



2018

28-30 JUNE
VIENNA, AUSTRIA

**SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE**

Non-Drug Treatment Approaches For Chemotherapy Neuropathy

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MASCC/ISOO

ANNUAL MEETING ON SUPPORTIVE CARE IN CANCER



www.mascc.org/meeting



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SUPPORTIVE CARE IN CANCER



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Faculty Disclosure

<input type="checkbox"/>	No, nothing to disclose
<input checked="" type="checkbox"/>	Yes, please specify:

<i>Company Name</i>	<i>Honoraria/ Expenses</i>	<i>Consulting/ Advisory Board</i>	<i>Funded Research</i>	<i>Royalties/ Patent</i>	<i>Stock Options</i>	<i>Ownership/ Equity Position</i>	<i>Employee</i>	<i>Other (please specify)</i>
Pledpharma AB	X							



Objectives

- To discuss currently available non pharmacologic **treatment** options for chemotherapy induced neuropathy
- To discuss future research strategies of **non pharmacologic modalities.**



Outline

- Introduction
- Cancer rehabilitation
- Exercise and Balance Training
- Integrative therapies: Acupuncture
- Neuro-stimulatory options
- Future Strategies



Introduction: Chemotherapy Induced Neuropathy (CIPN)



- Management Challenges
 - Insufficient understanding of mechanisms involved
 - Limited efficacy of traditional treatments
 - Pharmacologic interventions can have toxicities
 - Inadequate management of functional /whole body effects of CIPN

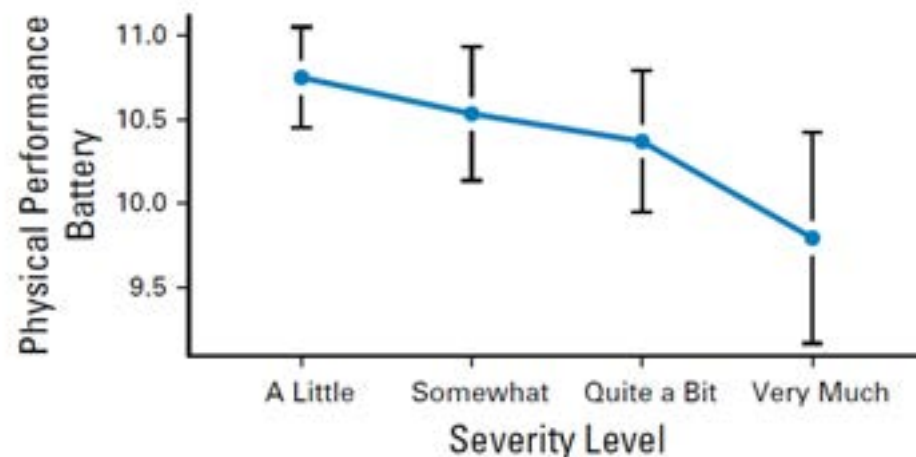
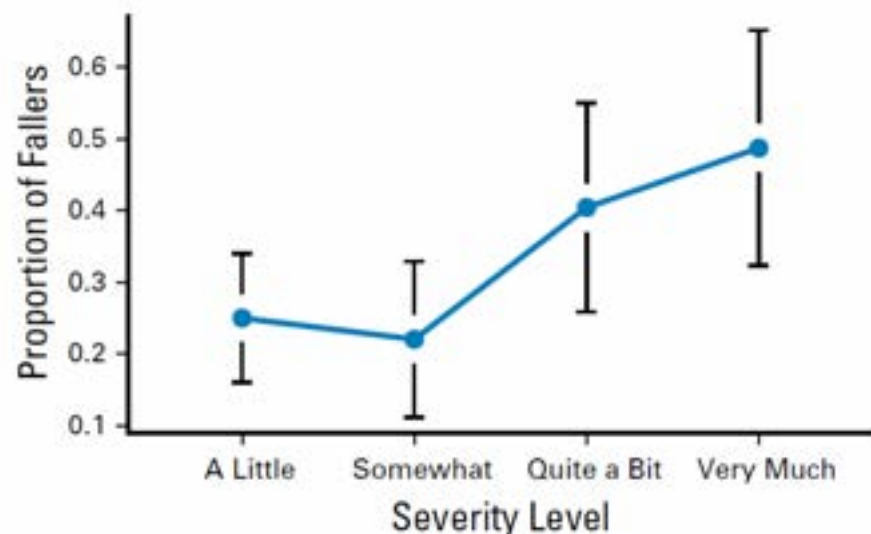


CIPN Effects are Not Solely Peripheral

- Functional impairments are common and are multifaceted
 - Gait and balance effects
 - Peripheral effects
 - Central effects
 - Neurocognitive effects



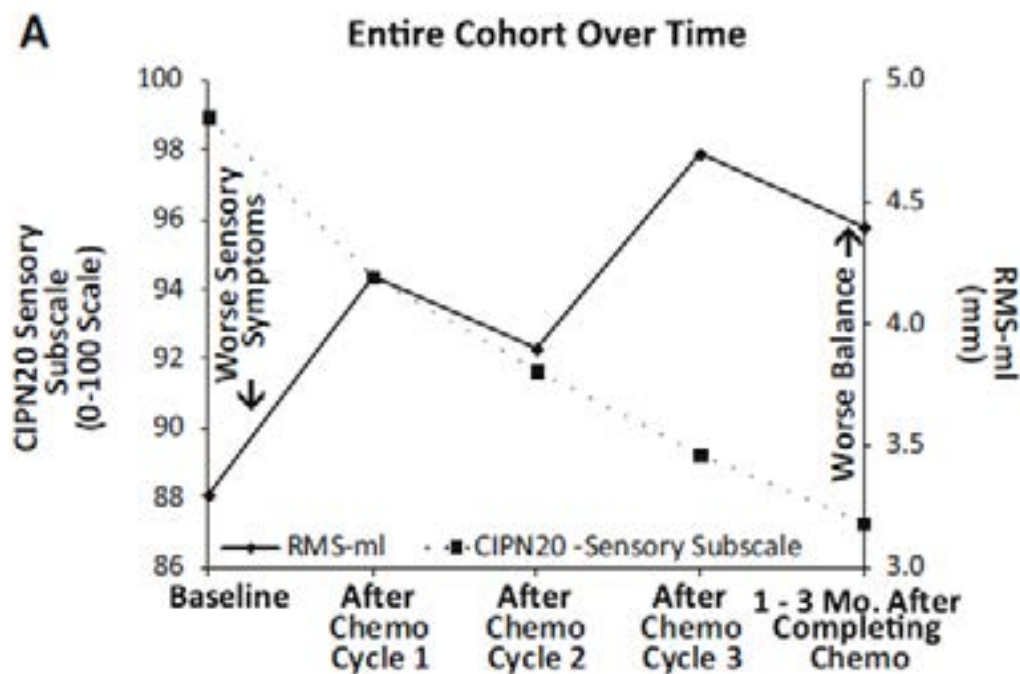
CIPN Associated Functional Deficits



Winters-Stone, et al JCO 2017



CIPN and Early Balance Changes



Monfort, SM..., Loprinzi, CL, Chaudhari, A Lustberg MB.
 Breast Cancer Research and Treatment, 2017



Role of non-pharmacologic interventions


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Cancer Rehab



Pharmacologic
options

CIPN

Exercise and Balance
training



New modalities under study
(Scrambler; acupuncture
others)
RESEARCH!



Outline

- Introduction
- **Cancer rehabilitation**
- Exercise and Balance Training
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Cancer Rehabilitation

- Restore functional capacity
- Primary prevention of disability
- Reducing impairment and disability
- Improve quality of life
- Foster independence



Cancer Rehab and CIPN

- Functional physical examination for gait and balance evaluation
 - Coordination
 - Proprioception
 - Strength
 - ROM
 - Balance
 - Transfers
 - Gait

Functional in office assessment

- Timed Get Up and Go test
- Berg Balance Scale
 - 14 item scale out of 56 points
 - Identifies low, medium, or high fall risk
- Six minute walk test



Outline

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Exercise Clinical Data



- Kleckner et al.: Phase III randomized controlled trial
 - 355 patients beginning taxane-, platinum-, or vinca alkaloid-based chemotherapy
 - Assigned to Chemotherapy or Chemotherapy & Exercise for Cancer Patients (EXCAP)
 - Standardized, personalized, moderate-intensity home-based 6-week progressive walking and resistance exercise program

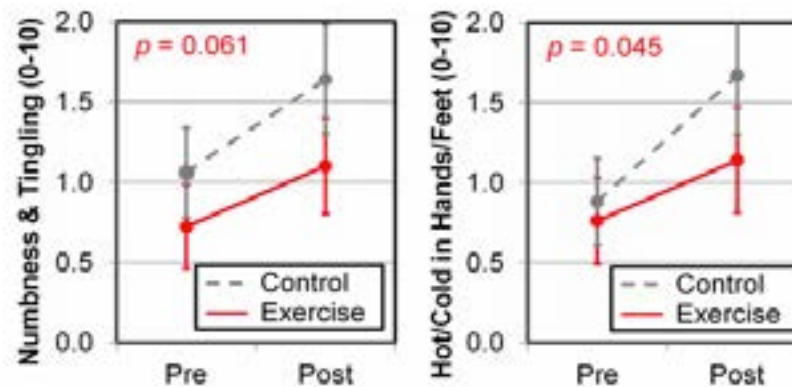
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Exercise Clinical Data

- Kleckner et al.: Results
 - Exercise protocol reduced CIPN symptoms of hot/coldness in hands/feet (-0.46 units, $p = 0.045$) compared to control
 - Exercise intervention reduced numbness and tingling (-0.42 units, $p = 0.061$) compared to control

Fig. 2 Exercise reduces the severity of CIPN symptoms per patient-reported numbness and tingling (left; trend-level effect) and hot/coldness in hands/feet (right). Error bars show 95% confidence intervals from 170 exercise patients and 185 control patients. The p values correspond to differences in exercise and control conditions from linear regression (Table 2)





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**Are there ways to make
exercise for CIPN more
appealing?**

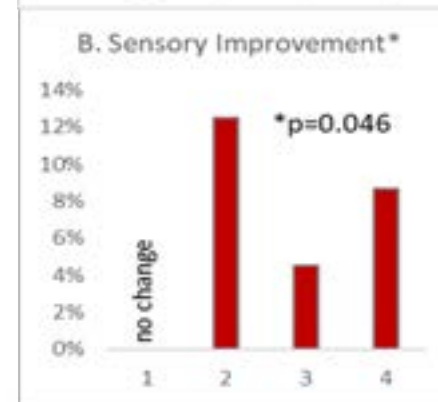
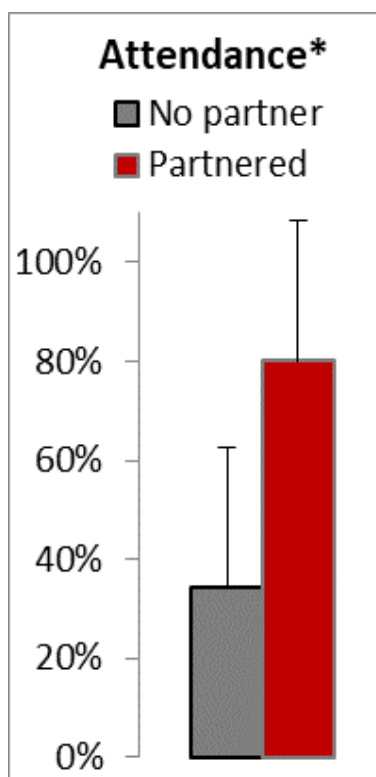
Emerging Exercise Modalities

- The art form of dance is particularly promising for functional rehabilitation
- provides an opportunity to practice balance and gait with cognitive problem solving (i.e., dual-tasking) in regard to spatial navigation
- Social interaction!



Exercise & Balance Training: Clinical Data

- Cancer survivors with neuropathy and postural control deficits at baseline
- Attended Tango classes



Exercise & Balance Training: Mechanism

- Exact mechanisms are still under study
- May treat CIPN through changes in inflammation and sensory pathways in the brain
- Exercise-induced changes in the brain may counteract central sensitization associated with neuropathic pain and reduce CIPN symptoms
- Preclinical and clinical studies are in process



Exercise and Balance Training: Future Directions



- Evaluate generalizability of findings to more severe CIPN patient populations
- Improve adherence with social /art based techniques
- Learn about optimal dose of exercise (type, duration, and intensity)
- A personalized exercise prescription tailored to patient and drug regimen



Outline

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Acupuncture and CIPN

- Absences of phase III randomized data in acupuncture and neuropathy
- Many patients are seeing services
- Small studies have been completed with some promising results

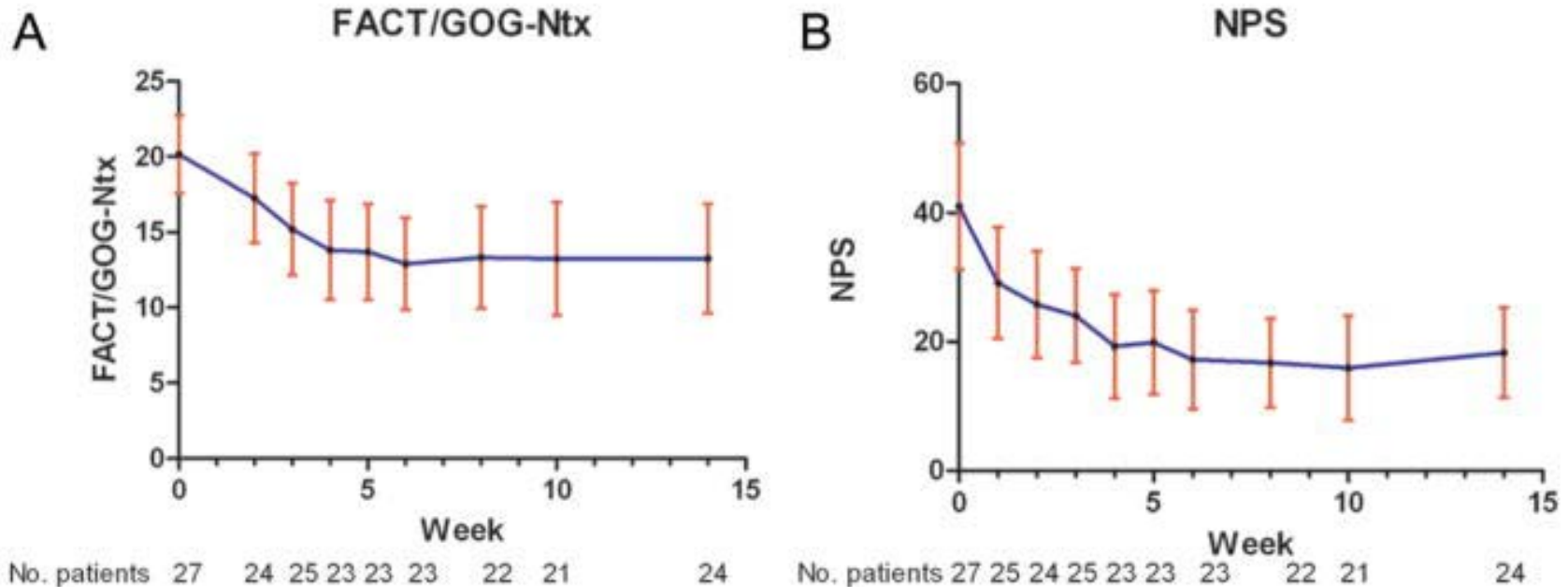


Acupuncture: Clinical Data

- Bao T. et al.: single arm prospective clinical trial pilot study
 - 27 multiple myeloma patients after Bortezomib treatment
 - Reported CIPN \geq grade 2 at baseline
 - Received 10 acupuncture treatments for 10 weeks (2 \times /week for 2 weeks, 1 \times /week for 4 weeks, and then biweekly for 4 weeks)
 - Outcome measures assessed with the Clinical Total Neuropathy Score (TNSc), Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOGNtx) questionnaire, and the Neuropathy Pain Scale (NPS)



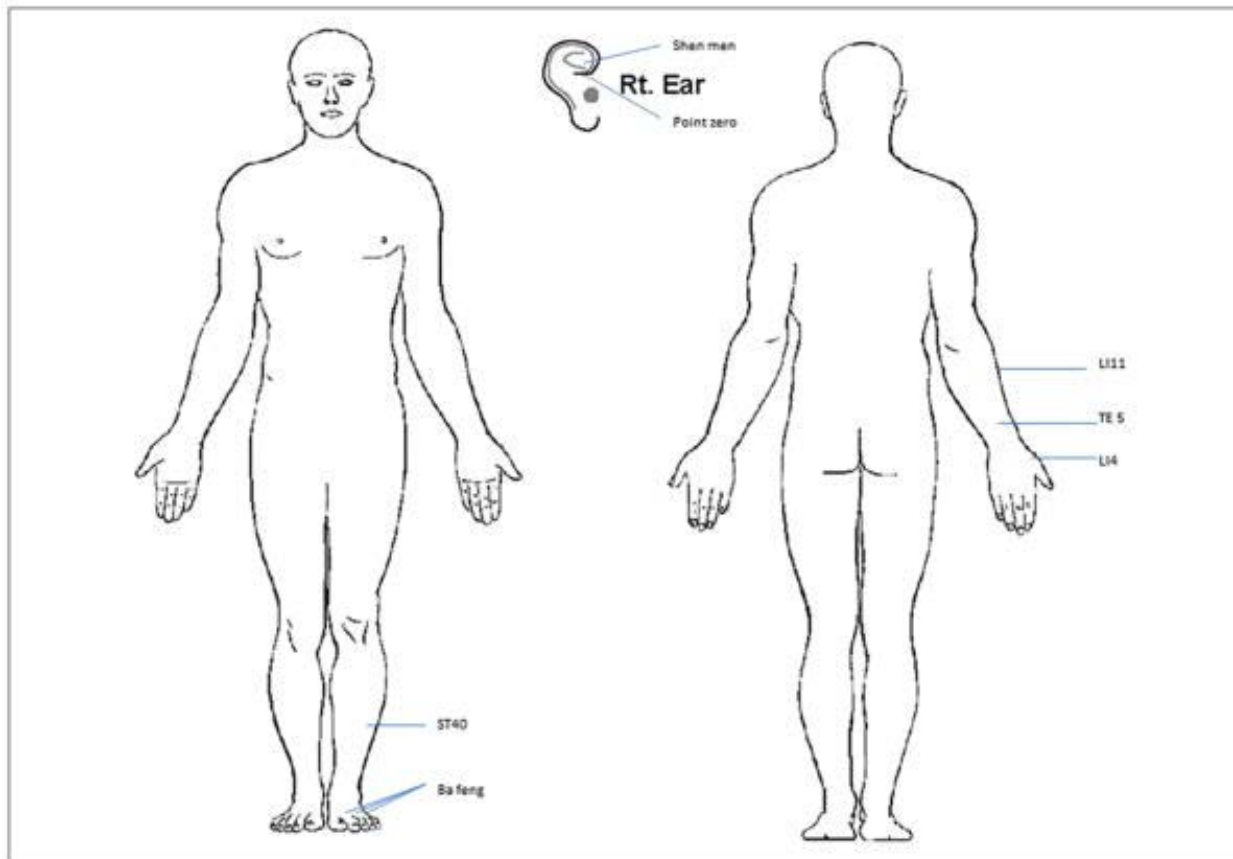
Acupuncture: Clinical Data



(A) Change in FACT/GOG-Ntx scores over 14 weeks. FACT/GOG-Ntx scores at each time point (means and 95% confidence intervals). (B) Change in NPS scores over 14 weeks. NPS scores at each time point (means and 95% confidence intervals).



Acupuncture: Clinical Data



Acupuncture point location map. Acupuncture needles were inserted 0.5 to 2 inches into the skin to reach *de qi* sensation and remained in the skin for 20 minutes.





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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline

Gary H. Lyman, Heather Greenlee, Kari Bohlke, Ting Bao, Angela M. DeMichele, Gary E. Deng, Judith M. Fouladbakhsh, Brigitte Gil, Dawn L. Hershman, Sami Mansfield, Dawn M. Mussallem, Karen M. Mustian, Erin Price, Susan Rafté, and Lorenzo Cohen



ASCO/SIO Clinical Practice Guideline 2018 for Integrative Therapies Breast Cancer



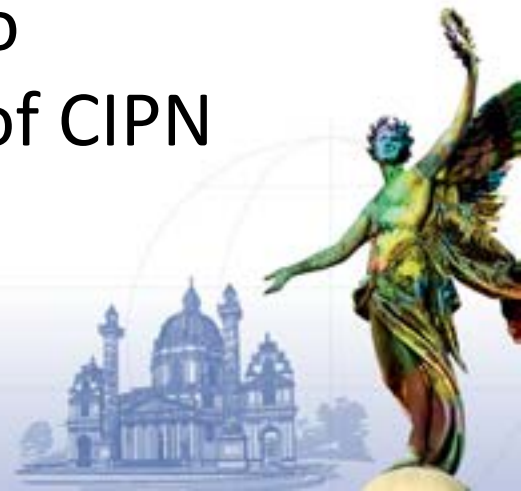
- Insufficient evidence for omega 3 fatty acids, vitamin E, acupuncture for treatment of CIPN
- Acetyl-L-carnitine is NOT recommended to prevent CIPN



Acupuncture: Future Directions

- Determine the precise mechanism of acupuncture
- Complete large, randomized, controlled trials of acupuncture to treat CIPN among cancer patients
- Development of best practice guidelines

Bottom line: currently insufficient data to recommend acupuncture for treatment of CIPN (ASCO/SIO, 2018)



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- **Neuro-stimulatory options**
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Neurostimulatory options and CIPN

- Transcutaneous Nerve Stimulation (TENS)
- Scrambler therapy
- Spinal cord stimulation



TENs

- Electrodes placed with intention to treat most symptomatic CIPN area
- A small battery operated unit with 2-4 leads applied to skin via sticky attachment pads.
- Available for patients to use at home, following some simple instructions.



Scrambler Therapy

- Scrambler Therapy:
 - Electrodes placed with intention to treat most symptomatic CIPN area
 - Initially placed in the pathway of nerves innervating areas of pain, tingling, and/or numbness, but not directly on symptomatic areas of skin.



Scrambler Therapy & TENs: Clinical Data

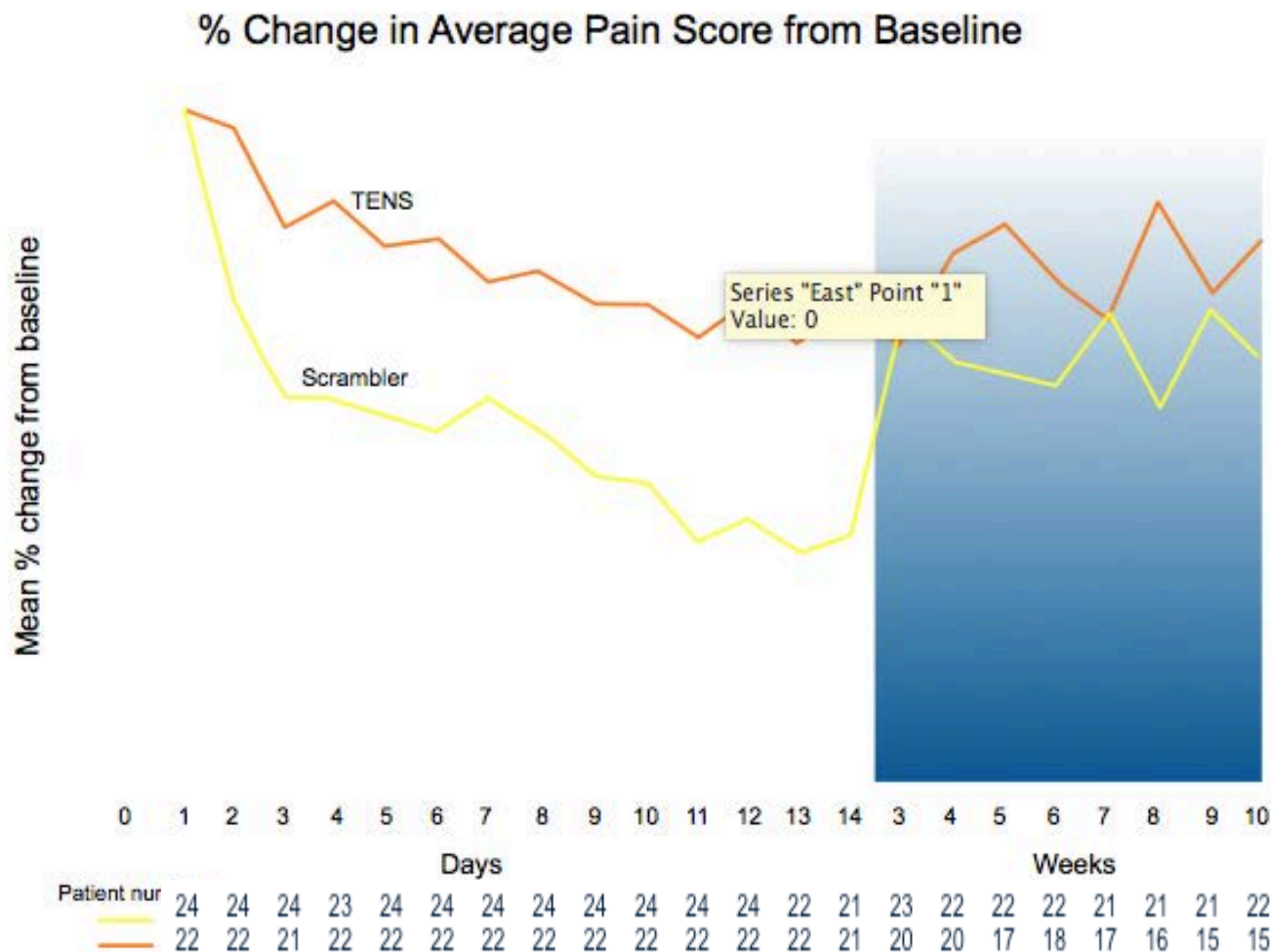


- Loprinzi, C. et al.: Randomized, Controlled Phase II Pilot Trial:
 - 50 patients accrued, 25 to each of the 2 study arms; 46 patients were evaluable.
 - At least 3 months since chemotherapy cessation
 - Moderate, chronic CIPN symptoms at baseline
 - Randomly assigned to receive scrambler therapy or trans-electrical nerve stimulation (TENs) for 2 weeks
 - Patient reported outcomes
 - Treatments were given for 30 minutes.
 - Treatments scheduled to be given for 10 consecutive weekdays.



Scrambler Therapy & TENS: Clinical Data

- Loprinzi, C. et al.: Results

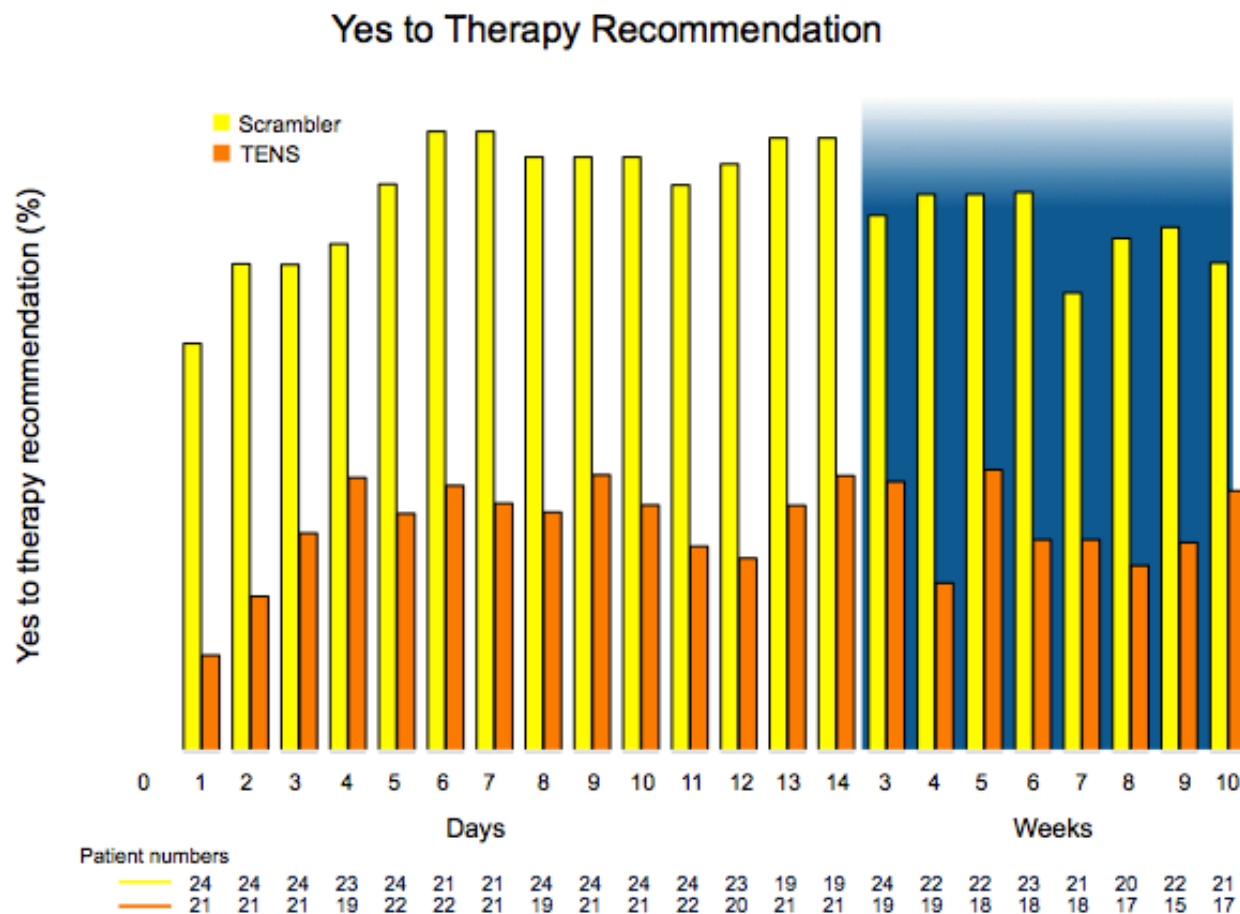


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Scrambler Therapy & TENs: Clinical Data

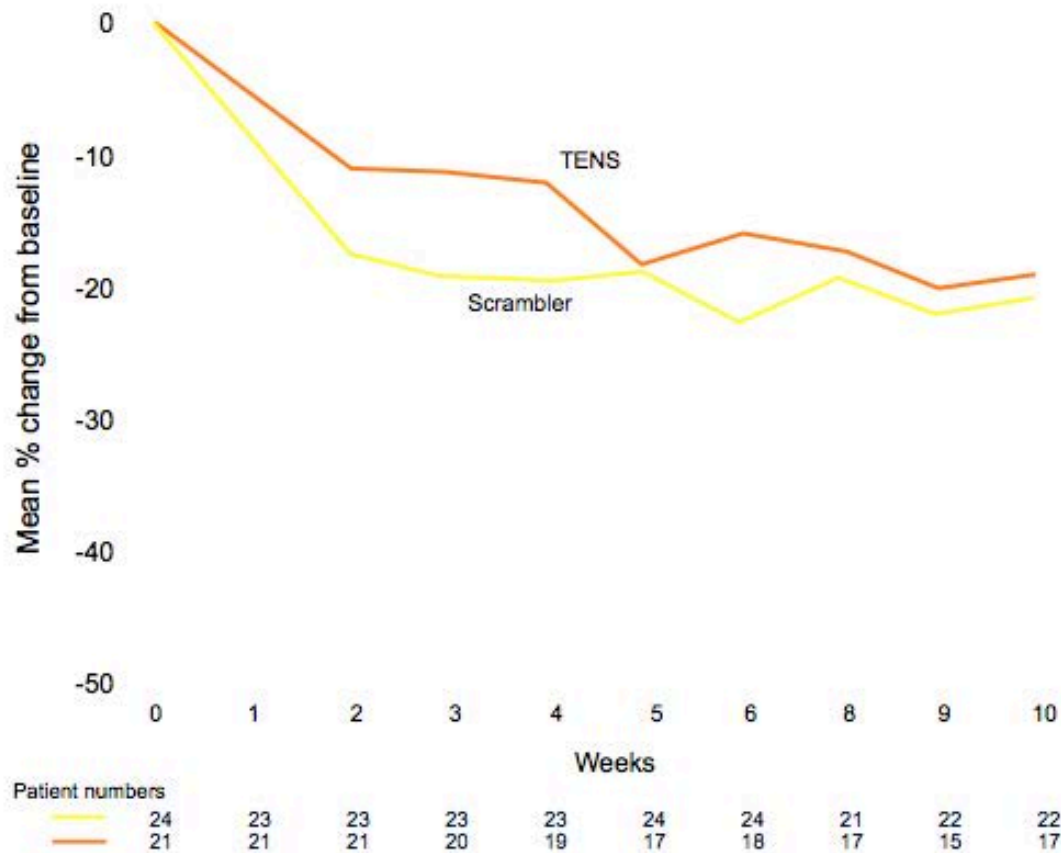
- Loprinzi, C. et al.: Results



Scrambler Therapy & TENs: Clinical Data

- Loprinzi, C. et al.: Results

Weekly % Change in EORTC QLQ-CIPN20 Sensory Scales



Scrambler Therapy & TENs: Clinical Data



- Loprinzi, C. et al.: Results Summary
 - Twice as many Scrambler-treated patients had at least a 50% documented improvement during the 2 treatment weeks from their baseline pain, tingling, and numbness scores in comparison to TENS-treated patients
 - Global Impression of Change scores for “neuropathy symptoms”, pain, and quality of life were similarly improved during the treatment weeks.
 - Scrambler group more likely than TENS group to recommend their treatment to others, both during the 2 week treatment period and the 8 week follow-up period ($P < 0.0001$).



Spinal Cord Stimulation

- Minimally invasive surgery
- Stimulator leads can be placed in many different regions
 - Most commonly in the epidural space to modulate the dorsal column of the spinal cord
- Modulates many different chemicals that work on pain
 - Increases GABA (helps to inhibit pain signals in the spinal cord)
 - Increases glycine
 - Decreases substance P



Neurostimulatory: Future Directions

- Evaluate optimal schedule for maintenance (scrambler)
- More data on spinal cord stimulation for painful CIPN needed
- Funding and availability of services
- Additional studies are needed to identify patients most likely to benefit from each type of neuro stimulatory approach



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- Acupuncture
- Scrambler Therapy and TENs
- **Future Strategies**



Future Strategies

- **Prior to treatment with neurotoxic chemo**
 - Evaluate risk (A CIPN Risk Calculator taking into account clinical and biological predictors)
 - Evaluate Function including balance and gait and mobility



Future Strategies

- **During neurotoxic chemotherapy**
 - Patient reported outcomes
 - Dose modifications if symptoms worsening
 - Functional assessment longitudinally
 - Optimize reversible risk factors (diabetic control, physical activity levels)
 - Early referral to cancer rehab services if symptom burden increasing



Future strategies

- **Post neurotoxic chemotherapy**
 - follow symptoms which can linger for years
 - Cancer rehabilitation
 - Exercise and balance training
 - Use of additional modalities for individualized symptom management





Creating a cancer-free world. *One person, one discovery at a time.*

The Ohio State University Comprehensive Cancer Center –
Arthur G. James Cancer Hospital and Richard J. Solove Research Institute



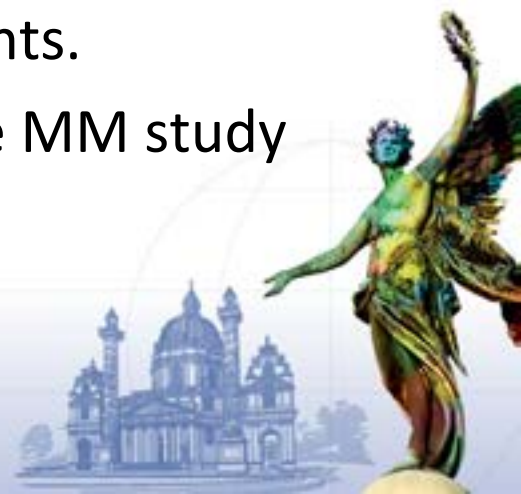
Thank you.

Questions?



Acupuncture: Mechanism

- Exact mechanism is under study
- May accelerate nerve regeneration
 - A positive correlation between the improvement in symptoms and nerve conduction function has been observed
- May affect inflammatory cytokines, neurotransmitters, or neurohormones.
 - Present study did not observe significant changes in these during the 10 weeks of acupuncture treatments.
 - Such changes may be difficult to detect in the MM study population



Scrambler Therapy & TENs:

Mechanism



- Scrambler Therapy:
 - Cutaneous neuro-stimulatory therapy
 - Exchanges endogenous pain information with synthetic “non-pain” / “normal-self” electrical signals
 - Signals hypothesized to move through peripheral afferent somatosensory C fibers to the brain, innervating the region of pain.
- TENs:
 - Cutaneous neuro-stimulatory therapy
 - Electrical current pulse along the intact surface of the skin to activate nerves below.
 - Increased analgesia occurs when a strong, non-painful electrical paraesthesia beneath the electrodes is achieved

