The Neuropathic Pain Symptom Inventory (NPSI): Development and clinical applications

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Webinar Hosts: Bio & Contact Information

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Agenda/Key Discussion Points

- Neuropathic pain – what is it and how do we assess it?
- Description of the NPSI, background, scoring guidelines
- Psychometric data
- Scope and clinical utility
- Available translations and conditions of use
- Questions and answers
Neuropathic pain definition

Pain caused by a lesion or disease of the somatosensory nervous system
Wide variety of aetiologies

- Shingles
- Diabetic Neuropathy
- Nerve trauma
- Surgery
- Radiculopathy
Neuropathic pain has specific:

- Clinical expression
- Pathophysiological mechanisms
- Response to treatment
Various combinations of Symptoms

Spontaneous pain

- ONGOING
  - Burning
  - Cold...

- PAROXYSMAL
  - Electric shocks
  - Stabbing...

Evoked pain

- ALLODYNIA
  - Non-nociceptive stimuli

- HYPERALGESIA
  - Nociceptive stimuli

mechanical and/or thermal

- dynamic
- static
- heat
- cold
Multiple pathophysiological mechanisms

Phenotypic changes
- Galanine, CCK, VIP
- NPY, alpha2delta...
- SP, CGRP, opioïdes

Ectopic discharges

Lesion

Fibre C

Fibre Aβ

Ectopic discharges

Phenotypic changes
- SP, CGRP

Hyperexcitability Nociceptive neurons

Glutamate peptides

Microglia activation

Reduced segmental inhibition
GABA, glycine, KKC2

Alteration of descending controls

The Challenge of Neuropathic Pain

Why?
Patients are treated in a uniform fashion despite the heterogeneity of neuropathic pain syndromes

Satisfactory pain relief in only 30-40% of patients

Identification of responders to each specific drug
Different combinations of symptoms may reflect different pathophysiological mechanisms and respond differently to treatment.

Bouhassira, 2001
Neuropathic pain has specific qualities reflecting its specific mechanisms.
Neuropathic Pain Assessment

Examination
- VAS
- NRS

Specific Questionnaires

Subjective

Quantitative Sensory Testing

Semi-objective

Electrophysiology

Functional Neuroimaging

Objective
Methods used in Pathophysiological Studies

**Microneurography**

Cline et al; 1989

**Laser evoked potentials**

Plaghki et al., 2004

**Functional Neuro-imaging**

**Skin Biopsies**

Arezzo et al., 1999

Predictive value for treatment Response?
Symptoms and Signs

- standard examination
- quantitative sensory testing (QST)
- specific questionnaires
Quantitative Sensory Testing

Detection and pain threshold

Responses to suprathreshold stimuli

Sensory deficits
Allodynia

Hyperalgesia

Pain Modulation
CPM
Limitations of QST

- No evaluation of spontaneous pain
- Inter-individual variations
- Normative data (Rolke et al., 2006) are not easy to apply to single patient
- Cooperation level and reliability of the patient
- Time-consuming
- Cost of the material
Neuropathic Pain Assessment: Beyond the VAS?

Development of specific neuropathic questionnaires for the measurement of relevant components of neuropathic pain syndromes:

- Spontaneous ongoing pain
- Spontaneous paroxysmal pain
- Evoked pain
Neuropathic Pain Symptom Inventory (NPSI)

Bouhassira et al., Pain, 2004

Main Objective:

Evaluation of the different components of NP:

- Spontaneous ongoing pains
- Paroxysmal pains
- Evoked pains
- Paresthesia/Dysesthesia
Development and validation of the Neuropathic Pain Symptom Inventory (NPSI)

176 patients with (« pure ») peripheral or central lesions

- Content validity (expert opinion)
- Face validity (patient opinion)
- Construct validity (factor analysis)
  - Test-retest Reliability
  - Sensitivity to change

Bouhassira et al., Pain, 2004
Development and validation of the Neuropathic Pain Symptom Inventory

Didier Bouhassira, Nadine Attal, Jacques Fernley, Hael Alehaan, Michèle Gautron, Etienne Masquelier, Sylvie Rostaing, Michel Lanteri-Minet, Elisabeth Collin, Jacques Grisart, François Boureau

- Burning
- Squeezing
- Pressure
- Electric Shocks
- Stabbing
- Pain provoked by brushing
- Pain provoked or increased by contact with cold
- Pain provoked or increased by pressure
- Pins and Needles
- Tingling

- 2 temporal items for spontaneous ongoing and paroxysmal pain

# Neuropathic Pain Symptom Inventory (NPSI)

## 10 sensory items quantified with NRS

**Q1/. Does your pain feel like burning ?**

<table>
<thead>
<tr>
<th>No burning</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst burning imaginable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Q2/. Does your pain feel like squeezing ?**

<table>
<thead>
<tr>
<th>No squeezing</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst squeezing imaginable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Q3/. Does your pain feel like pressure ?**

<table>
<thead>
<tr>
<th>No pressure</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst pressure imaginable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## 2 items related to the temporal aspect of pain

**Q4/. During the past 24 hours,** your spontaneous pain has been present :

Select the response that best describes your case

<table>
<thead>
<tr>
<th>Permanently</th>
<th>/ /</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between 8 and 12 hours</td>
<td>/ /</td>
</tr>
<tr>
<td>Between 4 and 7 hours</td>
<td>/ /</td>
</tr>
<tr>
<td>Between 1 and 3 hours</td>
<td>/ /</td>
</tr>
<tr>
<td>Less than 1 hour</td>
<td>/ /</td>
</tr>
<tr>
<td>% of variance explained</td>
<td>Factor 1</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>&quot;burning&quot;</td>
<td>0.07</td>
</tr>
<tr>
<td>&quot;pins and needles&quot;</td>
<td>0.09</td>
</tr>
<tr>
<td>&quot;tingling&quot;</td>
<td>0.08</td>
</tr>
<tr>
<td>&quot;electric shocks&quot;</td>
<td>0.11</td>
</tr>
<tr>
<td>&quot;stabbing&quot;</td>
<td>0.09</td>
</tr>
<tr>
<td>&quot;pressure&quot;</td>
<td>0.03</td>
</tr>
<tr>
<td>&quot;squeezing&quot;</td>
<td>0.08</td>
</tr>
<tr>
<td>&quot;evoked by brushing&quot;</td>
<td>0.80</td>
</tr>
<tr>
<td>&quot;evoked by pressure&quot;</td>
<td>0.85</td>
</tr>
<tr>
<td>&quot;evoked by cold stim.&quot;</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Neuropathic Pain Symptom Inventory (NPSI)

5 different dimensions
Bouhassira, Attal et al Pain 2004 (176 patients)
Attal et al Pain 2008 (482 patients)

Superficial spontaneous pain
  Burning

Deep spontaneous pain
  Squeezing, Pressure

Paroxysmal pain
  Electric Shocks
  Stabbing

Evoked pain
  Brush-evoked
  Cold- evoked
  Pressure-evoked

Paresthesia/dysesthesia
  Tingling
  Pins and Needles
NPSI Scoring

Each sensory descriptor is quantified (0-10) NRS

**Total score** = - sum of the 10 items

**5 subscores** = - Burning (superficial pain)
- Pressure/squeezing (deep pain)
- Paroxysmal pain
- Paresthesia/dysesthesia
- Evoked pain
Neuropathic pain: Are there distinct subtypes depending on the aetiology or anatomical lesion?

N. Attal\textsuperscript{a,b,*}, C. Fermanian\textsuperscript{c}, J. Fermanian\textsuperscript{d}, M. Lanteri-Minet\textsuperscript{e}, H. Alchaar\textsuperscript{a,b}, D. Boulhassira\textsuperscript{a,b}

The five neuropathic pain dimensions are present across neuropathic pain etiologies

<table>
<thead>
<tr>
<th></th>
<th>PHN</th>
<th>Diabetic</th>
<th>PPN</th>
<th>Nerve trauma</th>
<th>Radiculopathy</th>
<th>Trig. N</th>
<th>Spinal trauma</th>
<th>MS</th>
<th>Syrinx</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=49</td>
<td>n=35</td>
<td>n=53</td>
<td>n=110</td>
<td>n=43</td>
<td>n=18</td>
<td>n=25</td>
<td>n=32</td>
<td>n=40</td>
<td>n=31</td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>89.8</td>
<td>62.8</td>
<td>58.5</td>
<td>51.1</td>
<td>65.1</td>
<td>16.7</td>
<td>76</td>
<td>56.2</td>
<td>75</td>
<td>74.2</td>
</tr>
<tr>
<td>Deep pain</td>
<td>28.5</td>
<td>68.6</td>
<td>62.3</td>
<td>58</td>
<td>51.2</td>
<td>22.2</td>
<td>74</td>
<td>62.5</td>
<td>60</td>
<td>64.5</td>
</tr>
<tr>
<td>Paroxysmal pain</td>
<td>63.2</td>
<td>62.8</td>
<td>62.3</td>
<td>66.3</td>
<td>72</td>
<td>89.9</td>
<td>72</td>
<td>65.6</td>
<td>65</td>
<td>58</td>
</tr>
<tr>
<td>Evoked pain</td>
<td>91.9</td>
<td>51.5</td>
<td>64.1</td>
<td>76</td>
<td>44.2</td>
<td>61.1</td>
<td>70</td>
<td>75</td>
<td>62.5</td>
<td>74</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>30</td>
<td>82.9</td>
<td>84.9</td>
<td>86</td>
<td>81.4</td>
<td>33</td>
<td>80</td>
<td>84.4</td>
<td>87.5</td>
<td>83.9</td>
</tr>
</tbody>
</table>

No association between symptom combinations and aetiology
Multiple correspondence analysis (MCA) confirmed the lack of significant association between aetiologies and symptoms.

Strong clinical consistency of neuropathic pain as a « trans-aetiological » multidimensional entity.
NPSI sensitivity to change

Changes in NPSI total Score

Patient global impression of change
PGIC

Minimal clinically significant difference is: 20

Bouhassira et al., *Pain* 2004; Ranoux et al., *Ann Neurol* 2008
Comparison between NPSI and QST

Mechanical hyperalgesia

Cold hyperalgesia
Clinical applications of the NPSI

- The NPSI has been translated into more than 70 languages

<table>
<thead>
<tr>
<th>Available NPSI translations</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
</tr>
<tr>
<td>Spanish</td>
</tr>
<tr>
<td>Italian</td>
</tr>
<tr>
<td>German</td>
</tr>
<tr>
<td>Hungarian</td>
</tr>
<tr>
<td>Afrikaans</td>
</tr>
<tr>
<td>Croatian</td>
</tr>
<tr>
<td>Czech</td>
</tr>
</tbody>
</table>

- The NPSI multidimensional structure has been confirmed into several Languages: Italian (Padua et al. 2009); Spanish (Villoria et al., submitted), German (Sommer et al., submitted)

The NPSI has been used in over 50 international clinical trials
A randomized, double-blind, placebo-controlled trial of a chemokine receptor 2 (CCR2) antagonist in posttraumatic neuralgia

Jarkko Kalliomäki\textsuperscript{a,\ast}, Nadine Attal\textsuperscript{b,c}, Bror Jonzon\textsuperscript{a}, Flemming W. Bach\textsuperscript{d}, Karin Huizer\textsuperscript{a}, Stuart Ratcliffe\textsuperscript{e}, Britta Eriksson\textsuperscript{a}, Marcin Janecki\textsuperscript{f}, Andrei Danilov\textsuperscript{g}, Didier Bouhassira\textsuperscript{b,c}, for the AZD2423 PTN Study Group

Fig. 3. Mean daily pain scores during treatment. LS means and 80\% confidence intervals of daily NRS—Average Pain scores from days 1 to 28 in AZD2423 and placebo groups (mITT analysis set). Confidence intervals are shown every 4 days.

Fig. 4. Change in NPSI subscores from baseline to end of treatment. LS mean NPSI change and 80\% confidence intervals from treatment day 1 to 29 in AZD2423 and placebo groups (mITT analysis set).
Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial

Nadine Attal, Daniel C de Andrade, Frédéric Adam, Danièle Ranoux, Manoel J Teixeira, Ricardo Galhardoni, Irina Raicher, Nurcan Üçeyler, Claudia Sommer, Didier Bouhassira

A Paroxysmal pain

- Botulinum toxin A (n=25)
- Placebo (n=24)

B Allodynia

- Botulinum toxin A (n=33)
- Placebo (n=18)

Published Online
February 29, 2016
http://dx.doi.org/10.1016/S1474-4422(16)00017-X
Pooled results from 4 negative/weakly positive trials with pregabalin (n= 538 placebo ; n = 693 pregabalin)

Poststroke pain

![Graph showing mean pain score over weeks for Pregabalin and Placebo groups.](image)

*Fig. 2. Weekly mean pain score.*

Kim et al Pain 2010

HIV neuropathy

![Graph showing change in Numeric Pain Rating Scale score over time.](image)

Simpson et al Neurology 2010

Post traumatic neuropathic pain

![Bar chart showing pain levels at baseline and endpoint for Pregabalin and Placebo groups.](image)

Van Seventer et al E J Neurol 2010

Diabetic painful neuropathy

![Image of a hand with neuropathic pain symptoms.](image)

Protocol NoA0081071 clinicalstudyresults.org

Freeman, Bouhassira et al. submitted
Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs

Roy Freeman, Ralf Baron, Didier Bouhassira, Javier Cabrera, Birol Emir

Different treatment effects in patients with different sensory profiles?
Pregabalin better than placebo in two clusters
NPSI: Available Language Versions

- Original language of development:
  - French (France)

- Nearly 80 translations available, produced with a full linguistic validation methodology
<table>
<thead>
<tr>
<th>NPSI: Available Language Versions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afrikaans for South Africa</td>
</tr>
<tr>
<td>Armenian for Armenia</td>
</tr>
<tr>
<td>Bengali for India*</td>
</tr>
<tr>
<td>Bulgarian for Bulgaria*</td>
</tr>
<tr>
<td>Chinese for Hong Kong</td>
</tr>
<tr>
<td>Chinese for Malaysia</td>
</tr>
<tr>
<td>Chinese for Singapore</td>
</tr>
<tr>
<td>Chinese for Taiwan</td>
</tr>
<tr>
<td>Chinese for Taiwan</td>
</tr>
<tr>
<td>Croatian for Croatia*</td>
</tr>
<tr>
<td>Czech for Czech Republic</td>
</tr>
<tr>
<td>Danish for Denmark*</td>
</tr>
<tr>
<td>Dutch for Belgium (Flemish)*</td>
</tr>
<tr>
<td>Dutch for the Netherlands*</td>
</tr>
<tr>
<td>English for Australia*</td>
</tr>
<tr>
<td>English for Canada</td>
</tr>
<tr>
<td>English for India*</td>
</tr>
<tr>
<td>English for South Africa</td>
</tr>
<tr>
<td>English for the UK*</td>
</tr>
<tr>
<td>English for the USA</td>
</tr>
</tbody>
</table>

* Performed by Mapi
How to Access the NPSI

- Centralization of information and translations
- Licensing process
- Distribution
- Coordination of new translations

handled by Mapi Research Trust on behalf of Dr Bouhassira
NPSI: Conditions of Use

- Conditions of use available and detailed on PROQOLID via our ePROVIDE platform (https://eprovide.mapi-trust.org)

- Process:
  - Signature of a User Agreement for each study
  - Free access for Non-Funded Academic Users:
    — Easy and quick access to the NPSI for Non-Funded Academic Users via Online Distribution process on PROQOLID
  - Payment of access fees if the NPSI is used in:
    — Funded academic research
    — Large non-commercial organization research and evaluation
    — Commercial studies
  - When the process is completed, Mapi Research Trust delivers:
    — Needed language versions (if available)
    — Scoring instructions
For any questions on the NPSI:
- please visit on PROQOLID via our ePROVIDE platform (https://eprovide.mapi-trust.org)
Conclusion
Key Presentation Takeaways/Concluding Points

1. NPSI is simple and easy to use

2. NPSI allows a comprehensive assessment of neuropathic pain

3. NPSI has been largely used both in daily practice and in many multicenter international clinical trials

4. NPSI allows a multidimensional assessment of drug effects for a better identification and characterization of responders’ profile.

5. NPSI has been translated and validated in a large number of languages
Thank You!

Additional Questions? Ask our Webinar Hosts directly!

Host Information:
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Marie Dulac Trimoreau: mdulac@mapigroup.com

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