ECHO Diabetes

Diabetic Peripheral Neuropathy (DPN)

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Pre-question – select the correct option

Diabetic Peripheral Neuropathy in people with T2D

A. Is almost entirely due to effects of hyperglycemia
B. Is always associated with neuropathic pain
C. Is usually symmetric and progresses from most distal to proximal
D. Requires nerve conduction studies for diagnosis

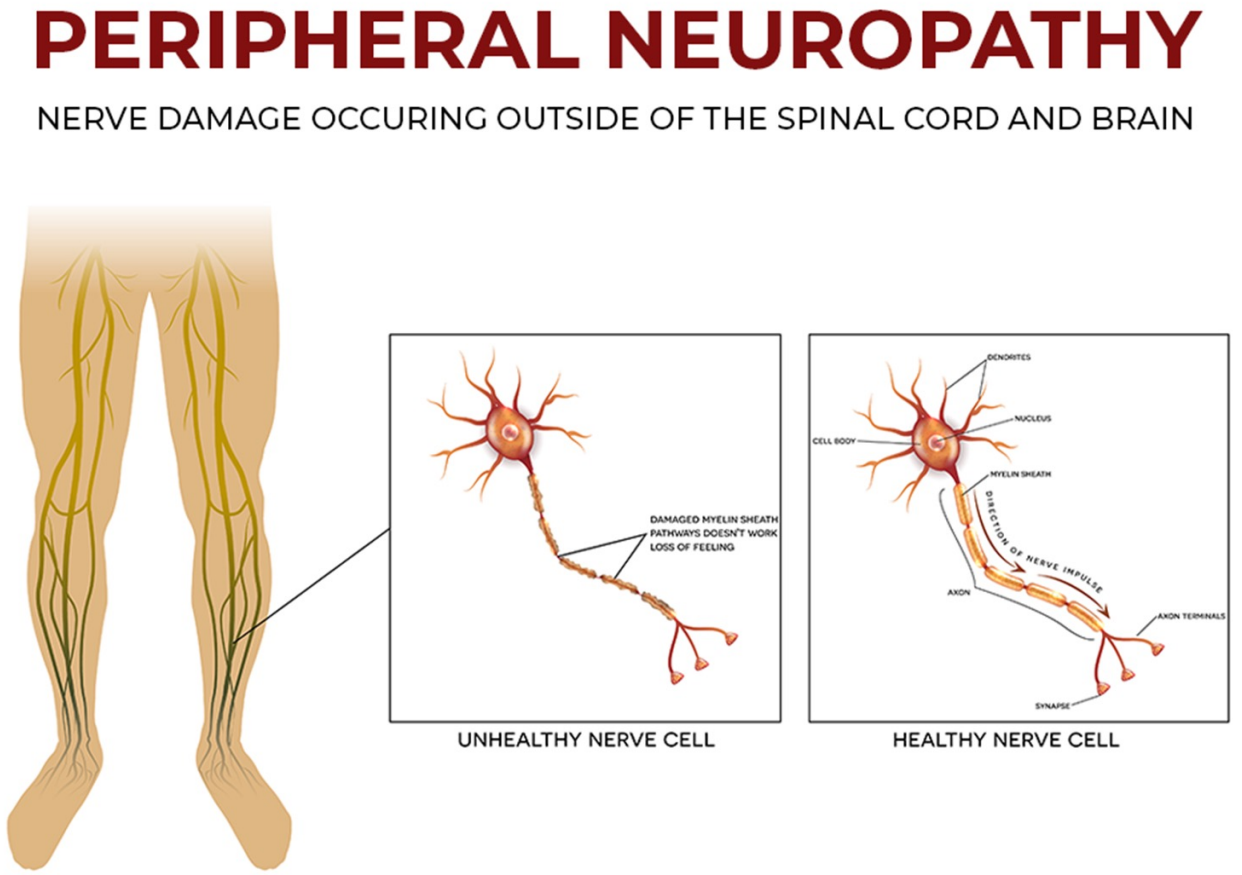
Diabetic Neuropathy
focus on Diabetic Peripheral Neuropathy

- **Diabetic neuropathy –** heterogenous group of disorders with an estimated lifetime prevalence exceeding 50% occurring in
  - adults with type 1 diabetes (at least 20% after 20 years)
  - adults with type 2 diabetes (at least 10%–15% of newly diagnosed T2D increasing to 50% after 10 years of disease duration)
  - young people with diabetes (~levels seen in adults with diabetes)
  - individuals with prediabetes (~10-30% of subjects)

- ***Diabetic peripheral neuropathy (DPN)*** *(*also called *diabetic polyneuropathy (DPN) & distal symmetric polyneuropathy (DSPN))*is the most common (~ 75% of all DN) and most studied form of DN
  - **DPN** affects multiple peripheral sensory and motor nerves that branch out from the spinal cord into the arms, hands, legs and feet.
    - Typically, the longest nerves — those that extend from the spine to the feet — are affected the most.

Background – Peripheral Nervous System

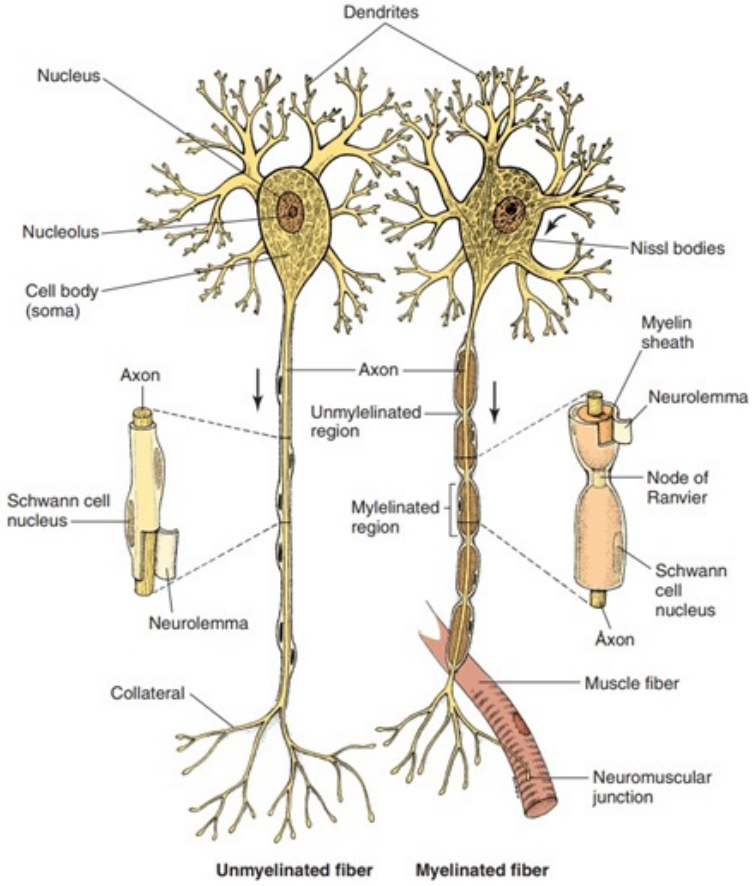
- Diabetes preferentially affects the ***peripheral nervous system*** (PNS), a likely reflection of the unique anatomy of the PNS.
  - PNS *sensory* neurons and their receptors *lie outside the blood-brain barrier* and are *more vulnerable to injury* resulting from diabetes than motor neurons, which lie within the barrier.
  - PNS axons are frequently ≥3 feet long (>20,000 times the length of their supporting cell bodies).
    - The process starts at the tip of toes & progresses in a “stocking & glove” pattern



DPN progresses distal → proximal

Background – Neurons

- "Small fibers"
  - small unmyelinated neurons known as C-fibers constitute most of the sensory axons in the PNS.
    - carry *nociceptive* information, particularly related to *heat* and *pain*
- "Large fibers"
  - small, thinly myelinated Aδ fibers
    - relay information on *touch, pressure,* and *cold*
  - fully myelinated fibers of different diameters, designated Aβ and Aα –
    - responsible for *vibratory* and *position sense*



DPN usually progresses small → large

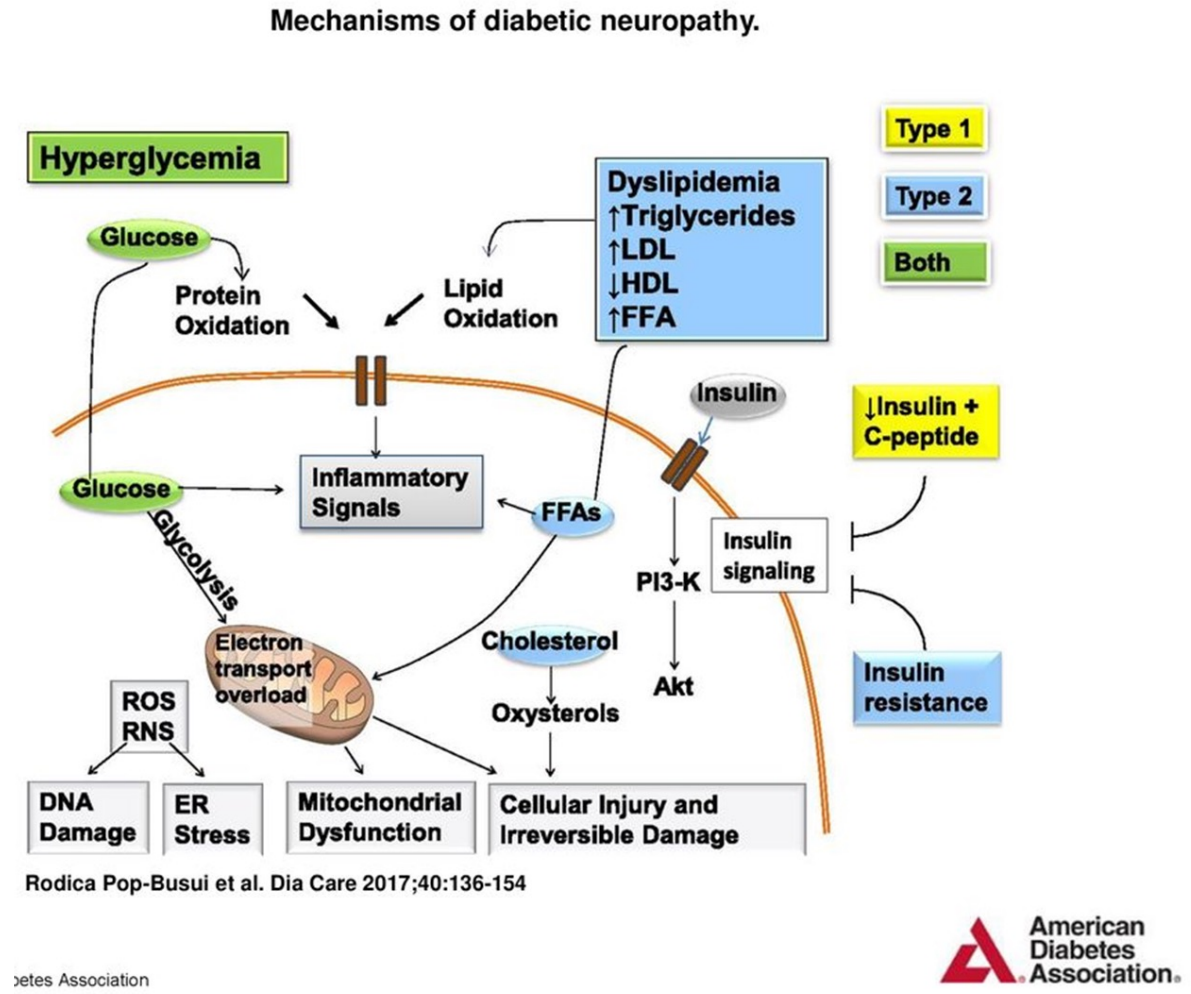
Background - Pathophysiology

"DPN has been associated with **glycemia, height** (perhaps as a proxy for nerve length), **smoking, blood pressure, weight, and lipid measures"**

- **Glycemic control** can prevent DPN in type 1 diabetes (78% relative risk reduction) & may modestly slow the progression of DPN in type 2 diabetes (5%–9% relative risk reduction)
- There is now consensus that *glycemic control alone cannot prevent the progression of DPN in patients with type 2 diabetes.*
- The **metabolic syndrome** has emerged as a crucial risk factor for neuropathy based on data from multiple clinical studies
  - The metabolic syndrome encompasses hyperglycemia, obesity, and dyslipidemia, and **the risk of developing neuropathy increases with the number of these components present in an individual.**
  - Clinical trials led to new thinking about the pathophysiology of diabetic neuropathy focused on the idea that **disruption in whole-nerve bioenergetics** (i.e., *how the nerve accesses energy along its entire length*) is **the crucial factor leading to disease.**

Background - Pathophysiology

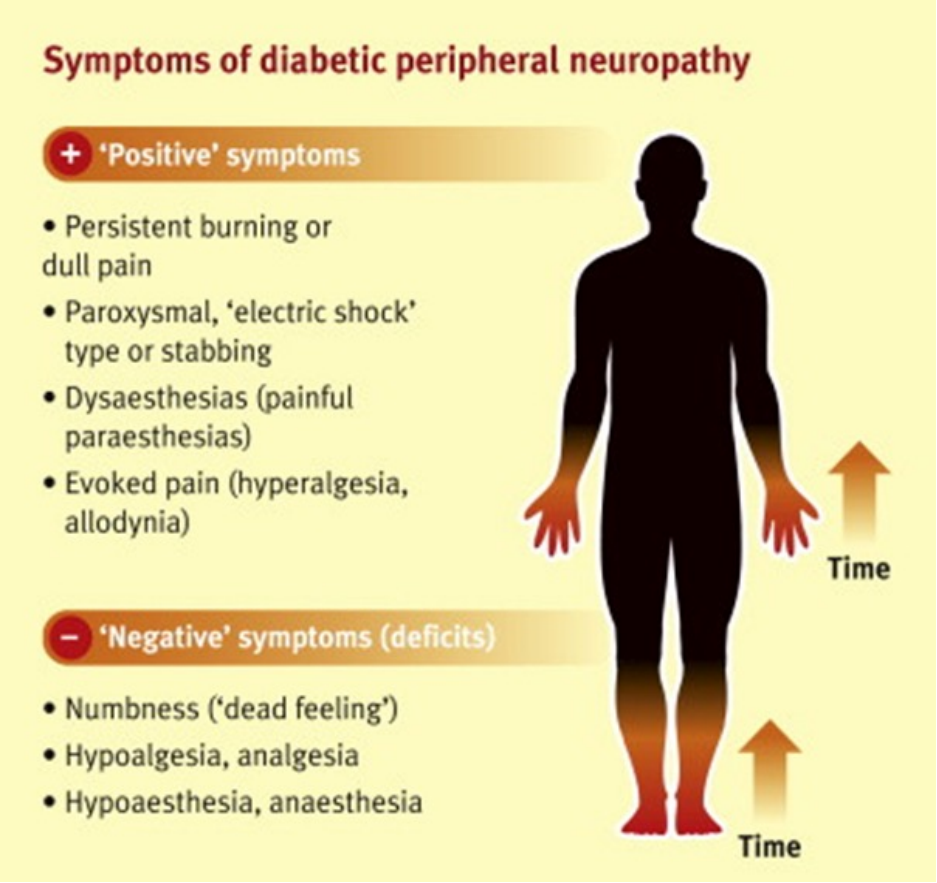
- In the diabetic environment, excess glucose and lipids disrupt the normal pathways used for their own breakdown & produce excess electron donors that the **mitochondria** are unable to process.
- The result is **bioenergetic failure** leading to inflammation, endoplasmic reticulum stress, ***apoptosis of neurons, and axonal failure.***



Background – Clinical Symptoms

- Early degeneration and loss of C fibers are evident in patients experiencing new-onset pain, burning, or prickling (dysesthesias) in their feet
  - Also exaggerated response to painful stimuli (hyperalgesia) and/or
  - pain evoked by contact with ordinarily unpainful stimuli such as socks, shoes, and bedclothes (allodynia)
- As the disease progresses, large fiber axonal loss eventually occurs, and patients experience numbness and loss of proprioception in the feet that travels upward over time.

This distal-to-proximal axonal loss and its accompanying symptoms are the hallmark of diabetic neuropathy.



Background – Clinical caveats -Lack of symptoms &/or signs

- 25–30% of people with diabetes will experience DPN pain (heralding *early* disease)
  - Characteristically, the pain is burning, lancinating, tingling, or shooting (electric shock–like); occurs with paresthesias; presents in varying combinations; and is typically worse at night.
  - Neuropathic pain may be present in individuals with newly diagnosed diabetes or even prediabetes
    - Consider screening patients with prediabetes who have symptoms of peripheral neuropathy.
  - Neuropathic pain may be present even in the absence of any neurological deficits
    - And with normal nerve conduction studies (NCS) (better at detecting large fiber deficits)
- DPN pain may be underreported
  - Some individuals may not voluntarily report some symptoms to their health care providers because of a variety of sociocultural factors
- Some people with DPN do not have pain

Women, members of some racial/ethnic minority groups, and individuals with type 2 diabetes appear to be at greater risk for developing DPN pain

Asymptomatic DPN

- Up to half of all people with DPN may be either asymptomatic or reluctant to report some symptoms.
  - In such cases, **neurological deficits** may be discovered during a routine clinical examination (emphasizing the importance of screening exam)
- Other individuals with neuropathic symptoms may become *asymptomatic later* in the course of the disease, as they experience ***severe sensory loss*** in all types of nerve fibers and develop **insensate** feet.
  - A serious consequence of insensate feet is an increased risk for ***painless injury***, leading to an increased risk for foot ulceration and amputation. For example,
    - objects lodged in the shoe, including a wrinkled stocking; unrecognized, increased pressure during walking and weight bearing; or
    - contact with very sharp or hot objects without the appropriate protection may produce blisters that erode through the skin and lead to more severe complications.
  - It is **the loss of the so-called "gift of pain"** that causes people with plantar neuropathic ulcers to unknowingly walk on their lesions, inducing chronicity that is frequently complicated by infection.

Acute (Subacute) Painful Diabetic Neuropathy

"treatment-induced neuropathy of diabetes"

- It is characterized by very severe neuropathic symptoms that typically occur within 2–4 weeks (occasionally up to 6+ weeks) after the achievement of rapid and sustained glycemic control with insulin, oral antidiabetic agents, or dietary measures. (A1c drop of >2% over 3 months or >4% over 6 months) - may be induced by
  - acute weight loss or diabetes treatment (this variety of neuropathy was originally called "insulin neuritis", but it can be precipitated by any treatment that rapidly improves glycemic control).
  - after normalization of blood glucose levels after simultaneous pancreas and kidney transplantation.
  - can follow an episode of ketoacidosis, and in young people, particularly females, it may be associated with eating disorders.
- Clinical presentation dominated by foot and lower-limb pain and progresses to constant burning dysesthesias and allodynia (small fiber) involving the legs in a stocking distribution. (Occasionally, the pain spreads to proximal sites, including the trunk)
- The prognosis of this acute form of painful neuropathy is good, typically with resolution of symptoms within 12 months.
  - However, pharmacological treatment of the severe symptoms is invariably required.
  - Despite the prominent pain, sensory loss may be mild or absent, there is no weakness, and reflexes are generally preserved.
- Can also have acute-onset autonomic symptoms (especially orthostatic hypotension)

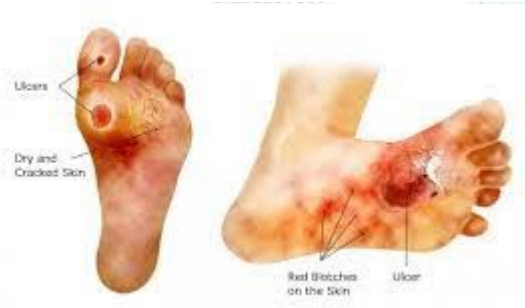
Background – Critical Points to Know

- DPN starts with the longest neurons and progresses
  - from distal → proximal
    - a specific symmetrical, distal-to-proximal pattern, starting at the tip of the toes and progressing proximally creating the typical "stocking-and-glove" clinical presentation
  - from "small fibers" (pain) → "large fibers" (loss of sensation & protection)
- Glucose is not the only factor contributing to nerve damage & loss
  - The metabolic syndrome components are critical factors

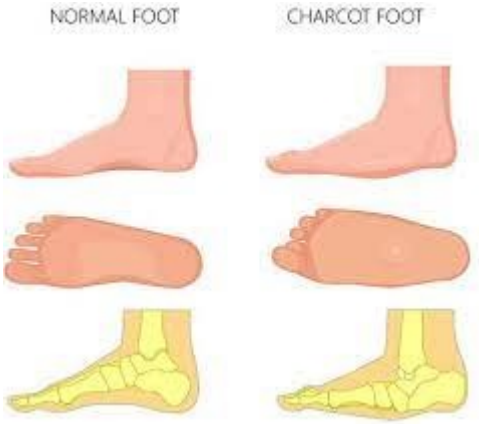
KEY POINTS

- Early injury and loss of small fibers, susceptible to energy flux, occur in people with diabetes, resulting in symptomatic pain and burning in their feet.
- As the disease progresses, larger nerve fibers also become injured by the lack of energy sources, and individuals experience numbness and loss of position sense in their feet.
- These signs and symptoms progress from the feet upward into the leg and reflect a distal-to-proximal fiber loss that is the hallmark of diabetic neuropathy.

Late Complications of DPN



- DPN is the most important cause of **foot ulceration**, and it is also a prerequisite in the development of **Charcot neuroarthropathy** (CN).
  - Foot ulceration and CN are both recognized as **late complications** of DSPN.
  - These late complications **drive amputation risk** and **economic costs** of diabetic neuropathy and are also predictors of **mortality**.
  - Mortality risk: 11% by 30 d & 18% by 90 d postop – 50% + by 5 years (overall 5-year mortality rate ranging from 29% to 69% following minor amputations and from 52% to 80% for patients with major amputations)
    - Age >65, especially >75 – CKD – CAD – Cerebral Vascular Ds – PAD – HF – De*pression*
  - *It is unclear if amputation hastens death or is a marker of underlying disease severity*



- DPN is also a major contributor to **falls and fractures**
  - More advanced small- and large-fiber dysfunction, with loss of sensory, proprioception, temperature discrimination, and pain, all ultimately lead to unsteadiness, recurrent minor injuries, and an increased risk of falls
  - These recurrent minor injuries may further contribute to the pathogenesis of CN.

Attention to Feet & Foot Care in DPN

- Due to a lack of treatments that target the underlying nerve damage, **prevention** is the key component of diabetes care.

- **Screening** for symptoms and signs of diabetic neuropathy is critical in clinical practice, as it may **detect the earliest stages** of neuropathy, enabling **early intervention**.

ADA Standards of Care 2022: Neuropathy – Screening

- 12.15 All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. B

- 12.16 Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either *temperature or pinprick sensation (small fiber function*) and *vibration sensation* using a 128-Hz tuning fork (for large fiber function). All patients should have *annual 10-g monofilament testing to identify feet at risk for ulceration and amputation.* B

When to screen for diabetic peripheral neuropathy

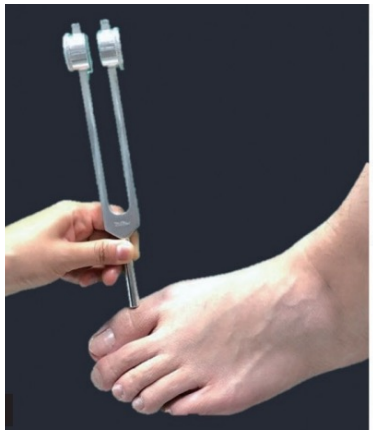
- **For type 1 diabetes**
  - Because diabetic peripheral neuropathy is uncommon within the first five years after onset of type 1 diabetes, annual screening for diabetic peripheral neuropathy should begin ***after five years of diabetes diagnosis***.
  - For children with type 1 diabetes, screening should be done once the child is past puberty and has had diabetes for at least five years.
- **For type 2 diabetes**
  - For people with type 2 diabetes, screening for diabetic peripheral neuropathy ***should begin right away, at diagnosis of diabetes***, and every year after that.

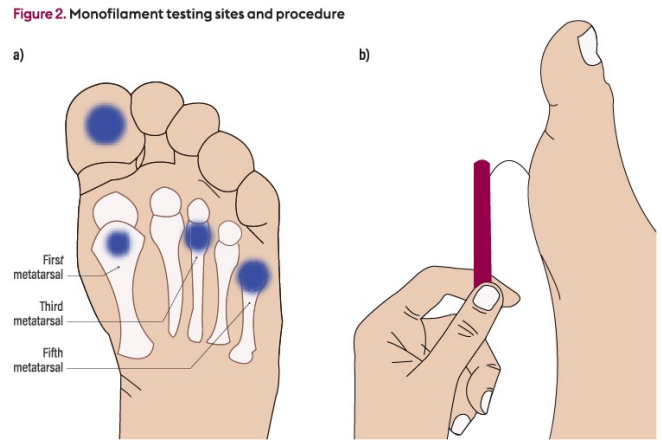
- Evaluate DPN-associated **small-fiber damage** by testing
  - pinprick sensation using a sharp object such as a safety pin
  - temperature threshold sensation with a cold metal object such as a tuning fork
- Evaluate DPN-associated **large-fiber damage** by assessing
  - vibration perception using a 128-Hz tuning fork
  - proprioception
  - light-touch pressure with a 10-g monofilament on the dorsal aspect of the great toe
  - bilateral ankle reflexes.

Monofilament testing

- Clinicians should use a standardized 10-g instrument and should apply the monofilament at the *dorsal aspect of the great toe* to ensure standardized assessment.
  - Although the 10-g monofilament is arguably the most often used test to screen for DPN in routine care, its ***use alone*** is ***not recommended*** for effective ***screening or diagnosis***, as the loss of light-touch sensation occurs in *advanced stages* of neuropathy
    - relying solely on this test could miss opportunities to implement early preventive care measures in many people with DPN.
  - Sensation testing with pin [or temperature] and vibration is more sensitive.
- Clinicians should note that the 10-g monofilament test included for the annual *DPN screening and diagnosis* is different than the *diagnosis of the "high-risk foot" for ulceration* (detection of LOPS), a late DPN complication (testing 4 sites on planter surface)

ADA Standards suggest both are important





Suggestions for doing a sensory exam

- All of these sensory modalities should be tested initially by application of the sensory stimulus to a body site where normal responses are expected, such as the forehead [*familiarity with what "it feels like"]*
- Then the stimulus is applied to the great toe and then moved proximally up the limb to the level where the sensation is felt to be normal.
- In addition, for many of these evaluations (e.g., vibration perception using a 128-Hz tuning fork or the 10-g monofilament) using a blinded, forced-choice testing procedure will reduce the potential for bias and increase the sensitivity of the evaluations.
  - This procedure involves applying a stimulus (either true vibration or just a touch with the tuning fork) at one of two times while a **patient's eyes are closed** and then asking whether the patient felt the stimulus at time A or time B.
    - Those with sensation loss may choose the incorrect time or state that they did not feel the stimulus either time.
  - All of these assessments should follow the typical DPN pattern***, starting distally (the dorsal aspect of the hallux) and moving proximally until a sensory threshold is identified***, with the same evaluations being performed on **both sides** to confirm a symmetrical, distal-to-proximal distribution
  - A combination of at **least two of these evaluations**, with at least ***one targeting small fibers and one targeting large fibers***, is recommended to screen for and diagnose DPN in routine clinical care

Exam

The following clinical tests may be used to assess small- and large-fiber function distal to proximal:

- Small-fiber function: pinprick and temperature sensation
- Large-fiber function: vibration perception, proprioception, 10-g monofilament, and ankle reflexes

DPN Diagnosis

- These tests not only screen for the presence of dysfunction but also predict future risk of complications.
- The diagnosis of DPN/DSPN is principally a clinical one.
  - A combination of typical symptomatology and symmetrical distal sensory loss or typical signs in the absence of symptoms in a patient with diabetes is highly suggestive of DPN
    - As up to half of the patients may be asymptomatic, a diagnosis may only be made on examination or, in some cases, when the patient presents with a painless foot ulcer.
  - Electrophysiologic testing or referral to a neurologist is *rarely needed* except in situations where the clinical features are atypical, or the diagnosis is unclear.
  - In all patients with diabetes and DPN, causes of neuropathy other than diabetes should be *considered*, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency (~30% of patients on metformin), hypothyroidism, renal disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy and vasculitis.

DPN can occur with other causes of peripheral neuropathy

When to Refer

- Although the norm in clinical care historically was to refer people with suspected DPN to a neurologist and to order electrophysiological testing to confirm the diagnosis, more recent evidence has shown that **these measures *are not necessary*** except in specific cases in which clinical features are atypical, onset is abrupt, and a different etiology is suspected
  - Specialized ***electrophysiological testing is usually not cost-effective***
    - high associated costs and typically long waiting times would place unnecessary additional burden on both people with DPN and the health care system.

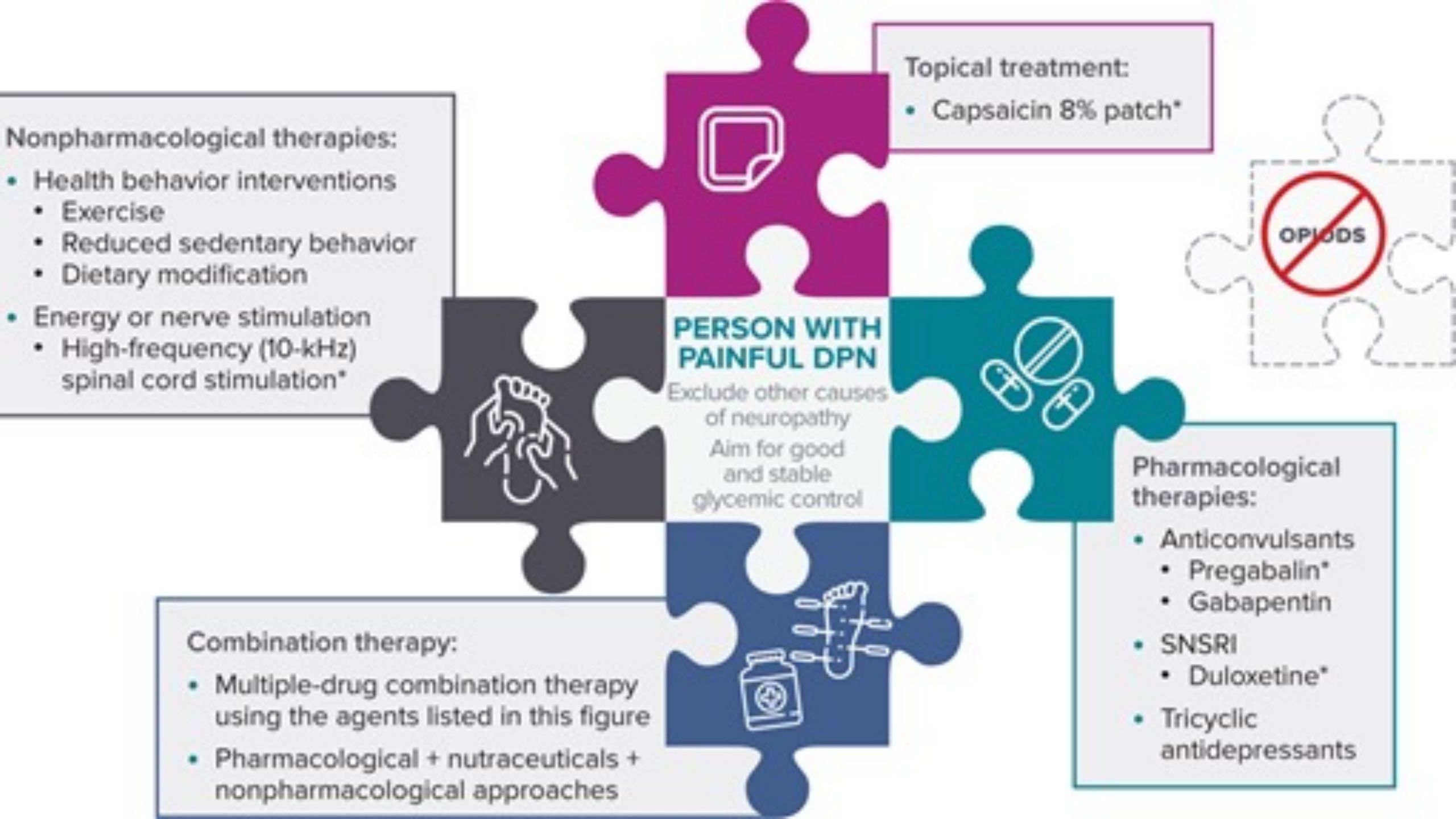
- A timely *referral to a neurologist* should be made in *atypical cases* involving
  - asymmetrical distribution of symptoms and clinical signs,
  - a motor predominance, or
  - an acute onset and rapid progression of signs such as severe weakness

ADA Standards of Care 2022: Neuropathy – Treatment

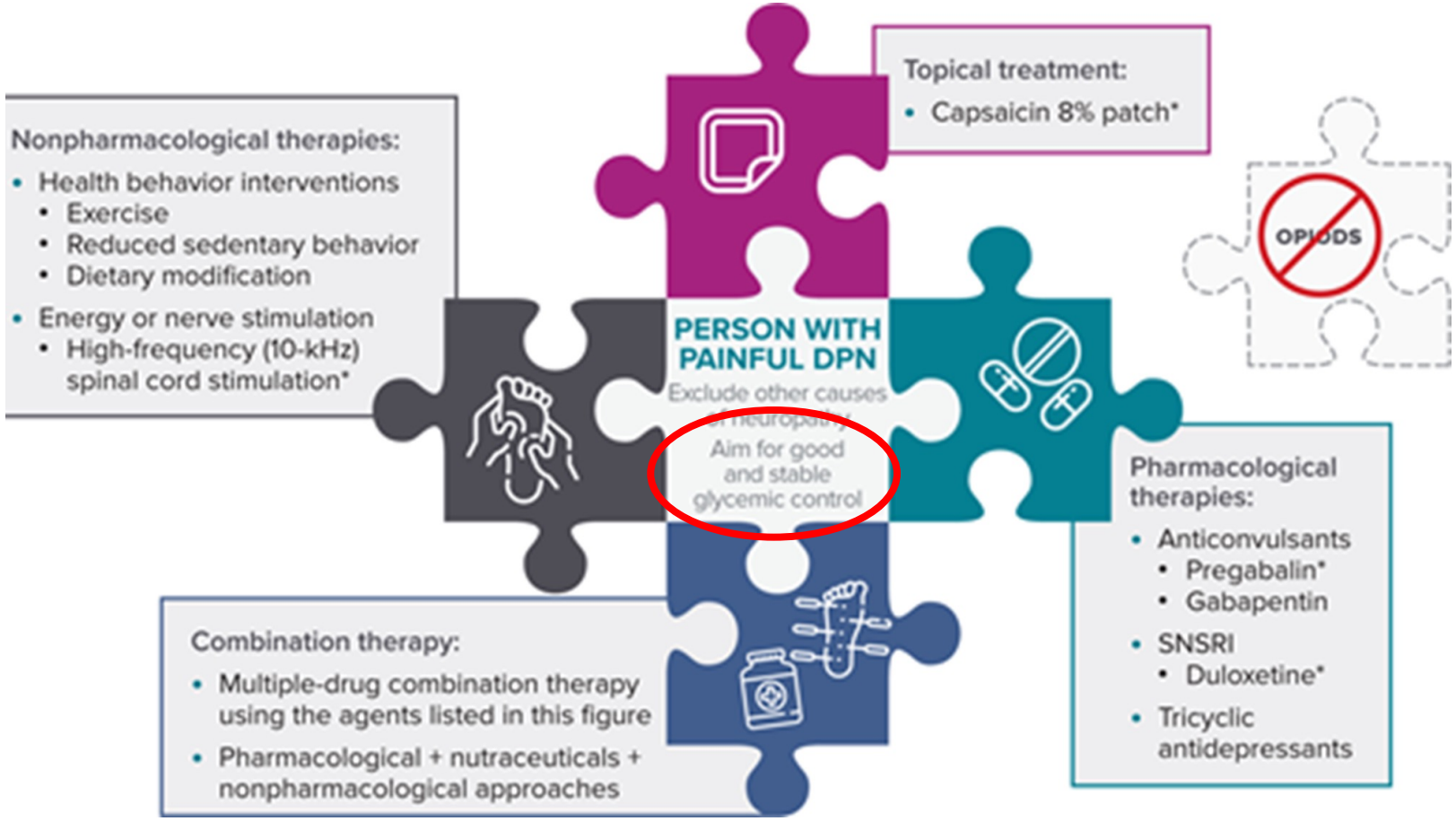
- 12.18 Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes (A) and to slow the progression of neuropathy in patients with type 2 diabetes (B)
- 12.19 Assess and treat patients to reduce pain B

Recommendations

- Consider either **pregabalin or duloxetine** as the initial approach in the symptomatic treatment for neuropathic pain in diabetes. A
  - Both have received regulatory approval for treatment of neuropathy
- **Gabapentin** may also be used as an effective initial approach, taking into account patients' socioeconomic status, comorbidities, and potential drug interactions. B
- Although not approved by the U.S. Food and Drug Administration, **tricyclic antidepressants** are also effective for neuropathic pain in diabetes but should be used with caution given the higher risk of serious side effects. B
- Given the high risks of addiction and other complications, the use of **opioids**, including tapentadol or tramadol, is ***not recommended*** as first- or second-line agents for treating the pain associated with DSPN. E
  - The opioid, tapentadol, has regulatory approval in the U.S. and Canada, but the evidence of its use is weaker


Topical treatment:
• Capsaicin 8% patch*
OPIOIDS
Nonpharmacological therapies:
• Health behavior interventions
• Exercise
• Reduced sedentary behavior
• Dietary modification
• Energy or nerve stimulation
• High-frequency (10-kHz) spinal cord stimulation*
PERSON WITH PAINFUL DPN
Exclude other causes of neuropathy
Aim for good and stable glycemic control
Pharmacological therapies:
• Anticonvulsants
• Pregabalin*
• Gabapentin
• SNSRI
• Duloxetine*
• Tricyclic antidepressants
Combination therapy:
• Multiple-drug combination therapy using the agents listed in this figure
• Pharmacological + nutraceuticals + nonpharmacological approaches

ADA https://diabetesjournals.org/compendia/article/2022/1/1/147001/Diagnosis-and-Treatment-of-Painful-Diabetic



AAN guidelines for DPN

- Updated 2021
- "the recommended drugs and topical treatments in this guideline *may not eliminate pain*, but they have been shown to *reduce* pain"
- "if one treatment class doesn't work try a different one, but do not use opioids."

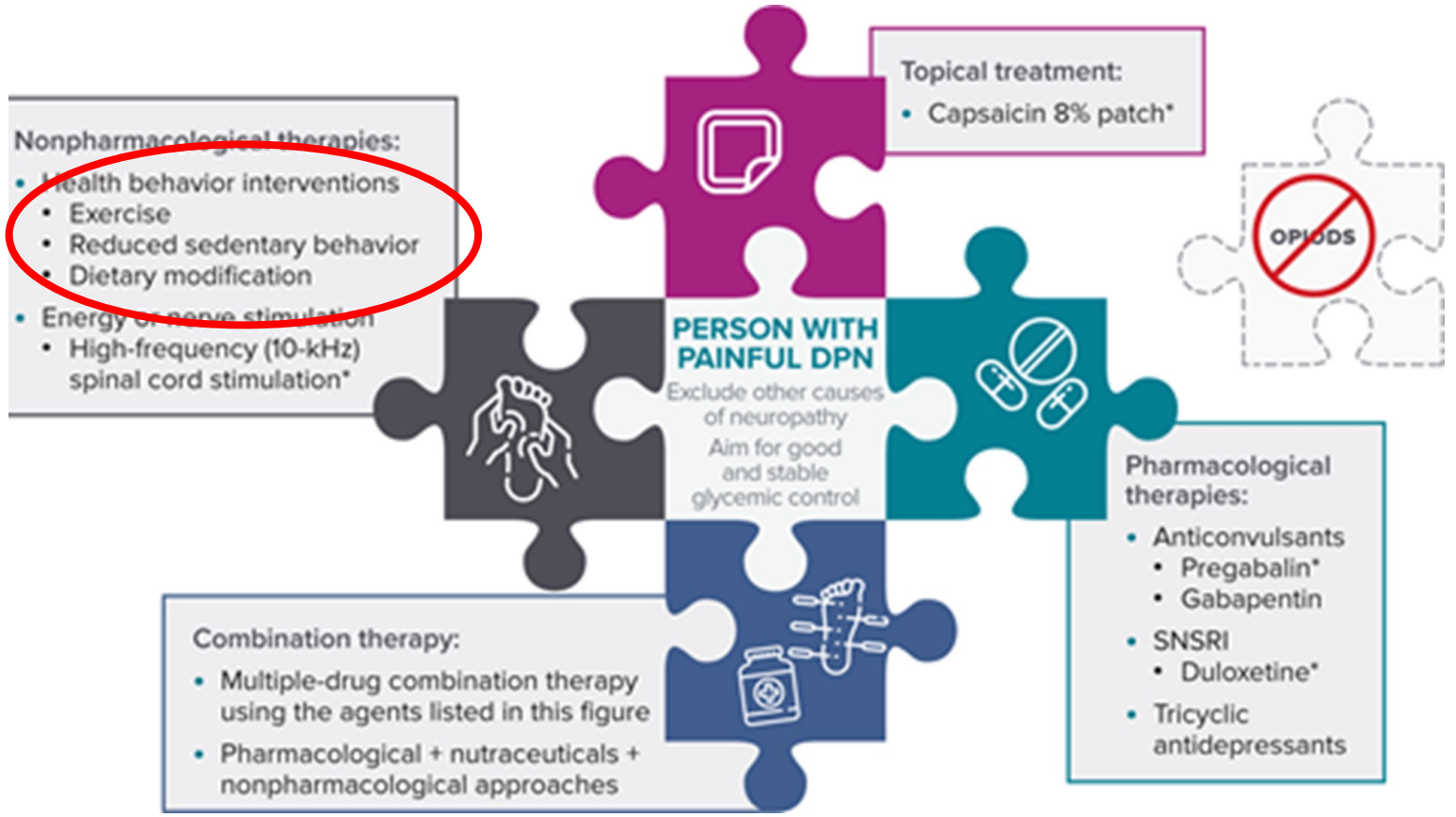
https://www.aan.com/Guidelines/home/GuidelineDetail/1037

"Aim for good & stable glycemic control" (Reduction in glucose variability)

- Studies suggested that stable glycemic control with few excursions into hyperglycemia or hypoglycemia was associated with *reduced pain scores*
- the ***stability of glycemic control*** may be more important than the actual level of control, as indicated by A1C, in the management of painful DPN.

Pro-inflammatory cytokines and free fatty acids released from enlarged adipocytes are neurotoxic to axons.

- Recommend a calorie-restricted diet high in anti-oxidants & plants (such as the DPP curriculum or Mediterranean diet) *



Exercise is perhaps the only intervention shown to improve the **regenerative capacity of small-diameter cutaneous sensory axons** in people with metabolic syndrome and those with diabetes.

- increase in intraepidermal nerve fiber density & regenerative capacity
- randomized trials of scheduled aerobic exercise using modes such as cycling, treadmill, and progressive walking programs have reported *significant improvement in pain scale scores, pain interference measures, and/or quality-of-life metrics*
- anti-sedentary behavioral modification is an alluring future research direction for DPN

Alpha-Lipoic Acid

- Not recommended in guidelines in US or Canada (but in guidelines in other countries)
  - ALA is suggested as an option in the ADA Clinical Compendia on Painful DPN

- Some studies show symptom relief in painful DPN using IV or oral ALA; some show improvement in neuropathy (in deficits) – (usually 600 mg QD but can increase to BID or TID if <30% improvement in pain)

- **Systematic Review** (Abubaker S A, Alonazy A M, Abdulrahman A (**June 08, 2022**) Effect of Alpha-Lipoic Acid in the Treatment of Diabetic Neuropathy: A Systematic Review. Cureus 14(6): e25750. doi:10.7759/cureus.25750)
  - ***Eight studies comprising 1,500 diabetic patients*** were evaluated in this systematic review. The ***findings were inconsistent*** among the literature concerning the effectiveness of α-lipoic acid in the treatment of diabetic neuropathy, with
    - three trials (37.5%) observing significant improvements in symptoms and
    - five trials (62.5%) not observing any notable results.
  - All studies found α-lipoic acid to be a safe and tolerable intervention, with no reported adverse effects.

  - The administration of α-lipoic acid may result in symptom reduction and offers a safe and tolerable treatment option.
    - However, there is *limited evidence* to support the beneficial outcomes of this approach.
    - Further trials are warranted to corroborate or contradict the hypothesis that α-lipoic acid is an effective intervention for the treatment of diabetic neuropathy.

Key Points - Summary

- DPN starts bilaterally with the longest neurons and progresses from distal to proximal (stocking-glove) and from "small fibers" (pain) to "large fibers" (loss of sensation & protection)
- Glycemia is not the only factor; Met Sn components are critical factors for the development of DPN
- DPN assessment should be performed annually starting at diagnosis for type 2 diabetes and 5 years after the diagnosis for type 1 diabetes.
  - People with prediabetes and young people with symptoms or signs of DPN should also be screened.
- Assessment should include a detailed history and at least two sensation and reflex tests.
  - Not all patients with DPN have pain – exam is critical for detection
  - Electrophysiological testing is rarely needed for people with typical signs and symptoms.
  - A complex differential is recommended, and ambiguous or atypical cases should be referred to a neurologist and/or have additional testing.
- Stabilizing glycemia (reducing glucose variability) can sometimes help improve pain
- Regular aerobic, strengthening, and balance exercise, alone or in combination; reduction of sedentary behavior; and dietary modification aimed at reducing calorie intake and increasing plant-based foods and polyunsaturated fats have all demonstrated positive outcomes for individuals with DPN.
- Effective pharmacological therapies for painful DPN include anti-epileptic agents (pregabalin and gabapentin) and anti-depressants (duloxetine and tricyclics), although often effective pain reduction requires higher doses that may be less tolerated or have a higher incidence of adverse effects.
  - For those with severe painful symptoms not responding to a single agent, combination therapy with two to three agents may be effective at much lower doses, as well as combinations of pharmacological and nonpharmacological approaches.
    - Caution in older patients and note autonomic neuropathy/ CAN is common in patients with DPN – increased orthostatic hypotension
- Avoid treatment with opioids

Post-question

Diabetic Peripheral Neuropathy in people with T2D

A. Is almost entirely due to effects of hyperglycemia
B. Is always associated with neuropathic pain
C. Is usually symmetric and progresses from most distal to proximal
D. Requires nerve conduction studies for diagnosis

Extra Slides

Nearly 50% of diabetes patients develop diabetic peripheral neuropathy (DPN) & 20% of type 2 diabetes patients have DPN *at diabetes presentation*

- Diabetes is the most common cause of peripheral neuropathy, accounting for 50% of cases.
- Most patients with *non-diabetic* neuropathy have ***cryptogenic sensory peripheral neuropathy (CSPN).***
  - A growing body of literature ***links prediabetes, obesity and metabolic syndrome*** to the risk of both DPN and CSPN. This association might be particularly strong in type 2 diabetes patients.
- There are no effective medical treatments for CSPN or DPN
  - ***Aggressive glycemic control*** is an effective approach to neuropathy risk reduction **only in *type 1 diabetes***
  - Several studies *suggest* ***lifestyle-based treatments*** *that integrate dietary counseling with exercise* might be a promising therapeutic approach **to *early DPN in type 2 diabetes and CSPN associated with prediabetes, obesity and metabolic syndrome.***

Risk factors for diabetic peripheral neuropathy

- High blood sugar levels
  - poor glycemic control in patients with type 1 or type 2 diabetes
- Cardiovascular disease risk factors including
  - smoking
  - hypertension
  - dyslipidemia, including isolated hypertriglyceridemia
  - obesity

MetS accelerates the rate of DPN *progression* in patients with established diabetes

- Obesity, hypertriglyceridemia and MetS were independent risk factors for early DPN independent of glycemic control
  - Obesity and triglycerides correlated with loss in IENFD (small unmyelinated axons),
  - Elevated hemoglobin A1C correlated with motor conduction velocity slowing on NCS (large myelinated axons),
  - Suggesting obesity and MetS might preferentially injure small fibers, whereas hyperglycemia might differentially impact large fibers

Treatment must extend beyond treatment of hyperglycemia and should be started as early in the disease course as possible.

- **MetS**, particularly ***hypertriglyceridemia and obesity,*** play a central role in peripheral nerve injury
- The most obvious therapeutic strategy ***is treatment of the underlying metabolic changes***
- The timing of treatment is also likely to be important, once established, neuropathy is difficult to reverse (can stabilize but not reverse)
  - CSPN-MetS is often painful, facilitating early recognition
  - Unmyelinated C fibers *regenerate* with much greater ease than large diameter fibers. Therefore, this population represents an ideal opportunity to explore potential therapeutic approaches.

Lifestyle-based Intervention for DPN

- The Impaired Glucose Tolerance Neuropathy Study utilized a lifestyle-based intervention with target ***weight loss of 7% and increased weekly exercise of at least 150 min for 1 year*** (per the Diabetes Prevention Program protocol)
  - Both objective (QSART and IENFD) and subjective (visual analog pain scale) measures showed that **metabolic improvement was associated with small nerve fiber improvement**. (intraepidermal nerve fiber density (IENFD) allows the morphological quantification of the unmyelinated C-fibers)
  - After 1 year of therapy, there was a significant improvement in IENFD and foot sweat volume using QSART
- After the lifestyle modification regimen, there was a ***significant improvement in axon regeneration rate*** (from 0.51 to 0.72 fibers/mm, $P < 0.002$). Those who achieved ***improvement in more MetS criteria experienced a greater degree of improvement***.
- These findings suggest that lifestyle modification exerts its positive effect at least in part through ***improvement in the ability of axons to regenerate.***

The effect of treating multiple metabolic risk factors on DPN

- The Steno-2 study randomized patients with type 2 diabetes to a ***multifactorial pharmacologic approach*** addressing hyperglycemia, hypertension, dyslipidemia and smoking cessation or simply to conventional therapy.
  - After 8 years of follow up, patients in the intervention arm had more marked reduction in hemoglobin A1c, systolic and diastolic blood pressure, serum cholesterol and triglycerides, and urine albumin excretion, with a nearly 50% reduction in the risk of cardiovascular and microvascular events.
  - Those in the conventional therapy group were also twice as likely to develop autonomic neuropathy compared with those in the treatment cohort
- An alternative approach to pharmacological treatment of multiple individual risk factors is implementation of ***lifestyle-based strategies aimed at improving diet, increasing exercise and reducing weight***

Lifestyle interventions for DPN

- The best models to date regarding parameters for an evidence-based, intensive lifestyle intervention come from the Diabetes Prevention Program (DPP), the Steno-2 Study, the Italian supervised treadmill study, and the University of Utah type 2 diabetes study.
  - The latter study recently reported ***nerve fiber regeneration*** in patients with type 2 diabetes engaged in an exercise program compared with loss of nerve fibers in those who only followed standard of care.
  - Overall, such an approach focuses on either exercise alone (supervised aerobic and/or resistance training) or combined dietary modification and exercise.
  - There is no consensus regarding dietary regimens, and although the DPP used a low-calorie, low-fat diet, others have championed a Mediterranean diet that is moderately lower in carbohydrate (45%) and higher in fat (35%–40%), with less than 10% of saturated fat

Effects of Sedentary Behavior

- Sedentary lifestyle is a major source of morbidity and a contributor to all-cause mortality in the general population.
  - It is associated with ***increased waist circumference, elevated lipid and cholesterol levels, and decreased glycemic control***
  - Prolonged sitting contributes to ***insulin resistance****, even in the setting of reduced caloric intake*
  - The limited use and contraction of postural support muscles also leads to ***reduced glucose uptake, unbalanced regulation of lipoprotein lipase, increased free fatty acid formation and toxic lipid secretion by the liver***
- An alternative approach to exercise-based lifestyle modification is to integrate strategies to reduce sedentary behavior.

“Metabolic Neuropathy”

- Patients with MetS and prediabetes are at elevated risk for CSPN, and CSPN patients are at increased risk for MetS and prediabetes.
- It has been suggested that CSPN-MetS and early DPN associated with type 2 diabetes represent a common disorder, which might be termed ‘***metabolic neuropathy***’.
- Although no pharmacological agent has been found to alter the natural history of DPN or CSPN-MetS, ***exercise-based lifestyle modification*** regiments have consistently shown promising results, likely because of enhanced peripheral nerve ***regenerative*** capacity.
- Although this approach might not be sustainable for many patients, integrating ***strategies to reduce sedentary behavior*** represent a promising alternative approach, as does ***pharmacological treatment aimed at weight loss and improved insulin sensitivity***.

References / Resources

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- ADA Standards of Care https://diabetesjournals.org/care/issue/45/Supplement_1
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- Rodica Pop-Busui,corresponding author1 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

- “*Oral and topical treatment of painful diabetic polyneuropathy practice guideline update summary*,” which was published in Neurology ® online on December 27, 2021, and appears in the January 4, 2022, print issue. Please refer to the full guideline at AAN.com/guidelines for more information, including for descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations.

Practical Neurology 01.04.22
AAN Guidelines for Diabetic Neuropathy Updated

The guideline recommends treatments from the following drug classes for nerve pain:

- tricyclic antidepressants (TCAs)
  - amitriptyline
  - nortriptyline
  - imipramine
- serotonin-norepinephrine reuptake inhibitors (SNRIs)
  - duloxetine
  - venlafaxine
  - desvenlafaxine
- gabapentinoids
  - gabapentin
  - pregabalin
- sodium channel blockers
  - carbamazepine
  - oxcarbazepine
  - lamotrigine
- lacosamide

- Supervised exercise improves cutaneous reinnervation capacity in metabolic syndrome patients
- J. Robinson Singleton MD,Robin L. Marcus PhD,Margaret K. Lessard BS,Justin E. Jackson MS,A. Gordon Smith MD
- First published: 12 November 2014 https://doi.org/10.1002/ana.24310Citations: 67

- https://drc.bmj.com/content/8/1/e001355 - Survival and factors predicting mortality after major and minor lower-extremity amputations among patients with diabetes: a population-based study using health information systems
- Silvia Cascini1, http://orcid.org/0000-0003-3385-1197Nera Agabiti1, Marina Davoli1, Luigi Uccioli2, Marco Meloni2, Laura Giurato2, Claudia Marino1, Anna Maria Bargagli1

- Thorud JC, Plemmons B, Buckley CJ, et al. Mortality After Nontraumatic Major Amputation Among Patients With Diabetes and Peripheral Vascular Disease: A Systematic Review. J Foot Ankle Surg 2016;55:591–9.doi:10.1053/j.jfas.2016.01.012pmid:http://www.ncbi.nlm.nih.gov/pubmed/26898398

Mortality after LEA

- A recent review considering long-term mortality after LEA reported an overall mortality rate of 48%, 61%, and 71%, at 1-year, 2-year, and 3-year follow-up, respectively, among patients with diabetes and peripheral vascular disease
- f the individuals 33% with major LEA died within 1 year and 65% within 4 years after the amputation. Among subjects enrolled after minor LEA, mortality rates at 1 and 4 years were 18% and 45%, respectively (data not shown). The median survival time varied significantly by age class for both groups of patients. In particular, among subjects with a major LEA, the survival time ranged from 30.6 months for the age group 35–54 to 16.8 months for those aged 85 years and older. Among subjects with a minor LEA, the median survival times were 38.4 months and 24.4 months for the age groups 35–54 and 85 years and older, respectively (online supplementary figure S1). Survival rate at 1 year after major LEA was 69% among men and 61% among women, decreasing to 35% and 31%, respectively, after 4 years. For patients who underwent minor LEA, the survival rate at 1 year was 83% among men and 79% among women, and 60% and 53%, respectively, for men and women after 4 years
- A recent systematic review reported an overall 5-year mortality rate ranging from 29% to 69% following minor amputations and from 52% to 80% for patients with major amputations

Spinal Cord Stimulators for painful DPN

- Spinal cord stimulation advances therapy for painful diabetic peripheral neuropathy (healio.com)

- FDA approves spinal cord stimulation for diabetic peripheral neuropathy chronic pain (healio.com)