Defining TMD for Clinical Care - The Horizon

Committee on Temporomandibular Disorders (TMD): From Research Discoveries to Clinical Treatment

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A Guiding Principle

Common chronic pain conditions – like TMD – present as a kaleidoscope of phenotypes that are temporally dynamic and result from GxE interactions.
High Psychological Distress

High State of Pain Amplification

Painful CPPCs

Persistent Pain

Acute Pain

Subclinical signs & symptoms

Mood

Anxiety

Depression

Stress response

Somatization

Neuro-endocrine function

Autonomic function

Impaired pain regulation

Pro-inflammatory state

ENVIRONMENTAL CONTRIBUTIONS

Physical trauma
abuse
infection
smoking

Psychological life stressors

Culture
health beliefs

Physical trauma
abuse
infection
smoking

Psychological life stressors

Culture
health beliefs

### Table 5. Published Estimates of Overlap Between Index Conditions and Other COPCs

<table>
<thead>
<tr>
<th>INDEX CASE</th>
<th>FM</th>
<th>IBS</th>
<th>TMD</th>
<th>CFS</th>
<th>VVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM</td>
<td>80^{37}</td>
<td></td>
<td>75^{82}</td>
<td>64^{2}</td>
<td>NA</td>
</tr>
<tr>
<td>IBS</td>
<td>41^{133}</td>
<td></td>
<td>16^{57}</td>
<td>14^{57}</td>
<td>NA</td>
</tr>
<tr>
<td>TMD</td>
<td>24^{133}</td>
<td>64^{2}</td>
<td></td>
<td>20^{2}</td>
<td>NA</td>
</tr>
<tr>
<td>CFS</td>
<td>55^{133}</td>
<td>58^{37}</td>
<td>42^{60}</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>VVD</td>
<td>23^{133}</td>
<td>25^{75}</td>
<td>20^{39}</td>
<td>8^{75}</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: COPC, chronic overlapping pain condition; FM, fibromyalgia; IBS, irritable bowel syndrome; TMD, temporomandibular disorders; CFS, chronic fatigue syndrome; VVD, vulvodynia; NA, not applicable.
Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study

Eric Bair¹,⁵, Shella Gaynor¹, Gary D. Slade¹,²,⁶, Richard Ohrbach¹, Roger B. Fillingim⁴, Joel D. Greenspan¹, Ronald Dubner¹, Shad B. Smith¹,²,⁶, Luda Diatchenko¹, William Maixner¹,⁵

Abstract
The classification of most chronic pain disorders gives emphasis to anatomical location of the pain to distinguish one disorder from the other (eg, back pain vs temporomandibular disorder [TMD]) or to define subtypes (eg, TMD myalgia vs arthralgia). However, anatomical criteria overlook etiology, potentially hampering treatment decisions. This study identified clusters of individuals using a comprehensive array of biopsychosocial measures. Data were collected from a case–control study of 1031 chronic TMD cases and 3247 TMD-free controls. Three subgroups were identified using supervised cluster analysis (referred to as the adaptive, pain-sensitive, and global symptoms clusters). Compared with the adaptive cluster, participants in the pain-sensitive cluster showed heightened sensitivity to experimental pain, and participants in the global symptoms cluster showed both greater pain sensitivity and greater psychological distress. Cluster membership was strongly associated with chronic TMD: 91.5% of TMD cases belonged to the pain-sensitive and global symptoms clusters, whereas 41.2% of controls belonged to the adaptive cluster. Temporomandibular disorder cases in the pain-sensitive and global symptoms clusters also showed greater pain intensity, jaw functional limitation, and more comorbid pain conditions. Similar results were obtained when the same methodology was applied to a smaller case–control study consisting of 199 chronic TMD cases and 201 TMD-free controls. During a median 3-year follow-up period of TMD-free individuals, participants in the global symptoms cluster had greater risk of developing first-onset TMD (hazard ratio = 2.8) compared with participants in the other 2 clusters. Cross-cohort predictive modeling was used to demonstrate the reliability of the clusters.

Keywords: Temporomandibular disorders, Clustering, Classification of chronic pain
Hazard Ratio (C1 vs C3) for First-Onset TMD

N = 2,731 TMD-free individuals; 260 onset cases

HR = 2.8; CI (2.3-3.9), p < 0.0001

Bair and Coworkers
### TMD Clinical Characteristics Based on Cluster Assignment

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>A Means (n=85)</th>
<th>PS Means (n=529)</th>
<th>GS Means (n=400)</th>
<th>Overall P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Facial Pain (months)</td>
<td>6.08</td>
<td>7.15</td>
<td>6.84</td>
<td>0.3318</td>
</tr>
<tr>
<td>Current Facial Pain (0-100)</td>
<td>15.63</td>
<td>18.42</td>
<td>29.46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Facial Pain Intensity 2 wks (0-100)</td>
<td>45.67</td>
<td>52.41</td>
<td>61.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Waking Day with Pain</td>
<td>35.41</td>
<td>32.63</td>
<td>48.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain Intensity 2 wks (0-20)</td>
<td>5.74</td>
<td>6.12</td>
<td>8.98</td>
<td>&lt;0.0001</td>
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<tr>
<td>Pain Unpleasantness 2 wks (0-20)</td>
<td>5.14</td>
<td>5.54</td>
<td>8.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Facial Pain Interference 2 wks (0-100)</td>
<td>12.50</td>
<td>19.80</td>
<td>30.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SF12v2 Physical Functioning Scale (0-100)</td>
<td>91.07</td>
<td>89.30</td>
<td>73.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. Orofacial sites tender to palpation (0-38)</td>
<td>15.61</td>
<td>21.61</td>
<td>25.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SF12v2 Mental Health Scale (0-100)</td>
<td>76.47</td>
<td>68.31</td>
<td>43.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. body sites tender to palpation (0-14)</td>
<td>4.16</td>
<td>5.53</td>
<td>7.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic pain in areas other than the face (%)</td>
<td>32.18</td>
<td>42.17</td>
<td>64.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Count of 20 comorbid conditions</td>
<td>1.14</td>
<td>1.91</td>
<td>4.25</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Bold Black = A different from PS; Bold Red = PS different from GS*

Proportions of TMD Cases and Controls in Each Cluster

Clusters and Comorbid Pain Conditions

Cluster 1
- No IBS (n=1307)
- No HA (n=15)
- No LBP (n=1322)

Cluster 2
- No IBS (n=2051)
- No HA (n=54)
- No LBP (n=1322)

Cluster 3
- No IBS (n=492)
- No HA (n=140)
- No LBP (n=523)

Cluster 1
- No VVS (n=1337)
- No HA (n=19)
- No LBP (n=1337)

Cluster 2
- No VVS (n=2171)
- No HA (n=86)
- No LBP (n=2171)

Cluster 3
- No VVS (n=539)
- No HA (n=89)
- No LBP (n=539)

Irritable Bowl Syndrome

Vulvodynia

Chronic Headache

Chronic Low Back Pain
OPPERA Omic Studies

• Inflammatory cytokines (e.g., MCP1, IL1b, IL1ra, IL8) are increased and the transcriptional factor TGFβ1 is decreased TMD patients

• Pathway analyses via DRG eQTL and GWAS findings reveal T&B cell signaling, Human Leukocyte Antigen (HLA) and SMAD1 alterations in TMD patients.

Ongoing Immunophenotyping

- GS cluster is elevated (p<0.05) relative to A cluster for:
  - HLA-DR+ Helper T Lymphocytes
  - Activated Helper T Lymphocytes
  - CD25 MFI on Transitional monocytes
  - CD25+ Transitional monocytes
  - HLA-DR MFI on Nonclassical monocytes
OPPERA I – Lessons Learned

1. *It is a misnomer and no longer appropriate to regard TMD solely as a localized orofacial pain condition.*

2. *It is pointless to envisage a single cause, nor even to expect that any one cause might be necessary or sufficient to explain TMD. For the majority of people with chronic TMD, the condition is a multisystem disorder with overlapping co-morbidity.*
Target Discovery
A few putative targets identified (reverse translation) or confirmed (forward translation) by human genetic studies

- COMT/ $\beta_2$
  - Completed POC
  - NCEs under development
- Novel opioid receptor splice variants (e.g., OPRM1/OPRM1-$\beta_2$)
  - NCE under development
- EGFR and associated downstream pathways
- Nicotinic receptors
- $\alpha_2\delta_2$ calcium channel subunit
- CA8
- KCNS1
- CGH1
- SCN9A/Nav1.7
- P2X7 receptor
- 5HT2a
CTPM and McGill Alliance Partners

- Secure cloud system
- HIPAA compliant
- Customizable & scalable
- Core Phenotypes:
  - Medical
  - Pain
  - Symptoms
  - Coping
  - Stress
  - Sleep
  - Risk factors
  - Satisfaction
- Biologics
- LabVantage LIMS
- PEDIGENE linkage
- Reports and Analyses
- EPIC DataMart linkage

Center for Translational Pain Medicine

Singapore Node
London Node
Montreal Node
University Maryland
Barriers to Discovery and Development

• Preclinical animal and human models
  – a need for models that capture the complexities and pathophysiology of human pain conditions

• Poor understanding of the human pathophysiology that underlie persistent pain conditions
  – a need for conceptual models that capture the complexities and heterogeneity of human pain conditions
  – a need for “big data”: cellular, animal, human
  – a need for bioinformatics tools
  – mechanisms to foster collaboration
Table 6. Number of Studies and Number of Patients Examined (Total N) Who Report an Increase in Pain Sensitivity Across Nociceptive Modalities and Across COPCs

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>FM</th>
<th>CFS</th>
<th>IBS</th>
<th>TTH</th>
<th>Migraine</th>
<th>TMD</th>
<th>MPS/RSTPS</th>
<th>PD</th>
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</thead>
<tbody>
<tr>
<td>Pressure (somatic)</td>
<td>15 (580)</td>
<td></td>
<td>4 (178)</td>
<td>3 (117)</td>
<td>2 (42)</td>
<td>9 (462)</td>
<td>1 (20)</td>
<td></td>
</tr>
<tr>
<td>Pressure (rectal)</td>
<td></td>
<td>26 (822)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat (somatic)</td>
<td>12 (480)</td>
<td>2 (21)</td>
<td>1 (50)</td>
<td>3 (117)</td>
<td>3 (76)</td>
<td>3 (137)</td>
<td>2 (42)</td>
<td></td>
</tr>
<tr>
<td>Heat (rectal)</td>
<td>1 (46)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Cold (somatic)</td>
<td>8 (255)</td>
<td>1 (33)</td>
<td></td>
<td>1 (41)</td>
<td></td>
<td></td>
<td>2 (184)</td>
<td></td>
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<tr>
<td>Electric (cutaneous)</td>
<td>4 (61)</td>
<td>1 (12)</td>
<td></td>
<td></td>
<td></td>
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<td>2 (36)</td>
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<tr>
<td>Electric (intramuscular)</td>
<td>2 (41)</td>
<td>1 (23)</td>
<td></td>
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<td>2 (36)</td>
<td>1 (10)</td>
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<td>Electric (spinal reflex)</td>
<td>2 (107)</td>
<td>1 (14)</td>
<td>1 (40)</td>
<td></td>
<td>1 (27)</td>
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<tr>
<td>Electric (rectal)</td>
<td>2 (21)</td>
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<td>Ischemic</td>
<td>1 (60)</td>
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<td>2 (72)</td>
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<td>Hypertonic saline</td>
<td>2 (41)</td>
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<td></td>
<td></td>
<td>1 (22)</td>
<td>1 (11)</td>
<td></td>
<td></td>
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<tr>
<td>Auditory stimulus</td>
<td>1 (20)</td>
<td></td>
<td>1 (15)</td>
<td></td>
<td>1 (65)</td>
<td></td>
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</table>

Abbreviations: COPC, chronic overlapping pain condition; FM, fibromyalgia syndrome; CFS, chronic fatigue syndrome; IBS, irritable bowel syndrome; TTH, tension type headache; TMD, temporomandibular disorders; MPS, myofascial pain syndrome; RSTPS, regional soft tissue pain syndrome; PD, primary dysmenorrhea.
<table>
<thead>
<tr>
<th></th>
<th>A, %</th>
<th>SE, %</th>
<th>n</th>
<th>PS, %</th>
<th>SE, %</th>
<th>n</th>
<th>GS, %</th>
<th>SE, %</th>
<th>n</th>
<th>P</th>
<th>A vs PS†</th>
<th>PS vs GS†</th>
<th>A vs GS†</th>
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<tr>
<td><strong>OPPERA cohort</strong></td>
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<td></td>
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<tr>
<td>Lifetime history of jaw injury</td>
<td>8.2</td>
<td>0.8</td>
<td>1339</td>
<td>11.5</td>
<td>0.7</td>
<td>1824</td>
<td>18.9</td>
<td>1.6</td>
<td>608</td>
<td>&lt;0.0001</td>
<td>0.0034</td>
<td>&lt;0.0001</td>
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<tr>
<td>Lifetime history of smoking</td>
<td>22.0</td>
<td>1.1</td>
<td>1426</td>
<td>24.7</td>
<td>1.0</td>
<td>2056</td>
<td>41.8</td>
<td>1.8</td>
<td>789</td>
<td>&lt;0.0001</td>
<td>0.0777</td>
<td>&lt;0.0001</td>
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<td>Lifetime history of hormonal contraceptive use (females)</td>
<td>64.9</td>
<td>2.0</td>
<td>579</td>
<td>70.1</td>
<td>1.2</td>
<td>1480</td>
<td>72.9</td>
<td>1.9</td>
<td>536</td>
<td>0.0121</td>
<td>0.0277</td>
<td>0.2285</td>
<td>0.0048</td>
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<tr>
<td>Current hormonal contraceptive use (females)</td>
<td>18.2</td>
<td>1.6</td>
<td>583</td>
<td>17.1</td>
<td>1.0</td>
<td>1494</td>
<td>11.7</td>
<td>1.4</td>
<td>540</td>
<td>0.0032</td>
<td>0.6166</td>
<td>0.0034</td>
<td>0.0030</td>
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<tr>
<td>Traumatic life event (LSL)</td>
<td>36.2</td>
<td>1.3</td>
<td>1421</td>
<td>40.1</td>
<td>1.1</td>
<td>2054</td>
<td>61.1</td>
<td>1.7</td>
<td>786</td>
<td>&lt;0.0001</td>
<td>0.0207</td>
<td>&lt;0.0001</td>
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<td><strong>UNC cohort</strong></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Lifetime history of jaw injury</td>
<td>28.9</td>
<td>3.7</td>
<td>152</td>
<td>32.6</td>
<td>4.0</td>
<td>138</td>
<td>44.1</td>
<td>6.5</td>
<td>59</td>
<td>0.1172</td>
<td>0.5839</td>
<td>0.1699</td>
<td>0.0535</td>
</tr>
<tr>
<td>Lifetime history of smoking</td>
<td>17.1</td>
<td>3.1</td>
<td>152</td>
<td>26.6</td>
<td>3.7</td>
<td>139</td>
<td>43.1</td>
<td>6.1</td>
<td>65</td>
<td>0.0004</td>
<td>0.0679</td>
<td>0.0286</td>
<td>0.0001</td>
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<tr>
<td>Traumatic life event (LSL)</td>
<td>25.6</td>
<td>3.4</td>
<td>164</td>
<td>27.3</td>
<td>3.6</td>
<td>154</td>
<td>41.5</td>
<td>5.4</td>
<td>82</td>
<td>0.0318</td>
<td>0.8345</td>
<td>0.0380</td>
<td>0.0168</td>
</tr>
</tbody>
</table>

* P value for the null hypothesis that the mean value of the risk factor does not differ between the 3 clusters.
† P value for the null hypothesis that the mean value of the risk factor does not differ between clusters, the A and PS (or the PS/GS or A/GS, respectively).
A, adaptive cluster; GS, global symptoms cluster; LSL, Lifetime Stressor List; PS, pain-sensitive cluster.