The Inconsolable Pain of Neuropathy

Megan Filoramo
APRN-BC, PGMT-BC, AP-PMN, IHWNC-BC
Maxim Pain Management

Disclosures

- I am a speaker for Nevro for non-surgical low back pain and painful diabetic neuropathy
- I am a speaker for Salix Pharmaceuticals for opioid induced constipation

- All relevant financial relationships have been mitigated.

Objectives

1. Review 3 pharmacologic options for the treatment of the pain of neuropathy.
2. Describe the benefits of neuromodulation for neuropathy.
3. Identify 2 non-pharmacologic treatment options.

What is neuropathy?

Neuropathic pain: a "pain arising as a direct consequence of a lesion or disease of the somatosensory system"

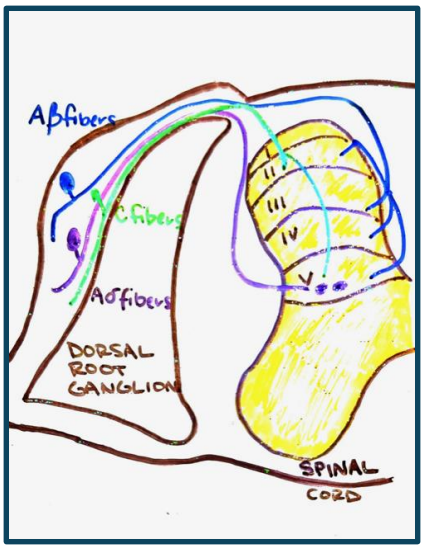
International Association for the Study of Pain

Sensory deficits/dysesthesias

International Association for the Study of Pain, neuropathic pain (NeP) is characterized by a "pain arising as a direct consequence of a lesion or disease of the somatosensory system"

Quick review of pain transduction/transmission

- C fibers: unmyelinated, slow-conducting, localize pain poorly
- Aδ fibers: thinly myelinated, faster-conducting, localize pain better than C fibers
- Aα and Aβ fibers: Larger, more thickly myelinated, primarily transmit information about proprioception and vibration



(Zeng, Alongkronrusmee & van Rijn, 2020)

Why we care?

Morbidities associated with diabetic neuropathy amount to more than $10 billion in the US.

Prevalence of neuropathic pain around 7-10% worldwide

AND…

(Zeng, Alongkronrusmee & van Rijn, 2020)

Morbidities associated with diabetic neuropathy amount to more than $10 billion in the US.

Any help is better than none

The prevalence of NeuP varies around the world, but has been cited as at a minimum of 3%,[2–4] and true prevalence has been estimated to be around 7%–10%. (Zeng, Alongkronrusmee & van Rijn, 2020)

“It feels like getting
hooked up to a car battery
and getting shocked”

“It is not a disease that you
want to have,
the pain is unbearable”

“I feel like a crappy mom because I can barely move around with my kids.”

“Every night is hell.”

"The pain is inconsolable"

Types of neuropathy

- Metabolic
- Toxic
- Disease based
- Idiopathic

Small Fiber vs Large Fiber

Small Fiber: C fiber and Aδ fibers

- alterations in lower-limb pinprick sensation
- visual analog scale pain score >40
- Biopsy: measuring intraepidermal nerve-fiber density

Large Fiber: Aα and Aβ fibers

- loss of tactile or vibratory skin sensation or tendon reflexes
- Nerve conduction studies primary measure Aβ fibers

It is primarily the Aδ and C fibers that are indiscriminately affected in the different types of neuropathies

Measuring which type of fibers are impacted is not trivial, but can be attempted by clinical examination;

Loss of tactile or vibratory skin sensation or tendon reflexes are indicative of large-fiber neuropathy

Whereas alterations in lower-limb pinprick sensation and a visual analog scale pain score >40 suggest small-fiber neuropathy.

Small-fiber neuropathy can also be determined by measuring intraepidermal nerve-fiber density following biopsy.

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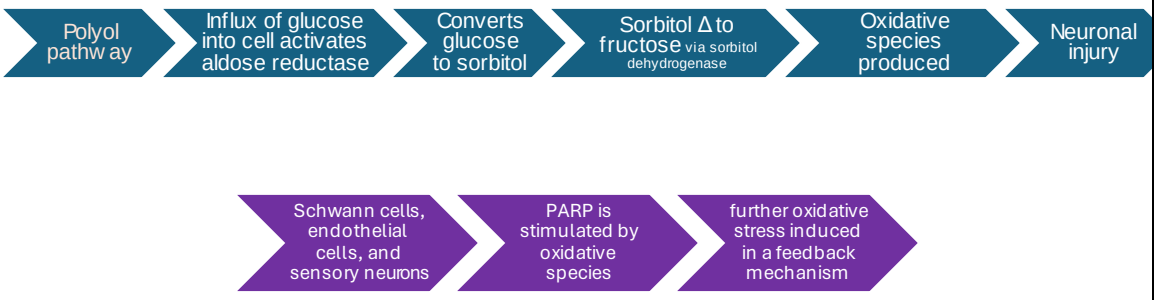
(Zeng, Alongkronrusmee & van Rijn, 2020)

Diabetic Neuropathy Mechanisms



PARP: a nuclear enzyme

can alter gene expression leading to impairment of neuronal conduction velocity, small-fiber neuropathy, hyperalgesia, and allodynia, as well as other diabetic complications

Diabetes or glucose intolerance can impair vasodilation and lead to ischemia, which is thought to be central to the pathogenesis of peripheral neuropathy
primarily small C fibers are affected by diabetes and glucose intolerance

On a molecular level, there are at least five prevailing mechanisms of how hyperglycemia leads to different complications of diabetes, with the polyol and PARP pathways being the most relevant to neuronal death.
In the polyol pathway, the influx of glucose into the cell activates aldose reductase to convert glucose to sorbitol.
Sorbitol is then converted to fructose via sorbitol dehydrogenase.
Both of these steps generate oxidative species that contribute to neuronal injury.
In Schwann cells, endothelial cells, and sensory neurons, PARP is stimulated by oxidative species and induces further oxidative stress in a feedback mechanism.
PARP is a nuclear enzyme that can also alter gene expression, leading to impairment of neuronal conduction velocity, small-fiber neuropathy hyperalgesia, and allodynia, as well as other diabetic complications.

Chemo-induced neuropathy

- Especially with Taxanes: one study showed 100% incidence of neuropathy in pts treated with paclitaxel (Zeng, Alongkronrusmee & van Rijn, 2020)
- Paclitaxel causes abnormal microtubule accumulation; leads to demyelination and inhibits regenerative capacities of neurons
- Risk Factors: (Hammond et al., 2020)
  - Previous chemo
  - Exposure to toxins
  - Genetic causes
  - Pre-existing nerve health
  - Mechanical entrapment neuropathies

CIPN is a small fiber sensory predominant neuropathy developing in the hands/feet that worsens with increasing dose and duration. It affects the Aβ, Aδ, and C-fiber function involved in light touch and vibration sense, thermal detection, and thermal pain. Symptoms include hypoesthesia, dysesthesias, hyperalgesia, allodynia, and neuropathic pain. At present, there are few effective treatment options for CIPN.

Risk factors for CIPN include previous chemotherapy, exposure to toxins, and genetic causes.3 One potential risk factor is preexisting nerve health.8 Mechanical entrapment neuropathies (such as carpal tunnel syndrome) and decreased neural excursion on nerve testing (such as postoperative nerve irritation from breast surgery) may sensitize the nerve to further injury with the chemotherapy drug and is termed the double crush injury or dual nerve disorder.9,10 Physical therapy is well established in orthopedics and plastic surgery for entrapment neuropathies, neuropathic pain, postoperative nerve repair, and regeneration.11-16 To improve nerve excursion across joints, improve pain, and decrease inflammation, therapists frequently add nerve gliding exercises to 899918

NNRXXX10.1177/1545968319899918Neurorehabilitation and Neural RepairHammond et al research-article2020 1 University of Manitoba, Winnipeg,

Manitoba, Canada 2 CancerCare Manitoba, Winnipeg, Manitoba, Canada Corresponding Author: Elizabeth Andersen Hammond, Department of Physical Therapy, College of Rehabilitation Sciences, Rady Faculty of Health Sciences, University of Manitoba, R106-771 McDermot Avenue, Winnipeg, Manitoba, Canada R3E 0T6. Email: elizabeth.hammond@umanitoba.ca An Exploratory Randomized Trial of Physical Therapy for the Treatment of Chemotherapy-Induced Peripheral Neuropathy Elizabeth Andersen Hammond, PhD1, , Marshall Pitz, MD1,2, Karen Steinfeld1, Pascal Lambert, MSc2, and Barbara Shay, PhD1 Abstract Background. Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of taxane treatment and cannot currently be prevented or adequately treated. Physical therapy is often used for neural rehabilitation following injury but has not been evaluated in this patient population. Methods. Single-blind, randomized controlled exploratory study compared standard care to a physical therapy home program (4 visits) throughout adjuvant taxane chemotherapy for stage I-III patients with breast cancer (n = 48). Patient questionnaires and quantitative sensory testing evaluated the treatment effect throughout chemotherapy to 6 months post treatment. Nonrandomized subgroup analysis observed effect of general exercise on sensory preservation comparing those reporting moderate exercise throughout chemotherapy to those that did not exercise regularly. Clinical Trial Registration. clinicaltrials.gov (NCT02239601). Results. The treatment group showed strong trends toward less pain (odds ratio [OR] 0.41, 95% confidence interval [CI] 0.17-1.01; P = .053) and pain decreased over time (OR 0.85, 95% CI 0.76-0.94; P = .002). Pain pressure thresholds (P = .034) and grip dynamometry (P < .001) were improved in the treatment group. For the nonrandomized subgroup analysis, participants reporting general exercise had preservation of vibration (Left P = .001, Right P = .001) and normal heat pain thresholds (Left P = .021, Right P = .039) compared with more sedentary participants. Conclusion. Physical therapy home program may improve CIPN pain in the upper extremity for patients with breast cancer, and general exercise throughout chemotherapy treatment was observed to have correlated to preservation of sensory function. Further research is required to confirm the impact of a physical therapy home program on CIPN symptoms. Keywords chemotherapy-induced peripheral neuropathy, CIPN, physical therapy, nerve gliding, neural gliding, nerve mobilizations, taxane 236 Neurorehabilitation and Neural Repair 34(3) the treatment plan.1

The physical therapy treatment group reported clinically relevant improvements (trending toward statistical significance) for CIPN pain on the NPRS, and statistically significant improvements in pain pressure thresholds, and grip strength compared to the control group. More studies needed
(Hammond et al., 2020)

Alcohol neuropathy

Occurs in 65% of pts with alcohol use disorder

Typically, symmetrical polyneuropathies in the lower distal extremities

- heavier abuse can progress to distal upper extremity symptoms

Cause may be multifactorial

- Nutritional: large-fiber neuropathy (vibration /proprioception) from thiamine deficiency
- Direct neurotoxic effect: acetaldehyde (neurotoxin formed when alcohol is metabolized) toxic effect on c-fibers (painful paresthesias, often in early disease)

(Zeng, Alongkronrusmee & van Rijn, 2020)

Acetaldehyde is a known neurotoxin that is formed when alcohol is metabolized by alcohol dehydrogenase. The precise mechanism underlying alcoholic neuropathy is yet to be fully elucidated. Some proposed explanations include direct neurotoxic effects of alcohol or its metabolite acetaldehyde[70] through activation of spinal cord microglia,[74] involvement of metabotropic glutamate 5 and opioid receptors[74,75] in the spinal cord, promotion of oxidative stress by the activity of alcohol-metabolizing enzymes in the liver,[76] and release of proinflammatory cytokines coupled with phosphorylation of protein kinase C[77] and extracellular signal-regulated kinases

One study suggested that a quantity more than 100 g/day over a number of years was likely to cause peripheral neuropathy
IMPORTANT TO ASK (1) How much alcohol do you drink? and (2) What is the length of the abuse? One shot, one beer, 1 glass of wine all 12-14gm of alcohol each

No specific lab test is available for diagnosis. Treatment should be focused on alcohol sobriety and replacement of key nutrients

Women are more likely to develop alcohol polyneuropathy and suffer from a more rapid onset and greater severity

One of the key nutrients inhibited by alcohol is thiamine, vitamin-B1. Thiamine serves as an important coenzyme in carbohydrate metabolism and neuron development. The lack of thiamine in the nervous system affects the cellular structure and can cause cell membrane damage and irregular ectopic cells. Other vitamin deficiencies seen with alcohol abuse include, but are not limited to, B-vitamins, folic acid, and vitamin-E.

Abstinence for several months up to a few years have shown both clinical examination and electroneurographic improvements, with most patients showing complete regain of function
(Zeng, Alongkronrusmee & van Rijn, 2020)

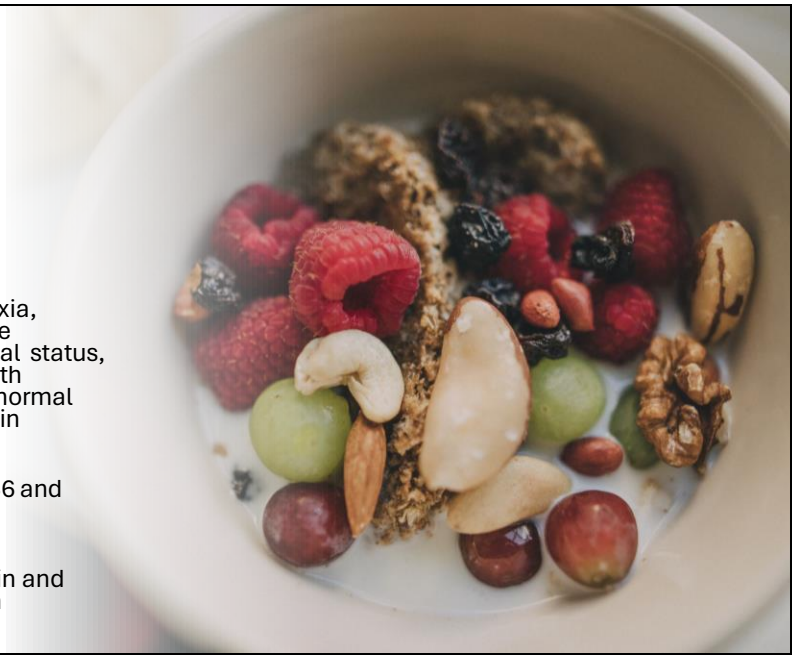
A note on alcohol neuropathy

"Abstinence for several months up to a few years have shown both clinical examination and electroneurographic improvements, with most patients showing complete regain of function."

Sadowski & Houck, 2022

Metabolic Neuropathy

- Can develop acutely
- Can include sensory ataxia, areflexia, variable muscle weakness, poor nutritional status, and weight loss, often with prolonged vomiting and normal cerebrospinal fluid protein
- Often with low Vitamin B6 and Thiamin
- Improved with weight gain and vitamin supplementation



This study describes clinical, laboratory, and electrodiagnostic features of a severe acute axonal polyneuropathy common to patients with acute nutritional deficiency in the setting of alcoholism, bariatric surgery (BS), or anorexia. *Methods*: Retrospective analysis of clinical, electrodiagnostic, and laboratory data of patients with acute axonal neuropathy. *Results*: Thirteen patients were identified with a severe, painful, sensory or sensorimotor axonal polyneuropathy that developed over 2–12 weeks with sensory ataxia, areflexia, variable muscle weakness, poor nutritional status, and weight loss, often with prolonged vomiting and normal cerebrospinal fluid protein. Vitamin B6 was low in half and thiamine was low in all patients when obtained before supplementation. Patients improved with weight gain and vitamin supplementation, with motor greater than sensory recovery. *Discussion*: We suggest that acute or subacute axonal neuropathy in patients with weight loss or vomiting associated with alcohol abuse, BS, or dietary deficiency is one syndrome, caused by micronutrient deficiencies. *Muscle Nerve* **57**: 33–39, 2018

Hammel 2018

Screening tools
CAGE

LABS

- Chemistry Panel
- Diabetes Testing
- Thiamine, Folate, and Vitamin-B12
  - Key in neuronal formation in PNS and CNS.
- Heavy Metal Toxicities
  - Can cause neuropathy in the extremities.
- Disease state: Lyme, HIV, Syphilis, ALS

•Chemistry Panel - Assess electrolytes which can cause peripheral neuropathies.
•Diabetes Testing - Diabetic neuropathy can have a similar presentation.
•Thiamine, Folate, and Vitamin-B12 Testing - Key nutrients in neuronal formation in both peripheral and central nervous systems.
•Heavy Metal Toxicities - Can commonly cause neuropathy in the extremities.
•HIV and Syphilis - Both diseases can have neuropathy in advanced presentations.
•Nerve Conduction Tests - Nerve conduction velocities are generally normal or mildly slow in early presentations and slowed in demyelinating conditions.
•Needle Electromyography (EMG) - Commonly seen with alcohol neuropathy and include positive sharp waves and/or fibrillation potentials and complex repetitive discharges.

Diagnostic scales

DN4: Douleur Neuropathique 4

- Score 1 point for every YES
- Test is positive if ≥ 4
- ≥ 4 sensitivity of 82.9% and a specificity of 89.9%.
- At score of 3, sensitivity and specificity are 84%

Does the pain have the following characteristics?	YES	NO
1. Burning	1	0
2. Painful Cold	1	0
3. Electric Shocks	1	0
Does the area of pain also have the following	**YES**	**NO**
4. Tingling?	1	0
5. Pins & Needles?	1	0
6. Numbness?	1	0
7.Itching	1	0
Exam	**YES**	**NO**
8. Decrease in touch sensation (soft brush)?	1	0
9. Decrease in prick sensation (von Frey hair #13)?	1	0
10. Does movement of a soft brush in the area cause or increase pain?	1	0

DN4 : Questionnaire initially written in French but immediately translated into English by the same team. The scale has been widely used since 2005 because of its simplicity. It evaluates neuropathic pain following central and peripheral neurological lesions.
It is also used for diagnostic purposes, allowing the clinician to determine if the pain is of neuropathic origin.
The questionnaire is composed of 4 questions with suggested responses to which "yes" or "no" must be replied.
This relates to the characterization of the pain (3 suggestions), associated symptoms in the zone (4 suggestions), the presence of hypoaesthesia in the zone (2 suggestions) and if the pain is provoked or increased by external stimulation (1 suggestion).
Each "yes" gives 1 point and each "no" gives no points. The score is thus out of 10.
If the score is greater or equal to 4, the test is positive with a sensitivity of 82.9% and a specificity of 89.9%.

At the cut-off of 4, DN4 displayed sensitivity of 80%, specificity of 92%, positive predictive value (PPV) of 82%, negative predictive value (NPV) of 91%, and likelihood ratio for a positive result (LR(+)) of 9.6. At the cut-off of 3, DN4-interview showed sensitivity and specificity of 84%, PPV of 71%, NPV of 92%, and LR(+) of 5.3.

S-LANSS: Leeds Assessment of Neuropathic Symptoms and Signs

Total score: Score of 12 or more suggests pain of predominantly neuropathic origin

1. In the area where you have pain, do you also have "pins and needles", tingling or prickling sensations?
   NO I don't get these sensations = 0
   YES I get these sensations = 5
2. Does the painful area change color (perhaps look mottled or more red) when the pain is particularly bad?
   NO The pain does not affect the color of my skin= 0
   YES I have noticed that the pain does make my skin look different from normal=5
3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.
   NO The pain does not make my skin abnormally sensitive to touch =0
   YES My skin in that area is particularly sensitive to touch= 3
4. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like "electric shocks", jumping and bursting might describe this.
   NO My pain does not really feel like this =0
   YES I get these sensations often = 2

LANSS cont.

5. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like "electric shocks", jumping and bursting might describe this.
   - NO My pain doesn't really feel like this= 0
   - YES I get these sensations often= 2
6. In the area where you have pain, does your skin feel unusually hot like a burning pain?
   - NO I don't have burning pain= 0
   - YES I get burning pain often= 1
7. Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?
   - The painful area feels no different from the non-painful area= 0
   - I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area=5
8. Gently press on the painful area with your fingertip and then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?
   - The painful area does not feel different from the non-painful area= 0
   - I feel numbness or tenderness in the painful area that is different from the non-painful area= 3

CAGE Questionnaire

- Have you ever felt you should **Cut Down** on your drinking?
- Have people **Annoyed** you by criticizing your drinking?
- Have you ever felt bad or **Guilty** about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**Eye opener**)?

A yes answer to two or more items has a sensitivity of 75% to 95% and a specificity of 84% to 97% for alcohol dependence.

EMG

Not always necessary for diagnosis

In ETOH - Commonly include positive sharp waves and/or fibrillation potentials and complex repetitive discharges

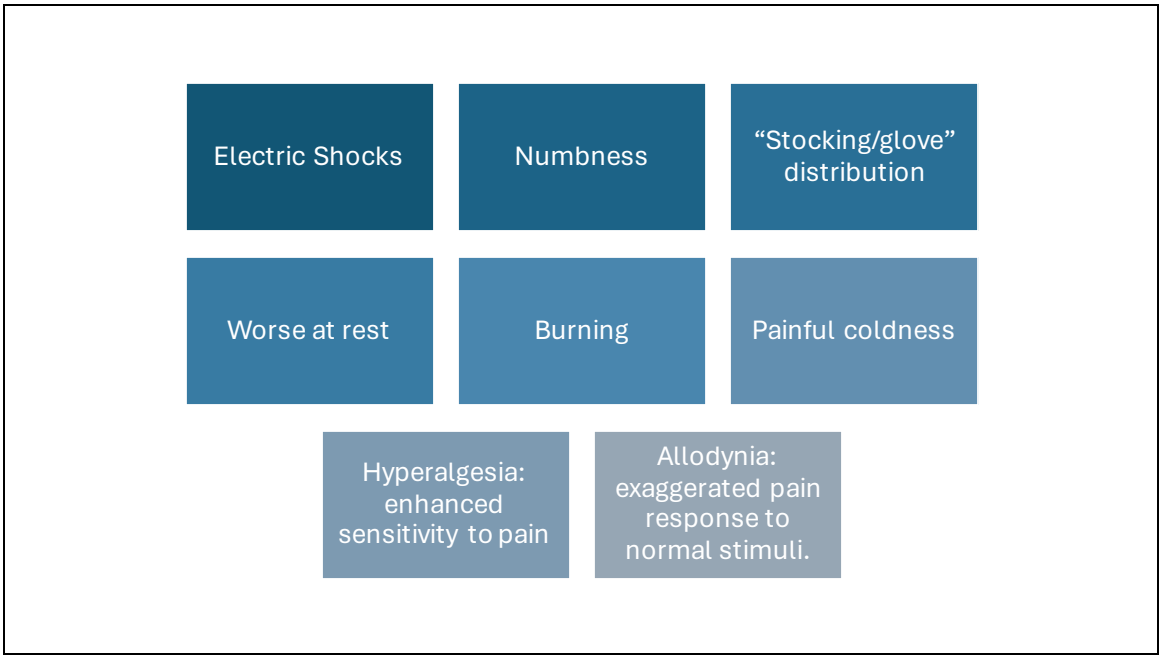
In ETOH

•Nerve Conduction Tests - Nerve conduction velocities are generally normal or mildly slow in early presentations and slowed in demyelinating conditions.

•Needle Electromyography (EMG) - Commonly seen with alcohol neuropathy and include positive sharp waves and/or fibrillation potentials and complex repetitive discharges.

What it feels like

hyperalgesia and allodynia, enhanced sensitivity to pain, and exaggerated pain response to normal stimuli. Zeng, Alongkronrusmee & van Rijn, 2020)



hyperalgesia and allodynia, enhanced sensitivity to pain, and exaggerated pain response to normal stimuli.

Which leads to

- Decreased physical activity
- Increased fatigue
- Sleep problems
- Worsening quality of life
- Increased mortality

These syndromes cause substantial morbidity, increased mortality, and pain in affected patients [10]. In particular, neuropathic pain causes spontaneous pain, allodynia, hyperalgesia, hyperpathia, decreased physical activity, increased fatigue, and sleep problems, which negatively affect the quality of life (Cho & Kim 2021)

Treatment

"Any help is better than none"

neuromodulation

It's electric

The American Association of Clinical Endocrinology (AACE) Guidelines Update 2022

High frequency (eg, 10 kHz) spinal cord stimulation is a nonpharmacological approach that may be effective in persons with painful DPN that failed at least one medication, as suggested by a recent large RCT, leading to FDA approval in 2021.

Lifestyle interventions including a combination of regular aerobic, strengthening, and balance exercises, reduction of sedentary behavior, and dietary modification aimed at reducing calorie intake and increasing plant-based and polyunsaturated fats are recommended. Neuromodulatory techniques such as high-frequency spinal cord stimulation and combining pharmacological with nonpharmacological.

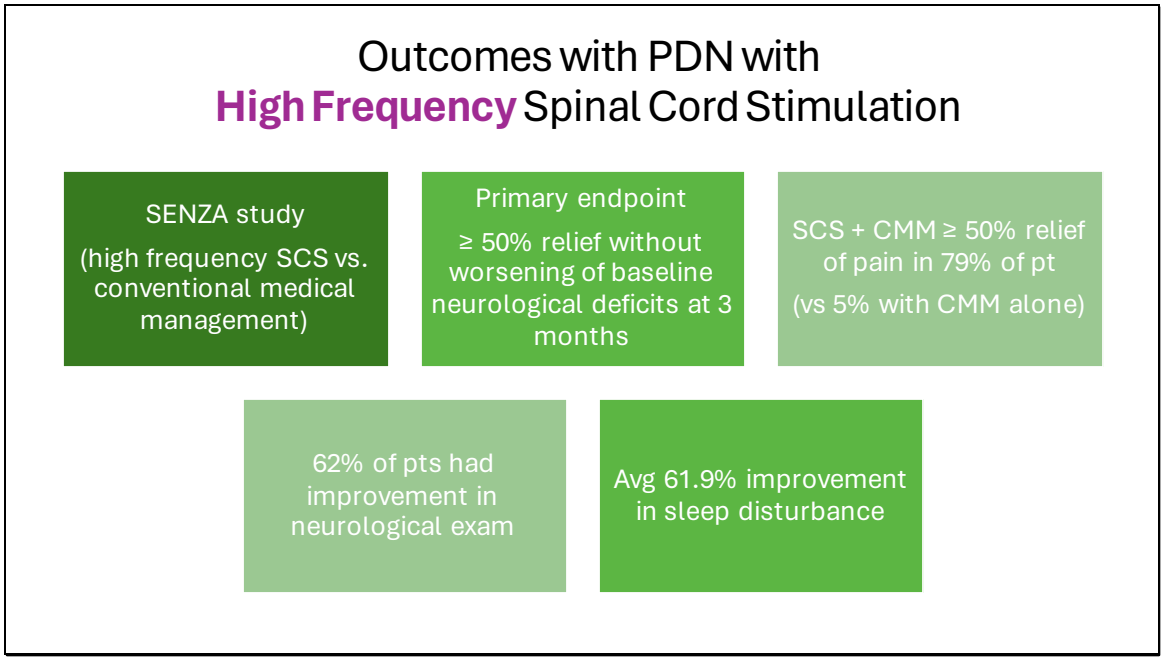
The American Association of Clinical Endocrinology (AACE) published its 2022 Guideline Update: Developing a Diabetes Mellitus Comprehensive Care Plan.1 The guideline features updated and new evidence-based clinical practice recommendations for diabetes at every stage. It now includes high-frequency (eg, 10 kHz) spinal cord stimulation as a treatment option for the treatment of refractory painful diabetic neuropathy.1. Blonde, L. et. al. AACE, Diabetes Guideline Update, Sept 2022.2.

The Recommendation (section 8.9 of guidelines) specifically states the following:

- High frequency (eg, 10 kHz) spinal cord stimulation is a nonpharmacological approach that may be effective in persons with painful DPN that failed at least one medication, as suggested by a recent large RCT, leading to FDA approval in 2021.
- Lifestyle interventions including a combination of regular aerobic, strengthening, and balance exercises, reduction of sedentary behavior, and dietary modification aimed at reducing calorie intake and increasing plant-based and polyunsaturated fats are recommended. Neuromodulatory techniques such as high-frequency spinal cord stimulation and combining

pharmacological with nonpharmacological.

Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan - 2022 Update Endocrine Practice10 kHz SCS in AACE 2022 Guideline



Diabetic outcomes with high frequency stimulation:
83% get at least 50% better improvement in dysesthesias
Improvements in secondary outcomes
Sleep
Pain interference in life
Quality of life

Design, setting, and participants: The prospective, multicenter, open-label SENZA-PDN randomized clinical trial compared conventional medical management (CMM) with 10-kHz SCS plus CMM. Participants with PDN for 1 year or more refractory to gabapentinoids and at least 1 other analgesic class, lower limb pain intensity of 5 cm or more on a 10-cm visual analogue scale (VAS), body mass index (calculated as weight in kilograms divided by height in meters squared) of 45 or less, hemoglobin A1c (HbA1c) of 10% or less, daily morphine equivalents of 120 mg or less, and medically appropriate for the procedure were recruited from clinic patient populations and digital advertising. Participants were enrolled from multiple sites across the US, including academic centers and community pain clinics, between August 2017 and August 2019 with 6-month follow-up and optional crossover at 6

months. Screening 430 patients resulted in 214 who were excluded or declined participation and 216 who were randomized. At 6-month follow-up, 187 patients were evaluated.

Results: Of 216 randomized patients, 136 (63.0%) were male, and the mean (SD) age was 60.8 (10.7) years. Additionally, the median (interquartile range) duration of diabetes and peripheral neuropathy were 10.9 (6.3-16.4) years and 5.6 (3.0-10.1) years, respectively. The primary end point assessed in the intention-to-treat population was met by 5 of 94 patients in the CMM group (5%) and 75 of 95 patients in the 10-kHz SCS plus CMM group (79%; difference, 73.6%; 95% CI, 64.2-83.0; P < .001). Infections requiring device explant occurred in 2 patients in the 10-kHz SCS plus CMM group (2%). For the CMM group, the mean pain VAS score was 7.0 cm (95% CI, 6.7-7.3) at baseline and 6.9 cm (95% CI, 6.5-7.3) at 6 months. For the 10-kHz SCS plus CMM group, the mean pain VAS score was 7.6 cm (95% CI, 7.3-7.9) at baseline and 1.7 cm (95% CI, 1.3-2.1) at 6 months. Investigators observed neurological examination improvements for 3 of 92 patients in the CMM group (3%) and 52 of 84 in the 10-kHz SCS plus CMM group (62%) at 6 months (difference, 58.6%; 95% CI, 47.6-69.6; P < .001).

Neuro assessment

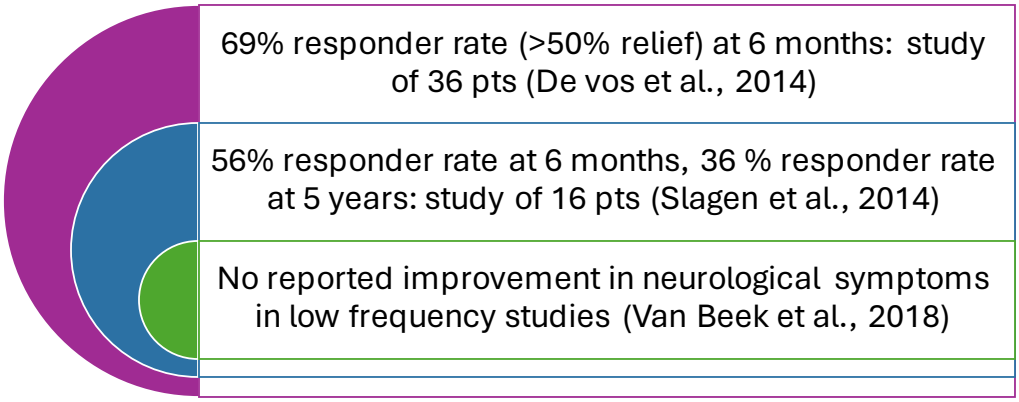
What did the patients look like?

Measure	Inclusion Criteria	Study Participants
Hgb AIC	<10%	7.4%
BMI	45	33.7
Duration of Diabetes		10.9 years
Duration of Neuropathy	1 year	5.6 years
VAS	≥ 5	7.3
Daily opioid MME	<120	

Patients with PDN were recruited across multiple sites in the US. Key inclusion criteria were PDN diagnosis with symptoms for 12 months or more that was refractory to treatment with gabapentin or pregabalin and at least 1 other class of analgesic, lower limb pain intensity of 5 cm or more on a 10-cm visual analogue scale (VAS), and medically suitable for the proposed procedure. All patients were psychologically evaluated and reviewed by independent medical monitors prior to randomization. Key exclusion criteria were hemoglobin A_{1c} (HbA1c) greater than 10%, body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 45, daily opioid dosage greater than 120 mg morphine equivalents, and upper limb pain intensity of 3 cm or more on a VAS.

Among 216 randomized patients, the mean (SD) HbA_{1c} was 7.4% (1.2) and mean (SD) body mass index was 33.7 (5.3). A total of 130 patients (60.2%) had suboptimally controlled diabetes. The median (interquartile range) duration of diabetes and peripheral neuropathy were 10.9 (6.3-16.4) years and 5.6 (3.0-10.1) years, respectively, before enrollment. There was a similar distribution of sex between groups (Table). Patients presented with moderate to severe neuropathic pain indicated by a mean (SD) baseline VAS score of 7.3 (1.6) cm and a mean (SD) DN4 score of 6.6 (1.8).

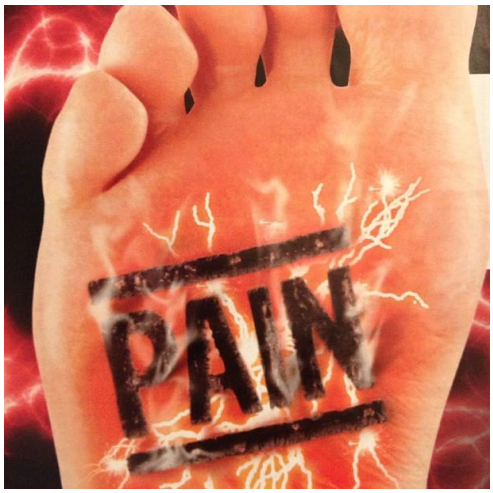
Outcomes in PDN with **low-frequency**/tonic SCS



(De vos et al., 2014. Slagen et al., 2014. Van Beek et al., 2018)

This is important even if you are not a prescriber- the patients will come to you with questions and concerns

Topical Capsaicin



- Brand patch is Qutenza
- TRPV1 channel agonist
- Indicated for the treatment of neuropathic pain associated with postherpetic neuralgia and with diabetic peripheral neuropathy
- For DPN: Apply up to 4 patches for 30 minutes on the feet. Repeat every 3 months or as warranted by the return of pain (not more frequently than every three months)
- Weeks 2-12 about 40% of patients had ≥ 30% relief

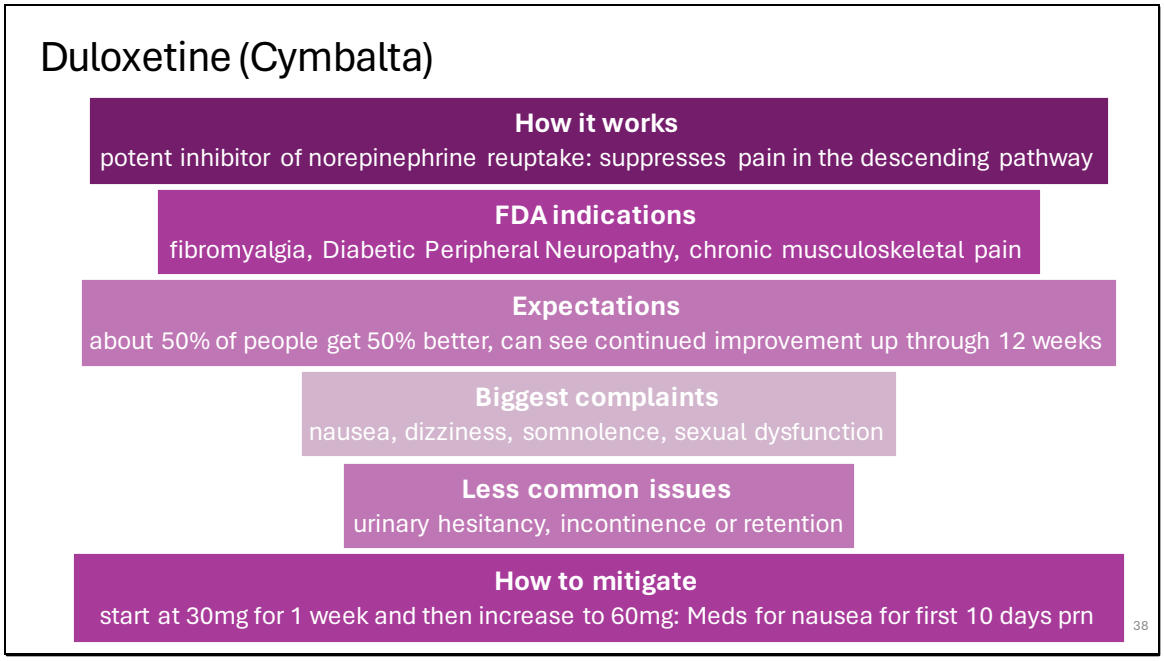
(Mou et al., 2013)

https://www.qutenza.com/pdfs/Qutenza_DPN_Administration_Guide_2023.pdf

QUTENZA is a TRPV1 channel agonist indicated for the treatment of neuropathic pain associated with postherpetic neuralgia (PHN) and neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet. (1)
Capsaicin is an agonist for the transient receptor potential vanilloid 1 receptor (TRPV1), which is an ion channel-receptor complex expressed on nociceptive nerve fibers in the skin. Topical administration of capsaicin causes an initial enhanced stimulation of the TRPV1-expressing cutaneous nociceptors that may be associated with painful sensations. This is followed by pain relief thought to be mediated by a reduction in TRPV1- expressing nociceptive nerve endings [see Clinical Pharmacology (12.2)]. Over the course of several months, there may be a gradual re-emergence of painful neuropathy thought to be due to TRPV1 nerve fiber reinnervation of the treated area.
Weeks

Capsaicin
(Mou et al., 2013)


You want me to take an ANTIDEPRESSANT?? ?

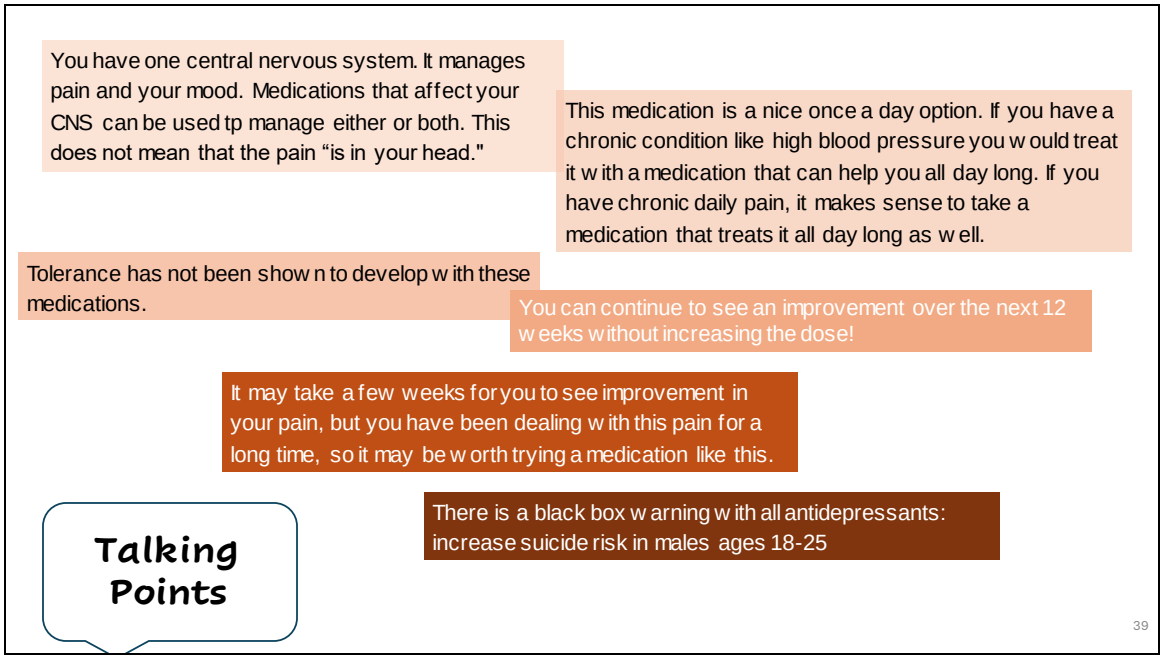


Usually the nausea associated with initiation of an SNRI will go away after the first few weeks and vomiting is unlikely. I really think this medication will help you so if you have nausea I would rather give you a medication for that to get you over the first few weeks than have you stop the medication.

How it works: potent inhibitor of neuronal serotonin and norepinephrine reuptake: norepinephrine suppresses pain in the descending pathway
FDA indications: fibromyalgia, Diabetic Peripheral Neuropathy, chronic musculoskeletal pain (studied in OA of the knee and chronic low back pain)
Expectations: about 50% of people get 50% better, can see continued improvement up through 12 weeks

Biggest complaints: nausea

How to mitigate: start at 30mg for 1 week and then increase to 60mg.
Medicate for nausea for first 10 days if needed



In the studies, the medication was titrated up to the right dose over the first 2 weeks. After that, the dose is kept the same but patients continue to see an increase in pain relief all the way up to the 12 week mark. The relief increases without increasing the dose!

Indeed, the FDA-conducted meta-analyses of 372 randomized clinical trials of antidepressants involving nearly 100,000 participants, which showed that rates of suicidal thinking or behavior was higher among patients assigned to antidepressants when compared with placebo, and in a subsequent age-stratified analysis it was shown that such increased risk was significant only among children and adolescents under the age of 18 years. There was no evidence of increased risk among adults older than 24 years, and, among adults 65 years of age or older, antidepressants had an apparent protective effect against the development of suicidal ideation and behavior.

Duloxetine: things to remember

- QD dosing = steady state in about 72hours
- Highly protein bound: Elimination through liver: CYP450 isozymes, CYP2D6 and CYP1A2
- Bioavailability reduced by about 1/3 in smokers. Dosage adjustment not recommended.
- Not recommended in end stage renal disease, Cr Cl<30ml/min, or with any hepatic impairment
- Serious side effect: increased risk of mydriasis, avoid in uncontrolled narrow-angle glaucoma

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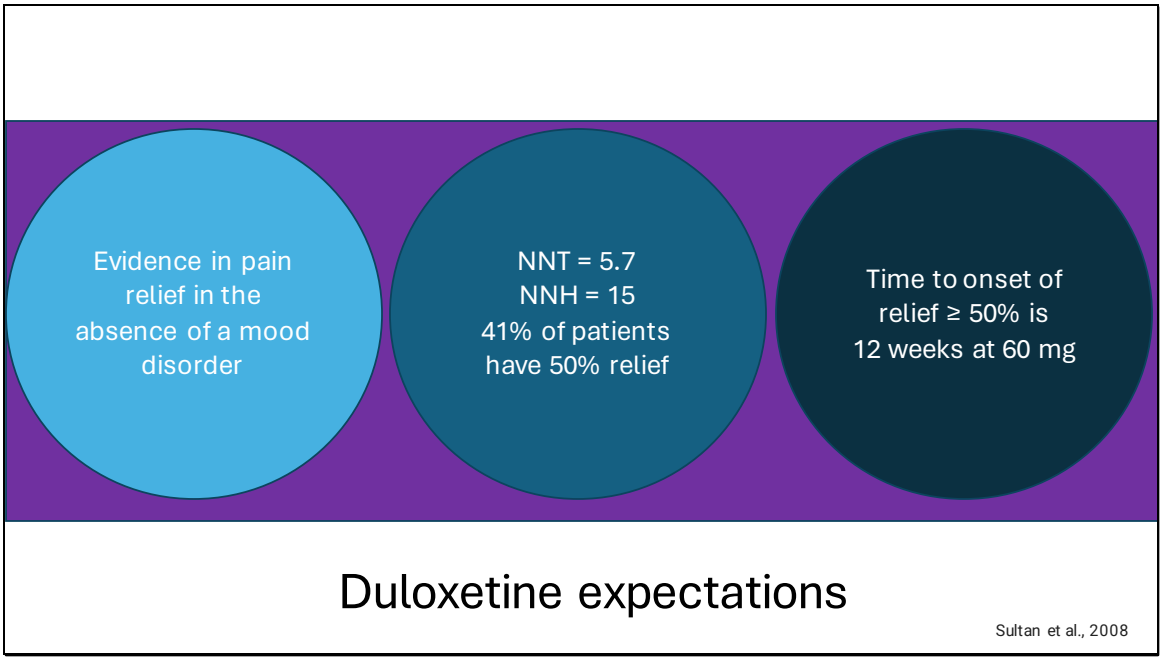


Results: The number needed to treat (NNT) for at least 50% pain relief at 12 to 13 weeks with duloxetine 60 mg versus placebo (1,211 patients in the total comparison) was 5.8 (95% CI 4.5 to 8.4), and for duloxetine 120 mg (1,410 patients) was 5.7 (4.5 to 5.7). There was no difference in NNTs between PDN and fibromyalgia. With all doses of duloxetine combined (20/60/120 mg) there were fewer withdrawals for lack of efficacy than with placebo (number needed to treat to prevent one withdrawal 20 (13 to 42)), but more withdrawals due to adverse events (number needed to harm (NNH) 15 (11 to 25)). Nausea, somnolence, constipation, and reduced appetite were all more common with duloxetine than placebo (NNH values 6.3, 11, 11, and 18 respectively). The results for duloxetine are compared with published data for other antidepressants in neuropathic pain.

Conclusion: Duloxetine is equally effective for the treatment of PDN and fibromyalgia, judged by the outcome of at least 50% pain relief over 12 weeks, and is well tolerated. The NNT of 6 for 50% pain relief suggests that this is likely to be a useful drug in these difficult-to-treat conditions, where typically only a minority of patients respond. Comparing duloxetine with antidepressants for pain relief in DPN shows inadequacies in the evidence for efficacy of antidepressants, which are currently recommended in PDN care pathways.

(Sultan et al., 2008)

Patients receiving duloxetine 60 mg QD and 60 mg BID had NNTs (95% CI) of 5.2 (3.8-8.3) and 4.9 (3.6-7.6), respectively, based on last observation carried forward; NNTs of 5.3 (3.8-8.3) for 60 mg QD and 5.7 (4.1-9.7) for 60 mg BID were obtained based on baseline observations carried forward. The NNHs (95% CI) based on discontinuation due to AEs were 17.5 (10.2-58.8) in the duloxetine 60-mg QD group and 8.8 (6.3-14.7) in the 60-mg BID group.

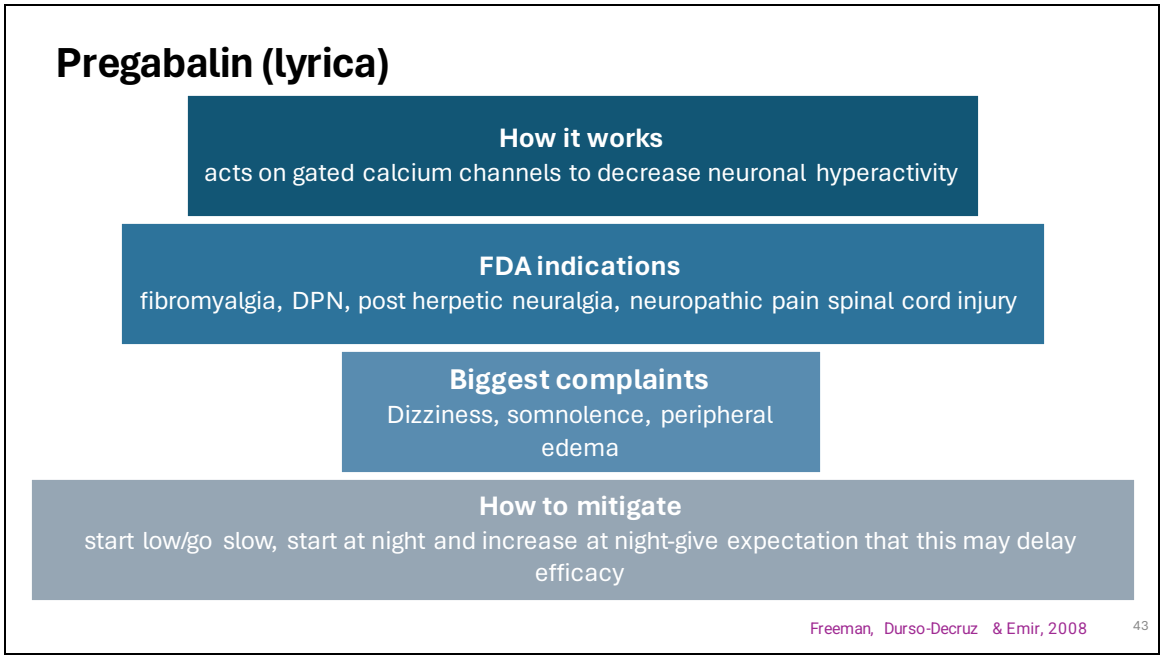
Kajdasz DK, Iyengar S, Desaiah D, et al 2007

Tricyclic Antidepressants not FDA approved for neuropathy

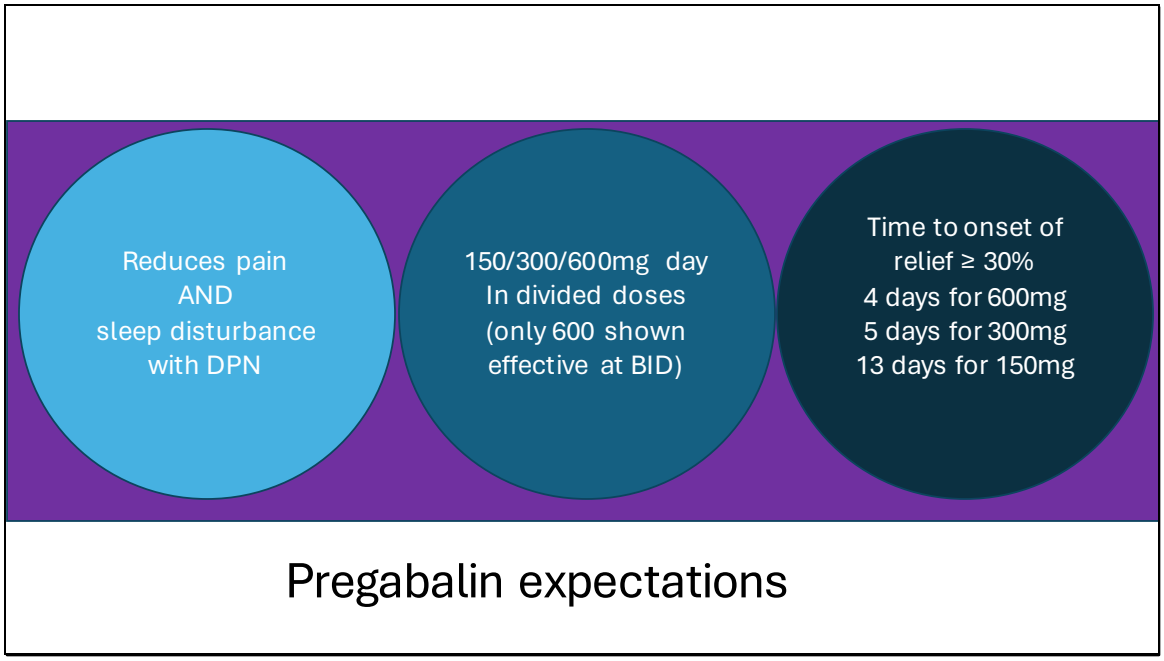
- MOA: block monamine reuptake (serotonin and norepinephrine)
- Dose: 10-90 mg day
- Most Common Adverse Effects: GI issues, orthostatic hypotension, dry mouth, urinary retention, QT prolongation
- Not a first line agent due to side effect profile
- Dosing at night may help with sleep

(Gupta et al., 2021, Staudt et al., 2022)

(Gupta et al., 2021, Staudt et al., 2022)



Pooled analysis showed that pregabalin significantly reduced pain and pain-related sleep interference associated with DPN (150, 300, and 600 mg/day administered TID vs. placebo, all P < or = 0.007). Only the 600 mg/day dosage showed efficacy when administered BID (P < or = 0.001). Pain and sleep interference reductions associated with pregabalin appear to be positively correlated with dosage; the greatest effect was observed in patients treated with 600 mg/day. Kaplan-Meier analysis revealed that the median time to onset of a sustained (> or =30% at end point) 1-point improvement was 4 days in patients treated with pregabalin at 600 mg/day, 5 days in patients treated with pregabalin at 300 mg/day, 13 days in patients treated with pregabalin at 150 mg/day, and 60 days in patients receiving placebo. The most common treatment-emergent adverse events were dizziness, somnolence, and peripheral edema.



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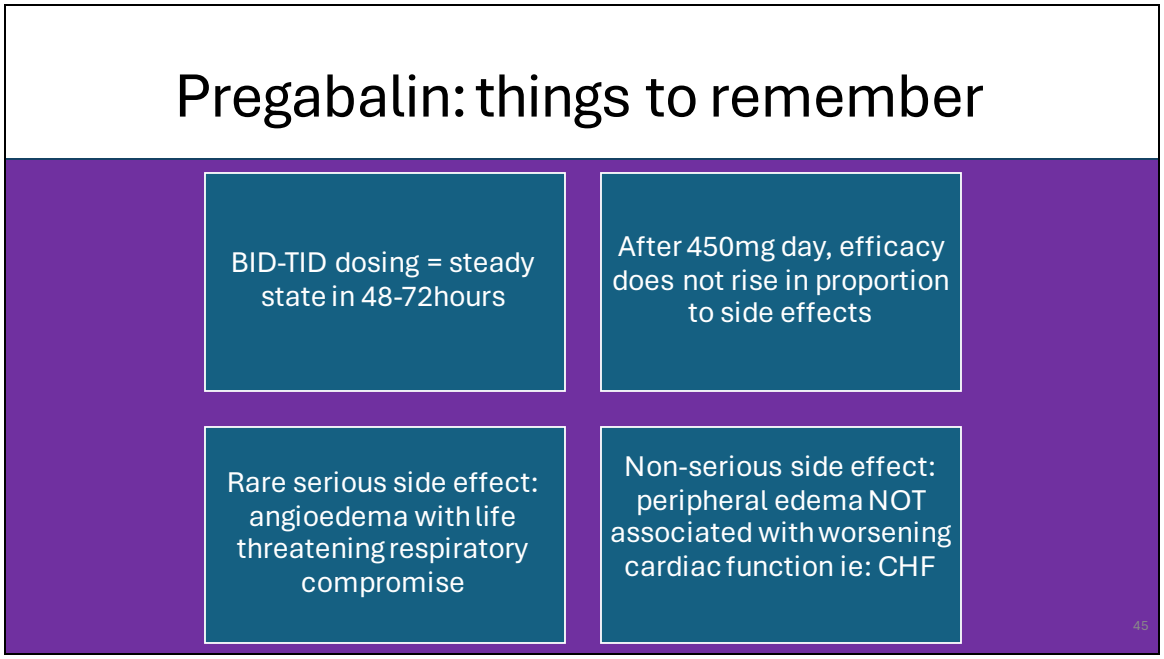
Freeman, Durso-Decruz & Emir, 2008

Time to onset of relief ≥ 30%4 days for

600mg 5 days for 300mg 13 days for 150mg



So what do we say to patients: it doesn't mean your heart is working harder.

Coaching Points

It's a nerve membrane stabilizer (it is actually doing something, not just blocking pain).

What's the big rush? You have been dealing with this for a long time.

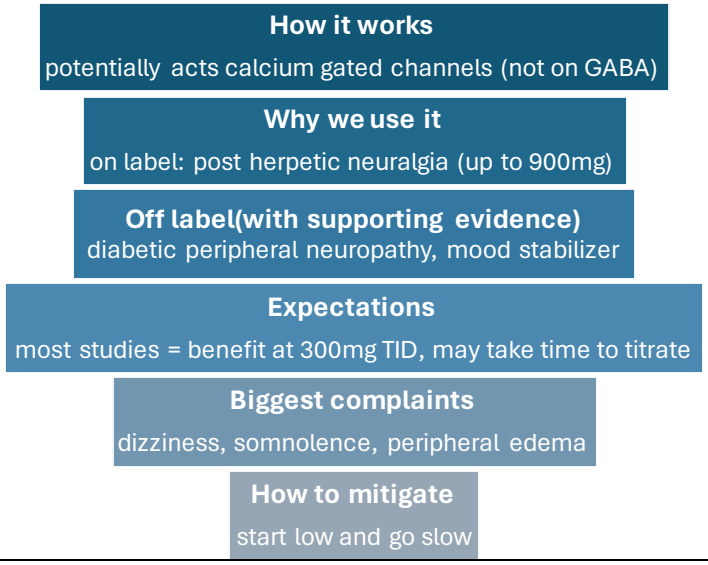
What are the pros and cons of not taking it?

Discuss the pros and cons of taking the medication.

Discuss the pros and cons of not taking the medication.

There are always both.

Gabapentin (short acting:Neurontin, long acting: Horizant & Gralise)



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adjunctive for partial onset seizures
We don't have unlimited options so don't rush the dosing- if we lose it as an option there aren't a ton of

Gabapentin: things to remember

- Long-acting formulations seem to be better tolerated but may have limited insurance coverage
- Gralise only indicated for PHN, Horizant indicated for PHN & restless leg syndrome
- 95% of gabapentin today prescribed for off-label indications : diabetic peripheral neuropathy, mood stabilizer

Rare but serious reactions

- Multiorgan Hypersensitivity Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): fever/rash/lymphadenopathy
- Anaphylaxis and angioedema: difficulty breathing, swelling of lips, throat, tongue, and hypotension

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5.1 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity Some of these reactions have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection.
Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. NEURONTIN should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Intrathecal Ziconotide

- Non-opioid/ Selective calcium channel blocker
  - Blocks the release of pro-nociceptive neurotransmitters in the dorsal horn
- FDA approved for treatment of refractory chronic pain
- Only administered intrathecally
- Tolerance and withdrawal do not develop
- Black box warning for potential severe psychiatric symptoms and neurological impairment

(Gupta et al., 2021)

To illustrate further the vital role of calcium channels in pain transmission, ziconotide is a selective calcium-channel blocker and potent analgesic. Ziconotide is FDA approved for the treatment of refractory chronic pain.[129] As ziconotide is a large peptide that cannot readily cross the blood–brain barrier, it can thus only be administered intrathecally. Intrathecal drug delivery can be used to manage chronic pain effectively, and may provide the most targeted approach with the fewest side effects.[1]

Opioids

Tapentadol (Nucynta)

- μ-opioid receptor agonist AND norepinephrine reuptake inhibition
- Improved GI impact over other opioids
- ER formulation FDA approved for pain associated with diabetic neuropathy when ATC opioid analgesic needed for extended period

Methadone

- Not FDA approved for neuropathic pain
- Evidence for benefit in neuropathic pain when conventional opioids failed

Levorphanol

- Not FDA approved for neuropathic pain
- Evidence of benefit equal to TCA and gabapentin when used around 9mg/d

cannabis

(Devit-Lee, 2017; Modesto-Lowe, Bojka & Alvarado, 2018)

THC/CBD metabolized by CYP450

- can inhibit or induce medications metabolized by this system
- >50% of pharmaceuticals metabolized via CYP450

Cochrane review in 2018

- 30% reduction in 39% of pts

Number Needed to Treat= 11

BUT

Number Needed to Harm = 10

More good data needed

Modesto-Lowe V, Bojka R, Alvarado, C. Cannabis for peripheral neuropathy: The good, the bad, and the unknown. *Cleveland Clinic Journal of Medicine* Dec 2018, 85 (12) 943-949; DOI: 10.3949/ccjm.85a.17115

Modifying response to injury

Following a nerve injury, neurons along the nociceptive pathway may become more reactive and responsive in a process known as sensitization.[21] The process involves a cascade of cellular events that result in sprouting of painsensitive nerve endings.[21,22]

Cannabinoids are thought to reduce pain by modifying these cellular events. They also inhibit nociceptive conduction in the dorsal horn of the spinal cord and in the ascending spinothalamic tract.[20] CB1 receptors found in nociceptive terminals along the peripheral nervous system impede pain conduction, while activation of CB2 receptors in immune cells decreases the release of nociceptive agents.

Cochrane review, 2018: 16 trials, 1,750 patients

A Cochrane review[34] analyzed 16 trials (in 1,750 patients) lasting 2 to 26 weeks. Treatments included an oromucosal spray with a plant-derived combination of THC and CBD, nabilone, inhaled herbal cannabis, and

plantderived THC.
With cannabis-based treatments, significantly more people achieved 50% or greater pain relief than with placebo (21% vs 17%, number needed to treat 20); 30% pain reduction was achieved in 39% of treated patients vs 33% of patients taking placebo (number needed to treat 11).
On the other hand, significantly more participants withdrew from studies because of adverse events with cannabis-based treatments than placebo (10% vs 5%), with psychiatric disorders occurring in 17% of patients receiving active treatment vs 5% of those receiving placebo (number needed to harm 10).
The primary studies suffered from methodologic limitations including small size, short duration, and inconsistency of formulations and study designs. Further evaluation of longterm efficacy, tolerability, and addiction potential is critical to determine the risk-benefit ratio

THC/CBD metabolized by CYP450
can inhibit or induce medications metabolized by this system

>50% of pharmaceuticals metabolized via CYP450
many by more than one CYP450 enzyme

THC is metabolized by CYP2C9, CYP2C19, (Theisen & Konieczny, 2019)

CYP2C9 is the primary enzyme responsible for metabolizing nonsteroidal antiinflammatory drugs (NSAIDs), oral antidiabetic agents, and angiotensin II receptor blockers (ARBs).
CYP2C9 also is the major enzyme involved in the disposition of warfarin.
https://www.pharmacytimes.com/publications/issue/2008/2008-03/2008-03-8462

https://www.projectcbd.org/medicine/cannabinoid-pharmaceutical-interactions-what-you-need-know

Clinically relevant changes in drug metabolism due to CBD are usually seen with high doses of pure CBD (Devit-Lee, 2017; Modesto-Lowe, Bojka & Alvarado, 2018)

Example: THC and CBD could decrease the metabolism of NSAIDs and thereby increase the side effects
CBD is metabolized by CYP2C19, CYP3A4(Theisen & Konieczny, 2019)

Warfarin can inhibit or induce THC/CBD, also use with caution with other sedative medications (Theisen & Konieczny, 2019)

Novel Agents more data needed

Alpha Lipoic Acid

- Potent antioxidant
- Reduces oxidative stress
- Improves microvascular blood flow
- Improves nerve conduction velocity
- In studies: improved sensory symptoms but no improvement of oxidative stress markers, inflammatory markers or nerve conduction

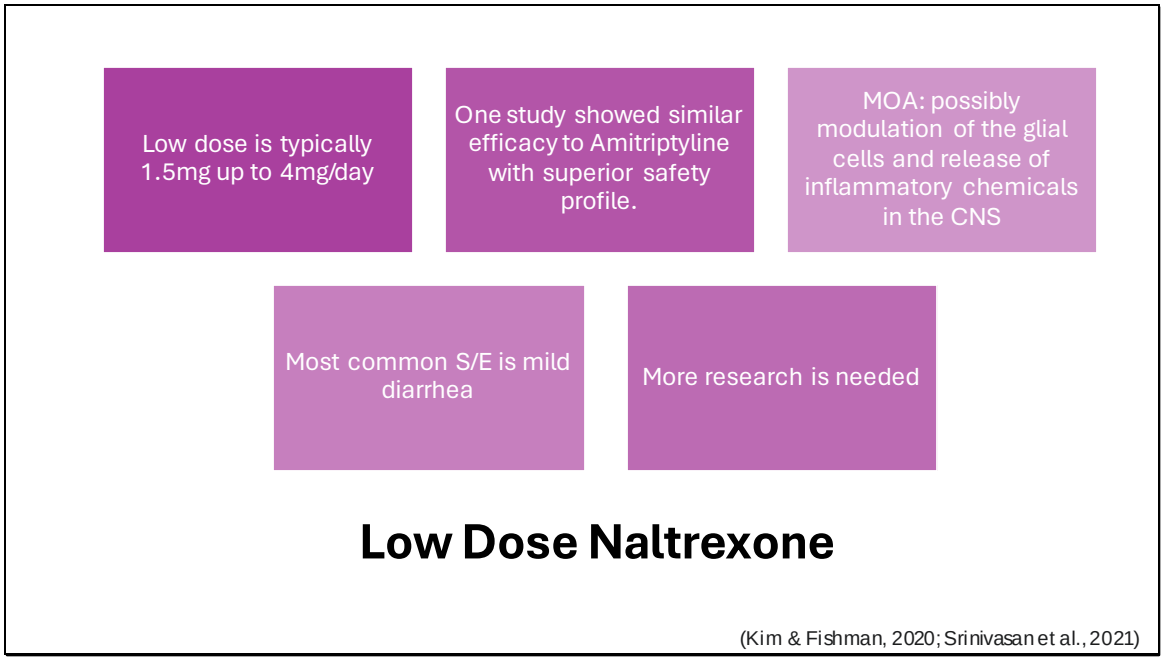
Actovegin

- Deproteinized ultrafiltrate of calf serum
- Potent anti-hypoxic effects
- Potential neuroprotective role
- Studies show improvement in neuropathic symptoms and vibration thresholds

(Staudt et al., 2022)

(Staudt et al., 2022)

Oral treatment with ALA for 5 weeks improved neuropathic symptoms and deficits in patients with DSP. An oral dose of 600 mg once daily appears to provide the optimum risk-to-benefit ratio.



Sixty-seven participants with painful diabetic neuropathy were randomized to receive either 2 mg naltrexone or 10 mg amitriptyline daily following a 2-week run-in period. The participants were followed up every 2 weeks for a total of 6 weeks. Up-titration was done (to 4 mg naltrexone or 25/50 mg amitriptyline) if the pain reduction was less than 20% on the visual analog scale (VAS) during the next follow-up visit. Efficacy was assessed using the change in VAS score at the end of 6 weeks from baseline. Safety was evaluated at each follow-up visit. After 2 weeks of washout period, the participants were crossed over to receive the comparator drug for another 6 weeks with similar evaluations.

Results

The difference (confidence interval) in the change in VAS score between groups from baseline was 1.64 (−0.92 to 4.20) in per-protocol analysis and 1.5 (−1.11 to 4.13) in intention-to-treat analysis. Eight and fifty-two adverse events were reported in the naltrexone and amitriptyline groups, respectively ($P < .001$). The most common adverse events were mild diarrhea with

naltrexone and somnolence with amitriptyline.

Conclusions

Low-dose naltrexone exhibited similar efficacy and a superior safety profile compared with amitriptyline in painful diabetic neuropathy.

(Kim & Fishman, 2020; Srinivasan et al., 2021)

Acupuncture
Herbals
Tapping
Meditation (requires a conversation about the nervous system)

Let's not forget about the person behind the dx

Mindfulness meditation and progressive relaxation (Izgu et al., 2020)

- 12 week study in PDN
- VAS scores significantly decreased
- In relaxation group, fatigue severity decreased

Acceptance and Commitment Therapy (ACT) (Taheri et al., 2020)

- Purpose is to face, accept and change the patient relationship with pain experience
- Research in chronic pain studies shows that it can decrease pain perception and pain severity
- 2 components: pain willingness and activity engagement

Taheri, A.A., Foroughi, A.A., Mohammadian, Y. *et al.*
The results indicated that acceptance and commitment therapy could be used as a psychological intervention besides pharmacotherapy to improve pain acceptance and reduce pain perception in patients with painful diabetic neuropathy.

One of the third-wave of cognitive behavioral therapies is acceptance and commitment therapy (ACT), which emphasizes
acceptance and willingness to experience unpleasant events.

pain acceptance consists of two elements: pain willingness and activity engagement. Pain willingness refer to strategies for adaption and
coping with pain. Activity engagement emphasizes continuing daily activities and taking actions towards values despite focusing on the unpleasant experiences of pain (Taheri et al., 2020)

Izgu, N., Gok Metin, Z., Karadas, C., Ozdemir, L., Metinarikan, N. and

Corapcıoglu, D. (2020),
VAS scores were significantly lower in the RG and MG at week 12 ($p < .05$) and were statistically significant in the RG at week 14. Additionally, fatigue severity decreased significantly in the RG at weeks 12 and 14, compared to that in the CG ($p < .05$). While no significant difference was found in the quality of life scores between the study groups at weeks 12 and 14 ($p > .05$), a significant improvement in quality of life scores in the RG were provided at week 12 compared to those at baseline and week 14 ($p < .05$).

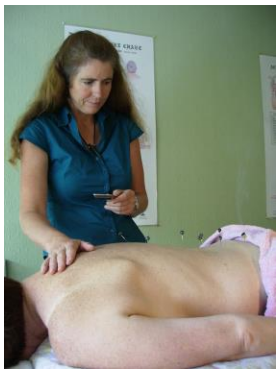
Acupuncture what do you have to lose?

CIPN (Huang et al., 2021)

- Evidence suggests that acupuncture can alleviate the neuropathic pain and improve touch perception thresholds

PDN (Cho & Kim, 2021)

- Systemic review of 10 human studies and 5 animal studies
- All studies at least 1 month of treatment, each session at least 20 min
- All showed significant improvement
- Minimal adverse effects: minor hematomas, temporary pain, swelling, numbness, nausea, cramps, and palpitations



Important point: single treatment is not sufficient, set reasonable expectations

This study evaluate the effect of manual acupuncture on CIPN. Twenty eligible breast cancer patients receiving taxane chemotherapy treatment were recruited and randomly divided into verum acupuncture and sham acupuncture groups. Each group received 15 treatments over 9 weeks. Quantitative tactile detection thresholds were measured.The between-group comparison of SWM revealed that the verum acupuncture group had more improvement of touch perception thresholds compared to the sham acupuncture group. The average pain severity in the BPI-SF of the verum acupuncture group was significantly lower than that of the sham acupuncture group. The results suggest that acupuncture can alleviate the neuropathic pain of CIPN and improve touch perception thresholds.

results suggest that a single acupuncture treatment may not be sufficient in attenuating diabetic neuropathy

Conclusion

The pain of neuropathy does not have to be inconsolable.

We have options, we just need to let our patients know about them…

and stay the course.

Let's Connect

Megan@NursingBeyondtheJob.com

or

LinkedIn: Megan Filoramo

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Image References

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