Diagnosing and Treating Pain Based on the Underlying Mechanism

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Disclosures

- Consulting
  - Pfizer, Pierre Fabre, Abbott, Cerephex, Tonix, Theravance, Zynerba, Samumed, Aptinyx, Daiichi Sankyo

- Research support
  - Pfizer, Cerephex, Aptinyx
Which person has pain?
Osteoarthritis of the knee - I

- Classic “peripheral” pain syndrome
- Poor relationship between structural abnormalities and symptoms\(^1\). In population-based studies:
  - 30 – 40% of individuals who have grade 3/4 K/L radiographic OA have no symptoms
  - 10% of individuals with severe pain have normal radiographs
- Psychological factors explain very little of the variance between symptoms and structure\(^2\)
- We sometimes delude ourselves into thinking that our current therapies are adequate
  - NSAIDs, acetaminophen, and even opioids have small effect sizes\(^3,4\)
  - Arthroplasty does not predictably relieve pain

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

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<td>Interstitial cystitis, bladder pain syndrome</td>
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Pain and sensory sensitivity in the population

- Like most other physiological processes, we have a “volume control” setting for how our brain and spinal cord processes pain \(^1\).

- This is likely set by the genes that we are born with \(^2-4\), and modified by neurohormonal factors and neural plasticity.

- The higher the volume control setting, the more pain we will experience, irrespective of peripheral nociceptive input.

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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

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.

   - No Pain
   - Jaw
   - Neck
   - Shoulder
   - Upper Back
   - Chest/Breast
   - Upper Arm
   - Lower Arm
   - Lower Back
   - Abdomen
   - Hip
   - Upper Leg
   - Lower Leg

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

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
- Face
- Neck
- Shoulder
- Upper Arm
- Lower Arm
- Elbow
- Wrist
- Hand
- Finger
- Hip
- Knee
- Ankle
- Foot
- Toe
- Nape
- Groin
- Groin
- Navel
- Lower Back
- Lower Leg
- Lower Leg
- Ankle
- Important:
- Sciatica - bilaterally.

- Left side:
  - Hip - Severe polyneuropathy after chemo for AML in 1990. Took some time, months - 1yr 2 yrs to recover to feel the ground.
  - Mid-thigh to feet
  - Mid ulnar forearm to fingers

- Right side:
  - Upper Leg
  - Lower Leg
  - Ankle

- Pain in back the priority. Need an epidural. Last one was difficult to get in allergic to sedatives, not sedated + no problems. Severe problems may be later after last epidural. Pain specific.

- GA plan of care changed per Dr. Davenport informed 1st visit to be done.
- No PE performed.

- Due to using cane from pain in plantar from GA surgery for carpal tunnel performed due to numb, back home to W1.
- Activity or just sore fingers due to stretching of people.

- No Pain

- List please for more info.
Fibromyalgia

Centralized pain in individuals with any chronic pain condition
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

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


19/31 potential FM score derived from how widespread pain is

12/31 potential FM score derived from co-morbid CNS-derived symptoms that accompany CNS pain
Each one point increase in fibromyalgianess led to:

- 9 mg greater oral morphine requirements during acute hospitalization (8 mg 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.
In LBP, responsiveness to duloxetine was strongly related to number of sites on the Michigan Body Map.

- Average number of sites of pain in this LBP study was 3 – 4
- At 14 weeks, using any measure of pain improvement, individuals with more body sites of pain were significantly more likely to respond

Relative response rate for responders (30% improvement in pain)

- MBM pain sites = 1 \( RR = 1.07 \)
- MBM sites = 2 \( 1.30 \)
- MBM sites = 3 \( 1.34 \)
- MBM sites = 4 \( 1.47 \)
- MBM sites > 5 \( 1.60 \)

In RA, the residual pain and fatigue seen despite treatment with biologics can be treated as such:

- In a large cohort of RA patients being treated at a US academic medical center, 47.3% continued to report having moderate to high levels of pain and fatigue. Most of these patients had minimal signs of inflammation but high levels of FM or Fmness.¹

- Using quantitative sensory testing, active inflammation was associated with heightened pain sensitivity at joints (peripheral sensitization), whereas poor sleep was associated with diffuse pain sensitivity as noted in FM (central sensitization or centralized pain).²

- In a cross-over trial of six weeks of milnacipran in RA patients, in the overall group there was no statistical improvement, but in the subgroup with the least inflammation (swollen joint count ≤ 1) milnacipran decrease average pain intensity more than placebo (95% CI -2.26 to -0.01, p = 0.04).³

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**Mixed Pain States**
Centralization Continuum

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

Peripheral

Acute pain
Osteoarthritis
RA
Ehler’s Danlos
Low back pain

Centralized

Fibromyalgia
Tension HA
TMJD
IBS
Pathophysiology of centralized pain states

- Most patients display augmented pain and sensory processing on quantitative sensory testing and functional neuroimaging$^{1,3}$
- Manifest by increased connectivity to pro-nociceptive brain regions and decreased connectivity to anti-nociceptive regions$^{2,3}$
- These abnormalities are being driven by imbalances in concentrations of CNS neurotransmitters that control sensory processing, sleep, alertness, affect, memory$^{3,4}$
- Autonomic, HPA, and peripheral abnormalities likely play a prominent role in some individuals

fMRI in Fibromyalgia

Pain Intensity

Fibromyalgia
Subjective Pain Control
Stimulus Pressure Control

Stimulus Intensity (kg/cm²)

14
12
10
8
6
4
2
0

1.5
2.5
3.5
4.5

STG=superior temporal gyri; SI=primary somatosensory cortex
SII=secondary somatosensory cortex; IPL=inferior parietal lobule.

Intrinsic Brain Connectivity is Altered in FM patients

- In FM, DMN and rEAN show greater intrinsic connectivity within component DMN (PCC), and rEAN (iPS) as well as limbic (insula), and sensorimotor (SII) regions outside conventional network boundaries.

- All FM vs. HC differences driven by greater connectivity for FM patients.

Napadow et al, *Arthritis Rheumatism* 2010
Changes in size and shape of brain regions indicate CNS neuroplasticity in chronic pain

- Apkarian\(^1\) was first to show that chronic pain may be associated with decrease of size of brain areas involved in pain processing

- More recently seen in virtually all other chronic pain states including headache,\(^2\) IBS,\(^3\) FM\(^4\)

- May be partially due to co-morbid mood disturbances\(^6\)

- Data from NIH MAPP network presented at 2016 IASP (Kutch et. al.) suggests increase in size of and connectivity to S1 may represent neural signature for widespreadness of pain

# Pharmacological Therapies for Fibromyalgia (i.e. Centralized Pain)

## Strong Evidence
- Dual reuptake inhibitors such as
  - Tricyclic compounds (amitriptyline, cyclobenzaprine)
  - SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?)
  - Gabapentinoids (e.g., pregabalin, gabapentin)

## Modest Evidence
- Tramadol
- Older less selective SSRIs
- Gamma hydroxybutyrate
- Low dose naltrexone
- Cannabinoids

## Weak Evidence
- Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)

## No Evidence
- Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin

*Modified from Clauw  *JAMA*. 2014*
CNS Neurotransmitters Influencing Pain

Arrows indicate direction in Fibromyalgia

Generally facilitate pain transmission

- Glutamate
- Substance P
- Nerve growth factor
- Serotonin \((5HT_{2a, 3a})\)

Gabapentinoids, ketamine, memantine

Generally inhibit pain transmission

- Descending anti-nociceptive pathways
  - Norepinephrine-serotonin \((5HT_{1a,b})\), dopamine
- Opioids
- Cannabinoids
- GABA

Anti-migraine drugs (–triptans), cyclobenzaprine

Gabapentinoids, ketamine, memantine

Gammahydroxybutyrate moderate alcohol consumption

Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study

Andrew Schrepf, Daniel E. Harper, Steven E. Harte, Heng Wang, Eric Ichesco, Johnson P. Hampson, Jon-Kar Zubieta, Daniel J. Clauw, Richard E. Harris

![Graphs showing correlation between DLPFC BOLD P.E. and DLPFC BP, pgACC/MFG BOLD P.E. and pgACC/MFG BP, sgACC BOLD P.E. and sgACC BP.](image)

D

![Brain images with highlighted areas and X-coordinates.](image)
Nobody knew that health care could be so complicated.
Hijacking the endogenous opioid system to treat pain: who thought it would be so complicated?

Daniel Clauw

In this issue, there is an especially interesting and important special review by Ballantyne and Sullivan entitled, “The discovery of endogenous opioid systems: what it has meant for the clinician’s understanding of pain and its treatment.” This review adds to these authors’ significant prior contributions to the pain field, as they are now proposing that many of the problems associated with opioid therapy can be understood mechanistically as being off-target effects on the endogenous opioid system. They describe how our emerging understanding of the endogenous opioid system might allow us to better understand how exogenous opioids can “hijack” this system to produce unexpected and undesired consequences, both when they are used for pain relief, and when they are misused or abused. They especially focus on how acute or chronic opioid therapy (COT) may impair some of the nonanalgesic functions of the endoge-

These issues of excess death and addiction, combined with a lack of any evidence of long-term efficacy, have led many of us in the pain field to question whether opioid should ever be used to treat chronic nonmalignant pain. We know of some patients with chronic pain who are on long-term high-dose opioid therapy who are doing well (ie, have good pain control and good functional status), but these patients are exceedingly rare. Instead, we see large numbers of individuals who want to keep taking opioids, although after we assess them, we conclude that the long-term side effects of these drugs far exceed any benefit they are receiving.

This review highlights why we may see some of the more insidious problems that occur with COT, which are summarized below.

Individuals on COT may continue to “need” opioids to replicate the functions of endogenous opioids that are no longer being
And what about those patients already on opioids?

- A slow gradual taper of opioids rarely leads to worsening of chronic pain
  - Use the patients own history to point out that opioids have not improved pain and function, or are leading to intolerable side effects

- Discern what symptom(s) opioids are treating

- Consider opioid-sparing drugs
  - Cannabinoids
  - Mixed opioids (tapentadol, buprenorphin
  - Gabapentinoids
How useful do you feel cannabinoids are for treating pain?

Worthless  

 Wonderful
Definitions

- **Cannabis** – A genus of flowering plants with three different species: indica, sativa, and ruderalis
  - Can be bred to have low amounts of psychoactive compounds (e.g. THC) that are used to make hemp, or high amounts that are used for recreational/medicinal purposes
  - Sativex is a oral spray that is a cannabis extract

- **Cannabinoid** – Compounds that act at cannabinoid receptors
  - Endocannabinoids – endogenous ligands produced naturally that bind to CB1 and CB2 receptors
  - Phytocannabinoids – plant origin (cannabis/marijuana)
    - At least 80 different cannabinoids in cannabis
  - Synthetic cannabinoids

CB, cannabinoid receptor; THC, tetrahydrocannabinol
Cannabis-derived cannabinoids

More than 80 known, with different strains having different relative concentrations

- **THC** (Synthetic forms include Dronabinol, Marinol, Nabilone)
  - The primary psychoactive cannabinoid in cannabis, and its metabolites are those assayed for in drug tests
  - Although it binds relatively equally to both the CB1 and CB2 receptors, most of its effects are associated with CB1 activity in brain

CB, cannabinoid receptor; THC, Tetrahydrocannabinol
CB, cannabinoid receptor

Cannabis-derived cannabinoids

- **Cannabidiol (CBD)**
  - Is not psychoactive and does not bind with any significant affinity to CB receptors, but yet has anticonvulsant and anti-inflammatory effects
  - Is actually thought to potentially protect against psychoactive effects of THC and hypothesized by some to be an effective anti-psychotic (although a recent Cochrane review concluded there was insufficient evidence of this)
  - May act as a indirect antagonist of CB agonists – but it does not seem to reduce activity of THC
  - Also acts as 5HT1a agonist which might be responsible for potential analgesic, antidepressant effects

5HT1a, 5-hydroxytriptamine 1A receptor; CB, cannabinoid receptor; THC, tetrahydrocannabinol
ZYN002 - Median Weekly Average Worst Knee Pain Score over Time - Males
ZYN002 - Median Weekly Average Worst Knee Pain Score over Time – Females
Proposed marketing program for medical cannabis

Cannabis plant talking to opium producing poppy plant

We don’t suck as bad as you do
Pragmatic Advice for Using Cannabinoids in 2017

- Where possible use a cannabinoid or cannabinoid extract of consistent and known potency
- Start with CBD alone and then go to low dose of low THC:high CBD strain and go up slowly
- Emerging evidence of U-shaped curve
- Oral dosing better once stable dose and strain identified
- The strongest recommendation based on current benefit: risk data is for the use of cannabinoids instead of opioids for neuropathic or centralized pain states
  - Data from US suggest that legalizing cannabis in a state leads to fairly dramatic reductions in opioid overdoses\(^1\)
- Use with caution in individuals under age 25

CBD, cannabidiol; THC, tetrahydrocannabinol

Treating Based on Mechanisms

Any combination may be present

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<td>-</td>
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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

Nonpharmacological Therapies are similar to those for any Chronic Pain State

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<td>Education</td>
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<td>Tender (trigger) point injections, flexibility exercise</td>
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<td>Aerobic exercise</td>
<td>Hypnotherapy, biofeedback, balneotherapy, yoga, Tai Chi</td>
<td>Neuromodulation</td>
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<td>Cognitive behavior therapy</td>
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Modified from Clauw  JAMA. 2014
Program features 10 CBT modules:
- Understanding Fibromyalgia
- Being Active
- Sleep
- Relaxation
- Time for You
- Setting Goals
- Pacing Yourself
- Thinking Differently
- Communicating
- Fibro Fog

In a RCT of 118 FM patients comparing the earlier version of this website plus usual care, to usual care alone, Williams demonstrated statistically significant improvements in pain (29% in the WEB group had 30% improvement in pain vs 8% in usual care, p=.009) and function (i.e., 31% in WEB-SM had .5 SD improvement in SF-36 PF vs. 6% in standard care, p<.002) Williams et. al. Pain. 2010;151(3):694-702
Summary

■ Most practitioners have historically considered chronic pain to be largely from peripheral nociceptive input (i.e. damage or inflammation)

■ When thinking about central factors in pain, many focus entirely on psychological factors

■ We now understand that non-psychological central nervous system factors can markedly increase (sensitization) or decrease pain sensitivity

■ The CNS is now thought of as “setting the volume control” or gain on pain processing and determining what nociception is felt as pain
Summary

- The most highly prevalent pain conditions in younger individuals are now thought to be more “central” than “peripheral”

- Centralized pain or central sensitization can also be identified in subsets of individuals with any nociceptive or neuropathic pain state

- This is not currently appreciated in clinical practice so there is marked overuse of treatments for acute/nociceptive pain (opioids, injections, surgery, biologics, DMARDs) for treating centralized pain

- Perhaps moving from considering FM a disease (i.e. the tip of the iceberg) to instead thinking of it as a CNS-driven pathophysiological process that can co-exist with any other disease or process would help the field, since current evidence strongly supports this notion
Future Research Directions

■ Does this approach really work?

■ Can we predict responsiveness to certain procedures using these measures?

■ Incorporating these approaches into prehab programs – especially aimed at high risk or high yield populations (individuals with high FM scores)
  ■ This a moment in time when individuals are maximally motivated to use behavioral interventions

■ Should non-pharmacological therapies be tailored to underlying mechanisms
How do we get there?

- Superimpose light phenotyping with PROs into ongoing clinical care
  - Don’t wait until you can incorporate into EHR – use superimposed research registries and web-based platforms such as Qualtrics to collect data

- Deep phenotyping with more sophisticated research methods on a subset of patients

- Need longitudinal data pre- and post-interventions to match with phenotypic information
Identifying and appropriately treating centralized pain is likely much more important.

You can ignore the tip of the iceberg – but ignore what is below the surface and you’re missing what is likely the most important CNS contributions to pain.