The misuse of analgesics and nonsteroidal anti-inflammatories in runners

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Abstract

Global participation in running has continued to grow over the last decade, with millions of people running weekly, regardless of distance. These events, particularly endurance running events, require months of progressive training and load adjustment, which, combined with other factors, increase the risk of developing running-related injuries. Inflammation is a natural biological response important for healing in musculoskeletal tissue; however, it may also contribute to the unpleasant experience of pain. Runners may suffer from exercise-induced pain and inflammation, necessitating using analgesics and nonsteroidal anti-inflammatories. Unfortunately, the inappropriate use of these drugs is frequently seen in athletes, which may impact their recovery after injury or general health status. This review presents in brief the current knowledge of running-related pathology and treatment thereof, including considerations of its misuse.

Keywords: analgesics, inflammation, nonsteroidal anti-inflammatories, pain, running

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Introduction

Running has grown in popularity over the last decade, with millions of individuals running weekly.[1] This popularity is observed for distances ranging from 5 km to ultra-marathon distances, where long-distance events require a greater degree of training when compared to shorter distances.[1] This increased demand for endurance running events, in combination with other factors, increases the risk of developing running-related injuries (RRI).[1] Athletes may suffer from exercise-induced pain and inflammation,[1-3] which are commonly observed with endurance running due to the nature of the event.[4] Inflammation is important for healing in musculoskeletal tissue; however, it may also contribute to pain, which can be an unpleasant experience.[3] Unfortunately, many athletes do not give themselves sufficient time to recover when injured or overworked, which results in support-seeking measures to get them back on their feet.[5] Pharmacologically, analgesics and anti-inflammatories, such as nonsteroidal anti-inflammatory drugs (NSAIDs), would generally be used to mitigate the effects of RRI and exercise-induced pain and inflammation.[1-3] Such pharmacotherapy is turned to due to their accessibility.[5] There are multiple studies which have assessed the frequency of use of NSAIDs during endurance events.[6-8] Many athletes believe that analgesics and anti-inflammatories improve performance and allow for the prophylactic management of injuries. Therefore, the use and misuse thereof are prevalent in sports, including endurance running.[5] Additionally, between 2009 and 2014, the number of individuals taking part in marathons increased worldwide by 13.25%, with average completion times indicating a high proportion of non-elite runners.[1] This more diverse range of runners includes individuals with comorbidities who may be more at risk of NSAID-associated adverse effects.[1]

Studies suggest that runners have poor knowledge of the correct use and associated side effects of analgesics and anti-inflammatories.[3-4,6] Athletes have been shown to take analgesics prior to a marathon, where such use has been associated with drug-induced side effects (including stomach cramps and gastrointestinal bleeding).[1] Analgesics, such as NSAIDs, may precipitate cardiovascular and gastrointestinal events, with gastric ulcers, myocardial infarctions and strokes being prominent concerns.[9] Moreover, the use of NSAIDs in athletes is believed to be detrimental to muscle healing and has a high risk of exceeding the recommended dosages.[6,9] This paper will review the prevalence of the use of analgesics and NSAIDs in runners and the associated risks in the context of running.

Inflammation and pain

Pain, an extremely complex phenomenon, is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[3] Pain is influenced by culture, previous pain events, mood and the ability to cope with the sensation.[3] There are two main types of pain: nociceptive and neuropathic pain.[10] Nociceptive pain is the result of neuronal activity in response to actual tissue damage or in stimuli that is potentially tissue-damaging.[11] Neuropathic pain is chronic and is characterised by nervous system lesions or dysfunction.[11-12] Neuropathic pain can be maintained by several mechanisms, with one common example being diabetic peripheral neuropathy present in 50% of diabetic patients.[11-12] Given the pathophysiological pathways involved, each type is treated differently from a pharmacotherapeutic vantage.[10] For example, depending on the severity, nociceptive pain will be treated with NSAIDs and opioids, whereas neuropathic pain is treated with antidepressants, anxiolytics or antiepileptic drugs (such as gabapentin).[10]

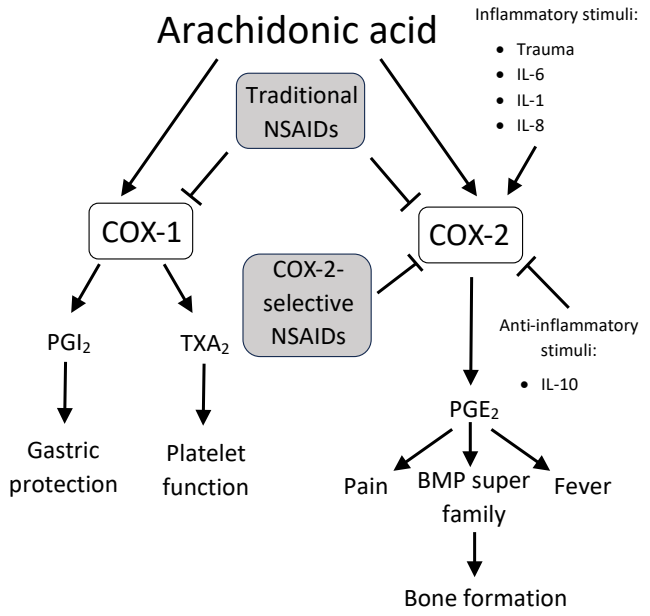

Figure 1: The synthesis of prostanoids and their associated biological effects.[15] TXA_2 = thromboxane A_2. COX-1 = cyclooxygenase-1; COX-2 = cyclooxygenase-2; PGI_2 = prostaglandin I_2; PGE_2 = prostaglandin E_2; IL-6 = interleukin-6; IL-1 = interleukin-1; IL-8 = interleukin-8; IL-10 = interleukin-10; NSAIDs = nonsteroidal anti-inflammatories; BMP = bone morphogenetic protein.

There are two forms of pain: acute pain, which has a limited duration, and chronic pain, which persists beyond the accepted time of healing.[3] When tissue injury occurs, phospholipids are released from the cell membrane and converted to arachidonic acid by the enzyme phospholipase A_2.[13] Arachidonic acid is then converted by the enzyme cyclooxygenase (COX) into various prostanoids, including prostaglandins (PGs).[13] The PGs are responsible for mediating pain and inflammation, e.g. those resulting from sports injuries.[3]

The COX enzyme is available in two isoforms: COX-1 and COX-2 (Figure 1).[13] Both isoforms are found throughout the body.[2] The COX-1 isoform is constitutively expressed and serves a homeostatic role.[2,13] In the gut, PGs, specifically PGE_2, play a role in gastro-protection and maintenance of several key functions of the GI tract.[13] Additionally, the prostanoids thromboxane A_2, PGs (E_1, E_2 and E_3) and prostacyclin play a role in platelet aggregation.[13] The PGE_2 also plays an important role in sodium and water retention in the kidney.[13] The COX-2 isoform is released by pro-inflammatory cytokines, mitogens and endotoxins in inflammatory cells.[13-14] Once stimulated, COX-2 produces the PGs, which are responsible for pain and inflammation.[13] Therefore, inhibition of COX-2 using NSAIDs helps to mitigate the pain and inflammation mediated by the COX-2-produced PGs.[13]

Muscle soreness versus muscle injury in running

Muscle soreness induced by prolonged exercise, as in the case of marathon running, is referred to as early-onset muscle soreness (EOMS).[16] The muscle soreness and damage markers in EOMS are different from those seen in delayed-onset muscle soreness, seen after eccentric muscle contraction, which occurs during resistance training.[16] Running longer distances, such as marathons, places enormous mechanical stress on one's body, which leads to muscle damage.[16] For example, gastrocnemius damage has been reported after a marathon due to the mechanical stress of the distance.[16] Increased creatinine kinase and lactate dehydrogenase plasma concentrations after a marathon are indicators of cellular damage which persist for approximately four days after a marathon, suggesting the muscle soreness will subside after several days.[16] It is apparent that muscle soreness induced by running long distances is a natural physiological response to the mechanical stress placed on the body whilst running.[16]

Running injuries may be defined in several ways,[17] for example, an injury requiring medical attention,[18] by the time needed for an athlete to return to running, or by a feeling of pain or discomfort.[17,19,20] A drawback to running is the relatively high risk of injury between 19% and 79%, which is variable due to the ambiguity in defining an injury, the difference in study populations, and follow-up periods.[21] Running is one of the most common sport activities to cause injuries of the lower back and leg.[21] Poorly perfused tissues, such as ligaments, tendons and cartilage, are at a higher risk of injury as they adapt more slowly than muscles to an increased mechanical load.[21]

Treatment of sports injuries

Initial treatment

The treatment of injuries in runners should combine five strategies which are aimed at treating the present injury as well as preventing its recurrence or the occurrence of a different injury.[22] Importantly, these strategies do not necessarily infer pharmacological treatment, but rather non-pharmacological measures. The five strategies are 1) appropriate medical care, 2) athlete education, 3) cross-training, 4) specific exercise and 5) programmed return to running (Table I).[22]

Pharmacological treatment

The World Health Organization's three-step pain ladder determines the appropriate pharmacological medical care depending on the level of pain experienced on a ten-point scale.[28] There are several analgesics and anti-inflammatories, which are commonly used to treat pain and inflammation, such as NSAIDs (e.g. ibuprofen and celecoxib) and opioids (e.g. codeine and tramadol), as single agents or in combination.[3] The most commonly used analgesics and anti-inflammatories and their associated side effects are discussed in Table II.

Nonsteroidal anti-inflammatories

In the majority of cases, NSAIDs are the drugs of choice for the treatment of sports injuries.[3] The NSAIDs are widely used in sports medicine and are the first line of use to decrease pain, swelling and inflammation caused by a soft tissue injury.[3] The NSAIDs exhibit anti-inflammatory and analgesic effects by reducing PG formation due to inhibition of COX.[13] The NSAIDs are available in

Table I: The different forms of recovery strategies that should be applied concurrently to ensure the healing of an injury and to prevent possible recurrence.

Recovery strategy	Description
Medical care	Basic to all forms of treatment are some types of rest for the injured part, usually ice and aspirin or some form of NSAID.[22] Remedial exercise with some form of stretching and strengthening should be included.[23] Complete rest is not suggested as it will result in musculoskeletal atrophy and impaired function.[22]
Athlete education	The single most important factor in reducing both the incidence and recurrence of injuries to endurance athletes.[22] The athlete must understand the reason(s) for the injury, the treatment plan and how to prevent further injury.[22] Athletes should understand that proper technique, proper progression and age-related considerations are all within their control.[22] Athlete education can be accomplished in conjunction with competitions through pre-race communication, pre-race discussions as well as through articles in popular running magazines.
Cross-training	Cross-training means alternative activity or concurrent training in more than one type of activity.[23] The main benefit of cross-training is the central adaptations (mainly cardiovascular) to training. For an injured runner, cross-training allows for the injury to heal while allowing the athlete to maintain a high level of fitness. However, the peripheral adaptations from running will be lost.[23] Therefore, once the injury is healed, the athlete should gradually reduce the time spent on the alternative activity while gradually increasing the time spent running.[23] Cross-training activities include swimming, pool running (may have carry-over benefits), cycling, rowing or any other activity that reduces eccentric and impact loading.[23]
Specific exercises	Specific remedial exercises should be started as soon as the acute inflammatory stage is past.[24] There should be no pain associated with specific exercise retraining. Stretching exercises should be implemented to develop appropriate ranges of motion since injury to tendons or muscles usually results in scarring and consequent shortening. Stretching should be done when muscle temperature has been elevated by a whole-body warm-up. It has been reported that cold stretches may increase the risk of injury.[25] An appropriate technique would be to stretch for 6 seconds followed by 6 seconds of relaxation, repeated ten times. Eccentric strength training, in which the muscle lengthens against resistance, is helpful during rehabilitation and in treating tendinitis.[26]
Return to training	Since peripheral adaptation is lost, even with cross-training, the return to running should be controlled and gradual. The progression thereof depends on the specific injury and the time taken off. Initially, runners should do 15 minutes of slow running every other day, with 5-minute increases weekly. When 40 minutes of painless running is achieved, the distance can be increased by the 10% rule. By following these guidelines, 80% of runners will be able to return to running within three months.[27]

various formulations, including tablets, creams, ointments, sprays, gels and patches.[3]

The NSAIDs are associated with significant gastrointestinal and renal side effects, among other concerns (Table II).[7] Furthermore, NSAIDs may cause water retention and hyponatraemia, causing them to interact with anti-hypertensive medication.[3] Traditional NSAIDs, those that inhibit both COX-1 and COX-2, are commonly associated with more distributed side effects due to their non-selective inhibition of COX, which includes more severe gastrointestinal side effects.[3] Newer agents, such as the COX-2-selective NSAIDs (COXIBs), are more selective for COX-2 and are effective at decreasing pain and allowing a quicker return to activity and rehabilitation.[29-31] The COXIBs also have a reduced frequency of gastrointestinal and renal side effects.[32] Although traditional NSAIDs and COXIBs have similar efficacy in the clinical setting, COXIBs are a safer choice due to their gastrointestinal safety profile.[32] However, COXIBs are associated with an increased risk of thrombosis (due to the inhibition of prostacyclin), increased blood

Table II: The commonly used oral analgesics and anti-inflammatories and their recommended doses and their commonly associated side effects.[38]

Drug (product example[s])	Recommended dose	Side effects
Aspirin (Bayer Aspirin®)	325 to 650 mg every 4 to 6 hours, with a maximum daily dose of 4 g.	Indigestion, stomach aches and bleeding or bruising more easily than normal.
Celecoxib (Celexib®)	200 mg daily or 100 mg every 12 hours. The maximum daily dose is 400 mg per day.	Stomach pain, constipation, diarrhea, heartburn, nausea, vomiting, dizziness, headache, respiratory tract infection.
Diclofenac (Voltaren®)	50 mg every 8 hours, with a maximum daily dose of 150 mg.	Nausea, vomiting, diarrhea, vertigo, headaches, stomach aches, loss of appetite and mild rash.
Ibuprofen (Deep Relief®)	400 mg every 4 to 6 hours. The maximum daily dose is 3 200 mg (acute) or 2 400 mg (chronic)	Headaches, dizziness, nausea, vomiting and indigestion.
Indomethacin (Arthrexib®)	Immediate release: 25 to 50 mg every 8 to 12 hours. Controlled release: 75 mg once or twice daily. The maximum dose is 150 mg per day.	Stomach pain, diarrhoea, indigestion, nausea and vomiting.
Meloxicam (Loxiflam®)	7.5 to 15 mg once daily. The maximum daily dose is 15 mg.	Diarrhea and indigestion.
Naproxen (Aleve®)	250 to 500 mg every 12 hours (naproxen based) or 275 to 550 mg every 12 hours (naproxen sodium)	Confusion, headaches, ringing in the ears, changes in vision, tiredness, dizziness and rashes.
Paracetamol (Panado®, Dischem Paracetamol®)	Adults: 650 to 1 000 mg every 6 hours with a maximum of 4 g/day Children: 15 mg/kg body weight every 6 hours with a maximum of 60 mg/kg body weight per day.	Nausea, vomiting and constipation.

pressure, oedema and congestive heart failure.[3,32-33] Additionally, COXIBs are more costly, which may be a reason patients opt for traditional NSAIDs.[34]

All of the risks associated with selective or non-selective NSAIDs are a major concern; however, it appears that athletes opt for analgesic use due to their perceptions of improved performance and prophylactic management of injuries.[35] The use and misuse of analgesics is prevalent in sports due to a lack of adequate knowledge of the effects and side effects of these agents.[36] Moreover, the use of analgesics and anti-inflammatories is speculated to delay muscle recovery as the PGs inhibited by drugs such as NSAIDs are important in the turnover of protein for protein synthesis during muscle repair.[3]

When looking at aspirin specifically, analgesic and antipyretic effects appear at doses up to 300 mg, while anti-inflammatory effects occur at higher doses alongside an increased risk for gastrointestinal side effects (e.g. gastric ulcers).[3] Aspirin's use in sports is limited due to its ability to inhibit platelet aggregation, which may increase bleeding,[3] where a single dose of 100 mg aspirin abolishes thromboxane A_2 production by COX-1 on blood platelets, inhibiting blood clotting, which may precipitate bleeding.[37]

Paracetamol

Paracetamol displays both antipyretic and analgesic effects but lacks anti-inflammatory or anti-clotting properties as it specifically inhibits the COX-3 isoform (predominantly found in the central nervous system and in the heart).[3] The use of paracetamol in acute sports injuries is reported to be safe up to a 3 to 4 g/day dose, with the incidence of side effects being similar to that of the placebo.[39] However, an overdose of paracetamol can cause severe hepatic necrosis.[40]

Opioids

Opioids mimic the actions of endogenous opioid peptides by interacting with the μ, δ and κ receptors.[41] These receptors are coupled to G_i proteins, which close N-type voltage-operated calcium channels and open calcium-dependent potassium channels, resulting in hyperpolarisation-induced reduction of neuronal excitability.[41] Activation of the opioid receptors also decreases cyclic adenosine monophosphate (cAMP) production, which modulates the release of nociceptive neurotransmitters such as substance P.[41]

Codeine, a potent opioid analgesic,[39] is often used in combination with aspirin or paracetamol.[30] However, it is reserved for more severe pain due to its addictive properties.[39,42-43] Tramadol, also an opioid, is effective in the treatment of neuropathic pain,[12] but it has been suggested that it may have a lower efficacy and a greater incidence of side effects compared to the COXIBs when treating lower back pain.[44] The use of tramadol in sports medicine is more appropriate in severe injuries when additional analgesia is needed.[3]

The use of analgesics in runners

Athletes, including cyclists, runners and triathletes, have indicated the use of NSAIDs prior to, during and after sporting events.[9] Furthermore, 33% of runners use analgesics to aid recovery from an RRI.[45] The use of analgesics in runners ranges from 64 to 71%.[5,9] Moreover, 35 to 57%, 11 to 56%, and 56 to 80% of runners take analgesics prior to, during, and after a run, respectively.[5-6,9] Athletes competing in ultra-distance marathons are more likely to use NSAIDs during the event than those running marathons and half-marathons.[6] The most commonly used analgesics include NSAIDs (ibuprofen, diclofenac, naproxen and celecoxib and aspirin) and paracetamol.[4,6] Myprodol®, a combination of paracetamol, ibuprofen and codeine, is commonly used by runners during a run.[5] Some runners believe that taking a single analgesic is not effective in relieving muscle and joint pain. Hence, they opt for the use of a combination of analgesics.[5] For example, runners may take Myprodol® in combination with diclofenac, or some runners take diclofenac and ibuprofen in combination during a run.[5] The use of analgesics in runners is significantly higher in those individuals who reported a previous RRI,[5] where a RRI is a three-fold predictive factor for use of analgesics compared to other factors.[5] Concerningly, runners have also reported taking excessive doses of NSAIDs available over-the-counter.[4] In one study, diclofenac was taken at a dose of > 100 mg, whereas ibuprofen was taken at 800 mg (twice the recommended daily dose).[4] Approximately 3.4% of runners have reported exceeding the recommended daily dose of NSAIDs.[1] In 2009, it was reported that analgesics were the most common category of drug in acute overdose in adult patients (10%).[46] Paracetamol alone or in combination accounted for 42% of acute overdose cases for the analgesics group, and NSAIDs accounted for 33% of cases.[46] Ibuprofen is the most common NSAID taken in cases of overdose (81%) followed by naproxen (11%).[46]

Analgesics are mainly accessed over the counter by 90% of runners, with 45% doing so without the recommendations of a healthcare professional.[5] Pharmacists are only responsible for 25% of the recommendations, with friends and family being responsible for 19%.[5] In South Africa, analgesic use appears to be increased in runners as they believe that many other runners are using them.[5] There is limited knowledge about analgesics and the associated side effects thereof,[4-5] where approximately 93% of runners are not aware of the risk of using analgesics in connection with endurance sports.[4] Furthermore, South African-based runners have good attitudes towards the use of analgesics but lack knowledge of their specific side effects, effects and drug interactions.[45] This then translates into bad practices regarding analgesic use.[45] For example, in one study 68% of South African runners used analgesics in running despite showing good attitudes towards the use thereof.[45] It has been shown that being part of a sports club is a predictor of self-medication.[45]

The incidence of side effects from analgesics is significantly higher in marathon runners compared to half-marathon runners (18% vs 7%).[4] The incidence of analgesic-related side effects is 4 to 10

times higher when compared to a control cohort during a run.[4] Common analgesic-related side effects include gastrointestinal cramps, haematuria and cardiovascular events (arrhythmia and palpitations), with gastrointestinal cramps and cardiovascular events being the most frequent.[4] Moreover, gastrointestinal cramps in runners taking analgesics are frequently blamed for race withdrawal.[4] Increasing the dose of analgesics used during a race increases the onset of side effects by three-fold.[4] The drug-related incidence of side effects during a race is most frequent with ibuprofen, aspirin and diclofenac.[4] Aspirin has been associated with numerous cases of gastrointestinal and kidney bleeding (49% of individuals reported this occurred during a race when aspirin was taken at high doses).[4] In some cases, side effects experienced from analgesic use during a marathon required hospital admittance.[4] Interestingly, it has also been reported that NSAID use decreases the amount of collagen synthesised after prolonged running.[47] It was found that twice daily ingestion of 100 mg of the NSAID indomethacin significantly reduced the levels of pro-collagen type I N-terminal propeptide, an important peptide in collagen turnover, in the patellar tendon after a 32 km run compared to the control group.[47]

Recently, there has been controversy in the world of endurance sports when the use of ibuprofen was banned in the Ultra Tour de Mount Blanc, one of the world's leading sports events, due to "negative health risks".[48] Studies reported that kidney injury was frequent in ultra-marathon runners with an association between NSAID use and acute renal injury/failure.[49] The use of NSAIDs was present in approximately 79 to 80% of acute renal failure cases.[50] The NSAID indomethacin has been shown to cause a significant reduction in renal blood flow during exercise and post-exercise, which caused a marked elevation in the mean arterial pressure and renal vascular resistance.[51] Exercise increases the amount of vasoconstriction-inducing hormones and renal sympathetic neuronal activity, which is modulated by renal prostaglandins.[51] Thus, blocking the production of these prostaglandins by using NSAIDs results in reduced renal blood flow.[51] Interestingly, this phenomenon only occurs during exercise and not under normal/basal conditions.[51]

Historically, the Comrades Marathon reports the highest incidence of acute renal failure in any sporting event in the world (2/10 000 runners).[50] The highest reported incidence of acute renal failure of 10/10 000 runners was in the 1986 Comrades Marathon.[50] In such instances, the cases vary from unrecognised failure that persists for around ten days after the Comrades Marathon to significant renal damage requiring extended hospitalisation and peritoneal dialysis.[50] The reason for this occurrence is deemed to be due to dehydration secondary to inadequate fluid intake and/or diarrhoea, vomiting, rhabdomyolysis and the use of analgesics (such as paracetamol and NSAIDs).[50] In a case study on four individuals who were admitted to the hospital for acute renal failure after having run the 2010 Comrades Marathon, it was found that three of the four individuals ingested NSAIDs during the race, whilst the fourth individual ingested a muscle relaxant.[50] The patients all presented with hyponatraemia one to four days after the race finished.[50] The authors suggested that the hyponatraemia was secondary to acute renal failure (ARF), which produced dilutional hyponatraemia secondary to protracted anuria/oliguria.[52] It was suggested that rhabdomyolysis, exercise-induced hyponatraemia and NSAID use may have caused the ARF.[50] However, more research needs to be conducted on this cohort of athletes to identify the factors placing these athletes at risk of life-threatening medical complications such as exercise-induced hyponatraemia and ARF.[50]

Conclusion

Findings reveal that NSAIDs are an easily accessible drug for runners to prevent or treat RRIs or exercise-induced inflammation and pain; however, many runners do not understand how these drugs exert their effects and what risks may be present. Importantly, there is a lack of knowledge of the side effects associated with such drugs in the context of endurance running. Athletes tend to use higher doses of analgesics, particularly NSAIDs such as ibuprofen and diclofenac, than those recommended and may engage in polypharmacy. The analgesics are obtained over-the-counter without the recommendation of a healthcare professional.

While injury is a predictor for use of NSAIDs, runners appear to be using NSAIDs to participate in events, to push through injuries by increasing pain tolerance and to deal with post-event soreness. The high use of NSAIDs without full knowledge of side effects, contraindications or cautions for use is a major concern. The lack of evidence for the benefits of using NSAIDs in exercise means that some runners are making poor benefit-harm decisions. Recreational runners appear to have an unmet need for more information on NSAIDs, which can be filled out by organisers of sports events or healthcare professionals (such as pharmacists, physiotherapists, sports practitioners, and biokineticists). The high use of NSAIDs before and during endurance running events is concerning, given the greater physiological stresses associated with these events. The organisers of endurance running events, as well as popular running media platforms, should consider providing athletes and coaches with evidence-based advice on the use of NSAIDs, as well as tracking systems for adverse effects experienced during events.

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