



**Great
Debates
& Updates**

Diabetic Foot



Diabetic Peripheral Neuropathy: What You Can't Feel Can Hurt You

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President-Elect Medicine and Science American Diabetes Association

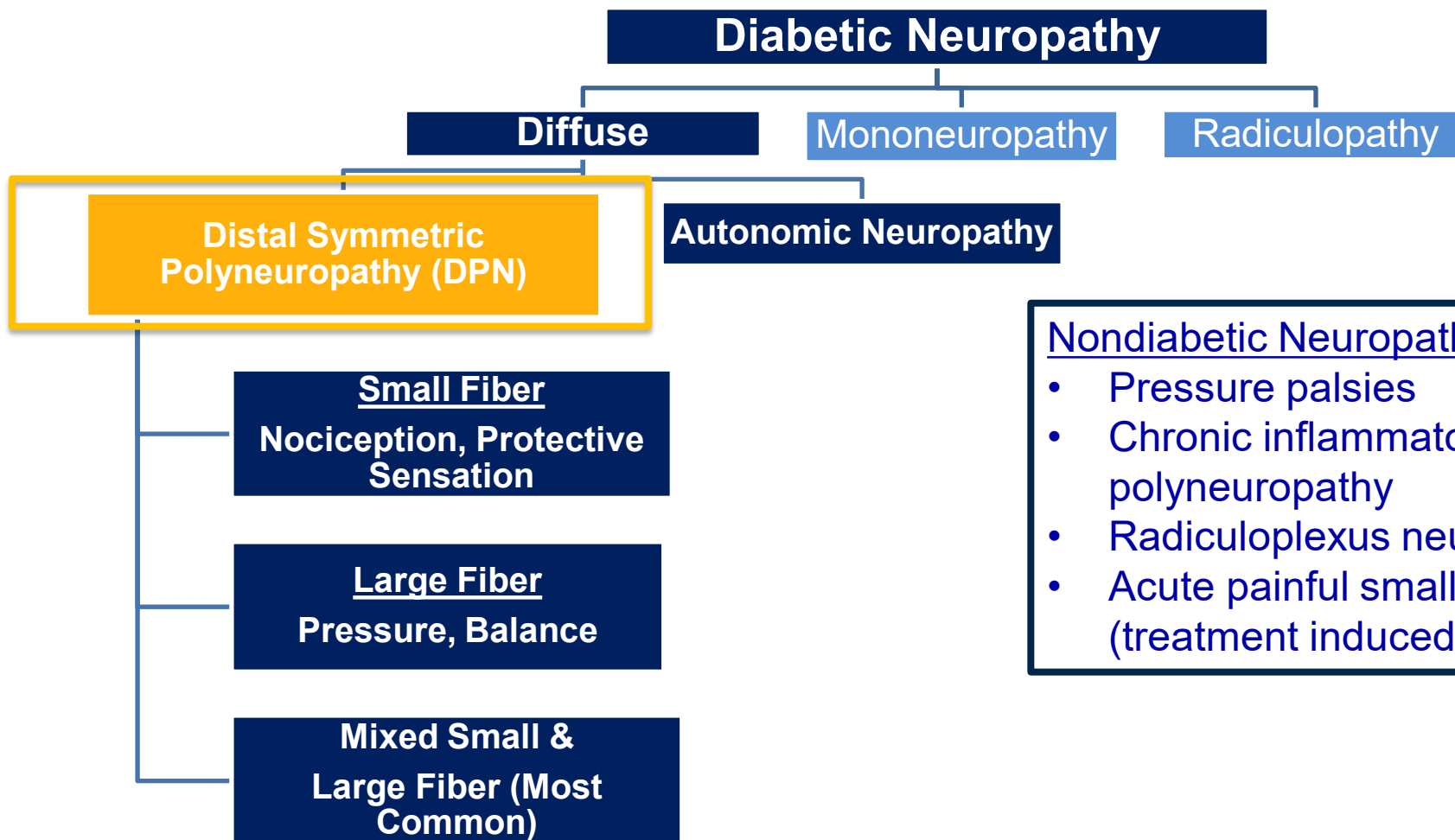
Disclosures

Rodica Busui, MD, PhD: Averitas Pharma, Boehringer-Ingelheim, Nevro, Novo-Nordisk, Procter & Gamble, Regenacy, Roche; Grant/research support: NIDDK, American Diabetes Association, JDRF

Outline

- Diabetic peripheral neuropathy: What is it and how prevalent is it?
- Clinical impact: Individual and societal impact – what one can't feel can hurt

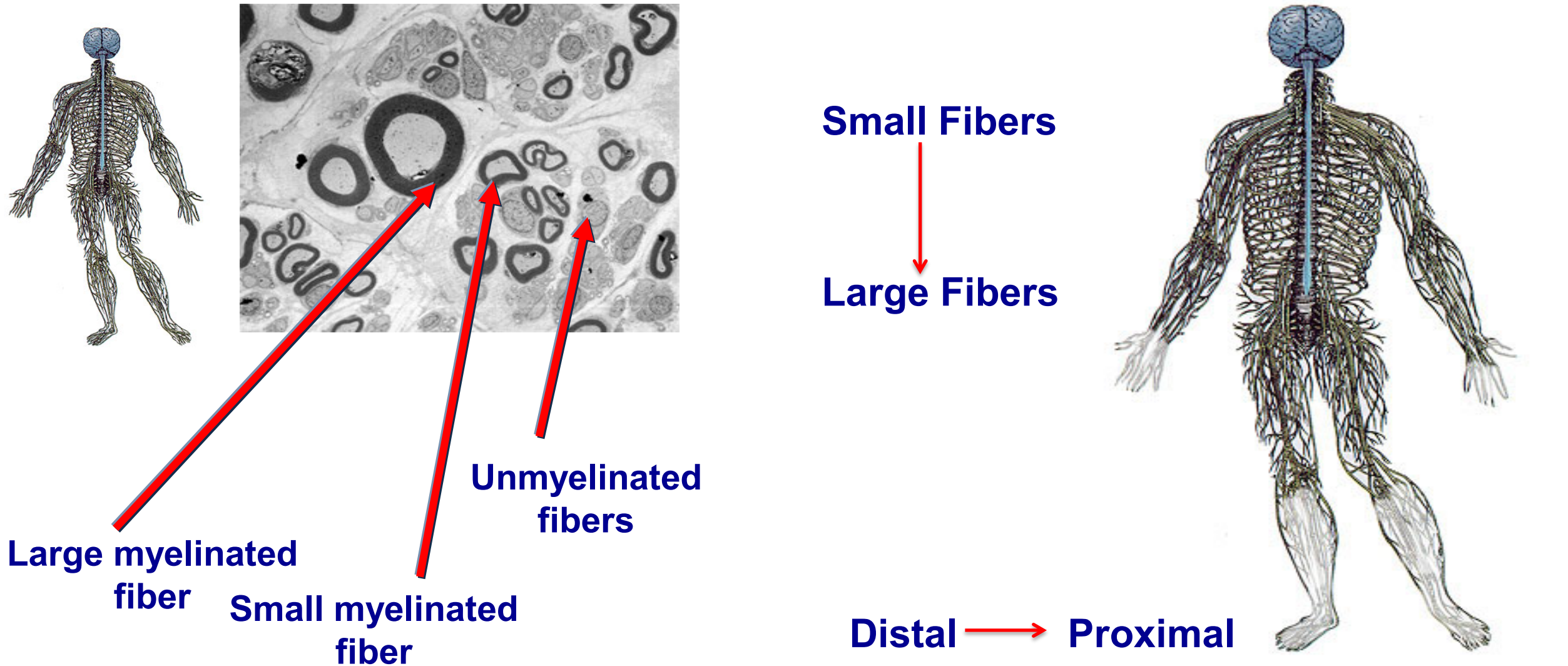
Diabetic Neuropathies-Broad Spectrum



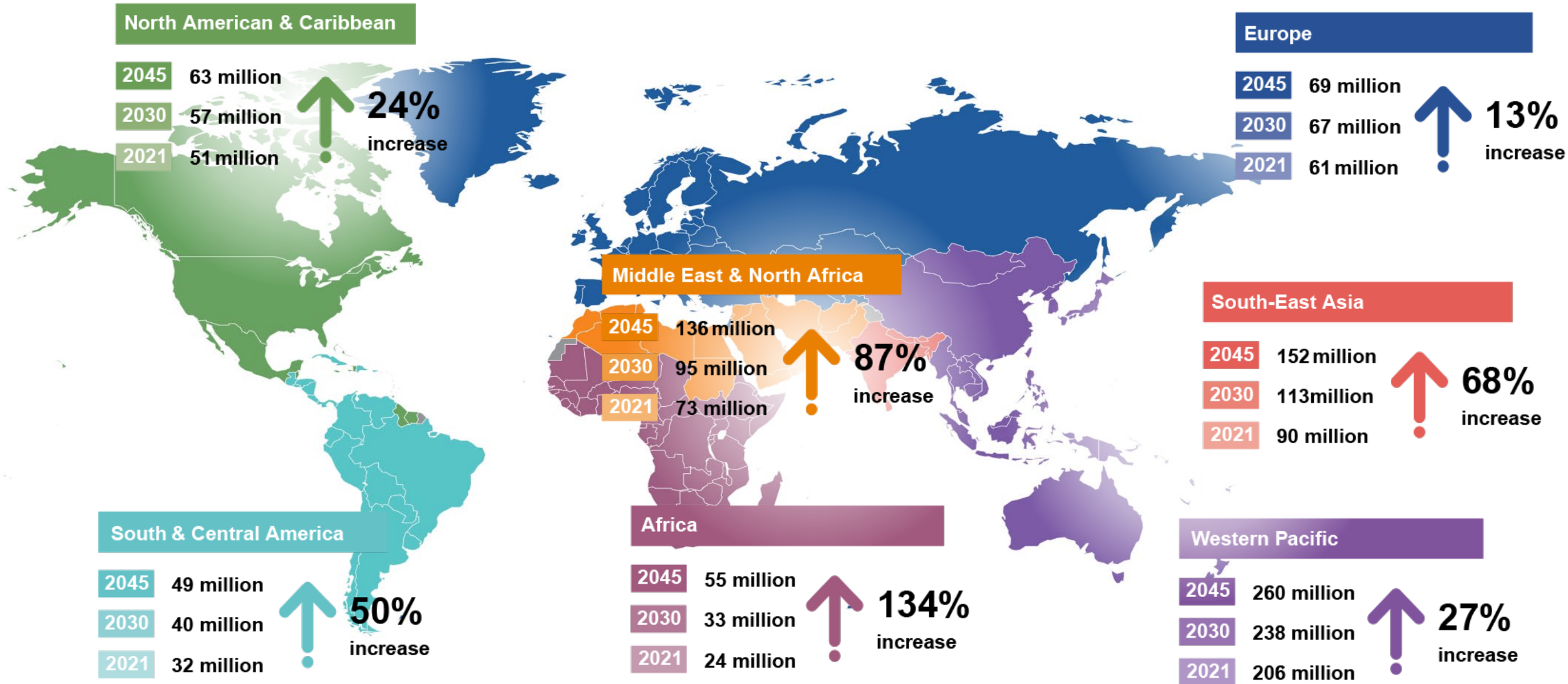
Nondiabetic Neuropathies common in diabetes

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

Diabetic Peripheral Neuropathy (DPN)

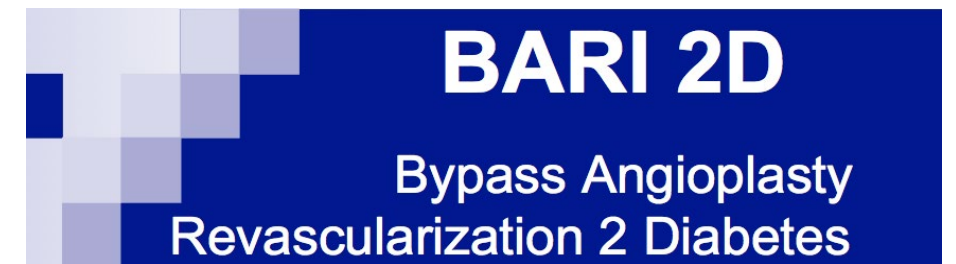
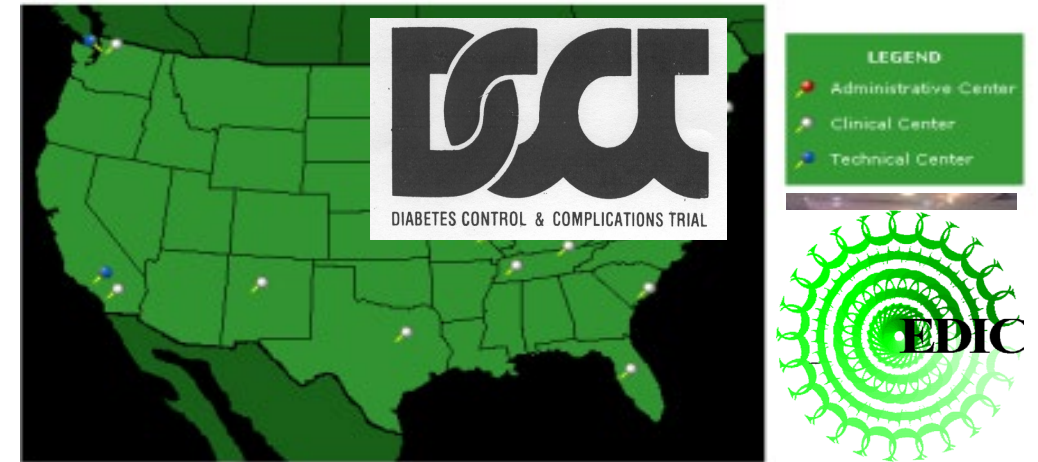


Diabetes Global Epidemiology 2022





diabeteslongevity.ca

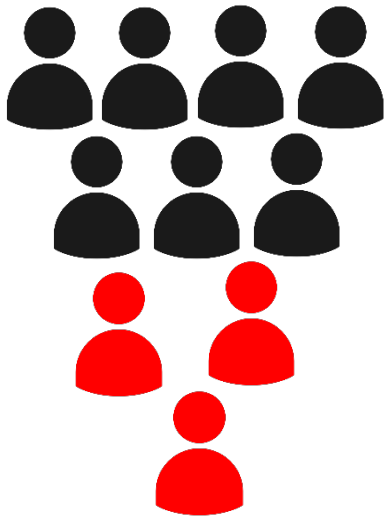


Magnitude of the Problem: Prevalence of Neuropathy in Diabetes

> 10,000 T1D

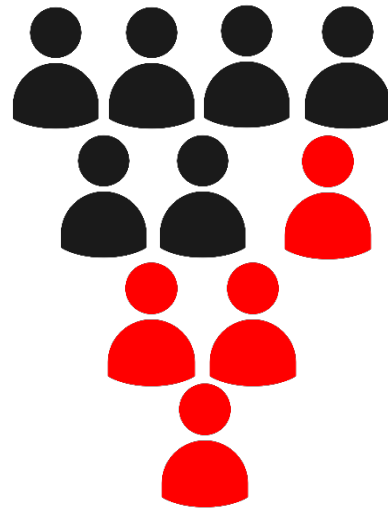
Type 1 Diabetes

DPN



Up to 30% after
>25 years of diabetes

Autonomic Neuropathy

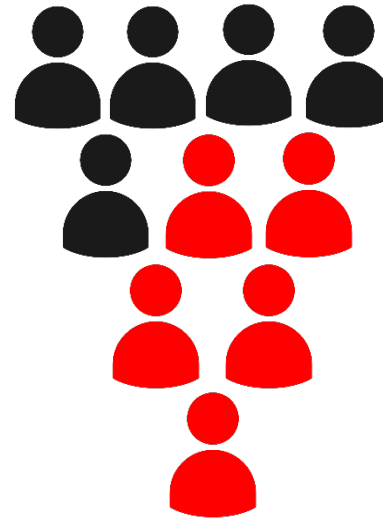


Up to 40% after
>25 years of diabetes

Type 2 Diabetes

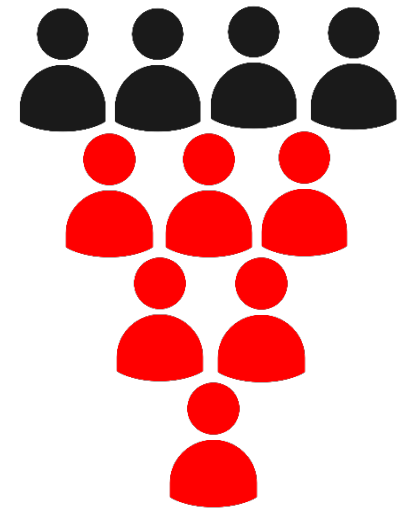
> 30,000 T2D

DPN



Up to 50% after 10
years of T2D

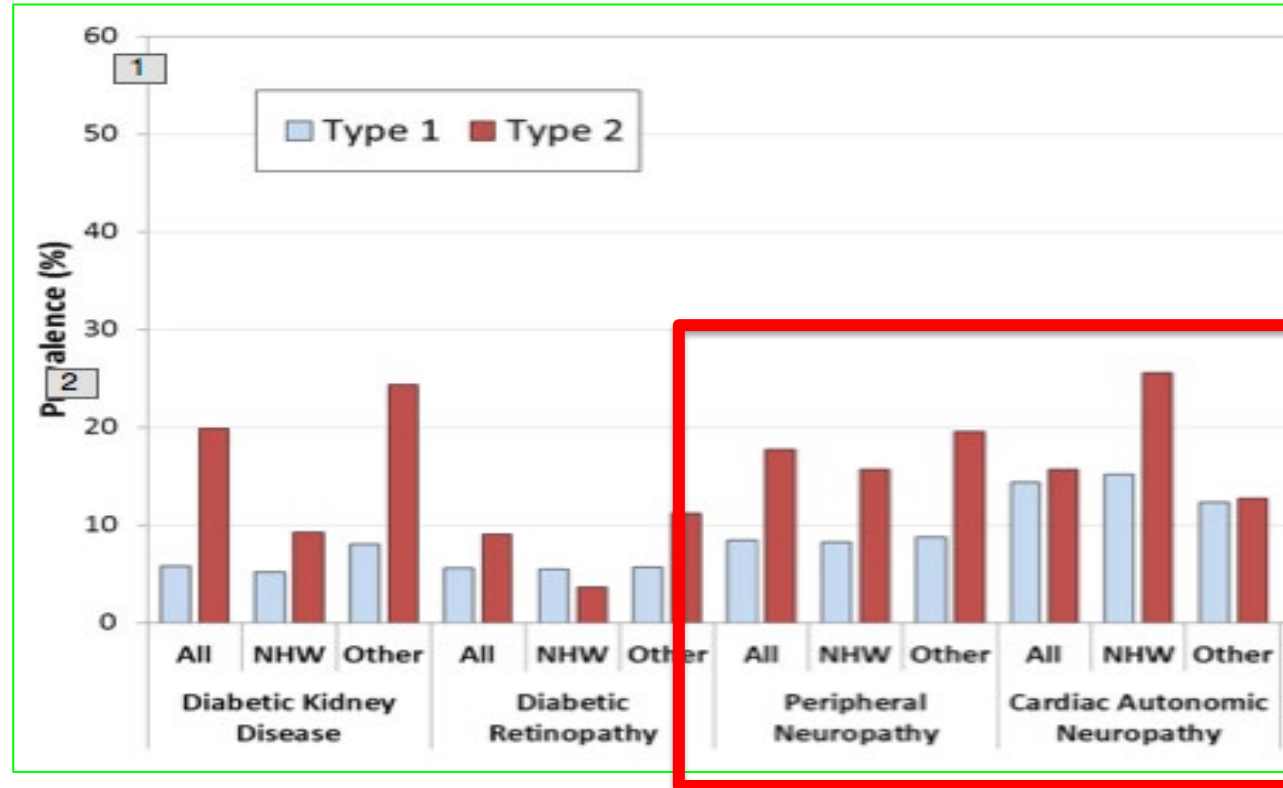
Autonomic Neuropathy



Up to 60% after
15 years of T2D

DPN and CAN Are Prevalent in Youth

High prevalence rates in youth with T1D and T2D



Up to 20%

DPN: MNSI

CAN: Deep breathing,
HRV

Outline

- Diabetic peripheral neuropathy: What is it and how prevalent is it?
- Clinical impact: Individual and societal impact – what one can't feel can hurt

Large Myelinated Fibers and Clinical Care Impact



Large Myelinated
Fibers

Nerve Function

- Pressure
- Balance

What One Can't Feel Can Hurt!

Falls and fractures associated with type 2 diabetic polyneuropathy: A cross-sectional nationwide questionnaire study

Karolina Snopek Khan^{1,2*}, Diana Hedevang Christensen^{1,3}, Sia Kromann Nicolaisen³, Sandra Sif Gylfadottir^{1,4}, Troels Staehelin Jensen^{1,4}, Jens Steen Nielsen^{1,5,6}, Reimar Wernich Thomsen³, Henning Andersen^{1,2}

¹Department of Clinical Medicine, International Diabetic Neuropathy Consortium, Aarhus University, Aarhus, Denmark; ²Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; ³Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; ⁴Department of Clinical Medicine, Danish Pain Research Center, Aarhus University, Aarhus, Denmark; ⁵The Danish Center for Strategic Research in Type 2 Diabetes, Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark; and ⁶Research Unit of SDCO, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Keywords

Diabetic polyneuropathy, Falls, Fractures

ABSTRACT

Aims/Introduction: To examine the prevalence of falls and fractures, and the association with symptoms of diabetic polyneuropathy (DPN) in patients with recently diagnosed type 2 diabetes.

Symposium/Special Issue

The Impact of Diabetic Neuropathy on Activities of Daily Living, Postural Balance and Risk of Falls - A Systematic Review

Karolina Snopek Khan, PhD, MD¹ and Henning Andersen, PhD, MD²

Abstract

Objective: The objective of this review is to discuss a compilation of the currently available literature regarding the impact of diabetic neuropathy (DN) on activities of daily living (ADL), postural stability, and risk of falls.

Methods: A systematic electronic search strategy was conducted on PubMed/MEDLINE database, Cochrane Library, and Embase in March 2020. This narrative review included clinical cross-sectional studies assessing ADL, postural balance, and falls in adults with DN. All studies underwent a quality assessment based on the Newcastle Ottawa scale developed to assess

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1–6
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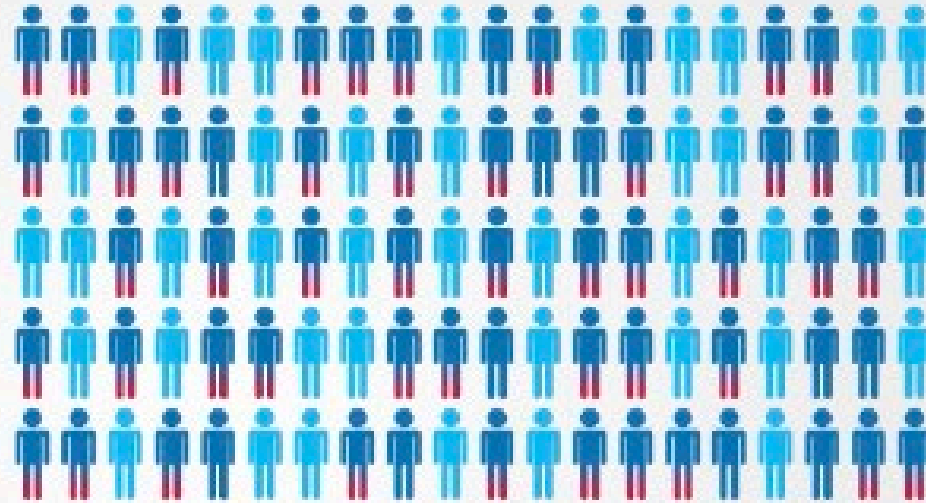
- Individuals with DPN have an increased risk of falling due to poor balance and function
- Assessments of postural stability, gait, and other functional should be included in an effective fall prevention program in individuals with DPN population

Advanced DPN Complications

Diabetic foot ulcers



Foot Problems' Incidence



80%

of diabetic patients have
peripheral diabetic neuropathy.¹

DPN – Can Hurt Badly

10,000 T2D ACCORD

Amputations, death

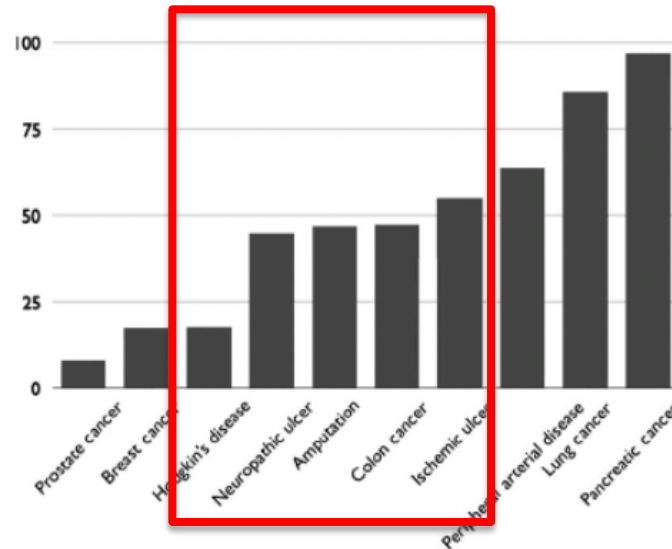
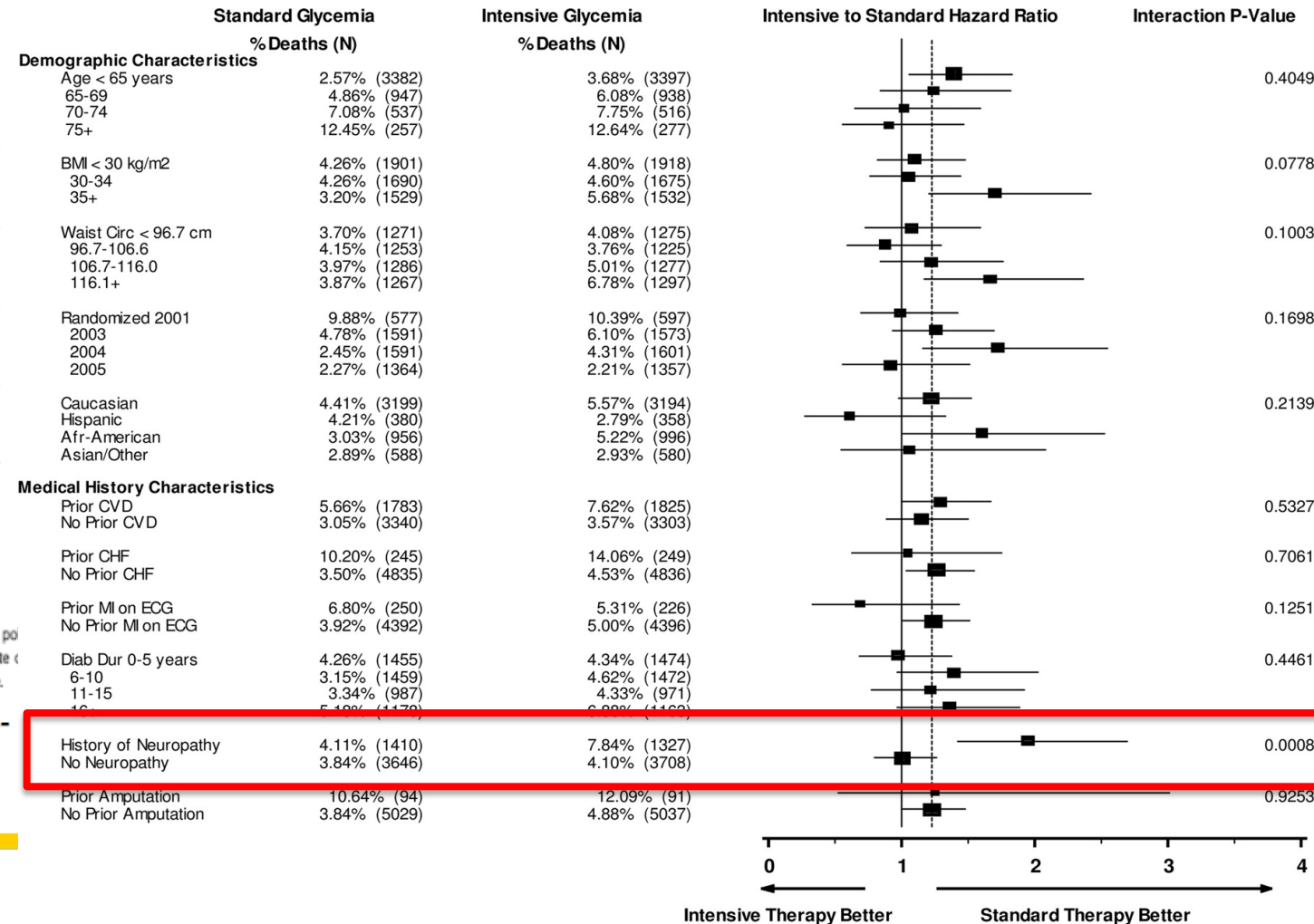
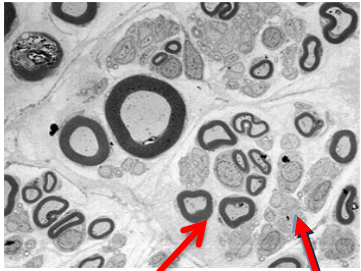


Figure 1. Five-year mortality (%). Perhaps now is the time to change our discussion with health-care administrators, politicians, and especially ourselves. The disease state that many of us treat routinely is, quite literally, killing our patients at a rate comparable to cancer. Addressing this issue aggressively may alter this and make a difference for millions of people worldwide.

Armstrong DG, Wrobel JS, Robbins JM. Are diabetes-related wounds and amputations worse than cancer? *IWJ*, 2007; 4(4) 286-7



Small Fibers and Clinical Care Impact



**Small
Myelinated**

**Unmyelinated
fibers**

Nerve Function

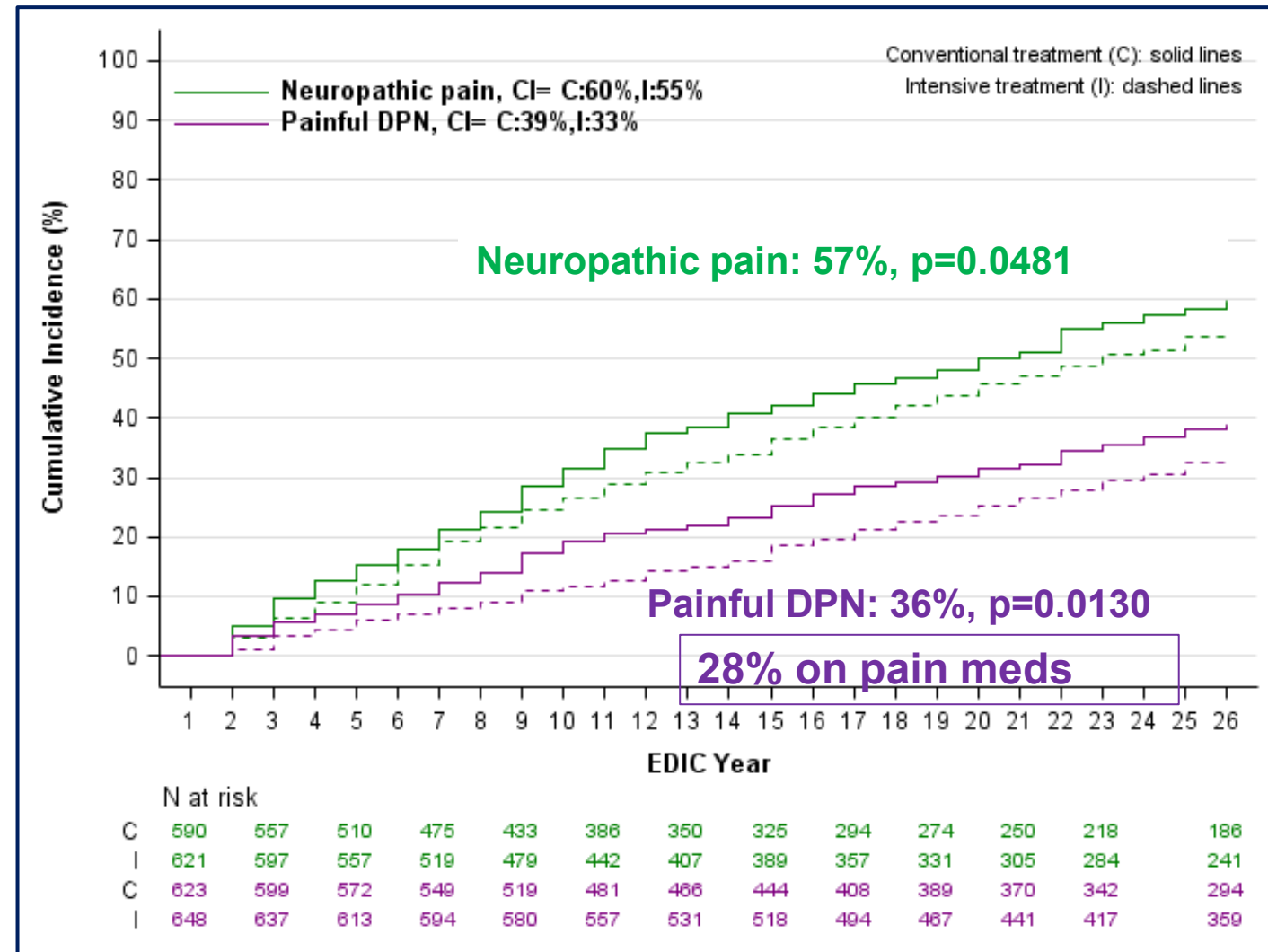
- Nociception (pain and temperature)
- Protective sensations

Painful DPN Is Prevalent

Neuropathic pain

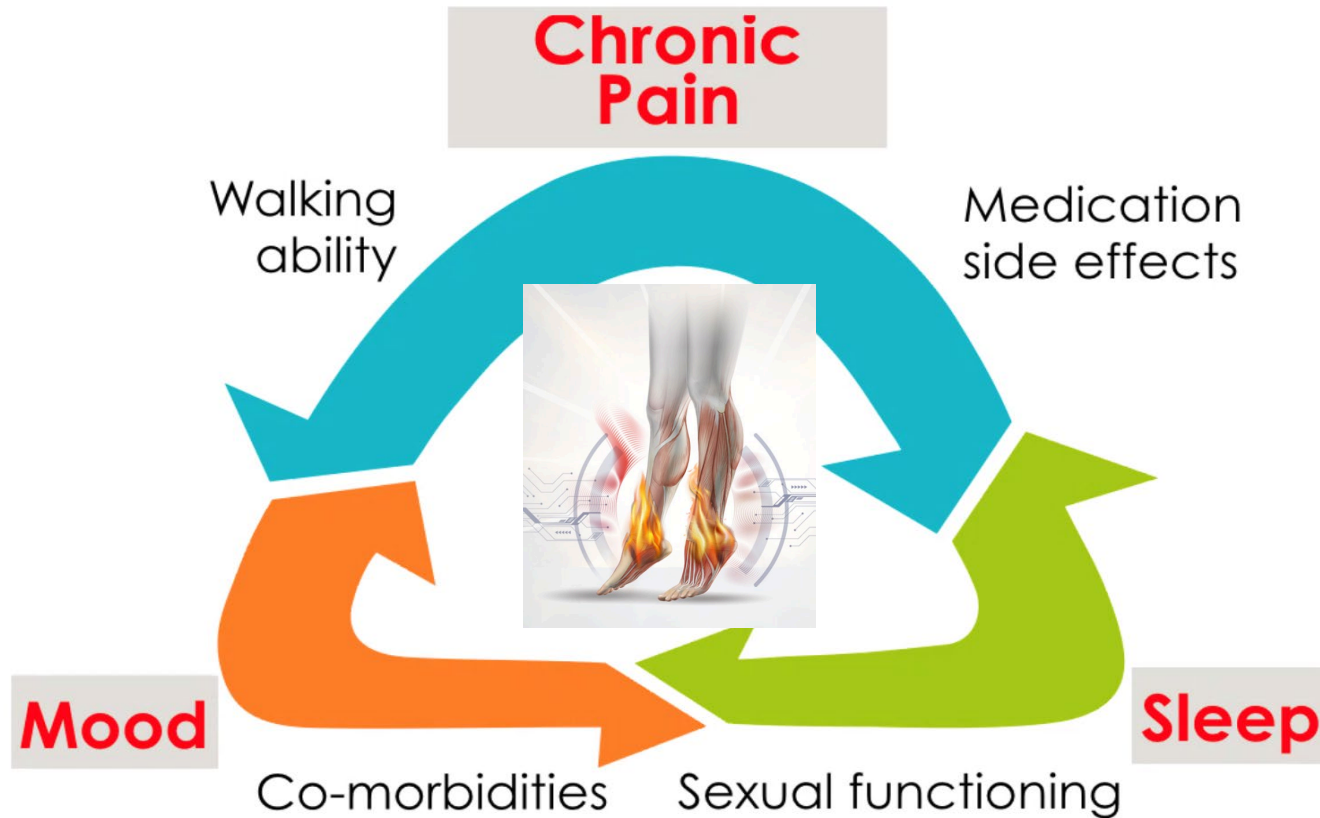
Q2: “Do you ever have any burning pain in your legs and/or feet?”

Q6: “Does it hurt when the bed covers touch your skin?”



What One Can't Feel Can Hurt – Painful DPN

Painful diabetic neuropathy:
a disabling problem for many patients



Patient reported
outcomes – Quality
of Life



Painful DPN – A Serious Challenge

europaean journal of neurology

the official journal of the europaean academy of neurology

European Journal of Neurology 2010; 17: 1113–1123

doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal^{a,b}, G. Cruccu^{a,c}, R. Baron^{a,d}, M. Haanpää^{a,e}, P. Hansson^{a,f}, T. S. Jensen^{a,g} and T. Nurmikko^{a,h}

NeuPSIG recommendations

Lancet Neurol 2015; 162–73

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

Nanna B Finnerup*, Nadine Attal*, Simon Haroutounian, Ewan McNicol, Ralf Baron, Robert H Dworkin, Ian Gilron, Maija Haanpää, Per Hansson, Troels S Jensen, Peter R Kamerman, Karen Lund, Andrew Moore, Srinivasa N Raja, Andrew S C Rice, Michael Rowbotham, Emily Sena, Philip Siddall, Blair H Smith, Mark Wallace

Diabetic Neuropathy: A Position Statement by the American Diabetes Association

Diabetes Care 2017;40:136–154 | DOI: 10.2337/dc16-2042

Rodica Pop-Busui,¹ Andrew J.M. Boulton,² Eva L. Feldman,³ Vera Bril,⁴ Roy Freeman,⁵ Rayaz A. Malik,⁶ Jay M. Sosenko,⁷ and Dan Ziegler⁸

CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, GA Finley MD, A Furlan MD PhD, I Gilron MD MSc, A Gordon MD, PK Morley-Forster MD, BJ Sessle MDS PhD, P Squire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, OD Williamson MBBS

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journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Review

Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: International expert consensus recommendations



Dan Ziegler^{a,b,*}, Solomon Tesfaye^c, Vincenza Spallone^d, Irina Gurieva^{e,f}, Juma Al Kaabi^{g,h}, Boris Mankovskyⁱ, Emil Martinka^{j,k}, Gabriela Radulian^l, Khue Thy Nguyen^m, Alin O Stirbanⁿ, Tsvetalina Tankova^o, Tamás Varkonyi^p, Roy Freeman^q, Péter Kempler^r, Andrew JM Boulton^s

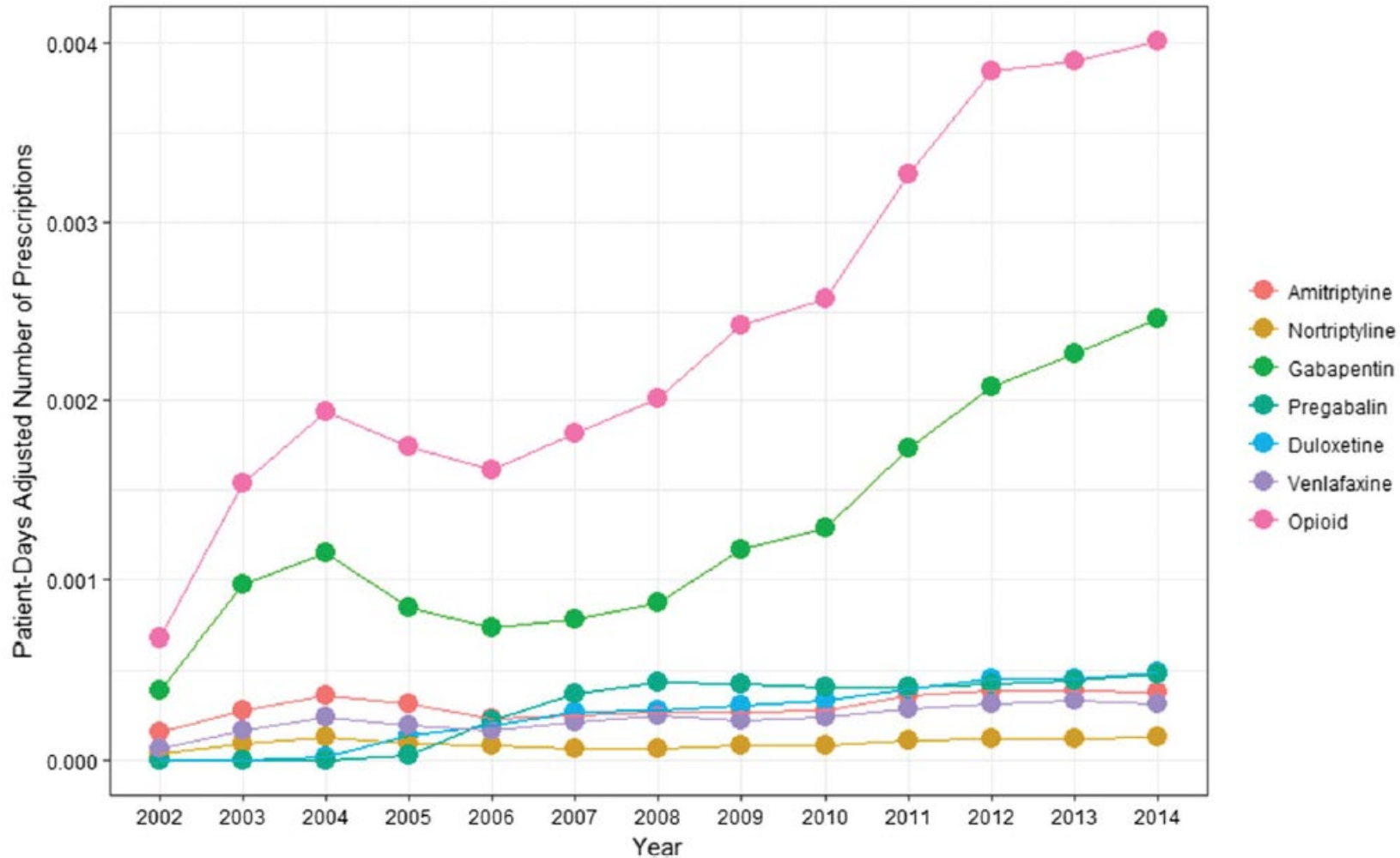


Painful DPN – A Serious Challenge

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

Adapted from Pop-Busui R, et al. *Diabetes Care*. 2017;40(1):136-154.

Opioid Use for Neuropathy Pain Is Increasing



Opioid-Related Death: A New Health Care Challenge and Burden

HEALTH

A grim tally soars: More than 50,000 overdose deaths in US

ASSOCIATED PRESS / DECEMBER 9, 2016



The US Food and Drug Administration (FDA) this week announced a new plan to refocus its efforts on curbing opioid-related deaths.

There were 18 893 deaths involving prescription opioids in the US in 2014, up 16% from 2013, according to the National Center for Health Statistics (NCHS). The administration believes synthetic opioids contributed to the increase in prescription opioid-related deaths. Deaths

involving buprenorphine, fentanyl and tramadol increased from 2013-2014.



There were 18 893 deaths involving prescription opioids in the US in 2014.

American Journal of Case Reports

Received: 2017.04.05
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Cardiac Arrest Following Drug Abuse with Intravenous Tapentadol: Case Report and Literature Review

ISSN 1941-5923

© Am J Case Rep, 2017; 18: 817-821

DOI: 10.12659/AJCR.904695

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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ACD 2 George Lominadze
ABCDF 2 Konstantin Millerman

1 Department of Medicine (Pulmonary and Critical Care Medicine), Bronx-Lebanon Hospital Center Affiliated with Icahn School of Medicine at Mount Sinai, Bronx, NY, USA.
2 Division of Critical Care Medicine, New York Presbyterian-Lawrence Hospital Center Affiliated with Columbia University College of Physician and Surgeons, Bronxville, NY, USA.

- Up to 28-33% of patients receive an opioid as a first-line agent for painful DPN

Patil PR, et al. *Clin J Pain*. 2015;31(5):414-24. Hoffman EM, et al. *JAMA Neurology*. 2017;74(7):773-79. Khaja M, et al. *Am J Case Reports*. 2017;18:817-821.

Great
Debates
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Diabetic
Foot

Prescription of Opioids and Mortality in Patients with Chronic Non-cancer Pain

Table 3. Mortality According to Underlying Cause of Death

Deaths	Anticonvulsant or Cyclic Antidepressant (Person-Years of Follow-up = 8066)		Long-Acting Opioid (Person-Years of Follow-up = 11 070)		Adjusted Hazard Ratio (95% CI) ^a	Adjusted Risk Difference (95% CI) ^{a,b}	P Value
	Deaths	Incidence per 10 000 Person-Years	Deaths	Incidence per 10 000 Person-Years			
All	87	107.9	185	167.1	1.64 (1.26 to 2.12)	68.5 (28.2 to 120.7)	<.001
Out-of-hospital	60	74.4	154	139.1	1.90 (1.40 to 2.58)	67.1 (30.1 to 117.3)	<.001
Unintentional overdose ^c	7	8.7	34	30.7	3.37 (1.47 to 7.70)	20.6 (4.1 to 58.1)	.004
Other causes	53	65.7	120	108.4	1.72 (1.24 to 2.39)	47.4 (15.7 to 91.4)	.001
Cardiovascular	36	44.6	79	71.4	1.65 (1.10 to 2.46)	28.9 (4.6 to 65.3)	.02
Respiratory	3	3.7	10	9.0	3.00 (0.81 to 11.09)	7.4 (−0.7 to 37.5)	.10
Other injury	11	13.6	19	17.2	1.15 (0.54 to 2.47)	2.1 (−6.3 to 20.0)	.72
Other	3	3.7	12	10.8	3.72 (1.04 to 13.30)	10.1 (0.2 to 45.7)	.04
Hospital	27	33.5	31	28.0	1.00 (0.59 to 1.69)	0 (−13.6 to 23.1)	>.99

^a Adjusted for baseline propensity score decile, age, and calendar year during follow-up.

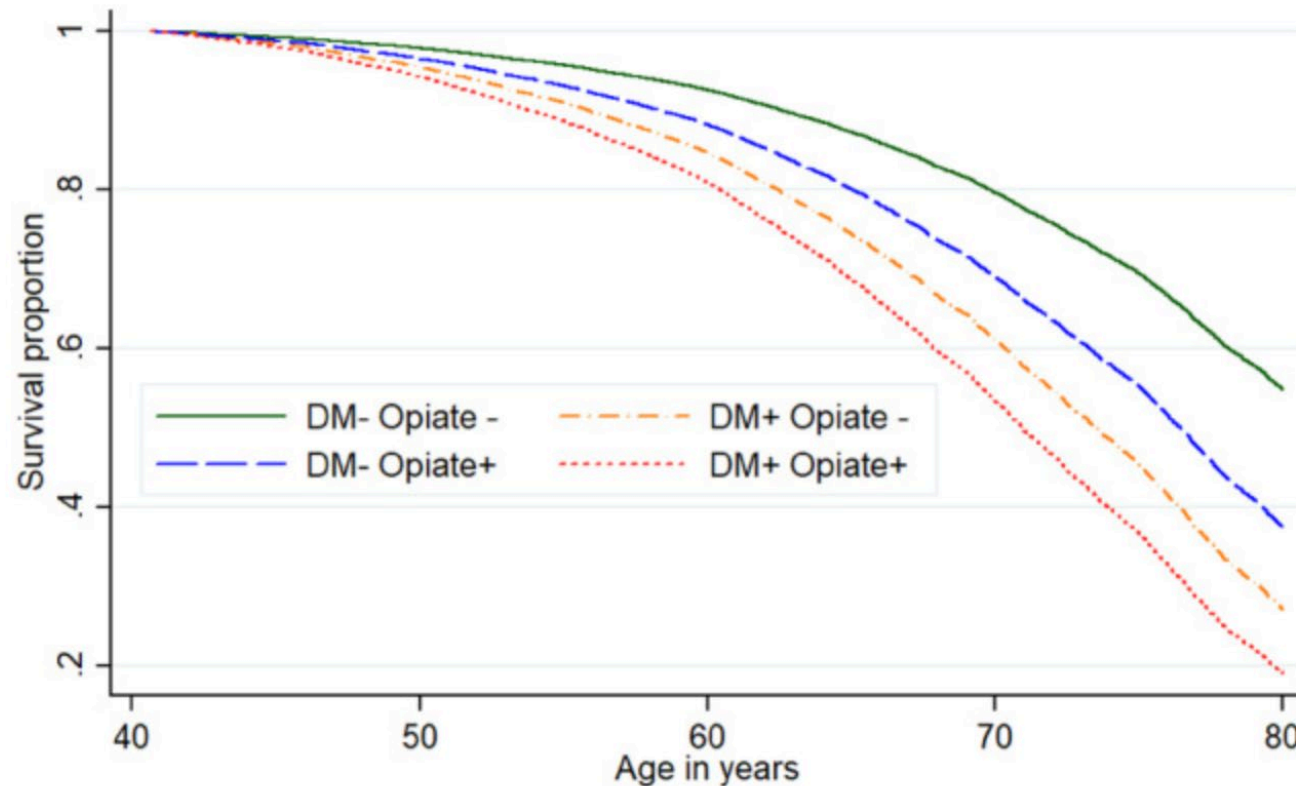
^b Risk differences for the specific causes of death do not sum because the regression model parameters are estimated separately for each cause.

^c The cohort excluded patients with a diagnosis of or procedure for treatment of

substance abuse other than nicotine or alcohol as well as those prescribed buprenorphine. Because such patients would plausibly have increased risk of overdose, overdose mortality in the study cohort is likely to be lower than that in a more general patient population.

Opiate Use and Mortality Among People With and without Diabetes

50 045 people—aged 40–75, 28 811 women, 8487 opiate users, 3548 diabetic patients—were followed during a median of 11.1 years, with over 99% success follow-up

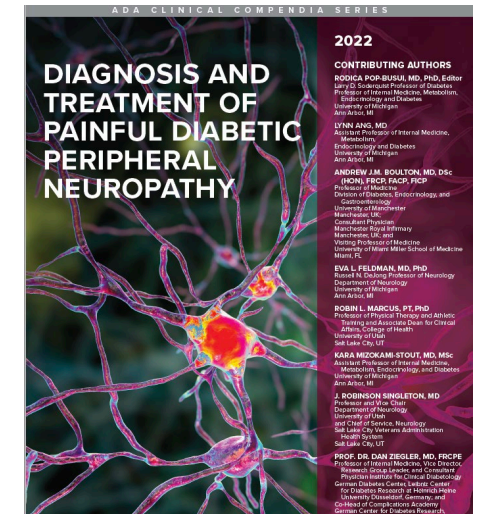
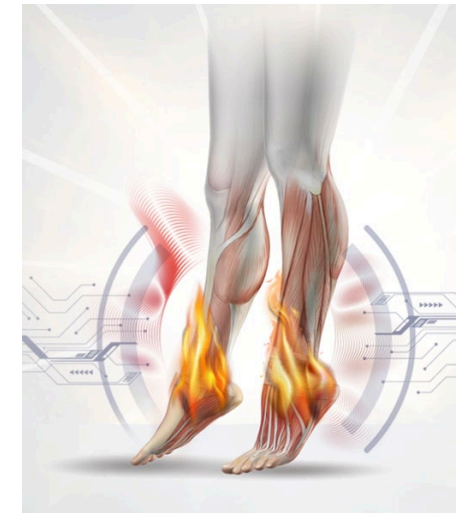
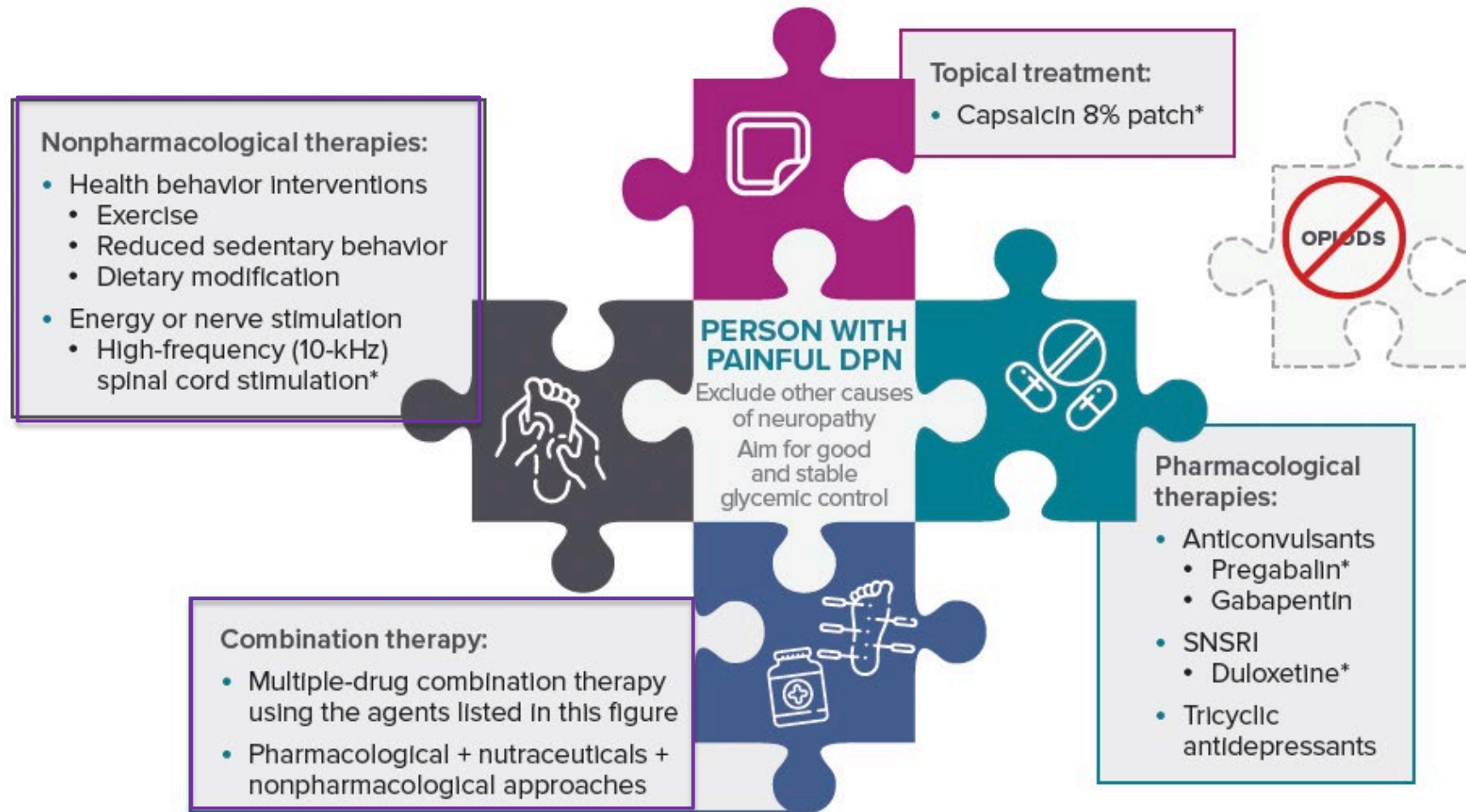


Opioid Therapy, Adverse Outcomes, and Mortality Among Patients with Polyneuropathy

Population-based cohort 2006-2016

Adverse Outcome	Opioid Treatment, No. (%)		HR (95% CI)	Adjusted HR (95% CI)
	<90 d (n = 1452)	≥90 d (n = 541)		
Depression	633 (43.6)	341 (63.0)	1.97 (1.68-2.30)	1.53 (1.29-1.82)
Abuse				
Alcohol	109 (7.5)	54 (10.0)	1.63 (1.10-2.39)	1.38 (0.90-2.11)
Opioid	2 (0.1)	9 (1.7)	10.66 (2.71-70.27)	3.97 (0.87-28.9)
Other substance	27 (1.9)	25 (4.6)	2.37 (1.29-4.36)	1.81 (0.92-3.58)
Overdose				
Opioid	4 (0.3)	14 (2.6)	8.29 (2.93-29.44)	5.12 (1.63-19.62)
Other substance	24 (1.7)	22 (4.1)	2.53 (1.37-4.65)	1.82 (0.92-3.6)
Dependence				
Opioid	20 (1.4)	39 (7.2)	5.59 (3.20-10.18)	2.85 (1.54-5.47)
Other substance	129 (8.9)	95 (17.6)	2.41 (1.73-3.34)	1.73 (1.21-2.49)
Deceased by 11/25/16	530 (36.5)	256 (47.3)	1.22 (1.05-1.41)	0.99 (0.84-1.16)

Algorithm for Treatment of Pain in DPN



Summary:

What You Can't Feel Can Hurt You

- The DPN associated nerve damage and loss lead to
 - Loss of sensation
 - Loss of balance
 - Loss of daily function
 - Increased risk for falls and fractures
 - Ulcers, amputations
 - Severe neuropathic pain
 - Polypharmacy, costs, side effects, dependance
 - Anxiety, depression, lack of sleep
 - Death

Thank you!

Research Participants!

All collaborators: Michigan and worldwide!



<https://medicine.umich.edu/dept/intmed/divisions/metabolism-endocrinology-diabetes/research/clinical-research/program-clinical-research-on-diabetes-care-complications>

Debate: Diabetic Peripheral Neuropathy What You Can't Feel Can Hurt You

- Nothing to debate here, right?...



Dr Crystal Holmes

- Is our neuropathy messaging working?
- Screening tool – why are we not using?
- Are we considering social determinants of health in our neuropathy work up, treatment plans and future discoveries for neuropathy?



Neuropathy Messaging

Are we asking the right
questions & giving the correct
feedback to patients?

Get the **pressure** off your foot ulcer with **offloading devices**:

- **Offloading devices** are what you wear on your foot and what you use to help you get around.
- Too much pressure causes ulcerations.
- 85% of diabetic foot and leg amputations are caused by a foot ulcer.
- The longer your foot ulcer stays open, the greater your risk is for infection and amputation.
- The more pressure you get off your foot ulcer, the faster it will heal.
- If you do not get the pressure off your foot ulcer it may never heal.
- **Work with your doctor to get the right foot gear and assistive device to heal your ulcer today!**



Volume 70, Issue Supplement_1

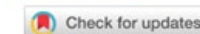
1 June 2021



OR: FOOT CARE—LOWER EXTREMITIES | JUNE 01 2021

267-OR: Assessing Patient Knowledge about Diabetic Foot Ulcer Offloading **FREE**

REBECCA A. BURMEISTER; CRYSTAL HOLMES; CHRISTINE JAROCKI; TYSON STROM; GARNEISHA M. TORRENCE; BRIAN M. SCHMIDT



Diabetes 2021;70(Supplement_1):267-OR

<https://doi.org/10.2337/db21-267-OR>

Patient Version

MICHIGAN NEUROPATHY SCREENING INSTRUMENT

A. History (To be completed by the person with diabetes)

Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check yes or no based on how you usually feel. Thank you.

- Are you legs and/or feet numb? ☐ Yes ☐ No
- Do you ever have any burning pain in your legs and/or feet? ☐ Yes ☐ No
- Are your feet too sensitive to touch? ☐ Yes ☐ No
- Do you get muscle cramps in your legs and/or feet? ☐ Yes ☐ No
- Do you ever have any prickling feelings in your legs or feet? ☐ Yes ☐ No
- Does it hurt when the bed covers touch your skin? ☐ Yes ☐ No
- When you get into the tub or shower, are you able to tell the hot water from the cold water? ☐ Yes ☐ No
- Have you ever had an open sore on your foot? ☐ Yes ☐ No
- Has your doctor ever told you that you have diabetic neuropathy? ☐ Yes ☐ No
- Do you feel weak all over most of the time? ☐ Yes ☐ No
- Are your symptoms worse at night? ☐ Yes ☐ No
- Do your legs hurt when you walk? ☐ Yes ☐ No
- Are you able to sense your feet when you walk? ☐ Yes ☐ No
- Is the skin on your feet so dry that it cracks open? ☐ Yes ☐ No
- Have you ever had an amputation? ☐ Yes ☐ No

Total: _____

MICHIGAN NEUROPATHY SCREENING INSTRUMENT

B. Physical Assessment (To be completed by health professional)

1. Appearance of Feet

Right			Left		
a. Normal	<input type="checkbox"/> 0	<input type="checkbox"/> Yes <input type="checkbox"/> 1 No	Normal	<input type="checkbox"/> 0	<input type="checkbox"/> Yes <input type="checkbox"/> 1 No
b. If no, check all that apply:			If no, check all that apply:		
Deformities	<input type="checkbox"/>		Deformities	<input type="checkbox"/>	
Dry skin, callus	<input type="checkbox"/>		Dry skin, callus	<input type="checkbox"/>	
Infection	<input type="checkbox"/>		Infection	<input type="checkbox"/>	
Fissure	<input type="checkbox"/>		Fissure	<input type="checkbox"/>	
Other	<input type="checkbox"/>		Other	<input type="checkbox"/>	
specify:	_____		specify:	_____	

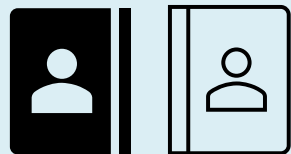
	Right			Left		
	Absent <input type="checkbox"/> 0	Present <input type="checkbox"/> 1		Absent <input type="checkbox"/> 0	Present <input type="checkbox"/> 1	
2. Ulceration						
3. Ankle Reflexes	Present <input type="checkbox"/> 0	Present/ Reinforcement <input type="checkbox"/> 0.5	Absent <input type="checkbox"/> 1	Present <input type="checkbox"/> 0	Present/ Reinforcement <input type="checkbox"/> 0.5	Absent <input type="checkbox"/> 1
4. Vibration perception at great toe	Present <input type="checkbox"/> 0	Decreased <input type="checkbox"/> 0.5	Absent <input type="checkbox"/> 1	Present <input type="checkbox"/> 0	Decreased <input type="checkbox"/> 0.5	Absent <input type="checkbox"/> 1
5. Monofilament	Normal <input type="checkbox"/> 0	Reduced <input type="checkbox"/> 0.5	Absent <input type="checkbox"/> 1	Normal <input type="checkbox"/> 0	Reduced <input type="checkbox"/> 0.5	Absent <input type="checkbox"/> 1

Signature: _____ Total Score _____ /10 Points

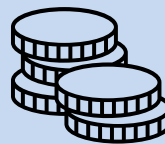
Why is not used in clinical care ?



Debate & dialogue: Social determinants of health & diabetic neuropathy



Race



Income



Education



Food insecurity



Housing



Support



Access to care

Non-Traditional Risk Factors DPN : Social Determinants of Health



T1D Exchange Cohort

>25,000 T1D

Characteristics of Participants with and without DPN

	MNSIq-DPN	Non-MNSIq DPN	P-value
Income \geq 75,000	38%	59%	N/A*
\geq Bachelor's Degree	54%	68%	<0.001
Private Insurance	58%	83%	<0.001

*Correlated with insurance and education level, not included in the multivariate analysis.

Scottish Cohort

>100,000 T1D



Individuals who lived in more deprived areas had significantly higher odds of having DPN than those living in less deprived areas:
OR 2.61 [95% CI 2.21–3.08]-
adjusted for age, sex, and diabetes duration,

Multiple adjustments this association remained :
OR 2.17 [95% CI 1.78–2.65]

Socioeconomic position (SEP) is strongly associated with DFU outcomes

Predictors of amputation in people with DFUs

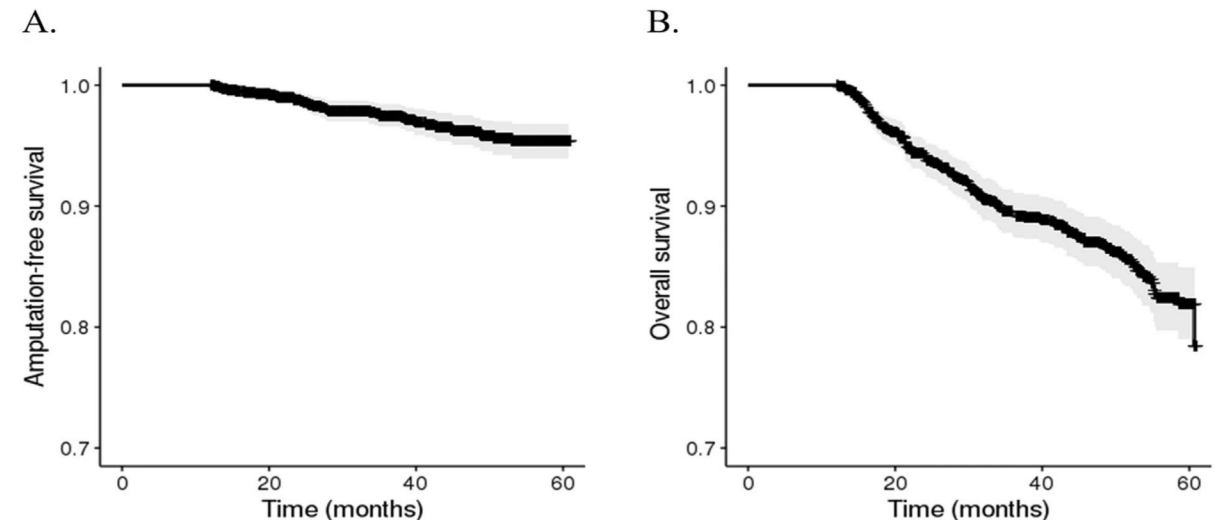
- **Low SEP (HR 5.13; $p = 0.018$),**
- Male sex (hazard ratio [HR], 2.41; $p < 0.01$),
- Circulatory complications (HR 2.14; $p = 0.020$)
- Ophthalmopathy (HR, 1.89; $p = 0.028$),

Predictors of Mortality in people with DFUs

- **Low SEP (HR 2.65; $p < 0.01$)**
- Circulatory complications (HR: 1.74; $p < 0.01$)
- Older age (HR: 1.06)

Fig. 2

From: [Association between socioeconomic position and diabetic foot ulcer outcomes: a population-based cohort study in South Korea](#)

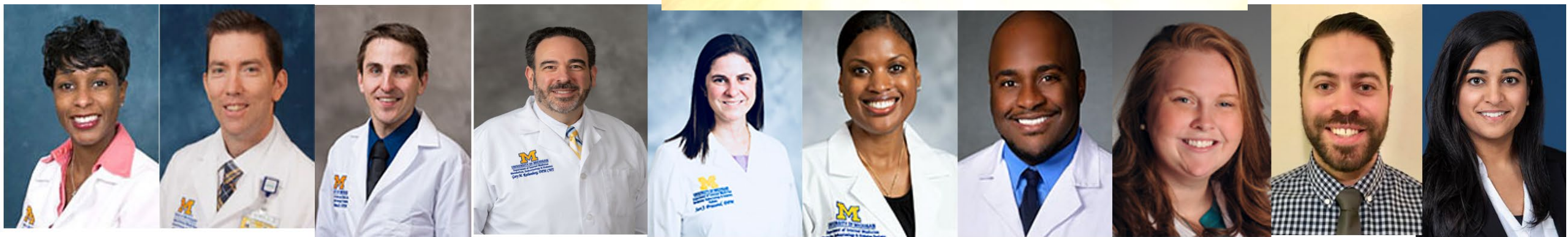


Kaplan-Meier plots for (a) amputation-free survival and (b) overall survival of patients with diabetic foot ulcers

Thank You to my Team

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Great
Debates
& Updates

Diabetic
Foot

Thank You