Functional Impairments in Patients with Chemotherapy-Induced Peripheral Neuropathy (CIPN)

The Evidence for Clinical Assessment and Rehabilitation

Betty Smoot, PT, DPTSc, MAS
Associate Professor
Department of Physical Therapy and Rehabilitation Science
University of California, San Francisco
Objectives

For adults with CIPN:

1. Identify key clinical self-report and performance based outcome measures for pain, balance, and gait.
2. Describe functional impairments and limitations.
3. Discuss patient-reported management strategies.
4. Describe current evidence for selected interventions used in the management of pain, balance, and gait.
Significance

- Over 14 million cancer survivors in the US; estimated to increase to 19 million by 2024. (ACS, 2014)
- Patients may be referred to PT for treatment of CIPN.
- CIPN may be a co-morbid condition for patients referred to PT for other impairments.
Decreased proprioception

Pain

Decreased touch, temperature and vibratory sensation

Muscle fatigue, mild distal weakness

Muscle cramps

Vestibular dysfunction

Autonomic dysfunction

Muscle cramps, muscle fatigue, mild distal weakness, decreased proprioception, pain, decreased touch, temperature and vibratory sensation, vestibular dysfunction, autonomic dysfunction

Functional limitations

Gerwandter, 2013; Tofthagen, 2012; Wampler, 2007; Kneis, 2015; Mols, 2014
Assessment

- Neurophysiologic tests of PNS function: EMG, NCS, QST
  - Limitations: Pain, cost, limited correlation w/patient reports. (Stubblefield, 2009)
- Clinical assessment
  - H & P
  - Practitioner based grading systems
    - The NCI Common Terminology Criteria for Adverse Events
    - Total Neuropathy Scale
    - mTNS - Modified total neuropathy score, without the NCS
- Subjective patient based measures of pain and function
  - FACT/GOG-Ntx - Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
  - EORTC QLQ CIPN-20 - sensory (9), motor (8), autonomic (3)
- Objective measures of function
Diagnostic classification:

Common Terminology Criteria for Adverse Events

- **Peripheral sensory neuropathy**
  - Grade 1: asymptomatic; loss of DTR; paresthesia
  - Grade 2: moderate symptoms, limiting IADL
  - Grade 3: severe symptoms, limiting self care ADL; AD indicated
  - Grade 4: life threatening

- **Peripheral motor neuropathy**
  - Grade 1: asymptomatic, clinical or diagnostic observation only; intervention not indicated
  - Grade 2: moderate symptoms; limiting IADL
  - Grade 3: severe symptoms, limiting self care ADL; AD indicated
  - Grade 4: life threatening
Outcomes Assessment: EDGE Taskforce

• Valid, reliable, responsive tests and measures are essential in establishing effectiveness of an intervention.

• CSM 2015: APTA Oncology Section EDGE taskforce on Breast Cancer Outcomes presented Clinical Measures of CIPN, Balance, and Functional Mobility
# EDGE taskforce ratings scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Recommendation Level</th>
<th>Rating Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4</strong></td>
<td>Highly recommend</td>
<td>Good psychometric properties &amp; clinical utility; used in research in BC populations</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Recommend</td>
<td>Good psychometric properties &amp; clinical utility; no published research using this outcome in BC populations</td>
</tr>
<tr>
<td><strong>2A</strong></td>
<td>Unable to recommend at this time</td>
<td>Insufficient information; the measure has been used in research on individuals with or post BC</td>
</tr>
<tr>
<td><strong>2B</strong></td>
<td>Unable to recommend at this time</td>
<td>Insufficient information; no published evidence that the measure has been applied to research on individuals with or post BC</td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>Do not recommend</td>
<td>Poor psychometric and/or poor clinical utility</td>
</tr>
</tbody>
</table>

Fisher, Hile, Huang, Davies, 2015
EDGE taskforce: Clinical Measures of CIPN

- Two clinically useful 2a measures included:
  - EORTC QLQ CIPN-20
  - mTNS

- One measure was rated “4”
    - 11 item (0 to 4), supplemental questionnaire
    - Validated in breast and ovarian cancer populations
### FACT-GOG-NTx (Additional Questions)

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have numbness or tingling in my hands</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I have numbness or tingling in my feet</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I feel discomfort in my hands</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I feel discomfort in my feet</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I have joint pain or muscle cramps</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I feel weak all over</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I have trouble hearing</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I get a ringing or buzzing in my ears</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I have trouble buttoning buttons</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I have trouble feeling the shape of small objects when they are in my hand</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I have trouble walking</td>
<td>0 1 2 3 4</td>
</tr>
</tbody>
</table>
EDGE taskforce: Clinical Measures of Balance

- No “4”s
- Two measures received a “3” (recommended)

FAB Scale
- 10 performance-based activities, 0 to 4 point scale
- Scored 0-40 (higher = better)
- 12 minutes or less

TUG – timed up and go
- 5 minutes or less

2a: Berg Balance Scale; Balance Evaluation Systems Test
EDGE taskforce: Clinical Measures of Functional Mobility

- 4 measures received a rating of “4” (highly recommended)
  - 2 minute walk test
  - 6 minute walk test
  - TUG
  - 5 times sit to stand
Findings from the CIN study

- Descriptive, longitudinal study (n = 218)
  - Adults $\geq 18$ years of age who had completed their course of a platinum or taxane CTx
  - Change in sensation or pain in hands or feet for $\geq 3$ months duration
  - Pain severity or a pain quality score of $\geq 3$

- Objective functional measures included:
  - Hands: Purdue Pegboard Test, Grip strength
  - Feet: FABS, TUG

- Self-management strategies
Pegboard test

- Number of pins in in 30 seconds
  - Dominant hand: 14.02 (2.40)
  - Non-dominant hand: 13.50 (2.23)
  - Dominant > non-dominant ($p < 0.001$)

Normative data: 60 - 69 years
Females
- Dominant: 14.4 pins (2.15)
- Non-dominant: 13.9 pins (2.19)
Males
- Dominant: 13.6 pins (1.74)
- Non-dominant: 13.1 pins (1.56)

mean age 60.4 (10.3)

Agnew, 1988
Grip strength

• Entire sample  n=212
  • Dominant hand: 25.3kg (9.0)
  • Non-dominant hand: 24.0 kg (8.4)

• Female (n=181)
  • Dominant hand: 22.7 kg (5.5)
  • Non-dominant hand: 21.9 kg (5.4)

• Male (n=31)
  • Dominant hand: 40.6 kg (10.2)
  • Non-dominant hand: 36.8 kg (11.1)

Dominant > non-dominant (p < 0.001)

Normative data: 60-64 years

• Right: 25.9 kg (22.2 - 29.6)
• Left: 23.0 kg (18.6 - 27.3)

Normative data: 60-64 years

• Right: 41.7 kg (36.8 - 46.7)
• Left: 38.7 kg (33.4 - 44.0)

mean age 60.4 (10.3)
### Consolidated grip strength reference values for females

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Source references</th>
<th>Total subjects (n)</th>
<th>Left (lb) mean (95% CI)</th>
<th>Left (kg) mean (95% CI)</th>
<th>Right (lb) mean (95% CI)</th>
<th>Right (kg) mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–24</td>
<td>[5,7,9,11,16]</td>
<td>133</td>
<td>61.4 (51.0–71.8)</td>
<td>27.9 (23.1–32.6)</td>
<td>67.4 (58.9–75.8)</td>
<td>30.6 (26.7–34.4)</td>
</tr>
<tr>
<td>25–29</td>
<td>[5–7,10,16]</td>
<td>142</td>
<td>68.0 (59.9–76.0)</td>
<td>30.8 (27.2–34.5)</td>
<td>74.5 (65.1–83.9)</td>
<td>33.8 (29.5–38.1)</td>
</tr>
<tr>
<td>30–34</td>
<td>[5–7,10,16]</td>
<td>141</td>
<td>70.0 (64.0–75.9)</td>
<td>31.8 (29.0–34.4)</td>
<td>74.5 (63.8–85.1)</td>
<td>33.8 (28.9–38.6)</td>
</tr>
<tr>
<td>35–39</td>
<td>[5–7,10,16]</td>
<td>142</td>
<td>66.5 (56.9–76.1)</td>
<td>30.2 (25.8–34.5)</td>
<td>73.1 (63.0–83.3)</td>
<td>33.2 (28.6–37.8)</td>
</tr>
<tr>
<td>40–44</td>
<td>[5–7,10,16]</td>
<td>133</td>
<td>64.5 (54.0–74.9)</td>
<td>29.3 (24.5–34.0)</td>
<td>72.3 (61.7–82.9)</td>
<td>32.8 (28.0–37.6)</td>
</tr>
<tr>
<td>45–49</td>
<td>[5–7,10,16]</td>
<td>133</td>
<td>67.8 (56.8–78.8)</td>
<td>30.8 (25.8–35.7)</td>
<td>74.8 (63.7–85.9)</td>
<td>33.9 (28.9–39.0)</td>
</tr>
<tr>
<td>50–54</td>
<td>[5–7,10,16]</td>
<td>116</td>
<td>63.4 (52.9–73.9)</td>
<td>28.8 (24.0–33.5)</td>
<td>68.2 (58.8–77.5)</td>
<td>30.9 (26.7–35.2)</td>
</tr>
<tr>
<td>55–59</td>
<td>[5–7,10,14,16]</td>
<td>123</td>
<td>60.0 (54.3–65.1)</td>
<td>27.2 (24.6–29.5)</td>
<td>66.0 (58.1–74.0)</td>
<td>29.9 (26.4–33.6)</td>
</tr>
<tr>
<td>60–64</td>
<td>[5,7,8,10,12,16]</td>
<td>132</td>
<td>50.6 (41.0–60.1)</td>
<td>23.0 (18.6–27.3)</td>
<td>57.1 (48.9–65.3)</td>
<td>25.9 (22.2–29.6)</td>
</tr>
<tr>
<td>65–69</td>
<td>[5,7,8,11–13,16]</td>
<td>118</td>
<td>50.4 (43.1–57.7)</td>
<td>22.9 (19.6–26.2)</td>
<td>56.5 (49.6–63.4)</td>
<td>25.6 (22.5–28.8)</td>
</tr>
<tr>
<td>70–74</td>
<td>[5,7,9,11–13,16]</td>
<td>166</td>
<td>49.9 (42.5–57.8)</td>
<td>22.5 (19.1–25.8)</td>
<td>53.4 (45.6–61.3)</td>
<td>24.2 (20.7–27.8)</td>
</tr>
<tr>
<td>75+</td>
<td>[5,7,9,11–13,15,16]</td>
<td>361</td>
<td>46.6 (38.5–54.8)</td>
<td>16.4 (14.7–18.1)</td>
<td>39.6 (35.3–43.9)</td>
<td>18.0 (16.0–19.9)</td>
</tr>
</tbody>
</table>

### Consolidated grip strength reference values for males

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Source references</th>
<th>Total subjects (n)</th>
<th>Left (lb) mean (95% CI)</th>
<th>Left (kg) mean (95% CI)</th>
<th>Right (lb) mean (95% CI)</th>
<th>Right (kg) mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–24</td>
<td>[5,7,9,11,16]</td>
<td>134</td>
<td>104.6 (85.5–123.6)</td>
<td>47.4 (38.8–56.1)</td>
<td>117.6 (99.6–135.6)</td>
<td>53.3 (45.2–61.5)</td>
</tr>
<tr>
<td>25–29</td>
<td>[5,7,10,16]</td>
<td>149</td>
<td>110.2 (90.5–129.9)</td>
<td>50.0 (41.1–58.9)</td>
<td>119.0 (97.7–140.3)</td>
<td>53.9 (44.3–63.6)</td>
</tr>
<tr>
<td>30–34</td>
<td>[5,7,10,16]</td>
<td>120</td>
<td>108.4 (89.1–127.6)</td>
<td>49.2 (40.4–57.9)</td>
<td>116.4 (97.2–135.6)</td>
<td>53.8 (44.1–61.5)</td>
</tr>
<tr>
<td>35–39</td>
<td>[5,7,10,16]</td>
<td>117</td>
<td>113.7 (97.1–130.8)</td>
<td>51.6 (44.0–59.3)</td>
<td>117.6 (97.0–138.1)</td>
<td>53.3 (44.0–62.6)</td>
</tr>
<tr>
<td>40–44</td>
<td>[5,7,10,16]</td>
<td>111</td>
<td>109.7 (93.7–125.8)</td>
<td>49.8 (42.5–57.1)</td>
<td>119.4 (103.9–135.0)</td>
<td>54.1 (47.1–61.2)</td>
</tr>
<tr>
<td>45–49</td>
<td>[5,7,10,16]</td>
<td>110</td>
<td>107.4 (88.9–126.0)</td>
<td>48.7 (40.3–57.2)</td>
<td>111.1 (93.7–128.5)</td>
<td>50.4 (42.5–58.3)</td>
</tr>
<tr>
<td>50–54</td>
<td>[5,7,10,16]</td>
<td>100</td>
<td>99.7 (86.8–112.7)</td>
<td>45.2 (39.4–51.1)</td>
<td>111.4 (97.4–125.4)</td>
<td>50.6 (44.2–56.9)</td>
</tr>
<tr>
<td>55–59</td>
<td>[5,7,10,16]</td>
<td>100</td>
<td>90.4 (74.3–106.6)</td>
<td>41.0 (33.7–48.4)</td>
<td>97.2 (80.9–113.4)</td>
<td>44.1 (36.7–51.4)</td>
</tr>
<tr>
<td>60–64</td>
<td>[5,7,8,10,16]</td>
<td>120</td>
<td>85.4 (72.7–97.1)</td>
<td>38.7 (33.4–44.0)</td>
<td>92.0 (81.1–103.0)</td>
<td>41.7 (36.8–46.7)</td>
</tr>
<tr>
<td>65–69</td>
<td>[5,7,8,16]</td>
<td>82</td>
<td>85.2 (72.7–97.1)</td>
<td>38.1 (32.0–44.4)</td>
<td>91.9 (78.1–105.7)</td>
<td>41.7 (35.4–47.9)</td>
</tr>
<tr>
<td>70–74</td>
<td>[5,7,9,11,16]</td>
<td>120</td>
<td>85.2 (72.7–97.1)</td>
<td>36.2 (30.3–42.1)</td>
<td>84.3 (70.5–98.0)</td>
<td>38.2 (32.0–44.5)</td>
</tr>
<tr>
<td>75+</td>
<td>[5,7,9,11,15,16]</td>
<td>217</td>
<td>65.6 (54.7–76.4)</td>
<td>29.8 (24.8–34.7)</td>
<td>61.7 (53.2–68.4)</td>
<td>28.0 (21.7–31.0)</td>
</tr>
</tbody>
</table>
FABS

- 0 to 40 scale, higher is better
  - Median 35 (range 0-40)
  - Cut off score for fall risk is \( \leq 25/40 \) points (Hernandez, 2008)
  - 14.2% (31/218) of participants scored 25 or less.

To be continued...
TUG

- Timed distance to stand - walk - turn - walk - sit
  - Mean 8.1 seconds (2.7); Median 7.5 seconds (range 4-20)
  - Cut off score for fall risk ≥13.5 seconds in community-dwelling older adults (Shumway-Cook, 2000)
  - 8.3% (12/218) of participants had times ≥ 13.5 seconds
Self-management

- 25 questions (plus other)
- Strategies to reduce pain (yes/no)
- How effective (0 to 10)
## Self-management - feet

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Used % (n)</th>
<th>Improvement (0 to 10 scale) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Took a walk</td>
<td>73.6 (159)</td>
<td>2.5 (2.4)</td>
</tr>
<tr>
<td>Read</td>
<td>69.2 (151)</td>
<td>1.4 (2.2)</td>
</tr>
<tr>
<td>Listened to the radio or music</td>
<td>63.2 (137)</td>
<td>1.5 (2.1)</td>
</tr>
<tr>
<td>Watched television</td>
<td>67.4 (147)</td>
<td>1.5 (2.1)</td>
</tr>
<tr>
<td>Exercised</td>
<td>57.1 (124)</td>
<td>2.6 (2.6)</td>
</tr>
<tr>
<td>Decreased activity</td>
<td>47.2 (102)</td>
<td>3.4 (2.5)</td>
</tr>
<tr>
<td>Did relaxation or meditation</td>
<td>40.4 (88)</td>
<td>3.0 (2.4)</td>
</tr>
<tr>
<td>Took hot bath</td>
<td>34.4 (75)</td>
<td>4.0 (2.5)</td>
</tr>
<tr>
<td>Used heating pad</td>
<td>20.2 (44)</td>
<td>4.6 (2.4)</td>
</tr>
<tr>
<td>Drank alcohol</td>
<td>31.3 (68)</td>
<td>0.9 (1.7)</td>
</tr>
<tr>
<td>Had a massage</td>
<td>30.1 (67)</td>
<td>4.3 (2.8)</td>
</tr>
</tbody>
</table>
## Self-management - hands

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Used % (n)</th>
<th>Improvement (0 to 10 scale) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Took a walk</td>
<td>57.3 (125)</td>
<td>1.5 (2.1)</td>
</tr>
<tr>
<td>Read</td>
<td>54.1 (118)</td>
<td>1.0 (1.8)</td>
</tr>
<tr>
<td>Listened to the radio or music</td>
<td>55.5 (117)</td>
<td>1.2 (2.0)</td>
</tr>
<tr>
<td>Watched television</td>
<td>57.8 (126)</td>
<td>1.2 (2.0)</td>
</tr>
<tr>
<td>Exercised</td>
<td>46.3 (100)</td>
<td>1.9 (2.3)</td>
</tr>
<tr>
<td>Decreased activity</td>
<td>42.5 (90)</td>
<td>2.7 (2.4)</td>
</tr>
<tr>
<td>Did relaxation or meditation</td>
<td>35.3 (77)</td>
<td>2.8 (4.0)</td>
</tr>
<tr>
<td>Took hot bath</td>
<td>31.7 (69)</td>
<td>3.5 (2.8)</td>
</tr>
<tr>
<td>Used heating pad</td>
<td>18.4 (40)</td>
<td>4.0 (2.3)</td>
</tr>
<tr>
<td>Drank alcohol</td>
<td>26.1 (57)</td>
<td>0.7 (1.5)</td>
</tr>
<tr>
<td>Had a massage</td>
<td>21.7 (47)</td>
<td>4.2 (3.0)</td>
</tr>
</tbody>
</table>
Additional responses - feet

• 40% of respondents provided additional information

• Recurring themes:
  • Self massage to feet (median score 6, range 2 to 8)
  • Change in shoe-wear and/or socks
  • Heat/warmth

"As I have been filling out this questionnaire, I've realized that although I'm aware of my condition all the time I have learned to largely ignore it in the same way that I largely ignore the floaters is my eyes." (6.4 years of foot pain)
Additional responses - hands

• 38% of respondents provided additional information

• Recurring themes:
  • Self massage to hands (median score 6, range 2 to 8)
  • Hand/finger exercises/ROM
  • Heat/warmth

“I am an instructor in American Sign Language. This requires using my mind to push through the pain and numbness in order to teach, but sometimes I "slur" my signs.”
27% of patients reported functional impairment

Gewandter, 2013

12% & 20% of patients with CIPN reported recent falls

Tofthagen, 2012; Gewandter, 2013

Poorer postural control, FABS, TUG

Wampler, 2007; Kneis, 2015

Falls

Social role impairment; decreased QOL

Mols, 2014
Goals of rehab

- Manage symptoms to promote physical activity
- Reduce impairments
- Restore function (objective and perceived)
- Improve quality of life
Review of current evidence

• 2014 ASCO guidelines for prevention and management of CIPN

• Systematic review of RCTs 1990-2013

  • Prevention (42 RCTs) - no conclusive or consistent clinically meaningful benefit was found for any chemo-protectants, anti-convulsants, anti-depressants, supplements.

  • Treatment (6 RCTs) - of all the anti-depressants, anti-convulsants, topical gels only **Duloxetine** (SNRI – anti-depressant) met the criteria for recommendation in clinical practice.

  • No non-pharmacological intervention studies met criteria for inclusion in the review.

  • However, acupuncture and electrical stimulation were mentioned.
Review of current evidence

- National Comprehensive Cancer Network
- Task Force Report 2009
  - Management of symptoms - pharmacological
  - Management of symptoms - non-pharmacological
    - Neuro-stimulation therapies
    - Complementary & alternative medicine therapies
  - Management of functional deficits

Stubblefield et al, 2009
Review of current evidence for pain

- **TENS** (Stubblefield, 2009)
  - "Scrambler therapy" (Smith 2010; Pachman, 2015)
- **Acupuncture** (Stubblefield, 2009; Franconi, 2013)
- **Heat**
  - Quasi experimental study - foot bathing vs massage (Park, 2015)
- **Massage**
  - Case study (Cunningham, 2011)
  - Pending...

Studies are ongoing
Review of current evidence function

• Preliminary evidence suggests physical rehabilitation
  • may improve balance and mobility in patients with persistent CIPN
  • may be helpful with self management of pain and other symptoms  
    (Wampler, 2005; Hile abstract 2010)
Review of current evidence function

- Animal studies:
  - Study of effect of a rigorous treadmill exercise program started 1 week before administration of paclitaxel and continued throughout the study in a mouse model of CIPN showed that exercise can partially reduce features of paclitaxel-induced axonal degeneration (Park JS, 2015)

- Clinical studies:
  - Balance training
    - CIPN causes balance impairments related to sensorimotor dysfunction
    - Sensorimotor training has the potential to influence neuromuscular mechanisms to improve balance performance. (Kneis, 2015)
  - 36 week RCT in patients being treated for lymphoma, comparing multimodal exercise to controls. (Streckmann, 2013)
    - Found improvements in all outcomes (QOL, balance, strength)
    - 25% had CIPN
Moving forward

• Evidence for rehabilitation and exercise in the management of existing CIPN and resulting functional impairment is limited.

• But the need for maintaining or increasing physical activity after cancer treatment cannot be under-estimated.

• We need to work with our patients to find strategies to help manage symptoms while encouraging physical activity.

• Need for continued research to address gaps.

• Continuing education opportunities for clinicians...
References

• Bohannon R, et al. Physiotherapy. 2006; 92:11-15
• Cunningham J, et al. Case report of a patient with chemotherapy induced peripheral neuropathy treated it’s mama Herod (massage)' support Care Cancer. 2011; 19:1473-1476
• Hile ES, Mick ME, Daughenbaugh A. Treadmill Training Improves Pain and Mobility in a Case of Persistent CIPN (abstract). Rehabil Oncol. 2014;32(2).
References

• Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community dwelling older adults using the Timed Up & Go Test. Phys Ther. 2000 Sep;80(9):896-903.