Medical Academy Journal (2022) 1: 26-33
https://doi.org/10.56823/OJLM6692

MEDICAL ACADEMY journal

Pain management with paracetamol and ibuprofen in combination

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Received: December 6th, 2022
Accepted: December 9th, 2022
Published online: December 15th, 2022

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ABSTRACT

Introduction: Pain is not limited to the activation of nociceptors but it is also influenced by psychological and physical factors through imbalance between inhibitory and stimulatory pathways.

Methods: Medical literature about the physiopathology and treatment of pain, with a particular focus on mechanical and inflammatory musculoskeletal pain, was reviewed and combined with the expert opinion of the author.

Results: Analgesic therapy that combines drugs with different mechanisms of action can increase the efficacy while decreasing the side effects. Several studies have shown that the combination of paracetamol and ibuprofen (resulting in a central analgesic and a peripheral anti-inflammatory action) provides superior efficacy and better safety profile than separate drugs. In 2019 a board of experts recommended this combination as the most suitable in treating mild-moderate musculoskeletal pain. Paracetamol/Ibuprofen combination is also indicated in musculoskeletal inflammatory pain associated and worsened by muscle contraction, like low back pain, chronic joint pain, osteoarthritis, tendinopathy due to rotator cuff syndrome; the combination is able to counteract both the inflammatory process and the descending stimulatory pathway.

Conclusions: The combination of paracetamol and ibuprofen shows efficacy and tolerability in different types of pain and is indicated as a first-line analgesic treatment in various morbid conditions.

Keywords: Pain treatment, musculoskeletal pain, ibuprofen, paracetamol

INTRODUCTION

The various types of pain: focus on inflammatory pain and somatic muscle pain.

According to International Association of Study of Pain (IASP) definition, pain is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[1]. This definition implies that pain is not an objective sensation but subjectively conditioned by numerous personal factors.

There are different types of pain: nociceptive pain, linked to actual or potential tissue damage, and neuropathic pain, which results from injury to the peripheral receptor, afferent fiber, or central nervous system[2].

Pain pathways

There are specific anatomical structures for pain transmission and modulation. The cell body of the neurons is responsible for perceiving painful stimulus and is located in the dorsal root ganglion (DRG). The peripheral axons innervate the tissues, and their extremities constitute the receptors that react to painful stimuli (nociceptors), while the central axons enter the spinal cord **(Fig. 1)**. Through synaptic connection with the neurons of the spinothalamic tract the axon transfers information to the thalamus, which in turn transmits the impulse to the limbic system (involved in the affective and emotional dimension of pain) and to the somatosensory cortex[3].

Nociceptors can be activated by three types of stimuli: mechanical, thermal and chemical. As for the latter, various substances capable of activating nociceptors are produced in the inflamed tissues, such as potassium and histamine released by damaged tissues or by polymorphonuclear cells migrated from blood vessels, and bradykinins, prostaglandins and leukotrienes, synthesized by enzymes activated by the damaged tissue[2]. Most clinically significant pain is generated by stimuli from the musculoskeletal or deep visceral tissues.

Once a pain signal from the ascending pathway reaches the somatosensory cortex, it triggers the descending pain modulatory system, that can be facilitatory or inhibitory on the pain perception[4]. The imbalance between the descending facilitatory and inhibitory systems is involved in the onset of chronic pain[5].

The sensation of pain is not limited to the activation of nociceptors but is also processed according to several factors: multiple personal, physical, hormonal, psychological and social factors (acting on the balance between inhibitory and facilitatory systems) can impact the perception of pain and its intensity, defining what is called "pain threshold"[4,6]. Psychological and physical factors are not entirely separate in their effects on the maintenance of pain. For example, stress and anxiety increase muscle contraction and would thus be expected to exacerbate any pain problem. The experience of pain determines a broad central involvement, which also involves the patient's cognitive system and his affective and relational system[2].

Somatic, mechanical musculoskeletal pain arises from structural changes located in the bones, joints, muscles, tendons; it can be described as a dull pain, sometimes intermittent and often radiate around the injured area to a larger area of the body. It can be chronic, but more often, it has an acute onset. Examples of deep somatic pain include fracture-related pain and post-operative pain[7].

Inflammatory pain is caused by an underlying inflammatory disease, such as inflammatory arthritis[8]. Prostaglandins and other proinflammatory mediators like IL-1, IL-6, TNF al-

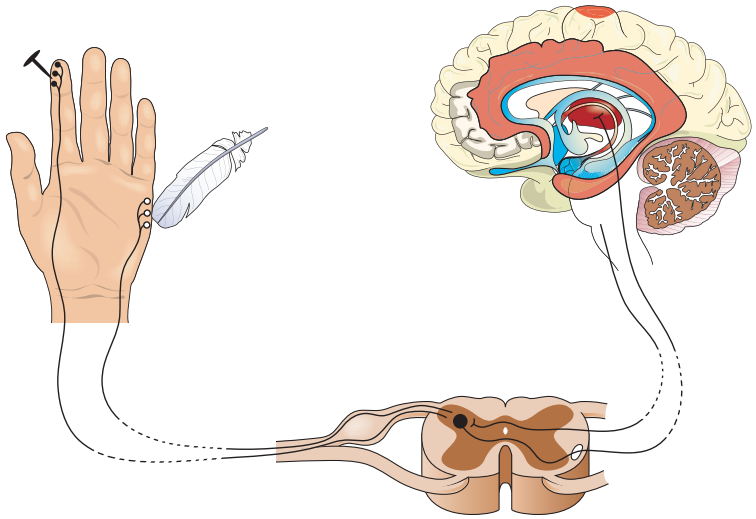

Figure 1. Schematic drawing of pain pathways.

pha, can be released either by peripheric immune cells or spinal glial cells (microglia e astrocytes), and not only sensitize nociceptors and produce hyperalgesia, but also increase pain through central mechanisms[4]. Drugs that interfere with prostaglandin synthesis and inflammatory markers release inhibit bone pain by inhibiting this sensitization[7].

The early differential diagnosis between inflammatory and somatic pain is crucial for a correct clinical approach, as the management and treatment of the two conditions can be different. According to a panel of experts from the Assessment of SpondyloArthritis international Society (ASAS), the typical characteristics of Inflammatory Back Pain (IBP) are: improvement with exercise but not with rest, pain at night, insidious onset, often before 40 years of age[8].

Regarding the duration of pain, it can be acute or chronic. Musculoskeletal disorders are one of the leading causes of chronic pain, and its most frequent manifestations are chronic back pain and pain caused by osteoarthritis and different inflammatory diseases, including rheumatoid arthritis[9].

Efficacy and safety of the Paracetamol / Ibuprofen combination in multimodal pain therapy.

In managing mild to moderate pain, analgesic therapy that combines drugs with different mechanisms of action (multimodal analgesia) can increase the efficacy while decreasing the side effects[10].

Paracetamol is the active metabolite of two older antipyretic drugs, acetanilide and phenacetin; it is one of the most commonly used analgesics and antipyretic medications across the world, in adults as well as in children and is included on the World Health Organization's List of Essential Medicines[11]. It inhibits the synthesis of phenoxyl radical, essential for cyclooxygenase activity of COX-2, and consequently the PGs synthesis[12,13]. Paracetamol easily crosses the blood-brain barrier, reaches the hypothalamic vessels and exerts its antipyretic action[14]. The analgesic effect is mediated by its primary metabolite, AM404, which is formed in the spinal cord and in some supraspinal and cerebral areas, and can inhibit the reuptake of anandamide, the primary endogenous cannabinoid **(Fig. 2)**[15,16]. Paracetamol is an effective pain reliever and antipyretic, but it has no antiinflammatory activity as its action is inhibited by the high concentrations of arachidonic acid found in inflamed tissues[14,17]. Paracetamol is one of the best-known and most used antipyretic and analgesic drugs, at a dose of 500-1000 mg, with a maximum of 3000 mg in 24 hours; due to its efficacy and tolerability, it is also often used in combination with other drugs[9].

Ibuprofen is a derivative of propionic acid, which, like other NSAIDs, has analgesic, antiinflammatory and antipyretic

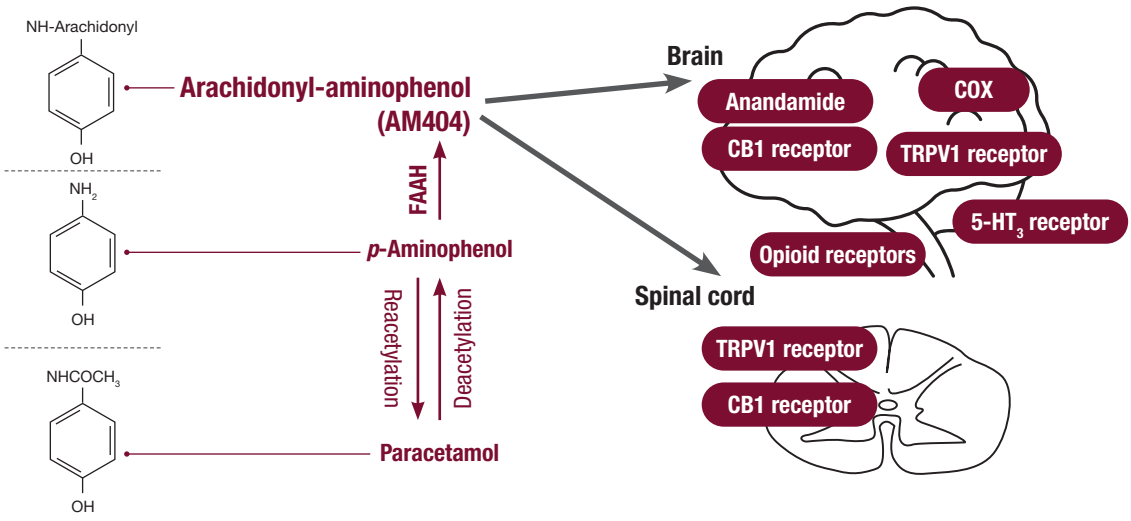

Figure 2. Paracetamol mechanism of action (modified from 15)

activity. Its therapeutic effects are linked to the inhibitory action of the cyclooxygenase enzyme Cox1 and COX2, with the consequence of a block of conversion of arachidonic acid into prostaglandins and thromboxane A2 synthesis[13,18].

The pharmacokinetic properties of paracetamol and ibuprofen (P/I) do not influence each other, and the two drugs have a very similar T_{max} and $T_{1/2,}$ with no effect of food on the absorption **(Fig. 3)**[18].

A fixed-dose combination of P/I has been shown to provide superior analgesia than paracetamol or ibuprofen alone while also exhibiting a better safety profile of both drugs when used at higher doses[18,19]. The two drugs have different mechanisms of action, and the combination results in a central analgesic effect and a peripheral anti-inflammatory effect[9].

Several studies have shown the efficacy and safety of the combination P/I. A Cochrane systematic review analyzed three comparative studies on the combination P/I in the treatment of acute post-oral surgery pain (tooth extraction); the analyzed studies included various comparisons: ibuprofen 200 mg + paracetamol 500 mg with placebo, ibuprofen 400 mg + paracetamol 1000 mg with placebo, ibuprofen 400 mg + paracetamol 1000 mg with ibuprofen 400 mg alone, with an overall number of 1647 of participants and 4 groups of treatment (P/I 200/500, P/I 400/1000, placebo, ibuprofen)[13]. The combination P/I showed superior efficacy and safety than ibuprofen alone and placebo, with a higher proportion of participants achieving at least 50% maximum pain relief over 6 hours, lower rate and longer time to rescue medication, and lower incidence of adverse events (30% for P/I 200/500, 29% for P/I 400/1000, 48% for placebo)[13]. A randomized clinical trial on 556 patients undergoing hip arthroplasty showed a significant reduction in the use of morphine in the first 24 hours after surgery in patients treated with P/I combination compared to the single components in monotherapy[20]. Gigliotti et al. in 2019, based on the rationale for use, complementary mechanisms of action and the results of clinical studies, recommended the combination of P/I as the most suitable in treating mild-moderate musculoskeletal pain[9].

Aspecific low back pain: etiology and therapeutic indications.

Low back pain is a frequent condition in clinical practice and represents a significant cause of disability (11-15% of the population)[2]. The prevalence of intermittent low back pain is 84%, while chronic low back pain is about 23%. Back pain is defined as nonspecific (90% of cases of low back pain) if no definite pathologies are recognizable, such as disc herniation, infections, osteoporosis, rheumatoid arthritis or tumors; low back pain can be caused by the pain

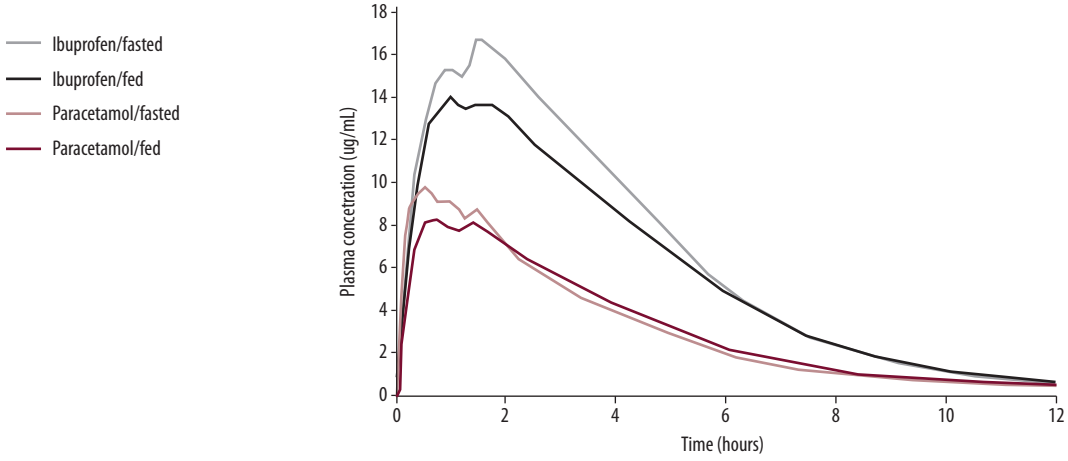

Figure 3. Mean plasma concentrations of paracetamol and ibuprofen after administration of fixed-dose combination, fasted and fed (modified from 18)

of myofascial structures, vertebral disc, facet joint, and sacroiliac joint, but also psychological factors can be involved[21]. In many cases, the patient with low back pain not only presents a nociceptive pain (resulting from the compression or irritation of the nerves involved) but also often manifests a diffuse muscle spasm of the paravertebral muscles due to reflexing mechanisms or problems postural; this contributes to increasing pain, creating a vicious circle[2,22]. For these patients, the most effective therapy should be multidisciplinary and include not only multimodal pharmacological but also psychological and physical treatments[21]. Pharmacological treatment often includes medications such as paracetamol and NSAIDs, muscle relaxants, gabapentin, topical analgesics, and opioids, according to the patient's characteristics and the severity of pain[23]. Also, in this indication, the efficacy of the combination P/I have been shown by clinical studies. A randomized trial was conducted on 80 patients suffering from low back pain, treated with ibuprofen alone (400 mg TID) or with P/I (325 mg/200 mg TID) for three days, with a follow-up of 10 days overall. The results showed a statistically significant better efficacy of the combination over ibuprofen alone ($p<0.045$) and a lower finger-to-floor distance in patients on combined therapy (4.7 cm vs 8.3 cm, $p=0.03$) **(Fig. 4)** at the end of follow up. Both the treatments were well tolerated, with minor gastric intolerability in one patient on combined therapy and two patients on ibuprofen monotherapy[24]. A survey on 121 specialists (of these 89 (74%) responded before the deadline: 39 pain specialists (44%), 16 physiatrists (18%), 13 orthopedic surgeons (15%), 11 general practitioners (12%), 4 occupational physicians (4.5%), 3 neurosurgeons/neurologists (3.5%), 1 rheumatologist (1%), 1 biotechnologist (1%), and 1 gynecologist (1%)) showed that 84% of them considered NSAIDs/paracetamol as the first-choice pharmacological treatment for low back pain **(Fig. 5)**[25].

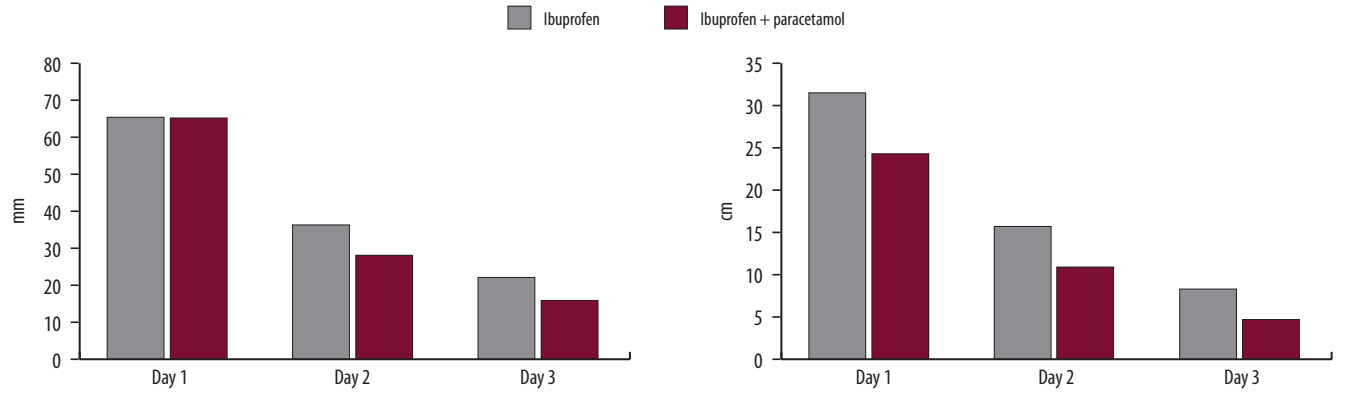

Figure 4. Change in pain intensity (left) and finger-to-floor distance (right) in patients treated with ibuprofen or the combination ibuprofen/paracetamol for low back pain (modified from 24)

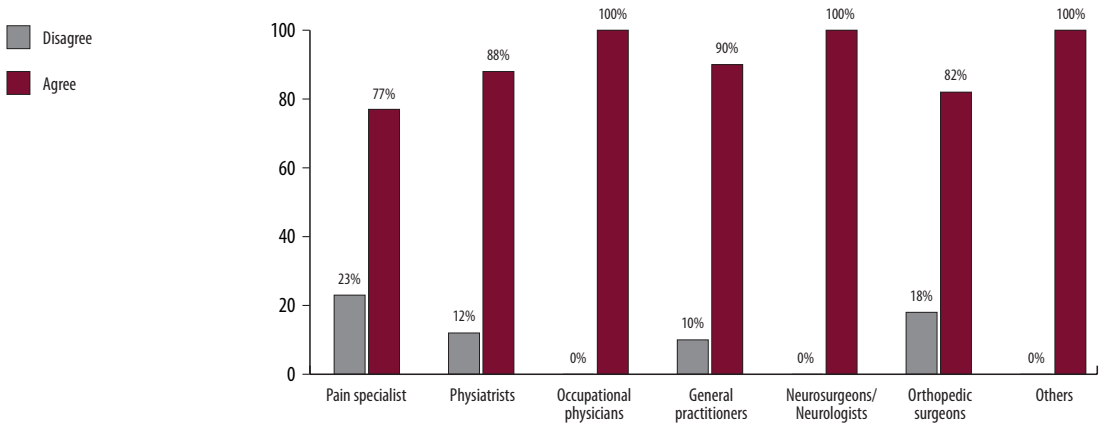

Figure 5. NSAIDs/paracetamol as first-line treatment for low back pain (modified from 25)

Joint pain associated with muscle spasm: the opportunity of the multimodal approach.

In chronic joint pain, the persistence of nociceptor activity induces contraction of the muscles innervated by the same spinal segment: at the level of the limbs, the contraction mainly affects the flexor muscles[2]. This mechanism is often involved in sustaining pain in the absence of ongoing tissue damage, and both peripheral mechanisms and hyperexcitability of the central nervous system might contribute to maintaining it[26]. In chronic pain patients, small, quite painful muscle areas are common. The pressure on these irritable spots (myofascial trigger points) can induce pain in the skeletal muscles, even in distant places, by activating the spinal reflex and muscle contraction[2].

For this reason, an association of drugs with a central and peripheral mechanism of action, and possibly with a muscle relaxant drug (in acute pain) or a tricyclic antidepressant (in chronic forms), is the more suitable choice. Paracetamol has a lower analgesic action and no anti-inflammatory action compared to NSAIDs, but it is often preferred due to its better tolerability. On the other hand, the administration of NSAIDs often raises concerns about gastric tolerability and drug interactions in case of multiple treatments (frequent in elderly patients). Multimodal therapy, with a combination of paracetamol and reduced doses of NSAIDs, can exploit the different mechanisms of actions (central and peripheric), increasing tolerability and compliance.

Osteoarthritis: treatment with antiinflammatories drugs combined with central analgesics for concomitant muscle spasms.

Osteoarthritis (OA) is a common, degenerative disease that affects more than 300 million people worldwide and is a leading cause of disability among older adults[27]. It can affect any joint but impacts most frequently the knee, hip, spine, and hand joints and is characterized by cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, leading to pain, stiffness, swelling and muscle spasms; these alterations lead to decreased range of motion and loss of normal joint function[27,28]. The management of osteoarthritis is challenging: several guidelines recommend a multidisciplinary treatment, including exercise, weight loss for overweight/obese patients, manipulation and stretching, particularly for osteoarthritis of the hip, local heat or cold applications, walking sticks, joint bracing and orthoses, transcutaneous electrical nerve stimulation (TENS)[27-29]. Pharmacological treatment involves the chronic use of analgesic and anti-inflammatory drugs, such as paracetamol and NSAIDs. In patients not responding to this first-line approach, opioids and corticosteroids (oral or as intra-articular injection) are indicated[27-29]. Also, the use of paracetamol and NSAIDs in knee osteoarthrosis is recommended by American Association of Orthopedic Surgeons[30]. The multimodal approach is particularly suitable for transitioning from acute, localized pain to chronic, widespread pain[9]. A board of experts (orthopedic surgeons) recommends the combination of P/I in transient exacerbation of the chronic disease with mild to moderate pain[9].

Rotator cuff syndrome: tendinopathy associated with muscle spasms, the results of multimodal therapy.

Rotator Cuff Tendinopathy is a common shoulder problem which can be caused by a single traumatic event (e.g. fall trauma or direct impact), or by chronic overload and/or a degenerative process affecting the musculotendinous and bone structures. It is responsible for 65-70% of shoulder pain complaints, which affects about 19.0 per 1000 patients per year[31]. According to some authors, the incidence increases with age[32], but instability or rotator cuff tendinopathy is more common < 35 years, while > 35 rotator cuff tears, adhesive capsulitis, osteoarthritis are more frequently responsible for the symptoms[33].

In addition to alterations in the anatomical structures involved, muscle spasms can aggravate pain and limit joint function[31]. In chronic forms, this can be treated with interferential treatments using a mid-frequency electrical signal or hot packs that improve the oxygenation of tissues[34,35]; in case of acute injury, ice therapy is indicated[35]. For the management of pain and inflammation, both paracetamol and NSAIDs are recommended[31].

CONCLUSIONS

Multimodal analgesia involves the use of different classes of analgesics to provide better overall efficacy than the individual components, using reduced dosages and thus inducing fewer side effects. An example of multimodal therapy is the combination of paracetamol and ibuprofen since ibuprofen exerts an analgesic and anti-inflammatory effect through the central and peripheral mode of action, while paracetamol has a central analgesic. This combination has shown efficacy and tolerability in different types of pain and is indicated in the literature as the first-line analgesic treatment in various morbid conditions.

REFERENCES

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S et al. The Revised IASP definition of pain: concepts, challenges, and compromises. Pain 2020;161(9):1976–82. doi: 10.1097/j.pain.0000000000001939.
2. Institute of Medicine (US) Committee on Pain, Disability, and Chronic Illness Behavior. Anatomy and Physiology of Pain. In: Osterweis M, Kleinman A, Mechanic D (Eds), Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives; National Academies Press, Washington (DC) 1987:123-45. doi: 10.17226/991.
3. Patapoutian A, Tate S, and Woolf CJ. Transient receptor potential channels: targeting pain at the source. Nature Reviews Drug Discovery 2009;8:55-68. doi: 10.1038/nrd2757.
4. Staud R. The important role of CNS facilitation and inhibition for chronic pain. International journal of clinical rheumatology. 2013 Dec 1;8(6):639-46. doi: 10.2217/ijr.13.57.
5. Kwon M, Altin M, Duenas H, Alev L. The role of descending inhibitory pathways on chronic pain modulation and clinical implications. Pain Pract 2014;14(7):656-67. doi: 10.1111/papr.12145.
6. Mills SE, Nicolson KP, and Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019;123(2):e273–e283. doi: 10.1016/j.bja.2019.03.023.
7. Carver AC, Foley KM. Types of Pain. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK12991/
8. Sieper J, van der Heijde, Landewe R, Brandt J, Burgos-Vagas, Collantes-Estevez E et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis. 2009;68(6):784-8. doi: 10.1136/ard.2008.101501.
9. Gigliotti S, Sante G, Putaggio G, Di Bisceglie L, Grimaldi G, Gentile F et al. Management of musuloskeletal pain in the setting of territorial orthopedics. Minerva Ortopedica e Traumatologica 2020;71(1):23-31.
10. Altman RD. A rationale for combining acetaminophen and NSAIDs for mild-to-moderate pain. Clin Exp Rheumatol 2004;22(1): 110–7.
11. World Health Organization. World Health Organization Model List of Essential Medicines. 2017. http://www.who.int/medicines/publications/essentialmedicines/en/
12. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacol. 2013; 21:201–32. doi: 10.1007/s10787-013-0172-x.
13. Derry CJ, Derry S, Moore RAE. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database of Systematic Reviews 2013; 6:Art. No.: CD010210. doi: 10.1002/14651858.CD010210.pub2.
14. Bonezzi C, Lora Aprile P, Fornasari D. Terapia farmacologica combinata del dolore: l'asso nella manica del medico di medicina generale. Rivista Società Italiana di Medicina Generale 2017;6(24):25-32.
15. Ohashi N and Kohno T. Analgesic Effect of Acetaminophen: A Review of Known and Novel Mechanisms of Action. Front Pharmacol 2020;11:580289. doi: 10.3389/fphar.2020.580289.
16. Mattia C, Coluzzi F. A look inside the association codeine-paracetamol: clinical pharmacology supports analgesic efficacy. Eur Rev Med Pharmacol Sc 2015;19:507-16.
17. Mazaleuskaya LL, Sangkuhl K, Thorn CF, FitzGerald GA, Altman RB, and Klein TE. PharmGKB summary: Pathways of acetaminophen metabolism at the therapeutic versus toxic doses. Pharmacogenet Genomics 2015;25(8):416–26. doi: 10.1097/FPC.0000000000000150.
18. Atkinson HC, Currie J, Moodie J, Carson S, Evans S, Worthington JP et al. Combination paracetamol and ibuprofen for pain relief after oral surgery: a dose ranging study. Eur J Clin Pharmacol 2015;71(5):579-87. doi: 10.1007/s00228-015-1827-x.
19. Merry AF, Gibbs RD, Edwards J, Ting GS, Frampton C, Davies E, Anderson BJ. Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. Br J Anaesth 2010;104(1):80-8. doi: 10.1093/bja/aep338
20. Thybo HE, et al. Effect of Combination of Paracetamol (Acetaminophen) and Ibuprofen vs Either Alone on Patient-Controlled

Morphine Consumption in the First 24 Hours After Total Hip Arthroplasty The PANSAID Randomized Clinical Trial. JAMA 2019;321(6):562-71. doi: 10.1001/jama.2018.22039.

21. Urits I, Burshtein A, Sharma M, Testa L, Gold PA, Orhurhu V et al. Low Back Pain, a Comprehensive Review: Pathophysiology, Diagnosis, and Treatment. Curr Pain Headache Rep 2019;23(3):23. doi: 10.1007/s11916-019-0757-1.
22. Roland MO. A critical review of the evidence for a pain-spasm-pain cycle in spinal disorders. Clin Biomech 1986;1(2):102-9. doi: 10.1016/0268-0033(86)90085-9.
23. Musich S, Wang SS, Slindee LB, Keown K, Hawkins K, Yeh CS. Using Pain Medication Intensity to Stratify Back Pain Among Older Adults Pain Medicine 2019; 20: 252–66. doi: 10.1093/pm/pny007.
24. Ostojic P, Radunovic G, Lazovic M, Tomanovic-Vujadinovic S. Ibuprofen plus paracetamol versus ibuprofen in acute low back pain: a randomized open label multicenter clinical study. Acta Reumatol Port 2017;42(1):18-25.
25. Varrassi G, Moretti B, Pace MC, Evangelista P, Iolascon G. Common Clinical Practice for Low Back Pain Treatment: A Modified Delphi Study. Pain Ther 2021;10(1):589-604. doi: 10.1007/s40122-021-00249-w.
26. Hirayama J, Yamagata M, Ogata S, Shimizu K, Ikeda Y, Takahashi K. Relationship between low-back pain, muscle spasm and pressure pain thresholds in patients with lumbar disc herniation. Eur Spine J 2006;15(1):41-7. doi: 10.1007/s00586-004-0813-2.
27. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care & Research 2020;72(2):149–62. doi: 10.1002/acr.24131.
28. Buelt A, Narducci DM. Osteoarthritis Management: Updated Guidelines from the American College of Rheumatology and Arthritis Foundation. Am Fam Physician 2021;103(2):120-1.
29. Conaghan PG, Dickson J, Grant RL, on behalf of the Guideline Development Group Care and management of osteoarthritis in adults: summary of NICE guidance. BMJ 2008;336:502-3. doi: 10.1136/bmj.39490.608009.AD.
30. Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. J Am Acad Orthop Surg 2022;30(9):e721-e729. doi: 10.5435/JAAOS-D-21-01233.
31. Kate Hopman, Lee Krahe, Sue Lukersmith,, Alexander McColl, Kris Vine1. Clinical Practice Guidelines for the Management of Rotator Cuff Syndrome in the Workplace. The University of New South Wales, Medicine, Rural Clinical School, Port Macquarie Campus 2013. https://rcs.med.unsw.edu.au/sites/default/files/rcs/page/RotatorCuffSyndromeGuidelines.pdf
32. Roquelaure Y, Bodin J, Ha C, Petit Le Manac'h A, Descatha A, Chastang JF, et al. Personal, biomechanical, and psychosocial risk factors for rotator cuff syndrome in a working population. Scand J Work Environ Health. 2011;37(6):502-11. doi: 10.5271/sjweh.3179.
33. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA. The demographic and morphological features of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. J Bone Joint Surg Am 2006;88(8):1699-704. doi: 10.2106/JBJS.E.00835.
34. Fuentes JP, Armijo Olivo S, Magee DJ, Gross DP. Effectiveness of interferential current therapy in the management of musculoskeletal pain: a systematic review and meta-analysis. Phys Ther 2010;90(9):1219-38. doi: 10.2522/ptj.20090335.
35. Mac Auley DC. Ice therapy: how good is the evidence? Int J Sports Med 2001;22(5):379-84. doi: 10.1055/s-2001-15656.

DISCLOSURES

Medical writing support was provided by Maria Carla Marrè Brunenghi, an independent medical writer, on behalf of Ma.CRO Lifescience Srl. The publication was supported by an unconditional grant by Angelini Pharma S.p.A

Conflict of Interests: The Author has been a speaker and author of sponsored editorials on the topic of pain for several companies.