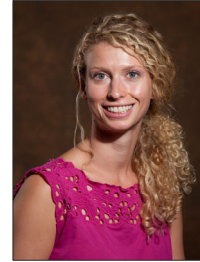




Managing Neuropathy after Transplant

Celebrating a Second Chance at Life Survivorship Symposium

April 17- 23, 2021



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University of Utah Health

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MANAGING NEUROPATHY AFTER TRANSPLANT

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INTRODUCTION

What is peripheral neuropathy?

Symptoms associated with peripheral neuropathy

Other forms of neuropathy

Diagnostic tools

Risk factors

Treatment related causes of neuropathy

Treatment options

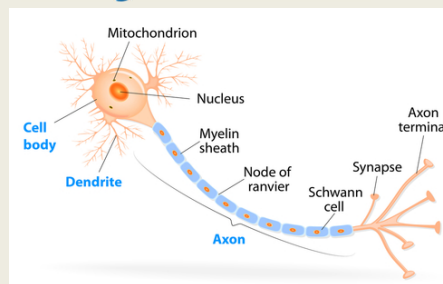


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PERIPHERAL NEUROPATHY: DEFINITION

- Damage to the peripheral nerves
- Typically affects the longest nerves first “stocking-glove” neuropathy

→ **Why is that?**



<http://www.richardsonthebrain.com/neuron-structures/>



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SYMPTOMS

- Symptoms depend on which type of nerves are affected
 - Smallest fibers (C and A-delta): Pain, temperature
 - pain, burning, tingling, pins-needles, shocks,
 - Most common, esp. **early** in course
 - Autonomic nerves (A-delta):
 - Orthostatic hypotension, GI/GU and sexual dysfunction
 - Large fiber sensory nerves (A-beta): touch, pressure
 - Numbness, imbalance, difficulty with vibration sensation
 - Motor nerves (A-alpha): proprioception, motor
 - Weakness, muscle atrophy (later on)
 - **Often a combination of above**

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AUTONOMIC NEUROPATHY

- Nerves that control **involuntary bodily functions**:

Decreased sweating
 Difficulty adjusting to the dark

Lightheadedness with standing
 (orthostatic hypotension)

Digestive issues (diarrhea,
 constipation, poor appetite)

Urinary issues (retention,
 frequency, urgency)

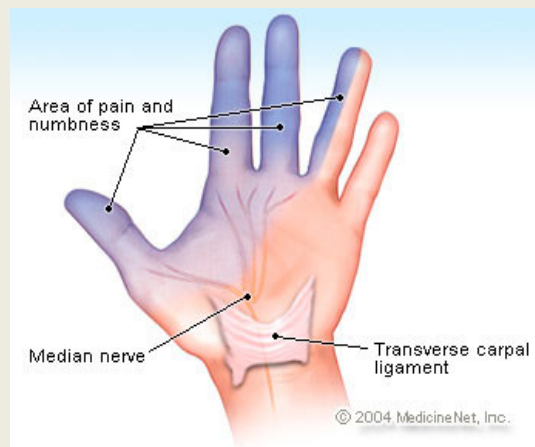
Sexual dysfunction

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

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CARPAL TUNNEL SYNDROME

- Compression of the median nerve at the wrist
- Numbness on palmar thumb/index and middle finger
- Action induced/episodic numbness, pain and grip weakness
- Good treatment options



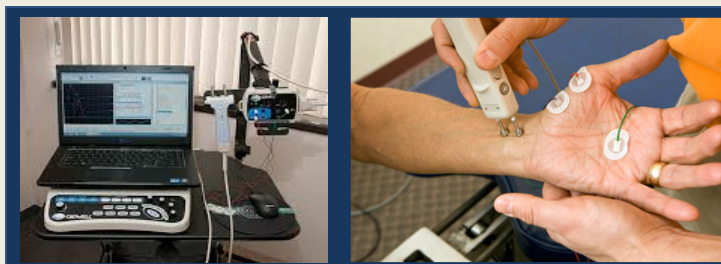
Carpal Tunnel Syndrome



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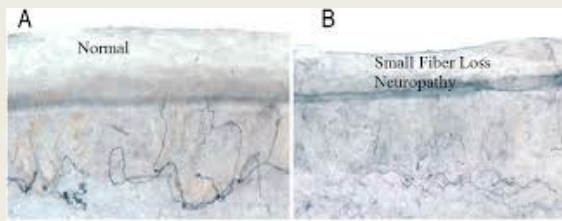
DIAGNOSIS

- **Neurologic exam** (done in clinic):
 - 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



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DIAGNOSIS



- Skin biopsy:
 - Small section of skin from three leg sites
 - Measure density of the small nerve fibers in the skin (epidermis)
- Laboratory evaluation: rule out factors which increase risk of neuropathy
 - Diabetes, vitamin B12 deficiency, high cholesterol, amyloidosis



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AUTONOMIC NEUROPATHY: DIAGNOSIS

- Usually based on typical clinical history: (underdiagnosed)
- Autonomic testing:
 - Orthostatic vital signs
 - Autonomic lab:
 - Heart rate variability
 - Quantitative sweating
 - Tilt table test



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QUALITY OF LIFE


Considerable impact on physical and psychological wellbeing

- Poor balance →
 - Loss of recreation
 - Loss of independence
 - Loss of employment
- Burden of chronic pain →
 - Depression/Anxiety/Insomnia/Isolation

Underestimated by clinicians

Starting to gain traction in clinical trials...

- With improved treatment and survival, researchers are more often including measures of quality of life




Sonneveld, Leukemia 2013

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RISK FACTORS

- Personal Risk Factors:
 - Pre-existing neuropathy
 - Sensory changes (during chemo)
 - Smoking
 - Abnormal kidney function
 - Obesity
- Acquired Risk Factors:
 - Diabetes
 - Vitamin B12 deficiency
 - High cholesterol



Serethy, PAIN 2014

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TREATMENT-RELATED CAUSES OF NEUROPATHY



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WHEN CAN NEUROPATHY OCCUR?

- Initially, from the underlying cancer
 - Multiple myeloma: 15-20% have neuropathy
- Chemotherapy
- During Transplant
- Graft vs Host Disease



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CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

- **Bortezomib (Velcade)**
 - Usually occurs within the first few courses, plateau ~ cycle 5
 - Common: 35-50% of patients
 - Painful
- **Thalidomide**
 - Common: 23-50% reported
 - More likely to cause weakness and constipation
- **Lenalidomide**
 - Less neurotoxic
- **Vincristine?**
 - 30-40% Sensory and motor neuropathy, 1/3 with autonomic neuropathy



Argyriou Blood 2008

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TRANSPLANT-RELATED NEUROPATHY

- Immune-mediated neuropathies = complication of auto-HSCT
 - Rare (0.36%) in a study of 3,305 patients
 - Varied presentation
 - Focal severe neuropathies
 - Eg. facial nerve, ocular nerve
 - Plexopathy (disorder affecting a network of nerves as they extend through the arm or leg)



<https://palmitoylethanolamideblog.com/plexopathy/>

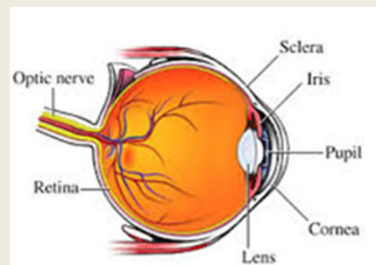


Mohyuddin, Acta haematologica 2016

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AFTER TRANSPLANT: IMMUNE SUPPRESSANTS

- **Tacrolimus** and cyclosporine- optic neuropathy
- **Sirolimus** –mostly just in combination
- **Prednisone**- muscle weakness
- **TNF-alpha** (etanercept, infliximab & adalimumab): Guillain-Barre syndrome, cranial neuropathies, central demyelination



Ruggiu Medicine, 2017; Kraus, PLOS, 2012

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AFTER THE TRANSPLANT: CHRONIC GVHD

- Peripheral nervous system involvement
 - Immune neuropathies; significant weakness <1%
 - Muscle cramps 16% (but underreported) in chronic GVHD
- Central nervous system involvement
 - Rare



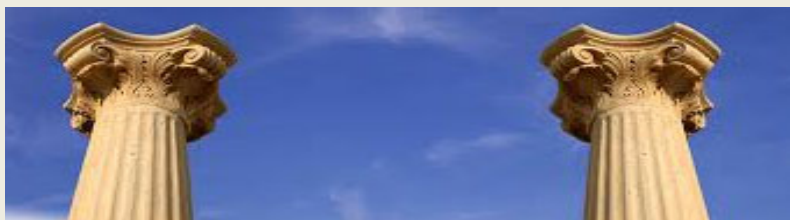
Ruggiu Medicine, 2017; Kraus, PLOS, 2012

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TWO TENETS OF TREATMENT

Target/prevent the underlying disease course

Target symptoms



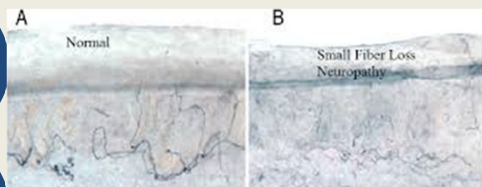
- Treat the multiple myeloma/ POEMS/amyloid
- Treat comorbid risk factors: diabetes, high cholesterol & low vitamin B12
- Exercise

- Topical
- Oral prescriptions
- Alternative/complementary



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EXERCISE AND NEUROPATHY WHAT'S THE EVIDENCE?



Initial nerve fiber density in all patients



Standard Counseling (40)

Exercise (60)

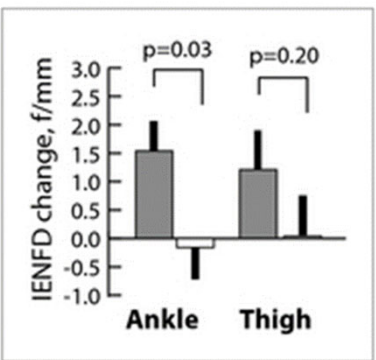
After 12 months, nerve fiber density repeated



Singleton, ANNALS 2014

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EXERCISE AND NEUROPATHY WHAT'S THE EVIDENCE?



Standard Counseling (40)

Exercise (60)

Singleton, ANNALS




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TOPICAL TREATMENT

- Lidocaine ointment/lidocaine patch
- Capsaicin
 - Active ingredient of chili
- Compounded ointment:
 - P4 cream: (Ketamine, gabapentin, amitriptyline, baclofen, clonidine, nifedipine, tetracaine)
- CBD ointment/tincture – **legality varies by state**
 - Sativex (THC/CBD spray)- UK study found decreased pain and increased sleep
 - Nabilone (oral) –CA study also successful reduction of pain, anxiety, depression

Successful in mice




Nurmikko, Pain 2007; Toth, Pain 2012



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ORAL PRESCRIPTIONS





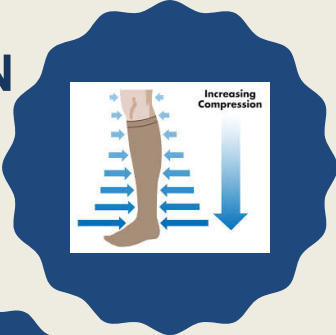
- Gabapentin (Neurontin):**
 - The good: low cost (**\$12-24/mo**), high efficacy
 - The bad: mild sedation “head fog” esp initially, swelling
- Amitriptyline (Elavil) vs Nortriptyline**
 - The good: low cost (**\$4-12/mo**), also helps insomnia and depression
 - The bad: dry mouth, constipation, sedation
- Pregabalin (Lyrica) = next generation of gabapentin**
 - The good: less “head fog”
 - The bad: \$\$\$ (**\$44-400/mo**)
- Duloxetine (Cymbalta)***
 - The good: Also helps with chronic pain and depression
 - The bad: \$\$\$ (**\$60-200/mo**)
- Oxycodone, tramadol** generally 2nd or 3rd line 2/2 SE profile & addiction potential

Callaghan, Ann Intern Med 2014, GoodRx.com

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AUTONOMIC NEUROPATHY: ORTHOSTATIC HYPOTENSION

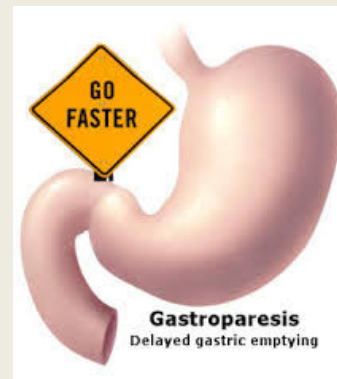
- Treatment:
 - Compression stockings (At least 15-20mmHg)
 - Abdominal binders
 - Optimizing hydration (2-3 Liters/day)
 - Optimizing salt intake (3+ grams per day)
 - Raise head of bed by 10-20 degrees
 - Meds to keep blood pressure from dropping (midodrine and florinef)



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AUTONOMIC NEUROPATHY: OTHER SYMPTOMS

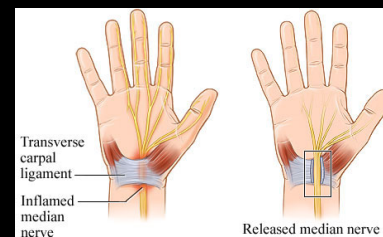
- Gastroparesis: delayed emptying due to loss of normal gut motility
 - Dietary modifications
 - Small, regular meals
 - Low fat, low insoluble fiber
 - Liquid nutrition
 - Avoid carbonated beverages, smoking and alcohol
 - Hydration
 - Prokinetic meds (Reglan 15 min before a meal)
- Urinary Frequency/Urgency/Incontinence
 - Medications: terazosin, oxybutynin etc.
- Erectile dysfunction
 - Medications: Viagra, Cialis etc.



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CARPAL TUNNEL SYNDROME

- Treatment
 - Neutral wrist splint (worn at night)
 - Steroid injections
 - Physical therapy
 - Carpal tunnel release surgery




webMD


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COMPLEMENTARY & ALTERNATIVE MEDICINE




Supplements




Physical therapy


COMPLEMENTARY MEDICINE




Meditation




Massage



Acupuncture



Electrotherapy



Brami, Critical Rev in Onc/Hem 2016; Franconi, Ev based Complementary and Alternative medicine 2013

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THANK YOU



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Questions?

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