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Managing Neuropathy after Transplant

Celebrating a Second Chance at Life Survivorship Symposium

July 11-17, 2020

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Massachusetts General Hospital

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What you need to know about chemotherapy-induced peripheral neuropathy (CIPN)

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Disclosures

- None

Overview

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- Define chemotherapy-induced peripheral neuropathy
- Review risk factors, prevalence and common culprits
- Discuss symptoms
- Review treatment strategies

What is neuropathy?

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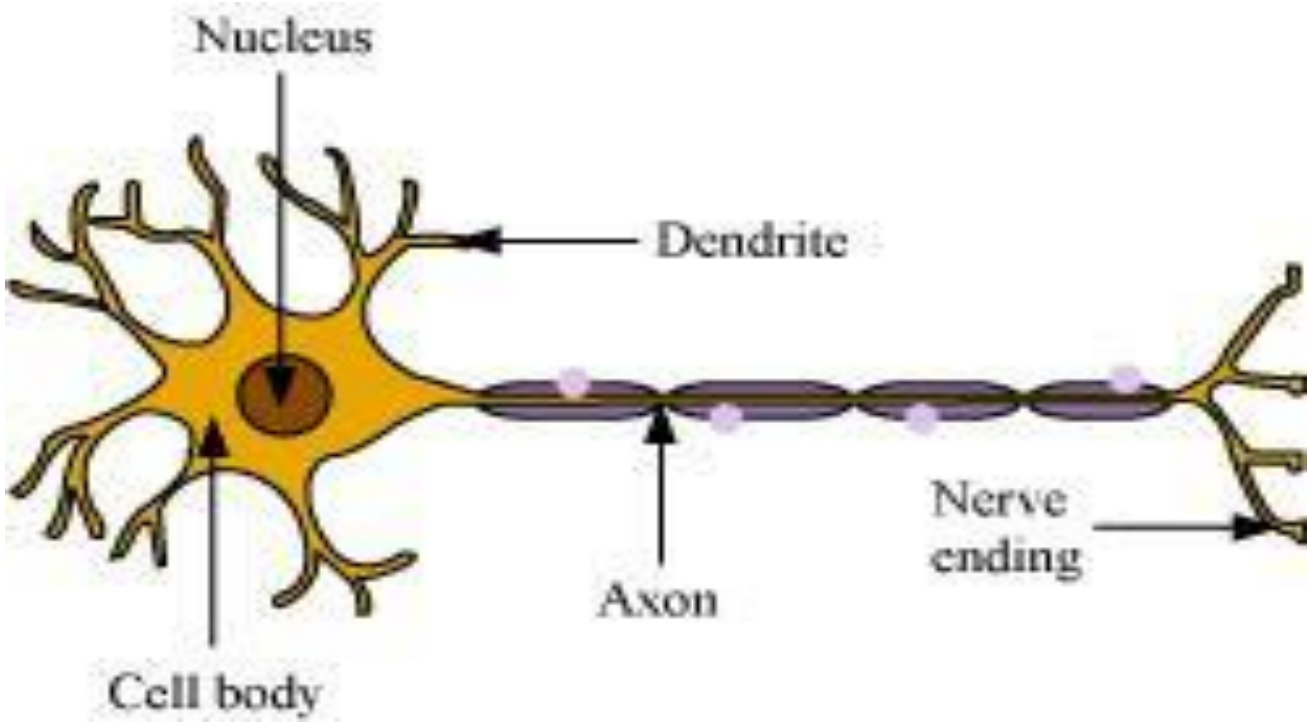
- Damage or dysfunction of peripheral nerves
- Nerves control sensation, movement, and "autonomics"



How common is neuropathy after chemotherapy?

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- At the end of one month: 68.1%
- At the end of 3 months: 60%
- At the end of 6 months: 30%

Seretny, Marta, et al. "Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis."*PAIN*® 155.12 (2014): 2461-2470.

Risk factors

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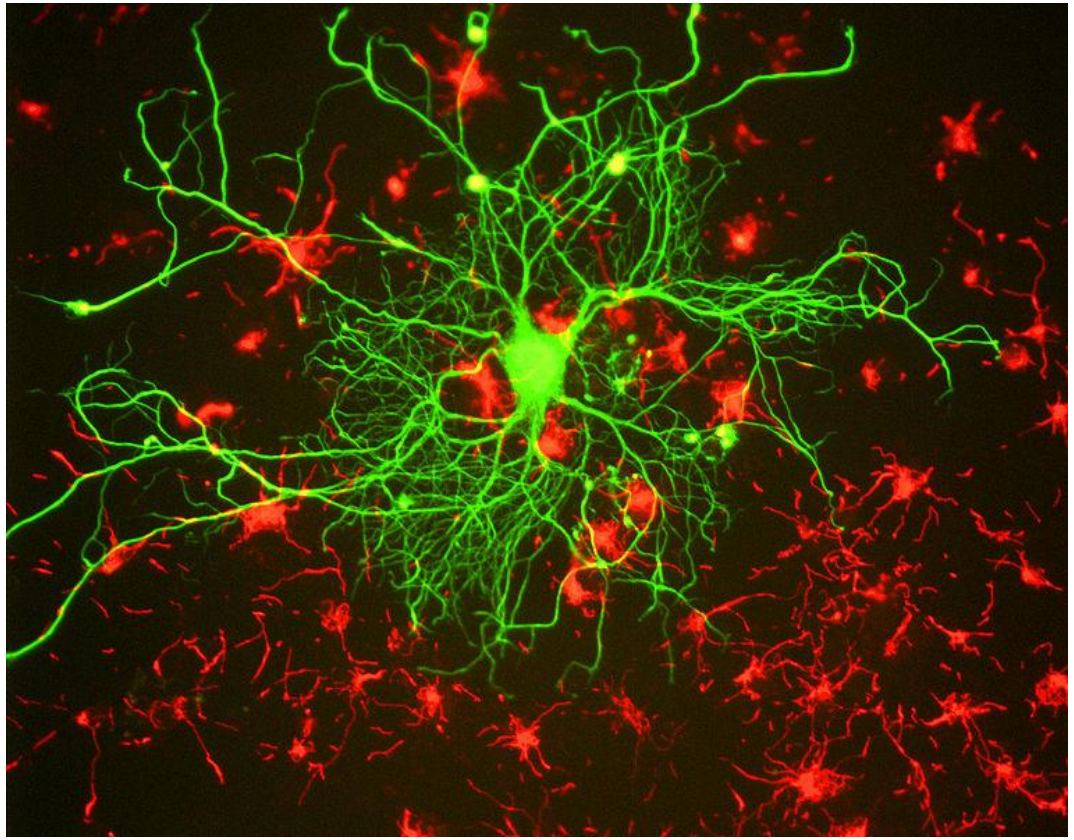
- Risk Factors
  - Baseline neuropathy
  - Age
  - Smoking history
  - Decreased creatinine clearance
  - Sensory changes during chemotherapy



- Seretny, Marta, et al. "Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis."*PAIN*® 155.12 (2014): 2461-2470.
- Han, Yaqin, and Maree T. Smith. "Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN)." *Frontiers in pharmacology* 4 (2013).
- Miltenburg, N. C., and W. Boogerd. "Chemotherapy-induced neuropathy: a comprehensive survey." *Cancer treatment reviews* 40.7 (2014): 872-882.

Symptoms

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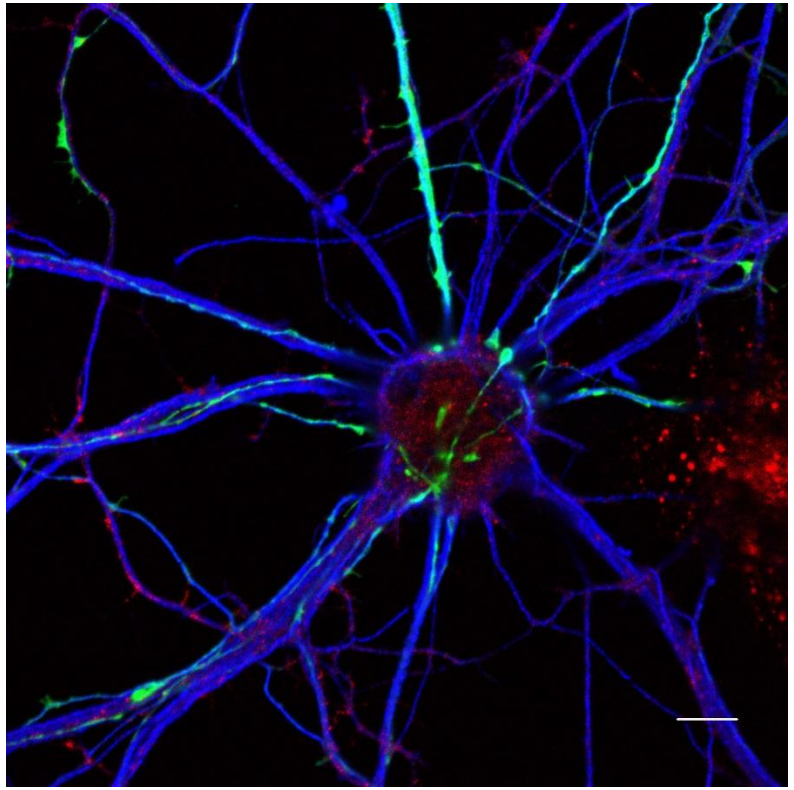
- Acute or Slowly Progressive
- Why are sensory nerves more affected than motor nerves?
  - Cell bodies located in DRG, which is outside of the blood-brain barrier



Symptom profile

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- **<u>Positive</u> and/or <u>Negative</u> symptoms**
- **Positive**
  - Pain (shock, burn, stab, lancing)
  - Dysesthesia, hypersensitivity
  - Tingling
  - Pruritis, cramping
- **Negative**
  - Numbness
  - Impaired proprioception/balance
  - Weakness including foot drop

Detecting neuropathy

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- History
  - Symptoms
  - Functional status
  - Comorbidities
  - Family history
- Exam – check motor, sensory, balance, gait
- NCS/EMG

Diagnosing CIPN

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- Diagnosis of **exclusion -** make sure you are not missing:
  - Diabetes
  - Vitamin deficiencies or toxicities
  - Thyroid issues
  - Less common things

Which drugs cause neuropathy?

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- Vincristine
- Platinum agents
- Bortezomib
- Thalidomide
- Taxoids (i.e. Taxol/docetaxel)
- Suramin
- Others

Who manages neuropathy?

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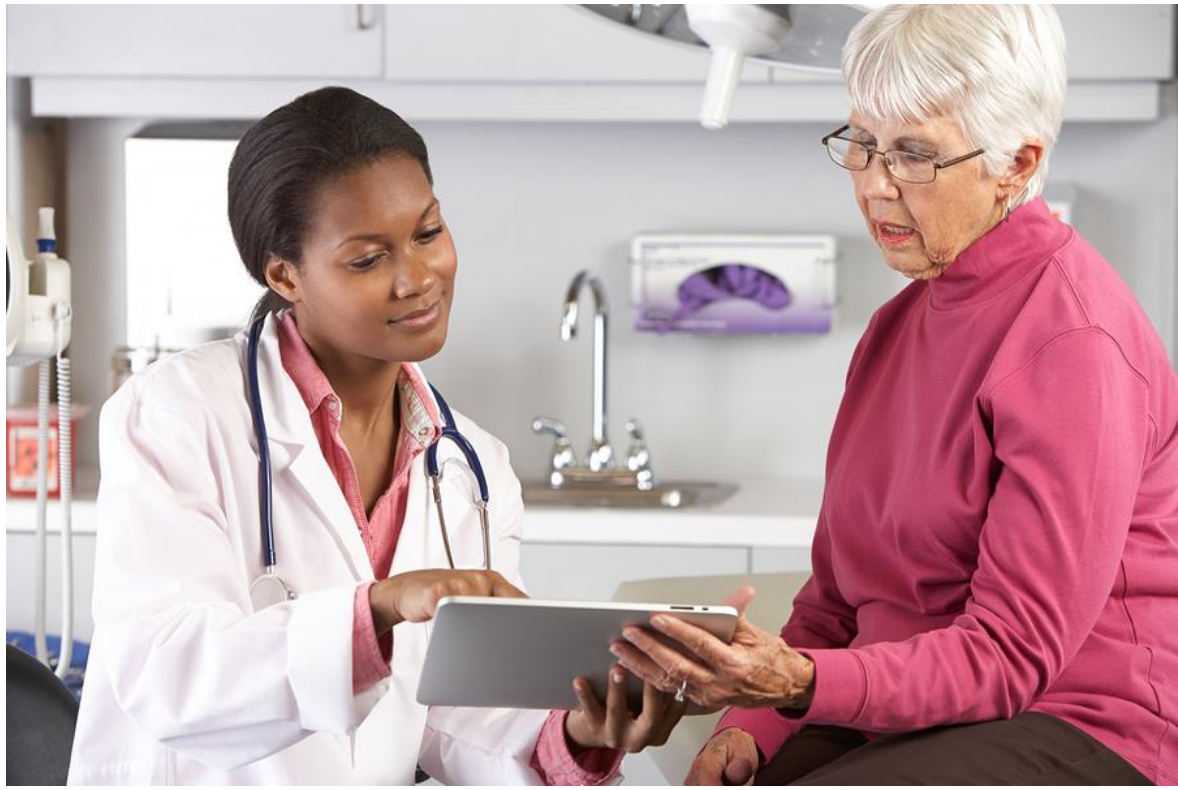
- Physiatry
  - Otherwise known as Physical Medicine and Rehabilitation Specialists
- Neurology/neuro-oncology



Why care about neuropathy?

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- Almost **70%** of patients experienced neuropathy **one month** after chemotherapy
- **6 months** after completing chemotherapy, **30%** of patients reported ongoing neuropathy

Seretny, Marta, et al. "Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis."*PAIN*® 155.12 (2014): 2461-2470.

Why care about neuropathy?

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- Quality of life
- Function
- Safety

Why care about CIPN?

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- Quality of life
  - Patients who have neuropathy from chemotherapy report **worse** quality of life
  - **More** symptoms of neuropathy = **worse** quality of life

- Tofthagen, Cindy, et al. "Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors." *Supportive Care in Cancer* 21.12 (2013): 3307-3313.
- Mols, Floortje, et al. "Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review." *Supportive Care in Cancer* 22.8 (2014): 2261-2269.

Why care about CIPN?

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- Function
  - Worse performance on functional tests
  - Walking slower = increased fall risk
  - Reduced independence with activities of daily living

- Winters-Stone KM et al. Falls, functioning and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. J Clin Oncology. 35(23). 2017. 2604-2610.
- Kolb, N.A., Smith, A.G., Singleton, J.R., Beck, S.L., Stoddard, G.J., Brown, S. and Mooney, K., 2016. The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling. *JAMA neurology*, *73*(7), pp.860-866.

Why care about CIPN?

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- Safety
  - Approximately **17%** of patients with neuropathy from chemotherapy fall
  - **Increased** odds of falling by 1.8 – 3x

- Winters-Stone KM et al. Falls, functioning and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. J Clin Oncology. 35(23). 2017. 2604-2610.
- Kolb, N.A., Smith, A.G., Singleton, J.R., Beck, S.L., Stoddard, G.J., Brown, S. and Mooney, K., 2016. The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling. *JAMA neurology*, *73*(7), pp.860-866.
- Argyriou, A.A., Bruna, J., Anastopoulou, G.G., Velasco, R., Litsardopoulos, P. and Kalofonos, H.P., 2019. Assessing risk factors of falls in cancer patients with chemotherapy-induced peripheral neurotoxicity. *Supportive care in cancer*, pp.1-5.

Who falls with CIPN?

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- Almost **12%** in 3 months
- Impaired proprioception, gait, foot drop
- Higher cumulative chemo dose
- Higher number of neuropathic symptoms and CIPN scale scores
- Motor>Sensory symptoms
- **27% reported functional impairment**

- Gewandter, J.S., Fan, L., Magnuson, A., Mustian, K., Peppone, L., Heckler, C., Hopkins, J., Tejani, M., Morrow, G.R. and Mohile, S.G., 2013. Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study. *Supportive care in cancer*, *21*(7), pp.2059-2066.

Any prevention techniques?

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- Short answer - no
- Amifostine
  - FDA approved to reduce chemotherapy toxicity
  - **Limited evidence** that it helps
- Vitamin E
  - The jury is out.
- Others being investigated

- Laumet, G., Edralin, J., Dantzer, R., Heihnen, C. and Kavelaars, A., 2018. Educated CD8+ T cells prevent chemotherapy-induced peripheral neuropathy (CIPN). *The Journal of Pain*, *19*(3), p.S8.
- Gewandter, J.S., Brell, J., Cavaletti, G., Dougherty, P.M., Evans, S., Howie, L., McDermott, M.P., O'Mara, A., Smith, A.G., Dastros-Pitei, D. and Gauthier, L.R., 2018. Trial designs for chemotherapy-induced peripheral neuropathy prevention: ACTTION recommendations. *Neurology*, *91*(9), pp.403-413.

How can you treat neuropathy?

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- Dose reduction or decreased frequency of chemotherapy
- If there is a contributing cause, treat it

Barton, D.L., Wos, E.J., Qin, R., Mattar, B.I., Green, N.B., Lanier, K.S., Bearden, J.D., Kugler, J.W., Hoff, K.L., Reddy, P.S. and Rowland, K.M., 2011. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Supportive Care in Cancer*, *19*(6), pp.833-841.

How can you treat neuropathy?

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- Medications:
  - **Duloxetine**, venlafaxine, amitriptyline, nortriptyline
  - **Gabapentin**, pregabalin
  - Topicals such as capsaicin, lidocaine or mix of baclofen, amitriptyline and ketamine

Barton, D.L., Wos, E.J., Qin, R., Mattar, B.I., Green, N.B., Lanier, K.S., Bearden, J.D., Kugler, J.W., Hoff, K.L., Reddy, P.S. and Rowland, K.M., 2011. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Supportive Care in Cancer*, *19*(6), pp.833-841.

CIPN: Treatment

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- **Exercise**
  - Helps symptoms
  - Improve QOL and ADL independence
- During chemotherapy administration, those who exercised experienced **symptoms less commonly** and also **less severe symptoms** compared to those who did not exercise

- Zimmer, P., Trebing, S., Timmers-Trebing, U., Schenk, A., Paust, R., Bloch, W., Rudolph, R., Streckmann, F. and Baumann, F.T., 2018. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. *Supportive Care in Cancer*, *26*(2), pp.615-624.
- Kleckner, I.R., Kamen, C., Gewandter, J.S., Mohile, N.A., Heckler, C.E., Culakova, E., Fung, C., Janelsins, M.C., Asare, M., Lin, P.J. and Reddy, P.S., 2018. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. *Supportive Care in Cancer*, *26*(4), pp.1019-1028.

Exercise guidelines for cancer survivors

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- Guidelines published by the American College of Sports Medicine in 2010:
  - Participate in at least **150 minutes** of moderate intensity aerobic exercise per week
  - Include **strengthening and flexibility** exercises

Updates from 2019

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- Moderate to vigorous activity **reduces** cancer risk
- Frequency: **150-300** minutes per week
- Prescription recommendation:
  - Moderate-intensity aerobic and/or resistance exercise
  - At least **3 times per week**
  - At least **30 minutes**

Campbell, K.L., Winters-Stone, K.M., Patel, A.V., Gerber, L.H., Matthews, C.E., May, A.M., Stuiver, M.M., Stout, N.L., Schmitz, K.H. and Morris, G.S., 2019. An Executive Summary of Reports From an International Multidisciplinary Roundtable on Exercise and Cancer: Evidence, Guidelines, and Implementation. *Rehabilitation Oncology*, *37*(4), pp.144-152.

General exercise prescription

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- **Aerobic exercise training:**
  - 150 minutes of moderate-intensity exercise or 75 minutes of vigorous-intensity exercise per week
- **Strength training:**
  - 2-3 sessions per week for major muscle groups
- **Flexibility:**
  - Stretch major muscle groups and tendons on days that other exercises are performed

Schmitz 2010

BUT…

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- Before you start exercising, you should be **screened** by a physician
- **Why?**
  - Prevent injury
  - Tailor your exercise program to achieve your goals

https://www.google.com/search?q=exercise&rlz=1C1GCEU_enUS820US821&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjn0cnNptzgAhWGm-AKHR2oAoQQ_AUIDigB&biw=1920&bih=1089#imgrc=8AydrYoqTg6ohM:

Schmitz 2010

CIPN: Rehab interventions

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- Start with static standing, then add simple manipulation, then walking, then manipulation while walking
- Work on gait training and LE strengthening and proprioception

- Monfort, S.M., Pan, X., Patrick, R., Ramaswamy, B., Wesolowski, R., Naughton, M.J., Loprinzi, C.L., Chaudhari, A.M. and Lustberg, M.B., 2017. Gait, balance, and patient-reported outcomes during taxane-based chemotherapy in early-stage breast cancer patients. *Breast cancer research and treatment*, *164*(1), pp.69-77.
- Wong, R., Major, P. and Sagar, S., 2016. Phase 2 study of acupuncture-like transcutaneous nerve stimulation for chemotherapy-induced peripheral neuropathy. *Integrative cancer therapies*, *15*(2), pp.153-164.

CIPN: Rehab interventions

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- Hand therapy through a specially trained occupational therapist can also be helpful to focus on:
  - Strengthening fine motor
  - Neuromuscular re-education
  - Adaptive equipment

- Monfort, S.M., Pan, X., Patrick, R., Ramaswamy, B., Wesolowski, R., Naughton, M.J., Loprinzi, C.L., Chaudhari, A.M. and Lustberg, M.B., 2017. Gait, balance, and patient-reported outcomes during taxane-based chemotherapy in early-stage breast cancer patients. *Breast cancer research and treatment*, *164*(1), pp.69-77.
- Wong, R., Major, P. and Sagar, S., 2016. Phase 2 study of acupuncture-like transcutaneous nerve stimulation for chemotherapy-induced peripheral neuropathy. *Integrative cancer therapies*, *15*(2), pp.153-164.

CIPN: Rehab interventions

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- Desensitization and TENS
- Laser therapy (photobiomodulation)
- Scrambler therapy being actively researched
- Can trial AFOs for foot drop **or** proprioception
- Ambulatory aids
- Compression socks, wool socks
- Trial acupuncture
- <u>Skin checks</u>

- Pusan, S. and Abdi, S., 2018. Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. *Pain physician*, *21*, pp.571-592.
- Smith, T.J., Razzak, A.R., Blackford, A.L., Ensminger, J., Saiki, C., Longo-Schoberlein, D. and Loprinzi, C.L., 2019. A Pilot Randomized Sham-Controlled Trial of MC5-A Scrambler Therapy in the Treatment of Chronic Chemotherapy-Induced Peripheral Neuropathy (CIPN). *Journal of palliative care*, p.0825859719827589.

QUESTIONS?

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Questions?

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