Defining TMD for Clinical Care

Daniel J. Clauw M.D.
dclauw@umich.edu
Professor of Anesthesiology, Medicine (Rheumatology), and Psychiatry
Director, Chronic Pain and Fatigue Research Center
The University of Michigan
Disclosures

- Consulting
  - Pfizer, Tonix, Theravance, Zynerba, Samumed, Aptinyx, Daiichi Sankyo, Intec, Regeneron, Teva

- Research support
  - Pfizer, Cerephex, Aptinyx

- Litigation
  - Retained by State of Oklahoma in litigation against opioid manufacturers
Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification

William Maixner,* ‡ Roger B. Fillingim,† David A. Williams,§ Shad B. Smith,* ‡ and Gary D. Slade,* ‡,∥

*Center for Pain Research and Innovation, ‡Department of Dental Ecology, ∥Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
†Center for Translational Pain Medicine, Department of Anesthesiology, Duke University, Durham, North Carolina.
§Pain Research and Intervention Center of Excellence, University of Florida, Gainesville, Florida.
∥Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan.

Abstract: There is increasing recognition that many if not most common chronic pain conditions are heterogeneous with a high degree of overlap or coprevalence of other common pain conditions along with influences from biopsychosocial factors. At present, very little attention is given to the high degree of overlap of many common pain conditions when recruiting for clinical trials. As such, many if not most patients enrolled into clinical studies are not representative of most chronic pain patients. The failure to account for the heterogeneous and overlapping nature of most common pain conditions may limit treatment success and will affect future research and practice.
Chronic Overlapping Pain Conditions

- Most highly prevalent pain conditions in individuals under age 50
  - Fibromyalgia
  - Chronic fatigue syndrome
  - Irritable bowel
  - TMJ Disorder
  - Headache
  - Interstitial cystitis
  - Low back pain
  - Endometriosis
  - Vulvodynia

- Same central mechanisms play significant roles in all pain conditions, even those with known peripheral contributions
Evolution of Thinking Regarding Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Pathophysiology poorly understood and thought to be psychological in nature

- Chronic widespread pain
- Tenderness in ≥11 of 18 tender points

- Final common pathway (i.e. pain centralization)
- Part of a much larger continuum
- Not just pain
- Pathophysiology fairly well understood and is a CNS process that is independent from classic psychological factors
# Mechanistic Characterization of Pain

Variable degrees of any mechanism can contribute in any disease

<table>
<thead>
<tr>
<th></th>
<th>Nociceptive</th>
<th>Neuropathic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Inflammation or damage</td>
<td>Nerve damage or entrapment</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Pain is well localized, consistent effect of activity on pain</td>
<td>Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling</td>
</tr>
<tr>
<td><strong>Screening tools</strong></td>
<td>NSAIDs, injections, surgery, ? opioids</td>
<td>PainDETECT</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>NSAIDs, injections, surgery, ? opioids</td>
<td>Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs</td>
</tr>
<tr>
<td><strong>Classic examples</strong></td>
<td>Osteoarthritis, Autoimmune disorders, Cancer pain</td>
<td>Diabetic painful neuropathy, Post-herpetic neuralgia, Sciatica, Carpal tunnel syndrome</td>
</tr>
</tbody>
</table>

**Mixed Pain States**
Fibromyalgia-ness

- Term coined by Wolfe to indicate that the symptoms of FM occur as a continuum in the population rather than being present or absent \(^1\)

- In rheumatic disorders such as osteoarthritis, rheumatoid arthritis, lupus, low back pain, etc. this score is more predictive of pain levels and disability than more objective measures of disease \(^2,^3\)

- Domain overlaps with somatization in many regards, and there are many questionnaires that collect somatic symptom counts as a surrogate for this construct

Fibromyalgia

Centralized pain in individuals with any chronic pain condition
CNS Pain Volume Control

Low Setting

NO PAIN

Peripheral pain signals

CNS Pain Volume Control

High Setting

HIGH PAIN

Central pain signals

ADVANCED DISPLACEMENT

NORMAL
Concept of “Fibromyalgia-ness”

Fibromyalgia Symptoms (Modified ACR 2010 Fibromyalgia Diagnostic Criteria)

1. Please indicate below if you have had pain or tenderness over the past 7 days in each of the areas listed below. Check the boxes in the diagram below for each area in which you have had pain or tenderness. Be sure to mark right and left sides separately.

Left
- Jaw
- Shoulder
- Upper Arm
- Upper Back
- Chest/Breast
- Abdomen
- Lower Back
- Hip
- Lower Leg
- Ankle

Right
- Jaw
- Shoulder
- Upper Arm
- Upper Back
- Chest/Breast
- Abdomen
- Lower Back
- Hip
- Lower Leg
- Ankle

2. Using the following scale, indicate for each item your severity over the past week by checking the appropriate box.
   - No problem
   - Slight or mild problems: generally mild or intermittent
   - Moderate: considerable problems; often present and/or at a moderate level
   - Severe: continuous, life-disturbing problems

   a. Fatigue
   b. Trouble thinking or remembering
   c. Waking up tired (unrefreshed)

3. During the past 6 months have you had any of the following symptoms?
   - No
   - Yes
   a. Pain or cramps in lower abdomen
   b. Depression
   c. Headache

4. Have the symptoms in questions 2-3 and pain been present at a similar level for at least 3 months?
   - No
   - Yes

5. Do you have a disorder that would otherwise explain the pain?
   - No
   - Yes

Centralization Continuum

Proportion of individuals in chronic pain states that have centralized their pain

Peripheral

Acute pain  Osteoarthritis  SC disease  Fibromyalgia
  RA  Ehler’s Danlos  Tension HA
  Low back pain  TMJD  IBS

Centralized

Interstitial cystitis
Interstitial Cystitis

Tertiles of body pain distribution:
local, intermediate, widespread

Non-Neuroimaging (N=334)

Neuroimaging (N=110)

Validation
FM (N=23)
HC (N=49)
Increased Gray Matter Volume in and Connectivity to Sensory Cortex In Widespread Pain
Neurological Signature of Widespread Pain
Includes Sensory and Insular Cortices
Sub-threshold FM is Highly Predictive of Surgery and Opioid Non-responsiveness in Patients Undergoing Arthroplasty and Hysterectomy

■ Primary hypothesis of studies is the measures of centralized pain in OA (FMness) will predict failure to respond to arthroplasty and hysterectomy

■ Extensive preoperative phenotype using validated self-report measures of pain, mood, and function

■ Two outcomes of interest:
  ■ Postoperative opioid consumption
  ■ Pain relief from procedure at 6 months

Knee

Lower
Michigan Body Map

On the image below, identify all the areas of your body where you have felt persistent or recurrent pain present for the last 3 months or longer.

- Head
- Shoulder
- Elbow
- Wrist
- Finger
- Back
- Hip
- Knee
- Ankle
- Foot

No Pain

* Sciatica - bilaterally.

- Pain in back vertebral area.
- Need an epidural. Last one was performed.
- Difficulty getting in, getting up, sitting, standing, walking. Has temporary relief of pain.

© 2004 Regents of the University of Michigan
Mismatch Between Injury and Pain

- Collaboration with S. Aronovich, DMD
- Prospective study on patients being treated for TMD
- n=68 with MRI of temporomandibular joints

Harper et al. (Manuscript in preparation)
Variables Analyzed

- Age
- Sex
- Surgery (Knee vs Hip)
- Primary anesthetic (GA vs neuraxial)
- Home opioids (IVME)
- Pain severity (BPI)
  - Overall
  - Surgical site
- Neuropathic pain score (PainDETECT)
- Depression (HADS)
- Anxiety (HADS)
- Catastrophizing
- Physical function-WOMAC
“Fibromyalgia-ness” can be scored 0-31

<table>
<thead>
<tr>
<th>FM Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>19/31</td>
<td>Potential FM score derived from how widespread pain is</td>
</tr>
<tr>
<td>12/31</td>
<td>Potential FM score derived from co-morbid CNS-derived symptoms that accompany CNS pain</td>
</tr>
</tbody>
</table>

Each one point increase in fibromyalgianess led to:

- 9 mg greater oral morphine requirements during acute hospitalization (8mg greater when all individuals taking opioids as outpatients excluded)
- 20 – 25% greater likelihood of failing to respond to knee or hip arthroplasty (judged by either 50% improvement in pain or much better or very much better on patient global)
- These phenomenon were linear across entire scale up to a score of approximately 18 - and equally strong after individuals who met criteria for FM were excluded
- This phenomenon was much stronger than and largely independent of classic psychological factors
Compared to Patient A with localized pain and no somatic symptoms, Patient B would need 90mg more Oral Morphine Equivalents during first 48 hours of hospitalization, and would be 5X less likely to have 50% improvement in pain at 6 months.

Classic psychological factors are playing a much larger role in individuals who meet criteria for FM than those with “sub-threshold” FM.
Arthroscopic Surgery in TMD

- After controlling for baseline pain, those who had WPI <3 had significantly more improvement in their pain after intervention compared to those with WPI ≥ 3 ($R^2 = .586$, $p<.05$)

Carver, Harper, Aronovich (Manuscript in Preparation)
### Treating Based on Mechanisms

*Any combination may be present*

<table>
<thead>
<tr>
<th></th>
<th>Peripheral (nociceptive)</th>
<th>Neuropathic</th>
<th>Centralized Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Surgery/Injections</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Tricyclics</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>SNRIs</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Gabapentinoid</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>CBD</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>THC</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Symptoms of Pain, Fatigue, etc.
- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing

Functional Consequences of Symptoms
- Increased stress
- Decreased activity
- Poor sleep
- Obesity
- Maladaptive illness behaviors

Dually Focused Treatment
- Pharmacological therapies to improve symptoms
- Nonpharmacological therapies to address dysfunction

Summary

- When clinically defining TMDs, one of key issues will be whether individuals have pain and symptoms confined to the face, or whether – and to what extent – this is a more centralized, systemic process.

- Phenotype is easily identifiable and includes multifocal pain, fatigue, sleep, memory and sensory sensitivity issues.

- Even though there are many causes for centralized pain (think hypertension) this demarcation can already be helpful clinically in guiding treatment by matching underlying mechanism(s) with treatments targeting those mechanisms.

Lessons from old guy in this field:

- Nothing about any of these conditions is yes or no.
- This is not peripheral vs central – it is peripheral plus central.
- This is not a primary psychological problem.

- Assess psychological factors independently – some people have them (especially as they have pain and symptoms longer), some do not.