Mechanism-Based Approaches to Understanding the Epidemic of Chronic Pain

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Overview of Presentation

• Chronic pain as an epidemic

• Biopsychosocial mechanisms of pain

• Risk factors for chronic pain

• Examples of mechanism-based epidemiology
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
## Prevalence of Chronic Pain in Norway

<table>
<thead>
<tr>
<th>Citation</th>
<th>Definition</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rustoen, et al, 2004, Eur J Pain 8: 555-65</td>
<td>“Do you generally have pain?” (Yes) and duration &gt; 3 months</td>
<td>24.4%</td>
<td>Gender, education, chronic illness, were related to chronic pain</td>
</tr>
<tr>
<td>Breivik, et al, 2006, Eur J Pain 10: 287-333</td>
<td>Pain: (a) &gt; 6 months, (b) in the last month, (c) at least twice/wk, (d) rated ≥ 5/10</td>
<td>30%</td>
<td>Norway had highest prevalence among 16 European countries</td>
</tr>
<tr>
<td>Hoftun, et al, 2011, PAIN 152: 2259-62</td>
<td>Pain unrelated to any known disease or injury, at least 1/wk during the last 3 mos.</td>
<td>44.4%</td>
<td>Young-HUNT Study, only adolescents, aged 13-18.</td>
</tr>
<tr>
<td>Landmark, et al, 2012, PAIN 153: 1368-73</td>
<td>Moderate pain or more on at least 3 of the 4 quarterly measurements from baseline to 9-month follow-up</td>
<td>26%</td>
<td>HUNT-Pain Study</td>
</tr>
<tr>
<td>Johansen, et al, 2012, PAIN 153: 1390-96</td>
<td>Persistent post surgical pain: (1) surgery 3 to 36 months prior to survey, (2) present pain in area of surgery rated ≥ 1/10</td>
<td>40.4%</td>
<td>Tromso VI Study: Post-surgical pain only (22.2% mild, 11.7% moderate, 6.6% severe)</td>
</tr>
<tr>
<td>Olsen, et al, 2013, PAIN 154: 257-62.</td>
<td>Persistent or constantly recurrent pain lasting 3 months or longer</td>
<td>31.8%</td>
<td>Tromso VI Study</td>
</tr>
</tbody>
</table>
Increasing Prevalence of Chronic Low Back Pain
(Frebruger, et al, 2009 Arch Int Med 169: 251-58)

CLBP: (1) pain and activity limitations nearly every day for the past 3 months or (2) more than 24 episodes of pain that limited activity for 1 day or more in the past year
**Increasing Prevalence of Knee Pain**


Knee Pain: Pain lasting at least a month in or around the knee, including the back of the knee during the past 12 months. Only adults ≥ 70 years of age included.
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What Do We Mean by “Mechanism?”
## Etiology Versus Mechanisms

<table>
<thead>
<tr>
<th>Etiology</th>
<th>General Mechanisms</th>
<th>Specific Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic peripheral neuropathy</strong></td>
<td>Peripheral nerve damage, altered central pain processing</td>
<td>TRP channels</td>
</tr>
<tr>
<td><strong>Knee Osteoarthritis</strong></td>
<td>Peripheral inflammation &amp; mechanical nociception, Central sensitization</td>
<td>Specific cytokines, matrix metalloproteinases</td>
</tr>
<tr>
<td><strong>Fibromyalgia</strong></td>
<td>Central and/or peripheral sensitization</td>
<td>Altered serotonergic function</td>
</tr>
</tbody>
</table>
“Pain mechanisms” include multiple dynamic processes in the periphery, spinal cord and the brain.
Psychological Factors also Represent Mechanisms

Methods for Identifying Pain Mechanisms in Humans

• Diagnostic tests to identify peripheral generators (e.g. skin biopsies for small fiber neuropathy)

• Pharmacologic approaches

• Distinct symptom clusters in patients with the same diagnosis

• **Quantitative sensory testing (QST)**

• **Genetic markers**

• Brain imaging
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Factors Associated with Both Chronic and Pain Sensitivity

• Demographic factors
  – Sex/gender
  – Age
  – Race/ethnicity

• Genetic Factors

• Psychological Factors
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</td>
<td>Sweden</td>
<td>12-month</td>
<td>38%</td>
<td>31%</td>
</tr>
<tr>
<td>Blythe</td>
<td>Australia</td>
<td>6-month</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Bouhassira</td>
<td>France</td>
<td>Current</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Breivik</td>
<td>Europe</td>
<td>6-month</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Gerdle</td>
<td>Sweden</td>
<td>3-month</td>
<td>59%</td>
<td>48%</td>
</tr>
<tr>
<td>Rustoen</td>
<td>Norway</td>
<td>Current</td>
<td>28%</td>
<td>23%</td>
</tr>
<tr>
<td>Smith</td>
<td>United Kingdom</td>
<td>Current</td>
<td>52%</td>
<td>49%</td>
</tr>
<tr>
<td>Tsang</td>
<td>17 countries</td>
<td>12-month</td>
<td>45%</td>
<td>31%</td>
</tr>
<tr>
<td>Von Korff</td>
<td>United States</td>
<td>12-month</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Wijnhoven</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. *Blyth et al did not indicate the significance of the difference.*
Sex Differences in Experimental Pain Measures
ETHNIC DIFFERENCES
Race and Ethnic Group Differences in Pain Prevalence

Pain that has lasted 3 months or longer

Women

Men

Prevalence (%)
Pain Prevalence and Severity Among Older Individuals
(Reyes-Gibby, et al, 2007, J Pain, 8:75-84)

Pain Prevalence: “Are you often troubled with pain?”

- **NH-Whites (n=11,021)**
- **NH-Blacks (n=1,804)**
- **Hispanics (n=952)**

The chart shows the prevalence of pain among older individuals categorized by race and pain severity.
Comorbid Pains Across Race/Ethnicity Among People with TMJ Pain

Number of Comorbid Pain Conditions (headache, neck pain, low back pain, joint pain)

Prevalence (%)

![Bar chart showing effect size for different pain responses (Heat, Cold, Ischemic, Pressure, Electrical) for AA vs. NHW. The chart compares unweighted and weighted effect sizes.](chart.png)
Does Pain Increase with Age?
Chronic Pain and Age


![Bar chart showing prevalence of chronic pain by age group.]

**Age Group**
- < 60
- 60-70
- 70-80
- > 80

**Prevalence (%)**

- **Any Pain**
- **Moderate to Severe**

Any Pain = “Are you often troubled with pain?”
Chronic Pain Across the Lifespan

Interview of 17,543 Australians

Chronic pain = Pain experienced every day for three months in the six months prior to interview
Prevalence of Osteoarthritis Across Age Groups

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)
PSYCHOLOGICAL FACTORS
Psychological Factors and Risk for Low Back Pain
(Linton, 2000, Spine, 25:1148-56)

1. Psychosocial variables associated with reported onset of back and neck pain and transition from acute to chronic pain disability. (Level A evidence)

2. Psychosocial variables generally have more impact than biomedical or biomechanical factors on back pain disability. (Level A)

3. Cognitive factors (attitudes, cognitive style, fear avoidance beliefs) (Level A)

4. Self-perceived poor health (Level A)

5. Depression, anxiety, negative emotions (Level A)

6. Personality and traits (Level C)

7. Sexual and/or physical abuse (Level D)

8. Psychosocial factors as risk factors for long-term pain and disability. (Level A)

Level A: evidence from two or more good-quality prospective studies
Level C: inconclusive data
Level D: no studies available meeting criteria
Pain Catastrophizing

• Catastrophizing refers to an exaggerated negative mental set brought to bear during actual or anticipated painful experience (Sullivan et al, 2001, Clin J Pain. 17: 52-64).

• Catastrophizing predicts:
GENETIC INFLUENCES
Heritability of Pain Phenotypes  
(Nielsen, et al., 2012, Clin Genetics, 82: 331-40)

<table>
<thead>
<tr>
<th>Pain Phenotype</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>46%</td>
</tr>
<tr>
<td>Low Back Pain</td>
<td>38%</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>39%</td>
</tr>
<tr>
<td>Irritable Bowel Syndrome</td>
<td>27%</td>
</tr>
<tr>
<td>Chronic Widespread Pain</td>
<td>~50%</td>
</tr>
<tr>
<td>Experimental Pain Phenotypes</td>
<td>0 – 55%</td>
</tr>
<tr>
<td>Cold Pressor Pain</td>
<td>~50%</td>
</tr>
</tbody>
</table>
INTERACTIONS
Prevalence of Migraine by Sex and Age

(Lipton, et al, 2001 Headache, 41: 646-57)
Sex X genotype interaction, p < 0.05

**OPRM1 A118G Genotype and Heat Pain Ratings among Females and Males** (Fillingim, et al, 2005, J Pain 6:159-67)

![Bar chart showing numerical pain ratings for males and females with AA and AG/GG genotypes.](chart.png)

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

![Graph showing VAS Pain Ratings (0-10) for Male and Female with AA and AG/GG categories.]

- Male:
  - AA: [Average rating with error bars]
  - AG/GG: [Average rating with error bars]

- Female:
  - AA: [Average rating with error bars]
  - AG/GG: [Average rating with error bars]
Combined Influences of \textit{COMT} and Catastrophizing on Shoulder Pain (George, et al, 2008)

- 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

![Graphs showing pain intensity pre- and post-operatively for different groups based on pain catastrophizing and COMT haplotype.](image-url)
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Orofacial Pain: Prospective Evaluation and Risk Assessment

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Charles Knott: Data Coordinating Center

External Advisory Committee
Gary Macfarlane, Chair

Funded by NIH/NIDCR: U01 DE017018
Study designs for first-onset and chronic TMD

Inception cohort: 3,263 people without TMD

Prospective cohort study of first-onset TMD.
3-monthly screening questionnaires of all people. Clinical assessment of each person who screens positively and one matched control who screens negatively

Baseline case-control study of chronic TMD

260 incident cases of first-onset TMD

Community-based recruitment of healthy volunteers
Four U.S. study sites
Baltimore, MD; Buffalo, NY; Chapel Hill, NC; Gainesville, FL

Study-wide screening enrollment criteria
aged 18-44 years
no significant medical conditions
no recent facial injury
First Onset TMD: Age, Gender, Race Associations

![Graph showing standardized hazard ratio for Age, Gender, and Race](graph.png)
Psychosocial Predictors of First Onset TMD

Standardized Hazard Ratio (± 95% CI)

- Pill Global Score
- SCL 90R Somatization
- Trait Anxiety Inventory
- PTSD Symptoms
- SCL 90R Obs Compuls
- Depression
- Perceived Stress Scale
- SCL 90R Anxiety
- EPQ-R Paranoid
- SCL 90R Neuroticism
- Interpers Sens
- LES Negative Impact
- POMS-BI Negative Affect
- SCL 90R Hostility
- State Anxiety Inventory
- SCL 90R Phobia
- SCL 90R Psychotic
- POMS-BI Positive Affect
Standardized Hazard Ratios (adjusted for sex, age, race/ethnicity, and study site) for TMD Incidence Related to QST Measures
# The Tromsø Study

<table>
<thead>
<tr>
<th>Wave</th>
<th>Year</th>
<th>N</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tromsø I</td>
<td>1974</td>
<td>6,595</td>
<td>20-49</td>
</tr>
<tr>
<td>Tromsø II</td>
<td>1979-80</td>
<td>16,621</td>
<td>20-54</td>
</tr>
<tr>
<td>Tromsø III</td>
<td>1986-87</td>
<td>21,826</td>
<td>12-67</td>
</tr>
<tr>
<td>Tromsø IV</td>
<td>1994-95</td>
<td>27,158</td>
<td>25-97</td>
</tr>
<tr>
<td>Tromsø V</td>
<td>2001-02</td>
<td>8,130</td>
<td>30-89</td>
</tr>
<tr>
<td><strong>Tromsø VI</strong></td>
<td><strong>2007-08</strong></td>
<td><strong>12,984</strong></td>
<td><strong>30-87</strong></td>
</tr>
</tbody>
</table>

[WWW.TROMSOUNDERSOKELSEN.NO](http://WWW.TROMSOUNDERSOKELSEN.NO)
Pain tests

• Pain sensitivity:
  – Cold-pressor test 106s, NRS every 8s (N = 10,486)
  – Pressure pain threshold x 3
  – Heat pain threshold x 3
  – Finometer blood-pressure monitoring
Chronic Pain Prevalence by Gender and Age: Tromso VI

![Graph showing chronic pain prevalence by gender and age. The graph displays the prevalence of chronic pain among women and men across different age groups (30-44, 45-54, 55-64, 65-74, 75+). The prevalence is represented on the y-axis, and the age groups are on the x-axis. The graph indicates that women have a higher prevalence of chronic pain compared to men across all age groups.]
Cold Pain Tolerance: Chronic pain vs. Control

Chronic pain, HR = 1.15, p < 0.001

Pain free
Cold Pain Tolerance: # Painful Body Sites

6+ sites, HR = 1.52, p < 0.001
4-5 sites, HR = 1.31, p < 0.001
2-3 sites, HR = 1.11, n.s.
1 site, HR = 0.96, n.s.
Pain free
Chronic Pain, Blood Pressure and Pain Sensitivity

Among people without chronic pain, higher blood pressure was more strongly associated with reduced sensitivity (i.e. lower pain ratings) to cold pain than in people with chronic pain.

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)
Summary

• Chronic pain is the most prevalent and costly public health condition affecting the western world.

• Multiple biopsychosocial mechanisms contribute to chronic pain.

• Mechanism-based epidemiological studies, such as OPPERA and Tromso, can be instrumental in uncovering the mechanisms and consequences of chronic pain disorders.