URBAŃSKI, Wojciech, DOLATA, Natalia, BALCER, Bartosz, KRUCZKOWSKA, Adrianna, BULZACKI, Emil, CEBULA, Agnieszka, WEIMANN, Maja, STOSIEK, Aleksandra, PAKUŁA, Mateusz and LISZKA, Pawel. NSAIDs in Sports Medicine: Balancing Quick Relief with Long-Term Health Impacts. Quality in Sport. 2024;36:56892. eISSN 2450-3118. https://doi.org/10.12775/OS.2024.36.56892

https://apcz.umk.pl/QS/article/view/56892

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.

Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).

Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.

Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

© The Authors 2024;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (http://creativecommons.org/licenses/by-nc-sa/4.0/) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 10.12.2024. Revised: 24.12.2024. Accepted: 24.12.2024. Published: 24.12.2024.

NSAIDs in Sports Medicine: Balancing Quick Relief with Long-Term Health Impacts

Wojciech Urbański

Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

https://orcid.org/0009-0008-6559-7510

wojciech.urbanski04@gmail.com

Natalia Dolata

Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

https://orcid.org/0009-0003-9564-9231

nataliadolata1998@gmail.com

Bartosz Balcer

Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

https://orcid.org/0009-0003-2994-3918

bartosz.balcer10@gmail.com

Adrianna Kruczkowska

Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

https://orcid.org/0000-0003-0549-0849

publikacja.a.kruczkowska@gmail.com

Emil Bulzacki

Nicolaus Copernicus Memorial Hospital, Pabianicka 62, 93-513 Łódź, Poland

https://orcid.org/0009-0009-4303-7114

emilbulzacki1@gmail.com

Agnieszka Cebula

Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland https://orcid.org/0009-0002-7966-6333

cebulaaga@interia.pl

Maja Weimann

Internship at Copernicus Hospital, Nowe Ogrody 1/6, 80-803, Gdańsk, Poland

https://orcid.org/0009-0004-1375-1337

majaweimann.priv@gmail.com

Aleksandra Stosiek

Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland https://orcid.org/0009-0001-9276-3528

aleksandra.stosiek@gmail.com

Mateusz Pakuła

Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

https://orcid.org/0009-0001-1792-0378

lek.m.pakula@gmail.com

Paweł Liszka

Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland https://orcid.org/0009-0003-5465-3656

liszkapawel99@gmail.com

Abstract:

Introduction and Purpose

Nonsteroidal anti-inflammatory drugs (NSAIDs) are regularly used in sports medicine to manage pain and inflammation caused by acute and chronic injuries. Their mechanism involves inhibition of cyclooxygenase (COX) enzymes, reducing the body's natural inflammatory response. This review aims to analyze the effects of NSAID use in sports contexts, focusing on short- and long-term benefits and risks, specifically concerning tissue healing, athletic performance, and general health outcomes.

Materials and Methods

We reviewed studies from PubMed, Google Scholar and ResearchGate, focusing on key search terms including NSAIDs in sports injuries, NSAID mechanism, short-term and long-term effects of NSAIDs, athletic performance and NSAID, pain management in sports, NSAID side-effects and NSAID alternatives

Conclusions

Short-term NSAID use can provide effective pain relief and support functional recovery, benefiting professional and recreational athletes in their sports. However, prolonged use may decrease natural tissue healing abilities, increase susceptibility to various side effects, and potentially affect long-term performance. Alternative pain management strategies are recommended to complement NSAID use, providing athletes with safer, long-term options for recovery. This review highlights the need for a balanced approach to NSAID usage, recommending cautious decision making among sportspeople, coaches, and healthcare workers.

Keywords: NSAIDs in sports injuries, NSAID mechanism, short-term and long-term effects of NSAIDs, athletic performance and NSAIDs, pain management in sports, NSAID side effects and NSAID alternatives

Introduction:

The common use of nonsteroidal anti-inflammatory drugs (NSAIDs) in sports varies from elite athletes to amateur enthusiasts and serves as a first action to manage pain and inflammation.

Studies demonstrate that NSAIDs are frequently used because of their rapid pain relief, which allows athletes to continue high-performance levels or return to activity quickly after injuries [1]. Approximately 65% of surveyed athletes report regular use of NSAIDs to manage chronic pain or recurring injuries resulting from intensive physical activity, especially during diverse disciplines sport events [1]. NSAIDs work by inhibiting cyclooxygenase (COX) enzymes-COX-1 and COX-2-that play essential roles in the body's inflammatory response by producing prostaglandins, compounds that promote pain, fever, and inflammation [2]. However, this mechanism, while effective, can also lead to various side effects, impacting both acute and long-term health outcomes. Former Olympic athletes reported high NSAID usage during their careers in a cohort study of over 3,000 retired Olympians [3]. NSAID use is not limited to Olympic professionals. According to Ray Tricker, 50% of all college athletes surveyed felt they overused these anti-inflammatory drugs [4]. This trend is particularly concerning as it may potentially lead to long-term health complications such as gastrointestinal [5] or renal damage [6]. Prolonged NSAID use has been linked to potential disruptions in the natural inflammatory response essential for healing [7], which has significant implications for athletes' recovery and performance sustainability. Considering this, despite their popularity, NSAIDs raise critical questions about balancing short-term benefits with long-term risks, particularly in the context of tissue healing, organ health, and overall athletic performance. This review will explore the physiological mechanisms of NSAIDs, their short- and long-term impacts on athletic performance, and alternative pain management strategies. Through a comprehensive examination, this work targets to provide evidence-based recommendations to optimize pain management and support athletes' overall health.

Mechanism of Action of NSAIDs:

Nonsteroidal anti-inflammatory drugs (NSAIDs) function primarily by inhibiting the cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, both of which play well defined roles in the body's physiological and inflammatory responses because they are responsible for arachidonic acid metabolism that results in the production of prostaglandins and thromboxane [8]. COX-1 is involved in maintaining normal cellular functions, such as protecting the gastric mucosa, supporting platelet aggregation, and regulating kidney function. COX-2, on the other hand, is typically upregulated in response to injury or inflammation and is primarily responsible for producing pro-inflammatory prostaglandins that mediate pain and swelling [8].

COX Enzyme Inhibition and Pain Relief

NSAIDs reduce pain and inflammation by blocking the production of prostaglandins through the inhibition of COX enzymes. By reducing prostaglandin levels, NSAIDs diminish symptoms such as pain and swelling, making them particularly beneficial in sports contexts where rapid pain relief is needed for continued performance which results in frequent drug usage among athletes that look for analgesic while struggling with various injuries [9]. Studies have shown that the degree of COX inhibition correlates with the effectiveness of pain relief, although this can vary significantly depending on the specific NSAID and its selectivity for COX-1 versus COX-2 [10].

Selective vs. Non-Selective NSAIDs

There are two primary categories of NSAIDs: selective COX-2 inhibitors and non-selective NSAIDs, which inhibit both COX-1 and COX-2. Non-selective NSAIDs, such as aspirin, ibuprofen, ketoprofen and naproxen inhibit both enzymes, providing robust anti-inflammatory effects but with a higher risk of gastrointestinal side effects due to COX-1 inhibition [11]. Selective COX-2 inhibitors, like celecoxib, parecoxib or etoricoxib were developed to reduce these side effects by sparing COX-1 and targeting only COX-2, which is primarily responsible for the inflammatory response [8]. Although selective NSAIDs have less gastrointestinal complications, they have been associated with the same cardiovascular dangers, especially in individuals with pre-existing risks.[12].

Physiological Impact on Inflammation and Healing

The inhibition of COX-2 by NSAIDs impacts the body's natural healing processes. Prostaglandins play a crucial role in signalling pathways that promote tissue repair and regeneration; by suppressing these signals, NSAIDs may delay tissue repair, particularly in muscle, tendon, and bone injuries. This effect has been observed in animal models, where prolonged NSAID use impaired muscle recovery by disrupting satellite cell proliferation, essential for muscle regeneration [13] further found that NSAID use could impede bone healing by reducing osteogenesis, presenting a risk for athletes recovering from fractures.

Short-Term Benefits of NSAIDs in Sports

In the short term, NSAIDs offer significant benefits for athletes dealing with pain and inflammation resulting from injuries.

Pain Relief and Improved Functionality- NSAIDs are highly effective in providing rapid pain relief, allowing athletes to manage discomfort and maintain performance during physical activities [14]. Studies confirm that NSAIDs can alleviate pain symptoms within hours, making them particularly valuable for managing acute sports injuries, where athletes benefit from quick pain management to minimize interruptions in training or competition calendars [15]. NSAIDs are especially beneficial in high-impact sports like football [16] where dynamic contact between players can cause musculoskeletal impact and schedules are demanding.

Reduction of Inflammation and Soreness

By inhibiting COX enzymes, NSAIDs decrease prostaglandin production, reducing inflammation and swelling in injured tissues. This effect enhances mobility and promotes a quicker initial recovery phase [17].

Temporary Performance Enhancement

For athletes with minor injuries, NSAIDs enable continued high-level performance by temporarily alleviating pain and supporting strength and endurance maintenance. However, it is critical to recognize that while NSAIDs offer temporary relief, they do not address the underlying injury; misuse could lead to aggravated conditions [18].

Short-Term Risks of NSAID Use in Sports

Despite the immediate benefits, short-term NSAID use also poses risks if not carefully monitored.

Gastrointestinal Complications

Non-selective NSAIDs, which inhibit both COX-1 and COX-2, may disturb gastric protective mechanisms, leading to discomfort, stomach mucosa layers damaging, and, in severe cases, gastrointestinal bleeding. Regular NSAID use or high doses heighten these risks, with research indicating that even short-term use can lead to measurable gastrointestinal issues among high-performance athletes [5,19].

Potential Cardiovascular Effects

While short-term NSAID use is generally safe, studies suggest a slight risk of cardiovascular events, particularly in individuals with pre-existing cardiovascular conditions. However, research has shown that side effects depend on NSAID doses and consumption duration [20].

Interference with Natural Healing Processes

NSAIDs' suppression of prostaglandins can disrupt essential inflammation, delaying tissue repair. Studies indicate that premature inflammation reduction may impair muscle regeneration and slow the healing of tendons and ligaments[11].

Long-Term Consequences of NSAID Use in Athletic Populations

Long-Term Benefits

For athletes managing chronic conditions or persistent pain, NSAIDs offer long-term relief, allowing for consistent training and enhanced quality of life. Research indicates that when used judiciously, NSAIDs enable athletes suffering from chronic musculoskeletal issues to sustain higher levels of physical function [21]. Additionally, NSAIDs can be used as an alternative pain treatment to opioids which have highly addictive properties [22].

Long-Term Risks

Organ-Specific Health Risks - Chronic NSAID use presents substantial risks to organ health, which will be explored in the following paragraph. It has been shown that glomerular filtration rate and renal blood flow are reduced during physical exercise [22]. By inhibiting COX enzymes, leading to a reduction in prostaglandin synthesis, NSAIDs might cause further decrease in glomerular filtration rate (GFR) and renal blood flow, heightening the risk of renal impairment. Prolonged NSAID use has been associated with chronic kidney damage, and their contribution to electrolyte imbalances, such as hyponatremia, is particularly concerning for endurance athletes, including marathon runners. This underscores the need for careful consideration of NSAID use in high-intensity or long-duration physical activities [24]. Prostaglandins play a protective role by stimulating mucus and bicarbonate production and maintaining adequate blood flow to the gastric mucosa. Because COX enzyme inhibition leads to reduced prostaglandins synthesis, chronic use of NSAIDs diminishes these protective factors, leading to mucosal erosion and increased susceptibility to ulceration. Studies have demonstrated that up to 50% of athletes using NSAIDs regularly can experience nuisance

dyspeptic symptoms [25]. Athletes, especially endurance runners, are at greater risk due to the combined effects of physical stress and reduced splanchnic blood flow[26]. Serious major complications, including peptic ulcers disease or GI bleeding have also been documented in cases of prolonged use without medical supervision [27]. Hepatotoxicity is much less common but raises another potential concern, because NSAIDs are metabolized in the liver, athletes with pre-existing issues may face liver damage [28].

Impact on Bone and Tissue Healing

Prostaglandins are also essential for bone repair. Studies have demonstrated that nonsteroidal anti-inflammatory drugs delay fracture healing by interfering with the recruitment and differentiation of osteoblasts, the cells responsible for new bone formation. The reduction in prostaglandin levels caused by NSAIDs impairs the inflammatory phase of bone healing, an essential precursor to the reparative and remodelling stages [29]. Additionally, long-term NSAID usage has been shown to increase the risk of nonunion or incomplete healing in high-stress scenarios often faced by athletes, such as repetitive loading or overtraining [29,30].

Psychological Dependence and Overuse

Athletes may develop psychological reliance on NSAIDs, viewing them as essential to their training regimen. This dependency can discourage athletes from exploring alternative pain management strategies that might be safer in the long term. Some studies suggest that athletes often take NSAIDs with a low awareness of the effects and side-effects, not just for pain relief but also as a preventive measure, leading to chronic overuse. [31]

Cardiovascular Risks

Long-term NSAID use, especially selective COX-2 inhibitors, has been associated with increased cardiovascular risks, such as hypertension, myocardial infarction, and stroke. This is particularly concerning for athletes with pre-existing cardiovascular conditions. Studies emphasize that while selective COX-2 inhibitors reduce gastrointestinal risks, they may elevate cardiovascular risks, a significant concern for athletes whose cardiovascular systems are already strained from intense physical activity [16, 32, 33].

Alternative Pain Management Strategies

For athletes seeking safer options for managing pain and inflammation, various alternative methods provide relief without the long-term risks associated with NSAIDs.

Physical Therapy and Manual Techniques

Physical therapy is widely recommended as a non-pharmacological approach to pain management in sports. Techniques such as manual therapy and intermittent pneumatic compression provided some immediate subjective benefits in improving muscle fatigue, as well as pain and soreness [34]. Study shows that 10-minute massage performed 3 hours after an eccentric exercise not only diminishes muscle soreness but also reduces plasma creatine kinase activity [35]. Additionally, dry needling has proven effective in supporting recovery or promoting muscle repair and function [36]. Another necessary component of physical therapy which is documented to allow return to function and full performance is strength and

conditioning program suited for specific injury requirements [37]. All the mentioned methods, whether applied individually or in combination, can provide aid in rehabilitation and recovery for athletes, reducing their reliance on NSAIDs use.

Cryotherapy

Cold therapy (cryotherapy) is commonly applied post-injury to reduce inflammation and pain. By constricting blood vessels, cryotherapy helps control swelling and numb the affected area, providing immediate relief. Studies indicate that cryotherapy can effectively manage muscle soreness and pain [38, 39].

Topical instead of oral NSAID use

Topical application enables effective drug delivery while minimizing the risks of gastrointestinal, renal, and cardiovascular side effects. Numerous innovative formulations, such as supersaturation, microemulsions, gels, have been developed to enhance the skin's absorption and ensure the drug reaches its target site efficiently. Research indicates that transdermal ibuprofen delivery not only outperforms placebo but also matches the effectiveness of oral ibuprofen, with significantly fewer and less severe adverse effects. Additionally, the reduced likelihood of complications and hospitalization makes topical ibuprofen a potentially more cost-effective option [40].

Dietary Supplements and Nutrients

Diet plays a critical role in preventing injuries, enhancing recovery, and optimizing performance among athletes. A well-balanced diet rich in essential nutrients supports tissue repair, reduces inflammation, and accelerates recovery from training-induced muscle damage. Adequate protein intake aids in muscle regeneration. Omega-3 fatty acids and foods like tart cherry juice and turmeric can lower injury risk by reducing inflammation. Moreover, tailored supplementation, such as creatine or branched-chain amino acids, further enhances performance and recovery. Overall, a strategic nutritional approach ensures athletes maintain peak physical condition, reduce downtime from injuries, and achieve their performance goals [41].

Mind-Body Techniques

Pain perception is significantly influenced by psychological factors, making mind-body techniques a supplement of holistic pain management. Practices like mindfulness and meditation after brief training have demonstrated subjective pain reduction [42]. Those methods could serve as a valuable tool for empowering patients to manage and regulate their individual pain experiences instead of using NSAID drugs.

Quality Sleep Routine

Sleep is a crucial factor in post-exercise recovery, influencing performance and promoting injury recovery. Studies highlight the benefits of adequate sleep, naps, and sleep-hygiene practices. However, many athletes fail to meet recommended sleep durations, impacting recovery and increasing injury odds. Poor sleep habits have been linked to low energy availability and nutritional deficiencies. Pre-sleep nutrition strategies, including casein protein, high-glycaemic index meals, and melatonin-rich foods, enhance sleep quality and muscle protein synthesis [43].

Discussion and Conclusion

The use of NSAIDs in sports medicine presents a challenging balance between the immediate advantages of pain relief and inflammation reduction and the potential risks associated with prolonged use. In the short term, NSAIDs provide athletes with effective pain management and enhanced functionality, often essential for those who require prompt relief to continue training or competing. However, risks associated with short-term NSAID use, including gastrointestinal side effects, underscore the importance of cautious application and regular monitoring.Long-term NSAID usage introduces additional health risks, particularly concerning organ health, tissue repair, and potential dependency. Prolonged NSAID use has been shown to impair bone and muscle healing processes, elevate risks of renal and hepatic complications, and increase the likelihood of cardiovascular issues in predisposed individuals. Given these findings, a conservative approach to NSAID use is recommended, particularly for athletes involved in endurance and contact sports, who may face higher cumulative health impacts over time.

Recommendations

Judicious NSAID Use- NSAID application should be limited to short-term usage, under close medical supervision, mitigate adverse effects. to Monitoring and Alternative Approaches- Regular health assessments and consideration of alternative pain management strategies, such as physical therapy, cryotherapy, dietary supplementation, and mind-body techniques, are advised. These approaches can reduce NSAID reliance sustainable and support health and recovery. Further Research- Continued investigation into the effects of NSAID use across different sports disciplines is essential. Further studies should also explore safer pharmacological alternatives specifically tailored to meet the unique physical demands of athletes.

Disclosure

Author Contributions: Wojciech Urbański, Natalia Dolata, Bartosz Balcer, Adrianna Kruczkowska, Emil Bulzacki, Agnieszka Cebula, Maja Weimann, Aleksandra Stosiek, Mateusz Pakuła, Paweł Liszka

Conceptualization: Wojciech Urbański, Bartosz Balcer

Methodology: Natalia Dolata, Adrianna Kruczkowska

Software: Emil Bulzacki, Mateusz Pakuła, Paweł Liszka

Check: Bartosz Balcer, Maja Weimann, Aleksandra Stosiek

Formal analysis: Natalia Dolata, Adrianna Kruczkowska

Investigation: Emil Bulzacki, Maja Weimann

Resources: Wojciech Urbański, Mateusz Pakuła, Paweł Liszka, Aleksandra Stosiek

Data curation: Emil Bulzacki, Adrianna Kruczkowska, Mateusz Pakuła

Writing- rough preparation: Wojciech Urbański, Maja Weimann

Writing- review and editing: Bartosz Balcer, Agnieszka Cebula

Supervision: Wojciech Urbański, Agnieszka Cebula

Project administration: Natalia Dolata, Agnieszka Cebula, Aleksandra Stosiek

All authors have read and agreed with the published version of the manuscript.

Funding Statement

The study did not receive special funding.

Institutional Review Board Statement Not applicable.

Informed Consent Statement Not applicable.

Data Availability Statement The data presented in this study is available upon request from the corresponding author.

Acknowledgments

Not applicable.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

References

- Brennan R, Wazaify M, Shawabkeh H, Boardley I, McVeigh J, Van Hout M. A scoping review of non-medical and extra-medical use of non-steroidal anti-inflammatory drugs (NSAIDs). *Drug Safety*. 2021;44:937–953. <u>https://doi.org/10.1007/s40264-021-01085-</u><u>9.</u>
- Machado GC, Underwood M.Abdel-Shaheed C, O Day R. Non-steroidal antiinflammatory drugs (NSAIDs) for musculoskeletal pain. *BMJ*. 2021;104:372. <u>https://doi.org/10.1136/bmj.n104</u>.
- 3. Palmer D, Cooper DJ, Emery C, Batt ME, Engebretsen L, Scamell BE, Schamasch P, Shroff M, Soligard T, Steffen K, Whittaker JL, Budgett R. Self-reported sports injuries and later-life health status in 3357 retired Olympians from 131 countries: a cross-sectional survey among those competing in the games. *Br J Sports Med*. 2021;55(1):46-51. https://doi.org/10.1136/bjsports-2019-101772

- Tricker R. Painkilling Drugs in Collegiate Athletics: Knowledge, Attitudes, and Use of Student Athletes. J. Drug Educ. 2000, 30, 313–324. <u>https://doi.org/10.2190/N1K3-V8BK-90GH-TTHU</u>
- 5. Lilly KF. Athletes, NSAID, Coxibs, and the Gastrointestinal Tract. *Curr. Sports Med.* Rep. 2010, 9, 103–105. <u>https://doi.org/10.1249/jsr.0b013e3181d405a9</u>.
- 6. Hörl WH.Nonsteroidal anti-inflammatory drugs and the kidney. *Pharmaceuticals* (2010) 3, 2291–2321. <u>https://doi.org/10.3390/ph3072291</u>.
- 7. Ziltener J-L, Leal S, Fournier P-E. Non-steroidal anti-inflammatory drugs for athletes: An update. *Ann Phys Rehabil Med.* (2010);53(4):278-82. <u>https://doi.org/10.1016/j.rehab.2010.03.001</u>
- 8. Ribeiro H, Rodrigues I, Napoleão L, Lira L, Marques D, Veríssimo M, Andrade JP, Dourado M. Non-steroidal anti-inflammatory drugs (NSAIDs), pain and aging: Adjusting prescription to patient features. *Biomed Pharmacother*. (2022);150, 112958. https://doi.org/10.1016/j.biopha.2022.112958
- Larsen AC, Pedersen JR, Møller M, Storm LK, Koes B, Thorlund JB. The impact of injuries on sports-related analgesic use in Danish youth elite athletes: A 4-week prospective cohort study. J Sci *Med Sport*. 2024 Aug 15:S1440-2440(24)00486-9. <u>https://doi.org/10.1016/j.jsams.2024.08.201</u>
- Er Y, Faki A. Different chemical structures and physiological/pathological roles of cyclooxygenases. *Rambam Maimonides Med J.* 2021;12(3) <u>https://doi.org/10.5041/RMMJ.10426</u>
- 11. Sinniah A, Yazid S, Flower RJ. From NSAIDs to glucocorticoids and beyond. *Cells*. 2021;10(12):3524. <u>https://doi.org/10.3390/cells10123524</u>
- 12. Singh G, Scolnik M. Combination therapy versus celecoxib, a single selective COX-2 agent, to reduce gastrointestinal toxicity in arthritic patients: patient and cost-effectiveness considerations. *Open Access Rheumatol.* 2011;3:53-62. <u>https://doi.org/10.2147/oarrr.s14568</u>
- Bondesen BA, Mills ST, Pavlath GK. The COX-2 pathway regulates growth of atrophied muscle via multiple mechanisms. Am J Physiol Cell Physiol.Jun;290(6):C16511659 <u>https://doi.org/10.1152/ajpcell.00518.2005</u>
- 14. Holgado D, Hopker J, Sanabria D, Zabala M. Analgesics and sport performance: Beyond the pain-modulating effects. *PM R*. 2018;10(1):72–82. <u>https://doi.org/10.1016/j.pmrj.2017.07.068</u>
- 15. Meyer-Glitza PS, Langer T, Wieder O. Non-steroidal anti-inflammatory drug use in endurance sports: balancing performance and health implications. *OSF Preprints* 2023;(9) <u>http://dx.doi.org/10.31219/osf.io/b24nr</u>
- 16. Tso J, Hollowed C, Liu C, Alkhoder A, Dommisse M, Gowani Z, Miller A, Nguyen G, Nguyen P, Prabakaran G, Wehbe M, Galante A, Gilson CR, Clark C, Marshall T, Patterson G, Quyyumi AA, Baggish AL, Kim JH. Nonsteroidal Anti-inflammatory Drugs and Cardiovascular Risk in American Football. *Med Sci Sports Exerc.* 2020 Dec;52(12):2522-2528. <u>https://doi.org/10.1249/mss.00000000002404</u>
- 17. Tscholl PM, Gard S, Schindler M. A sensible approach to the use of NSAIDs in sports medicine. *Sports Med.* 2019 Nov; <u>https://doi.org/10.34045/SSEM/2017/8</u>
- Pham H, Spaniol F. The efficacy of non-steroidal anti-inflammatory drugs in athletes for injury management, training response, and athletic performance: A systematic review. *Sports*. 2024;12(11):302. <u>https://doi.org/10.3390/sports12110302</u>
- 19. Waterman JJ, Kapur R. Upper gastrointestinal issues in athletes. *Curr Sports Med Rep.* 2012;11(2):99-104. <u>https://doi.org/10.1249/jsr.0b013e318249c311</u>

- Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332(7553):1302–1308. <u>https://doi.org/10.1136/bmj.332.7553.1302</u>
- Pedersen JR, Andreucci A, Thorlund JB, Koes B, Møller M, Storm LK, Bricca A. Prevalence, frequency, adverse events, and reasons for analgesic use in youth athletes: A systematic review and meta-analysis of 44,381 athletes. *J Sci Med Sport*. 2022 Oct;25(10):810-819 <u>https://doi.org/10.1016/j.jsams.2022.08.018</u>
- Leone James E, Maurer-Starks Suanne, Wise Kimberly A, Muse Daniel A. (2019). Opioids, Acute Pain Management, Athletes, and Policy. *Bridgewater Review*. 38(2), 4-9.
- 23. Baker J, Cotter JD, Gerrard DF, Bell ML, Walker RJ. Effects of indomethacin and celecoxib on renal function in athletes. *Med Sci Sports Exerc*. 2005 May;37(5):712-7. https://doi.org/10.1249/01.mss.0000162700.66214.ce
- 24. Lipman GS, Shea K, Christensen M, Phillips C, Burns P, Higbee R, Koskenoja V, Eifling K, Krabak BJ. Ibuprofen versus placebo effect on acute kidney injury in ultramarathons: a randomised controlled trial. *Emerg Med J*. 2017 Oct;34(10):637-642. https://doi.org/10.1136/emermed-2016-206353
- 25. Shoor S. Athletes, nonsteroidal anti-inflammatory drugs, coxibs, and the gastrointestinal tract. *Curr Sports Med Rep.* 2002;1(2):107–15. <u>https://doi.org/10.1249/00149619-200204000-00008</u>
- 26. Van Wijck K, Lenaerts K, Grootjans J, Wijnands KAP, Poeze M, Van Loon LJC, et al. Physiology and pathophysiology of splanchnic hypoperfusion and intestinal injury during exercise: strategies for evaluation and prevention. *Am J Physiol Gastrointest Liver Physiol.* <u>https://doi.org/10.1152/ajpgi.00066.2012</u>
- 27. Papantoniou K, Michailides C, Bali M, Papantoniou P, Thomopoulos K. Gastrointestinal bleeding in athletes. *Ann Gastroenterol*. 2023;36(3):267–274. https://doi.org/10.20524/aog.2023.0788
- García Rodríguez LA, Pérez Gutthann S, Walker AM, Lueck L. The role of nonsteroidal anti-inflammatory drugs in acute liver injury. *BMJ*. 1992;305(6858):865–8. doi: <u>https://doi.org/10.1136/bmj.305.6858.865</u>
- Vuolteenaho K, Moilanen T, Moilanen E. Non-steroidal anti-inflammatory drugs, COX-2, and the bone healing process. *Basic Clin Pharmacol Toxicol*. 2008;102(1):10– 4. <u>https://doi.org/10.1111/j.1742-7843.2007.00149.x</u>
- Lisowska B, Kosson D, Domaracka K. Positives and negatives of NSAIDs in bone healing: The effects on repair. *Drug Des Devel Ther*. 2018;12:3267–74. <u>https://doi.org/10.2147/DDDT.S164565</u>
- 31. Gorski T, Cadore EL, Pinto SS, da Silva EM, Correa CS, Beltrami FG, Kruel LF. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med.* 2011;45(2):85–90.
 - https://doi.org/10.1136/bjsm.2009.062166
- 32. Schweiger V, Niederseer D, Schmied C, Attenhofer-Jost C, Caselli S. Athletes and hypertension. *Curr Cardiol Rep.* 2021;23(12):176. <u>https://doi.org/10.1007/s11886-021-01608-x</u>
- 33. Warden SJ. Prophylactic use of NSAIDs by athletes: a risk/benefit assessment. *Phys* Sportsmed. 2010;38(1):132–8. <u>https://doi.org/10.3810/psm.2010.04.1770</u>
- 34. Heapy AM, Hoffman MD, Verhagen HH, Thompson SW, Dhamija P, Sandford FJ, Cooper MC. A randomized controlled trial of manual therapy and pneumatic

compression for recovery from prolonged running - an extended study. *Res Sports Med.* 2018;26(3):354–364 <u>https://doi.org/10.1080/15438627.2018.1447469</u>

- 35. Zainuddin Z, Newton M, Sacco P, Nosaka K. Effects of massage on delayed-onset muscle soreness, swelling, and recovery of muscle function. *J Athl Train*. 2005;40(3):174–80.
- 36. Tang CT, Song B. Acupuncture and dry needling for sports performance and recovery. *Curr Sports Med Rep.* 2022;21(6):213–8. <u>https://doi.org/10.1249/jsr.000000000000968</u>
- 37. Reiman MP, Lorenz DS. Integration of strength and conditioning principles into a rehabilitation program. *Int J Sports Phys Ther*. 2011;6(3):241–53.
- Dupuy O, Douzi W, Theurot D, Bosquet L, Dugué B. An evidence-based approach for choosing post-exercise recovery techniques to reduce markers of muscle damage, soreness, fatigue, and inflammation: A systematic review with meta-analysis. *Front Physiol.* 2018;9:403. <u>https://doi.org/10.3389/fphys.2018.00403</u>
- Bailey DM, Erith SJ, Griffin PJ, Dowson A, Brewer DS, Gant N, Williams C. Influence of cold-water immersion on indices of muscle damage following prolonged intermittent shuttle running. J Sports Sci. 2007;25(11):1163–70. https://doi.org/10.1080/02640410600982659
- 40. Manoukian MAC, Migdal CW, Tembhekar AR, Harris JA, DeMesa C. Topical administration of ibuprofen for injured athletes: considerations, formulations, and comparison to oral delivery. *Sports Med Open.* 2017;3(1):36. https://doi.org/10.1186/s40798-017-0103-2
- Wang L, Meng Q, Su CH. From food supplements to functional foods: Emerging perspectives on post-exercise recovery nutrition. *Nutrients*. 2024;16(23):4081. <u>https://doi.org/10.3390/nu16234081</u>
- 42. Zeidan F, Vago DR. Mindfulness meditation-based pain relief: a mechanistic account. *Ann N Y Acad Sci.* 2016;1373(1):114–27. <u>https://doi.org/10.1111/nyas.13153</u>
- Bonilla DA, Pérez-Idárraga A, Odriozola-Martínez A, Kreider RB. The 4R's framework of nutritional strategies for post-exercise recovery: A review with emphasis on new generation of carbohydrates. *Int J Environ Res Public Health*. 2020;18(1):103. <u>https://doi.org/10.3390/ijerph18010103</u>