Challenges and Hurdles to Translational Pain Research

NIH Pain Consortium
11th Annual Symposium

Bethesda, MD
Pain – So what’s the problem?

- It’s **common**
  - Chronic pain - ~25% of the population, >50% of veterans, overall prevalence is increasing as is disability
  - Acute pain - Moderate-severe in ~30% postoperatively
  - Cancer pain - >50% all stages, >30% after cure

- It’s **costly**
  - Chronic pain - $600B annually in the US, and costs are increasing faster than overall healthcare
  - Acute pain - Discharge, readmission, recovery, complications
  - Cancer pain - Direct + Indirect ~$900/mo

- It’s **difficult to treat**
  - Drug Trials - <50% of participants receive >50% pain relief
  - Multiple treatments and multimodal treatment is common
  - Functional improvements difficult to demonstrate
What then are the options for treatment?

Many medicines, few cures
Benjamin Franklin
### Numbers Needed to Treat/Harm (NNT/NNH)

#### Acute Pain, 50% Relief

Oxford League Table, 2007

#### Chronic Pain, 50% Relief

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>NNT 50% relief</th>
<th>NNH</th>
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</thead>
<tbody>
<tr>
<td>Opioids 1,2</td>
<td>Neuropathic pain</td>
<td>2.5, 4.3, 12</td>
<td>4.2, -8.3</td>
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<tr>
<td>Tramadol 3,4</td>
<td>Neuropathic pain Post-surgical</td>
<td>3.4, 4.7, 12</td>
<td>8.3</td>
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<tr>
<td>TCAs: Amitryptiline5</td>
<td>Neuropathic pain</td>
<td>3.6, 12</td>
<td>6 (minor) - 28 (major)</td>
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<tr>
<td>Nortryptiline</td>
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<tr>
<td>Gabapentins 6,7</td>
<td>Neuropathic pain Central Neuropathic</td>
<td>7.2, 7.7, 12</td>
<td>3.7 (minor)</td>
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<tr>
<td>Pregabalins 8,9</td>
<td>Diabetic neuropathy</td>
<td>5, 5.8, 9, 9</td>
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<tr>
<td>SNRIs: Venlafaxine</td>
<td>Neuropathic pain PostHerpeticNeuralgia</td>
<td>13-22, 9</td>
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<tr>
<td>Duloxetine10</td>
<td></td>
<td></td>
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<tr>
<td>Paracetamol11</td>
<td>Chronic arthritis</td>
<td>4-5, 11</td>
<td>12 (GI SEs)</td>
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<tr>
<td>Lignocaine patch12</td>
<td>Peripheral Neuropathic Pain</td>
<td>4.4, 10.6</td>
<td>Minimal</td>
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<tr>
<td>Capsaicin patch13</td>
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## What has changed in 20 years?

<table>
<thead>
<tr>
<th>1996</th>
<th>2016</th>
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<tbody>
<tr>
<td>NSAIDS</td>
<td>Same (COX2)</td>
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<tr>
<td>Acetaminophen</td>
<td>Same (IV)</td>
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<tr>
<td>Opioids</td>
<td>Same (Formulations)</td>
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<tr>
<td>Antidepressants</td>
<td>Same (More SNRI’s)</td>
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<tr>
<td>Gabapentin</td>
<td>Same (Pregabalin)</td>
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<tr>
<td>Tramadol</td>
<td>Same (Tapentadol)</td>
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<tr>
<td>Capsaicin</td>
<td>Same (Patch)</td>
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<tr>
<td>Lidocaine</td>
<td>Same (Patch)</td>
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<tr>
<td>Omega connotoxin</td>
<td>Omega connotoxin</td>
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<tr>
<td>Botulinum toxin</td>
<td>Botulinum toxin</td>
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</table>
What approaches were used in trials? (A very Short List)

- **CCR2 antagonists**
  - Posttraumatic neuralgia
- **TRPV1 antagonists**
  - AMG 517 (others), Hyperthermia
  - OA, Dental pain, GERD
- **FAAH1 antagonists**
  - OA
- **NK1 antagonists**
  - Postoperative pain
  - PDN
- **“Glial inhibitors”** (Minocycline, Propentofylline)
  - Persistent pain after discectomy, Hand surgery, Radiculopathy
  - PHN
Goal: Optimize preclinical testing to make translation to specific human pain states most likely.
The Reproducibility of Preclinical Testing

“At least 50% of published studies, even those in top-tier academic journals, can't be repeated with the same conclusions by an industrial lab.”

Bruce Booth, venture capitalist, 2011

Bayer Healthcare, 67 laboratory projects
The Cost of Irreproducibility

- If 50% of preclinical research is irreproducible, over $28B is wasted per year in the US alone.

Freedman et al. PLOS Biology, 2015
Reporting Guidelines

- Contributing problem: Failure to describe research methods and to report results appropriately
- Guidelines:

**CONSORT** - Consolidated Standards of Reporting (clinical) Trials

**ARRIVE** - Animals in Research: Reporting In Vivo Experiments

**PPRECISE** - Animals in Preclinical Pain Research: Reporting and Methodological Guidelines

**NIH** - “Rigor and Reproducibility:” Scientific premise, rigor of approach, biological variables, resources and reagents
<table>
<thead>
<tr>
<th>ARRIVE Checklist</th>
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<tr>
<td><strong>(20 Items)</strong></td>
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<tr>
<td><strong>Title</strong></td>
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<td>o Accurate</td>
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<tr>
<td><strong>Abstract</strong></td>
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<tr>
<td>o Concise key details</td>
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<tr>
<td><strong>Methods</strong></td>
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<tr>
<td>o Ethical statement</td>
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<td>o Study design</td>
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<tr>
<td>o Specific methods</td>
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<tr>
<td>o Animal details</td>
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<tr>
<td>o Blinding and randomization</td>
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<td>o Statistics</td>
<td></td>
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<tr>
<td><strong>Results</strong></td>
<td></td>
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<tr>
<td>o Health and weight</td>
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<tr>
<td>o Numbers analyzed and excluded</td>
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<tr>
<td>o Precision and variance</td>
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<tr>
<td>o Adverse events</td>
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<tr>
<td><strong>Discussion</strong></td>
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<td>o Interpretation</td>
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<tr>
<td>o Generalization</td>
<td></td>
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<tr>
<td>o Funding sources</td>
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Acceptance of ARRIVE Guidelines

**SURGE IN SUPPORT FOR STUDY GUIDELINES**
In 2015, more than 150 journals signed up to the ARRIVE checklist for animal studies — the highest number of signatories in a single year since it was released.
Addressing the Preclinical Challenge

- **Models**
  - Are the models valid and reliable?
  - How is the pain-related physiology of the mouse/rat similar or distinct from humans?
  - Are commonly occurring comorbidities included?
  - Are the PK/PD properties of the model similar to humans?

- **Measures**
  - Are the measures valid?
  - Does the response provide and accurate index of a relevant dimension of pain?
  - Is the targeted dimension of pain important to the clinical condition being modeled?
Preclinical Models
(Face Validity)

Does the model resemble what we see in the clinic?

Shingles/PHN
Arthritis
Surgery
CRPS
Nerve Injury
CFA
Incision
Fracture/Cast
The most common etiological factors linked to CRPS are distal limb fracture and immobilization.

Under anesthesia, the distal tibia is fractured and placed in a reinforced cast for 3 (mice) to 4 (rats) weeks.

- Spontaneous extravasation/edema
- Warmth
- Epidermal thickening
- Osteopenea
- Allodynia/unweighting
- Spontaneous pain
- Innate/adaptive immune activation
- Anxiety and memory changes

CRPS: The Rodent Fracture-Cast Model
Clinical data: Several small controlled trials – alendronate, clodronate, pamidronate and neridronate

Zoledronate? – Animal data useful for FDA approval

Ahmad and Kumar, 2015: Monthly zoledronate reduces pain in CRPS I after electrical burn
**Example: Autoimmunity Translation**

- **Autoimmunity in CRPS**
  - Anti-mACh, beta-2, alpha-1, anti-nuclear antibodies
  - Some patients treated with IVIG
Preclinical Models
(Influence of Sex)

- **Human sex dependence:**
  - Disease prevalence
  - Pain severity
  - Comorbidity susceptibility
  - Analgesic responsiveness/side effect profile

- **Animal model sex dependence:**
  - Degree/duration of nociceptive sensitization
  - Environmental effects
  - Analgesic sensitivity
  - Pathogenic mechanisms

- **NIH:** Sex (and other biological variables) should be represented in preclinical studies
Preclinical Models
(Influence of Sex)

Sorge et al., 2015
Preclinical Models
(Influence of Genetics, Human Observations)

- **Twin studies, heritability**
  - Pain sensitivity: <10% (mechanical) to >60% (cold pressor)
  - Pain syndromes: 25% IBS, 35% axial spine pain, 50% migraine
  - Analgesic sensitivity: 12% morphine (heat), 60% morphine (cold)
  - Side effects: 30% morphine (RR), 59% morphine (nausea)

- **Monogenic (Medelian) pain disorders**
  - SCN9A: Activating (more pain), Inactivating (no pain)
  - Hereditary sensory neuropathies (HSNs), Several genes
  - Fam. hemiplegic migraine, CACNA1A, ATP1A2, SCN1A

- **Gene association studies**
  - COMT, GCH1, MC1R, OPRM1 (pain phenotypes)
  - MDR, CYP2D6 (analgesic responses)
Preclinical Models
(Influence of Genetics)

LaCroix-Fralish et al., 2009
Preclinical Models
(Influence of Genetics)

Chu et al., 2009
Preclinical Models
(Non-rodent species)

- **Rodents offer:**
  - Cost/time advantages
  - Genetic opportunities
  - Social acceptability

- **Large animals (dogs, horses, primates) offer:**
  - Physiology, pharmacology, PK/PD more similar to humans (sometimes)
  - The natural occurrence of similar diseases, e.g. OA
  - Some functions more easily studied, e.g. gait
  - Ability to work with complex behaviors/cognitive tasks
  - Better size for some testing, e.g. structural/functional imaging

- **Available models**
  - Acute nociception (dogs, primates)
  - Algogen injection (primates)
  - UV sensitization (pigs)
  - OA, ACL injury (dogs)
  - L6, L9 primate nerve ligation model (primates)
Preclinical Measures
(Reflexive Testing)

- “Reflexive” or “evoked” testing
  - Mechanical, e.g. von Frey filaments
  - Thermal, e.g. thermal plantar
  - Very quick, straightforward, objective
  - Inexpensive

- Problems?
  - Nociceptive fiber types activated
  - Generally skin tissue targeted
  - Clinical complaint: “My pain is almost always there and it limits what I do, my ability to think, being with my family, my sleep and makes me feel depressed.”
Analgesia vs. Anti-hyperalgesia

- Twenty-two subjects with CRPS
- Allodynia and hyperalgesia assessed
- Clonidine 100ug or adenosine 2mg intrathecal

Rauck et al. Pain. 2015
Preclinical Measures
(Spontaneous/Ongoing Pain)

“Body Language”
- Flinching, guarding
- Postural changes/weight bearing
- Face analysis
- Ultrasonic vocalizations

Langford et al., 2010
Preclinical Measures
(Spontaneous/Ongoing Testing)

- Conditioned Place Preference

- Other “operant” assays:
  - Reward-conflict – receiving a reward with corresponding aversive stimulus
  - Avoidance-escape – forced selection between alternative aversive stimuli (one nociceptive)

Navratileva and Porreca, 2014
Blockade of hypersensitivity is not the same as blocking ongoing pain.

Spinal MK-801 does not induce CPP

At a dose that fully reverses thermal hypersensitivity

Spinal ω-conotoxin induces CPP

Spinal ω-conotoxin paired chamber

Courtesy Dr. Frank Porreca
Preclinical Measures
(Memory and Social Interactions)

Tajerian et al., 2015
Preclinical Measures
(Functional Testing)

- **Gait analysis:**
  - Incision, Osteo and Rheumatoid arthritis, Multiple sclerosis, CRPS, Chemotherapy-induced pain, Neuropathic pain
  - Analgesics reversed gait abnormalities in some but not all models, e.g. SNI, incision.

Vincelette et al., 2007
Preclinical Models
(Breadth of Experimental Factors)

- **For discovery**
  - Stringently standardize experimental conditions.
  - Use multiple rigorous, complementary approaches focused on a clear hypothesis, e.g. pharmacological, genetic, biochemical, electrophysiological, optogenetic, etc.

- **For translation** we may specifically examine the impact of:
  - Sex
  - Genetics, species
  - Age
  - Disease comorbidities
  - “Psychological” comorbidities
  - PK/PD
<table>
<thead>
<tr>
<th>IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials</th>
<th>IMMPAAS: Initiative on Methods, Measurement, and Pain Assessment in Animal Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong>&lt;br&gt;○ Patient report, analgesic use</td>
<td><strong>Pain</strong>&lt;br&gt;○ Evoked, spontaneous, operant</td>
</tr>
<tr>
<td><strong>Physical function</strong>&lt;br&gt;○ Interference scales</td>
<td><strong>Physical function</strong>&lt;br&gt;○ Activity, gait, running</td>
</tr>
<tr>
<td><strong>Emotional function</strong>&lt;br&gt;○ Depression, anxiety</td>
<td><strong>Emotional/cognitive function</strong>&lt;br&gt;○ Depression, anxiety, memory</td>
</tr>
<tr>
<td><strong>Pt. impression of change</strong>&lt;br&gt;○ PGIC scale</td>
<td><strong>Side effects, PK/PD, toxicity</strong>&lt;br&gt;○ Sedation, balance, organ tox.</td>
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<tr>
<td><strong>Symptoms/adv. events</strong>&lt;br&gt;○ Active/passive capture</td>
<td><strong>Subjects, reporting</strong>&lt;br&gt;○ ARRIVE</td>
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<tr>
<td><strong>Participants, reporting</strong>&lt;br&gt;○ CONSORT</td>
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Thank you