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Pain and Rheumatoid Arthritis

Yvonne C. Lee, MD, MMSc
April 26, 2024

Disclosures

- Current
  - Stock in CVS Health Corp, GE Healthcare

- Past
  - Grant from Pfizer
  - Receipt of Medical Writing Services from Sanofi-Genzyme
  - Stock in Cigna-Express Scripts

Overview

- The problem of pain in patients with RA
- Definitions, categorization, and mechanisms
- Nociplastic pain in RA – evidence and implications
- Risk factors for nociplastic pain in RA – implications for prevention
- Recommendations for
  - Assessing nociplastic pain in RA
  - Managing nociplastic pain in RA
- Emerging areas in pain management for RA

Setting the stage…

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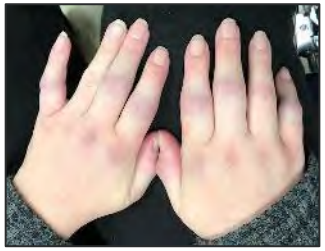


Credit: Kevin Deane

Stock Image (PowerPoint)

<u>Clinically Suspect Arthralgia</u>
30 yo woman
Joint pain
Fatigue
Finding it difficult to care for newborn baby
No joint swelling

<u>Early RA</u>
Continues to have joint pain
Now has joint swelling
Stiff all morning
Fatigue
Not sleeping well

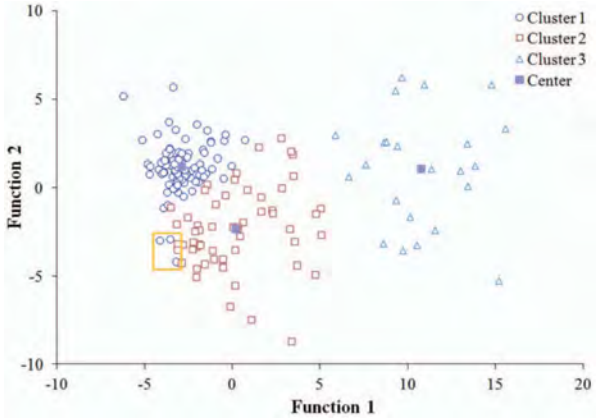
Stock Image (PowerPoint)

Paths Diverge

Subgrouping of Patients With Rheumatoid Arthritis Based on Pain, Fatigue, Inflammation, and Psychosocial Factors

Yvonne C. Lee,[1] Michelle L. Frits,[1] Christine K. Iannaccone,[1] Michael E. Weinblatt,[1] Nancy A. Shadick,[1] David A. Williams,[2] and Jing Cui[1]

- Cluster 1: 89 (53%) individuals w/ low levels of inflammation, pain, fatigue, depression, anxiety, sleep problems
- Cluster 2: 57 (33%) individuals w/ minimal inflammation but high pain, fatigue, depression, anxiety, sleep problems
- Cluster 3: 23 (14%) individuals w/ high inflammation, pain and fatigue



Population: 169 established RA patients (median disease duration 13 years)

Lee YC et al. Arthritis Rheum, 2014

Let's Talk About Pain…

SPECIAL ARTICLE

Report of the American College of Rheumatology Pain Management Task Force

AMERICAN COLLEGE OF RHEUMATOLOGY PAIN MANAGEMENT TASK FORCE

- Many rheumatologists are uncomfortable treating pain
- Most were not taught how to evaluate/manage pain during training
- Most approach pain by concentrating therapy on reducing joint inflammation

Inflammation

Pain

Borenstein D et al. Arthritis Care Res (2010); 62: 590-9.

What do rheumatologists do about the pain?

A. Dance with the one who brung ya (i.e., intensify DMARD therapy)

B. Turf - Refer back to PCP

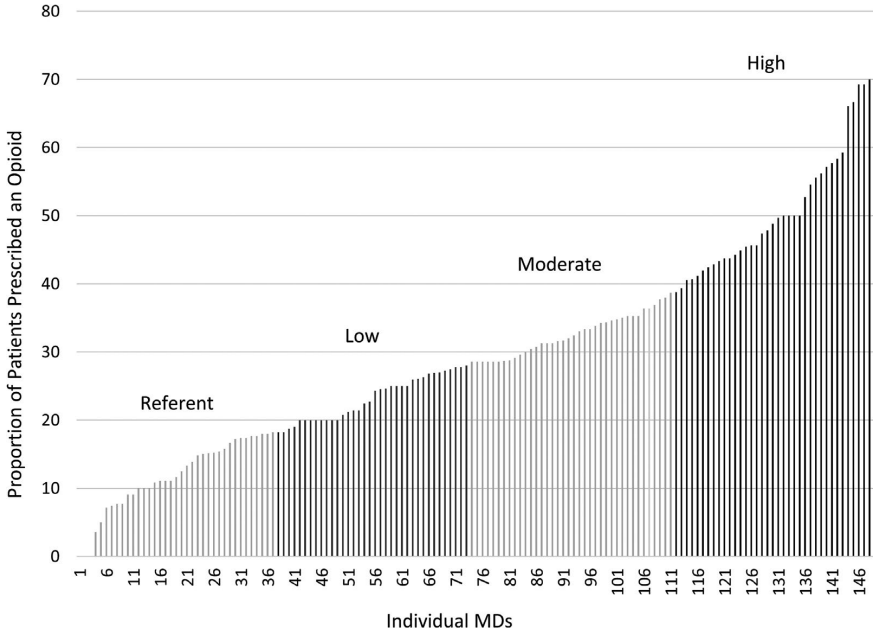
C. Turf - Refer to Pain Management

D. Prescribe pain medications

Let's Talk About Pain Meds…

- Significant variability in if/how rheumatologists manage pain
  - 2001-2016: Opioid usage among patients seen by rheumatologists in Corrona varied from 0-70%
    - Lowest: 0-18%
    - Low: >18-28%
    - Moderate: >28-38%
    - High: >38%

Patient-Reported Opioid Usage by MD



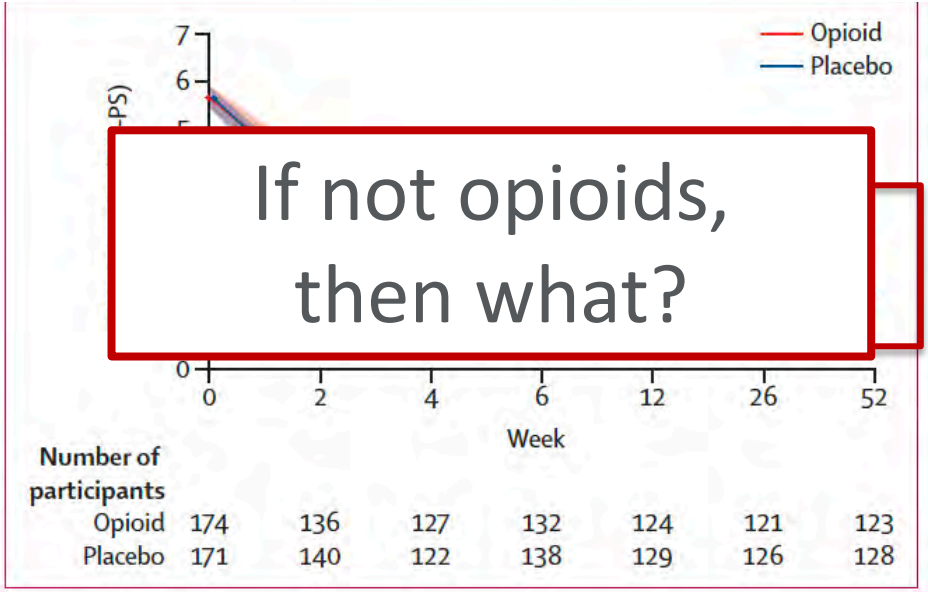
Lee YC et al. Arthritis Rheumatol, 2020

But Opioids Don't Work Either

- 1st placebo-controlled RCT of an opioid without addition of another pain med for acute low back and neck pain
- At 6 weeks (primary endpoint), no difference in pain
- At 52 weeks, small significant difference, favoring placebo

Opioid analgesia for acute low back pain and neck pain (the OPAL trial): a randomised placebo-controlled trial

*Caitlin M P Jones, Richard O Day, Bart W Koes, Jane Latimer, Chris G Maher, Andrew J McLachlan, Laurent Billot, Sana Shan, Chung-Wei Christine Lin, on behalf of the OPAL Investigators and Coordinators**



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Jones CMP et al. Lancet, 2023

Pain: Definitions, Categorization, and Mechanisms

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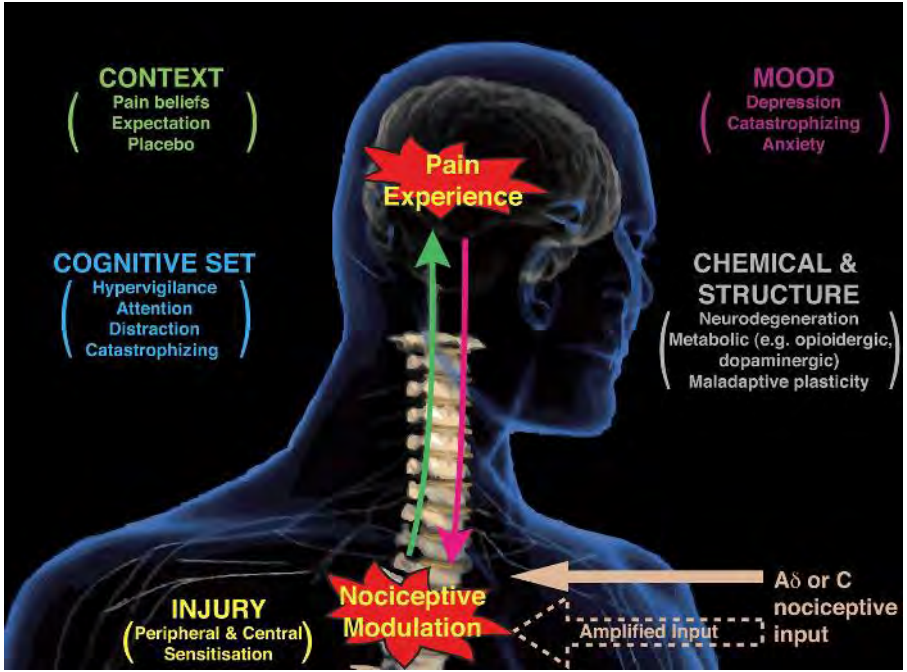
Pain – What is it?

- The IASP defines pain as:

"An unpleasant sensory and emotional experience with, or resembling that associated with, actual or potential tissue damage"

  - "Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors"



https://www.cell.com/fulltext/S0896-6273(07)00533-8

https://www.iasp-pain.org/resources/terminology/

How do we assess pain?

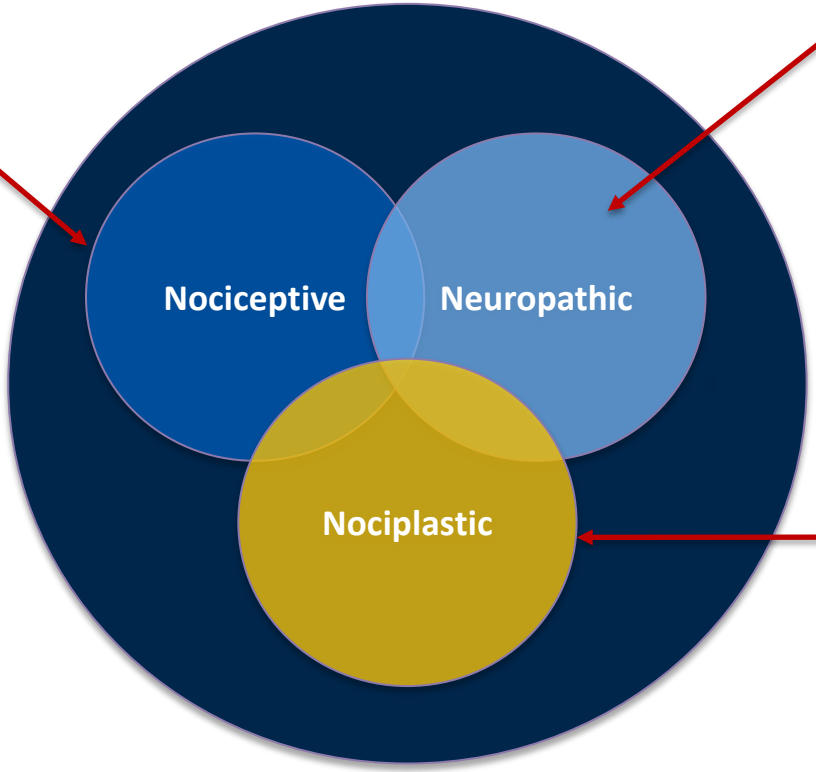
- People have different anchors
- Pain may fluctuate
- Pain may occur in different locations
- Many different types of pain

Pain Categorization

Psychological
Social
Cultural

Credit: Kevin Deane

Examples
Joint Inflammation
Digital ulcers



Stock Image (PowerPoint)

Examples
Carpal tunnel syndrome
Mononeuritis multiplex
Sciatic radiculopathy

Stock Image (PowerPoint)

Examples
Fibromyalgia
Irritable Bowel Syndrome

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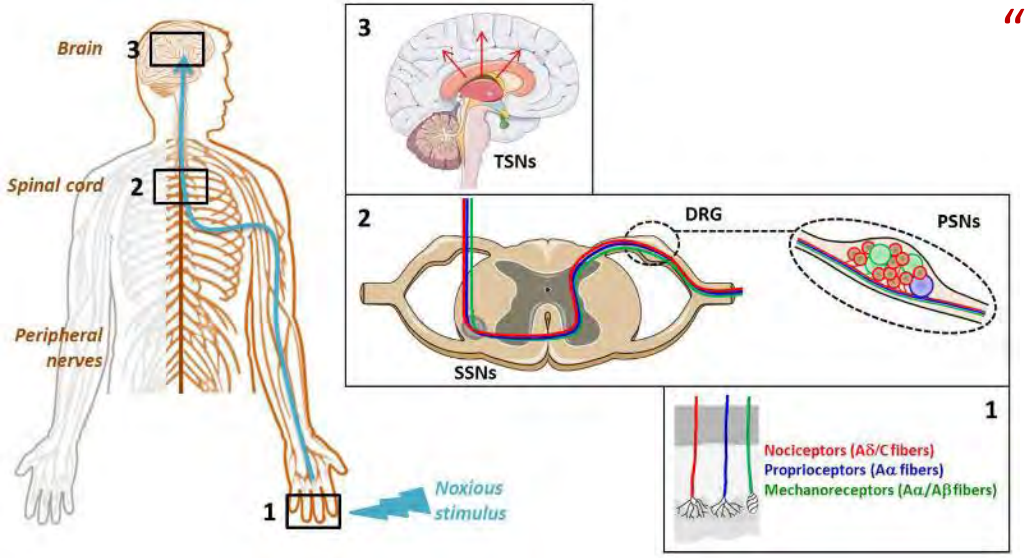
Nociceptive Pain

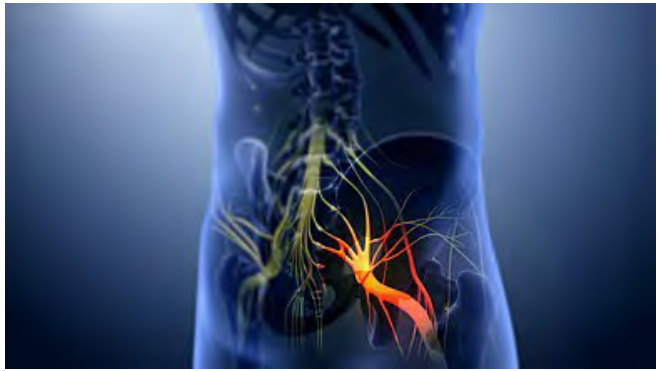
- Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors



"Pain working the way it should"

Neuropathic Pain

- Pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system
- Distribution tends to follow dermatomes
- Responsive to locally targeted treatments of nerves

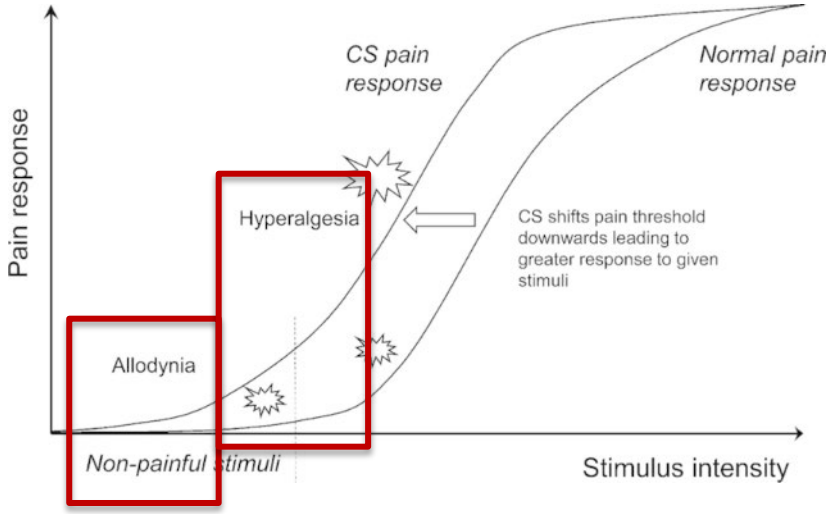


Nociplastic Pain

- Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain

Stock Image (PowerPoint)

- "Volume Control" Problem
- Global problem with sensory processing



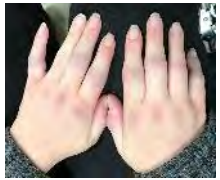
Sandkuher J. Physiol Rev (2009); 8:707-58.

Mechanisms of Nociplastic Pain

Bottom Up

- Ascending pathways (primarily facilitation of pain)
- Stimulated by peripheral input
- May resolve when nociceptive input is removed
- Secondary fibromyalgia

Stock Image (PowerPoint)



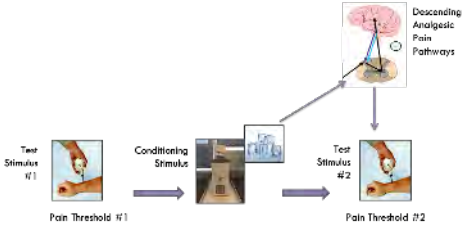
Credit: Kevin Deane

Top Down

- Descending pathways (primarily inhibition of pain)
- Genetics
- Prior experiences
- Expectations
- Emotion/mood
- Does not resolve when nociceptive input is removed
- Primary fibromyalgia

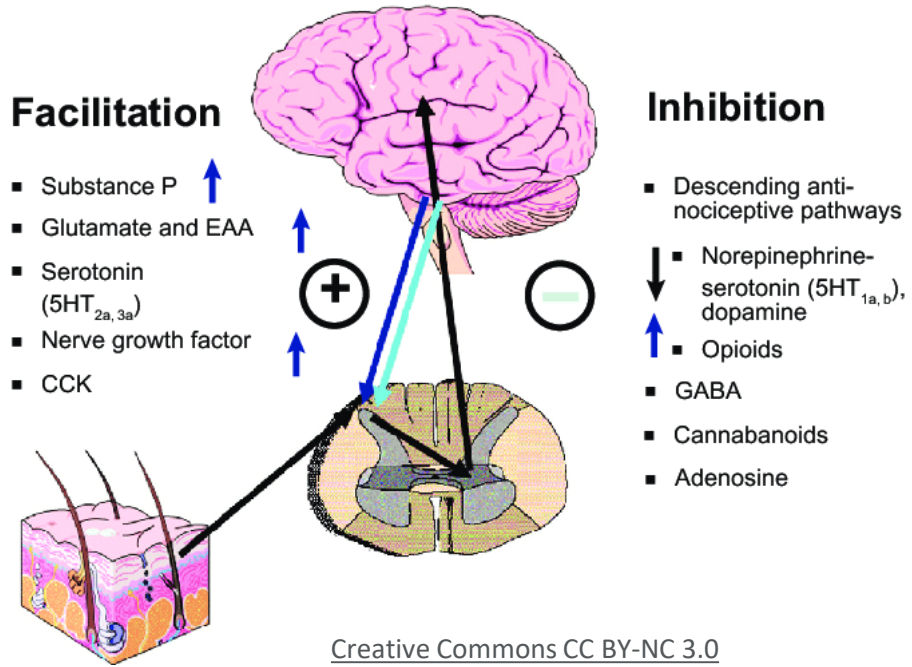
Assessing Nociplastic Pain Mechanisms

- Quantitative Sensory Testing (QST)
  - Pressure Pain Thresholds (PPTs): Overall pain sensitivity
    - Lower pain thresholds = Higher pain sensitivity
  - Temporal Summation (TS): Ascending pain facilitatory pathways
    - Higher temporal summation = Greater pain facilitation
  - Conditioned Pain Modulation (CPM): Descending inhibitory pathways
    - Lower CPM = Inefficient pain inhibition



Implications for Treatment

Gabapentinoids; treatment of underlying condition



TCAs, SNRIs, Tramadol

Smith HS et al. J Central Nervous System Dis, 2010

Nociplastic Pain in RA: Evidence and Implications

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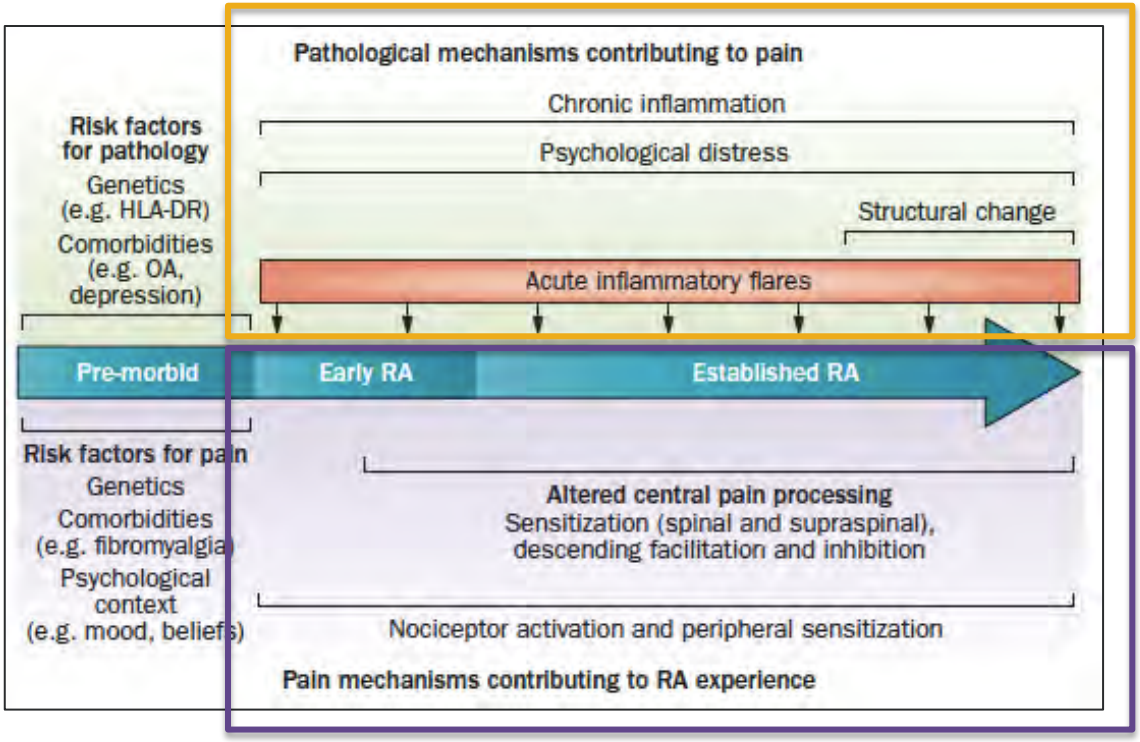
Bringing it Back to RA



Nociceptive Pain

Nociplastic Pain

Stock Image (PowerPoint)

Walsh DA and McWilliams DF, Nature Rev Rheumatol. (2014). 10:581-92.

Prevalence of Fibromyalgia (Nociplastic Pain)

General population: 2%

Chronic DWSP	% prevalence of FMS (mean)	% prevalence of FMS (range)
Rheumatoid arthritis	15.4	12.2–19.8
SLE	16.2	5.0–25.3
Ankylosing spondylitis*	30.4	10.8–50.0
Osteoarthritis	11.0	—
Diabetes mellitus*	17.5	17.0–18.0
Endometriosis	5.9	—
Hypothyroidism	34.0	—
Crohn's disease	26.0	3.0–49.0
Ulcerative colitis	11.4	3.7–49.0

SLE: systemic lupus erythematosus.
*Female patients only.

Yunus MB. Pain Res and Treatment, 2012

Nociplastic Pain in Rheumatoid Arthritis

PPT site	Median (IQR) kg/cm^2		β	P
	RA (N = 58)	Controls (N = 54)		
Wrist	6.8 (4.8, 8.8)	8.1 (6.0, 10.3)	-1.06	**0.03**
Knee	7.5 (5.9, 11.0)	9.4 (7.3, 11.0)	-1.17	**0.01**
Thumbnail	6.7 (5.0, 9.8)	8.1 (5.7, 9.8)	-0.53	0.31
Trapezius	5.2 (3.8, 7.9)	6.4 (4.2, 9.3)	-0.61	0.23

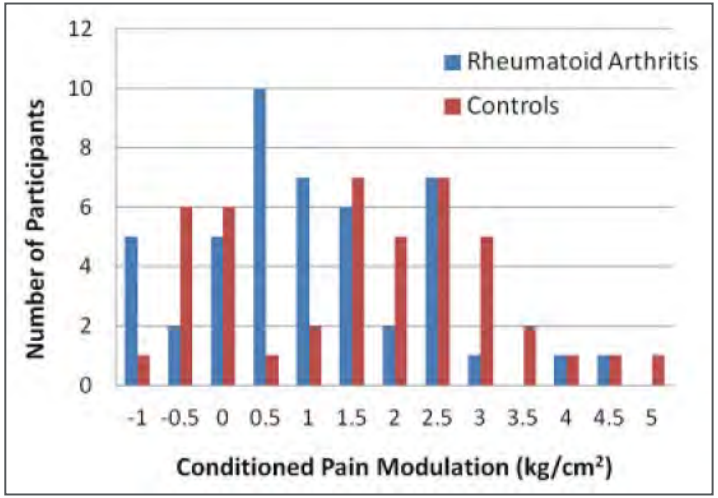
Sensitization at the level of the joints

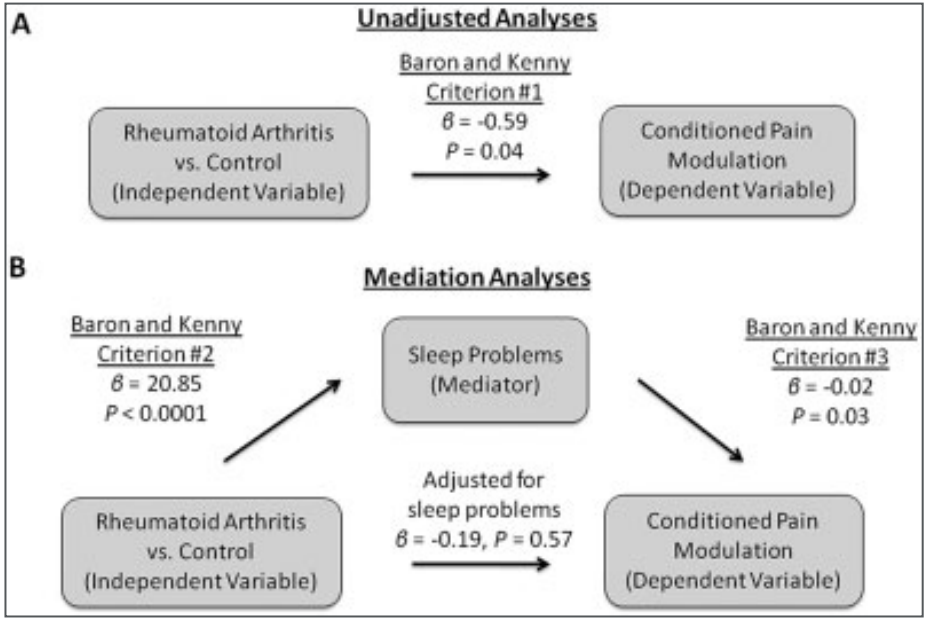
Sensitization mediated by the CNS

Lee YC et al. Arthritis Rheum. 2013; 65:59-68

Nociplastic Pain in Rheumatoid Arthritis

RA median CPM: 0.5 kg/cm^2 (IQR -0.1, 1.6)
Control median CPM: 1.5 kg/cm^2 (IQR -0.1, 2.5)
P = 0.04





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Lee YC et al. Arthritis Rheum. 2013; 65:59-68

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol.72,No.8,August2020,pp1122–1129
DOI 10.1002/acr.23994

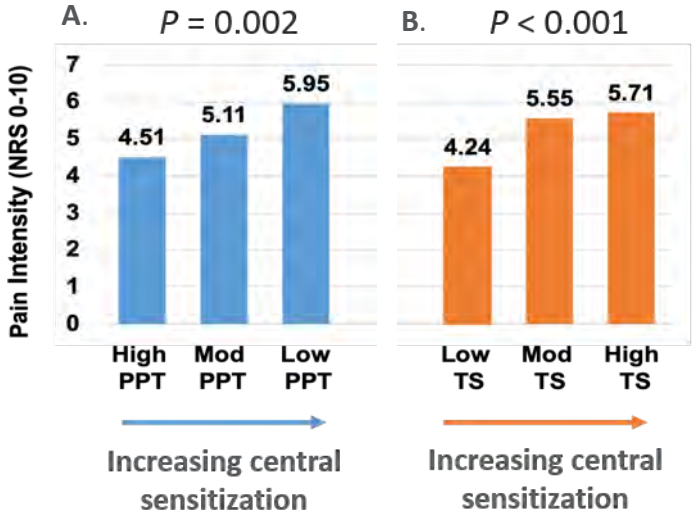
Association of Pain Centralization and Patient-Reported Pain in Active Rheumatoid Arthritis

Andrew C. Heisler,[1] Jing Song,[1] Dorothy D. Dunlop,[1] Alyssa Wohlfahrt,[2] Clifton O. Bingham III,[3] Marcy B. Bolster,[4] Daniel J. Clauw,[5] Wendy Marder,[5] Kristine Phillips,[6] Tuhina Neogi,[7] and Yvonne C. Lee[1]

A. Heisler

- Increasing central sensitization measured by trapezius PPT (indicator of overall central sensitization) was associated with increasing pain intensity

- Increasing pain facilitation measured by temporal summation was associated with increasing pain intensity



Arthritis Care & Research
Vol. 70, No. 2, February 2018, pp 197–204
DOI 10.1002/acr.23266

ORIGINAL ARTICLE

Association
Disease Acti
Arthritis: A

YVONNE C. LEE,[1] CLIFT
KRISTINE PHILLIPS,[3] M
BING LU,[1] ALYSSA WO

Pain sensitization may contribute to amplification of disease activity scores

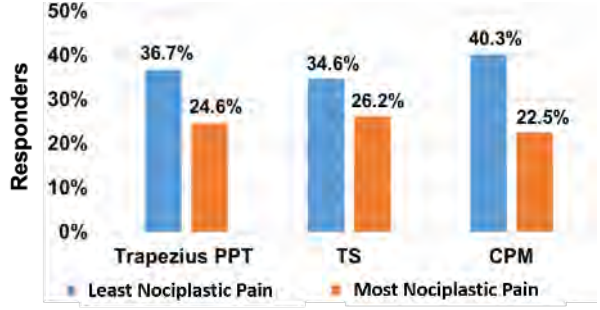
This may be particularly evident among patients with comorbid fibromyalgia

- Low PPTs (high pa…igh pain facilitation) were …
  - Associations see…easures and tender joint cou…
  - In analyses stratified by fibromyalgia status, β-coefficients for association were 2x higher than β-coefficients in patients with RA and no concomitant fibromyalgia

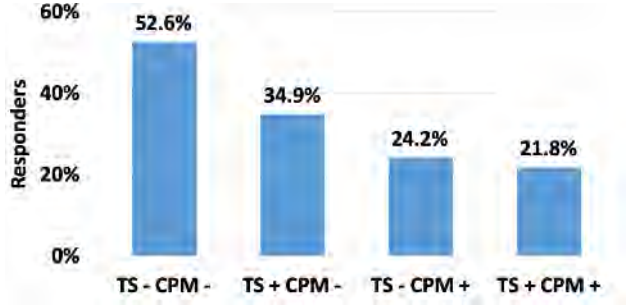
Are CNS Abnormalities Associated with Clinically Meaningful Outcomes? (Response)

A. Heisler

- Patients with higher nociplastic pain (assessed separately by trapezius PPT, TS, CPM) had lower rates of good EULAR response



- Patients with abnormalities in both pain facilitation (TS) and pain inhibition (CPM) were less likely to respond than those without these abnormalities



Heisler AC et al. Arthritis Rheumatol, 2020

Risks Factors for Nociplastic Pain in RA: Implications for Prevention

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Mechanisms of Nociplastic Pain

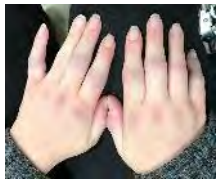
Bottom Up

- Ascending pathways (primarily facilitation of pain)
- Stimulated by peripheral input
- May resolve when nociceptive input is removed
- Secondary fibromyalgia

Stock Image (PowerPoint)

?

Chronic Pain Unresponsive to DMARD Therapy



Credit: Kevin Deane

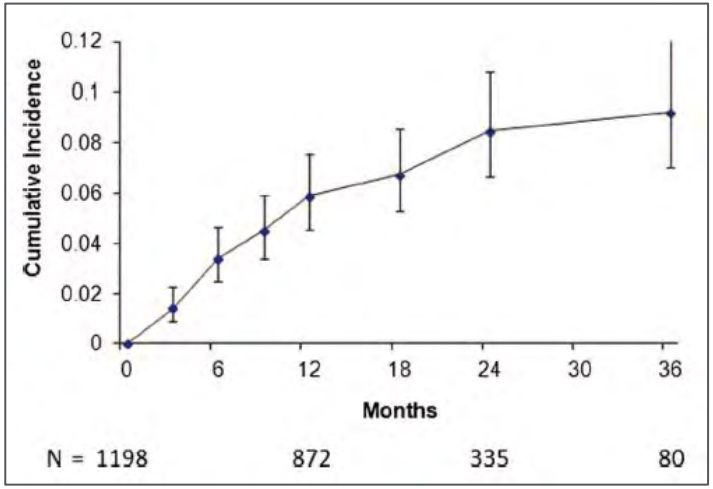
Top Down

- Descending pathways (primarily inhibition of pain)
- Genetics
- Prior experiences
- Expectations
- Emotion/mood
- Does not resolve when nociceptive input is removed
- Primary fibromyalgia

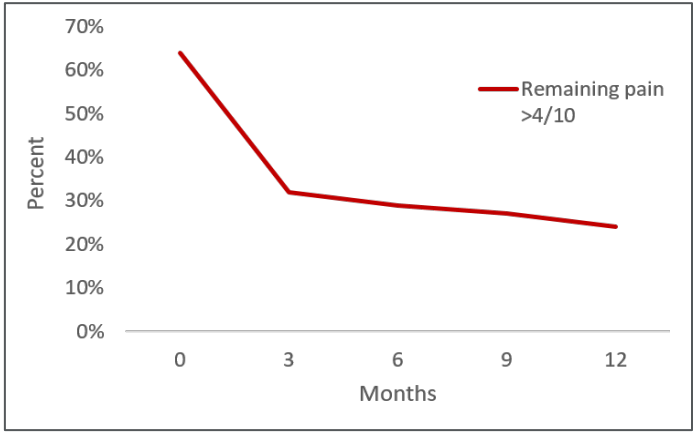
Acute to Chronic Pain Transition

CATCH CANADIAN EARLY ARTHRITIS COHORT

- The incidence of FM is highest in the 1st 24 months after diagnosis of inflammatory arthritis



- 24% of early RA patients continue to have pain above the Patient Acceptable Symptom State (>4/10) after 12 months



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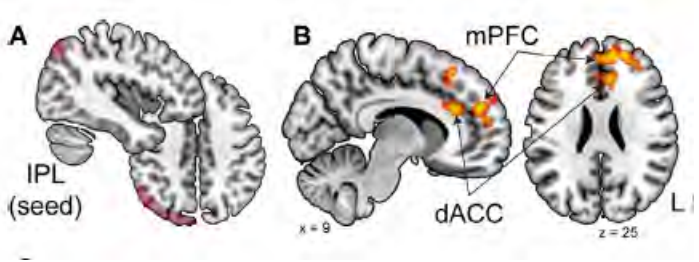
Lee YC et al. Ann Rheum Dis, 2013

Association of Inflammation With Pronociceptive Brain Connections in Rheumatoid Arthritis Patients With Concomitant Fibromyalgia

Chelsea M. Kaplan,[1] Andrew Schrepf,[1] Eric Ichesco,[1] Tony Larkin,[1] Steven E. Harte,[1] Richard E. Harris,[1] Alison D. Murray,[2] Gordon D. Waiter,[2] Daniel J. Clauw,[1] and Neil Basu[3]

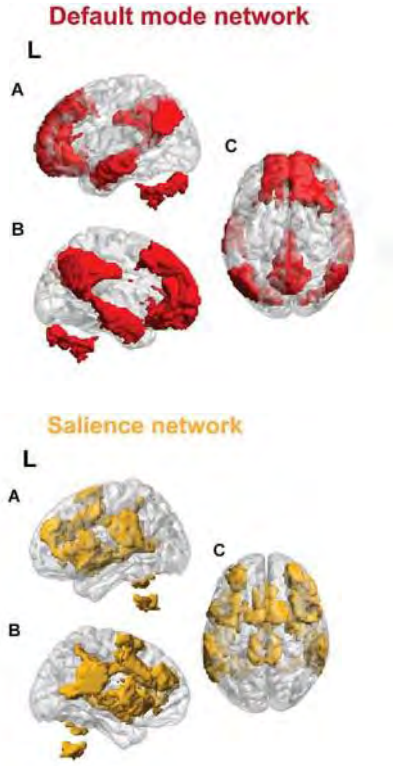
- Compared to patients with RA alone, patients with RA and FM had increased functional connectivity between:
  - Left inferior parietal lobule (DMN) and anterior cingulate cortex (SLN)
  - Left inferior parietal lobule (DMN) and the medial prefrontal cortex (DMN)



Kaplan C et al. Arthritis Care Res, 2020

What are these brain areas?

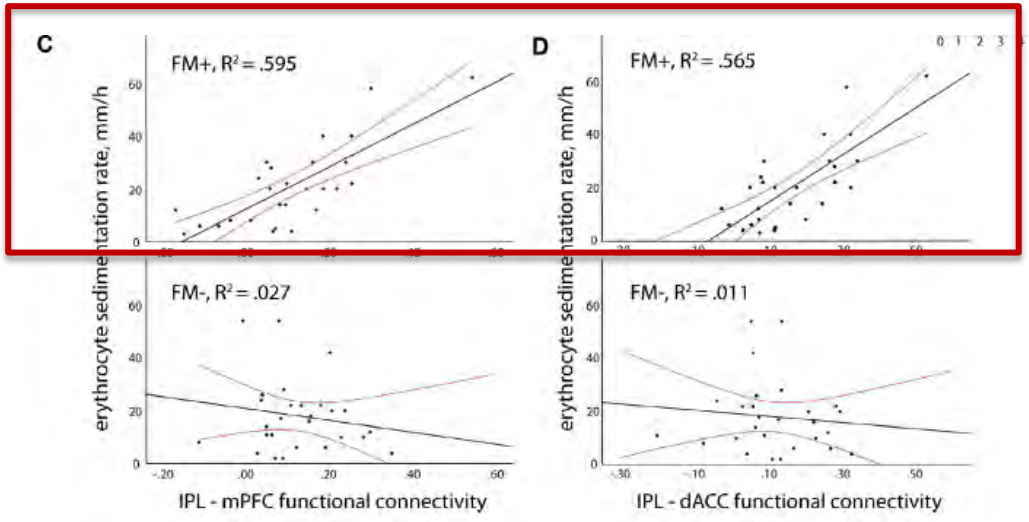
- Default Mode Network (DMN): network of brain regions active at rest and engaged in self-referential thought
  - **Inferior parietal lobule (LP)**
  - **Medial prefrontal cortex (MPFC)**
  - Posterior cingulate cortex (PCC)
- Salience Network (SLN): network of brain regions involved in detection and filtering of important stimuli
  - **Anterior Cingulate Cortex (ACC)**
  - Anterior insula (AINS)



Schimmelpfennig J et al. Front Hum Neurosci, 2023

Functional Connectivity in Established RA

- ESR was correlated with connectivity between inferior parietal lobule-anterior cingulate cortex (DMN-SLN) and inferior parietal lobule-medial prefrontal cortex (DMN-DMN) among patients with RA and FM but not among those with RA only



Differential brain responses to systemic inflammation may influence whether patients with RA transition from acute episodes of inflammatory pain to a chronic, non-inflammatory pain state (i.e., secondary FM)

Kaplan C et al. Arthritis Care Res, 2020

Poor Sleep Predicts Pain Despite DMARD Tx

CATCH CANADIAN EARLY ARTHRITIS COHORT

- Poor Sleep
- Pain Intensity
- Disability

Baseline characteristics	Remaining Pain[1] OR (95% CI)
Age (for change of 10 yrs)	0.8 (0.7, 1.0)
Baseline pain intensity > 4/10	**2.1 (1.3, 3.4)**
Sleep problems, quartiles	
≥0 and ≤2	REF
>2 and ≤5	**1.8 (1.1, 3.1)**
>5 and ≤8	**1.8 (1.1, 3.0)**
>8 and ≤10	**2.2 (1.2, 3.9)**
Missing	0.6 (0.1, 5.6)
HAQ-DI	**1.5 (1.1, 2.0)**
Number of comorbidities	1.1 (1.0, 1.3)
Non-MTX csDMARD use	0.8 (0.6, 1.1)

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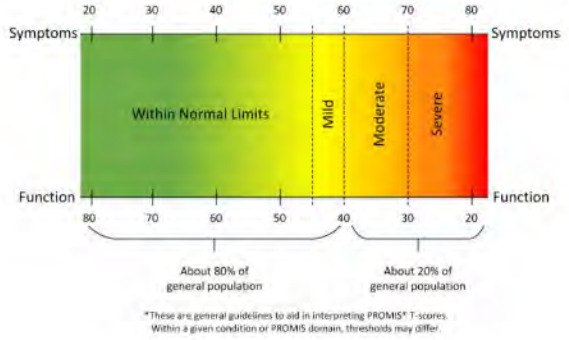
Lee YC et al. Arthritis Rheumatol, 2018; 70 (suppl)

Poor Sleep Predicts Pain Despite DMARD Tx

J. Song

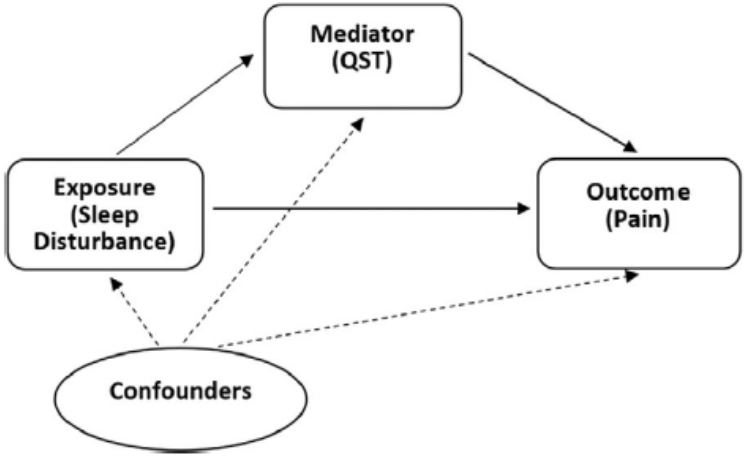
- Replicated in CPIRA
  - Baseline PROMIS sleep disturbance predicted subsequent pain intensity (12-weeks after starting a DMARD), adjusting for age, sex, BMI, RA duration, comorbidities, depression, swollen joint count, and steroid use
    - Every 5-unit difference in baseline PROMIS sleep disturbance score was associated with a 0.32 difference in 12-week pain intensity
    - 15-unit difference in baseline PROMIS sleep disturbance score needed for 1-unit change (MCID) in 12-week pain intensity



Song J et al. Arthritis Care Res (Hoboken), 2023

Poor Sleep Predicts Pain Despite DMARD Tx

J. Song



- Measures of pain sensitization, assessed in separate models, partially mediated relationship between sleep and pain
  - Temporal summation: 19.5%
  - Knee PPT: 19.1%
  - Trapezius PPT: 15.5%
  - Wrist PPT: 11.6%
  - Thumbnail PPT: 10%

A substantial proportion of the effect is mediated by unmeasured factors

Song J et al. Arthritis Care Res (Hoboken), 2023

Summary

- Potential risk factors for the development of nociplastic pain
  - Peripheral and/or systemic inflammation
  - Factors associated with disease
    - Poor sleep
    - Pain itself
    - Decreased physical activity
    - Increased stress

Recommendations for Assessing Nociplastic Pain in RA

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Fibromyalgia Assessment

- "I know it when I see it"
- In a university rheumatology clinic (n = 497)
  - 20.9% received an ICD-9 diagnosis of fibromyalgia
  - 24.3% satisfied 2010 ACR Preliminary Diagnostic Criteria
  - Physicians failed to identify 60 ACR criteria-positive patients (50%)
  - Physicians incorrectly identified 43 ACR criteria-negative patients (11%)

Wolfe F et al. Arthritis Care Res, 2019

But what are the Fibromyalgia Criteria?

THE AMERICAN COLLEGE OF RHEUMATOLOGY 1990 CRITERIA FOR THE CLASSIFICATION OF FIBROMYALGIA

Report of the Multicenter Criteria Committee

The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity

FREDERICK WOLFE,[1] DANIEL J. CLAUW,[2] MARY-ANN FITZCHARLES,[3] DON L. GOLDENBERG,[4] ROBERT S. KATZ,[5] PHILIP MEASE,[6] ANTHONY S. RUSSELL,[7] I. JON RUSSELL,[8] JOHN B. WINFIELD,[9] AND MUHAMMAD B. YUNUS[10]

Fibromyalgia Criteria and Severity Scales for Clinical and Epidemiological Studies: A Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia

FREDERICK WOLFE, DANIEL J. CLAUW, MARY-ANN FITZCHARLES, DON L. GOLDENBERG, WINFRIED HÄUSER, ROBERT S. KATZ, PHILIP MEASE, ANTHONY S. RUSSELL, I. JON RUSSELL, and JOHN B. WINFIELD

Wolfe F et al. Arthritis Rheum, 1990;
Wolfe F et al. Arthritis Care Res, 2010; Wolfe F et al. J Rheum, 2011

But what are the Fibromyalgia Criteria?

2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria

Frederick Wolfe, MD[a,b,*], Daniel J. Clauw, MD[c], Mary-Ann Fitzcharles, MD[d], Don L. Goldenberg, MD[e,f], Winfried Häuser, MD[g,h], Robert L. Katz, MD[i], Philip J. Mease, MD[j,k], Anthony S. Russell, MD[l], Irwin Jon Russell, MD, PhD[m], Brian Walitt, MD, MPH[n]

AAPT Diagnostic Criteria for Fibromyalgia

Lesley M. Arnold,* Robert M. Bennett,† Leslie J. Crofford,‡ Linda E. Dean,§ Daniel J. Clauw,¶ Don L. Goldenberg,|| Mary-Ann Fitzcharles,** Eduardo S. Paiva,†† Roland Staud,‡‡ Piercarlo Sarzi-Puttini,§§ Dan Buskila,¶¶ and Gary J. Macfarlane§

Wolfe F et al. Sem Arthritis Rheum, 2016
Arnold LM et al. J Pain, 2019

But what are the Fibromyalgia Criteria?

EDITORIAL

Time to Stop the Fibromyalgia Criteria Wars and Refocus on Identifying and Treating Individuals With This Type of Pain Earlier in Their Illness

Daniel Clauw

- Either the ACR 2016 criteria or the AAPT criteria will suffice
- Development of AAPT criteria may have been more methodologically rigorous
- However, the 2011/2016 ACR Survey Criteria can be scored as a continuous quantitative measure

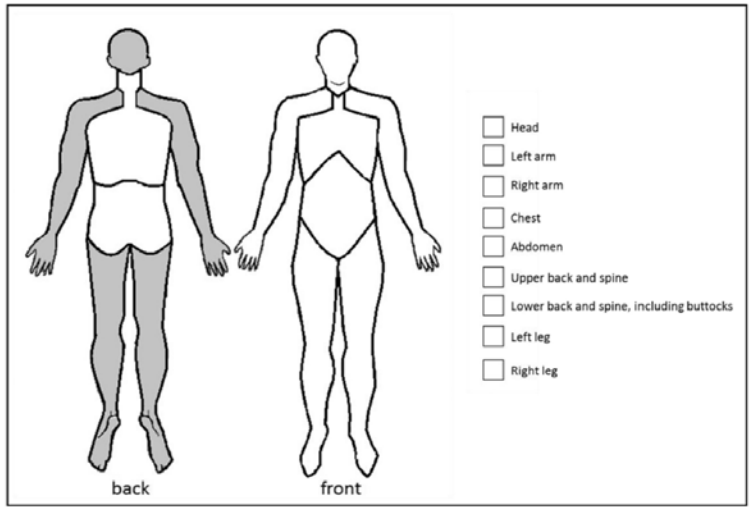
Clauw DJ. Arthritis Care Res, 2021

ACTTION-APS (AAPT) Diagnostic Criteria

Table 1. AAPT Diagnostic Criteria for Fibromyalgia

Dimension 1: Core Diagnostic Criteria

1. MSP defined as 6 or more pain sites from a total of 9 possible sites (see Fig 1)
2. Moderate to severe sleep problems OR fatigue
3. MSP plus fatigue or sleep problems must have been present for at least 3 months



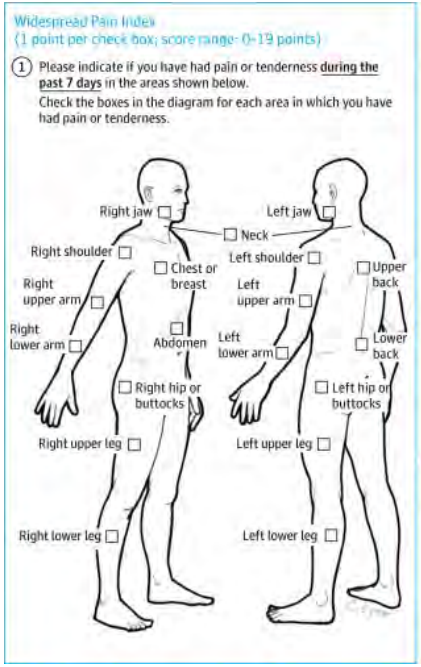
- "Moderate to severe sleep problems or fatigue" is assessed by the healthcare professional
- Dichotomous yes/no result

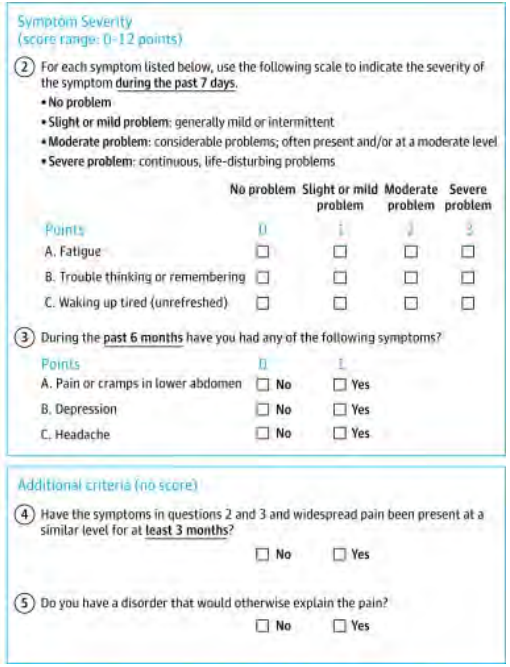
Arnold LM et al., J Pain, 2019

ACR Fibromyalgia Criteria

Fibromyalgia Survey Criteria

Widespread Pain Index (0-19)





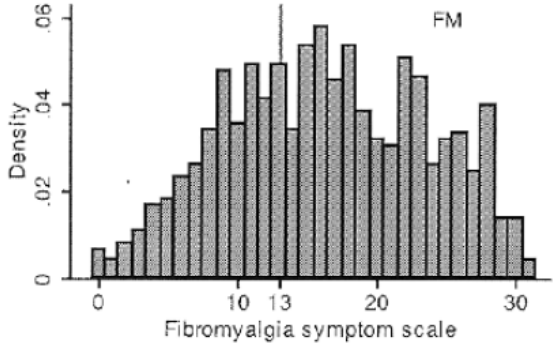
Symptom Severity Scale (0-12)

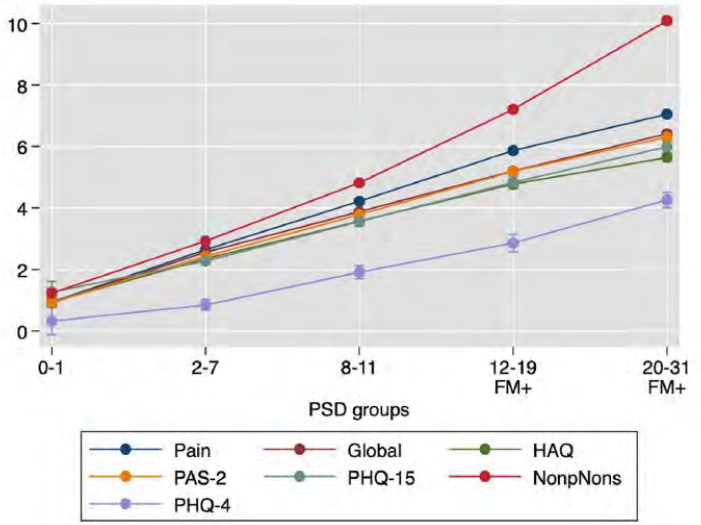
Fibromyalgia Survey Scale = WPI + SSS (0-31)

Clauw DJ. JAMA, 2014

ACR Fibromyalgia Criteria

- Continuous distribution of FM Survey Scores

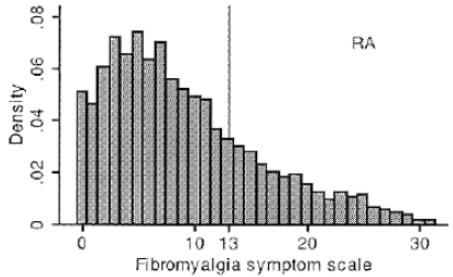




Wolfe F et al. J Rheumatol, 2011
Wolfe F et al. Sem Arthritis Rheum 2023

Fibromyalgia Survey Scale in RA

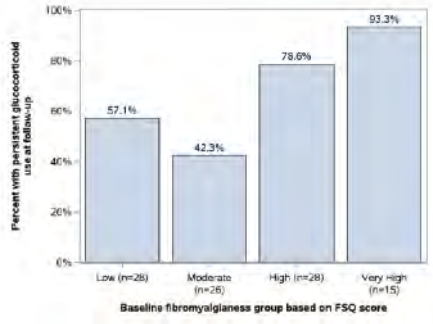
FM Survey Scale has a continuous distribution in RA



FM Survey Scale is associated with DAS28 3 months after DMARD initiation/switch

Model	B[a]	β[a]	*P*	Adjusted R^2
Model 1[b]	0.09 (0.06-0.12)	0.39 (0.26-0.52)	< 0.001	0.15
Model 2[c]	0.04 (0.01-0.07)	0.16 (0.03-0.29)	0.01	0.42
Model 3[d]	0.04 (0.01-0.07)	0.17 (0.04-0.30)	0.01	0.41

FM Survey Scale is associated with steroid use after DMARD initiation/switch



Low: 0-7
Moderate: 8-10
High 11-15
Very high > 15

Wolfe F et al. J Rheumatol, 2011; Gorzewski A et al, J Rheumatol, 2022; Wallace B et al, Rheumatology, 2022

Summary of the Fibromyalgia Criteria

- Apply one of the published diagnostic criteria
  - ACR 2016 Criteria
  - AAPT Criteria
- Think about fibromyalgia as a continuous measure of nociplastic pain

Assessment Using Commonly Obtained Measures of RA

- Tender minus swollen joint count ≥ 7
- Swollen to tender joint count ratio < 0.5
- DAS28-P

Assessment Using Commonly Obtained Measures of RA

- Subjective: 42 yo woman with seropositive RA on methotrexate presents with increasing pain and fatigue; rates global disease activity as 7/10; interested in talking about escalating DMARD therapy

Objective:

Tender joint count: 8
Swollen joint count: 1
Physician global assessment: 2/10
CRP: 0.3 mg/dL
ESR: 20 mm/hr

Impact of Pain on Assessment of Disease Activity

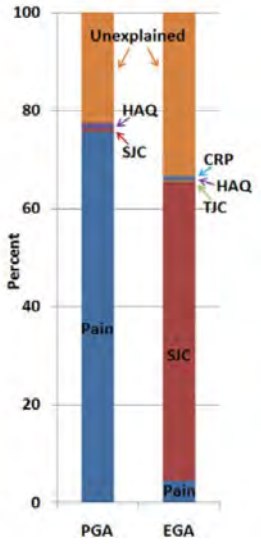
Measures of RA disease activity

- CDAI = TJC28 + SJC28 + PGA + MDGA — 18 (moderate)
- SDAI = TJC28 + SJC28 + PGA + MDGA + CRP — 18.3 (moderate)
- DAS28-ESR = 0.56 x √(TJC28) + 0.28 x √(SJC28) + 0.014 x PGA + 0.70 x ln(ESR) — 4.9 (moderate)
- DAS28-CRP = 0.56 x √(TJC28) + 0.28 x √(SJC28) + 0.014 x PGA + 0.36 x ln(CRP+1) = 0.96 — 4.3 (moderate)

Impact of Pain on Composite Disease Activity Measures

- Composite Disease Activity Scores
  - CDAI: TJC(28) + SJC(28) + Pt Global(10) + MD Global(10)
  - SDAI: TJC(28) + SJC(28) + Pt Global(10) + MD Global(10) + CRP(10) (mg/dL)

Explained Variance in Pt Global and MD Global



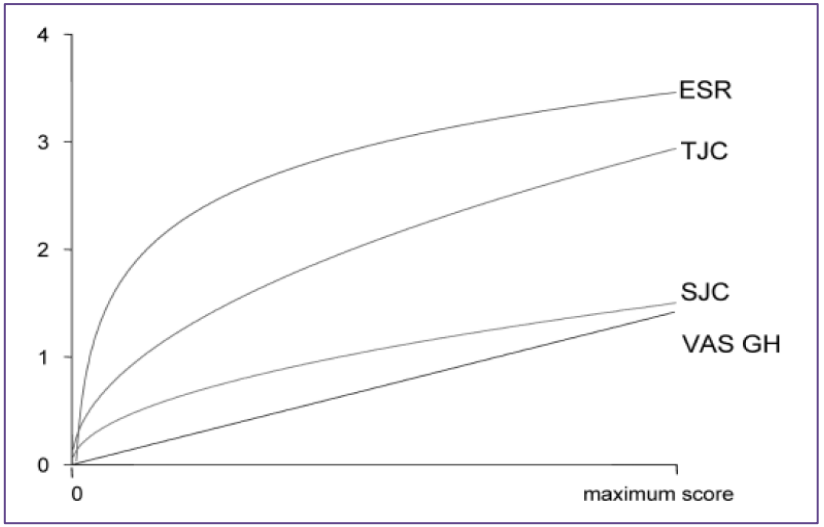
Studenic P et al. Arthritis Rheum 2012

Impact of Pain on Composite Disease Activity Measures

DAS28(4)-ESR:
0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.70 *ln(ESR) + 0.014 Pt Global(10)

DAS28(4)-CRP:
0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36 *ln(CRP+1) + 0.014 Pt Global(10) + 0.96

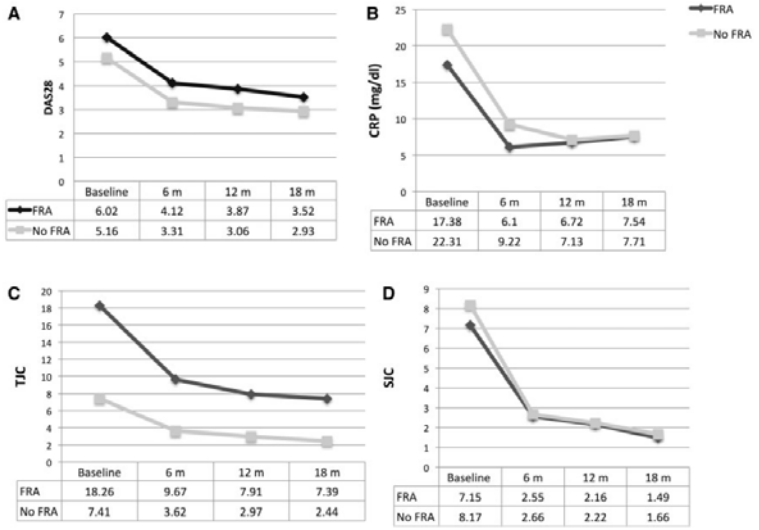
Contribution to the total DAS28 score
(x-axis: 0 to max range of plotted variable; y-axis: Units of DAS28)



Ton et al. J Rheum, 2012

Tender – Swollen Joint Count Difference (TJC – SJC)

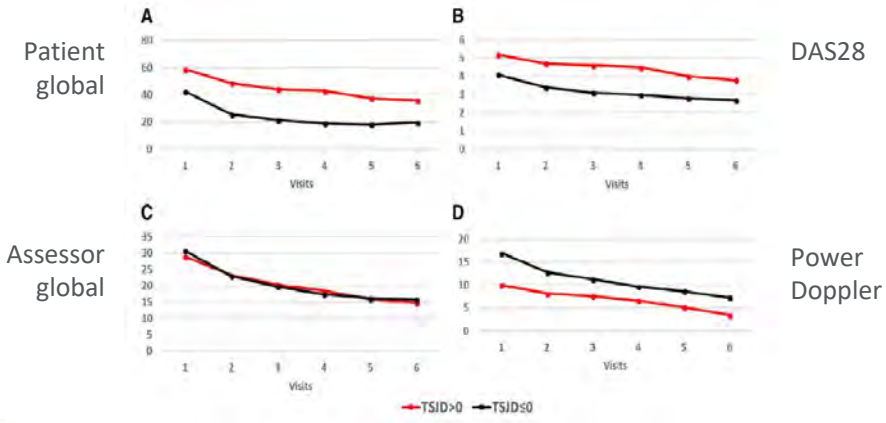
- Optimal threshold of ≥ 7 predicted presence of ≥ 11 tender points with 72% sensitivity and 98% specificity
- Patients with TJC-SJC ≥ 7 were significantly less likely to achieve LDA (RR 0.77, 95% CI 0.63, 0.94) and remission (RR 0.61, 95% CI 0.46, 0.81)



Pollard et al. Rheumatology, 2010; Duran et al. Rheumatol, 2015

Tender – Swollen Joint Count Difference (TJC – SJC)

- Patients with predominantly tender joints (TJC-SJC > 0) had
  - Higher patient global score and higher DAS28 scores than patients with TJC-SJC ≤ 0
  - No differences in assessor global assessment
  - **Lower** power Doppler scores



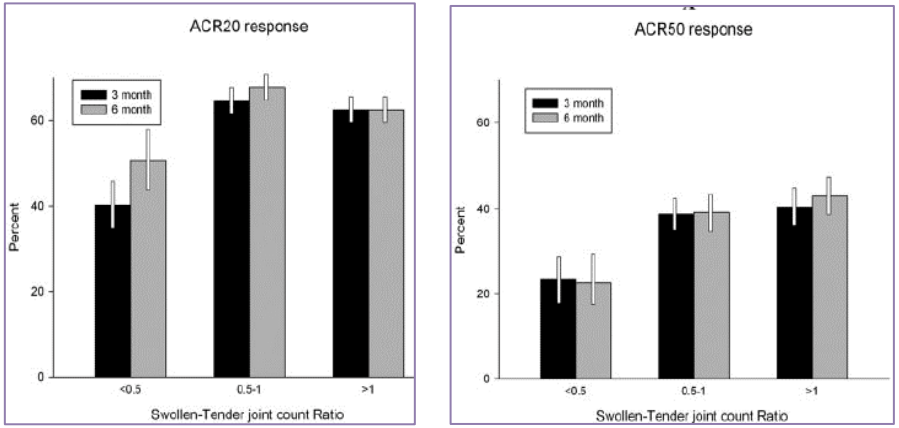
Hammer H et al. AC&R, 2020

TJC – SJC Practical Points

- TJC-SJC ≥ 7 may be a practical way for identifying RA patients with fibromyalgia (nociplastic pain)
- Among patients with TJC-SJC ≥ 7 who do not achieve LDA or remission, may want to consider placing more weight on SJC and inflammatory markers
- Consider MSK ultrasound

Swollen to Tender Ratio

- Thresholds determined by distribution plots of STR
  - Cluster of patients with STR of 0.5 or 1.0
  - Low < 0.5, Moderate 0.5-1.0, High > 1.0



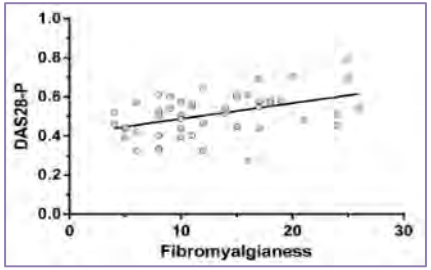
Kristensen et al. AC&R, 2014

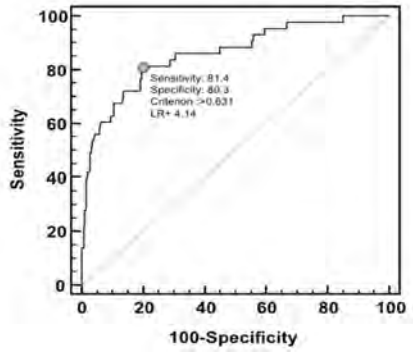
DAS28 – Patient-Reported (DAS28-P)

- Fraction of the total DAS28 score contributed by patient-reported components (TJC and patient global assessment)

$$\frac{(0.56 \times \sqrt{TJC}) + (0.014 \times GH)}{(0.28 \times \sqrt{SJC}) + (0.56 \times \sqrt{TJC}) + (0.7 \times \ln(ESR)) + (0.014 \times GH)}$$

- Has been shown to predict pain response but not necessarily treatment response





McWilliams et al. AC&R, 2012; McWilliams and Walsh BMC Musculoskeletal Disorders 2016; Jurgens et al. AC&R 2015; Son et al. Clin Rheumatol, 2017

Recommendations for Managing Nociplastic Pain in RA

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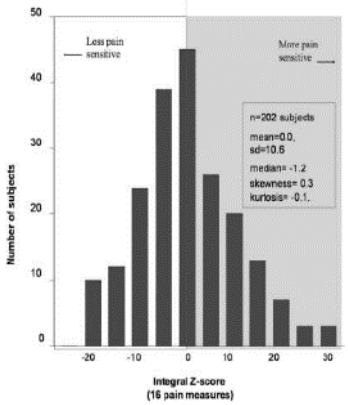
Patient Education

- Break down defenses

- Use facts to explain the situation in a non-judgmental manner
  - Pain sensitivity has a bell-shaped curve, similar to height or blood pressure
  - 14% of variation in the FM score can be explained by genetic variation



Dutta D et al. Arthritis Rheumatol, 2020; Clauw DJ. Best Pract Res Clin Rheumatol, 2015; Clauw DJ. JAMA, 2014; Diatchenko et al., Human Molecular Genetics, 2005

Patient Education

- Secure patient “buy in”

Stock Image (PowerPoint)

- Demonstrate relevance to patient’s own personal experiences
  - “Normal” life changes (e.g., getting a job and not being as physically active; having children and not sleeping as much)
  - Acute pain event (e.g., car accident)

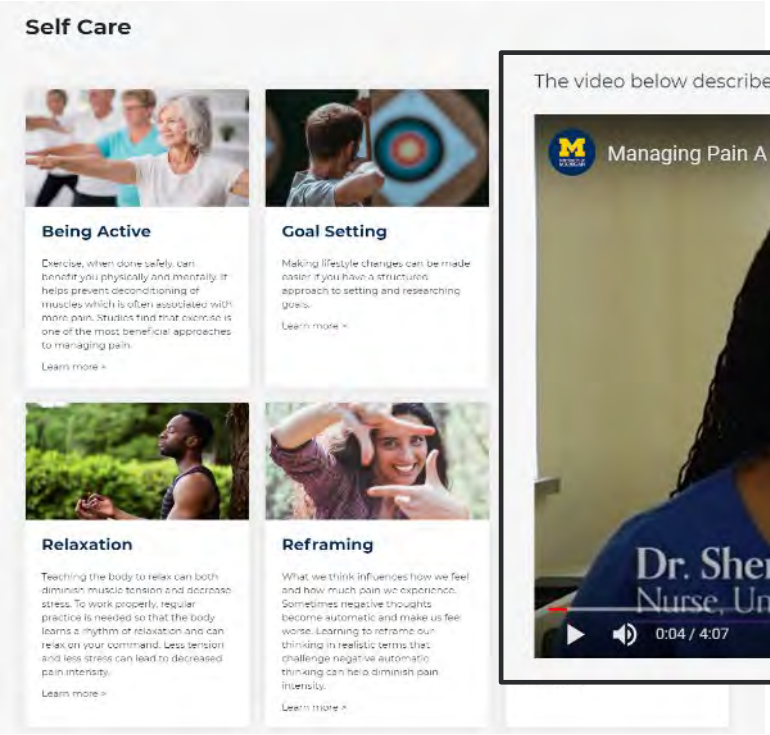
Clauw DJ. Best Pract Res Clin Rheumatol, 2015; Clauw DJ. JAMA, 2014

Patient Education Resources

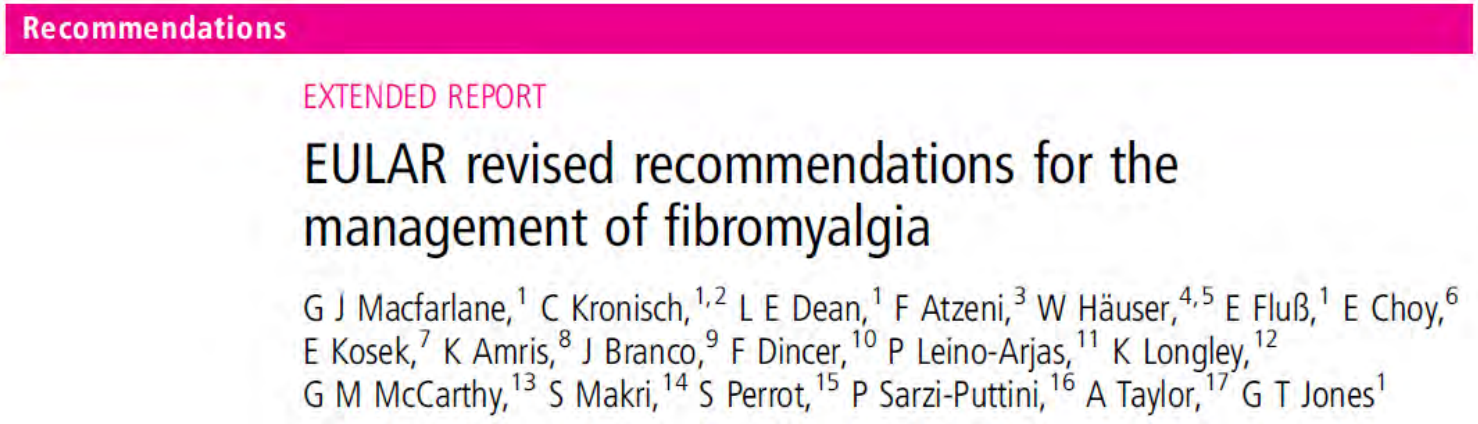
Northwestern Medicine
Feinberg School of Medicine

Fibroguide.med.umich.edu

Patient Education Resources



Treatment Options

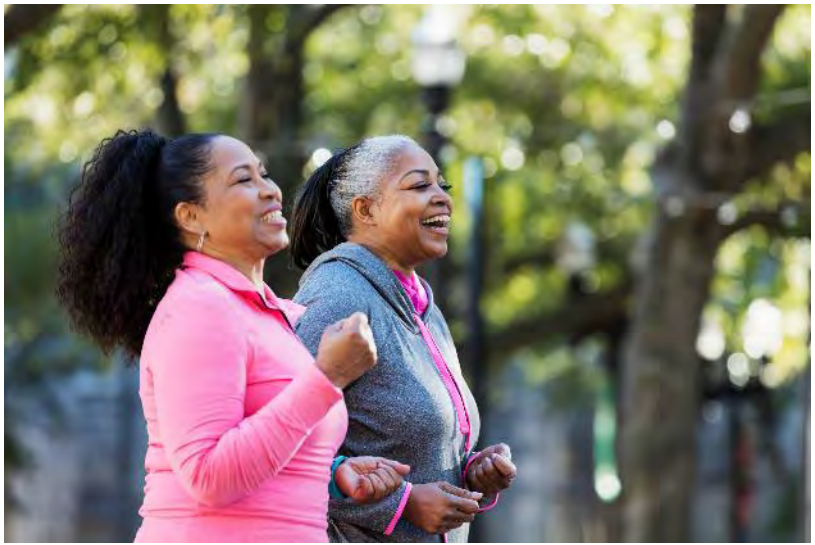


- Overarching principles
  - Fibromyalgia should be recognized as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features
  - Management often requires a combination of non-pharmacologic and pharmacologic modalities tailored to the patient

Macfarlane GH et al. Ann Rheum Dis, 2017

Non-Pharmacologic Strategies (Strong Recommendation)

- Exercise: 100% agreement from working group members



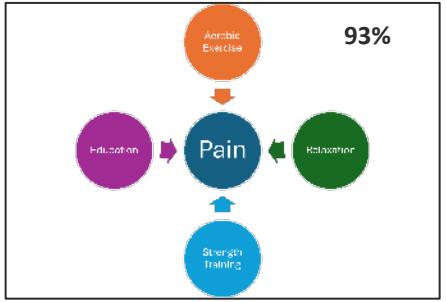
Stock Image (PowerPoint)

- Based on 20 reviews including up to 34 trials and at least 2494 participants
- Consistent results for aerobic and strengthening exercises

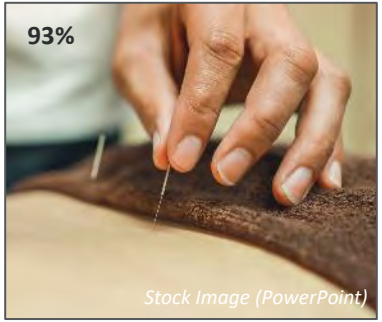
Macfarlane GH et al. Ann Rheum Dis, 2017

Non-Pharmacologic Strategies (Weak Recommendation)

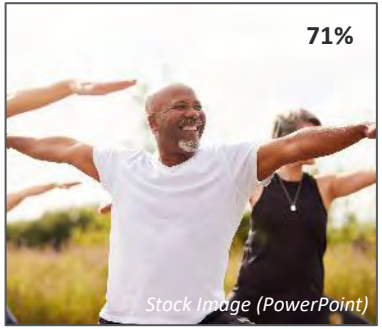
CBT/Multicomponent



Specific Physical Therapies



Meditative Movement



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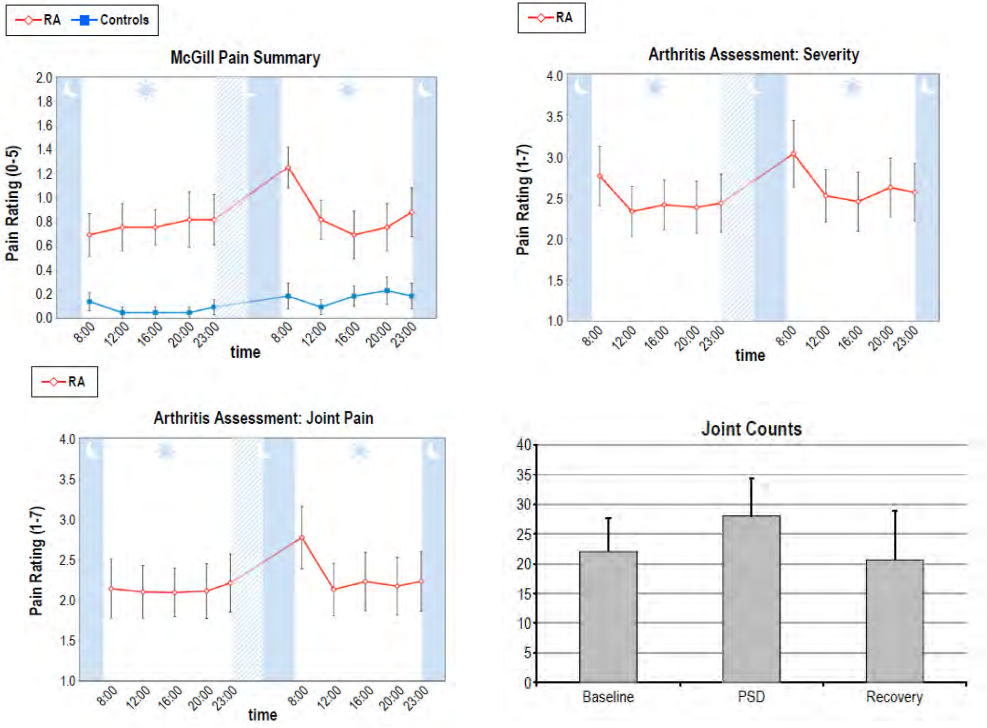
Macfarlane GH et al. Ann Rheum Dis, 2017

Sleep and Rheumatoid Arthritis

- We have previously shown that
  - Sleep disturbances may mediate the relationship between RA and inefficient descending pain inhibition
  - Sleep disturbances predict pain intensity
    - In patients with early RA
    - In patients with established disease starting a new DMARD
  - Abnormalities in QST assessments of nociplastic pain mediate relationship between sleep disturbances and pain intensity

Predictors of Next Day Pain

- 27 RA patients and 27 controls
- Between-groups laboratory study with assessment of pain and mood before and after partial night sleep deprivation (PSD)
  - Adaptation night
  - Baseline night (sleep from 23:00-7:00)
  - PSD night (awake between 23:00-3:00)
  - Recovery night (sleep from 23:00-7:00)



Irwin MR et al., Sleep, 2012

Nonpharmacological Treatments of Insomnia for Pain

- Meta-analysis of studies of CBT-I in patients with cancer and non-cancer (back pain, arthritis, fibromyalgia)
- Results
  - Large improvements in sleep quality
  - Small reductions in pain

A

Study or Subgroup	Sleep treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Currie et al., 2000	1.35	1	32	0.5	1	28	9.4%	0.84 [0.31, 1.37]	2000
Savard et al., 2005a	1.7	1	27	1.02	1	30	9.3%	0.67 [0.14, 1.21]	2005
Edinger et al., 2005	0.79	1	16	0.03	1	9	7.1%	0.73 [−0.11, 1.58]	2005
Espie et al., 2008	0.92	1	74	0.09	1	40	10.3%	0.82 [0.42, 1.22]	2008
Berger et al., 2009b	0.36	1	90	−0.01	1	85	10.9%	0.37 [0.07, 0.67]	2009
Barsevick et al., 2010	0.01	1	142	−0.1	1	134	11.2%	0.11 [−0.13, 0.35]	2010
Jungquist et al., 2010	0.77	1	19	0.45	1	9	7.4%	0.31 [−0.49, 1.11]	2010
Miró et al., 2011	0.93	1	20	0.31	1	20	8.6%	0.61 [−0.03, 1.24]	2011
Ritterband et al., 2012	2.18	1	14	0.33	1	14	6.8%	1.80 [0.90, 2.69]	2012
Martinez et al., 2014	1.14	1	29	0.47	1	22	9.1%	0.66 [0.09, 1.23]	2014
Garland 2014	2.56	1	47	0.62	1	64	9.9%	1.93 [1.47, 2.38]	2014
Total (95% CI)			**510**			**455**	**100.0%**	**0.78 [0.42, 1.13]**	

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 60.74$, df = 10 ($P < 0.00001$); $I^2 = 84\%$
Test for overall effect: $Z = 4.28$ ($P < 0.0001$)

Std. Mean Difference IV, Random, 95% CI
−2 −1 0 1 2
Favors [Control] Favors [Sleep Tx]

B

Study or Subgroup	Sleep treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Currie et al., 2000	0.67	1	32	0.3	1	28	12.5%	0.37 [−0.15, 0.88]	2000
Edinger et al., 2005	0.23	1	15	−0.48	1	9	4.5%	0.69 [−0.17, 1.54]	2005
Barsevick et al., 2010	−0.12	1	142	−0.25	1	134	58.7%	0.13 [−0.11, 0.37]	2010
Jungquist et al., 2010	0.23	1	19	0.25	1	9	5.2%	−0.02 [−0.81, 0.77]	2010
Miró et al., 2011	0.24	1	20	0	1	20	8.5%	0.24 [−0.39, 0.86]	2011
Martinez et al., 2014	0.3	1	29	0.19	1	22	10.7%	0.11 [−0.45, 0.66]	2014
Total (95% CI)			**257**			**222**	**100.0%**	**0.18 [0.00, 0.36]**	

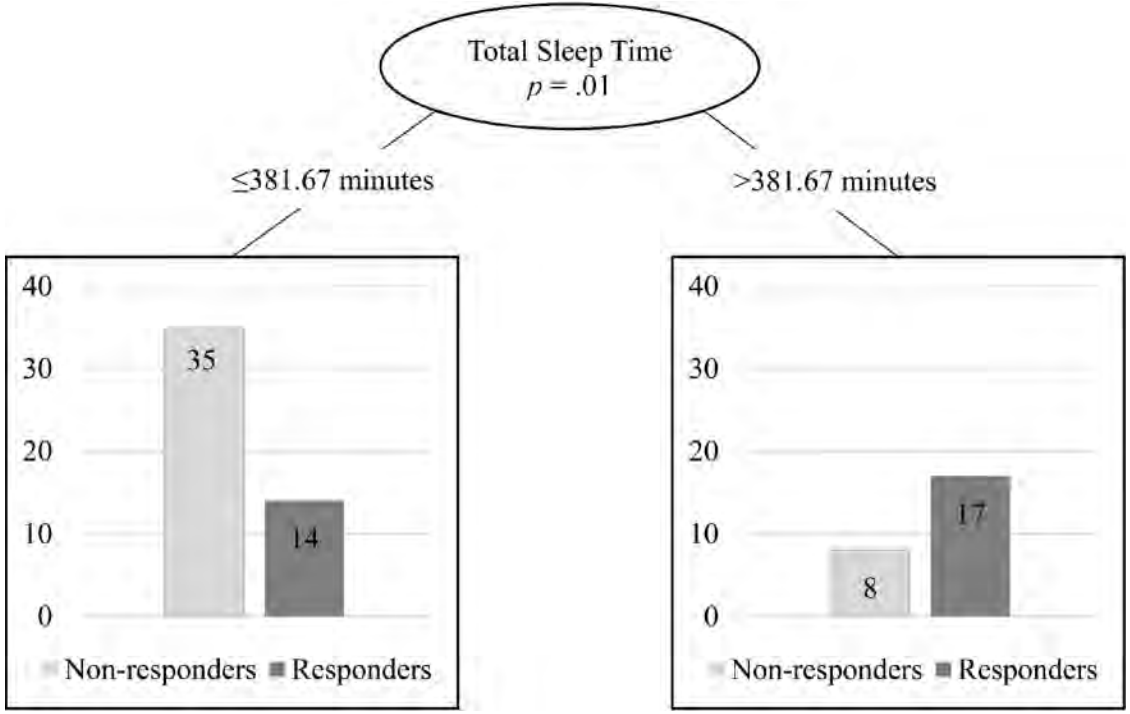
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.36$, df = 5 ($P = 0.80$); $I^2 = 0\%$
Test for overall effect: $Z = 1.98$ ($P = 0.05$)

Std. Mean Difference IV, Random, 95% CI
−2 −1 0 1 2
Favors [Control] Favors [Sleep Tx]

Tang NKY et al. SLEEP, 2015

Nonpharmacological Treatments of Insomnia for Pain

- Participants who achieved at least 381 min (6.4 hrs) of sleep at mid-treatment were significantly more likely to be pain responders

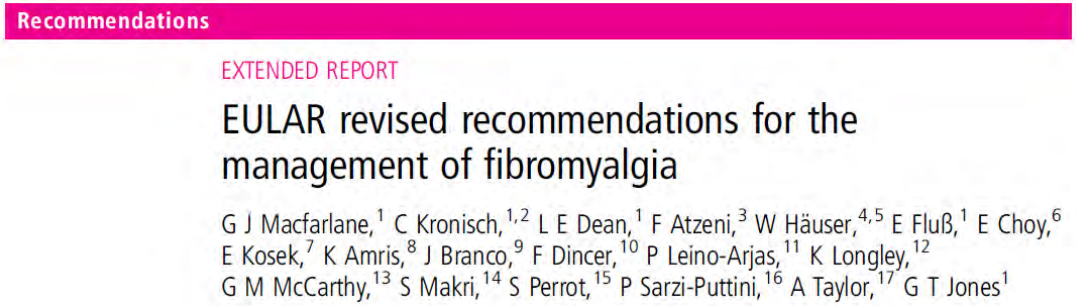


Salwen JK et al. , SLEEP, 2017

Treating Sleep to Improve Pain

- Improving sleep likely will improve pain
- However, thus far, improvements in pain are small
- Future studies to determine
  - Whether thresholds for sleep improvements need to be met
  - Whether specific types of sleep disturbances (e.g., sleep fragmentation vs. sleep duration) are more associated with pain
  - Whether multi-component therapies are needed

Pharmacologic Strategies



Recommendations

EXTENDED REPORT

EULAR revised recommendations for the management of fibromyalgia

G J Macfarlane,[1] C Kronisch,[1,2] L E Dean,[1] F Atzeni,[3] W Häuser,[4,5] E Fluß,[1] E Choy,[6] E Kosek,[7] K Amris,[8] J Branco,[9] F Dincer,[10] P Leino-Arjas,[11] K Longley,[12] G M McCarthy,[13] S Makri,[14] S Perrot,[15] P Sarzi-Puttini,[16] A Taylor,[17] G T Jones[1]

- No strong recommendations
- Weak recommendations for
  - Amitriptyline (low dose) – 100% agreement
  - Duloxetine/milnacipran – 100% agreement
  - Tramadol – 100% agreement
  - Pregabalin – 94% agreement
  - Cyclobenzaprine – 75% agreement

OPIOIDS DON'T WORK FOR NOCIPLASTIC PAIN

Macfarlane GH et al. Ann Rheum Dis, 2017

TCAs for Pain in RA

Tricyclic antidepressants	Nine RCTs in inflammatory arthritis (eight in RA) found no evidence of short-term (<1 week) benefit Conflicting evidence found in trials of duration >1 week, with minor AEs that did not result in discontinuation	Richards *et al.* (2012)[172]

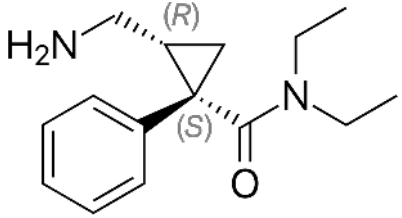
- Caveats
- Most studies were published in 1980s in patients with active disease receiving minimal DMARD therapy
- Common side effects: Somnolence, dizziness, dry mouth, nausea, constipation (advise patients to hydrate well)

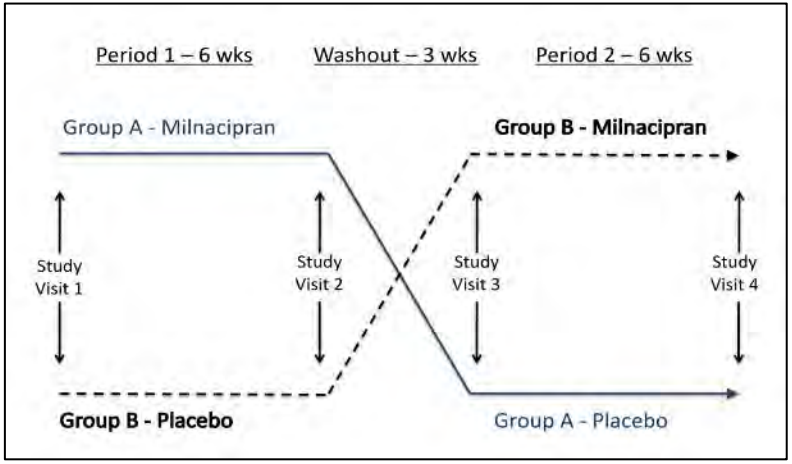
Richards B et al. J Rheumatol, 2012

SNRIs for Pain in Patients with RA

Effect of Milnacipran on Pain in Patients with Rheumatoid Arthritis with Widespread Pain: A Randomized Blinded Crossover Trial

Yvonne C. Lee, Elena Massarotti, Robert R. Edwards, Bing Lu, ChihChin Liu, Yuanyu Lo, Alyssa Wohlfahrt, Nancy D. Kim, Daniel J. Clauw, and Daniel H. Solomon





- Intervention: Milnacipran, an SNRI, approved for treatment of FM
- Study population:
  - Diagnosis of RA
  - Pain at ≥ 5 body sites on the Regional Pain Scale
  - Pain intensity ≥ 4 out of 10

Lee YC et al. J Rheumatol. 2016

SNRIs for Pain in Patients with RA

- Primary Analysis (N = 32)

	Placebo	Milnacipran	P
BPI Pain Intensity	-0.3 (2.0)	-0.7 (1.7)	0.37
Thumbnail PPT	**-0.02 (1.4)**	**0.7 (1.4)**	**0.04**

- Subgroup Analysis (SJC ≤ 1; N = 22)

	Placebo	Milnacipran	P
BPI Pain Intensity	**0.1 (1.9)**	**-1.0 (1.6)**	**0.04**
Thumbnail PPT	**-0.1 (1.2)**	**0.9 (1.4)**	**0.003**

- Importance of appropriately phenotyping pain in patients with rheumatic diseases

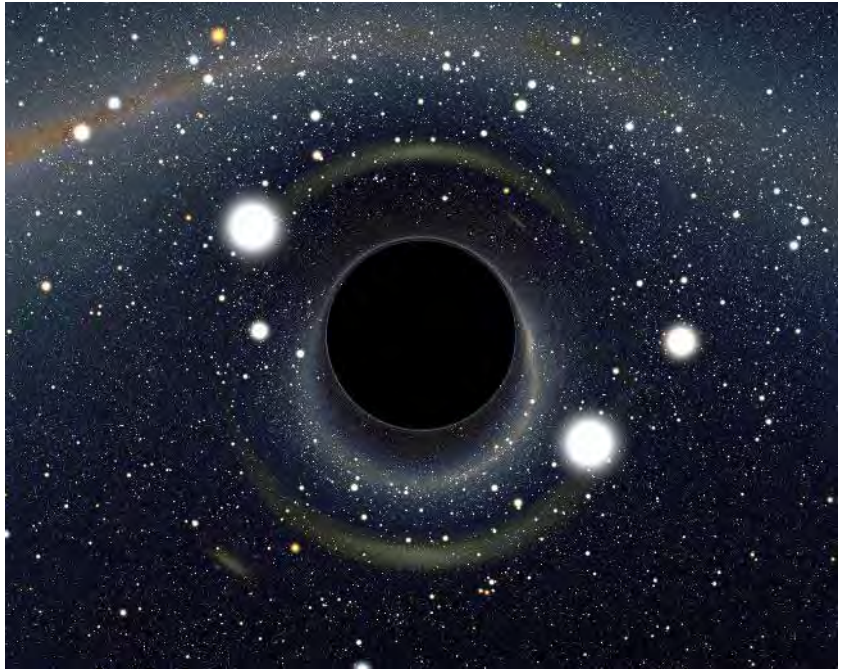
Lee YC et al. J Rheumatol. 2016

Adverse Effects of Milnacipran in RA

- Of the 41 pts who were randomized and received ≥ 1 dose of milnacipran/placebo, 24 (58%) reported ≥ 1 adverse effect
  - Nausea (27% on milnacipran, 7% on placebo)
  - Loss of appetite (10% on milnacipran, 0% on placebo)
  - Vomiting (7% on milnacipran, 0% on placebo)
  - Sleep problems (7% on milnacipran, 5% on placebo)
  - Urinary hesitation (5% on milnacipran, 0% on placebo)

Lee YC et al. J Rheumatol. 2016

Anticonvulsants for Pain in RA



Pharmacologic Strategies – Dosing

- TCAs
  - Amitriptyline: Start at 10 mg qhs, increase as needed up to 75 mg qhs
- SNRIs
  - Duloxetine: Start at 30 mg daily, increase as needed up to 60 mg daily
  - Milnacipran: Start at 12.5 mg daily, increase as needed to 100 mg twice daily
- Alpha-2-delta Ligands
  - Pregabalin: Start at 75 mg bid, increase to max of 150 mg qAM and 300 mg qPM
  - Gabapentin 100-300 mg qhs, may need doses in range of 1200-2400 mg daily (divided)

Emerging Areas for Pain Management in RA

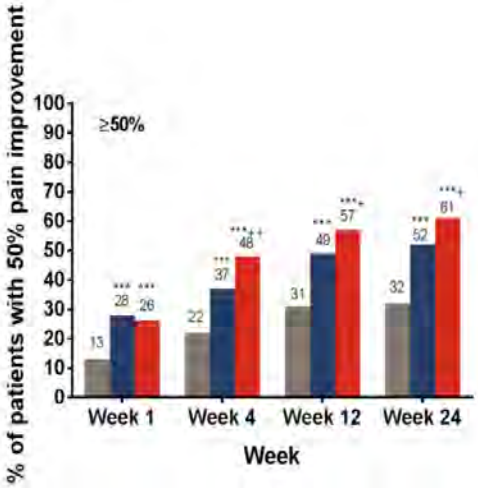
JAK Inhibitors

Cannabinoids

JAK Inhibitors (baricitinib, upadacitinb) and Pain

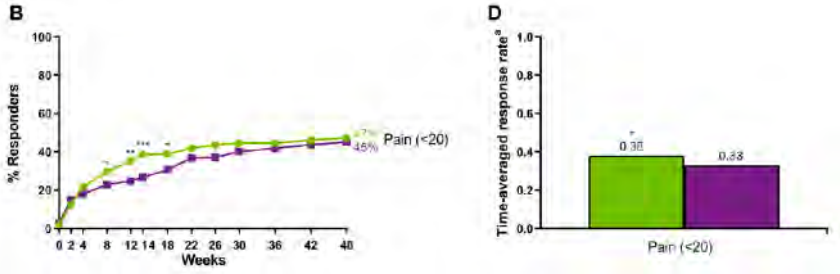
Achieving Pain Control in Rheumatoid Arthritis with Baricitinib or Adalimumab Plus Methotrexate: Results from the RA-BEAM Trial

Population: MTX-IR



Impact of initial therapy with upadacitinib or adalimumab on achievement of 48-week treatment goals in patients with rheumatoid arthritis: *post hoc* analysis of SELECT-COMPARE

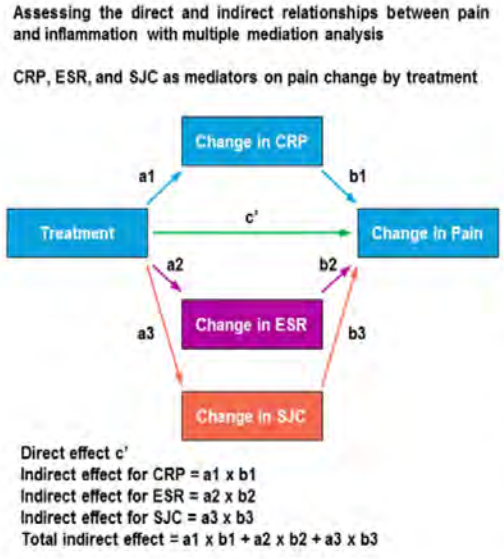
Population: MTX-IR

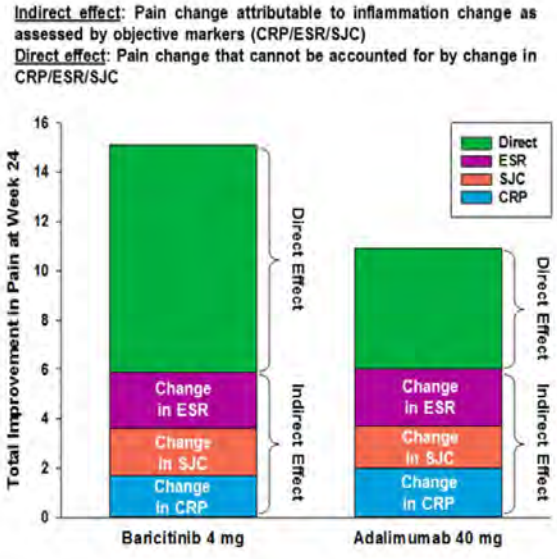


Taylor PC et al. J Clin Med, 2019; Mysler E et al. Rheumatology (Oxford), 2022

JAK Inhibitors and Pain

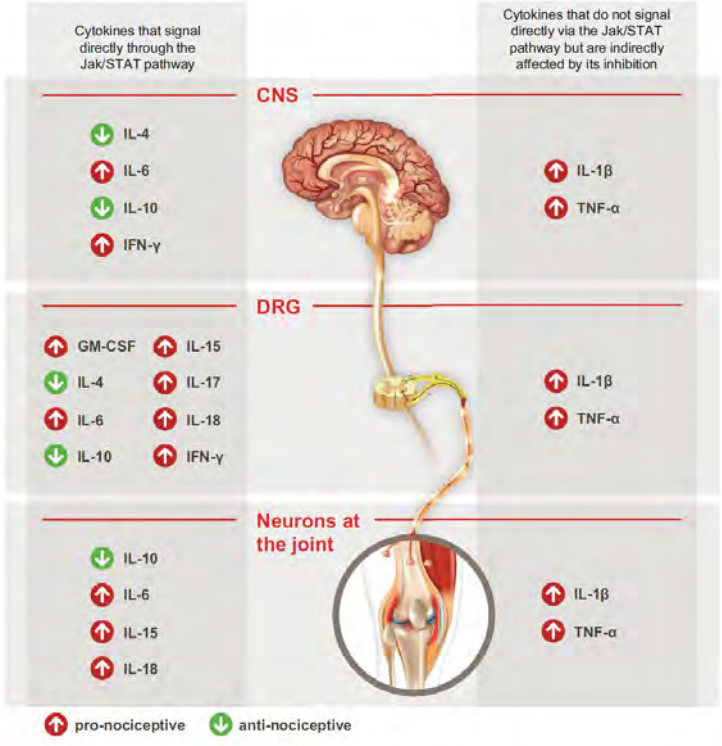
- Mediation analysis: The majority (60%) of the effect of baricitinib on pain seemed to be occurring via “non-inflammatory” pathways





Taylor PC et al. J Clin Med, 2019

JAK Inhibitors and Pain



- JAK inhibitors may act directly or indirectly to decrease pain via multiple pathways
  - CNS
  - Dorsal root ganglion
  - Peripheral nerves (at the joints)

Simon LS et al. Sem Arthritis Rheum 51: 278-84, 2021

JAK Inhibitors (tofacitinib) and Pain

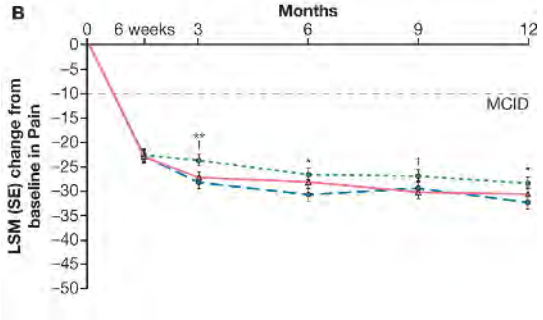
RMD Open
Rheumatic & Musculoskeletal Diseases

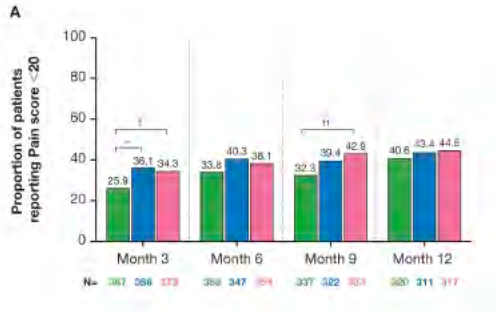
ORIGINAL ARTICLE

Patient-reported outcomes for tofacitinib with and without methotrexate, or adalimumab with methotrexate, in rheumatoid arthritis: a phase IIIB/IV trial

ORAL Strategy

- Population: MTX-IR
- Comparison
  - Tofacitinib mono
  - Tofacitinib + MTX
  - Adalimumab + MTX





Northwestern Medicine
Feinberg School of Medicine

Strand V et al. RMD Open, 2019.

JAK Inhibitors and Pain

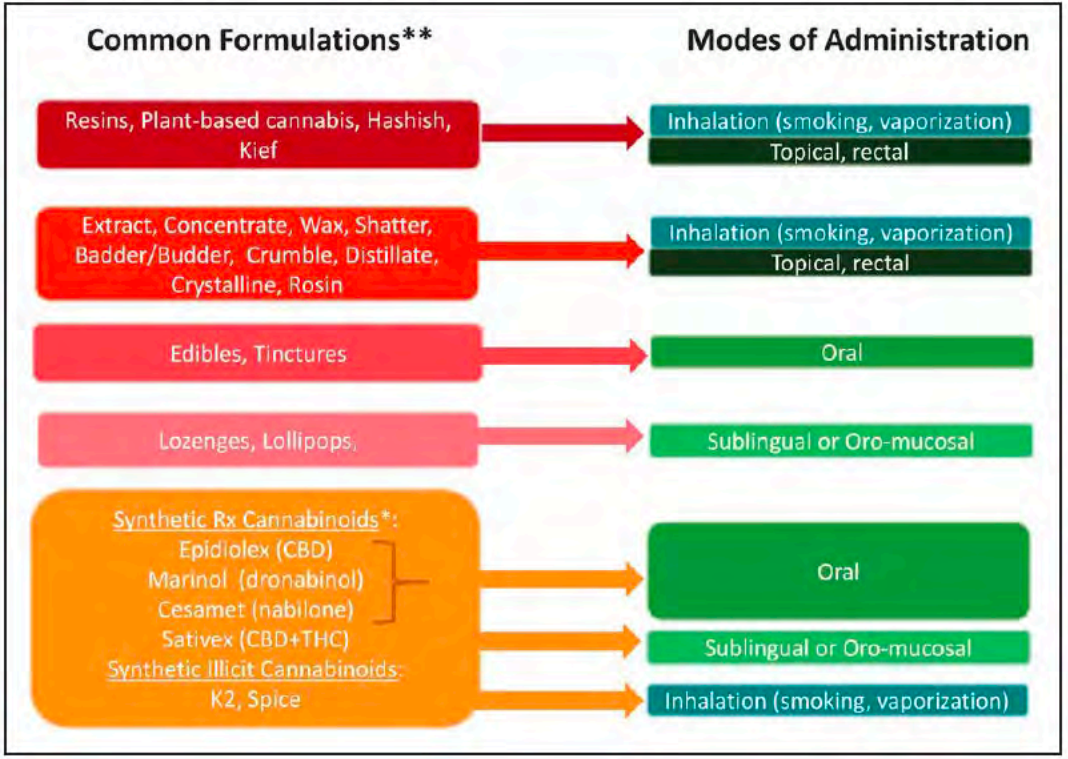
- Jury is still out
- Open questions
  - Differences between JAK inhibitors?
  - Differences between JAK inhibitors and non-TNF biologics?
  - Differences between study populations (MTX-IR, TNF-IR, etc)?
  - If there are differences, are differences really due to “non-inflammatory” pathways?

Cannabinoids and Pain

- Cannabis sativa
  - >100 identified cannabinoid molecules
    - Tetrahydrocannabinol (THC)
      - Main psychotropic constituent of cannabis
    - Cannabidiol (CBD)
    - Both THC and CBD have potential for analgesic and anti-inflammatory effects

Current Formulations and Modes of Administration

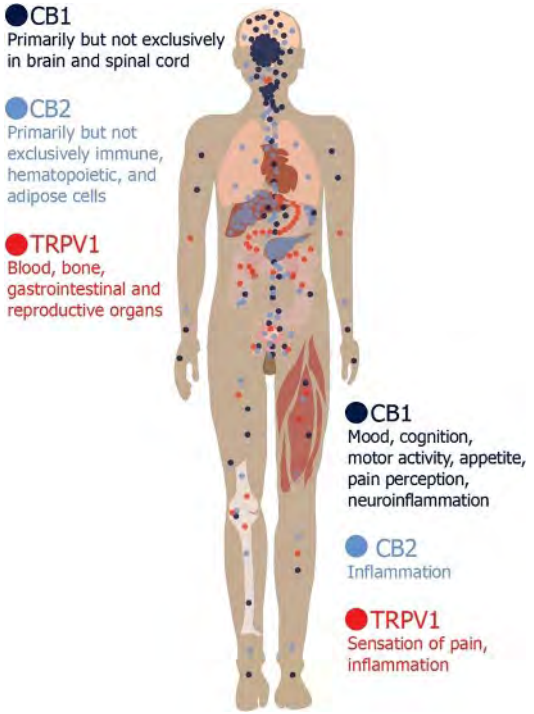
- Since 2006, attitudes toward recreational and medicinal cannabis use have rapidly evolved
- At the state level, cannabis has moved from illicit to decriminalized to legalized
- Rise in cannabis availability and use



Page et al. Circulation, 2020

Mechanisms for Cannabinoids and Pain

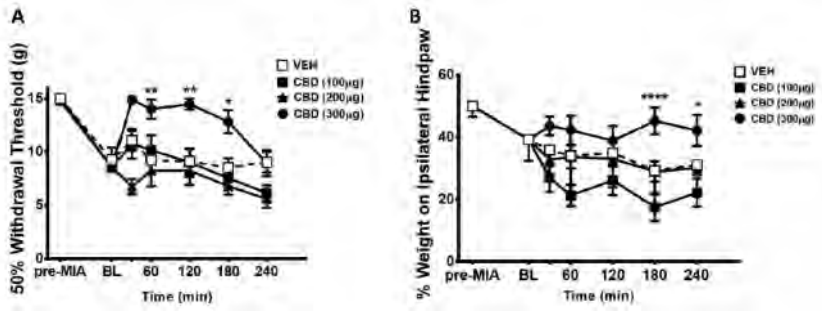
- Complex and not well understood
- Cannabinoid receptors
  - CB1: Mood, cognition, pain perception, neuroinflammation
  - CB2: Inflammation
- Other receptors
  - TRPV1: Pain sensation; inflammation



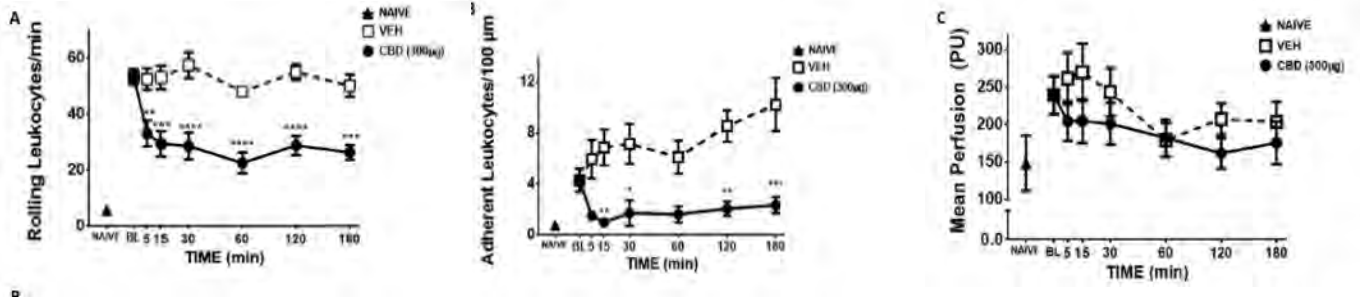
Nowell WB et al. Curr Rheumatol Rep, 2022
Fitzcharles MA et al, Arthritris Care Res (Hoboken), 2023

Preclinical data on CBD and Pain and Inflammation

Pain



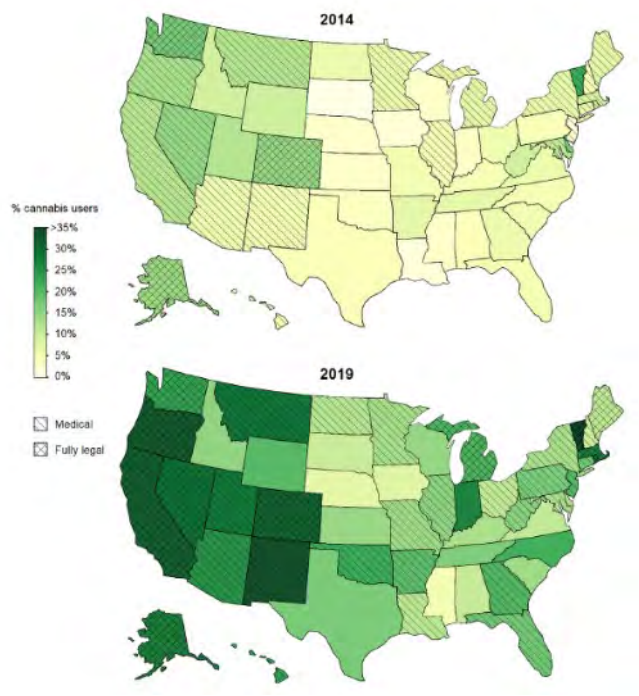
Inflammation



Philpott HT et al., PAIN, 2017

Cannabis Use in Patients with Rheumatic Diseases

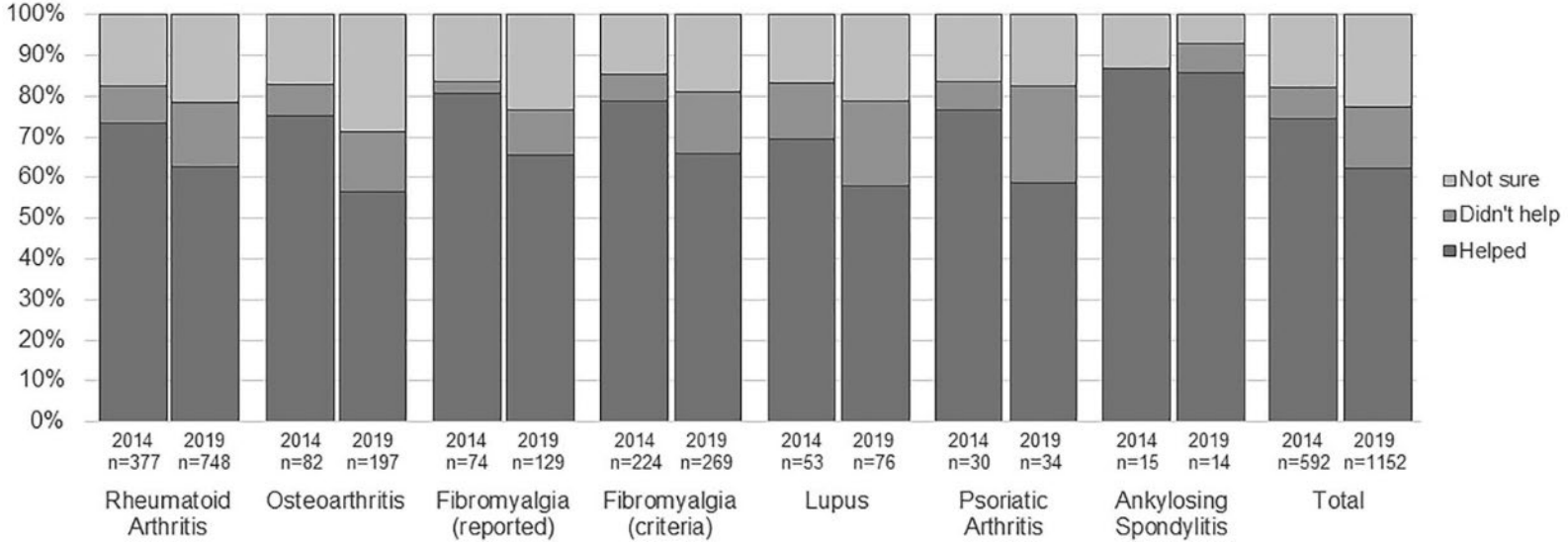
- Study in FORWARD, the National Databank for Rheumatic Diseases
- Cannabis use nearly tripled from 6.3% in 2014 to 18.4% in 2019



Wipfler K et al. Arthritis Care res 2022

Cannabis Use in Patients with Rheumatic Diseases

- Most users (74%and 62%in 2014 and 2019, respectively) reported that cannabis was effective in the relief of arthritis symptoms.



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Wipfler K et al. Arthritis Care res 2022

Cannabis-Based Medicines and Pain in RA

Rheumatology 2006;45:50–52
Advance Access publication 9 November 2005
doi:10.1093/rheumatology/kei183

Concise Report

Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis

D. R. Blake, P. Robson[1], M. Ho[2], R. W. Jubb[3] and C. S. McCabe

- Cannabis-based medicine (synthetic): Sativex (oromucosal spray w/ 2.7 mg THC and 2.5 mg CBD); not available in US

TABLE 2. Efficacy endpoints: difference between change from baseline between CBM and placebo after 5 weeks of treatment

Efficacy endpoint	Baseline (mean/median)[a]		Endpoint (mean/median)[a]		Difference (mean/median[a])	95% confidence interval	*P*
	CBM	Placebo	CBM	Placebo			
Morning pain on movement[a]	7.0	6.7	4.8	5.3	−0.95	−1.83, −0.02	0.044
Morning pain at rest[a]	5.3	5.3	3.1	4.1	−1.04	−1.90, −0.18	0.018
Morning stiffness[a]	3.5	3.8	3.0	3.2	−0.09	−0.58, 0.23	0.454
Quality of sleep	5.7	5.8	3.4	4.6	−1.17	−2.20, −0.14	0.027
DAS 28	5.9	6.0	5.0	5.9	−0.76	−1.23, −0.28	0.002
SF-MPQ, total intensity of pain[a] (a)	15.0	20.0	10.5	13.0	3.00	−3.00, 9.00	0.302
SF-MPQ, intensity of pain at present[a] (b)	48.0	50.0	33.0	50.0	−3.00	−18.0, 9.00	0.574
SF-MPQ, pain at present (c)	3.2	3.2	2.6	3.3	−0.72	−1.30, −0.14	0.016

Blake DR et al, Rheumatology 2006

Clinical data on CBD and Pain and Inflammation

PAIN®

VIDEO

Abstract

Cannabidiol (CBD) is increasingly used as analgesic medication although the recent International Association for the Study of Pain Presidential Task Force on cannabis and cannabinoid analgesia found a lack of trials examining CBD for pain management. This trial examines CBD as add-on analgesic therapy in patients with hand osteoarthritis or psoriatic arthritis experiencing moderate pain intensity despite therapy. Using a randomized, double-blind, placebo-controlled design, patients received synthetic CBD 20 to 30 mg or placebo daily for 12 weeks. The primary outcome was pain intensity during the past 24 hours (0-100 mm); safety outcomes were percentage of patients experiencing adverse events and a characterization of serious adverse events. Explorative outcomes included change in Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale (PCS), and Health Assessment Questionnaire Disability Index. One hundred thirty-six patients were randomized, of which 129 were included in the primary analysis. Between-group difference in pain intensity at 12 weeks was 0.23 mm (95% confidence interval −9.41 to 9.90; $P = 0.96$). Twenty-two percent patients receiving CBD and 21% receiving placebo experienced a reduction in pain intensity of more than 30 mm. We found neither clinically nor statistically significant effects of CBD for pain intensity in patients with hand osteoarthritis and psoriatic arthritis when compared with placebo. In addition, no statistically significant effects were found on sleep quality, depression, anxiety, or pain catastrophizing scores.

Keywords: Cannabidiol, Joint pain, Psoriatic arthritis, Hand osteoarthritis, Medical cannabis

Summary of Cannabinoids and Pain

- Encouraging preclinical data but not great clinical data → more research needed
- In the meantime, patients will ask…
  - Encourage patients to obtain a product with certification of Good Manufacturing Practices
  - Avoid smoking/vaping
  - Start treatment with a low dose at nighttime
  - No good data on dosing but should have < 0.3% THC

Fitzcharles MA et al., Arthritis Care Res, 2023

Summary

- Pain in patients with RA is complicated and may include nociceptive, neuropathic, and nociplastic pain
- Nociplastic pain may affect assessment of RA disease activity and should be taken into account when considering DMARD changes
- Data regarding treatments directed at CNS pain processing in RA are sparse
  - Make sure inflammatory disease is well controlled
  - Make sure to educate patients and discuss non-pharmacologic strategies
  - Consider amitriptyline and SNRIs if non-pharmacologic strategies are insufficient

Acknowledgments

Lee Research Group

CPIRA Network

Funding Sources: NIH R01 AR064850-10 (including STAR supplement), NIH R21 A080351-02, NIH K24 AR080840-02, RRF Innovative Research Grant