Chemotherapy-Induced Peripheral Neuropathy (CIPN) Measurement Approaches

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PhD Program Director
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## Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mundipharma</td>
<td>x</td>
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<tr>
<td>ASCO</td>
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<tr>
<td>Columbia University</td>
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</tr>
</tbody>
</table>
CIPN has been a difficult side effect to measure.
Measurement Challenges

- Don’t tell, don’t ask
- Lack skills
- No standardized approach
- Lack access to best measures
- Hardwired use of unreliable grading scales
  - Under-estimate severity
  - Measurement error in clinical trials

Hershman, et al., 2014; Gewandter, et al., 2017; Postma, et al., 1998; Griffith, et al., 2010; Cavaletti, et al., 2010; Smith, et al., 2013; Albers, et al., 2011
Symmetrical Distal to Proximal Extension of Signs and Symptoms

Stubblefield, et al., 2009

Neurotoxic Drugs & Our Nervous Systems

Injury

Descending pathway

Brain

Ascending pathways

Peripheral nerve

C-fiber

A-beta fiber

A-delta fiber

Dorsal horn

Spinal cord

Adapted with permission from WebMD Scientific American Medicine.
Measurement Approaches

• There is no “gold standard” approach for clinical and research settings.

• A comprehensive approach improves validity.
  – Objective measurement of large and small fibers
  – Distal to proximal extension
  – Patient-reported outcomes (PRO)
  – Function assessment

• Must have strong psychometric properties

England, et al., 2005; EFNS/PNS, 2010; Alberti, et al., 2014; Griffith, et al., 2010; Cavaletti, et al., 2010
Objective Measures

Clinical neurologic exam, quantitative sensory testing (QST), nerve conduction studies (NCS), electromyography (EMG), skin biopsy
Total Neuropathy Score (TNS)

- The only comprehensive composite tool to be extensively tested in patients receiving neurotoxic chemotherapy
  - Reliable, valid, sensitive, & responsive

- Multidimensional
  - Symptoms - Proximal Extension Tingling, Numbness, Pain
  - Signs – e.g., Reflexes, Vibration & Pin Sensibility, Strength
  - NCS and QST - Optional

- Abbreviated versions can be used in clinical practice to assess adults and children.

## 5-itemTNS Scoring

<table>
<thead>
<tr>
<th>Item</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom extension (tingling)</td>
<td>None</td>
<td>Symptoms from toes to midfoot (not including heel)</td>
<td>Symptoms from midfoot to ankle</td>
<td>Symptoms extend above ankle to knee without upper extremity symptoms</td>
<td>Symptoms above knee or concurrent lower and upper extremity symptoms</td>
</tr>
<tr>
<td>Symptom extension (numbness)</td>
<td>None</td>
<td>Symptoms from toes to midfoot (not including heel)</td>
<td>Symptoms from midfoot to ankle</td>
<td>Symptoms extend above ankle to knee without upper extremity symptoms</td>
<td>Symptoms above knee or concurrent lower and upper extremity symptoms</td>
</tr>
<tr>
<td>Symptom extension (neuropathic pain)</td>
<td>None</td>
<td>Symptoms from toes to midfoot (not including heel)</td>
<td>Symptoms from midfoot to ankle</td>
<td>Symptoms extend above ankle to knee without upper extremity symptoms</td>
<td>Symptoms above knee or concurrent lower and upper extremity symptoms</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td>Normal</td>
<td>Ankle reflex reduced</td>
<td>Ankle reflex absent</td>
<td>Ankle reflex absent or others reduced</td>
<td>All reflexes absent</td>
</tr>
<tr>
<td>Vibration sensibility</td>
<td>Normal</td>
<td>Absent or decreased from toes to midfoot (not including heel)</td>
<td>Absent or decreased from midfoot to ankle</td>
<td>Absent or decreased above ankle to knee</td>
<td>Absent or decreased above knee or in lower and upper extremities concurrently</td>
</tr>
</tbody>
</table>

*Note. Based on information from Chaudhry et al., 1994; Cornblath et al., 1999; Lavoie Smith et al., 2011; Smith et al., 2008, 2010.*

Smith, et al., 2013.
TNS-PV Responsiveness

- Sample: Children ages 1-18 receiving vincristine for ALL

TNS Versus Grading Scale Scores by Week

- Smith, et al., 2013
  - N = 65

Sample:
- Children ages 1-18 receiving vincristine for ALL
Testing Vibration Sensibility

Feasible to perform in individuals ≥ 6 years of age

Use weighted 128Hz Tuning Fork

Smith, et al., 2013, *Cancer Nursing*; Smith et al., 2013, *Clinical Journal of Oncology Nursing*
Grading Scale Problems

- OK for screening but . . .
- Under-reports severity when compared to patient report
- Poor sensitivity & responsiveness
- No operational definitions, poor reliability
- Imprecisely captures progression
  - Preclinical and clinical signs/sx in same grade
  - Distal to proximal extension
  - What about pain?

# Sensory Neuropathy

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No signs or symptoms</td>
<td>Asymptomatic: loss of deep tendon reflexes or paresthesia</td>
<td>Moderate symptoms: limiting instrumental ADL</td>
<td>Severe symptoms: limiting self care ADL</td>
<td>Life-threatening consequences: urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

Published: May 28, 2009 (v4.02: Sept. 15, 2009)  
National Institutes of Health; National Cancer Institute
PRO Measures

Seven Measures: The most extensively tested are the FACT-GOG/NTX & EORTC QLQ-CIPN20.
FACT GOG-NTX

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>ADDITIONAL CONCERNS</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have numbness or tingling in my hands.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have numbness or tingling in my feet.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel discomfort in my hands.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel discomfort in my feet.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have joint pain or muscle cramps</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel weak all over.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble hearing.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I get a ringing or buzzing in my ears.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble buttoning buttons.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble feeling the shape of small objects when they are in my hand</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble walking.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>QLQ CIPN20</td>
<td>Not at All</td>
<td>A Little</td>
<td>Quite a Bit</td>
<td>Very Much</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>31. Did you have tingling fingers or hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>32. Did you have tingling toes or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>33. Did you have numbness in your fingers or hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>34. Did you have numbness in your toes or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>35. Did you have shooting or burning pain in your fingers or hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>36. Did you have shooting or burning pain in your toes or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>37. Did you have cramps in your hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>38. Did you have cramps in your feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>39. Did you have problems standing or walking because of difficulty feeling the ground under your feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>40. Did you have difficulty distinguishing between hot and cold water?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>41. Did you have a problem holding a pen, which made writing difficult?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>42. Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>43. Did you have difficulty opening a jar or bottle because of weakness in your hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>44. Did you have difficulty walking because your feet dropped downwards?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
QLQ CIPN20 (cont.)

During the past week:

45. Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?

   Not at All  A Little  Quite a Bit  Very Much
   1          2          3          4

46. Were you dizzy when standing up from a sitting or lying position?

   Not at All  A Little  Quite a Bit  Very Much
   1          2          3          4

47. Did you have blurred vision?

   Not at All  A Little  Quite a Bit  Very Much
   1          2          3          4

48. Did you have difficulty hearing?

   Not at All  A Little  Quite a Bit  Very Much
   1          2          3          4

Please answer the following question only if you drive a car

49. Did you have difficulty using the pedals?

   Not at All  A Little  Quite a Bit  Very Much
   1          2          3          4

Please answer the following question only if you are a man

50. Did you have difficulty getting or maintaining an erection?

   Not at All  A Little  Quite a Bit  Very Much
   1          2          3          4
## Comparison of FACT GOG/NTX with CIPN20

<table>
<thead>
<tr>
<th></th>
<th>FACT GOG/NTX/NTX12</th>
<th>QLQ-CIPN20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Studies</strong></td>
<td><strong>10</strong></td>
<td><strong>9</strong></td>
</tr>
<tr>
<td><strong>Properties Tested</strong></td>
<td>ICR, Contrasting Group, Content, Structural, Contrasting Groups, &amp; Convergent Validity, Sensitivity &amp; Specificity, Responsiveness</td>
<td>ICR &amp; Test-Retest Reliability; Content, Structural, Contrasting Group, &amp; Convergent Validity, Sensitivity, Responsiveness, Mode Equivalence, Item Response</td>
</tr>
<tr>
<td><strong>Languages</strong></td>
<td>Numerous</td>
<td>Numerous</td>
</tr>
<tr>
<td><strong>Neuropathy Types</strong></td>
<td>Taxanes, Platinums, Vinblastine, Bortezomib</td>
<td>Taxanes, Platinums, Vincas, Bortezomib</td>
</tr>
</tbody>
</table>
| **Strengths**         | Feasible for multisite trials 
Brief (11/12-items, 4-items) | Feasible for multisite trials 
Brief (20-items) but longer than FACT. |
| **Weaknesses**        | Some items may not be neuropathy-specific         | Lack of Consensus About Autonomic & Driving items; Disordered response thresholds |
Rasch Analysis-Response Ordering

1= not at all
2= a little
3= quite a bit
4= very much

www.mascc.org/meeting
Small Objects

Foot Drop

Pedals

Erection
What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST in the past 7 days?

How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities in the past 7 days?

1. Not At All
2. 
3. 
4. Very Much

Concurrent validity when compared to QLQ CIPN20

Knoerl et al., 2017
# Function Measures

Examples: Timed Up-and-Go (TUG), 9-Hole Peg Test, Bumps Test

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assesses functional outcomes such as walking and balance, hand dexterity and sensory function.</td>
<td>Requires special training and equipment</td>
</tr>
<tr>
<td>Useful for research settings</td>
<td>Time-consuming</td>
</tr>
<tr>
<td></td>
<td>Limited psychometric testing in CIPN</td>
</tr>
</tbody>
</table>

Kennedy, et al., 2011; Stubblefield, et al., 2009; Mannil et al., 2014; Gilchrist, et al., 2016; Caronni, et al., 2016
# Summary

No Consensus About Measurement Approaches But Many Good Options

## Practice Settings:
- **At Baseline, During Rx, & In Survivors**
  - CTCAE
  - PRO-CTCAE
  - ★ 5-item TNS

## Research Settings:
- Objective Measures
  - FACT GOG/NTX or QLQ-CIPN20
- Functional Measures
  - PRO-CTCAE
Thank you!