

## **Should patients with rheumatic diseases take pain medication in order to engage in exercise?**

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Pain is the main symptom in most rheumatic and musculoskeletal diseases (RMDs). It has debilitating effects in terms of mobility, physical function, sleep, mood, fatigue and overall quality of life. This is why pain and its associates are some of the predominant outcomes evaluated regularly in response to pharmaceutical or any other interventions involved in the management of RMDs.

The source of pain in RMDs seems to be mainly inflammation and/or damage of affected joints, while changes in central nervous system processing contribute significantly to its chronicity [reviewed comprehensively by Salaffi and colleagues (1)]. In line with this, the implementation of treat-to target approaches seem to effectively reduce pain scores (2), most likely by suppressing inflammation in the short term and inhibiting joint damage in the longer term. In general, patients treated with disease modifying anti-rheumatic drugs (DMARDs) experience alleviation in pain in the short term, with follow-up long-term studies suggesting that their effects on pain are much less clear (3). Joint replacement, on the other hand, can also reduce pain, supporting the notion that treating structural and functional joint disease-induced alterations can also significantly reduce pain in RMDs (4).

It is alarming that 75% of European and 82% of US patients with rheumatoid arthritis report moderate-to-severe pain in the last two months (5), irrespective of treatment or disease duration. Despite a significant amount of research in this area, pain still remains a challenging area of investigation, without a clear understanding of how it can be drastically and effectively managed. The lack of significant progress on how best to treat this important outcome is denoted in recent efforts, such as the 2018 European League Against Rheumatism (EULAR) recommendations on pain management in RMDs (6).

Exercise, a part of the general spectrum of physical activity, is planned and structured physical activity done with the intention to improve health outcomes. Exercise improves health outcomes in a dose-dependent manner; thus, higher exercise intensities will have better health effects compared to lower exercise intensities. However, the concept of “high-intensity exercise” is perceived by many patients with RMDs as something they should avoid, as they fear that it may exacerbate disease symptoms and joint damage (7), a view that RMD professionals lack the confidence to appropriately address in their consultations with RMD patients (8). This is despite a great number of research studies demonstrating that exercise (even high-intensity), not only is safe, but can also ameliorate disease-related symptoms [such as pain and fatigue (9, 10)] and systemic aspects of RMDs [such as cardiovascular risk and rheumatoid cachexia (9, 11, 12)]. However, it is important to note that patients with RMDs report pain as one of the main barriers that stops them from engaging in exercise (7). This may be because patients fear that exercise may induce further joint damage, particularly when the exercises are painful; however, painful exercises may have the potential to reconceptualize pain related fear and as a result, help these patients to engage in such activities (13).

Blocking tumor necrosis factor alpha (TNF $\alpha$ ) via anti-TNF $\alpha$  medication seems to result in an increased engagement in physical activity in rheumatic diseases (14); if this is because of reductions in pain and/or symptom alleviation, still remains to be investigated. Given the multiple benefits of physical activity and exercise in RMDs with pain being an important barrier for lack of engagement, the question arises as to whether patients should increase their

intake of pain relief medication in order to engage in exercise. In the absence of any robust studies in this field of investigation, the short answer is no, and this is for the following reasons:

*Exercise may potentially reduce pain as an intervention in itself:* Exercise *per se* is an intervention that seems to have beneficial effects in alleviating pain in people with rheumatic disease. A 2009 meta-analysis in the Cochrane Library has evaluated the effects of aerobic and strength training on pain outcomes in rheumatoid arthritis patients (9) and revealed that pain can be reduced by an absolute 6% after 12 weeks of exercising; whether this represents a clinically significant reduction is uncertain. In general, exercise can induce analgesia via activating central inhibitory pathways. Serotonin, opioids and N-methyl-D-aspartate (NMDA) related mechanisms that act on the rostral ventromedial medulla [a group of neurons located in the middle line of the medulla oblongata (in the brainstem)] can be induced by exercising (15) with pain-reducing effects in exercising adults. Although this establishes biological plausibility, a recent 2017 umbrella Cochrane review (including 21 reviews with 381 included studies and 37,143 patients with chronic pain) suggested an overall favourable effect of exercise in reducing pain severity, but this is small to moderate and not consistently observed in all studies (16). In contrast, a 2017 meta-analysis from a EULAR Taskforce conducted specifically in people with RMDs suggested that exercise associated with more uniformly positive effects on pain management (6), which is a positive finding and specific to RMDs. As such, because pain has great within-person variability, not only within a day but also between days (17), perhaps engaging people with RMDs in exercise at times when pain is experienced less, should be considered as an option prior to giving pain-relief medication in order to engage in exercise.

*Increasing pain relief medication may have adverse effects:* Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most commonly prescribed drugs for managing pain in RMDs but their use can be unfortunately associated with gastrointestinal side-effects (18), increased cardiovascular risk and premature mortality (19). Even in healthy athletes, who tend to use NSAIDs to alleviate exercise-induced pain, a small relevant study demonstrated that administration of ibuprofen aggravates the exercise-induced small intestinal injury (20) while NSAIDs seem ineffective in alleviating pain from muscle damage (21). The latter, is a very frequent phenomenon caused by high-intensity exercise but is actually necessary for beneficial physiological adaptations (e.g. muscle mass increase) that can improve balance, cachexia (loss of muscle mass), functional disability and other outcomes in people with RMDs. Significantly fewer side-effects are seen with the use of acetaminophen (paracetamol) vs. NSAIDs in athletes (22). However, in patients with RMDs that are already subjected to polypharmacy (23), this may not be an absolutely safe approach, as increases in acetaminophen use could potentially result in further side effects. Even in healthy adults, the usual recommended dose of 4 g/d of acetaminophen may associate with elevated aminotransferases (24). The most recent EULAR recommendations for managing pain in rheumatic conditions suggest usage of paracetamol, topical NSAIDs and capsaicin as first-line treatments, with the potential side-effects of NSAIDs to be taken into account when prescribing such agents (6).

*Drug treatment alone does not seem to be an ideal solution for pain care:* Compared to treatment advances in other areas of rheumatic diseases (e.g. inflammation control), pain management in RMDs is still in its infancy. Any enthusiasm around the usage of pain relief medications to facilitate and enable engagement in exercise should be tempered by the absence of relevant studies establishing either efficacy or safety in this particular context. Given that factors other than inflammation and joint damage, such as depression, obesity, demographic and social factors (1, 5) associate with pain in RMDs, it is likely that (any) medication on its

own is insufficient for pain management in people with RMDs. Educational interventions, exercise, orthotics, weight management, psychological interventions and other multidisciplinary approaches have been successfully used for the management of pain in RMDs (6), however, their utility in the context of exercise has not been assessed.

Pain is the cardinal symptom in most RMDs, has many dimensions and is one of the main barriers to exercise. Exercise, in turn, has multiple indisputable health benefits in this population, including reduced pain in RMDs. The use of pain medication alone as a means to enable people with RMDs to exercise cannot be supported at this stage, due to lack of evidence for efficacy and safety in this particular context. It is likely that a more comprehensive lifestyle approach alongside a reconceptualization of pain acting as a barrier to engage in such lifestyles are both necessary. Both the individual components (including pain medication) and the overall lifestyle approach need to be prospectively evaluated in studies designed specifically for the purpose.

### **Conflicts of Interest**

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## References

1. Salaffi F, Giacobazzi G, Di Carlo M. Chronic Pain in Inflammatory Arthritis: Mechanisms, Metrology, and Emerging Targets-A Focus on the JAK-STAT Pathway. *Pain Res Manag.* 2018;2018:8564215.
2. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Ewals JA, Han KH, Hazes JM, et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. *Arthritis Rheum.* 2009;61(1):4-12.
3. McWilliams DF, Walsh DA. Factors predicting pain and early discontinuation of tumour necrosis factor-alpha-inhibitors in people with rheumatoid arthritis: results from the British society for rheumatology biologics register. *BMC Musculoskelet Disord.* 2016;17:337.
4. Judge A, Arden NK, Cooper C, Kassim Javaid M, Carr AJ, Field RE, et al. Predictors of outcomes of total knee replacement surgery. *Rheumatology (Oxford).* 2012;51(10):1804-13.
5. Taylor P, Manger B, Alvaro-Gracia J, Johnstone R, Gomez-Reino J, Eberhardt E, et al. Patient perceptions concerning pain management in the treatment of rheumatoid arthritis. *J Int Med Res.* 2010;38(4):1213-24.
6. Geenen R, Overman CL, Christensen R, Asenlof P, Capela S, Huisinga KL, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. *Ann Rheum Dis.* 2018;77(6):797-807.
7. Veldhuijzen van Zanten JJ, Rouse PC, Hale ED, Ntoumanis N, Metsios GS, Duda JL, et al. Perceived Barriers, Facilitators and Benefits for Regular Physical Activity and Exercise in Patients with Rheumatoid Arthritis: A Review of the Literature. *Sports Med.* 2015;45(10):1401-12.
8. Iversen MD, Scanlon L, Frits M, Shadick NA, Sharby N. Perceptions of physical activity engagement among adults with rheumatoid arthritis and rheumatologists. *Int J Clin Rheumtol.* 2015;10(2):67-77.
9. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst Rev.* 2009(4):CD006853.
10. Rongen-van Dartel SA, Repping-Wuts H, Flendrie M, Bleijenberg G, Metsios GS, van den Hout WB, et al. Effect of Aerobic Exercise Training on Fatigue in Rheumatoid Arthritis: A Meta-Analysis. *Arthritis Care Res (Hoboken).* 2015;67(8):1054-62.
11. Metsios GS, Kitas GD. Physical activity, exercise and rheumatoid arthritis: Effectiveness, mechanisms and implementation. *Best Pract Res Clin Rheumatol.* 2018;32(5):669-82.
12. Summers GD, Metsios GS, Stavropoulos-Kalinoglou A, Kitas GD. Rheumatoid cachexia and cardiovascular disease. *Nat Rev Rheumatol.* 2010;6(8):445-51.
13. Smith BE, Hendrick P, Bateman M, Holden S, Littlewood C, Smith TO, et al. Musculoskeletal pain and exercise-challenging existing paradigms and introducing new. *Br J Sports Med.* 2019;53(14):907-12.
14. Metsios GS, Stavropoulos-Kalinoglou A, Douglas KM, Koutedakis Y, Nevill AM, Panoulas VF, et al. Blockade of tumour necrosis factor-alpha in rheumatoid arthritis: effects on components of rheumatoid cachexia. *Rheumatology (Oxford).* 2007;46(12):1824-7.
15. Lima LV, Abner TSS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. *J Physiol.* 2017;595(13):4141-50.
16. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2017;1:CD011279.

17. Schneider S, Junghaenel DU, Keefe FJ, Schwartz JE, Stone AA, Broderick JE. Individual differences in the day-to-day variability of pain, fatigue, and well-being in patients with rheumatic disease: associations with psychological variables. *Pain*. 2012;153(4):813-22.
18. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1995;123(4):241-9.
19. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340(24):1888-99.
20. Van Wijck K, Lenaerts K, Van Bijnen AA, Boonen B, Van Loon LJ, Dejong CH, et al. Aggravation of exercise-induced intestinal injury by Ibuprofen in athletes. *Med Sci Sports Exerc*. 2012;44(12):2257-62.
21. Donnelly AE, Maughan RJ, Whiting PH. Effects of ibuprofen on exercise-induced muscle soreness and indices of muscle damage. *Br J Sports Med*. 1990;24(3):191-5.
22. Esh CJ, Mauger AR, Palfreeman RA, Al-Janubi H, Taylor L. Acetaminophen (Paracetamol): Use beyond Pain Management and Dose Variability. *Front Physiol*. 2017;8:1092.
23. Treharne GJ, Douglas KM, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. *Musculoskeletal Care*. 2007;5(4):175-90.
24. Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *JAMA*. 2006;296(1):87-93.