The Challenges of Neuropathic Pain

Andrew SC Rice
• What is neuropathic pain?

• Challenges in the use of animal models to study neuropathic pain

• Ongoing systematic review and meta-analysis of neuropathy animal model publications
Persistent Pain

Nociceptive Pain
- Pain in response to a noxious stimulus
- Sensitivity to stimuli may be enhanced by inflammation

Neuropathic Pain
- Pain as a direct consequence of a lesion or disease affecting the somatosensory system
- Absence of a noxious stimulus
- No discernable biological function
- Disorder of nerve repair/regeneration?

Dry Beriberi

Thiamine (vitamin B₁) deficiency

”...intense burning of the feet and an exquisite sensitiveness which scarcely enables them to walk and they cannot sleep or get any rest...”

War Diaries of Weary Dunlop
Dunlop EE BMJ;1946;4474:481-6
Range of Underlying Diseases Associated with Neuropathic Pain

- Trauma to nervous system
- Peripheral neuropathies
  - Metabolic, dietary & toxic
- Infection
- CNS disease
- Tumours
- Nerve compression
- Genetic channelopathies
Key Features of Neuropathic Pain

- Pain occasionally generated in response to damage to sensory nervous system

- Pain in absence of a noxious stimulus:
  - Spontaneous continuous
  - Spontaneous paroxysmal (lancinating)
  - Evoked (stimulus dependant) pain

- Variably associated with sensory perturbations:
  - **Sensory Loss:**
    - Pain in areas of sensory loss - *Anaesthesia Dolorosa*
  - **Sensory gain:**
    - *Allodynia* – pain in response to an innocuous stimulus
    - *Hyperalgesia* – increased response to a painful stimulus

- Prevalence ~ 7%¹

- Usually severe and chronic²:
  - Mean duration 78 months
  - Mean pain intensity 6/10

¹ Torrance et al 2006; Smith et al 2007; Bouhassira et al 2008, Van Hecke et al 2014
² Backonja & Stacey 2004
NeuPSIG Meta-analysis of 229 RCTs in Neuropathic Pain 2014
Finnerup, Attal, Haroutounian, Nicol et al

**NNT 50% pain relief for drugs where > 50% of trials positive**
- ⋄ = % responding to placebo
- Circle size = number patients treated with active

**NNT**
External Validity

- **The Model:** Replicate disease
- **Outcome measures:** ethological relevance
- Animal choice: Healthy young, male, genetically similar, rodents as models of complex human disease
- Chronicity
- “Pain” outcome incidence and heterogeneity of clinical presentations
- Accounting for co-morbidity seen in patients
The Model:

Reproducing the Disease/Lesion
Animal Models of Traumatic Nerve Injury

Heterogeneous Pathologies Associated with Neuropathic Pain

- Trauma
- Ischaemia
- Infection/Inflammation
- Cancer
- Chemical injury, including drugs
- Metabolic and endocrine neuropathies
- Compression
- Idiopathic
Meta-Analysis of Neuropathic Pain Animal Models

PubMed 18611  Web of Science 11710  Biosis Citation Index 11271  Biosis Previews 11337  Embase 12227

Total 65156  Duplicates 31342

Unique references 33184

Included so far 4568

NeuPSIG Clinical SR 2014  229 RCTs
<table>
<thead>
<tr>
<th>Neuropathic pain model</th>
<th>Number of publications from screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Constriction Injury</td>
<td>1402</td>
</tr>
<tr>
<td>Spinal Nerve Ligation</td>
<td>916</td>
</tr>
<tr>
<td>Diabetes-induced</td>
<td>678</td>
</tr>
<tr>
<td>Partial Sciatic Nerve Ligation</td>
<td>396</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>384</td>
</tr>
<tr>
<td>Chemotherapy-induced</td>
<td>341</td>
</tr>
<tr>
<td>Spared Nerve Injury</td>
<td>228</td>
</tr>
<tr>
<td>Crush sciatic nerve</td>
<td>78</td>
</tr>
<tr>
<td>Trigeminal nerve ligation</td>
<td>70</td>
</tr>
<tr>
<td>Transection of the spinal nerve</td>
<td>54</td>
</tr>
<tr>
<td>Root ligation</td>
<td>46</td>
</tr>
<tr>
<td>Transection of the sciatic nerve</td>
<td>38</td>
</tr>
<tr>
<td>Herpes zoster-induced</td>
<td>35</td>
</tr>
<tr>
<td>Alcohol-induced</td>
<td>36</td>
</tr>
<tr>
<td>Anti-retroviral drug-induced</td>
<td>26</td>
</tr>
<tr>
<td>HIV-induced</td>
<td>27</td>
</tr>
<tr>
<td>CCI of infraorbital nerve</td>
<td>21</td>
</tr>
<tr>
<td>Root transection</td>
<td>20</td>
</tr>
</tbody>
</table>
External Validity

- **The Model**: Replicate disease

- **Outcome measures**: Ethological relevance

- Animal choice: Healthy young, male, genetically similar, rodents as models of complex human disease

- Chronicity

- “Pain” outcome incidence and heterogeneity of clinical presentations

- Accounting for co-morbidity seen in patients
Outcome Measures:
Reproducing the Clinical Signs Associated with Neuropathic Pain (*Not Symptoms!*)

- Presence/absence of pain cannot be directly measured in humans or animals. No biomarkers.

- Measurement of pain in patients reliant on “patient reported outcomes”

- Pain can only be inferred in animals by measuring changes in **ethologically relevant** behaviours characterised by appropriate pharmacological perturbations
Outcome Measures

Limb Withdrawal to Sensory Stimuli

- Mechanical
  - PWT (N)
  - Preop 7 day Post op

- Heat
  - PWL (Sec)

- Cold
  - % Response


- Left L5 spinal nerve transected
- Right sham control
# Portfolio of Neuropathic Pain Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Animal Efficacy Studies</th>
<th>Human RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evoked hypersensitivity</td>
<td>+</td>
<td>+/- (for baseline QST phenotyping)</td>
</tr>
<tr>
<td>Spontaneous continuous pain</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Usual 1º efficacy measure)</td>
</tr>
<tr>
<td>Spontaneous paroxysmal pain</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Physical function</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>• Emotional function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Circadian rhythm disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Global impression</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>
The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study

Dyveke T. Demant¹, Karen Lund¹, Jan Vollert⁵, Christoph Maier⁷, Märtha Segerdahl⁴⁵, Nanna B. Finnerup⁵, Troels S. Jensen⁵, Søren H. Sindrup⁴,*

**ITT Population**

<table>
<thead>
<tr>
<th>NNT 50% (95% CI)</th>
<th>Whole population</th>
<th>Non-irritable nociceptor</th>
<th>Irritable nociceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyneuropathy</strong></td>
<td>7.0 (4.2-22)</td>
<td>13 (5.2-∞)</td>
<td>3.9 (2.3-12)</td>
</tr>
<tr>
<td><strong>Nerve Injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PHN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagram (A)**

- Non-irritable nociceptor
- Irritable nociceptor
Norway Rat Social Structure
The “Breeding Deme”

McClintock 1987
THIGMOTAXIS IN OPEN FIELD

- **Construct:** Behavioural conflict - limiting exposure (to risk of predation) vs exploratory drive
- **Apparatus:** Open field arena

BURROWING

- **Construct:** Engagement in routine burrow maintenance activity of fossorial rodents
- **Apparatus:** gravel filled tube in cage
Propsective Multi-Centre Academic and Industry Validation of Burrowing Paradigm
Multicentre Validation Of CFA* Effect On Burrowing In Rats

Preliminary Whole Group Analysis

Group Sizes

Day 1:  CFA 113, Naïve 78, Saline 75
Day 10: CFA 97, Naïve 63, Saline 75

* CFA - 100μg in 100 μl intraplantar
Meta-Analysis of Neuropathic Pain Animal Models

AIMS

- Ascertain the quality of internal validity reporting
- Ascertain the impact of internal and external validity on reported outcome
- Estimate the magnitude and impact of publication bias

- Provide a publicly available community resource for experimental design eg:
  - Comparative efficiency of different models/outcomes
  - Robust data for sample size calculations
  - Identify tests which require fewer animals
  - Establish if a high burden of severity model can be replaced with one of lower impact
  - Influence of postoperative analgesia on outcome
  - Identify whether multiple tests are necessary
  - Establish whether the duration of experimentation may be shortened
887 included publications
Median reporting quality score 2 out of 8 and IQR (2-1).

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
<th>No. of publications /Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinded Assessment of Outcome</td>
<td>29</td>
<td>236/805</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>3</td>
<td>21/805</td>
</tr>
<tr>
<td>Randomisation - Drug</td>
<td>25</td>
<td>156/621</td>
</tr>
<tr>
<td>Randomisation - Model</td>
<td>9</td>
<td>69/805</td>
</tr>
<tr>
<td>Animal Welfare Regulations</td>
<td>88</td>
<td>706/805</td>
</tr>
<tr>
<td>Potential Conflicts of Interest</td>
<td>12</td>
<td>99/805</td>
</tr>
<tr>
<td>Animal exclusions</td>
<td>17</td>
<td>133/805</td>
</tr>
<tr>
<td>Sample Size Calculation</td>
<td>0.4</td>
<td>3/805</td>
</tr>
</tbody>
</table>
Publications And Quality

![Graph showing the number of publications and median quality scores over the years from 1988 to 2012. The x-axis represents the year, and the y-axis represents the number of publications. The graph also shows the median quality score for each year.](image)
### Publications reporting drug treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>71</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>47</td>
</tr>
<tr>
<td>MK-801</td>
<td>23</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>17</td>
</tr>
<tr>
<td>Naloxone</td>
<td>12</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>9</td>
</tr>
<tr>
<td>WIN 55,212-2</td>
<td>8</td>
</tr>
<tr>
<td>Tramadol</td>
<td>8</td>
</tr>
<tr>
<td>Ketamine</td>
<td>8</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>8</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>8</td>
</tr>
<tr>
<td>Drugs reported once</td>
<td>559</td>
</tr>
<tr>
<td>Other drugs (reported 2-8)</td>
<td>424</td>
</tr>
</tbody>
</table>
# Reporting Quality Across Models

<table>
<thead>
<tr>
<th>%</th>
<th>HIV</th>
<th>Antiretroviral</th>
<th>Alcohol</th>
<th>CIPN</th>
<th>CCI</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blinded Assessment of Outcome</strong></td>
<td>50</td>
<td>50</td>
<td>23</td>
<td>46</td>
<td>29</td>
<td>40</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Randomisation - Drug</td>
<td>25</td>
<td>43</td>
<td>18</td>
<td>18</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Randomisation - Model</td>
<td>25</td>
<td>17</td>
<td>9</td>
<td>12</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Animal Welfare Regulations</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>92</td>
<td>88</td>
<td>95</td>
</tr>
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<td>14</td>
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<td>25</td>
<td>0</td>
<td>9</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Sample Size Calculation</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>0.4</td>
<td>2</td>
</tr>
</tbody>
</table>
Experimental Bias In Animal Studies of Pain

Rice et al Pain 2008;139:241-5

• Located 14 reports in PAIN vols 128-30 (2007) which estimated pharmacological efficacy in an animal model

• Scored with modified Jadad tool\(^1\) that assesses presence and quality of:
  • Randomisation
  • Blinding
  • Reporting of withdrawals/dropouts
  • Power calculation

• Max. score 7
• > 5/7 required for inclusion in clinical systematic review

Results:

- 5/14 (36%) – described as “blinded”
- 4/14 (29%) – described as “randomised”
- 1/14 (7%) - reported withdrawals/dropouts
- 0/14 (0%) - described a power calculation

• Modified Jadad score:
  • 13/14 – scored 0/7
  • 1/14 – scored 1/7
  • 0/14 - scored >1/7

Re-analysis of data from 125 animal studies (Kontinen & Meerk 2003):\(^1\)

• 29% described as “randomised”
• 28% described as “blinded”

\(^1\) Rice et al in Systematic Reviews and Meta-Analyses in Pain.2007. IASP Press
ACKNOWLEDGEMENTS

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- Victoria Wallace
- Fauzia Hasnie
- Ewen Legg
- Tim Pheby
- Helena Angel-Scott
- Ran Xiong

External

- EUROPAIN WP2

- Edinburgh/CAMARADES:
  - Emily Sena
  - Gillian Currie
  - Malcolm MacLeod
CAMARADES: Bringing evidence to translational medicine

Hypothesis Generating
Descriptive Statistics
Exploratory observations

Hypothesis Testing
Inferential Statistics
Pre-Clinical Proof of Concept
Pre-Clinical Proof of Efficacy

Effect Sizes
P values

Replication (conceptual & independent)

Case Report
RCT
Meta-Analysis

Pre-Clinical
Clinical
HIV neuropathy (S1)

- Loss:
  - Cold Detection Threshold (Aδ fibre)
  - Warm Detection Threshold (C fibre)
  - Thermal Sensory Limen
  - Mechanical Detection Threshold (Aβ)
  - Vibration Detection Threshold (Aβ)

Gain: Nil
Efficacy Of Pregabalin In HIV Neuropathy Patient Subset With Pin Prick Hyperalgesia

Adapted from: Simpson et al Neurology 2010;74:413
Importance of Ethologically Relevant Outcome Measures
BURROWING

- Construct: Engagement in routine burrow maintenance activity of fossorial rodents
- Apparatus: gravel filled tube in cage