1st Annual MSKCC Cancer Rehabilitation Symposium

Managing Neuropathy to Promote Physical Activity

Tiffany Kendig, PT, DPT, MPH
Gabrielle Miskovitz, OTR/L, MS, CHT
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The presenters have no conflict of interest to report regarding any commercial product/manufacturer that may be referenced during this presentation.

Objectives

- Recognize mechanisms and presentation of CIPN
- Describe the impact of CIPN on function
- Identify key elements of examination
- Describe selected interventions to maximize outcomes

Peripheral Neuropathy

"A condition arising from damage and dysfunction of the peripheral nerves – the motor, sensory, and autonomic nerves that connect the brain and spinal cord to the rest of the body."

-Stubblefield et al., 2009; p.S1

Cancer-Related Etiology

- Direct effect
  - Infiltration
  - Compression
- Indirect effect
  - Paraneoplastic
  - Nutritional deficiencies
  - Metabolic disturbance
- Iatrogenic effect
  - Radiation
  - Immunosuppression
  - Bone marrow transplantation
  - ★Chemotherapy

Stubblefield et al., 2009; Stubblefield et al., 2012

Chemotherapy-Induced Peripheral Neuropathy

"Any injury, inflammation, or degeneration of the peripheral nerves because of the administration of a chemotherapeutic agent"

-Gilchrist 2012; p. 9

Neurotoxic Chemotherapeutics

- Ara-C, Ara-A, Ara-G
- Bortezomib
- Carboplatin
- Cisplatin
- Cytarabine
- Docetaxel
- Epothilones
- Etoposide
- Gemcitabine
- Hexamethylmelamine
- Ifosfamide
- Interferon-alpha
- Misonidazole
- Oxaliplatin
- Paclitaxel
- Procarbazine
- Suramin
- Thalidomide
- Vincristine
- Vinblastine
- Vinorelbine
- Vindesine

Hausheer et al., 2006; Lee & Wen, 2012; Lee & Wen, 2013

Neurotoxic Chemotherapeutics: Classes

Platinum Analogues	Vinca Alkaloids	Taxanes
• Cisplatin • Carboplatin • Oxaliplatin	• Vincristine • Vinblastine • Vinorelbine • Vindesine	• Paclitaxel • Abraxane • Docetaxel

Hausheer et al., 2006; Stubblefield et al., 2009; Wampler 2006

Neurotoxic Chemotherapeutics: Indications

Platinum Analogues	Vinca Alkaloids	Taxanes
• Ovarian • Lung • Testicular • Bladder • Colon • Colorectal	• Lymphoma • Leukemia • Multiple Myeloma • Breast • Lung	• Ovarian • Breast • Lung • Bladder • Prostate

Custodio 2008; Makker & Spriggs 2009; http://chemocare.com

Incidence

Class	Incidence
Platinum Analogues	Cisplatin: 28%-100% Carboplatin: 6-42% Oxaliplatin, acute: 85-95%
Vinca Alkaloids	30%-47%
Taxanes	Paclitaxel: 57%-83% Abraxane: 73% Docetaxel: 11%-64%

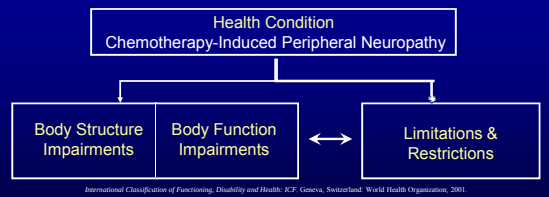
Stubblefield et al., 2009

Risk Factors

- Chemotherapeutic profile
  - Type
    - Taxanes: HR=2.22 (95% CI: 1.85-2.66)
    - Combination therapy: HR=3.33 (95% CI 2.05-5.05)
  - Dose
  - Duration
  - Schedule
- PNS integrity
  - Pre-existing dysfunction
  - Neurologic sequelae of cancer treatment

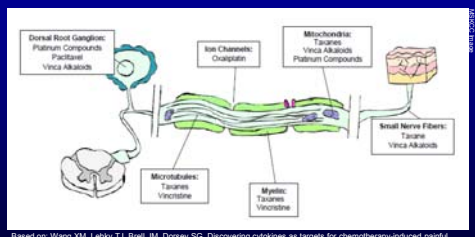
Hausheer et al., 2006; Stubblefield et al., 2009; Nurgalieva et al., 2010

The Big Picture



International Classification of Functioning, Disability and Health: ICF. Geneva, Switzerland: World Health Organization; 2001.

Mechanism



Based on: Wang XM, Lehky TJ, Brell JM, Dorsey SG: Discovering cytokines as targets for chemotherapy-induced painful peripheral neuropathy. *Cytokine*. 2012;59(1):3-9.

Body Structure Impairments

- Peripheral Nervous System

Sensory
- First and most affected

Motor
- Less often affected
- Associated with more severe sensory involvement
- Potential for re-generation

Autonomic
- Rarely affected

Hausheer et al., 2006; Stubblefield et al., 2009

Body Function Impairments

- Sensory
  - Numbness
  - Paresthesia
  - ↓ Thermal perception
  - ↓ Light touch
  - ↓ Position sense
  - ↓ Vibration
  - Pain
- Motor
  - ↓ Strength
  - Cramping
  - Muscle fatigue
- Autonomic
  - Orthostasis
  - Arrhythmia
  - Constipation
  - Incontinence

Hausheer et al., 2006; Hile et al., 2010; Stubblefield et al., 2009; Stubblefield et al., 2012

Body Function Impairments

- Neuropathic pain
  - Caused by nervous system lesion / dysfunction
  - No nociceptive stimulation required
  - Disproportionate to the stimulation of receptor

Merskey & Bogduk, 1994; Serra et al., 1999

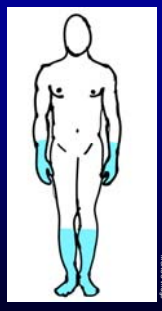
Positive vs. Negative Symptoms

- Positive Symptoms
  - Pain
    - Allodynia
    - Dysesthesia
    - Hyperesthesia
    - Hyperalgesia
    - Paresthesia
- Negative Symptoms
  - ↓ Strength
  - Sensory Loss
    - Numbness
    - ↓ Light touch
    - ↓ Position sense
    - ↓ Thermal perception
    - ↓ Vibration

Stubblefield et al., 2009; Stubblefield et al., 2012

Presentation: Hallmarks

- Distal
- Symmetric
- Length-dependent
- Stocking-glove distribution
- Sensory > motor
- Onset after chemotherapy
  - Progressive, rapid or coasting
- Dose-dependent



Custodio 2008; Hausheer et al., 2006; Stubblefield et al., 2009

Presentation: Platinum Compounds

Agent (Dose)	Sensory	Motor	Reflexes	Autonomic
Cisplatin (300 mg/m²)	• Numbness • Tingling • Pain • Paresthesias • Stocking-glove distribution • ↓ Proprioception • Ataxia with impaired gait	• WNL	• ↓ in proportion to sensory impairment	• Rare
Carboplatin (800-1600 mg/m²)	• Less severe but similar to Cisplatin	• WNL	• WNL	• Rare

Lee & Wen, 2012; Lee & Wen 2013; Stubblefield et al., 2009; Wampler 2006

Presentation: Platinum Compounds

Agent (Dose)	Sensory	Motor	Reflexes	Autonomic
Oxaliplatin, Acute (Any dose)	• Dysesthesia - cold-induced · mouth · throat · UE's	• Cramps • Muscle spasms, throat	• WNL	• None
Oxaliplatin, Chronic (750-850 mg/m²)	• Similar to Cisplatin	• WNL	• WNL	• Rare

Lee & Wen, 2012; Lee & Wen 2013; Stubblefield et al., 2009; Wampler 2006

Presentation: Vinca Alkaloids

Agent (Dose)	Sensory	Motor	Reflexes	Autonomic
Vincristine (4-10 mg) Vinblastine (4-10 mg) Vinorelbine (4-10 mg) Vindesine (4-10 mg)	• Tingling · distal · symmetric · LE's • UE's rarely affected	• Weakness · distal · symmetric • May progress to foot drop • Impaired gait	• ↓ / absent at ankle	• Constipation • Orthostatic hypotension

Lee & Wen, 2012; Lee & Wen 2013; Stubblefield et al., 2009; Wampler 2006

Presentation: Taxanes

Agent (Dose)	Sensory	Motor	Reflexes	Autonomic

Paclitaxel (100-300 mg/m²)
Docetaxel (75-100 mg/m²)
	• Numbness
	• Pain
	• Paresthesias
	• Stocking-glove distribution
	  ◦ Feet > hands
	• Ataxia
	• ↓ Vibration
	• ↓ Proprioception
		• Weakness
		  ◦ occasional
		• Impaired gait
			• ↓ Ankle	• Rare

Lee & Wen, 2012; Lee & Wen 2013; Stubblefield et al., 2009; Wampler 2006

Functional Implications

Balance	• ↓ Postural control s/p Taxane therapy • Impairment associated with high fall risk
Falls	• 11.9 – 20% of persons with CIPN • ↑ Risk with cumulative dose, cycle & ↑CIPN score
Mobility	• Standing, walking, running, stair negotiation • Sensory impairment associated w/ poor mobility in survivors (OR 1.65, 95% CI: 0.96-2.83)
ADL	• ↓ UE function • Cooking, cleaning, dressing, writing, typing, grooming
QOL	• 15-20% ↓ in health-related QOL scores

Gewandter et al., 2013; Hile et al., 2010; Marchese et al., 2011; Ness et al., 2013; Sasane et al., 2010; Stubblefield et al. 2009; Stubblefield et al., 2012; Thurman et al., 2008; Tofthagen et al., 2012; Wampler et al., 2005; Wampler et al. 2007; Winters-Stone et al., 2011

Functional Implications

- *"…worse than alopecia, pancytopenia & fatigue…"*
- *"least expected… most distressing & disabling…"*
- *"…made patients feel dependent, disabled & helpless"*

-Sasane et al., 2010; p. E16

Diagnostic Classification

Common Terminology Criteria for Adverse Events Version 4.03

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Motor Neuropathy	Asymptomatic, clinical or diagnostic observations only	Moderate symptoms; ***limiting instrumental ADL***	Severe symptoms; ***limiting self-care ADL; assistive device indicated***	Life-threatening consequences; urgent intervention indicated	Death
Sensory Neuropathy	Asymptomatic, Loss of DTR or paresthesia	Moderate symptoms; ***limiting instrumental ADL***	Severe symptoms, ***limiting self-care ADL***	Life-threatening consequences; urgent intervention indicated	Death
Paresthesias	Mild symptoms	Moderate symptoms; ***limiting instrumental ADL***	Severe symptoms, ***limiting self-care ADL***	--	--

Common Terminology Criteria for Adverse Events, version 4.03, June 2010, National Institutes of Health, National Cancer Institute, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Prognosis

Class	Recovery
Platinum Compounds	Cisplatin & Carboplatin: Partial recovery, possible "coasting" Oxaliplatin, acute: ≤1 week to resolve Oxaliplatin, chronic: 3 months to resolve, rare long-term persistence ↑ risk of sensory impairment as late effect (OR 1.62, 95% CI: 0.97-2.72)
Vinca Alkaloids	≤ 3 months to resolve Vincristine may continue ↑ risk of motor impairment as late effect (OR 1.66, 95% CI: 1.04-2.64)
Taxanes	≤3 months to resolve May continue

Lee & Wen, 2012; Lee & Wen 2013; Ness et al., 2013; Stubblefield et al., 2009

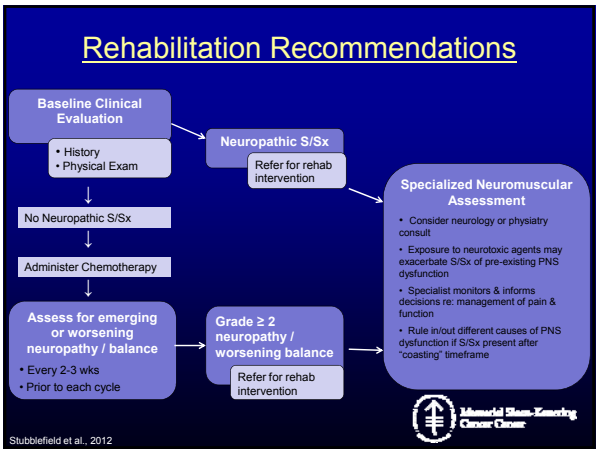
Management

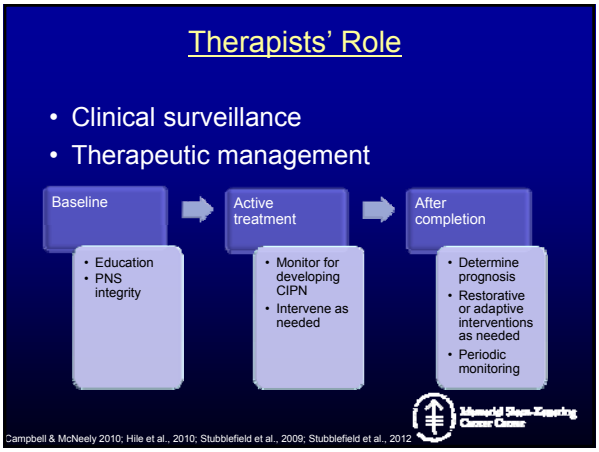
Prophylaxis
- Vitamin E
- Calcium/Magnesium
- Glutamine

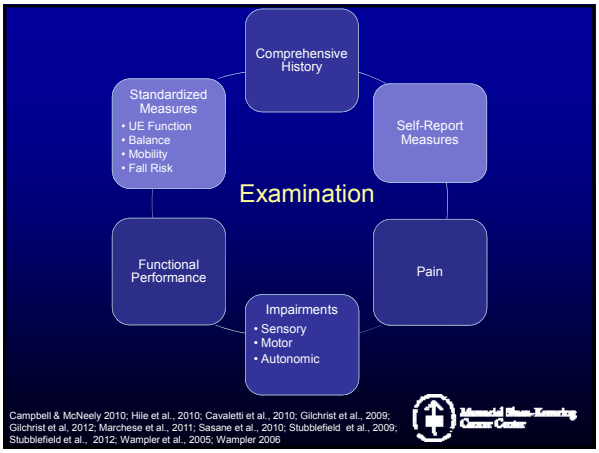
Negative Symptoms
- Education on safety
- Fall prevention
- Functional training
- Strengthening
- Physical activity

Positive Symptoms
- Pharmacologic
  - Anticonvulsants
  - Antidepressants
  - Topical anesthetics
  - Opioids
- Pain procedures
- Neuromuscular stimulation
- Complementary / Alternative medicine

Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007







Subjective: History

- Personal history
- Family history of hereditary neuropathy
- Alcohol use
- Comorbid conditions
  - DM
  - HIV
  - Guillain-Barre
  - CIDP
  - Radiculopathy

Stubblefield et al., 2009

Subjective: Neurotoxicity Profile

- Chemotherapeutic regimen
  - Temporal profile
- Symptoms
  - Type
  - Distribution
  - Severity
- Pain
- Time course
- Treatment implications

Stubblefield et al., 2009

Subjective: Direct Questioning

Symptoms

- Do you feel:
  - Numbness/tingling in hands/feet?
  - Pain in hand/feet? (rate 0-10)
  - Like having stockings/gloves on?
  - Weakness in arms/legs?
  - These sensations bother you or are getting worse?

Functional Performance

- Do you drop things often?
- Have you fallen recently?
- Do you have difficulty walking?
- Do you have difficulty climbing stairs?
- Do these sensations interfere with your work or daily activities?

Stubblefield et al., 2009

Self-Report Measures

Functional Assessment

- PNQ (Patient Neurotoxicity Questionnaire)
- FACT (Functional Assessment of Cancer Therapy)
  - Taxane
  - GOG-Ntx (Gynecologic Oncology Group- Neurotoxicity Scale)
  - GOG–Oxaliplatin Specific Ntx12

Pain

- VAS (Visual analogue scale)
- Brief Pain Inventory
- Neuropathic Pain Score
- LANSS (Leeds Assessment of Neuropathic Symptoms & Signs of Pain Scale)

Cavaletti et al, 2010; Smith et al., 2013; Marchese et al., 2011; Sasane et al., 2010; Stubblefield et al., 2009; Stubblefield et al., 2012

Visual Inspection

- Integument
  - Nail coloration
  - Skin integrity
- Posture
  - COG alignment
- Musculoskeletal abnormalities
  - Foot structure

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Marchese et al., 2011; Stubblefield et al., 2009

Impairments

Sensory

- Pain & temperature
  - Pin-prick sensitivity
- Vibration
  - Biothesiometer
  - 128 Hz tuning fork
- Light touch
  - Semmes-Weinstein Monofilaments
- Proprioception

Motor

- Distal muscle strength
  - MMT
  - Dynamometry
- Deep tendon reflexes

Autonomic

- Heart rate
- Orthostatic evaluation

Gilchrist et al., 2009; Kanji et al., 2010; Marchese et al., 2011; Sasane et al., 2010; Stubblefield et al., 2009; Stubblefield et al., 2012; Wampler 2006; Wampler et al., 2005

Composite Scales: Total Neuropathy Score (TNS) Scales

	TNS	mTNS	cTNS
Symptoms			
Sensory	✓	✓	✓
Motor	✓	✓	✓
Autonomic	✓		✓
Exam			
Pin sensibility	✓	✓	✓
Vibration	✓	✓	✓
Strength	✓	✓	✓
Deep tendon reflexes	✓	✓	✓
Nerve conduction studies	✓		

mTNS: Modified Total Neuropathy Score; cTNS: Clinical Total Neuropathy Score

Cavaletti et al, 2010; Gilchrist et al., 2009; Gilchrist et al., 2012; Marchese et al., 2011; Wampler et al. 2006; Wampler 2006

Composite Scales: Total Neuropathy Score (TNS) Scales

	0	1	2	3	4
Symptoms					
Sensory	None	Fingers or toes	Extends to ankle or wrist	Extends to knee or elbow	Above knees or elbows, or disabling
Motor	None	Slight difficulty	Moderate difficulty	Requires assist	Paralysis
Autonomic	0	1	2	3	4
Exam					
Pin sensibility	Normal	↓ fingers/toes	↓ up to wrist/ankle	↓ up to elbow/knee	↓ above elbow/knee
Vibration	Normal	↓ fingers/toes	↓ up to wrist/ankle	↓ up to elbow/knee	↓ above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
DTR	Normal	↓ ankle	Absent ankle	Ankle absent, others ↓	All absent

Cavaletti et al., 2010; Gilchrist 2012; Wampler et al., 2006

Functional Task Performance

- Deficits may be subtle or marked
- Quality is key

- Gait
  - Kinematics
  - Speed
  - Environment
- Name writing
- Buttoning

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Brach et al., 2011; Hile et al., 2010; Hile et al., 2012; Silver & Gilchrist, 2011; Richardson et al., 2005; Stubblefield et al., 2009 ; Tofthagen et al., 2012; Wampler et al., 2007

Standardized Measures: UE Function

- Grooved Peg Board
- Timed Pellet Retrieval

Stubblefield et al., 2009; Wampler et al., 2005; Wampler 2006; Wampler et al., 2007

Standardized Measures: Balance

- Sensory Organization Test (SOT)
  - Postural stability
  - COG alignment
  - Strategy analysis
  - Sensory analysis
  - Correlates with:
    - Fullerton Advanced Balance Scale (FABS)
    - Timed Up & Go (TUG)

Gilchrist et al., 2009; Wampler et al., 2005; Wampler 2006; Wampler et al., 2007

Standardized Measures: Balance

- BESTest
  - Biomechanical constraints
  - Stability limits and verticality
  - Anticipatory postural adjustments, transitions
  - Reactive postural responses
  - Sensory orientation
  - Dynamic balance during gait & cognitive effects

Horak 2009; www.rehabmeasures.org

Standardized Measures: Mobility

- Romberg
- Tandem Romberg
  - <10 sec
- Single leg stance
- Functional Reach
  - <25.4 cm
- Timed "Up & Go"
  - >13.5 sec
- Berg Balance Scale
  - <45/56
- Dynamic Gait Index
  - ≤19/24
- Fullerton Advanced Balance Scale
  - ≤25/40
- Short Physical Performance Battery

** Use caution with interpretation of fall risk*

Gilchrist et al., 2009; Hile et al., 2010; Hile et al., 2012; Jernigan et al., 2012; Marchese et al., 2011; Wampler et al., 2005; www.rehabmeasures.org

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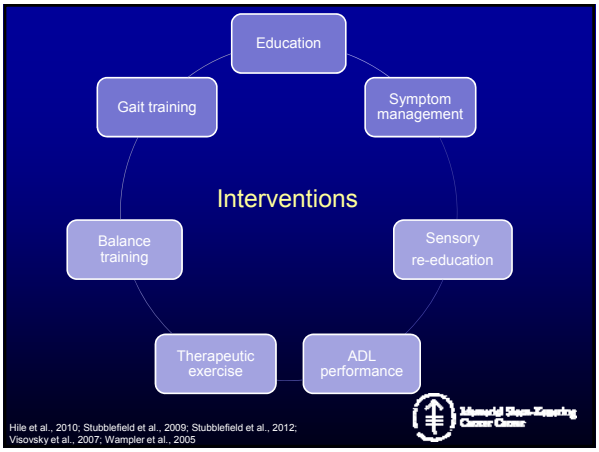

Hile et al., 2010; Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007; Wampler et al., 2005

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Education: Signs and Symptoms

- Recognize signs & symptoms
- Importance of continuous monitoring
- Report to healthcare provider for timely management

Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

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Education: Injury Prevention

- Skin protection
  - Regular self-inspection of hands & feet
    - Proper fit of footwear & orthotics
  - Protect against ischemic injury, thermal stress
    - Set water temperature < 120° F
    - Bath thermometer
    - Gloves with dishwashing
    - Potholders / mitts with hot & cold items
    - Caution with knives

Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

Education: Fall Prevention

- Fall prevention is key
- Visual compensation for somatosensory loss
  - Unfamiliar environments
  - Surface changes
  - Maximize visual contrast
- Proper footwear
  - Closed back and toe
  - No heels
  - Supportive insoles, not too soft
  - Non-skid soles

Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

Education: Fall Prevention

- Household modifications
  - Living Area
    - Secure or remove throw rugs
    - Clutter-free floors
    - Secure cords / wires
    - Adequate lighting
    - Nightlights
  - Kitchen
    - Store items within reach
  - Bathroom
    - Bathmat, non-slip surfaces
    - Grab bars
  - Stairs
    - Adequate lighting
    - Handrails
    - Clutter-free

Gillespie et al., 2012; Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

Symptom Management: Pain

- Pain management is key
- Neurostimulation therapies
  - Transcutaneous electrical nerve stimulation (TENS)
  - Electrical Stimulation (ES)
  - High Frequency (HF)
  - In diabetic PN:
    - ↓ pain, numbness, tingling
    - ↑ self-reported function
    - No adverse effects
    - Transient benefit

Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007; Wampler et al., 2005

Symptom Management: Paresthesia

- Cold Sensitivity
  - Room-temperature foods & drinks
  - Avoid iced or frozen food and drinks
  - Gloves to handle refrigerated/frozen item
  - Weather-appropriate protective clothing

Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

Symptom Management: Paresthesia

- Massage
- Textures
- Vibration
- Theraputty
- Compression
- Kinesiotape

Symptom Management: Autonomic

- Orthostatic Intolerance
  - Time to acclimate between positional changes
  - Dangle feet, ankle pumps prior to standing
  - Wait before leaving support surface
  - Compression stockings / abdominal binder
  - Hydration

Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

Sensory Re-education

- Desensitization
- Tactile gnosis
  - Rice
- Graded touch & coordination
  - There's an app for that!

Physical Function / ADL Performance

- Meals
  - Vegetable chopper
  - Large handled utensils
  - Automatic jar opener
- Dressing
  - Velcro closures
  - Button hook

Stubblefield et al., 2009

Physical Function / ADL Performance

- Writing
  - Pen grip
  - Dycem under paper

- Typing
  - Velcro or Dycem on computer keys

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Stubblefield et al., 2009

Therapeutic Exercise

- Multi-modal exercise
- No studies to date in CIPN
- In PN of varying etiologies:
  - ↑ function, muscle strength, balance, stance, functional reach, NCV
  - ↓ pain, fall risk
  - Reverse muscle loss
  - Potential neuro-protective effects

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Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

Therapeutic Exercise

- Strengthening
  - Intrinsics
  - Core
  - Proximal LE
  - Dynamic ankle stabilization
- Aerobic conditioning
- Stretching
  - Wrist/finger flexors
  - Toe flexors
  - Gastroc/soleus

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Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

Balance Training

- Balance training is key
- Wampler et al., 2005
  - 45-60 min, 2x/week for 4 weeks
  - ↑ self-perceived balance
- Comprehensive training:
  - Static
  - Dynamic
  - Context-Specific
  - Manipulation activities
  - LE strengthening

Wampler et al., 2005

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Stubblefield et al., 2009; Stubblefield et al., 2012; Wampler et al., 2005; Wampler 2006

Balance Training

- Additional considerations
  - Postural alignment
  - COG alignment
  - Postural adjustments
  - Movement strategies
  - Sensory strategies
  - Compensations

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Horak 2006

Gait Training

- Mobility training is key
- In diabetic PN:
  - SC, vertical surface, orthotic
  - ↑ gait characteristics (spatial & temporal)
- Quality
- Endurance tasks
- Environment
- Task constraints
- Assistive devices
- Orthotics

MSKCC photos

Richardson et al., 2004; Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

Gait Training

- Environment
  - Terrain / obstacles
  - Complexity
- Task constraints
  - Time
  - Physical load
- Assistive devices
  - Cane, walker
  - Somato-sensory input
- Orthotics
  - AFO, dorsiflexion assist, custom
  - Used for foot drop, ankle instability

Richardson et al., 2004; Stubblefield et al., 2009; Stubblefield et al., 2012; Visovsky et al., 2007

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The Bottom Line

Health Condition
Chemotherapy-Induced Peripheral Neuropathy

Body Structure Impairments	Body Function Impairments	Limitations & Restrictions
Peripheral Nervous System • Sensory nerves • Motor nerves • Autonomic nerves	Paresthesias Pain Loss of sensation Distal muscle weakness Loss of deep tendon reflexes Postural instability Orthostatic intolerance	Impaired balance Gait deviations • wide base of support • foot drop • toe drag Mobility limitations Falls Limited ADL/IADL performance • Dressing • Grooming • Writing • Typing • Driving

Hausheer et al., 2006; Hile et al., 2010; Marchese et al., 2011; Stubblefield et al., 2009; Nurgalieva et al., 2010; Tofthagen et al., 2012; Wampler 2006; Wampler et al., 2007

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The Bottom Line

- Clinical surveillance is necessary & on-going
- Key elements of evaluation include:
  - Direct questioning regarding symptoms
  - Impairment-level tests of PNS functions
  - Functional task analysis
  - Standardized measures of fall risk, mobility & balance
- Comprehensive interventions should include:
  - Adaptive and restorative strategies
  - Fall prevention, pain management, balance & mobility training

Campbell & McNeely 2010; Hile et al., 2010; Marchese et al., 2011; Stubblefield et al., 2009; Stubblefield et al., 2012; Wampler et al., 2005

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