Strategies to Manage Neuropathy after Transplant

Celebrating a Second Chance at Life Survivorship Symposium

April 27 – May 3, 2024

Kelsey Barrell MD
Assistant Professor in the Division of Neuromuscular Medicine, University of Utah

Introduction

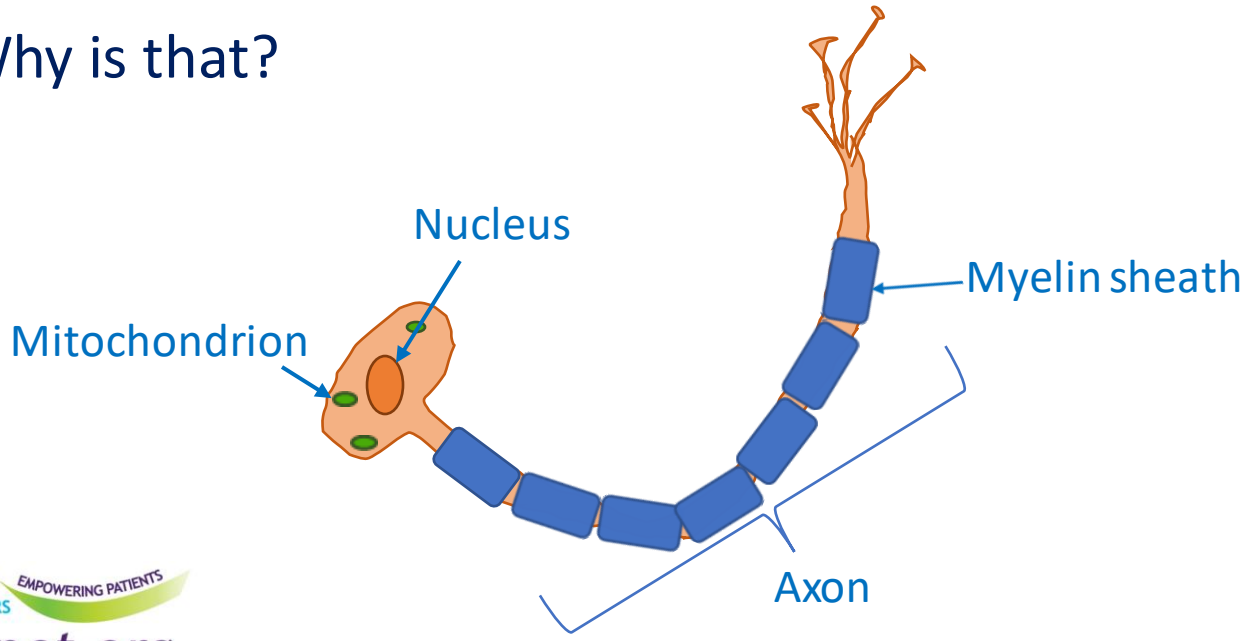
- What is peripheral neuropathy?
- What are the different types of neuropathy experienced post-transplant?
- Common symptoms of peripheral and autonomic neuropathy
- Causes of neuropathy during/after transplant
- How neuropathies are diagnosed
- Therapies to help manage symptoms
- Which providers manage neuropathy and how to find one

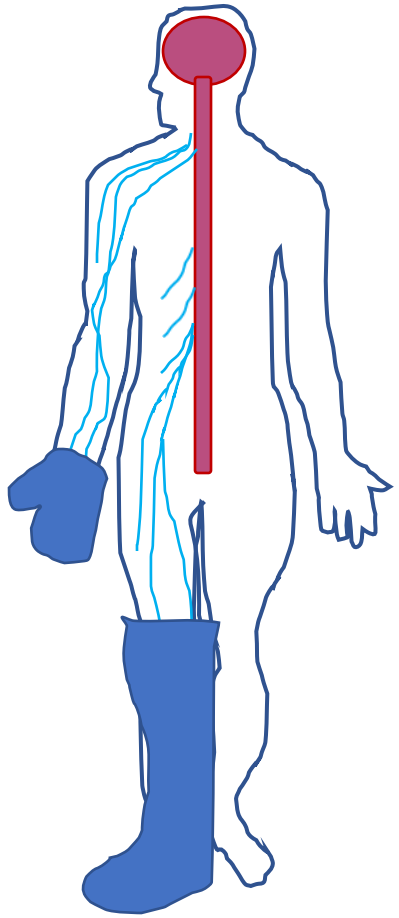
Neuropathy: Definition

- Damage to the peripheral nerves
- Typically affects the longest nerves first

  ie. “stocking glove pattern”

  - Why is that?



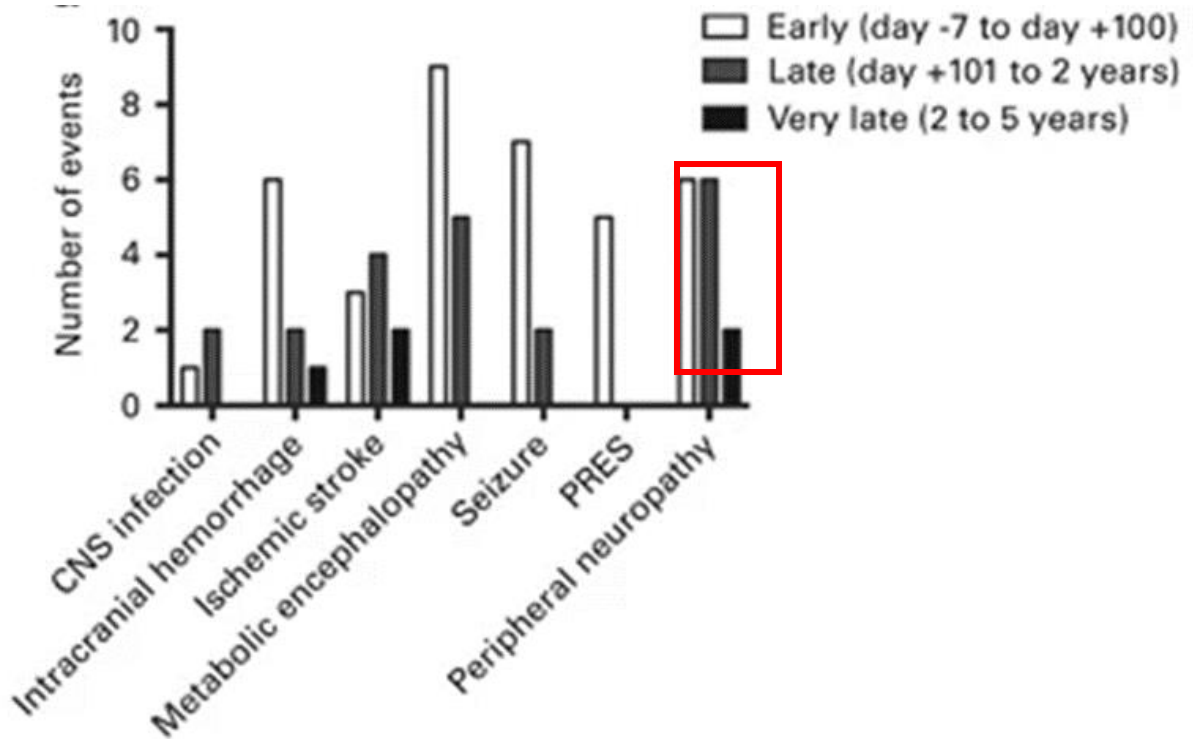


The Different Types of Neuropathy

- Peripheral neuropathy
- Autonomic neuropathy
- Mononeuropathy
- Plexopathy
- Optic neuropathy

Peripheral Neuropathy

- **Symptoms**: numbness/tingling/burning starting in toes +/- imbalance & weaknes
- Rare in stem cell transplant (1-5%)
- Most patients have a mild sensory predominant form
  - Rarely (~0.4%), patients have an immune mediated severe form with weakness



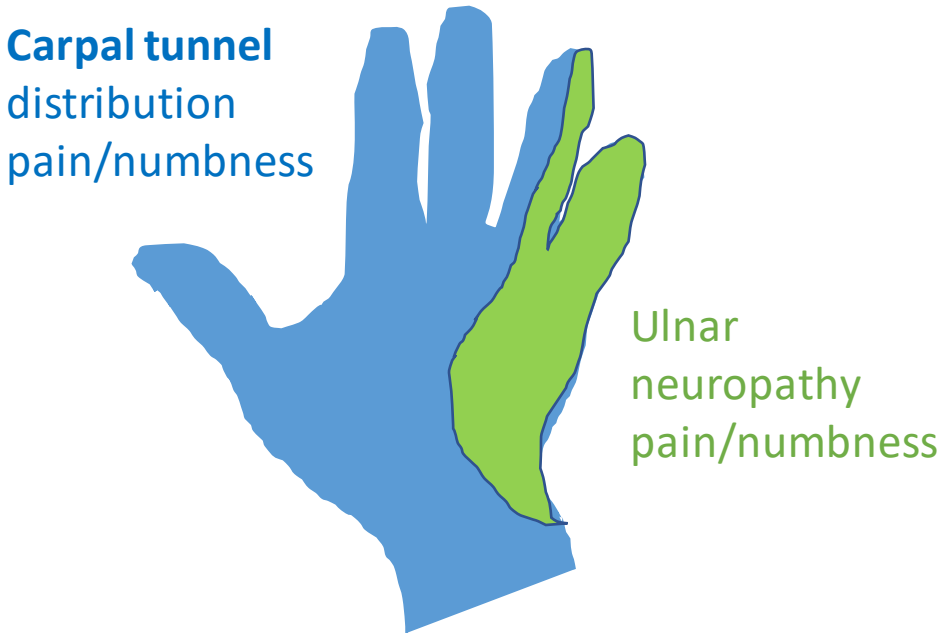
Dowling, 2018
Ruzhansky, 2015

Autonomic Neuropathy

- Nerves that control involuntary bodily functions
  - Blood pressure and heart rate regulation
  - Bowel and bladder function
  - Sexual function
  - Visual and sweating function
- Rare after HSCT
- *Can occur in setting of a plasma cell disorders (AL amyloidosis>multiple myeloma) vs chemotherapy

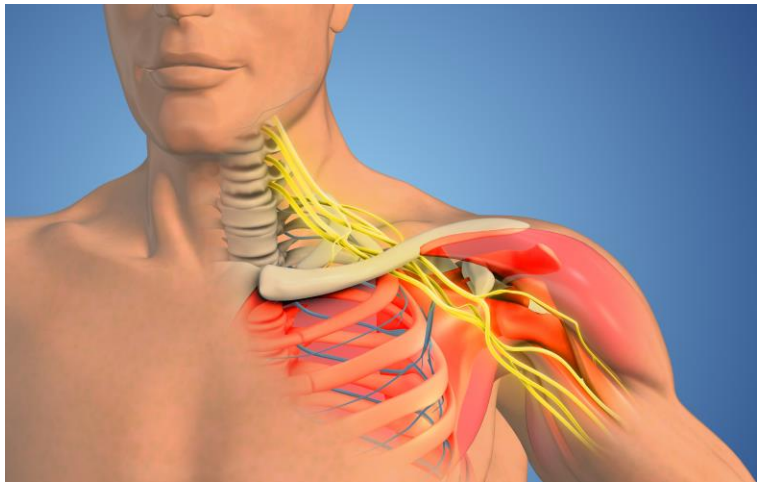
Mononeuropathies

- Mono = when a single nerve is injured
  - Usually due to compression
- Carpal tunnel syndrome is the #1 common form
- Ulnar neuropathy #2 common form
- Causes episodic focal numbness/tingling, worse at night or with activity
- Good treatment options (more later)



Plexopathy

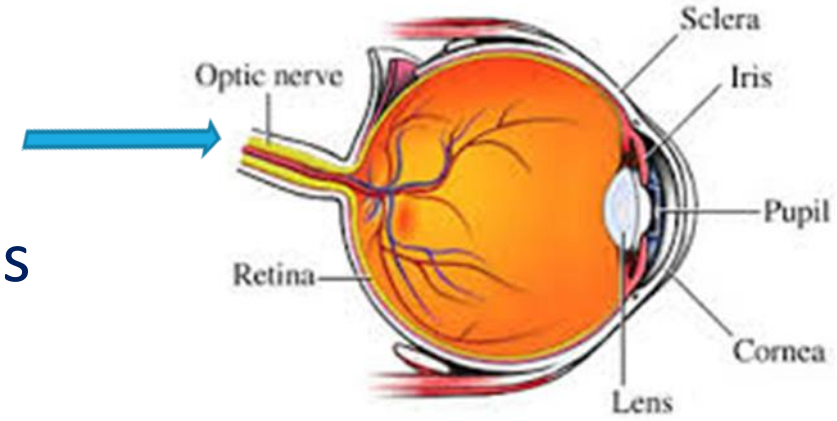
- Inflammation of a plexus (network) of nerves
  - Brachial plexus: upper arm
  - Lumbosacral plexus: pelvis
- Occurs earlier (<6 months) after transplant
- Symptoms: pain followed by weakness and numbness
- Theory: this represents an abnormal immune system
- Rare: 0.3-1% have immune neuropathies



Ren, 2019; Li, 2016

Optic Neuropathy

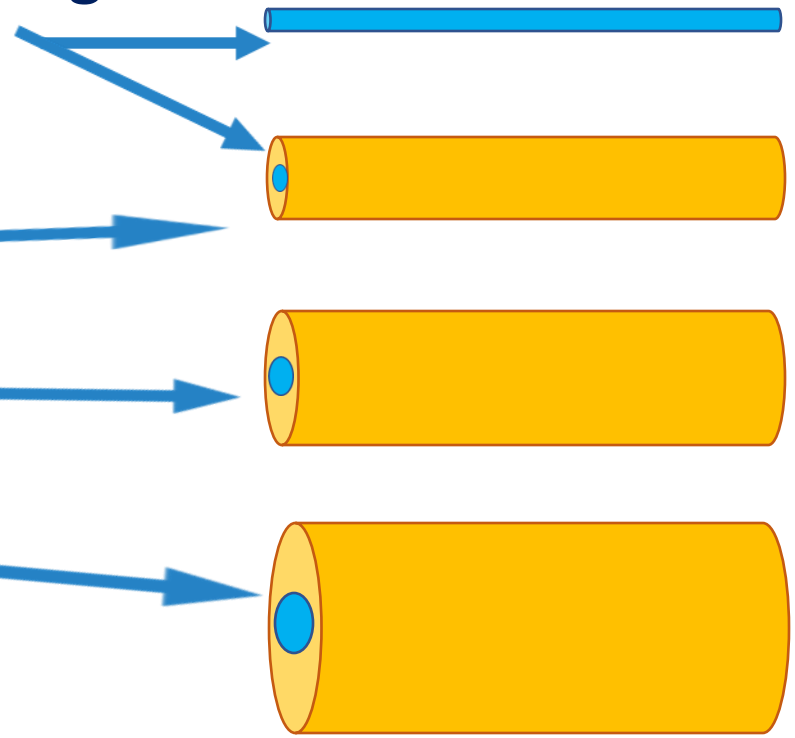
- Damage to the optic nerve (carries visual information from eye to brain)
- Most commonly due to treatment (tacrolimus or cyclosporine), rarely as complication of transplant
- Symptoms:
  - eye pain
  - reduced color vision
  - reduced vision



Symptoms of Peripheral Neuropathy

- **Small fiber neuropathy**: pain, burning, tingling
  - (more common, early in course)
- **Autonomic neuropathy**
- **Large fiber neuropathy**: numbness
- **Motor neuropathy**: weakness

<u>Often a combination</u>



Symptoms of Autonomic Neuropathy

"Fight or flight, rest and digest"

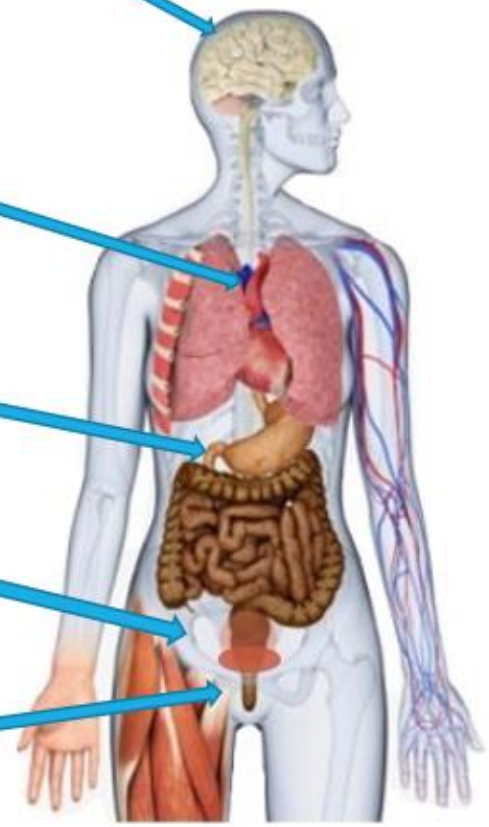
Decreased sweating
Difficulty adjusting to the dark

Lightheadedness with standing (orthostatic hypotension)

Digestive issues (diarrhea, constipation, poor appetite)

Urinary issues (retention, frequency, urgency)

Sexual dysfunction



http://animalia-life.club/animalia-view.html

Symptoms of Autonomic Neuropathy

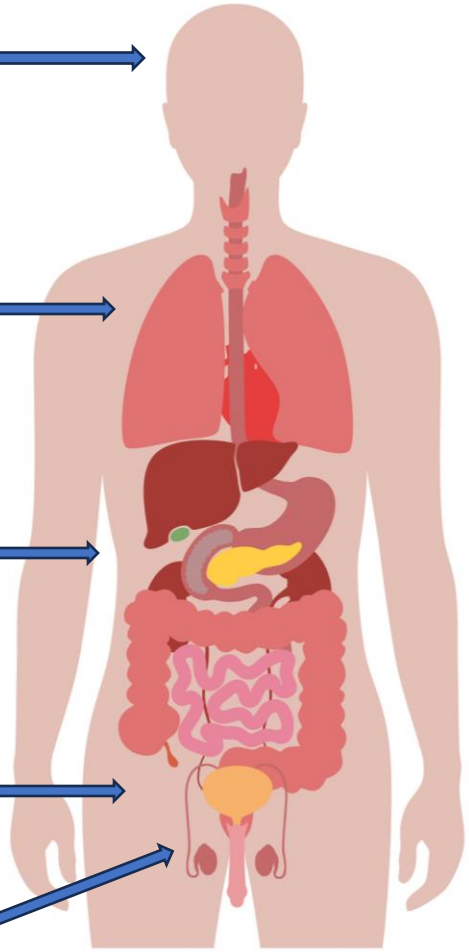
Decreased sweating
Difficulty adjusting to the dark

Lightheadedness with standing (orthostatic hypertension)

Digestive issues (diarrhea, constipation, poor appetite

Urinary issues (retention, frequency, urgency

Sexual dysfunction



"Fight or flight, rest and digest"

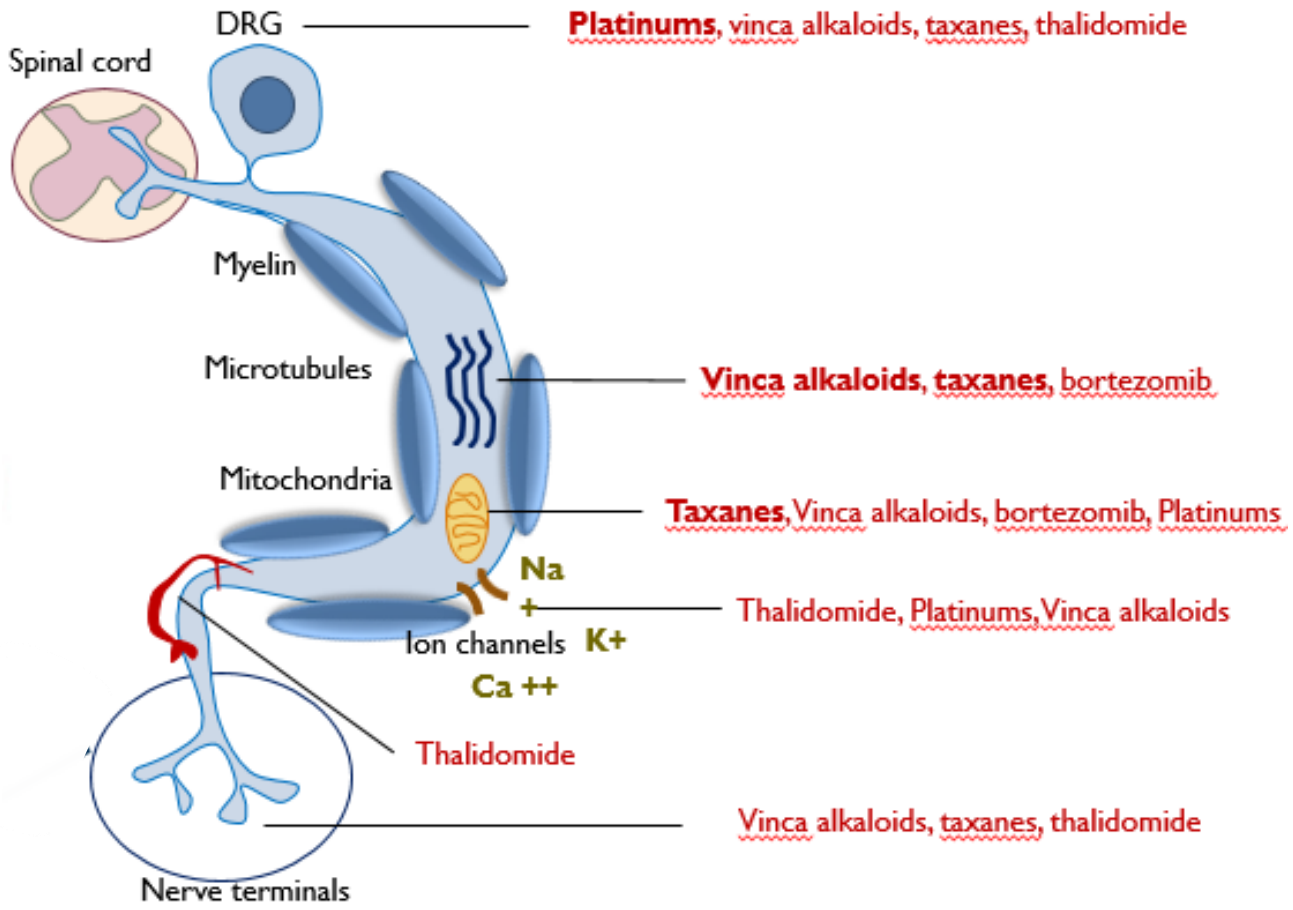
Causes of Neuropathy Before Transplant

- Neuropathy is a common complication of hematologic malignancies
  - Multiple myeloma: 15-20% have neuropathy
  - AL amyloidosis: ~40% have neuropathy
- Neuropathy is also common with chemotherapy

Chemotherapy-Induced Peripheral Neuropathy

- Bortezomib (Velcade): 35-50% develop neuropathy
  - Usually occurs within the first few courses, plateau ~ cycle 5
  - Painful!!!
- Thalidomide: 23-50% reported neuropathy (less with lenalidomide)
  - More likely to cause weakness and constipation
- Vincristine: 30-40% develop neuropathy
  - Sensory and motor neuropathy
  - 1/3 with autonomic neuropathy

Mechanisms Behind Chemotherapy-Induced Neurotoxicity



CA CANCER J CLIN 2013;63:419–437

Causes of Neuropathy During Transplant

- Usually related to immune-mediated neuropathies
  - The immune system reconstituting itself after transplant (immune dysregulation)
- Rare (0.36 – 1.04%)
  - Graft vs host disease is a risk factor as is CMV viral infection and unrelated donors
- Can affect the plexus (network of nerves), a spinal nerve root, a single nerve or multiple nerves.
- Treatment:
  - immune suppressants (steroids)
  - immune modulators (IVIG and plasma exchange)

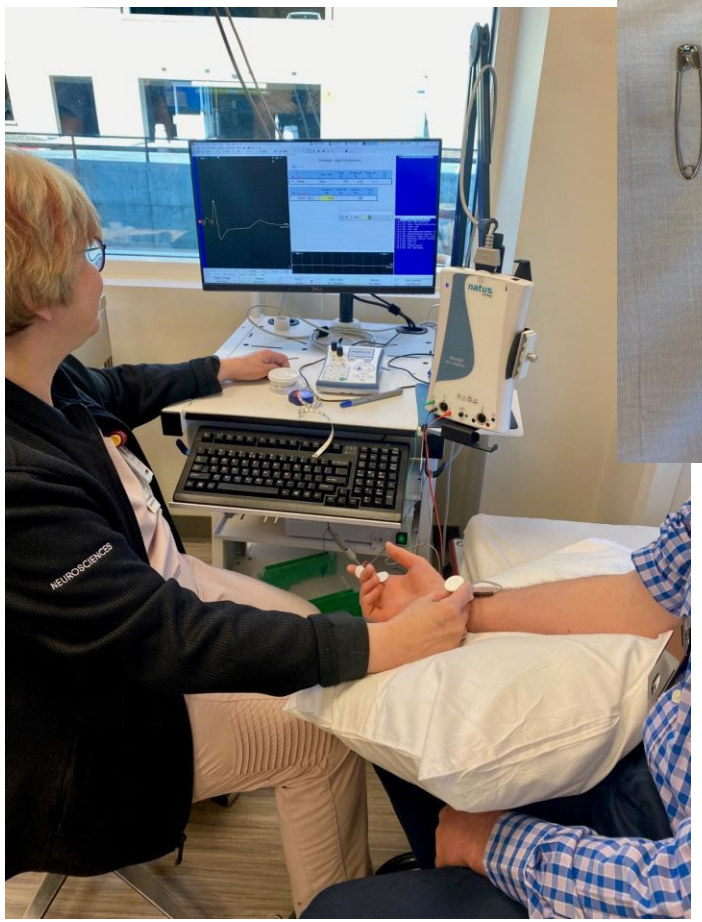
Mohyuddin 2016
Ren 2019

Causes of Neuropathy After Transplant

- Chronic graft vs host disease
  - <1% immune neuropathies
  - 16+ % muscle cramps
- Immune suppressant related:
  - Tacrolimus & cyclosporine- Optic neuropathy
  - TNF alpha (etanercept, infliximab, adalimumab)- immune neuropathies or cranial neuropathies
  - Prednisone- muscle weakness

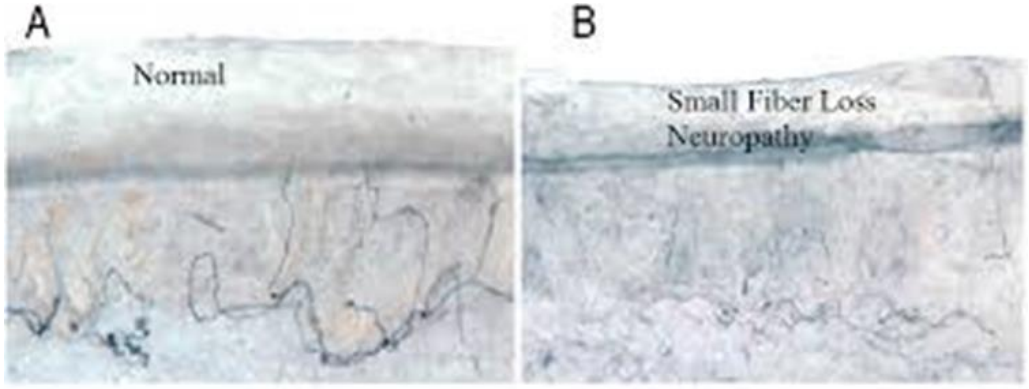
Diagnosis (Basic)

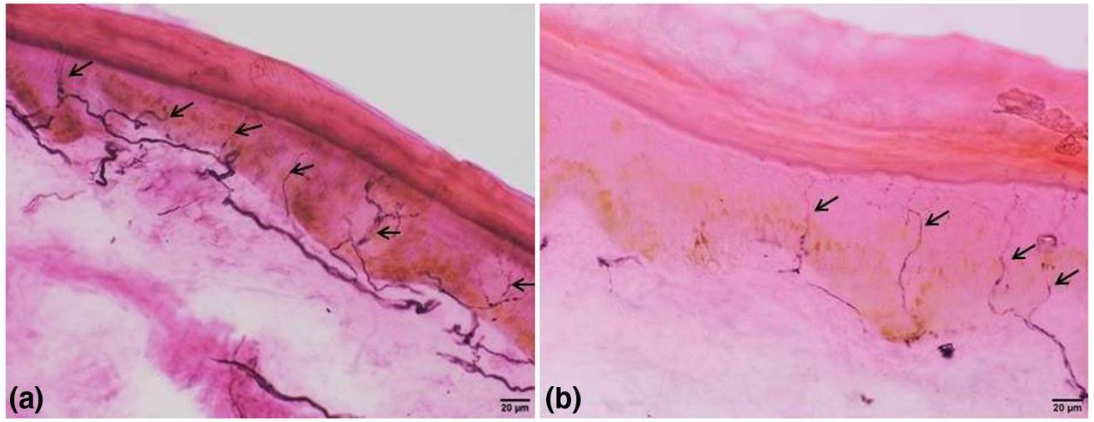
- Neurologic exam:
  - Check pinprick, fine touch, vibration and position sensation as well as reflexes, strength and balance
- Nerve conduction study/EMG
  - Electrical study measuring nerve function
  - Can be normal early on in course



Diagnosis continued

- Skin biopsy:
  - Small section of skin from three placed on the leg
  - Measure density of the small nerve fibers in the skin
- Laboratory evaluation:
  - Rule out factors which increase risk of neuropathy:
    - Diabetes, vitamin B12 deficiency, high cholesterol, alcohol

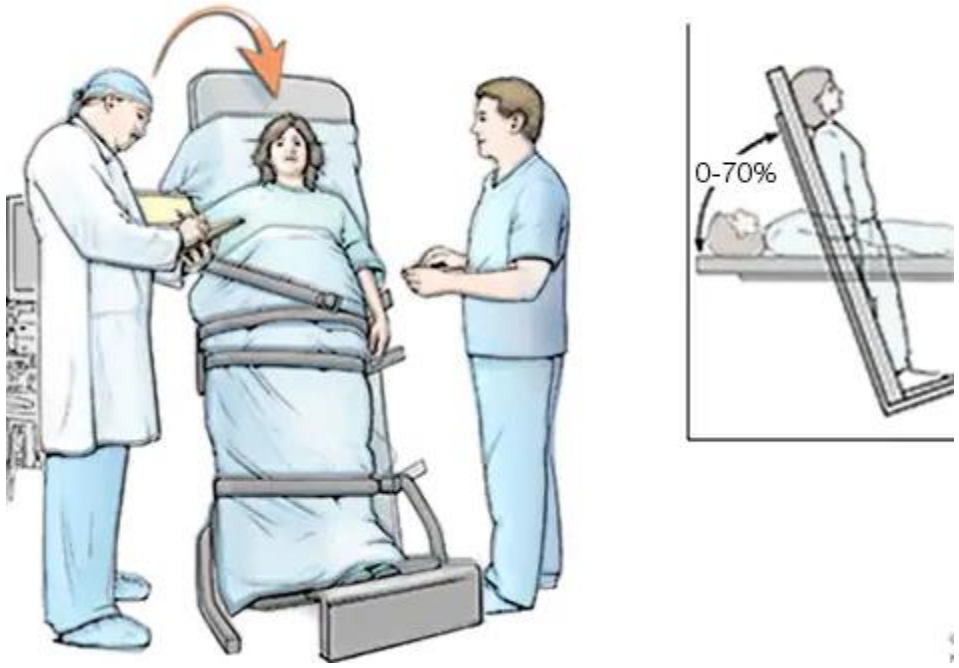




***IF a neuropathy progresses AFTER chemotherapy is stopped, look for common risk factors**

Diagnosing Autonomic Neuropathy

- Usually based on typical clinical history:
  - Lightheadedness with standing (orthostatic hypotension)
  - Gastrointestinal: early satiety, bloating, constipation or diarrhea,
  - Urinary/sexual: urinary frequency or incontinence, erectile dysfunction
- Autonomic lab testing
  - Checks blood pressure and heart rate during a tilt table test
  - Measures heart rate variability & quantifies



mayoclinic.org/tests-procedures/tilt-table-test/about/pac-20395124

Therapy Options: The Two Tenets

- Targeting/preventing the underlying disease course
  - Treating the underlying cancer: multiple myeloma/amyloidosis
  - Switching or decreasing chemotherapy
  - Treating the risk factors: diabetes, obesity, high cholesterol or low vitamin B12
  - Exercise! (more in a second)
- Targeting symptoms –especially painful features
  - Topical vs oral vs complementary treatments

Exercise- What's the Evidence?

- Well established in diabetic/pre-diabetic patients:

- In chemotherapy-induced neuropathy, 2 rodent studies show similar results

Singleton, 2014; Kleckner 2021, Park 2015

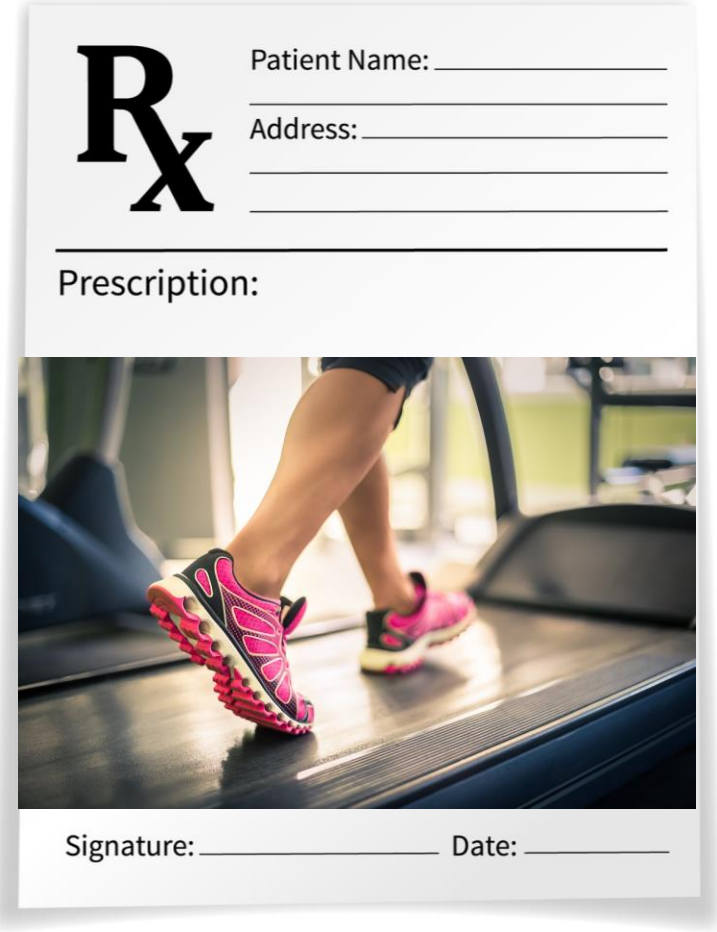
Exercise: Why Do It

- A recent systematic review found 16 controlled trials studying exercise, concluding:
  - Exercise can improve quality of life
  - Exercise can improve physical function (balance and strength)
  - Exercise can improve neuropathic pain
  - There are no major risks/side effects with exercise

Guo, 2023

Exercise Prescription

- Regular moderate aerobic fitness: **30 minutes 5 times a week**
  - Biking, walking, swimming, rowing, stairstepper etc
- Exercise to the point where you can't sing a song
- Overtime, you'll be able to push it a little more
  - As your fitness level increases, you can go further in the same amount of time
- Adding strength training and balance exercise= icing on the cake



Treatment: The American Society of Clinical Oncology (ASCO) Practice Guidelines (2020)

- **Duloxetine** to help with painful symptoms
- Outside the context of a clinical trial, no recommendations made on:
  - Acupuncture
  - Cryotherapy (frozen gloves and socks)
  - Compression therapy (tight glove)
  - Ganglioside-monosialic acid (fatty acid)

Loprinzi, 2020

Treatment: ASCO practice guidelines (2020) cont'd

- Clinicians should NOT offer the following for prevention:
  - All-trans retinoic acid
  - Calcium
  - Magnesium
  - L-carnosine
  - Glutamate
  - glutathione
  - Goshajinkigan
  - N-acetylcysteine
  - Omega-3 fatty acids
  - Vitamin B
  - Vitamin E

Loprinzi, 2020

Topical Treatment

- Over the counter:
  - Lidocaine 4-5% ointment/lidocaine patch
  - Salonpas
  - Aspercream
  - Biofreeze
  - Capsaicin- active ingredient of chili
  - CBD ointment/tincture: legality varies by state (if it has THC)

Prescription: compounded ointment

- P4 cream:
  - Ketamine
  - Gabapentin
  - Amitriptyline
  - Baclofen
  - Clonidine
  - Nifedipine
  - Tetracaine

Prescription treatments – Equal Efficacy!

- Gabapentin (Neurontin)
  - Low cost; side effects of mild sedation, possible swelling
- Amitriptyline (Elavil)
  - Low cost & helps insomnia/depression; side effect: dry mouth & constipation
- Pregabalin (Lyrica) = next generation of gabapentin
  - Less sedation compared to gabapentin but 10x more expensive
- **Duloxetine (Cymbalta)** Best studied in chemotherapy induced neuropathy
  - Can help with chronic pain and depression, but more expensive

Non-Pharmacological Options

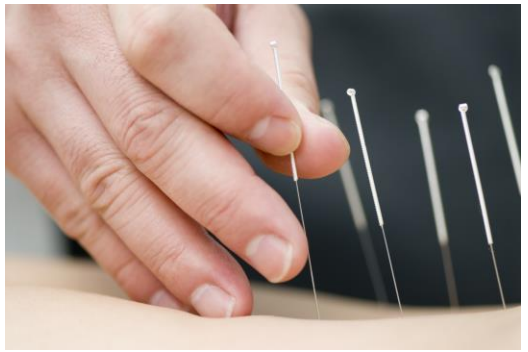
Supplements

Complementary Medicine

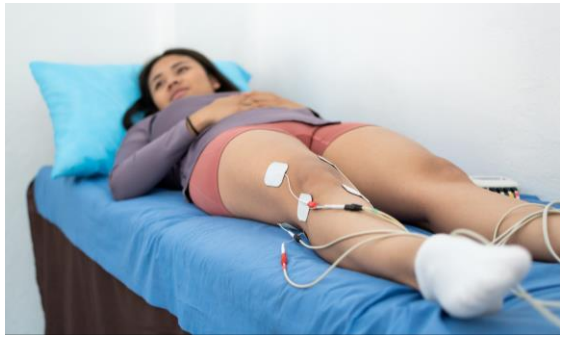
Physical Therapy

Meditation

Massage



Acupuncture

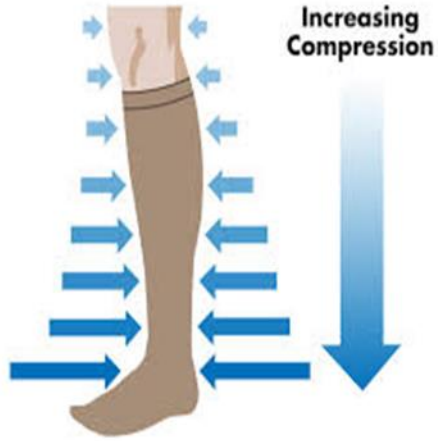


Electrotherapy

Brani 2016, Zhang 2023

Treatment of Autonomic Neuropathy Orthostatic Hypotension

- Compression stockings (At least 15-20mmHg)
- Abdominal binders
- Optimizing hydration (2-3 Liters/day) –if OK from a cardiac standpoint
- Optimizing salt intake (3+ grams per day) –if OK from a cardiac standpoint
- Raise head of bed by 10-20 degrees
- Medications: midodrine or florinef



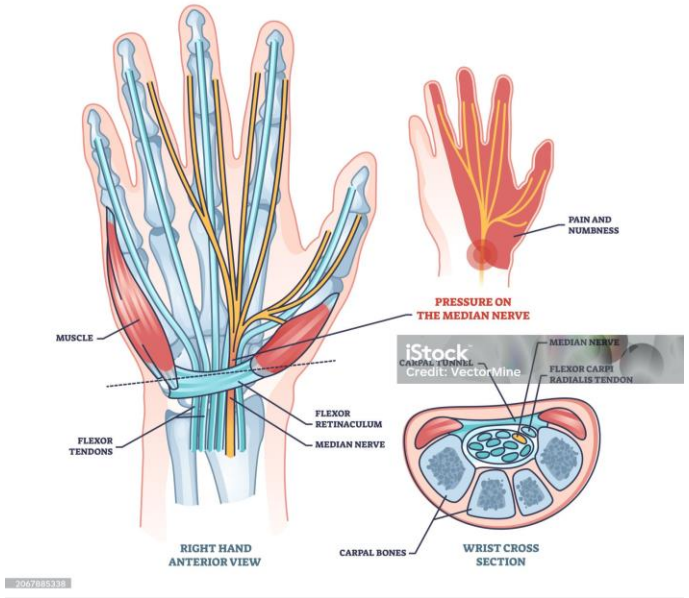
Treatment of Autonomic Neuropathy Gastroparesis, Incontinence, Erectile Dysfunction

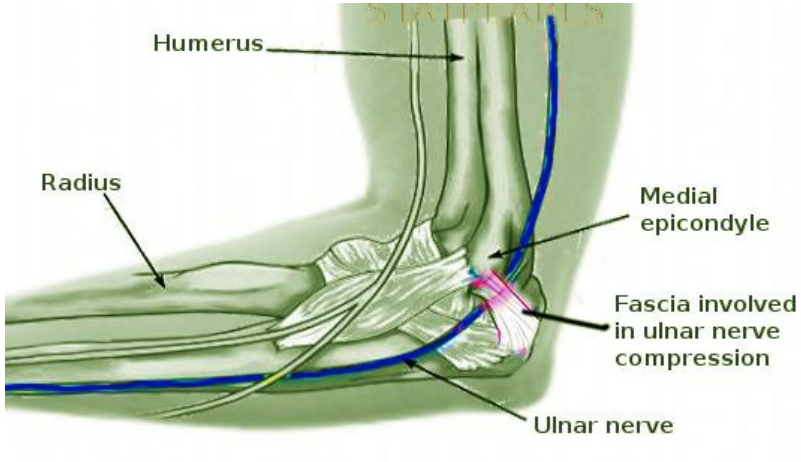
- Gastroparesis: delayed emptying due to loss of normal gut motility
  - Dietary modifications: small particle, low fat, regular meals, +/-liquid nutrition and increase hydration
  - Pro-kinetic meds (Reglan 15 min before a meal)
- Urinary Frequency/Urgency/Incontinence
  - Medications: terazosin, oxybutynin etc
- Erectile dysfunction
  - Medications: Viagra, Cialis etc.

Camilleri M. 2022

Treatment of Mononeuropathies

- Carpal tunnel syndrome
  - Neutral wrist splint (nightly x 6 weeks)
  - Steroid injections or carpal tunnel release
- Cubital tunnel (ulnar neuropathy)
  - Elbow brace (nightly x 6 weeks)
  - Ulnar release at the elbow





Who you gonna call?

- Talk to your hematologist/oncologist first
  - Many feel comfortable prescribing medications for nerve pain
- A neurologist can help confirm and manage neuropathy IF needed
  - If there is diagnostic uncertainty
  - Symptoms are severe
  - Neuropathic pain is not under control with 1st line agents
  - *This generally would just require a referral from your primary provider

References

Argyriou AA et al. Chemotherapy-induced peripheral neurotoxicity: management informed by pharmacogenetics. Nature Reviews Neurology 2017;13:492-504

Boland EG, Selvarajah D, Hunter M, Ezaydi Y, Tesfaye S, Ahmedzai SH, Snowden JA, Wilkinson ID. Central pain processing in chronic chemotherapy-induced peripheral neuropathy: a functional magnetic resonance imaging study. PLoS ONE 2014; 9(5):e96474.

Brami C et al. Natural products and complementary therapies for chemotherapy-induced peripheral neuropathy: a systematic review. Crit Rev Oncol Hematology 2016;98:325-334.

Camilleri M et al. ACG Clinical guidelines: gastroparesis. The American Journal of Gastroenterology 2022;117(8):1197-1220.

Dowling et al. Neurologic complications after allogeneic hematopoietic stem cell transplantation: risk factors and impact. Bone Marrow Transplant 2018;53:199-206.

Guo S et al. Effects of exercise on chemotherapy-induced peripheral neuropathy in cancer patients: a systematic review and meta-analysis. Journal of Cancer Survivorship 2023;17:318-331.

Li, Z et al. Immune-mediated complications after hematopoietic stem cell transplantation. Biology of Blood and Marrow Transplantation 2016:22;1368-1375.

Loprinzi et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. Journal of Clinical Oncology 2021;9:385-450

Kleckner IR et al. Systematic review of exercise for prevention and management of chemotherapy-induced peripheral neuropathy. Diagnosis, Management and Emerging Strategies for chemotherapy-Induced Neuropathy 2021; 183-241.

References

Kraus P.D. et al. Muscle cramps and neuropathies in patients with allogeneic hematopoietic stem cell transplantation and graft-versus-host disease.

Mohyuddin G.R. et al. Immune-Mediated Neuropathies following Autologous Stem Cell Transplantation for Multiple Myeloma: case series and Review of the literature. Acta Haematologica 2017;137:86-88.

Nurmikko T.J. et al. Sativex successfully treats neuropathic pain characterized by allodynia: a randomized, double-blind, placebo-controlled clinical trial. PAIN 2007 133;210—220.

Ren X et al. Incidence, risk factors, and outcomes of immune-mediated neuropathies following haploidentical hematopoietic stem cell transplantation. Biology of Blood and Marrow Transplantation 2019;25 (8)1629-1636.

Ruggiu M. Case report: central nervous system involvement of human graft versus host disease- Report of 7 cases and a review of literature. Medicine 2017;96:42.

Ruzhansky KM et al. Neuromuscular complications of hematopoietic stem cell transplantation, Muscle and nerve 2015;52(4):480-487.

Seretny M et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. PAIN 155 (2014) 2461-2470

Singleton et al. Exercise increases cutaneous nerve density in diabetic patients without neuropathy. Annals of clinical and Translational Neurology, 2014;1(10);844-849.

Zhang et al. Non-pharmacological therapy for chemotherapy-induced peripheral neurotoxicity: a network meta-analysis of randomized controlled trials. BMC Neurology 2023;23(433)

Questions?

Kelsey Barrell MD
Assistant Professor in the Division of Neuromuscular Medicine, University of Utah

Let Us Know How We Can Help You

Visit our website: bmtinfonet.org

Email us: help@bmtinfonet.org

Phone: 888-597-7674 or 847-433-3313

Find us on:

Facebook, facebook.com/bmtinfonet

X, twitter.com/BMTInfoNet