The Epidemic of Chronic Pain: Translational Challenges & Opportunities

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Clinical and Translational Science Institute
Overview of Presentation

• Chronic pain as an epidemic

• Translational approaches in pain research
  – Challenges
  – Opportunities

• Translational Bridges

• The way forward
What is Chronic Pain?

• Chronic pain has been recognized as that pain which persists past the normal time of healing (Bonica, 1953). In practice this may be less than one month, or more often, more than six months. With nonmalignant pain, three months is the most convenient point of division between acute and chronic pain, but for research purposes six months will often be preferred.

Merskey & Bogduk, Eds (1994). IASP Classification of Chronic Pain
Is Chronic Pain an Epidemic?

- Epidemic (noun): a disease or event whose incidence is beyond what is expected
  

- Epidemic (adj.): extremely prevalent; widespread
  
  Dictionary.com
Pain as a Public Health Problem

• Finding 2-1. Pain is a significant public health problem
  – Chronic pain alone affects at least 100 million U.S. adults, reduces quality of life, affects specific population groups
  – Pain costs society at least $560–635 billion annually (an amount equal to about $2,000 for everyone living in the United States)
Prevalence and Costs of Several Chronic Diseases in the United States

- **Cancer**
- **HIV/AIDS**
- **Heart Disease**
- **Diabetes**
- **Alzheimer's**
- **Chronic Pain**

**Prevalence**
- Point Prevalence (in millions)

**Annual Costs**
- 2010 Annual Costs (in billions)
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How Far Has the Pain Field Come in the Last 20+ Years?

• Mike S.
  – CLBP for several years
  – 2 unsuccessful surgeries
  – 45 year old former iron worker
  – < HS education, functionally illiterate
  – Panic disorder, depression
  – MI
Since January 1, 1992 there have been 63,633 articles published on “chronic pain.”
## Then vs. Now

<table>
<thead>
<tr>
<th></th>
<th>Then</th>
<th>Now</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical Options</strong></td>
<td>Lumbar fusion</td>
<td>Lumbar fusion</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td>NSAIDs, antidepressants, opioids (available, but not prescribed)</td>
<td>Similar classes of medications, but some new options (duloxetine, milnacipran), gabapentenoids.</td>
</tr>
<tr>
<td><strong>Neurostimulation</strong></td>
<td>Spinal cord stimulation (SCS)</td>
<td>SCS, noninvasive stimulation methods (tDCS, TMS) – but these are not widely available clinically</td>
</tr>
<tr>
<td><strong>Behavioral Approaches</strong></td>
<td>Multidisciplinary treatment</td>
<td>Multidisciplinary care is less available now</td>
</tr>
</tbody>
</table>
Why Such Limited Progress in 20+ Years?
Pain as a Symptom vs. a Disease

“While pain can serve as a warning to protect us from further harm, it also can contribute to severe and even relentless suffering, surpassing its underlying cause to become a disease in its own domains and dimensions.”

What Is Translational Pain Research?

- **T0** Discovery Research
  - Basic Neurobiology of Nociception
  - Preclinical Nociceptive Assays
  - Quantitative Sensory Testing

- **T1** Translation to Humans
  - Pharmacologic Probes
  - Brain Imaging
  - Genetic Associations

- **T2** Translation to Patients
  - Case-Control Studies
  - Genetic Associations
  - Prospective Cohort Studies
  - Phase II-III Clinical Trials

- **T3-4** Translation to Practice & Population
  - Implementation Science
  - Pragmatic Trials
  - Comparative Effectiveness Trials

- **T0** Reduced Pain in the Population
  - Identify New Molecular Targets
  - High Throughput Screening
  - Social Determinants of Health

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Translational Challenges & Opportunities

<table>
<thead>
<tr>
<th>Issue</th>
<th>Challenge</th>
<th>Opportunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain research is underfunded</td>
<td>XXX</td>
<td>XX</td>
</tr>
<tr>
<td>Preclinical pain models often fail to reflect clinical pain</td>
<td>XXX</td>
<td>XXX</td>
</tr>
<tr>
<td>Pain is a subjective experience</td>
<td>XXX</td>
<td>XXX</td>
</tr>
<tr>
<td>Pain is actively modulated by the CNS</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Pain is driven by multiple biopsychosocial processes</td>
<td>X</td>
<td>XXX</td>
</tr>
<tr>
<td>Pain is characterized by robust individual differences</td>
<td>XX</td>
<td>XXX</td>
</tr>
</tbody>
</table>
The First Translational Challenge

<table>
<thead>
<tr>
<th>Disease</th>
<th>2010 Annual Costs (in hundreds of billions)</th>
<th>2010 NIH Funding (in billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>3.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Cancer</td>
<td>6.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>1.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>
What’s Impeding Translational Pain Research?
Challenges to T1 Translation in Pain Research

- Reflex-based nociceptive assays
- Failure to model sources of variability in human pain responses (e.g. socioeconomic influences, psychological factors)
Pain is a Major Public Health Condition

But, Pain is Also a Private Health Condition

*There is no visible blood test or X ray to show a trauma. I do not look sick.*

- A person with chronic pain (IOM Report)
Pain as a Subjective Experience

“The neurologic signature for physical pain has been identified in a new study.”

Advantages of Self-Report Measures

• Self-report pain measures are reliable and valid

• Cost and convenience

• Epidemiological research

• Validate the person’s experience
Pain is Actively Modulated in the CNS


Descending pain pathway (Purves, 2001).
Psychosocial Factors Impact CNS Mechanisms

The Biopsychosocial Model of Pain

Biological Factors

Psychological Factors

Social Factors

Chronic Pain
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Seizing Opportunities in Translational Pain Research

Mechanisms  Pain Treatment
Translational Bridges in Pain Research

- Laboratory pain testing (or Quantitative Sensory Testing, QST)
- Genetics
- Brain Imaging
- Biopsychosocial factors
What is Quantitative Sensory Testing?

The assessment of perceptual and/or physiological responses to systematically applied and quantifiable sensory stimuli for the purpose of characterizing somatosensory function or dysfunction.
# Common Experimental Pain Modalities and Measures

<table>
<thead>
<tr>
<th><strong>Stimulus Modalities</strong></th>
<th><strong>Pain Measures</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical</td>
<td>Pain Threshold</td>
</tr>
<tr>
<td>Contact Thermal (heat, cold)</td>
<td>Pain Tolerance</td>
</tr>
<tr>
<td>Immersion Thermal (heat, cold)</td>
<td>Suprathreshold Scaling (e.g. VAS, NRS)</td>
</tr>
<tr>
<td>Mechanical/Pressure</td>
<td>Temporal Summation</td>
</tr>
<tr>
<td>Ischemic</td>
<td>Conditioned Pain Modulation</td>
</tr>
<tr>
<td>Chemical (e.g. capsaicin, hypertonic saline, glutamate)</td>
<td>Cerebral Responses (e.g. EEG, fMRI, PET)</td>
</tr>
<tr>
<td></td>
<td>Muscle Reflexes (e.g. R3 reflex)</td>
</tr>
</tbody>
</table>
Dad,

you’re a sick, sick man.

Thermal Pain Assessment

Dad, you’re a sick, sick man.
Ischemic Pain Assessment

Don’t let the smiles fool you, WE NEED HELP!
QST IS CLINICALLY RELEVANT
## Understanding Pain and Limitations in OsteoArthritic Disease (UPLOAD) Study

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thermal Pain Testing</strong></td>
<td>• Heat pain threshold &amp; tolerance</td>
</tr>
<tr>
<td></td>
<td>• Temporal summation (TS) at three temperatures</td>
</tr>
<tr>
<td><strong>Mechanical Pain Testing</strong></td>
<td>• Pressure pain thresholds</td>
</tr>
<tr>
<td></td>
<td>• Punctate mechanical pain &amp; TS</td>
</tr>
<tr>
<td><strong>Cold Pressor Pain</strong></td>
<td>• Cold pressor pain at 8, 12, 16 deg C</td>
</tr>
<tr>
<td></td>
<td>• Ratings obtained at 30 sec &amp; 1-minute</td>
</tr>
<tr>
<td><strong>Conditioned Pain Modulation</strong></td>
<td>• Heat TS (left hand) before &amp; after 1-minute immersion in cold water (right hand)</td>
</tr>
</tbody>
</table>
# Descriptive Statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>OA High Pain* (n=155)</th>
<th>OA Low Pain* (n=129)</th>
<th>Controls (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>55.4 (7.1)</td>
<td>58.4 (7.9)</td>
<td>57.4 (8.0)</td>
</tr>
<tr>
<td>Sex (% Female)</td>
<td>65.3</td>
<td>64.8</td>
<td>63.9</td>
</tr>
<tr>
<td>Race (% White)*</td>
<td>27.3</td>
<td>39.2</td>
<td>70.6</td>
</tr>
<tr>
<td><strong>Clinical Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCPS-Characteristic Pain (0-100)</td>
<td>67.7 (14.1)</td>
<td>30.6 (12.7)</td>
<td>10.2 (16.8)</td>
</tr>
<tr>
<td>GCPS-Disability (0-100)</td>
<td>59.7 (24.5)</td>
<td>24.6 (21.7)</td>
<td>2.1 (7.0)</td>
</tr>
<tr>
<td>WOMAC-Pain (0-20)</td>
<td>9.8 (4.1)</td>
<td>4.5 (2.8)</td>
<td>0.6 (1.7)</td>
</tr>
<tr>
<td>WOMAC-Physical Function (0-)</td>
<td>31.8 (13.7)</td>
<td>13.9 (10.2)</td>
<td>1.8 (4.8)</td>
</tr>
<tr>
<td>SPPB Total Score</td>
<td>9.2 (2.1)</td>
<td>10.5 (1.5)</td>
<td>10.9 (1.4)</td>
</tr>
<tr>
<td>CES-D Scores</td>
<td>11.8 (8.3)</td>
<td>7.6 (6.4)</td>
<td>6.5 (6.7)</td>
</tr>
</tbody>
</table>

* High vs. low OA pain based on median split of GCPS-Characteristic Pain Score (median=50)
Heat Pain Thresholds and Tolerances for OA Patients and Controls

Groups with unlike letters differ from each other, $p < 0.05$
Pressure Pain Thresholds for OA Patients and Controls

Groups with unlike letters differ from each other, p < 0.05
Punctate Mechanical Pain for OA Patients and Controls

*OA-High differs from the other two groups in both average rating and slope (p < 0.05)
Temporal Summation of Heat Pain for OA Patients and Controls

*OA-High differs from the other two groups in both average rating and slope (p < 0.05)
What are Individual Differences?

- Individual differences refer to variations across people in abilities, attitudes, experiences, behavior, and other potentially important biological or psychological responses.
Pain After Laparoscopic Cholecystectomy
(Bisgaard, et al, 2001)
Ratings of a 48 Degree Thermal Stimulus

Ratings (0-100) vs. Rank

Pain Rating (0-100)
Brain Correlates of Individual Differences in Pain

Individuals high in sensitivity to thermal pain (HIGH) showed more robust pain-related activation than those low in sensitivity (LOW) in the somatosensory (S1), anterior cingulate (ACC) and prefrontal (PCC) cortex.


A study of 116 healthy volunteers found that regional grey matter density in the following regions was negatively correlated with pain ratings of a 49 °C heat stimulus: bilateral precuneus, posterior cingulate cortex, inferior parietal lobule, intraparietal sulcus, and primary left somatosensory cortex.
GENDER DIFFERENCES
**Table 1. Prevalence of Chronic Pain in Representative Samples**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Prevalence</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman(^{30})</td>
<td>Sweden</td>
<td>12-month</td>
<td>38%</td>
<td>31%</td>
</tr>
<tr>
<td>Blythe(^{41,\ast})</td>
<td>Australia</td>
<td>6-month</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Bouhassira(^{44})</td>
<td>France</td>
<td>Current</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Breivik(^{47})</td>
<td>Europe</td>
<td>6-month</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Gerdle(^{158})</td>
<td>Sweden</td>
<td>3-month</td>
<td>59%</td>
<td>48%</td>
</tr>
<tr>
<td>Rustoen(^{351})</td>
<td>Norway</td>
<td>Current</td>
<td>28%</td>
<td>23%</td>
</tr>
<tr>
<td>Smith(^{377})</td>
<td>United Kingdom</td>
<td>Current</td>
<td>52%</td>
<td>49%</td>
</tr>
<tr>
<td>Tsang(^{415})</td>
<td>17 countries</td>
<td>12-month</td>
<td>45%</td>
<td>31%</td>
</tr>
<tr>
<td>Von Korff(^{427})</td>
<td>United States</td>
<td>12-month</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Wijnhoven(^{442})</td>
<td>Netherlands</td>
<td>12-month</td>
<td>49%</td>
<td>41%</td>
</tr>
</tbody>
</table>

**NOTE.** **Bolded** numbers reflect significant sex differences in prevalence.

\(^{\ast}\)Blyth et al did not indicate the significance of the difference.
STANDARDIZED PAIN MEASURES ACROSS MULTIPLE PAIN TASKS FOR FEMALES AND MALES

Mean=0, higher numbers reflect higher pain threshold or tolerance
Sex Differences in Experimental Pain Measures
Temporal Summation of Thermal Pain

$p < .005$, Trial X Sex Interaction
Does Pain Increase with Age?
Prevalence of Chronic Pain Across the Lifespan

N=42,249 from 17 countries.
Chronic pain=presence of at least one of the following in the past 12 months: arthritis or rheumatism, chronic back or neck pain, frequent or severe headaches, other chronic pain.
Chronic Pain Across the Lifespan
(Blyth, et al, 2001 *PAIN* 89: 127-34)

Interview of 17,543 Australians
Chronic pain=Pain experienced every day for three months in the six months prior to interview
Age-Related Differences in Pain Perception
(Edwards & Fillingim, 2003)

Pain responses compared across multiple modalities in 32 younger (22.4 years) and 34 older (62.2 years) adults.
Age-Related Differences in Conditioned Pain Modulation
(Riley, et al, 2010)
Prevalence of Migraine by Sex and Age

(Lipton, et al, 2001 Headache 41: 646-57)
GENETIC FACTORS
# Heritability of Pain and Analgesic Responses

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Heritability Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Clinical Pain Conditions (e.g. migraine, neck pain, back pain, widespread pain)</td>
<td>0.34 - 0.68</td>
</tr>
<tr>
<td>Experimental Pain (pressure pain, heat pain, cold pain, acid pain, hyperalgesia)</td>
<td>0.10 - 0.60</td>
</tr>
<tr>
<td>Opioid Analgesia (tested with heat and cold pain)</td>
<td>0.12 – 0.60</td>
</tr>
</tbody>
</table>
OPRM1 A118G Genotype and Pressure Pain Thresholds among Females and Males (Fillingim, et al, 2005, J Pain 6:159-67)

96 F (72 AA, 24 AG/GG)
71 M (59 AA, 12 AG/GG)

† Sex X genotype interaction, p’s = .09
* Genotype effect, all p’s < .05 for males
**OPRM1 A118G Genotype and Heat Pain Ratings among Females and Males** (Fillingim, et al, 2005, J Pain 6:159-67)

Sex X genotype interaction, p < 0.05
Studied 252 patients presenting with lumbar disc herniation and sciatica

Pain at 12 months was examined as a function of sex and A118G genotype
VAS Pain Ratings with Activity 12 Months after Lumbar Disc Herniation

VAS Ratings (0-10)

Male
Female

AA
AG/GG
**COMT Haplotype and Pain Sensitivity**

LPS=low pain sensitive, APS=average pain sensitive; HPS=high pain sensitive

PSYCHOLOGICAL FACTORS
Psychological Factors Predict Development of Chronic Pain

- Headache (Obermann, et al, 2010 *Cephalalgia* 30: 538-34)
Orofacial Pain: Prospective Evaluation and Risk Assessment

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High Psychological Distress

- Mood
- Anxiety
- Depression
- Stress response
- Somatization

High State of Pain Amplification

- Neuro-endocrine function
- Autonomic function
- Impaired pain regulation
- Pro-inflammatory state

Painful TMD

Persistent TMD

First-onset TMD

Subclinical signs & symptoms

ENVIRONMENTAL CONTRIBUTIONS

Physical environment
  • eg. trauma, infection

Social environment
  • eg. life stressors

Culture
  • eg. health beliefs

Demographics

Psychosocial Predictors of First Onset TMD

BIOPSYCHOSOCIAL INTERACTIONS
Combined Influences of \textit{COMT} and Catastrophizing on Shoulder Pain

- 58 (24 F, 34 M) patients with chronic shoulder pain, undergoing arthroscopic surgery

- Pre-operative testing
  - Psychological questionnaires (catastrophizing)
  - Psychophysical testing
  - Buccal swab for DNA (COMT diplotypes from Diatchenko, et al, 2005)

- Arthroscopic surgery
- Post-operative testing (3-5 months later)

Combined Influences of Pain Catastrophizing and COMT Haplotype

LPS=Low pain sensitive genotype; APS/HPS=Average/High pain sensitive genotype; PCS=Pain Catastrophizing Scale
Combined Influences of Psychological Factors and COMT Haplotype

Figure 2a-c – Prediction of 5-day upper extremity disability: interactions between genetic and psychological factors

Figures 2a and 2b
Overview of Presentation

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  – Opportunities

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Chronic Pain Disorders

Altered Pain Processing

Psychological Processes

Biological Processes

Genetic Factors

Environmental Exposures (e.g. trauma, surgery)

Effect Modifiers (e.g. sex, age, race)

Effect Modifiers (e.g. sex, age, race)
Future Directions

• Multiple approaches can facilitate translational pain research in the future:
  – QST
  – Brain Imaging
  – Genetics

• Translational pain research must address the multiple biopsychosocial mechanisms that contribute to chronic pain.

• We need far more T3-T4 pain research.

• Through interdisciplinary translational efforts, we can make rapid progress in addressing the epidemic of chronic pain.
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