The Science of Pain

Learning Objectives

- Understanding that pain in RA does not necessarily correlate with the degree of inflammation or disease activity
- Recognizing that pain in RA is driven by multiple mechanisms
- Identifying that pain in RA results from the interplay between inflammation and processing of pain signals, and the importance of treating both inflammation and pain

Are You Managing Your RA Patients' Pain as Well as Possible?

"Although most patients seen by rheumatologists have pain as their presenting complaint, most rheumatologists have little formal training about contemporary theories regarding pain processing or pain management."

Phillips K, Clauw DJ. *Arthritis Rheum*. 2013;65(2):291-302.

Up to 70% of RA Patients Rate Pain Improvement as Their First Priority Relative to Other Disease Symptoms[1]

Pain is commonly highlighted as their most important problem

Pain relief is rated as a top priority for improvement of health and quality of life (QoL)[2]

Pain can be associated with:[3]

- psychological distress
- impaired physical and social functioning
- decreased QoL
- increased health-care utilization

QoL: quality of life.

1. Heiberg T, et al. *Ann Rheum Dis.* 2005;64(2):191-195; 2. Bas DB, et al. *Pain Manag*. 2016;6(3):265-284; 3. Walsh DA, McWilliams DF. *Nat Rev Rheumatol*. 2014;10:581–592.

RA-related Pain is Not Only a Consequence of Inflammation in the Joints

- Joint pain continues to be a significant problem, despite good disease control with antirheumatic drugs and biologics
- Accumulating data suggest that RA is a complex of:
  - peripheral inflammation
  - structural and neurochemical changes within the joint and sensory nervous system
  - altered central pain processing

Pain does not necessarily correlate with the degree of inflammation or the type of pharmacological management[1]

1. Bas DB, et al. *Pain Manag*. 2016;6(3):265-284.

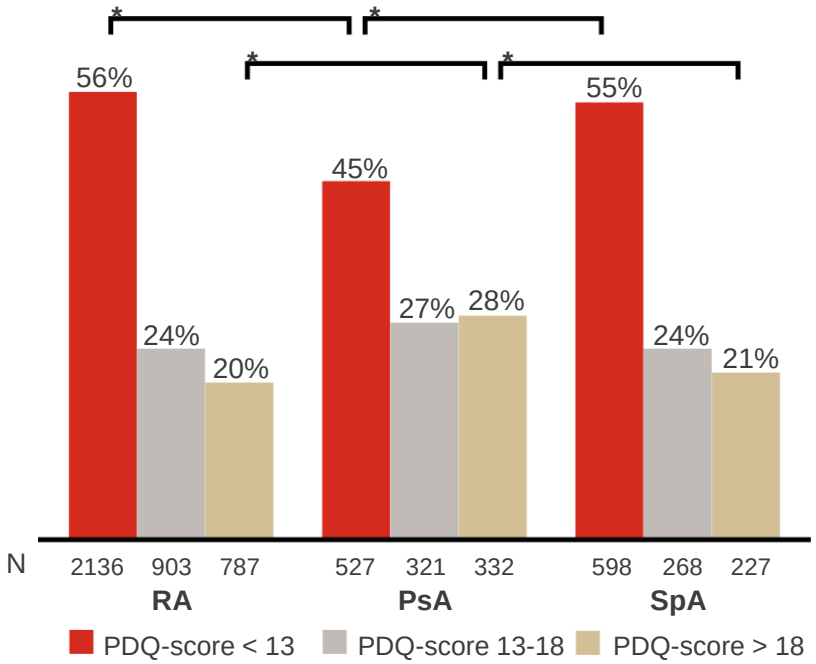
High Unmet Need For Arthritis Pain Relief Among RA Patients Despite Effective Treatment of Synovitis

- **34%** of patients were *very dissatisfied* with the level of control of their arthritis pain in the past 30 days
- **83%** of patients stated *increased pain in joints* as their main reason for making an unscheduled visit to their rheumatologists
- Patients were not satisfied with pain control even when disease activity was well controlled, despite being on biologics

N=755 RA patients and 501 rheumatologists: DESIGN EU Study

Taylor P, et al. *Ann Rheum Dis.* 2008;67(Suppl II):72.

Inflammatory Arthritis Patients Reported Clinically Significant Pain Despite Antirheumatic Therapy

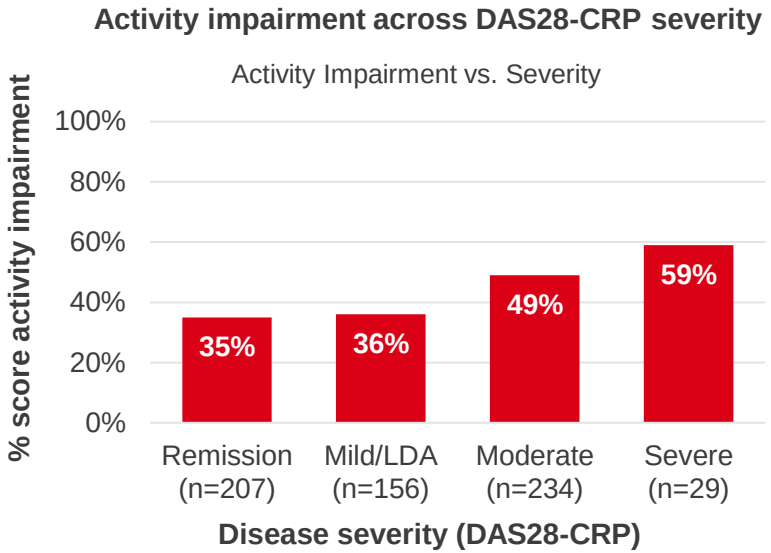


- PainDETECT questionnaire (PDQ) score was associated with composite disease activity and PROs but not with markers of inflammation (CRP and SJC)

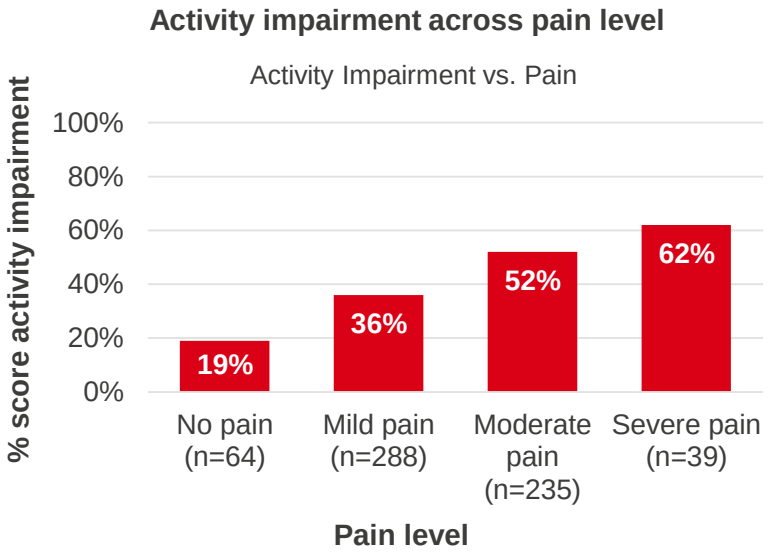
*P<0.001.
N=15,978; Cross-sectional survey including patients registered in DANBIO, >90% of adults treated with biologics/DMARDs due to rheumatic disease.
CRP: C-reactive protein; PDQ: painDETECT questionnaire is a patient-administered screening questionnaire originally developed to identify neuropathic pain; PROs: patient reported outcomes; SJC: swollen joint count.
Rifbjerg-Madsen S, et al. *PLoS One*. 2017;12(7):e0180014.

Pain and Disease Severity Have a Significant Impact on Work and Activity Impairment in RA

- With ⇧ **disease severity** patients experience greater activity impairment

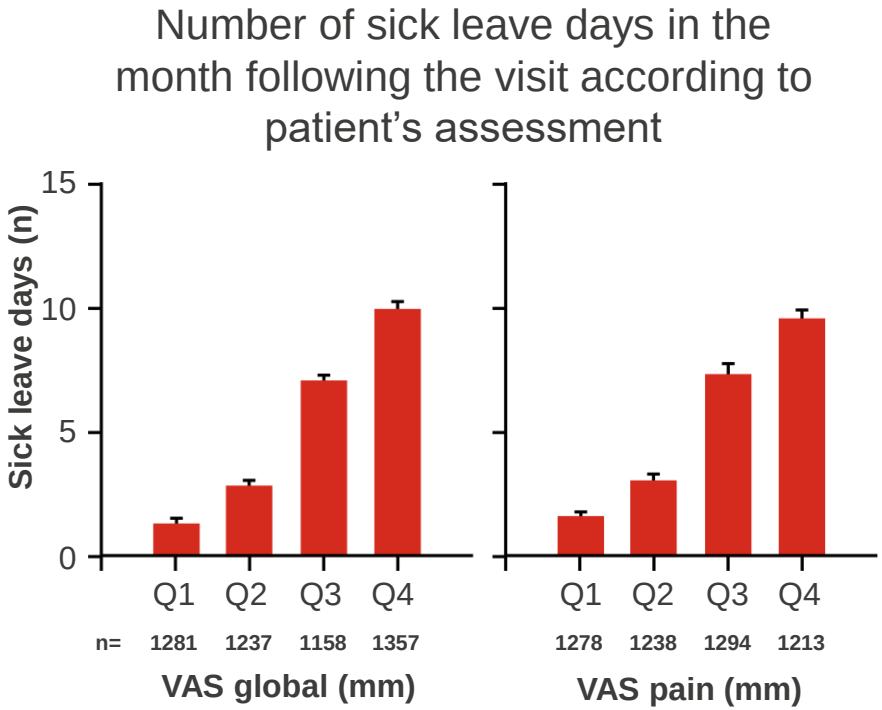


- With ⇧ **pain** patients experience greater activity impairment



CRP: C-reactive protein; DAS: disease activity score.
BRASS, a societal perspective observational RA dataset across 10 European countries; data on 646 patients included in analysis. Descriptive analysis used to explore associations based on data from the Work Productivity and Activity Impairment Questionnaire.
Galloway J, et al. *Ann Rheum Dis.* 2018;77:842.

Patient Assessment of Pain and Disease Activity are More Closely Correlated with Sick Leave than Physician Assessments



- Patient's assessed pain and disease activity, scored using a visual analog scale (VAS), had a greater relationship with subsequent sick leave in biologic treated patients with RA than physician assessed measures (SJC, ESR, CRP)
- Focusing on patient-reported outcomes/measures of pain and disease activity should be considered when targeting work loss or interventions to reduce it

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; VAS: visual analog scale.

Olofsson T, et al. *Arthritis Care Res (Hoboken).* 2018;70(11):1712-1716.

Pain Perception/Catastrophizing is Associated with a Reduced Chance of Achieving Remission in RA

- Pain perception/catastrophizing (includes negative cognitive and emotional response to pain) is not associated with clinical assessment or markers of inflammation (SJC, CRP)[1]
  - Strong association with PROs and disease activity measures[§] (P<0.001)

    N=209 initiated bDMARDs and followed for 12 months

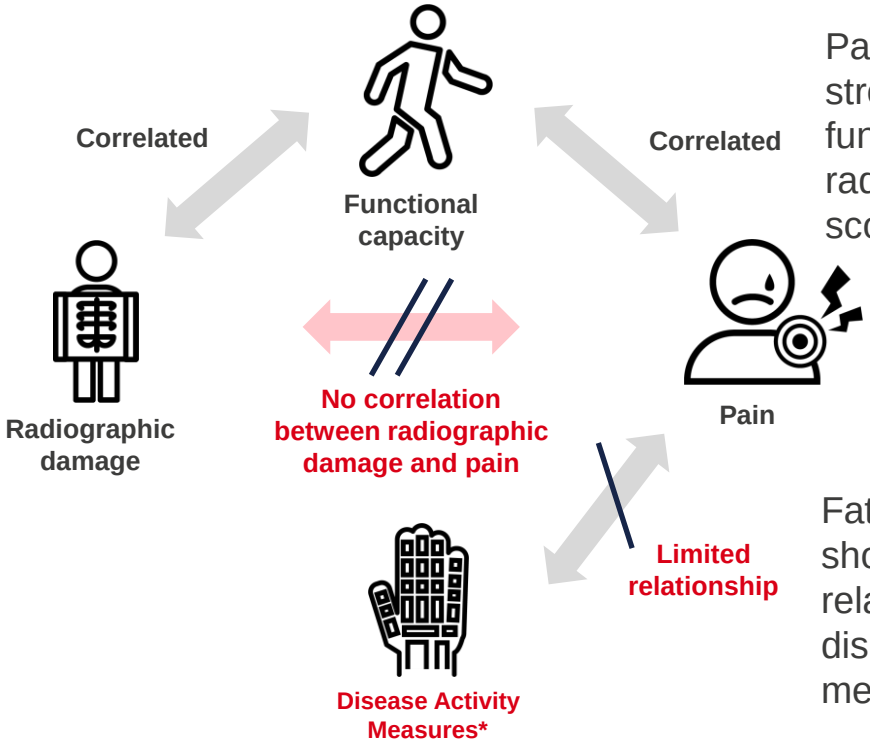
- **35%** of patients with RA did not consider their health improved despite achieving favourable clinical outcomes[^2]
  - Inadequate change in pain and fatigue (from baseline) was related to perception of no improvement

  N=210 Dutch remission induction cohort study* followed for 12 months

[§]Including DAS28, TJC, SJC, CRP, ultrasound; [^]Based on physician-assessed disease activity (SJC, TJC, CRP); *Dutch Rheumatoid Arthritis Monitoring remission induction cohort study.
CRP: C-reactive protein; PROs: patient reported outcomes; SJC: swollen joint count; TJC: tender joint count.
1. Hammer HB, et al. *Arthritis Care Res (Hoboken).* 2018;70(5):703-712; 2. Steunebrink LMM, et al. *Arthritis Care Res (Hoboken).* 2018;70(4):510-515.

Pain Does not Correlate with Damage, Disease Activity or Remission

Clinically significant pain may persist despite achieving DAS28 remission; **PGA, disability, fatigue, and sleep impairment** are strongly associated with pain severity[3]

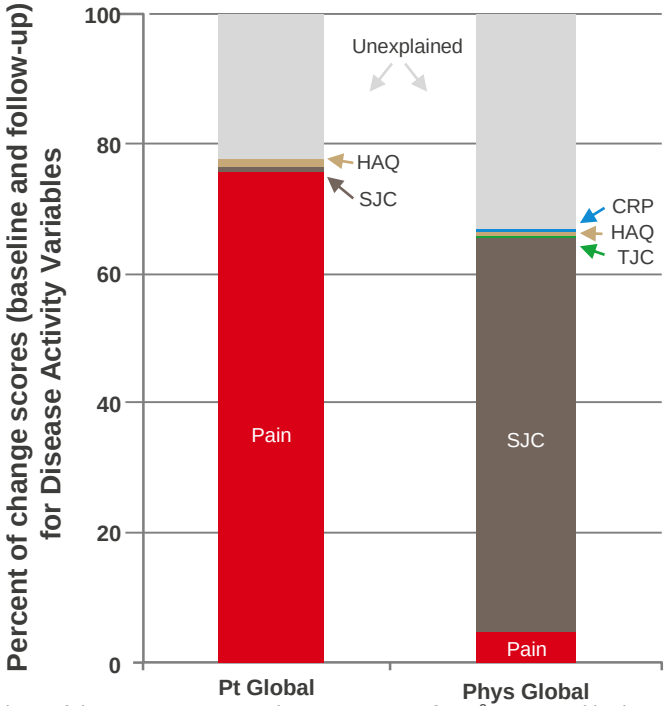


*tender joint count, swollen joint count, disease activity score, C-reactive protein, physicians global assessment.

DAS: disease activity score; PGA: patient global assessment.

1. Sokka T, et al. *Arthritis Rheum.* 2000;43(2):386-389; 2. Ferreira RJO, et al. *Arthritis Care Res (Hoboken).* 2018;70(3):369-378; 3. Lee YC, et al. *Arthritis Res Ther.* 2011;13:R83.

Pain and Swollen Joint Count Account for the Greatest Discrepancies Between Perceptions of RA Disease Activity



Pain is the main determinant for the patient global assessment (75.6%)

- Pain scores correlated very highly with PtGA (r=0.86, P<0.001); SJC correlated with PhGA (r=0.77, P<0.001)

Increased pain led to a discrepancy based on worse patient perceptions

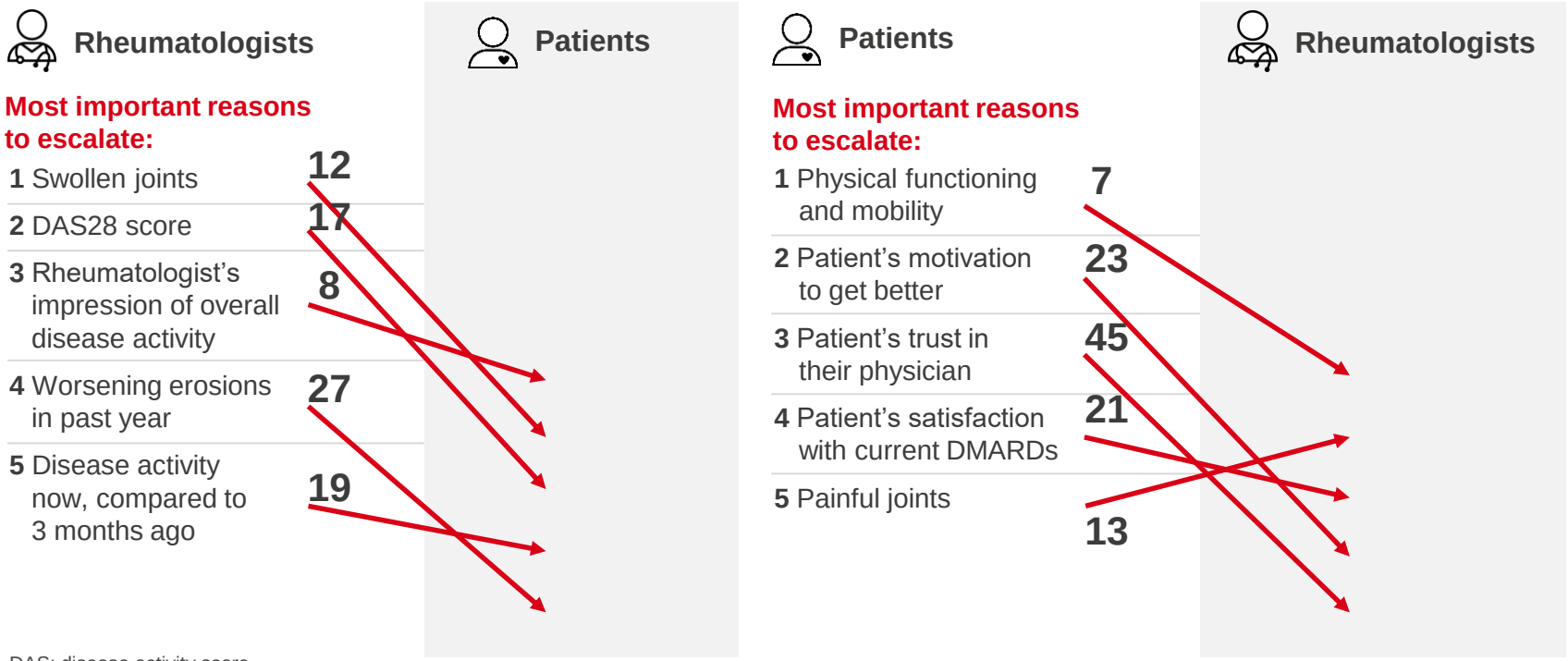
Values of the components are the percentage of ΔR^2 computed in the multivariate regression model. Values for the patient global assessment are 22.6% unexplained, 0% CRP, 1.3% HAQ, 0% TJC, 0.5% SJC, and 75.6% pain. Values for the physician global assessment are 33.3% unexplained, 0.4% CRP, 0.6% HAQ, 0.3% tender joint count, 60.9% swollen joint count, and 4.5% pain.

PtGA: patient global assessment; PhGA: physician global assessment; SJC: swollen joint count.

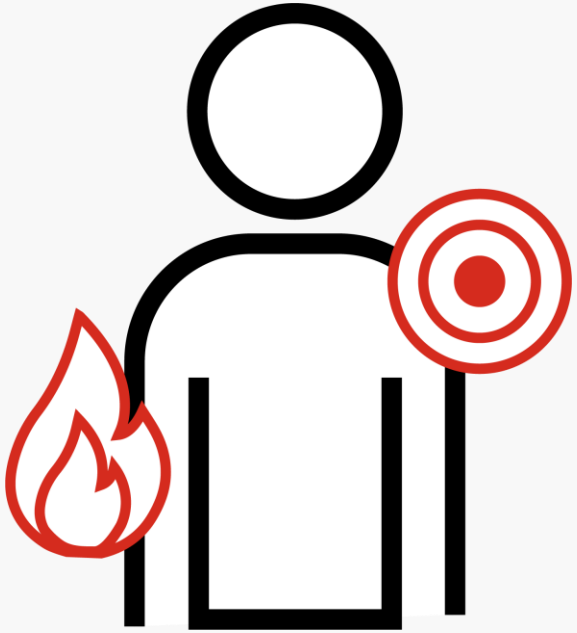
Studenic P, et al. *Arthritis Rheum*. 2012;64(9):2814-23.

Perspectives on RA Management

Factors influencing the decision to escalate care differ between rheumatologists and patients



DAS: disease activity score.
Maximum Difference Scaling survey administered to 106 rheumatologists and 213 patients with RA.
Van Hulst LTC, et al. *Arthritis Care Res*. 2011;63:1407-1414.



Relationship Between Inflammation and Pain

How Do You Define Pain and Inflammation?

Pain

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[1]
- *Latin: Poena (meaning a punishment, penalty, retribution; also torment, hardship, suffering)*[2]

Inflammation

- A local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, and pain[3]
- Serves as a mechanism initiating the elimination of noxious agents and of damaged tissue[3]
- *Latin: Inflammationem (meaning a kindling, a setting on fire)*[4]

1. www.iasp-pain.org; 2. https://www.etymonline.com/word/pain; 3. https://www.merriam-webster.com/dictionary/inflammation; 4. https://www.etymonline.com/word/inflammation.

Acute vs. Persistent/Chronic Pain

Acute pain

- Typically results from tissue damage
- Mitigated when the injury/condition has resolved and/or the tissue has healed

Persistent pain

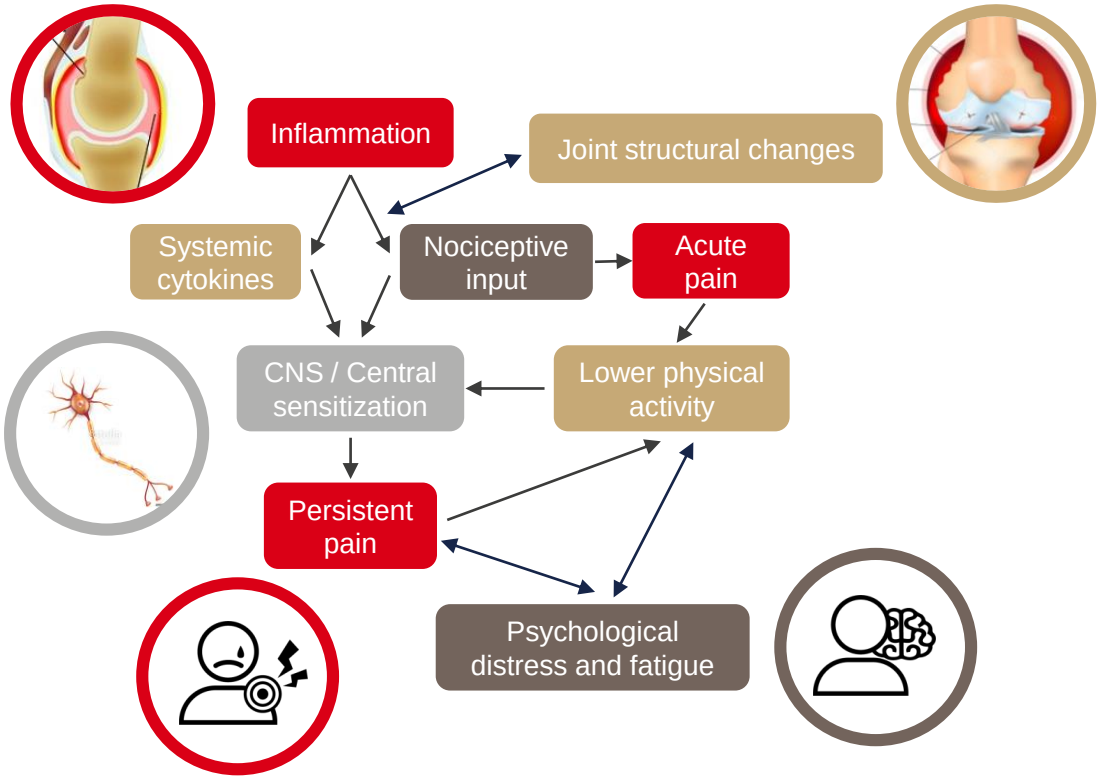
- "Chronic pain is not simply acute pain that has lasted longer; it is more likely to be influenced by input from the central nervous system."[1]
- Chronic pain defined as ≥3 month duration of symptoms
  - **Nociceptive pain:** linked to ongoing tissue damage and/or inflammation
  - **Neuropathic pain:** damage or injury to primary afferent and/or CNS neurons within the pain pathways
  - **Nociplastic pain:** occurs without apparent ongoing tissue or nervous system injury, and results from a remodelling of the nociceptive pathways

International Association for the Study of Pain.

1. Phillips K, Clauw DJ. *Arthritis Rheum*. 2013;65(2):291-302.

Pain in RA is Driven by Multiple Mechanisms

Pain results from interplay between joint pathology and processing of pain signals by peripheral nerves, spinal and supraspinal pain pathways



Walsh DA, McWilliams DF. *Nat Rev Rheumatol.* 2014;10:581-592; McWilliams DF, Walsh DA. *Clin Exp Rheumatol.* 2017;35(Suppl. 107):S94-S101; Boyden SD et al. *Curr Rheumatol Rep.* 2016;18:30.

Factors Impacting Pain Perception

Sleep disturbances affect between **38-86%** of individuals with RA

- May contribute to enhanced pain sensitivity

Depression affects **5-41%** of individuals with RA

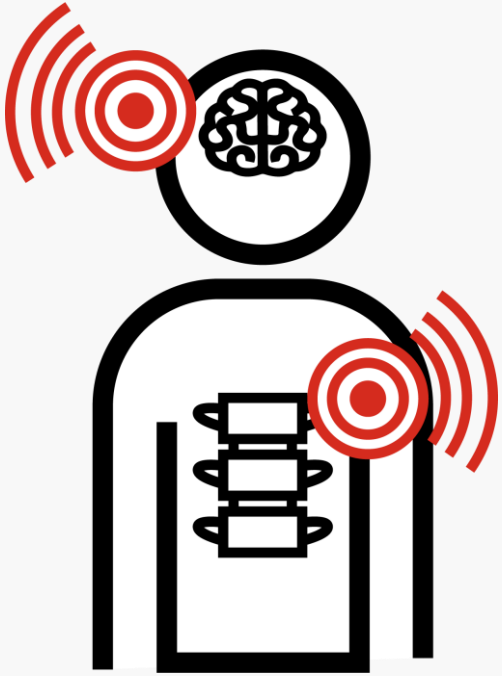
- Associated with higher pain scores
- Depressive symptoms predict slower rates of improvement in patient-reported pain and TJC

Symptoms of anxiety affect **23-46%** of individuals with RA

- Anxiety associated with higher pain scores

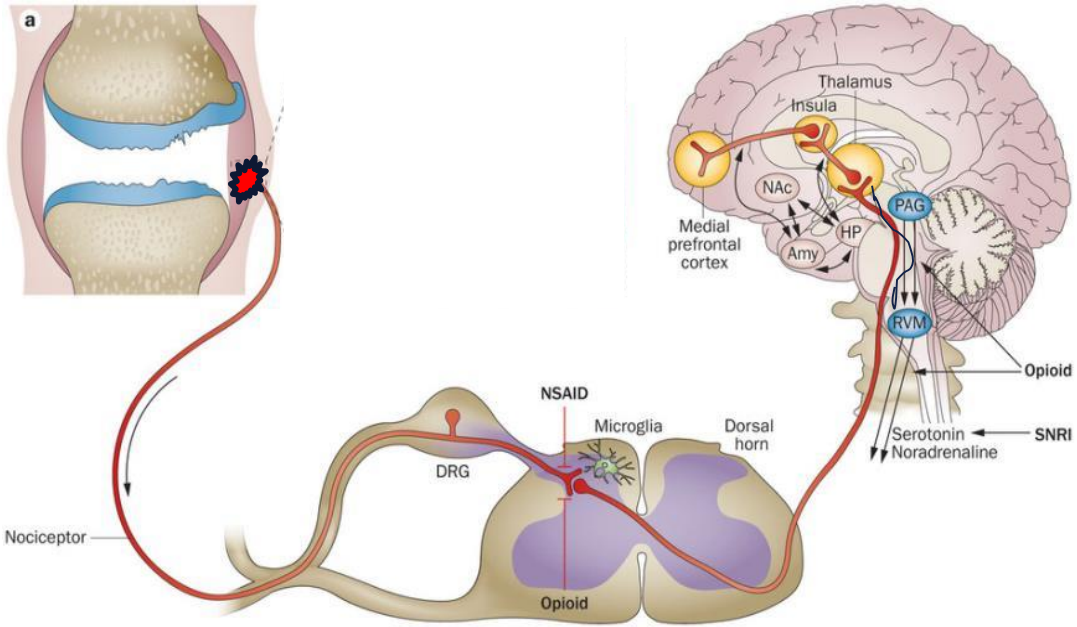
TJC: tender joint count.

Boyden SD, et al. *Curr Rheumatol Rep.* 2016;18:30.



Neurobiology of Pain Signalling

Pain Signals are Detected by Nociceptors in the Periphery and Transmitted to the Spinal Cord and Brain

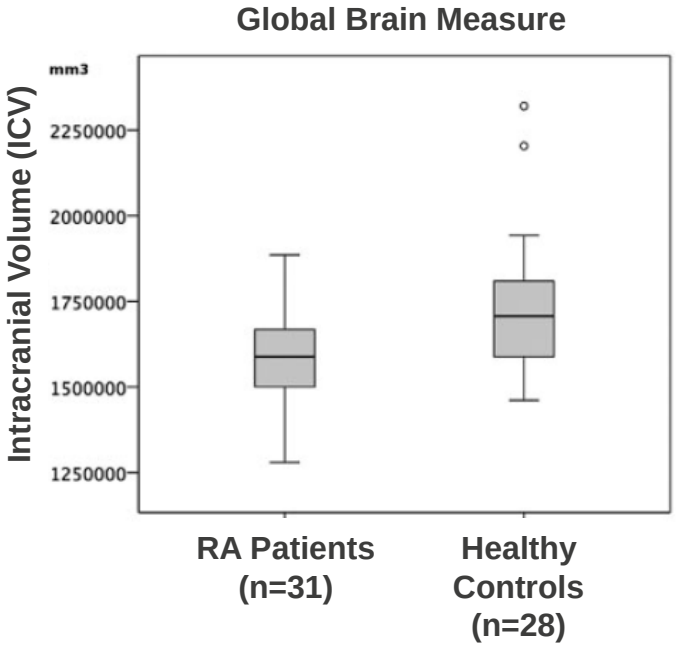


- Pain processing by the CNS can affect:
  - pain reporting
  - sensitivity
  - descriptive quality
  - intensity/severity
- All types of pain can be influenced by central factors

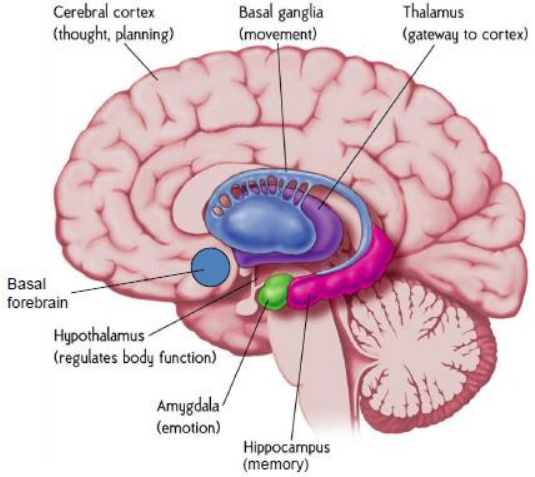
Amy: amygdala; CNS: central nervous system; DRG: dorsal root ganglion; GPCR: G-protein-coupled receptor; HP: hippocampus; NAc: nucleus accumbens; NGF: nerve growth factor; PAG: peri-aqueductal grey; PG: prostaglandin; RVM: rostral ventromedial medulla; SNRI: serotonin–noradrenaline reuptake inhibitor.

Malfait AM, Schnitzer TJ. *Nat Rev Rheumatol*. 2013;9(11):654-64; McWilliams DF, Walsh DA. *Clin Exp Rheumatol.* 2017;35(Suppl. 107):S94-S101.

RA is Associated with Changes in Brain Volume and Pain Processing



Volume changes in the subcortical grey matter (basal ganglia) may alter motor control or prolong pain processing, modulating pain processing and behaviour response to adverse stimuli



Data are shown as box plots. Each box represents the 25th and 75th percentiles (interquartile range [IQR]). Lines inside the boxes represent the median. Whiskers represent nonoutlier maxima and minima. Circles indicate outliers 3 IQR above the 75th percentile.

Wartolowska K, et al. *Arthritis Rheum.* 2012;64(2):371-379.

RA is a Mixed Pain State Based on Multiple Mechanisms

Neuroimaging and functional connectivity MRI data provide evidence that symptoms may be related to aberrant brain functional connectivity rather than classic inflammatory mechanisms

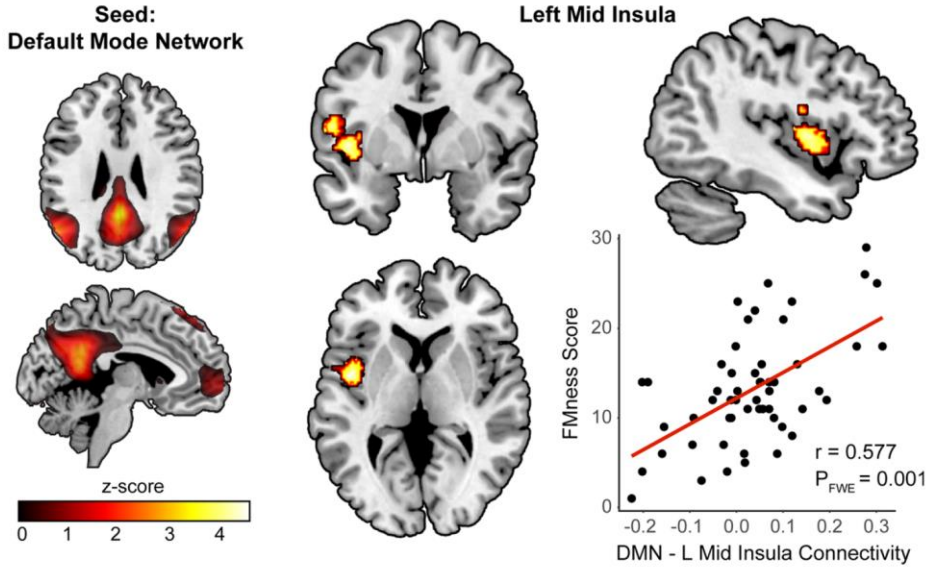
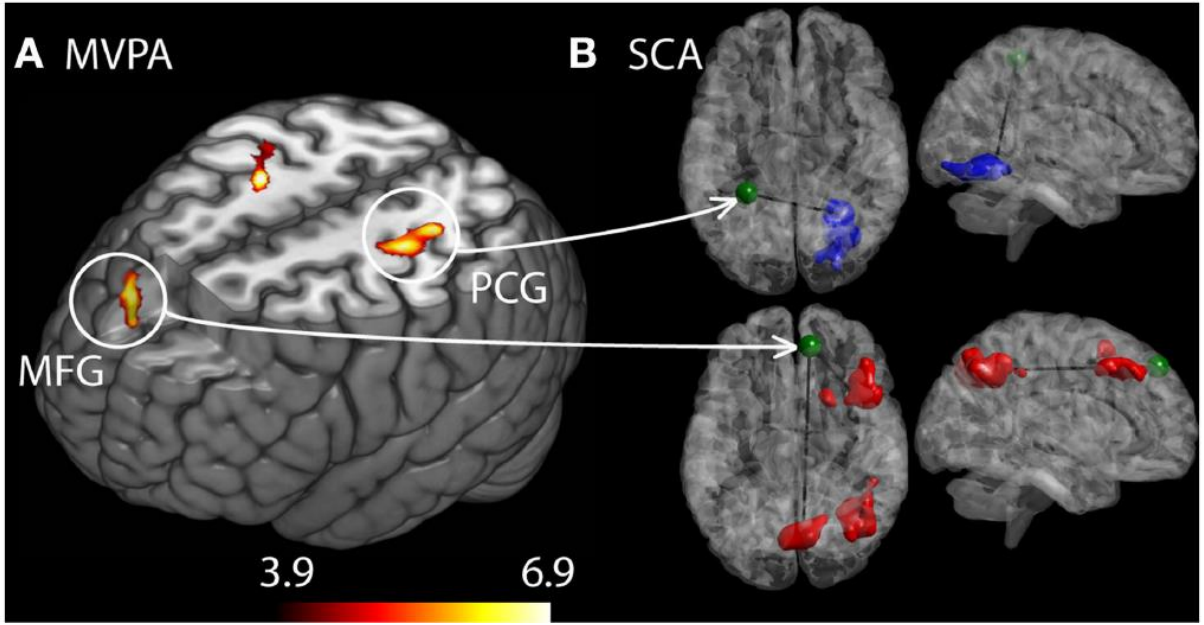


Figure 1. Increased brain connectivity between the default mode network (DMN) and left mid/posterior insula in rheumatoid arthritis patients is associated with fibromyalgianess (FMness). Scatterplots show positive correlations for interindividual differences in brain connectivity (Fisher-transformed r values) with the total FMness score. FWE = family-wise error.

Basu N, et al. *Arthritis Rheumatol*. 2018;70(7):1000-1007.

Increased Connectivity Between Brain Regions in RA Patients

Patients with RA also show increased sensitivity to supra-threshold pressure pain in affected joints and report a higher global pain intensity



RA identified increased functional connectivity
(differences in brain connectivity profile between RA and healthy cohorts indexed at a voxel level using multivariate pattern analysis (MVPA))

MFG: middle frontal gyrus; PCG: post central gyrus; SCA: seed-based correlation analysis.

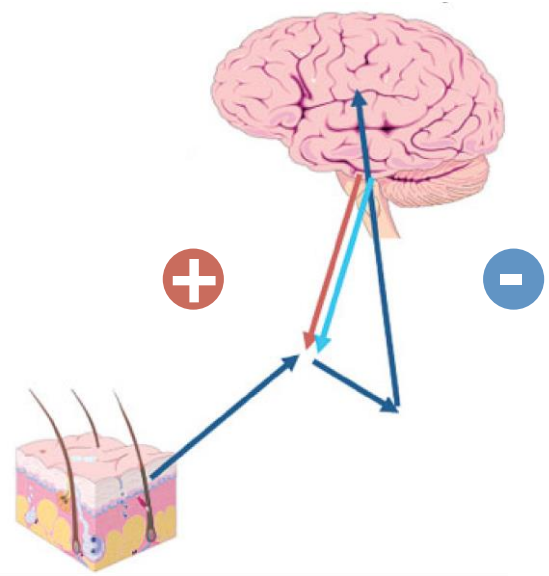
Flodin P, et al. *Front Hum Neurosci*. 2016;15(10):107.

Neurotransmitter Levels Influence Pain and Sensory Processing

Facilitation

Increase in:

- Substance P
- Glutamate and excitatory amino acid
- Serotonin
- Nerve growth factor



Inhibition

- Descending anti-nociceptive pathways
- Decrease in:
  - norepinephrine-serotonin, dopamine
  - γ-aminobutyric acid
- Cannabinoids

A person's "set point" for pain is determined by a variety of factors, neurotransmitters which facilitate pain transmission (turn up the gain), and neurotransmitters which inhibit pain transmission.

Phillips K, Clauw DJ. *Arthritis Rheum*. 2013;65(2):291-302.

Pain in RA Results from Interplay Between Joint Pathology and Pain Signals

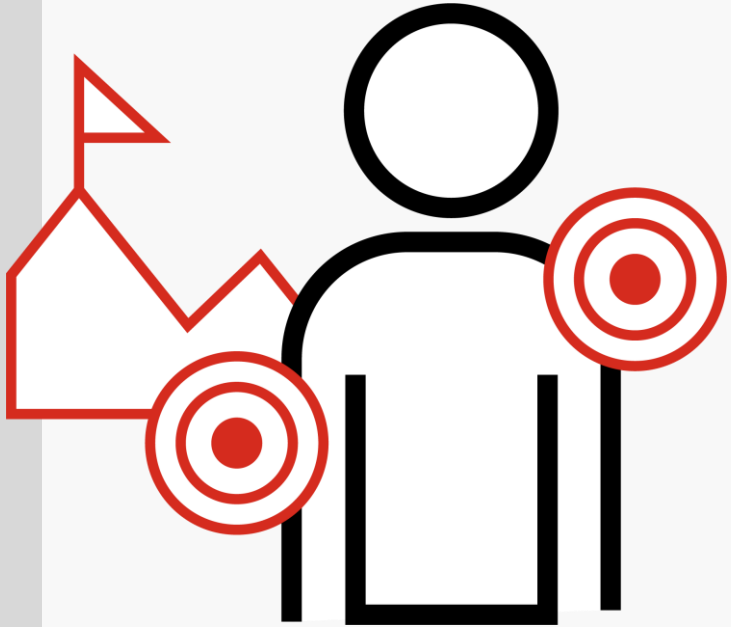
Pathological Mechanisms Contributing to Pain

RA pain has many facets:

- constant or intermittent
- localized or widespread
- often associated with psychological distress and fatigue

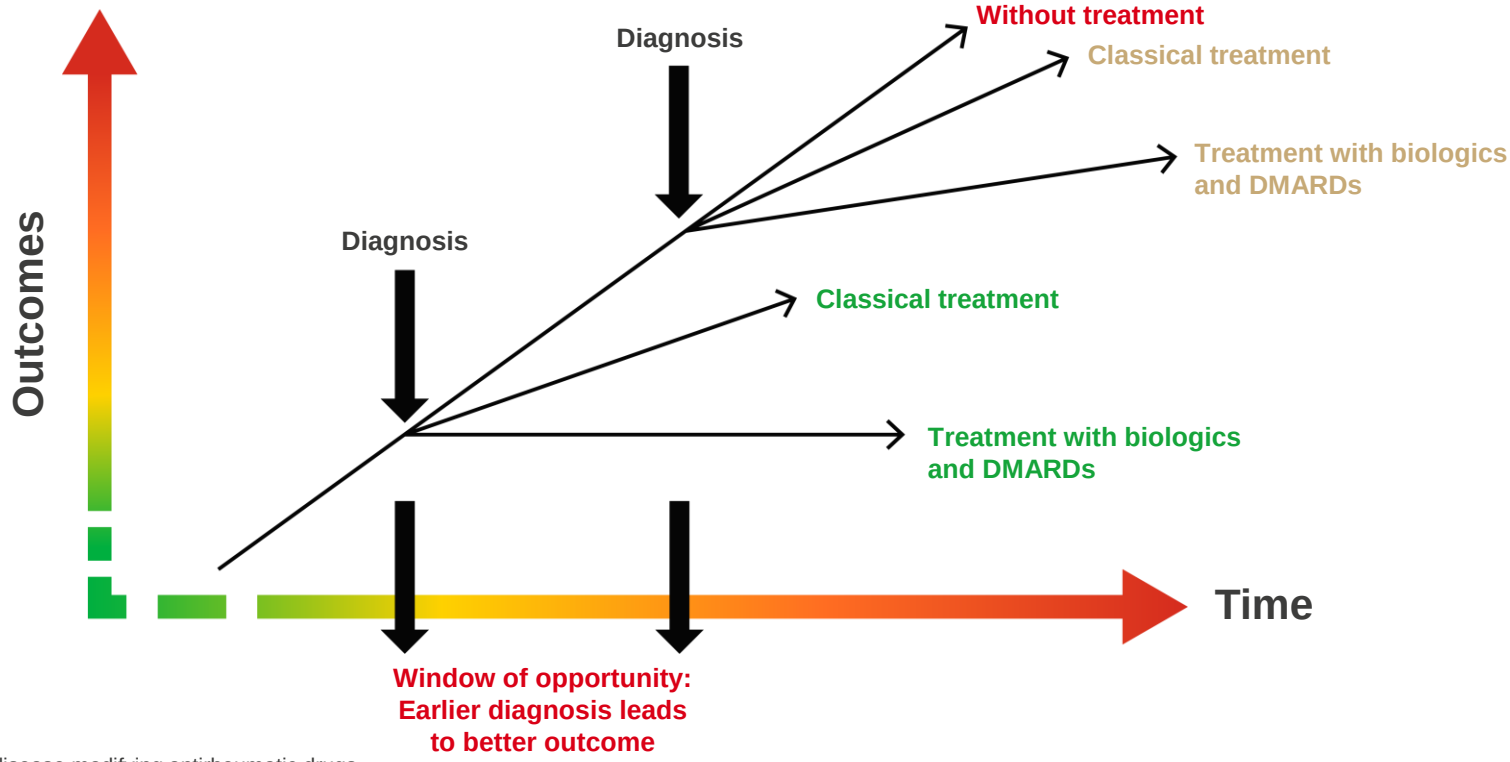
ACPA: anti-citrullinated protein antibody; CRP: C-reactive protein; RF: rheumatoid factor.

Walsh DA, McWilliam DF. *Nat Rev Rheumatol.* 2014;10:581-592.



Pain Management in RA: An Ongoing Challenge

Earlier Diagnosis and Effective Treatment Leads to Improved Outcomes



DMARDS: disease modifying antirheumatic drugs.

Monti S, et al. *RMD Open.* 2015;1:e000057.

Treatment of RA Needs to Focus Beyond the Joint

Articular disease

- Joint inflammation
- Cartilage degradation
- Bone erosion
- Loss of joint function

Psychosocial aspects

- Impaired HRQoL
- Fatigue
- Depression
- Cognitive dysfunction
- Reduced work performance
- Work disability

Comorbidities

- Cardiovascular disease
- Osteoporosis
- Lung disease
- Infection
- Malignancy

HRQoL: health-related quality of life.

Cutolo M, et al. *Sem Arthritis Rheum*. 2014;43(4):479-488.

Treatment and Management of Pain in RA patients

Multimodal management of RA pain includes pharmacological, psychological and exercise-based interventions.

Pharmacological

- Directly acting analgesic agents (e.g. NSAIDs, acetaminophen, opioids)
- Drugs that suppress inflammation (eg. coticosteroids) and reduce joint damage (e.g. csDMARDs, tsDMARDs, bDMARDs*)

Psychological

- Cognitive behavioral therapy (CBT)
- Mindfulness training
- Sleep interventions

Exercise-based Interventions

- Aerobic exercise
- Strength and resistance training

*conventional, targeted synthetic, target syntheitic, biologic biologic.

Walsh DA, McWilliams DF. *Nat Rev Rheumatol.* 2014;10:581-592; Geenen R, et al. *Ann Rheum Dis.* 2018;77:797-807.

Pharmacological Analgesics Offer Some Efficacy in RA

Analgesic agent	Summary of evidence in RA clinical trials
Acetaminophen	12 RCTs and one observational study in RA showed weak evidence of benefit over placebo and an additive benefit when used together with NSAIDs
NSAIDs	Weak evidence shows that physicians and patients prefer ibuprofen over acetaminophen; COX-2-selective and nonselective inhibitors seem to be equally efficacious in RA
Opioids	11 studies in RA, where four could be pooled to show opioids led to improved pain relief over placebo, but with an increased risk of AEs; high likelihood of bias
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
Nefopam	Two trials with risk of bias showed benefit of nefopam over placebo, but with associated AEs
Capsaicin	One trial found topical capsaicin was beneficial over placebo, but with some AEs

*Agents listed may not be licensed for use for RA pain in some countries.
AE: adverse event; COX: cyclooxygenase; RCT: randomized controlled trial.
Walsh DA, McWilliams DF. *Nat Rev Rheumatol.* 2014;10:581-592.

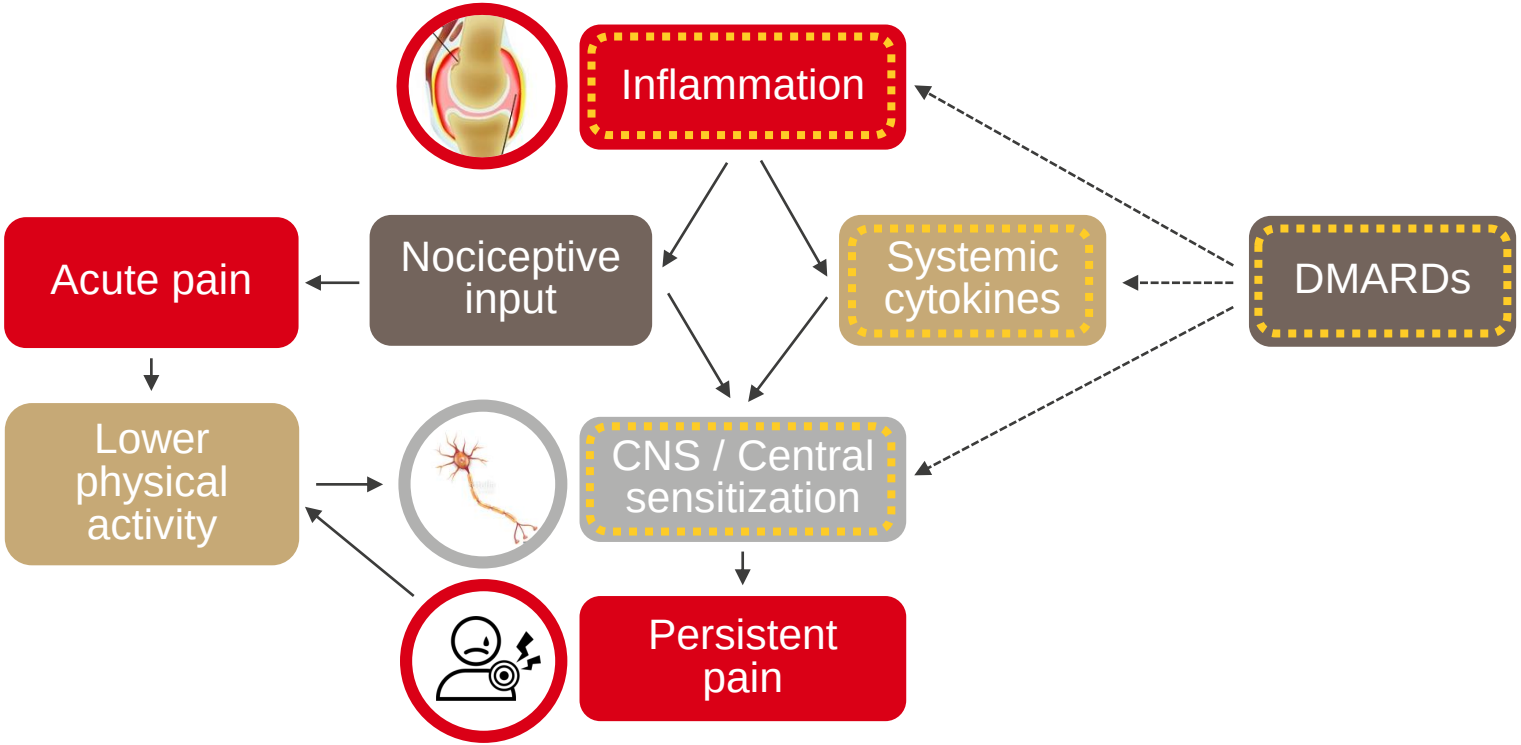
Control of Inflammation Does Not Translate Directly into Remission

Treatment should address 2 complementary domains:

- Control of inflammation with DMARDs → ↓ CRP and SJC
- Effect of disease* → improve patient global assessment using adjunctive therapies

*Includes persistent pain, fatigue, functional limitations, and psychological factors all contribute to elevated patient global assessment values in patients with controlled inflammation.
CRP: C-reactive protein; DMARDs: disease-modifying antirheumatic drugs; SJC: swollen joint count.
Dobkin PL, Boire G. *J Rheumatol.* 2018;45(5):585-587.

Possible Effects of Current Disease Modifying Agents on Improving RA Inflammation and Pain



Williams DF, Walsh DA. *Clin Exp Rheumatol.* 2017;35(Suppl. 107):S94-S101.

Role of Adjunctive Therapies in Pain and Remission

Existing adjunctive psychological interventions may lead to increased rates of sustained remission and improved long-term QoL

bDMARDs: biologic disease-modifying antirheumatic drugs; QoL: quality of life.

Dobkin PL, Boire G. *J Rheumatol.* 2018;45(5):585-587.

Psychological Interventions for Coping with Pain in RA

Cognitive-behavioral therapy (CBT)

- Focuses on changing unhelpful beliefs, encouraging productive coping strategies and facilitating behavioral change
- Improves disability and has small effects on reported pain severity

Mindfulness Training

- Aims to prevent adverse consequences without necessarily changing beliefs

Comparison of Strategies

- CBT better than mindfulness training for reported pain-control
- Mindfulness training more helpful than CBT for pain-coping and catastrophizing, especially in people with a history of depression

Mindfulness and CBT could be suited to different patient groups based on history of depression

CBT: cognitive behavioral therapy.

Walsh DA, McWilliams DF. *Nat Rev Rheumatol.* 2014;10:581-592.

Pain Management Strategies

Focusing patient attention is worth the conversation

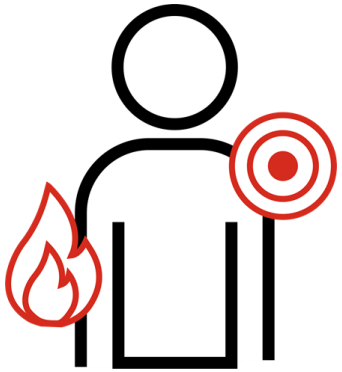
- Psychological management through mindfulness training helps develop coping strategies and supports pain reduction
- Sleep disturbances - even a 1 hour disruption affects pain levels
- Physical activity modifies central pain processing, reducing pain intensity

Several studies on ‘attention shifting’ for the acute pain experience have shown utility in helping patients not think about pain.

Walsh DA, McWilliams DF. *Nat Rev Rheumatol*. 2014;10:581–592.

Summary

- People with RA commonly highlight pain as their most significant issue
- Control of inflammation with DMARDs combined with adjunctive therapies (analgesics, psychologic interventions) may increase rates of sustained remission and improve long-term QoL
- Despite good control of inflammation, pain often remains problematic
  - Pain may persists despite remission
- Pain results from interplay between joint pathology and processing of pain signals; which is impacted by psychological distress and fatigue, joint damage, and comorbidities



DMARDs: disease-modifying antirheumatic drugs; QoL: quality of life.