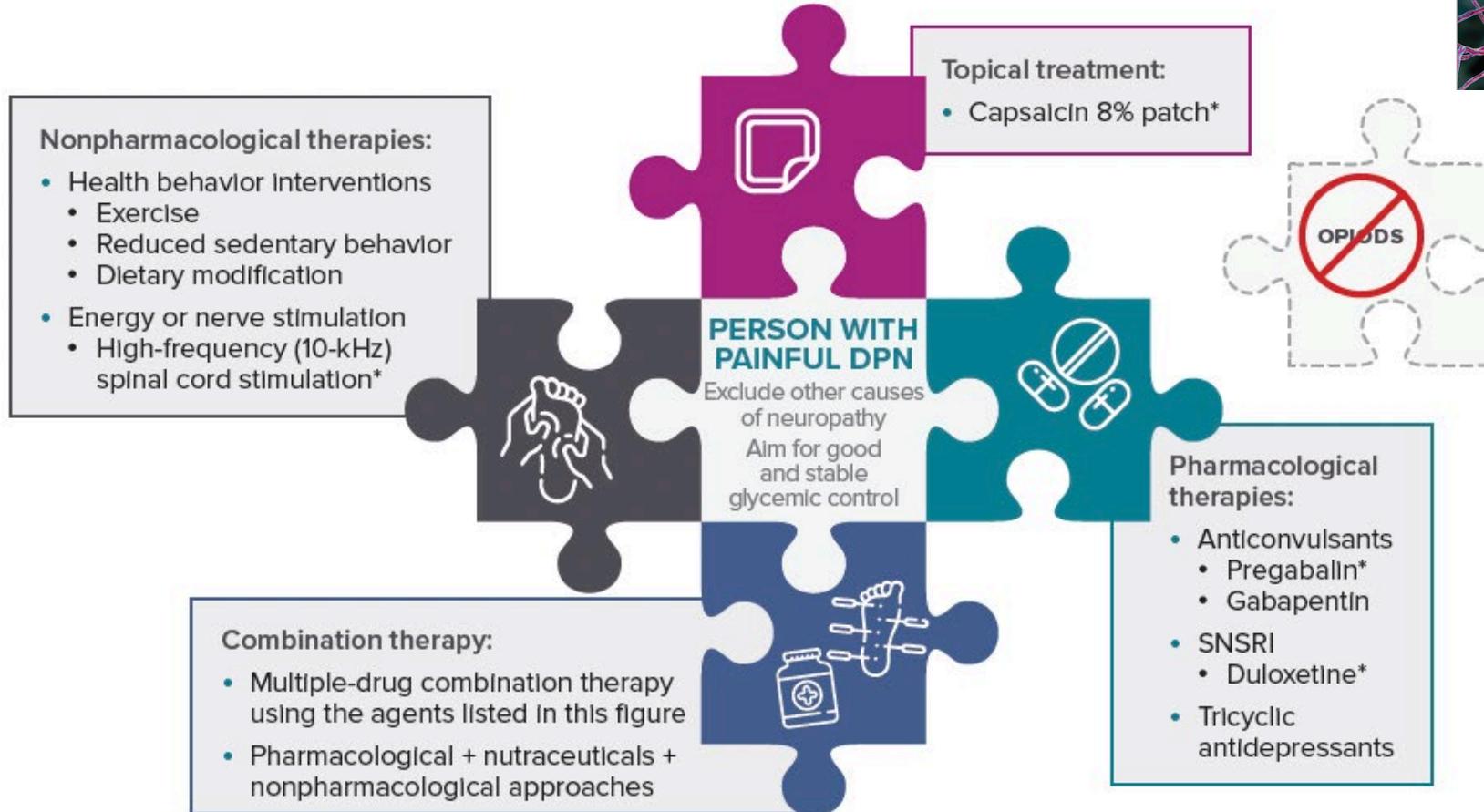
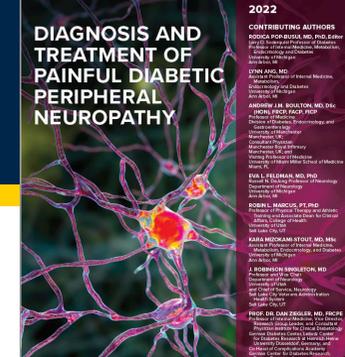
Dietary Modifications

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.

# 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 1<sup>st</sup> 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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