Signs and symptoms in neuropathic cancer pain: Inclusion criteria for clinical trials

Mike Bennett
Professor of Palliative Medicine
Lancaster University, UK
• Definitions and concepts

• Epidemiology of cancer neuropathic pain

• Assessment approaches

• Neuropathic signs and symptoms
  – in cancer patients
  – in clinical trials
Definitions and concepts
Definitions

• Neuropathic pain
  – Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system
  – ‘abnormal activation of pain pathways’

• Nociceptive pain
  – inflammatory pain
  – ‘normal activation of pain pathways’
• Old way of thinking about neuropathic pain
  – binary diagnosis of pain type

• New ways of thinking
  – pain mechanisms as a spectrum phenomena
  – varying strength of supporting evidence
Can pain can be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians

Michael I. Bennett a,*, Blair H. Smith b, Nicola Torrance b, Amanda J. Lee b
– more useful to regard pain as a spectrum phenomenon
  • pain can be more or less neuropathic
  • ‘pain of predominantly neuropathic origin = POPNO’

– this is particularly true in cancer neuropathic pain
Criteria to be evaluated for the diagnosis of neuropathic pain:
1. Pain with a distinct neuroanatomically plausible distribution?
2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system?
3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test?
4. Demonstration of the relevant lesion or disease by at least one confirmatory test?

Grading of certainty for the presence of neuropathic pain:
- Definite neuropathic pain: all criteria fulfilled (1 to 4);
- Probable neuropathic pain: 1 and 2, plus either 3 or 4;
- Possible neuropathic pain: 1 and 2, without confirmatory evidence from 3 or 4.

Treede et al, Neurology 2008
Epidemiology of cancer neuropathic pain
Epidemiology

- Neuropathic pain probably affects 40% of patients with cancer pain
  – vast majority have mixed mechanism pain

- ...and is associated with greater pain intensity

Caraceni and Portenoy Pain 1999
Grond et al Pain 1999
Aetiology

• ‘Standard’ cancer induced neuropathic pain
  – Direct invasion and damage
  – Para-neoplastic neuropathies

• ‘New’ types of cancer related neuropathic pain:
  – Cancer Induced Bone Pain (CIBP)
    – Unique state with inflammatory and neuropathic elements
  – Post chemotherapy
    – Axonal degeneration and demyelination

• Deeper understanding of these from animal models
• In developed countries, increasingly larger proportion of older people
Mechanisms

• In older people……
  – common co-morbid diseases causing neuropathic pain include
    • diabetic neuropathy
    • stroke
    • degenerative musculo-skeletal disorders

• Need to distinguish cancer neuropathic pain from neuropathic pain in cancer patients
Neuropathic pain and cancer

• The main difference is in the patient not the pain
  – more frail
  – changing pain picture
  – additional renal, hepatic or cognitive impairment

• Many diverse signs and symptoms can exist
Assessment approaches
Symptoms

- Trying to explain the pain is difficult, like hundreds of needles inside my head. I ended up trying to relate it to other pain I have suffered over my lifetime. For instance, ear infection at its worst, very bad migraine, tonsillitis. If you could imagine all this pain in one blast it is about right, maybe even worse. At this time of my life I was lucky if I managed to have 1 or 2 hours undisturbed sleep.

Freynhagen and Bennett, BMJ 2009
Screening or measurement?

• Screening or diagnostic tools
  – Assessment is qualitative
    • presence of a pain quality
  – Allocate patients to a category
    • neuropathic or not neuropathic

• Measurement tools
  – Assessment is quantitative
  – Provide measure of intensity of symptoms
Concept of screening tools

• Pain is a subjective phenomenon
  – …it makes sense to examine verbal description when diagnosing pain type

• Initial work supported anecdotal opinion
  – Classification of clinical pain descriptions by multiple group discriminant analysis
    *Dubuisson D, Melzack R, Exp Neurology 1976; 51: 480-487*
  – Study of verbal description in neuropathic pain
    *Boureau F, Doubrère JF, Luu M, Pain 1990; 42: 145-152*

• Growth in screening tools within last 7 years
Appendix A

THE LANSS PAIN SCALE
Leeds Assessment of Neuropathic Symptoms and Signs

NAME_________________________________________ DATE__________________________

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

• Think about how your pain has felt over the last week.
• Please say whether any of the descriptions match your pain exactly.

1) Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.
   a) NO - My pain doesn’t really feel like this......................................................... (0)
   b) YES - I get these sensations quite a lot.............................................................. (5)

2) Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.
   a) NO - My pain doesn’t affect the colour of my skin................................. (0)
   b) YES - I’ve noticed that the pain does make my skin look different from normal .... (5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.
   a) NO - My pain doesn’t make my skin abnormally sensitive in that area.......... (9)
   b) YES - My skin seems abnormally sensitive to touch in that area................... (3)
Current screening tools

- LANSS and S-LANSS
  - Bennett, Pain 2001
  - Bennett et al, J Pain 2005
- Neuropathic Pain Questionnaire (NPQ)
  - Krause, Backonja, Clin J Pain 2003
- DN4
  - Bouhassira et al, Pain 2005
- ID Pain
  - Portenoy, Curr Med Res Opin 2006
- PainDetect
  - Freynhagen et al, Curr Med Res Opin 2006
Topical review

Using screening tools to identify neuropathic pain

Michael I. Bennett a,*, Nadine Attal b, Miroslav M. Backonja c, Ralf Baron d, Didier Bouhassira b, Rainer Freynhagen e, Joachim Scholz f, Thomas R. Tölle g, Hans-Ulrich Wittchen h, Troels Staehelin Jensen i
# Common Features of Screening Tools

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>LANSS</th>
<th>NPQ</th>
<th>DN4</th>
<th>Pain Detect</th>
<th>IDPain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pricking, tingling, pins, and needles</strong></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>Electric shocks or shooting</strong></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>Hot or burning</strong></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>Numbness</strong></td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>Pain evoked by light touching</strong></td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>Painful cold or freezing pain</strong></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical examination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Brush allodynia</strong></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raised soft touch threshold</strong></td>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raised pinprick threshold</strong></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• StEP
  – 6 symptom questions
  – 10 examination items
  – Differentiates neuropathic Low Back Pain

  – Most discriminant features
    • Altered pin prick threshold
    • Reduced cold sensitivity
    • Positive straight leg raising test

  *Sholz et al, PLoS Medicine 2009*
Current screening tools

• Similar content, despite
  – developed in different contexts
  – different researchers
  – different validation methods

• Similar accuracy
  – Better with examination items
    • LANSS, DN4, StEP

• Powerful evidence to support this approach to recognising neuropathic pain
Development and validation of the Neuropathic Pain Symptom Inventory

Didier Bouhassira\textsuperscript{a,b,*}, Nadine Attal\textsuperscript{a,b}, Jacques Fermanian\textsuperscript{c}, Haiel Alchaar\textsuperscript{d}, Michèle Gautron\textsuperscript{a,b}, Etienne Masquelier\textsuperscript{e}, Sylvie Rostaing\textsuperscript{f}, Michel Lanteri-Minet\textsuperscript{d}, Elisabeth Collin\textsuperscript{g}, Jacques Grisart\textsuperscript{e}, François Boureau\textsuperscript{f}
Q1. Does your pain feel like burning?

| No burning | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst burning imaginable |

Q2. Does your pain feel like squeezing?

| No squeezing | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst squeezing imaginable |

Q3. Does your pain feel like pressure?

| No pressure | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst pressure imaginable |
Examination

- Limited bedside examination
  - reduced soft touch sensation
  - Allodynia

- More detailed approaches
  - QST = quantitative sensory testing
• MPS: mechanical pain sensitivity
• DMA: allodynia
• WUR: wind-up ratio

QST – Positive symptoms
- **MDT**: mechanical detection threshold
- **VDT**: vibration detection threshold
•QST – Small fibers

• CDT: cold detection threshold
• WDT: warm detection threshold
• TSL: thermal sensory limen
• CPT: cold pain threshold
• HPT: heat pain threshold
Neuropathic signs and symptoms - in cancer patients
• 453 hospitalised patients with cancer pain
• Selected from list of 12 descriptors
• Brief clinical examination for altered skin sensitivity
## Altered Skin Sensibility in the Area of Pain vs. Specific Pain Descriptors

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Pearson Correlation</th>
<th>Sig. (Two-Tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aching</td>
<td>-0.092</td>
<td>0.055</td>
</tr>
<tr>
<td>Throbbing</td>
<td>0.111</td>
<td>0.021</td>
</tr>
<tr>
<td>Piercing</td>
<td>0.065</td>
<td>0.174</td>
</tr>
<tr>
<td>Pounding</td>
<td>0.034</td>
<td>0.484</td>
</tr>
<tr>
<td>Stabbing</td>
<td>0.036</td>
<td>0.458</td>
</tr>
<tr>
<td>Burning</td>
<td>0.180</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stinging</td>
<td>0.239</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shooting</td>
<td>0.115</td>
<td>0.016</td>
</tr>
<tr>
<td>Squeezing</td>
<td>0.059</td>
<td>0.218</td>
</tr>
<tr>
<td>Hot/cold</td>
<td>0.083</td>
<td>0.084</td>
</tr>
<tr>
<td>Pressing</td>
<td>0.015</td>
<td>0.761</td>
</tr>
<tr>
<td>Cramping</td>
<td>0.171</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Identifying neuropathic pain in patients with head and neck cancer: use of the Leeds Assessment of Neuropathic Symptoms and Signs Scale

Jean Potter BSc MRCP   Irene J Higginson PhD FFPHM   John W Scadding MD FRCP¹
Columba Quigley MD MRCP²


SECTION OF PALLIATIVE CARE, 12 DECEMBER 2002

- 25 head and neck cancer patients
  – 86% accuracy (79% sensitivity, 100% specificity)

- need to validate different thresholds?
Tools for Identifying Cancer Pain of Predominantly Neuropathic Origin and Opioid Responsiveness in Cancer Patients

Sebastiano Mercadante,† Vittorio Gebbia,‡ Fabrizio David,† Federica Aielli,‡ Lucilla Verna,‡ Alessandra Casuccio,§ Giampiero Porzio,‡ Salvatore Mangione,§ and Patrizia Ferrera†
### Table 2. Relationship Between Clinical Diagnosis of Definite Neuropathic Pain (NP), Possible NP, and Unlikely NP and Values Of the Tools Examined

<table>
<thead>
<tr>
<th></th>
<th>Definite NP</th>
<th>Possible NP</th>
<th>Unlikely NP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 60</td>
<td>N = 37</td>
<td>N = 71</td>
</tr>
<tr>
<td>NPQ mean</td>
<td>0.14</td>
<td>-0.40</td>
<td>-0.25</td>
</tr>
<tr>
<td>(± SD)</td>
<td>(0.98)</td>
<td>(0.83)</td>
<td>(0.89)</td>
</tr>
<tr>
<td>NPQ-SF mean</td>
<td>0.0</td>
<td>-0.33</td>
<td>-0.34</td>
</tr>
<tr>
<td>(± SD)</td>
<td>(0.84)</td>
<td>(0.86)</td>
<td>(0.81)</td>
</tr>
<tr>
<td>NPSI mean</td>
<td>14.3</td>
<td>12.96</td>
<td>10.61</td>
</tr>
<tr>
<td>(± SD)</td>
<td>(7.39)</td>
<td>(8.03)</td>
<td>(5.23)</td>
</tr>
<tr>
<td>LANSS mean</td>
<td>8.2</td>
<td>5.25</td>
<td>4.098</td>
</tr>
<tr>
<td>(± SD)</td>
<td>(6.82)</td>
<td>(5.21)</td>
<td>(4.63)</td>
</tr>
</tbody>
</table>

Statistical significance:
- D vs P: .012
- D vs U: .013
- P vs U: .549
- D vs P: .060
- P vs U: .589
- D vs P: .221
- D vs U: .002
- P vs U: .196
- D vs P: .053
- D vs U: < .0005
- P vs U: .370
• ...but no comparison with definite, possible or probable categories

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>NPQ</td>
<td>50.8%</td>
<td>64.8%</td>
<td>13.1%</td>
</tr>
<tr>
<td></td>
<td>NPQ-SF</td>
<td>50.8%</td>
<td>60.6%</td>
<td>13.1%</td>
</tr>
<tr>
<td></td>
<td>LANSS</td>
<td>29.5%</td>
<td>91.4%</td>
<td>8.5%</td>
</tr>
<tr>
<td>T1</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 3. Sensitivity and Specificity of the Tools Examined, According to Their Diagnostic Cut-Off
Neuropathic signs and symptoms - in clinical trials
Problems in past trials

- Symptoms often not assessed or measured

- Clinical judgement of pain type only
  - no specific criteria

- Single symptom descriptors
  - Keskinbora trial
  - Caraceni trial
Fig. 1. Change in mean NRS scores throughout the study period.

*p<0.001, vs. baseline; $p<0.001, vs. Day 4; †p=0.0001 for intergroup comparison
Evidence from non-cancer trials

• LANSS sensitive to treatment changes?
  – RCT of transcranial magnetic stimulation in patients with trigeminal neuralgia and post-stroke pain

rTMS in trigeminal neuralgia and post-stroke pain syndrome

**TGN – VAS scores**

- Pre
- Post 1
- Post 2
- Post 3
- 2 weeks

**TGN – LANSS scores**

**PSP – VAS scores**

- Pre
- Post 1
- Post 2
- Post 3
- 2 weeks

**PSP – LANSS scores**
Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain

Okan Solak a,*, Muzaffer Metin b, Hidir Esme a, Özlem Solak c, Mehmet Yaman d, Atilla Pekcolaklar b, Atilla Gurses b, Vural Kavuncu c

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b Yedikule Training and Research Hospital for Pulmonary Diseases and Chest Surgery, Department of Thoracic Surgery, Istanbul, Turkey
c Afyon Kocatepe University, School of Medicine, Department of Physical Medicine and Rehabilitation, Afyon, Turkey
d Afyon Kocatepe University, School of Medicine, Department of Neurology, Afyon, Turkey

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Future clinical trials

• Inclusion criteria
  – Screening tools
  – ?Treede criteria
  – Modified QST

• Outcomes assessment
  – Measurement tools
Which tools or measures?

• We need to review evidence to support screening and measurement tools in cancer neuropathic pain

• We probably need to validate existing tools
  – new (lower) cut-off points needed?
  – against good clinical criteria (Treede)
    • screening tools can then be a proxy for these
Pragmatists

Purists
Research

• Future
  – Do patients that score positive on screening tools respond differently to therapy?
Thankyou

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