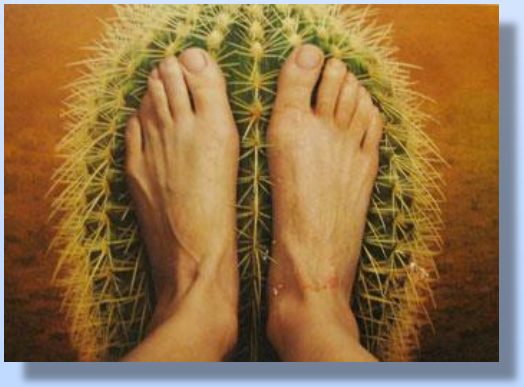
MAYO CLINIC

Living with Myeloma

Peripheral Neuropathy



Mark K. Edwin, M.D.
Palliative Medicine
Mayo Clinic in Arizona
March 18, 2017

 |

Disclosure

- None

MAYO CLINIC

Today's topics

1. What is peripheral neuropathy

2. Who gets it and how

3. Can it be prevented

4. How can it be treated

MAYO CLINIC

What is Peripheral Neuropathy?

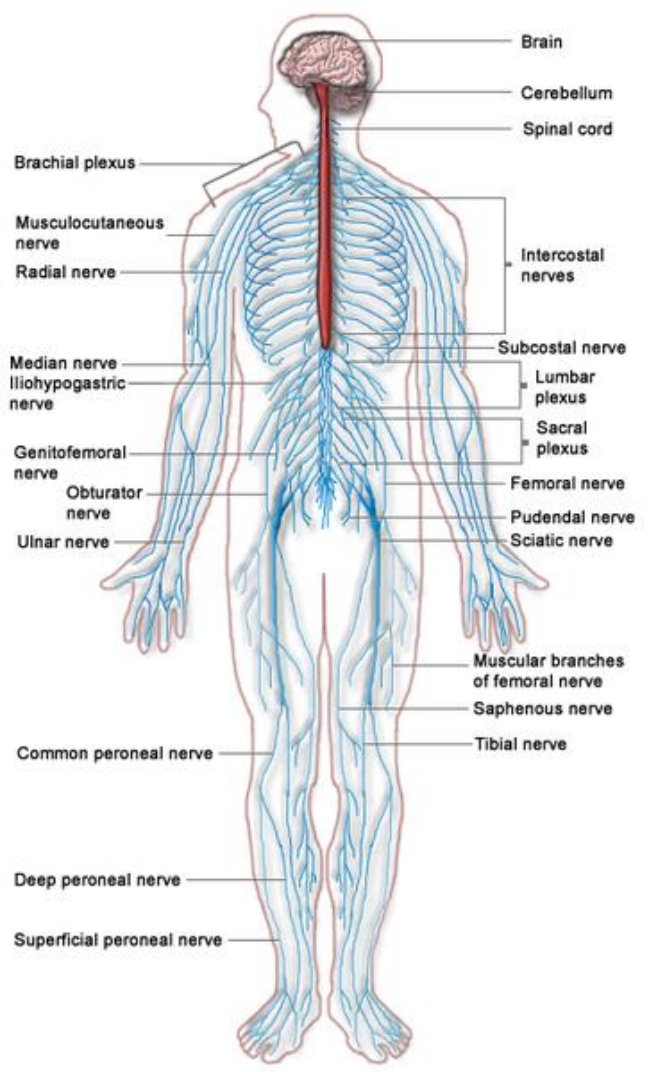
Damage to the peripheral nerves in the hands and feet resulting in:

numbness

tingling

pain

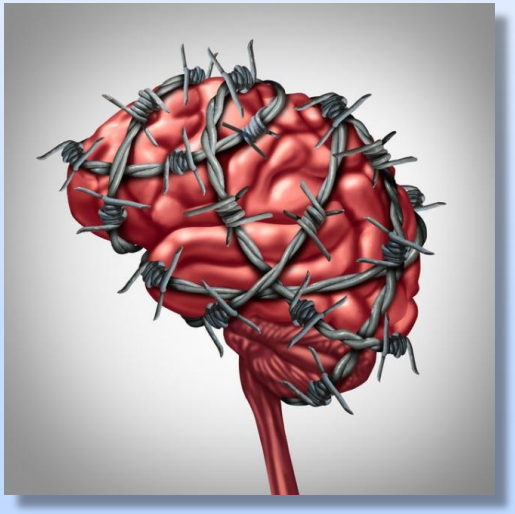
weakness



Red: Central Nervous System
Blue: Peripheral Nervous System

What causes nerve damage

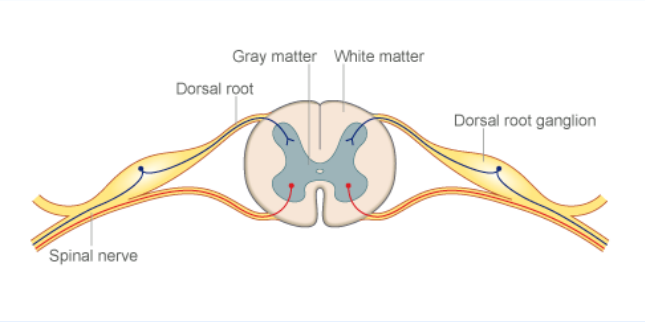
- Diabetes (most common)
- Chemotherapy (most common in this room)
- Tumors / Compression of the nerve itself
- Radiation therapy
- Shingles
- Thyroid abnormalities
- Low Vitamin B levels
- Alcohol
- Phantom Pain



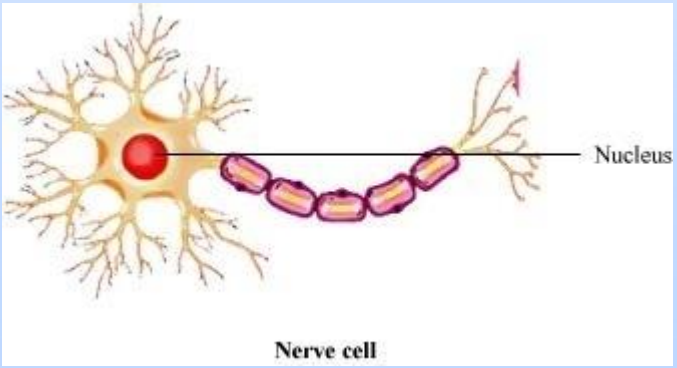
MAYO CLINIC

What Causes Peripheral Neuropathy

- Not fully understood



- Theories
  - Chemotherapy causes key nerve cells to die
  - Therapies disrupt the communication along the nerve pathways.



MAYO CLINIC

Neuropathic pain

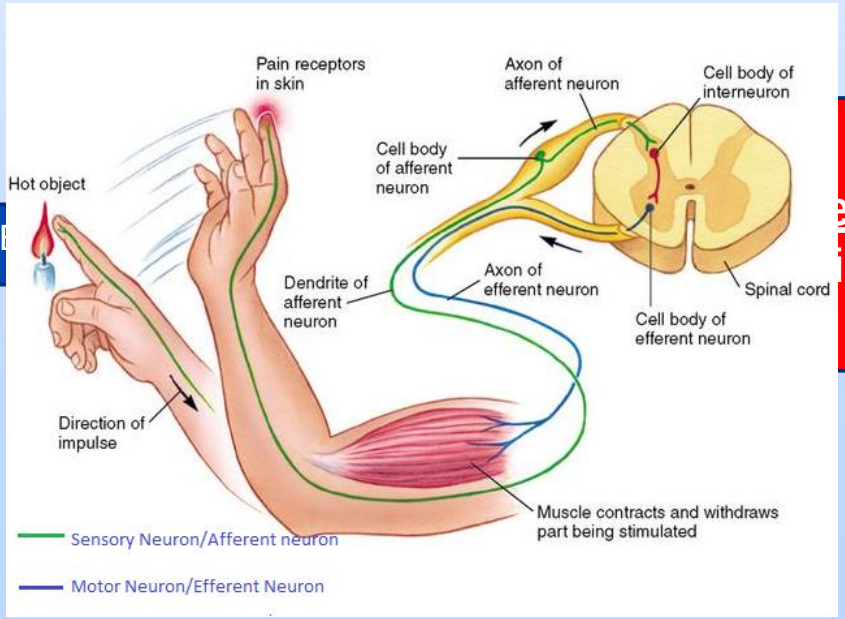
- Protective mechanism vs. Pathologic response

Injury / Trauma (Mechanical, Burn, Inflammation)

IMPULSE

Temporary symptoms trigger reflex to withdraw

ALTE



ersistent symptoms of iscomfort / numbness

MAYO CLINIC

The Challenge

- 4 million patients in US
- Impairs function
- Prolonged clinical course
- Less responsive to traditional analgesics

MAYO CLINIC

What are the symptoms?

- Pain
  - Stabbing
  - Tingling
  - Burning
- Loss of feeling
- Loss of dexterity
- Loss of balance
- Tremor
- Weakness

} Thalidomide causes in 30 – 40%

- Symptoms I hear from patients
  - Walking on a piece of wood
  - Walking on pebbles
  - Wearing a stocking / glove
  - Lose balance easily
  - Electric shock
  - Lightening bolt
  - Can't button my shirt

MAYO CLINIC

The Culprits: Chemotherapy Agents

- Bortezomib / Velcade®
- Carfilzomib / Kyprolis®

- Thalidomide
- Lenalidomide / Revlimid®
- Pomalidomide / Poalyst®

Seen in 40-75% of patients treated for 12 months

Mileshkin, L.,. (2006) Journal of Clinical Oncology, 24, 4507–4514

MAYO CLINIC

What increases the risk

- Chemotherapy related:
  - Frequency it is given
  - What dose is used
  - Route is it given
  - What is the cumulative dose
- Age
- Are there multiple risk factors are present?
  - Diabetes, HIV, vitamin deficiencies, Excess alcohol

MAYO CLINIC

What to expect

- Velcade
  - Good news!
    - Improves or resolves completely in 65% of patients in 4 months after treatment
  - Bad news
    - 35 % have persistent symptoms

MAYO CLINIC

Richardson PG, Br J Haematol 2009; 144:895.

Can we reduce the risk?

- Dosing adjustment of chemotherapy
- No agents are recommended for the prevention of CIPN
    - Vitamin E
    - Omega-3 fatty acids
    - Anti-depressant medications
- Exercise and acupuncture may be beneficial

Kleckner I, J Clin Oncol 34, 2016
Courneya KS,. Br J Cancer 2014; 111:1718.
Greenlee H. J Clin Oncol 34, 2016

Treatment Options

1. Medications
2. Topical agents
3. Cannabis
4. Nerve stimulators

MAYO CLINIC

Medications

1. Duloxetine (Cymbalta)
2. Gabapentin (Neurotin)
3. Pregabalin (Lyrica)
4. Tricyclic Anti-depressants
5. Opioids

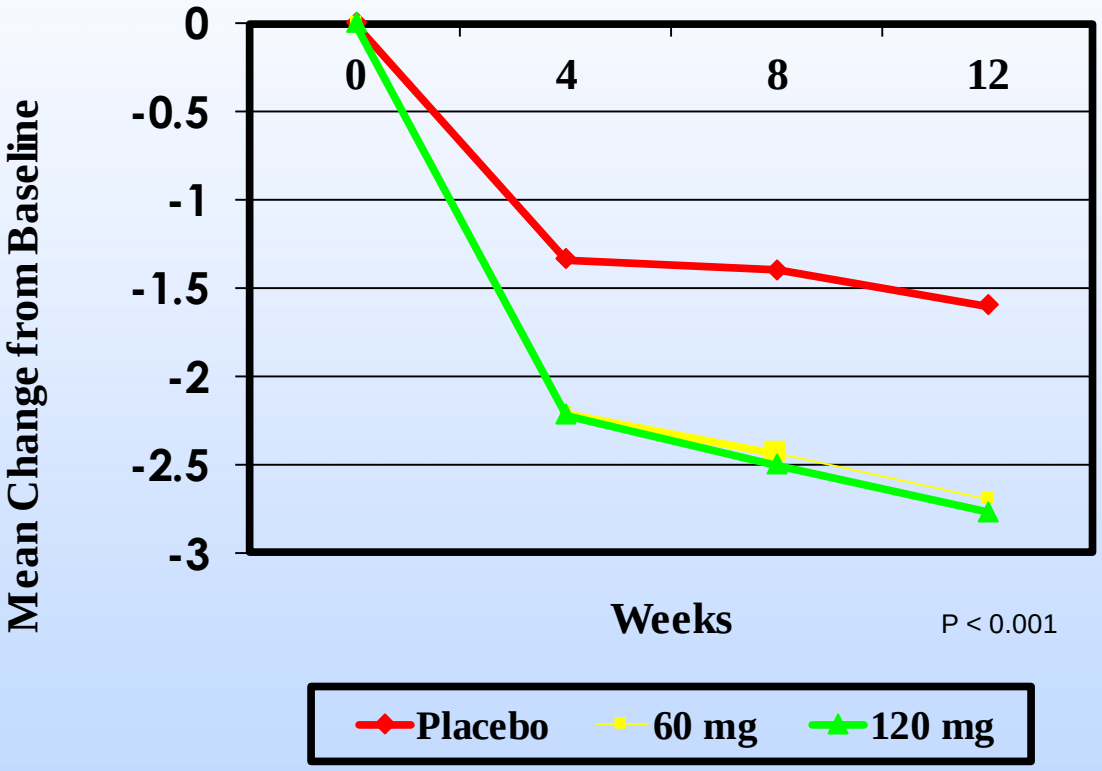
MAYO CLINIC

Medications – Cymbalta®

- First-tier treatment for CIPN
- Anti-depressant (SNRI)
- FDA approved
  - Depression, fibromyalgia and diabetic peripheral neuropathy
- Cautions
  - Elevation of BP
  - Lowers seizure threshold
  - Glaucoma

MAYO CLINIC

Medications - Cymbalta



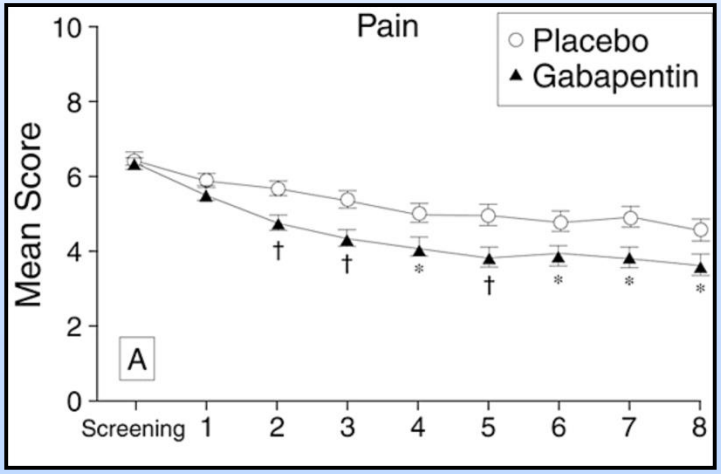
- 348 patients
- Randomized placebo controlled trial
- Endpoint: Relief from diabetic peripheral neuropathy
- 12 weeks
- Mean change in pain score
  - **-2.47 (0.18)**

Raskin J Am Acad Pain Med 6 (5) 346.

Medications - Neurontin / Lyrica

- Medications
  - Gabapentin (Neurontin®)
  - Pregabalin (Lyrica ®)
- Significant role in chronic, neuropathic pain

Gabapentin trial



CLINICAL FINDINGS

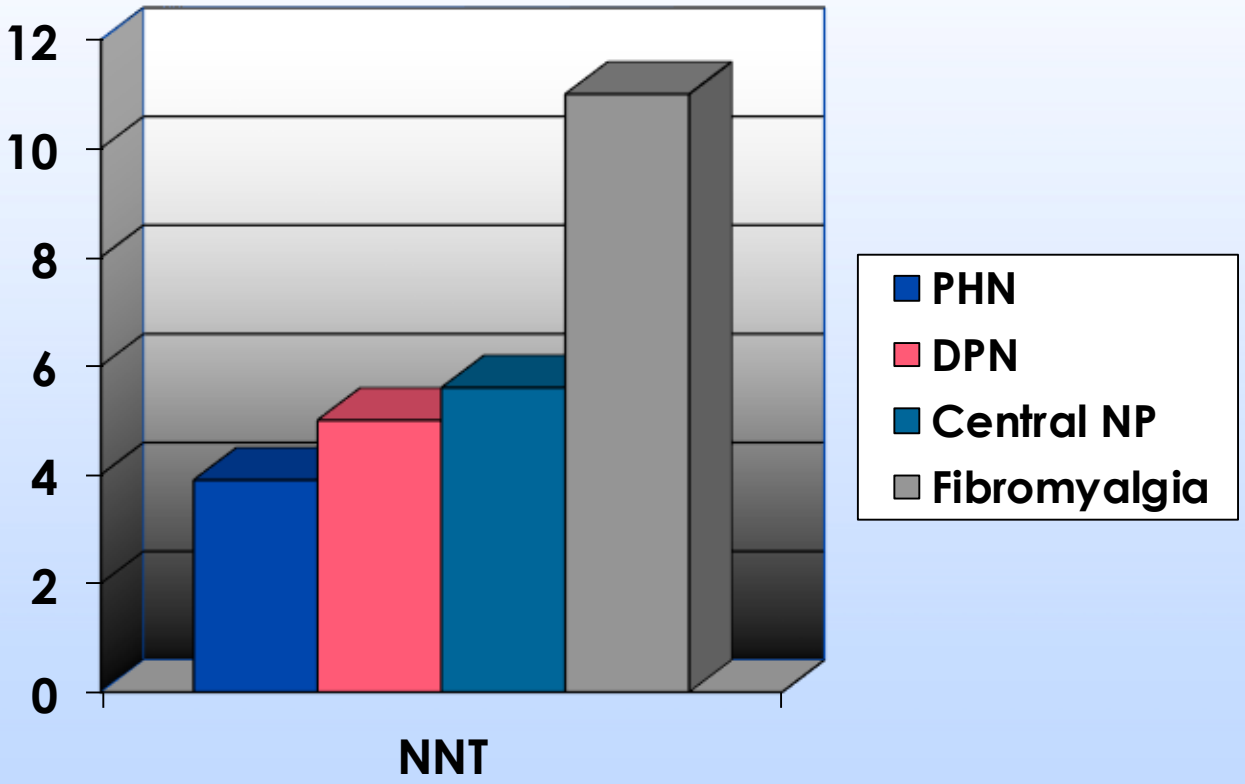
Statistically significant improvement

Mean pain scores dropped from 6.5 to 4

JAMA. 1998;280(21):1831-1836. doi:10.1001/jama.280.21.1831

MAYO CLINIC

Lyrica®



Cochrane Review of 17 RCT trials

NNT to achieve > 50% pain reduction from baseline using dose of 600mg daily

Moore RA Cochrane Database Syst Rev. 2009

Neurontin / Lyrica

- Testing in patients with chemotherapy-induced peripheral neuropathy
  - Double-blind, placebo-controlled cross over trial
  - No benefit

- Side Effect Profile
  - Dizziness (29%)
  - Somnelence (22%)
  - Swelling in the extremities (12%)

Smith EM, JAMA 2013; 309:1359.

MAYO CLINIC

Topical Agents

- Primary Goal
  - Selectively inhibit nerve function

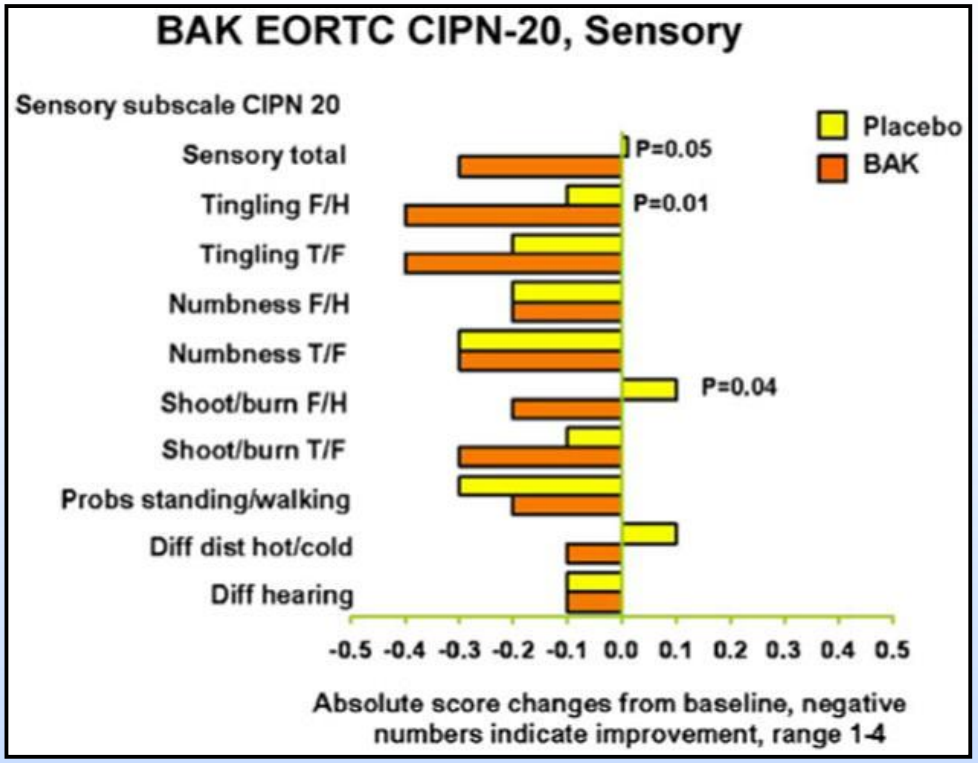
- Advantages
  - Avoid issues of stomach absorption
  - Ease of use
  - Limited interaction with other meds
  - Customize treatments
  - Limited toxicities / side effects

- Disadvantages
  - Cost
  - Area of distribution
  - Skin permeability

MAYO CLINIC

Topical Agents

- Recipe
  - Baclofen 10mg
  - Amitriptyline 40mg
  - Ketamine 20mg



Apply 3 times daily for 1 month

Modest improvements related to the symptoms of tingling, cramping, and shooting/burning pain in the hands as well as difficulty in holding a pen

.

Barton DL Support Care Cancer. 2011 Jun;19(6):833-41

MAYO CLINIC

Marijuana - Cannabis sativa

- *Cannabis sativa*
  - Plant originating in Central Asia
  - Psychotomimetic properties and
    - medical use for thousands of years
  - Flowers contain a series of compounds known as cannabinoids
  - Approved for medical use in Arizona in 2011

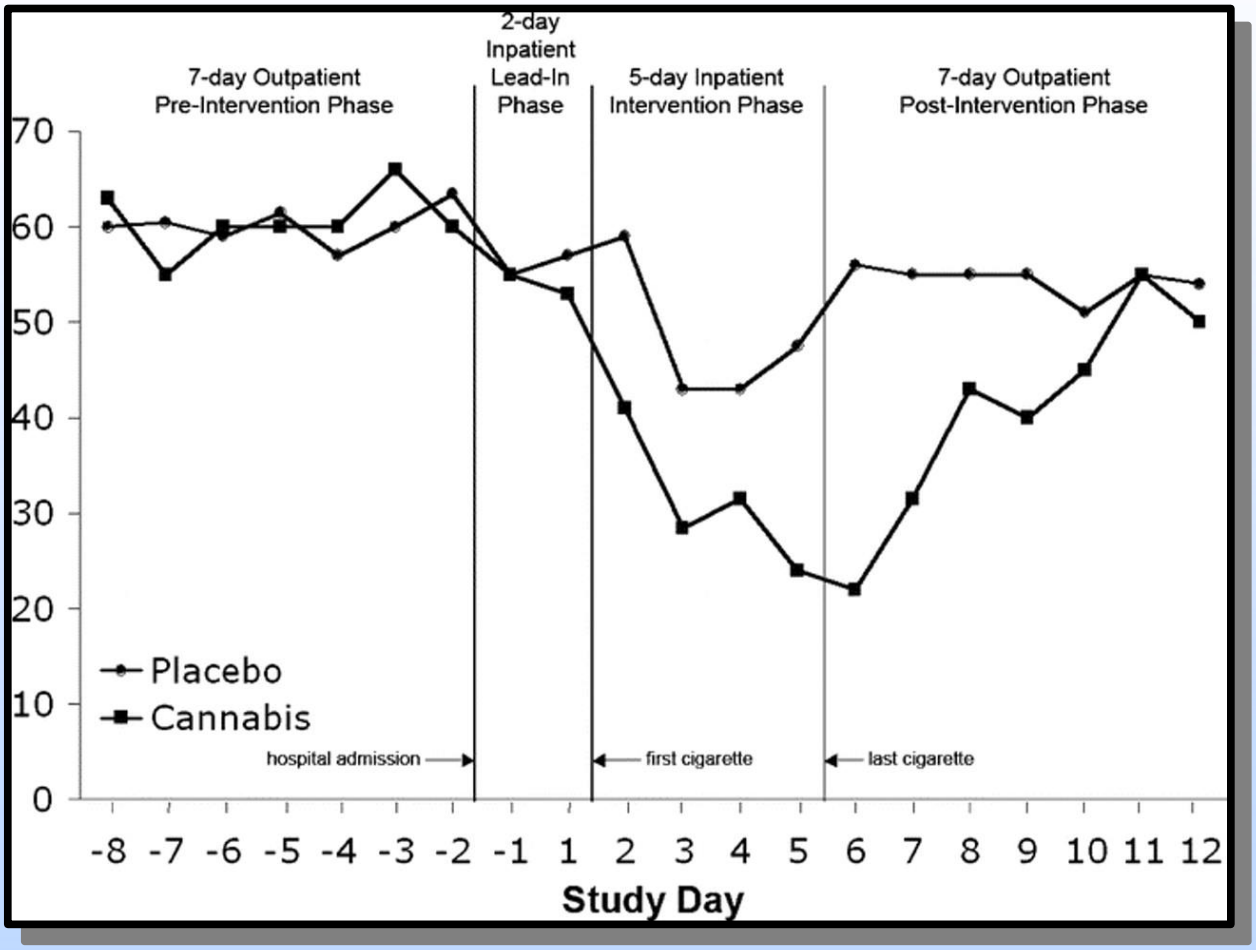
MAYO CLINIC

Inhaled cannabis

- Study in patients with painful HIV-induced neuropathy
- No studies in CIPN
- Study intervention
  - Randomized to inhaled cannabis vs placebo
  - Dose: inhaled medication.
    - Active agent: 3.56% THC
  - Dose: 1 cigarette 3 times daily
  - Uniform puff procedure

MAYO CLINIC

Pain Relief – Inhaled cannabis



Abrams D I et al. Neurology 2007;68:515-521

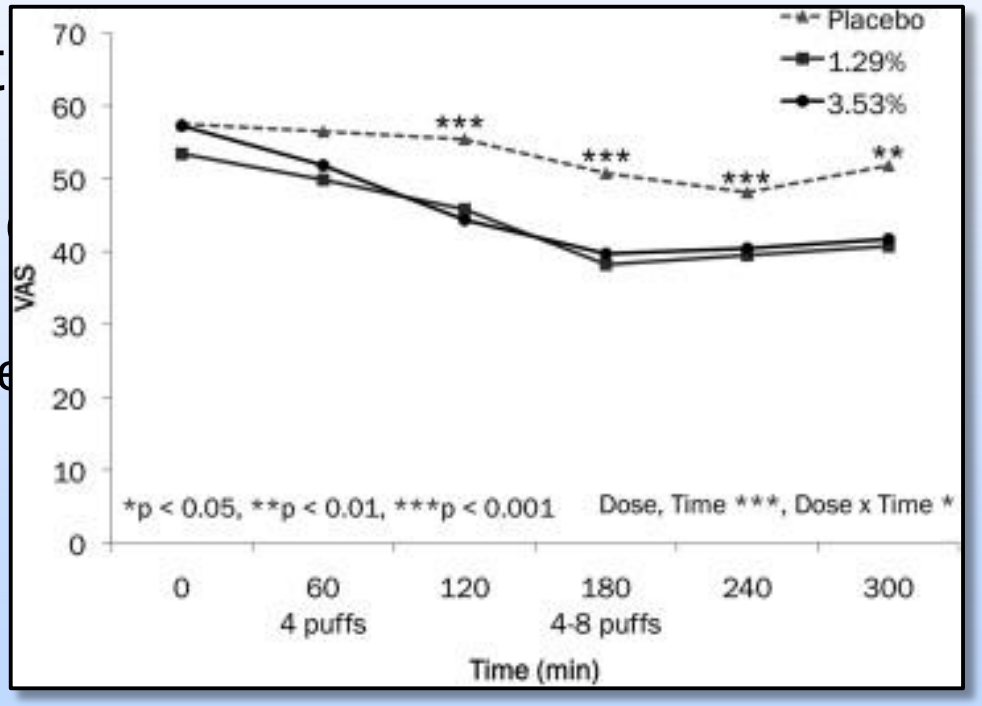
Vaporized Cannabis – Study 2

Purpose to assessing the dose

39 patients

Both cent

1. Low
2. High
3. Place



Barth W. The Journal of Pain, Volume 14, Issue 2, 2013, 136 - 148

Limited Studies on Cannabis

- Total of 5 randomized-controlled trials
  - 178 patient
  - Followed for up to 2 weeks
  - Neuropathy from multiple causes (not CIPN)
- Benefit appreciated by 1 in 5 patients

Andreae, MH Journal of Pain 16 (12) 2015

Scrambler Therapy

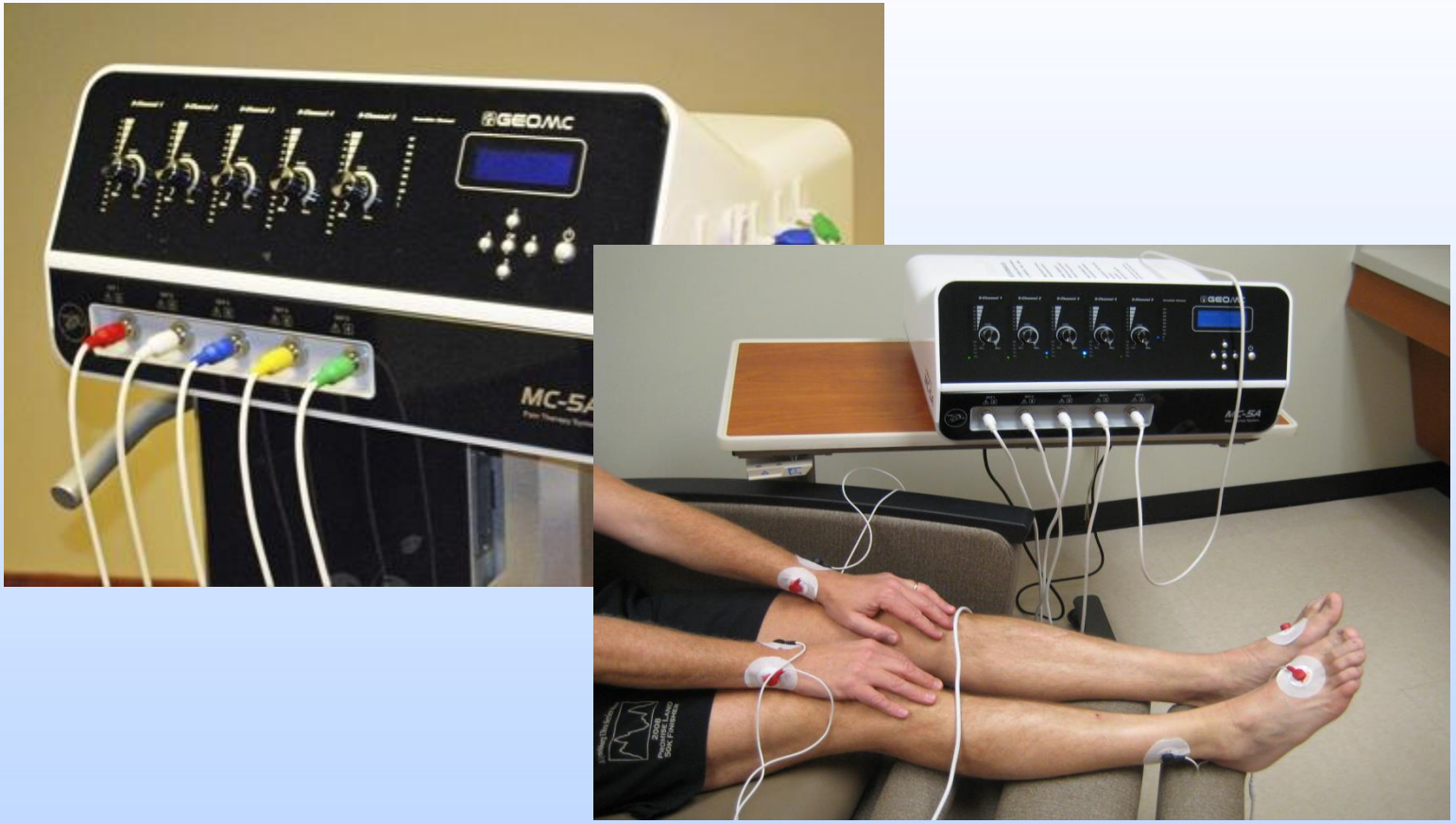
- New technique

- Theory:

  Block the transmission of pain signals by providing non-pain information to nerve fibers that have been receiving pain messages

MAYO CLINIC

Scrambler Therapy



MAYO CLINIC

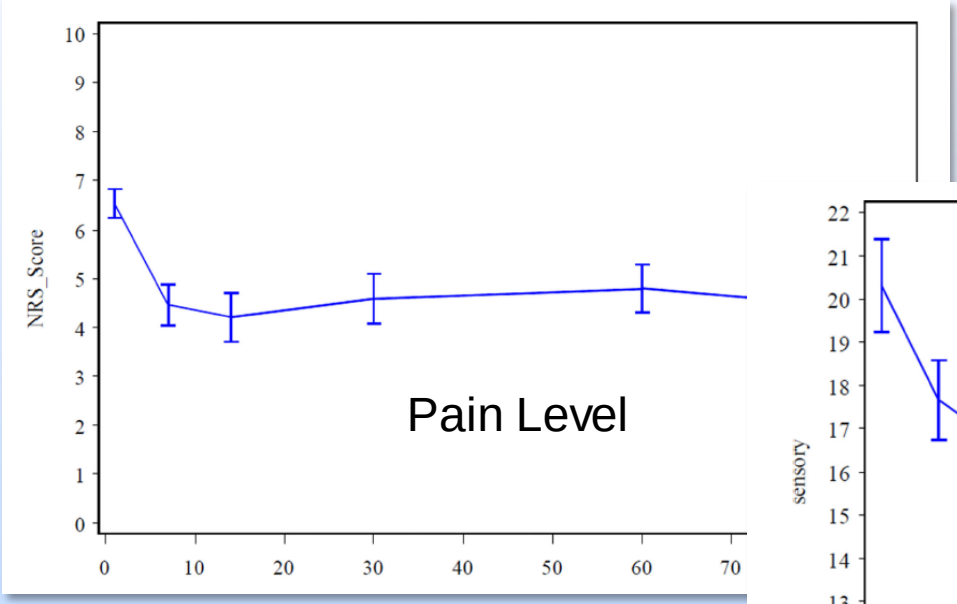
Scrambler Therapy

- Technique
  1. Apply electrodes
  2. Increase intensity until patient feels sensation (not pain)
  3. Treatment lasts 30 minutes
  4. Daily treatment for 10 days

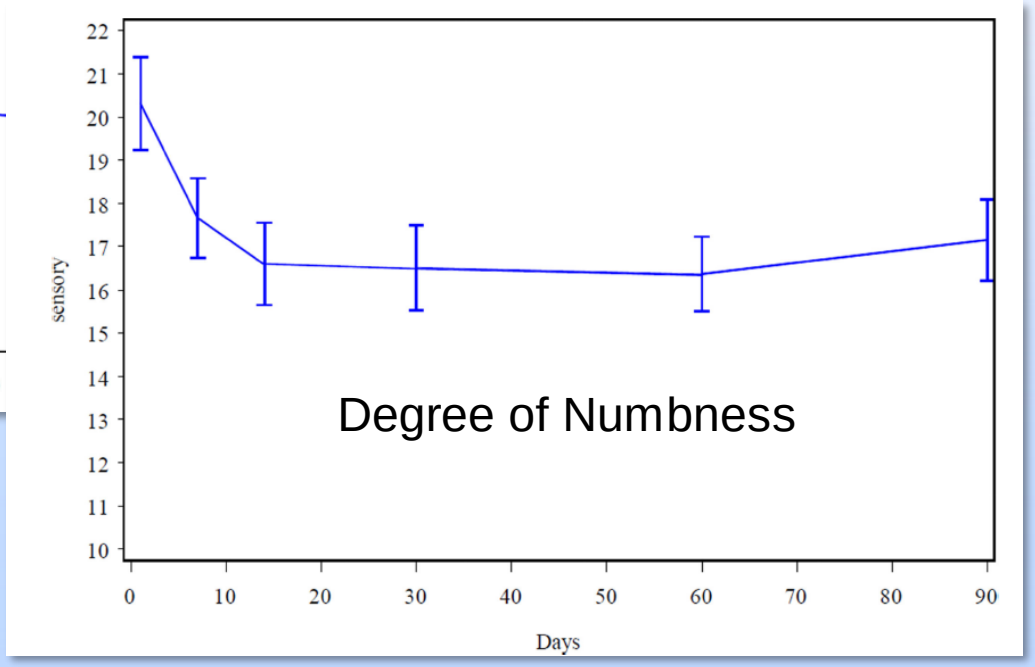
MAYO CLINIC

Results of Pilot Study – Johns Hopkins

- Small study of 39 patient with CIPN

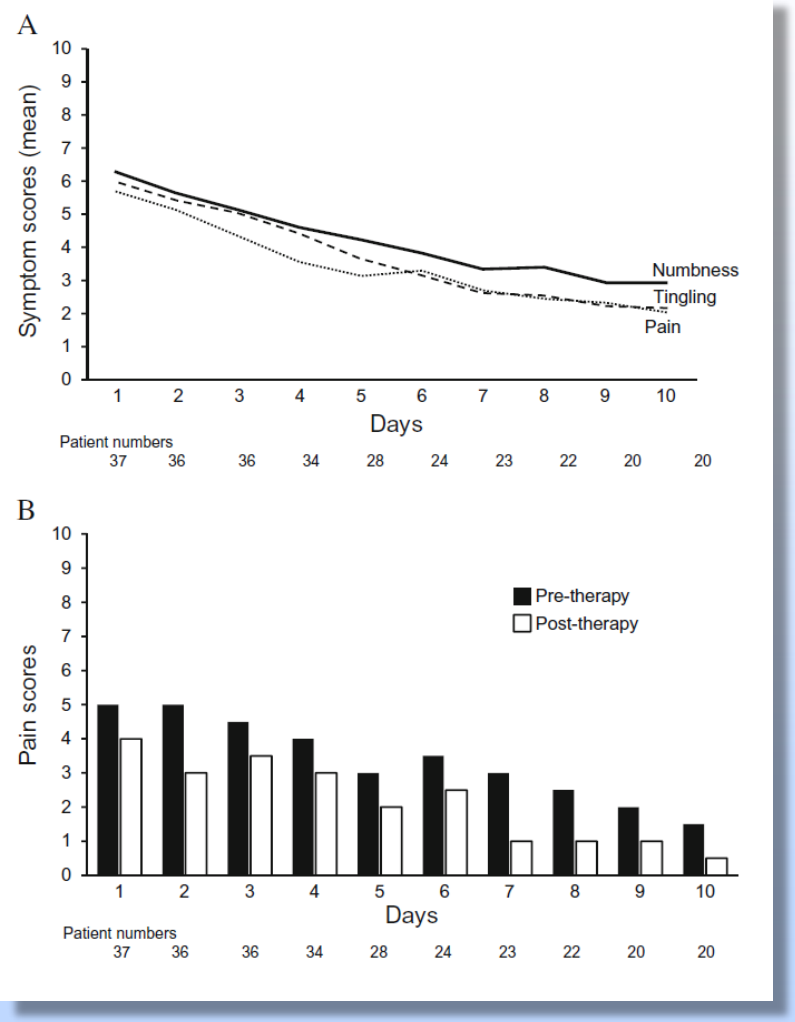


Average Pain Scores dropped 6.6 to 4.6



Smith T J Pain Palliat Care Pharm 2013 Dec 27(4)

Results of Pilot Study – Mayo Clinic



37 patients treated

10 treatments

Results

53% reduction in pain

44% reduction in tingling

37% reduction in numbness

C Loprinzi Supp Care Can 2015. 23

Not For Everyone

- Pacemakers
- Implantable pain pumps
- Metal implants (screws, plates, joints)
- History of epilepsy
- Irregular heart beat
- Skin breakdown
- Latex allergy

MAYO CLINIC

Cost and Availability

- Clinical trials at Mayo Clinic in Rochester and Johns Hopkins
- FDA clearance
- Clinically available at ~ 15 centers in the USA
- Costs: ~ $300 per session (10 sessions)
- Insurance coverage variable

MAYO CLINIC

Scrambler Benefits

- non-invasive
- painless
- benefit within 2 weeks
- ongoing pain control
- limited side effects

MAYO CLINIC

Take Home Points

- Limit Risks
- No agents for prevention
- Strongest evidence for Cymbalta
- Trial of Neurontin / Lyrica
- Cannabis
- Awaiting further data on Scrambler therapy

MAYO CLINIC

Thank you

Be Well