Abstract

Analgesics are widely used in sport to treat pain and inflammation associated with injury. However, there is growing evidence that some athletes might be taking these substances in an attempt to enhance performance. While the pharmacological action of analgesics and their use in treating pain with and without anti-inflammatory effect is well established, their effect on sport performance is debated. The aim of this review was to evaluate the evidence of whether analgesics are capable of enhancing exercise performance, and if so, to what extent. Paracetamol has been suggested to improve endurance and repeated sprint exercise performance by reducing the activation of higher brain structures involved in pain and cognitive/affective processing. Non-steroidal anti-inflammatory drugs (NSAIDs) affect both central and peripheral body systems, but investigation on their ergogenic effect on muscle strength development have provided equivocal results. The therapeutic use of glucocorticoids is indubitable, but clear evidence exists for a performance enhancing effect following short-term oral administration. Based upon the evidence presented in this review article, the ergogenic benefit of analgesics may warrant further consideration by regulatory bodies. In contrast to the aforementioned analgesics, there is a paucity of research on the use opioids such as tramadol on sporting performance.

Keywords

drug-use, anti-doping, pharmacological drugs, exercise induced pain

Introduction

There is little doubt that when exercise is performed above certain intensities, or over a prolonged period of time, it causes feeling of pain and discomfort. Sayings such as ‘no pain, no gain’ are often heard in relation to both training and competition settings across a variety of different sports. Indeed, these feelings of exercise-induced pain have been shown to have a negative effect on training and performance [1]. As a consequence, there has been a trend for athletes from all levels and ages to use pharmacological analgesics substances prior to training and competition up to 4-fold more than their age-matched general population [2]. The general term analgesic covers a variety of different pharmacological substances, including non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesic (such as paracetamol

and others), weak opioids (for example tramadol, codeine or morphine [3]) and orally administered or injected glucorticosteroids [4,5]. Indeed, paracetamol and NSAIDs are one of the most recurrent groups of pharmacological substances used by athletes ranging from 11 up to 92% [6,7]. For instance, it is common for athletes with minor injuries to continue training and even competing, by treating their minor health issues with analgesic [8].

The aforementioned negative association between pain and exercise capacity increases the likelihood of analgesic use as a method to increase the level of performance during competition [5,9]. Furthermore, the trends for more frequent use of analgesics in-competition vs. out-competition, use of more than one drug at the same time, and administration of these medications at supratherapeutic dosages, all suggest athletes may be using these analgesics as ergogenic aids [4,5]. Therefore, in contrast to the post-exercise use of analgesics to accelerate recovery, there is potential for their prophylactic use as a potential performance enhancing intervention. In comparison to what is known about the use of analgesics for treating sporting injury [10,11], much less is known about their effects on exercise related physiology and performance [12–14]. However, as analgesics exert a pharmacological action on key physiological systems related to exercise performance, a theoretical rationale exists whereby these drugs could provide a significant ergogenic effect.

Material and methods

The aim of this manuscript was to review the literature and evaluate the evidence for the ergogenic effect of analgesics, expected dosages, and potential side effects. A computer search of scientific databases (PubMed, Web of Science, ScienceDirect and Scopus) was made for English language articles investigating the use of analgesics in sport for all period of time up to September 2016. The following keywords were used in different combinations: “analgesics”, “paracetamol”, “acetaminophen”, “painkillers”, “NSAID”, “non-steroidal anti-inflammatory drugs”, “glucocorticoids”, “ibuprofen”, “tramadol”, “exercise”, “sport”, and “performance”. This search retrieved 1440 articles. All titles were scanned, and abstracts were read for article relevance. The reference lists of all included articles, were also searched for additional relevant papers. Articles with performance outcome, whether primary or secondary, in human healthy subjects, randomized, placebo controlled and double-blind methods were included. We considered performance as any measure of time, distance, power output, or muscle strength

(weight lifted, one repetition maximum (1RM) or number of repetitions). Following review of retrieved articles, 20 met the inclusion criteria.

Results

Paracetamol (Acetaminophen)

Summary of the evidence on performance

Paracetamol (also known as acetaminophen) is one of the most commonly used over-the-counter analgesics [10], although the mechanism by which it achieves its pain relieving effect is not completely understood. Paracetamol may exert its action via the cyclooxygenase pathway (COX) [15], but without significant anti-inflammatory activity, or inhibition of thromboxane production [10]. It is also known to block prostaglandin synthesis from arachidonic acid by inhibiting COX [13]. Paracetamol also might exert its analgesic effect by inhibiting voltage-gated calcium and sodium currents in primary sensory neurons via activation of spinal transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential cation cannel 1 (TRPV1) [16]. Ottani et al. [17] suggested that paracetamol could also have an effect on the endogenous cannabinoid system involving CB_1 receptors in the brain or spinal cord. Paracetamol might also inhibit pain sensation by decreasing the activation of higher brain structures (e.g. anterior cingulate cortex or prefrontal cortices) involved in pain and cognitive/affective processing [18].

Even though the exact mechanism of action is yet to be fully determined, some researchers have attempted to use paracetamol's analgesic effects as a method to reduce pain induced by exercise. The current available research is summarized in Table 1. Mauger et al. [19] found that 1.5g paracetamol ingestion increased cycling power output, and reduced the time required to complete a 16.1 km cycling time trial (26 min 15 s ± 1 min 36 s), compared to a placebo condition (26 min 45 s ± 2 min 2 s) in trained cyclists. The authors hypothesized that paracetamol may exert its effect by reducing perceived pain and rating of perceived exertion (RPE), although no differences were observed between conditions in their study. More recently, the influence of 1.5g paracetamol ingestion on exercise performance was examined during a series of "all-out" Wingate sprints [20]. Results demonstrated a 5% improvement in mean power output in the paracetamol (391 ± 74 W) compared to the placebo (372 ± 90 W) condition. Collectively, these studies suggest that, both short [20] and long duration [19] exercise performance can be improved

by paracetamol ingestion. An alternative explanation as to why paracetamol might improve exercise performance is via an increased cortico-spinal excitability, and thus higher force output from the muscular system [18,21]. Mauger and Hopker [21] demonstrated that paracetamol ingestion significantly increased the motor evoked potential and motor evoked area of the right first dorsal interossei muscle following transcranial magnetic stimulation of the motor cortex. However, more research is required to verify the pharmacological effects of paracetamol on cortico-spinal excitability and its potential to enhance whole body exercise performance.

Paracetamol also has a notable antipyretic effect, and has the potential to enhance exercise performance via a reduction in thermal stress of exercise in hot conditions [12]. Burtscher et al. [22], recruited 7 runners to perform a running time-to-exhaustion test in 30ºC and 50% relative humidity at an exercise intensity corresponding to the 70% VO_{2max} following ingestion of a single 500mg dose of paracetamol or a placebo. They found a smaller increase in core temperature after 20 min running following paracetamol ingestion, but no difference between conditions at exhaustion, or in terms of the exercise time-to-exhaustion performance. In a similar study, Mauger et al. [23] examined the influence of paracetamol on cycling time-to-exhaustion in 30 ºC and 50% relative humidity at 70% VO_{2max}. The authors measured core temperature (T_{core}), skin temperature (T_{skin}), body temperature (T_{body}) and thermal sensation. Results demonstrated an increased time-to-exhaustion in the paracetamol compared with placebo condition (23 ± 15 min vs. 19 ± 13 min). The authors concluded that the antipyretic effect of paracetamol was a useful mechanism to enhance performance by reducing T_{core}, T_{skin}, T_{body} and thermal sensation during exercise in the heat, in the absence of a pre-cooling mechanism at rest. However, Coombs et al. [24] failed to find any effect of paracetamol on thermoregulatory control or perceptual responses during exercise at a fixed rate of metabolic heat production in hot-humid condition. Interestingly their methodological design afforded a fixed level of heat production between participants over a standardized exercise duration, something not done by either of the aforementioned studies. Therefore, Coombs et al.[22] could separate the effects of the exercise on thermoregulatory responses from those attributable to the pharmacological action of the paracetamol. Thus, instead of paracetamol exerting a performance enhancing antipyretic effect, the findings of Mauger et al. [23] could be attributable to its aforementioned analgesic properties.

Key questions remain such as: the timing of paracetamol ingestion or dosage required to demonstrate an ergogenic effect; which pathways paracetamol acts for its' aforementioned analgesic, antipyretic, or

neuromuscular effects. The evidence showing the effects of paracetamol on exercise performance tend suggest a positive performance enhancing effect. However, the assumption that paracetamol might provide additional protection from heat-related increases in T_{core} are uncertain. Therefore, caution is advised when attempting to exploit the antipyretic effect of paracetamol during exercise in the heat.

Side effects

The pharmacokinetics of paracetamol do not appear to be modified by exercise, (i.e., plasma concentration, clearance and half-life) do not change during exercise compared to rest [25]. Paracetamol intake has not been associated with serious adverse events amongst most users [11], although some frequently reported mild to moderate side effects of short term administration within the therapeutic dose (maximum of 3g daily) include nausea, vomiting, diarrhoea and abdominal pain. Liver failure has been reported following an overdose of paracetamol (>10g) [26]. Long-term use of paracetamol has been associated with an increased risk of asthma [27]. In general, paracetamol has been deemed a safe drug when it is consumed within therapeutic dosages [28].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Summary of the evidence on performance

Research on NSAIDs in sport has primarily focused on their effects on exercise-induced muscle damage and soreness [29]. In contrast, there are limited studies that investigate the effects of NSAIDs on sport performance (Table 2). NSAIDs appear to have both central and peripheral affects by inhibiting cyclooxygenase oxidase (COX) activity [15]. Two COX enzymes have been identified in skeletal muscle (COX-1 and COX-2) [30]. Through COX inhibition, NSAIDs limit prostaglandin synthesis both centrally and peripherally, and subsequently mask its nociceptive effect [14]. New NSAIDs allow the selective inhibition of the COX-2 enzyme, which seems to more effectively counteract inflammatory reactions [31]. As a consequence of COX inhibition, NSAIDs assist in alleviating the swelling and pain of inflammation [32].

Burian & Geisslinger [14] suggest that NSAIDs normalise the increased pain threshold associated with inflammation, rather than reduce the "normal" pain threshold. Thus, the antinociceptive action of NSAIDs might more accurately be described as antihyperalgesic, rather than analgesic. From a sport

performance perspective, if athletes were to use NSAIDs prophylactically, they may be able to tolerate higher exercise induced pain levels or reduce post-exercise inflammation, providing the potential for greater training volume/intensity than could have been sustained naturally. Indeed, there is some evidence using indirect markers of inflammation, such as creatine kinase (CK) concentration or muscle soreness, that post-exercise inflammation is reduced after NSAID ingestion compared to placebo [33]. However, other studies have failed to find an influence of NSAID ingestion on muscle inflammatory cell concentrations [34].

Trappe et al. [35] found an enhanced adaptation to muscle strength training with NSAIDs versus placebo in older individuals (+60 years). Thirty-six participants were requested to ingest either 3 doses/day of ibuprofen (400 mg/dose, 1,200 mg total), paracetamol (1,500 mg, 1,500 mg, 1,000 mg, 4,000 mg total), or placebo, 3 days/week, over a 12 week period. All three groups increased their quadriceps muscle strength (1RM) from pre- to post-training, but strength gains were greater in the drug groups. The authors suggested that the skeletal muscle would have adapted to these COX-inhibiting drugs during resistance training in a way that ultimately promoted additional muscle hypertrophy and strength gains. As outlined above, one potential mechanism might be that the COX-inhibition enabled participants to work at greater levels of physiological stress within the muscle due to the higher tolerance of exercise induced pain levels, thus allowing them to complete more work per training session.

Baldwin et al. [36] recruited a group of elderly healthy, but non-resistance-trained individuals and asked them to ingest sodium naproxen (220 mg) or placebo (sucrose) three times a day for 10 days. The authors assessed the participants' 1RM and maximal isometric contraction 3 days after they had performed an eccentric exercise on a knee extension machine. The decrement in 1RM contraction was greater for placebo (-32 ± 9%) than for NSAIDs (-6 ± 8%) treatment, with similar findings for maximal isometric force (-24 ± 4% vs. -12 ± 7%). Muscle soreness was also perceived to be lower in a visual analogue scale after the 3 days of NSAIDs. The authors concluded that sodium naproxen attenuated the loss of muscle function following eccentric exercise by inhibiting the COX and subsequently reducing prostaglandin synthesis, which may have also attenuated the inflammatory response.

Contrary to the findings of Trappe et al. [35], Krentz et al**.** [37] reported no additional benefits of strength training with NSAIDs. Krentz et al**.** recruited 18 participants who were experienced in resistance training, and required them to perform alternate days of strength training on their right and left biceps, 5

days/week, for 6 weeks. Participants were required to ingest ibuprofen (two 200 mg tablets per day) immediately after training the biceps of one arm, and placebo after training the other arm the next day. ibuprofen ingestion was shown to have no effect on either 1RM strength or daily muscle soreness compared with placebo. The reasons for the divergent findings of Trappe et al. [35] and Krentz et al**.** [37] are unclear. However, differences in the study population (67 vs. 24 years), NSAID dose (1200mg/day vs 400mg/day), muscle group trained (quadriceps vs. biceps), the duration of the protocol (12 vs. 6 weeks), and training experience of participants (untrained vs. experienced), may all have contributed to the conflicting results.

The effect of NSAIDs on resistance exercise performance has also been studied using an acute dosage study methodology, with ibuprofen, flurbiprofen, and asprin all demonstrating no effect on exercise induced pain, or exercise performance [38–40]. Reasons for these negative findings are unclear, but it could be plausible that the muscle soreness experienced following exercise is independent from increases in prostaglandin synthesis and the inflammatory process affected by the NSAIDs.

There appears to be no conclusive evidence supporting the prophylactic use of NSAIDs taken prior to resistance training in order to reduce post-exercise inflammation or pain, and/or to increase exercise capacity. Despite the high incidence of the consumption of NSAIDs by athletes, the majority of studies have been conducted on recreationally active and elderly participants, with few on high-level athletes. Crucially, more robust designs and methodologies regarding the dose and timing of administration should be considered in future studies. Moreover, the majority of work on the use of NSAIDs during exercise and training has been undertaken on resistance-based activities. Further research should be conducted on endurance-based exercise performance.

Side effects

The use of NSAIDs within or above the therapeutic doses has been related to an increased risk of hyponatremia during exercise (6%) [41], kidney failures, bleeding ulcers, cardiovascular events (9%), gastrointestinal cramps (10%), bleeds (4%), permeability, and renal dysfunction [42]. Of major concern is the use of NSAIDs, in particular ketorolac (Toradol) [43], in sports involving physical contact/trauma. NSAIDs have been shown to possess an inhibitory effect on platelet function [44] meaning that the body’s blood clotting mechanisms may be reduced by up to 50% [45]. Moreover, long-term use of

NSAIDs has been associated with accelerated progression of hip and knee osteoarthritis [46]. Furthermore, NSAIDs may allow athletes to resume activity prematurely, and before full tissue healing has occurred, which could result in further damage [47]. As a consequence, frequent users of NSAIDs may have an elevated injury risk due to delays in tissue healing [48]. Limited research has also questioned whether long-term NSAIDs use might impair satellite cell activity or reduce the synthesis of the extracellular matrix (collagen) via the inhibition of COX activity [49].

Glucocorticoids

Summary of the Evidence on performance

Glucocorticoids remain one of the most controversial analgesics used in sport. Their therapeutic use in the treatment of pain and inflammation seems unquestionable [50], but they also have a powerful effect related to exercise performance at both central and peripheral levels. As a consequence glucocorticoids have the potential to be used as ergogenic aids [51]. Table 3 summaries the current available evidence of the effect of glucocorticoids on exercise performance. In two separate studies, Arlettaz et al. [52] and Le Panse et al. [53] investigated the effects of 7 days of prednisolone administration (oral dose 60mg/day and 50mg/day, respectively) on exercise performance during submaximal exercise (time to exhaustion at 70-75% VO_{2max}). Both studies found an improvement in time-to-exhaustion compared with a placebo condition (Arlettaz et al., prednisolone: 74.5 ± 9.5 min vs. placebo: 46.1 ± 3.3 min; Le Panse et al., prednisolone: 66.4 ± 8.4 min vs. prednisolone: 47.9 ± 6.7 min). Both sets of authors also found that adrenocorticotrophic hormone (ACTH), dehydroepiandrosterone (DHEA), growth hormone (GH) and prolactin (PRL) values were significantly decreased following the time-to-exhaustion test under the short-term prednisolone treatment. Insulin and glucose were significantly higher during the whole experiment, and lactate concentration increased significantly after 10 min exercise until 10 min of recovery under prednisolone treatment. Therefore, alterations in hormonal and metabolic parameters during exercise indicate that short-term glucocorticoid treatment induced both central and peripheral effects. Indeed, it is possible that prednisolone exerted a central effect by inducing alteration in either brain serotonin or dopaminergic activity at the onset of fatigue [54]. A reduction in serotonin activity has been shown to inhibit descending motor neurons and thus motor output from the locomotor muscles [54]. Peripherally, glucocorticoids increase fat oxidation and lower carbohydrate oxidation during submaximal exercise,

with a significant increase in energy expenditure possibly due to a reduction in respiratory exchange ratio [55]. Likewise, an increase in energy store mobilization has been demonstrated as a result of the change in hormonal balance after prednisolone ingestion [56].

Collomp et al. [57] recruited a group of 8 male recreational cyclists to perform four cycling trials at 70–75% VO_{2peak} until exhaustion before and after either oral prednisolone treatment or placebo, coupled with a standardised period of physical training (2 hours/day). Training associated with glucocorticoid treatment resulted in an 80% improvement in time-to-exhaustion performance after 1 week, as well as decreases in ACTH, DHEA, PRL, GH, TSH, free testosterone; and increment in blood glucose concentration. Similarly, Casuso et al. [58] assessed muscle function following a 5-day ingestion period (twice/day) of either 2 mg of dexamethasone or placebo, but in a one-legged kicking exercise, and whole body exercise performance, using 20-m shuttle run and 30 m sprint tests. One-leg kicking exercise time-to-exhaustion was longer and total running distance in the 20-m shuttle run test was improved. A possible explanation for these improvements in muscle function might be enhanced monosynaptic transmission between excitatory muscle afferents and spinal motor neurons [59], and corticospinal excitability [60].

In contrast to the findings outlined above, Kuipers et al. [61] studied the effects of 4 weeks of twice daily-inhaled budesonide or placebo on performance during a maximal graded exercise test after 2 and 4 weeks. The authors failed to find differences in maximal power output and in the measures with the profile of mood state questionnaire (POMS) between treatments, and Zorgati et al. [62] found no effect of oral corticosteroid ingestion on exercise performance, despite hormonal changes. Therefore, the route of administration may play a role in generating a potential ergogenic effect (oral vs. inhaled). As well as the route of administration, the mode (systematic vs. acute) may modify the effects. An acute dose of prednisolone (20mg) did not influence performance in time-to-exhaustion performance at either 70-75% VO_{2max} [63], or at 80-85% VO_{2max} [64].

In conclusion, the mechanisms by which short-term administration of glucocorticoids are able to improve exercise performance is not completely understood [52,53,57,60]. However, single acute doses do not appear to have the same performance enhancing effect as systematic short-term administration despite having found similar alterations in blood hormonal and metabolic parameters.

Side effects

Both short and long-term use of glucocorticoids show an alteration in normal release of hormones from the hypothalamic-pituitary-adrenal axis as previously described. In addition, if taken for longer durations, or on larger doses, glucocorticoids can have a negative effect on bone tissue, a catabolic effect on muscle tissue, and increase incidence of mood swings in users [65]. Long-term administration is capable to produce skin thinning and purpura, lipodystrophy, neuropsychiatric disorders, hypertension [65], memory impairment [66], Cushing syndrome (typical symptoms are weight gain, bruising, hypertension, diabetes and facial puffiness) [67], and inhibition of the immune response mediated by the rapid depletion of circulating T-cells and B-cells [68]. Moreover, withdrawal of the glucocorticoid treatment following their long-term use is a problem due to adrenal suppression, with a tapering regime being required [69].

Opioids

Summary of the evidence on performance

Tramadol

Tramadol is an analgesic medication, of the opioid type, used in the treatment of moderate to severe pain. Tramadol has a dual mechanism of action, being both an μ-opioid receptor agonist, and a serotonin and Norepinephrine reuptake inhibitor [3]. Activation of the μ-opioid receptor agonist can cause analgesia and sedation [70]. Likewise, by inhibiting serotonin and norepinephrine reuptake, tramadol reduces the ability of the brain to respond to sensory inputs [71]. It is therefore possible that tramadol could improve exercise performance via its effect on central brain areas associated with effort and pain perception, similar to the aforementioned *analgesics.* There is a wealth of literature on the effectiveness of tramadol in therapy of musculoskeletal pain [72]. In sports, the use of powerful analgesics drugs might enable athletes to exert themselves beyond their normal pain threshold. Indeed, there have been concerns raised in the media about the possible abuse of tramadol in the pro-cycling peloton as a prophylactic drug to relieve pain [73]. However there is a general lack of data to support significant use tramadol in sport, and we are not aware of any study that has investigated the effects of tramadol on sport performance.

Morphine and codeine

Morphine is known to be a powerful opioid (acting via similar pathways to Tramadol) and is currently prohibited by WADA. Morphine exerts its analgesic effect directly on the central nervous system, acting as a μ-opioid receptor agonist [74]. To the best of our knowledge, only one study [75] has investigated the effect of morphine using a double-blind procedure. Benedetti et al. [75] investigated the effect of morphine on a simulated sport competition (pain endurance during a submaximal effort tourniquet test applied to the arm) undertaken by 4 teams of 10 participants. The four teams went through 3 weeks of training, either with or without morphine administration. Then, on the day of competition, the team that ingested morphine during training demonstrated a higher pain tolerance than the other teams even though they were given a placebo substance prior to competition. The results of Benedetti et al.'s study suggests that participants were conditioned to morphine administration, with an inert placebo substance triggering an opioid-mediated enhancement of pain endurance and physical performance. This conditioned morphine-like placebo effect may have significant implications for anti-doping authorities as this practice would be considered entirely legal under anti-doping legislation, as morphine is only prohibited in-competition. Codeine is another opioid pain-reliever, similar to morphine, but it is no currently banned. Indeed, following ingestion a small amount of codeine is converted to morphine in the body [76]. The precise mechanism of action of codeine is not known; however, like morphine, codeine binds to receptors in the brain (opioid receptors) that are important for transmitting the sensation of pain throughout the body and brain [77]. Current research is limited to the use of VISCOPROFEN® that is a combination of hydrocodone (an opioid derived from codeine) and ibuprofen. Kraemer et al., [78] found that anaerobic performance was enhanced in the following days after induced muscle damaged with VISCOPROFEN® in comparison to ibuprofen and placebo. In addition, VanHeest et al., [79] found participants who ingested VISCOPROFEN®, had lower perceived pain at 72 hours after eccentric exercise induced muscle damage throughout a 5-day evaluation period. Interestingly however, VanHeest et al. [79] did not find an enhancement in aerobic performance. Further research should be conducted to evaluate whether morphine and codeine increase sport performance, and to provide more evidence of the opioid-mediated placebo response found by Benedetti et al. [75].

Side effects

Tramadol, morphine and codeine have several commonly reported adverse effects including nausea, dizziness, vomiting, and headache [80]. Of particular concern is the drowsiness reported following

tramadol administration which could lead to reduced perception, attention and vigilance [81]. These reductions in cognitive function during sports, such as cycling, are potentially catastrophic as reduced vigilance and lack of attention while riding might result in falls with potentially significant injury consequences. Indeed, tramadol intake has been suggested as a potential cause of falls in the pro-cycling peloton [82]. Moreover, it has been suggested that the use of tramadol alone or in combination with other medications may lead to sub-optimal performance in athletes [83]. Future studies should aim to shed light on whether tramadol may improve physical performance and if so, whether it is at the expense of reducing sustained attention and vigilance.

World Anti-Doping Agency (WADA) status

WADA is an independent agency composed and funded by the sports movement and governments of the World. WADA's key activities include education, development of anti-doping activities, and monitoring of the World Anti-Doping Code (the document synchronises anti-doping policies in all sports and in all countries). Table 4 summarizes the current status of these analgesics and their potential ergogenic effects.

Due to its analgesic effects and safety at therapeutic doses, paracetamol is one of the most easily accessible drugs for athletes to use. These conditions therefore present the opportunity for paracetamol to be misused by athletes due to its ergogenic effect [19,20,23]. Similarly, NSAID use is not currently considered as a doping violation in sport by WADA. It is difficult to form firm conclusions on the potential ergogenic effect of paracetamol and NSAIDs due to the degree of variation in the methodologies of the current research literature. As a consequence of the potentially damaging side effects outlined above, athletes and coaches should exert caution in their long-term use. However, given the current widespread use of paracetamol and NSAIDs across athletes of all standards [84], it appears that a cautionary approach to their use is not being taken.

Glucocorticoids are banned in-competition (when administered by oral, intravenous, intramuscular or rectal routes) by WADA, but they are permitted out-competition via any route of administration. The lack of evidence related to performance enhancement with glucocorticoids has allowed some to question whether they could be removed from the WADA list [85]. However, it is possible that if used during a period of training, glucocorticoids could increase the amount of work that an athlete is capable of completing, leading to an enhanced level of adaptation. Indeed, Pigozzi et al. [86], have suggested that

glucocorticoid use should be subject to a TUE during training. However, there is currently not enough evidence to support this suggestion, and it recommended that further research be conducted to investigate the effects of glucocorticoids within training type environments.

Finally, tramadol and codeine have been placed on WADA's Monitoring Program from 2012 to 2017 (Narcotics: in competition only) [87] in order to detect potential patterns of abuse, while morphine's use is currently prohibited.

Conclusions

The pharmacological effects of analgesics are well described in the scientific literature, but by comparison far less is known about how they might affect sporting performance. It seems that paracetamol and NSAIDs have the potential to improve exercise performance by decreasing the activation of higher brain structures and hence, reducing perception of effort and exercise induced pain. The therapeutic use of glucocorticoids is unquestionable in the treatment of inflammation associated with soft-tissue injury. However, some research has suggested the potential for these drugs to have ergogenic effects on both central and peripheral body systems, improving exercise performance. Nevertheless, one must be concerned about potential health consequences on long-term use of glucocorticoids. In contrast, little is known about the impact of tramadol during exercise. The available research suggests that the use of analgesics has become a common practice amongst athletes and physicians. It is recommended that detailed educational information on the medical and ethical use of analgesics in sport should be provided for physicians, coaches and athletes.

References

1 Parfitt G, Rose E a, Burgess WM. The psychological and physiological responses of sedentary individuals to prescribed and preferred intensity exercise. *Br J Health Psychol* 2006;**11**:39–53. doi:10.1348/135910705X43606

2 Alaranta A, Alaranta H, Heliövaara M, *et al.* Ample use of physician-prescribed medications in Finnish elite athletes. *Int J Sports Med* 2006;**27**:919–25. doi:10.1055/s-2006-923811

3 Bastami S, Haage P, Kronstrand R, *et al.* Pharmacogenetic aspects of tramadol pharmacokinetics and pharmacodynamics after a single oral dose. *Forensic Sci Int* 2014;**238**:125–32. doi:10.1016/j.forsciint.2014.03.003

4 Tscholl P, Alonso JM, Dollé G, *et al.* The use of drugs and nutritional supplements in top-level track and field athletes. *Am J Sports Med* 2010;**38**:133–40. doi:10.1177/0363546509344071

5 Da Silva ER, De Rose EH, Ribeiro JP, *et al.* Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007). *Br J Sports Med* 2009;**45**:91–4. doi:10.1136/bjsm.2009.065342

6 Taioli E. Use of permitted drugs in Italian professional soccer players. *Br J Sports Med* 2007;**41**:439–41. doi:10.1136/bjsm.2006.034405

7 Tsitsimpikou C, Jamurtas a, Fitch K, *et al.* Medication use by athletes during the Athens 2004 Paralympic Games. *Br J Sports Med* 2009;**43**:1062–6. doi:10.1136/bjsm.2009.062521

8 Gorski T, Cadore EL, Pinto SS, *et al.* Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med* 2011;**45**:85–90. doi:10.1136/bjsm.2009.062166

9 Bastian B, Jetten J, Hornsey MJ, *et al.* The Positive Consequences of Pain: A Biopsychosocial Approach. *Pers Soc Psychol Rev* 2014;**18**:256–79. doi:10.1177/1088868314527831

10 Anderson BJ. Paracetamol (Acetaminophen): Mechanisms of action. *Paediatr Anaesth* 2008;**18**:915–21. doi:10.1111/j.1460-9592.2008.02764.x

11 Prior MJ, Lavins BJ, Cooper K. A randomized, placebo-controlled trial of acetaminophen extended release for treatment of post-marathon muscle soreness. *Clin J*

Pain 2012;**28**:204–10. doi:10.1097/AJP.0b013e318227cc4f

12 Hinz B, Brune K. Antipyretic analgesics: Nonsteroidal antiinflammatory drugs, selective cox-2 inhibitors, paracetamol and pyrazolinones. *Handb Exp Pharmacol* 2007;**177**:65–93. doi:10.1007/978-3-540-33823-9_3

13 Aminoshariae A, Khan A. Acetaminophen: Old Drug, New Issues. *J Endod* 2015;**41**:588–93. doi:10.1016/j.joen.2015.01.024

14 Burian M, Geisslinger G. COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites. *Pharmacol Ther* 2005;**107**:139–54. doi:10.1016/j.pharmthera.2005.02.004

15 Ziltener JL, Leal S, Fournier PE. Non-steroidal anti-inflammatory drugs for athletes: An update. *Ann Phys Rehabil Med* 2010;**53**:278–88. doi:10.1016/j.rehab.2010.03.001

16 Andersson DA, Gentry C, Alenmyr L, *et al.* TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid Δ(9)-tetrahydrocannabiorcol. *Nat Commun* 2011;**2**:551. doi:10.1038/ncomms1559

17 Ottani A, Leone S, Sandrini M, *et al.* The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol* 2006;**531**:280–1. doi:10.1016/j.ejphar.2005.12.015

18 Pickering G, Kastler A, Macian N, *et al.* The brain signature of paracetamol in healthy volunteers: a double-blind randomized trial. *Drug Des Devel Ther* 2015;:3853. doi:10.2147/DDDT.S81004

19 Mauger AR, Jones AM, Williams C a. Influence of acetaminophen on performance during time trial cycling. *J Appl Physiol* 2010;**108**:98–104. doi:10.1152/japplphysiol.00761.2009

406 20 Foster J, Taylor L, Chrismas BCR, *et al.* The influence of acetaminophen on repeated
407 sprint cycling performance. *Eur J Appl Physiol* 2014;**114**:41–8. doi:10.1007/s00421-
408 013-2746-0

409 21 Mauger AR, Hopker JG. The effect of acetaminophen ingestion on cortico-spinal
410 excitability. *Can J Physiol Pharmacol* 2013;**91**:187–9. doi:10.1139/cjpp-2012-0213

411 22 Burtscher M, Gatterer H, Philippe M, *et al.* Effects of a single low-dose acetaminophen
412 on body temperature and running performance in the heat: A pilot project. *Int J Physiol*
413 *Pathophysiol Pharmacol* 2013;**5**:190–3.

414 23 Mauger AR, Taylor L, Harding C, *et al.* Acute acetaminophen (paracetamol) ingestion
415 improves time to exhaustion during exercise in the heat. *Exp Physiol* 2014;**99**:164–71.
416 doi:10.1113/expphysiol.2013.075275

417 24 Coombs GB, Cramer MN, Ravanelli NM, *et al.* Acute acetaminophen ingestion does not
418 alter core temperature or sweating during exercise in hot-humid conditions. *Scand J Med*
419 *Sci Sports* 2015;**25**:96–103. doi:10.1111/sms.12336

420 25 Lenz TL, Lenz NJ, Faulkner M a. Potential interactions between exercise and drug
421 therapy. *Sport Med* 2004;**34**:293–306. doi:10.2165/00007256-200434050-00002

422 26 Nourjah P, Ahmad SR, Karwoski C, *et al.* Estimates of acetaminophen (paracetomal)-
423 associated overdoses in the United States. *Pharmacoepidemiol Drug Saf* 2006;**15**:398–
424 405. doi:10.1002/pds.1191

425 27 Etminan M, Sadatsafavi M, Jafari S, *et al.* Acetaminophen Use and the Risk of Asthma
426 in Children and AdultsA Systematic Review and Metaanalysis. *CHEST J*
427 2009;**136**:1316–23. doi:10.1378/chest.09-0865

428 28 Bertolini A, Ferrari A, Ottani A, *et al.* Paracetamol: New vistas of an old drug. *CNS*
429 *Drug Rev* 2006;**12**:250–75. doi:10.1111/j.1527-3458.2006.00250.x

29 Schoenfeld DBJ. The Use of Nonsteroidal Anti-Inflammatory Drugs for Exercise-Induced Muscle Damage. *Sport Med* 2012;**42**:1017–28. doi:10.1007/BF03262309

30 Weinheimer EM, Jemiolo B, Carroll CC, *et al.* Resistance exercise and cyclooxygenase (COX) expression in human skeletal muscle: implications for COX-inhibiting drugs and protein synthesis. *Am J Physiol Regul Integr Comp Physiol* 2007;**292**:R2241-8. doi:10.1152/ajpregu.00718.2006

31 Warden SJ. Cyclo-oxygenase-2 inhibitors : beneficial or detrimental for athletes with acute musculoskeletal injuries? *Sports Med* 2005;**35**:271–83.

32 Vane JR, Botting RM. Mechanism of Action of Nonsteroidal Anti-inflammatory Drugs. *Am J Med* 1998;**104**:2S–8S. doi:10.1016/S0002-9343(97)00203-9

33 Tokmakidis SP, Kokkinidis EA, Smilios I, *et al.* The effects of ibuprofen on delayed muscle soreness and muscular performance after eccentric exercise. *J Strength Cond Res* 2003;**17**:53–9. doi:10.1519/1533-4287(2003)017<0053:TEOIOD>2.0.CO;2

34 Peterson JM, Trappe TA, Mylona E, *et al.* Ibuprofen and Acetaminophen: Effect on Muscle Inflammation after Eccentric Exercise. *Med Sci Sport Exerc* 2003;**35**:892–6. doi:10.1249/01.MSS.0000069917.51742.98

35 Trappe TA, Carroll CC, Dickinson JM, *et al.* Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. *Am J Physiol - Regul Integr Comp Physiol* 2011;**300**:R655–62. doi:10.1152/ajpregu.00611.2010

36 Baldwin AC, Stevenson SW, Dudley GA. Nonsteroidal Anti-Inflammatory Therapy After Eccentric Exercise in Healthy Older Individuals. *Journals Gerontol Ser A Biol Sci Med Sci* 2001;**56**:510–3. doi:10.1093/gerona/56.8.M510

37 Krentz JR, Quest B, Farthing JP, *et al.* The effects of ibuprofen on muscle hypertrophy, strength, and soreness during resistance training. *Appl Physiol Nutr Metab* 2008;**33**:470–

5. doi:10.1139/H08-019

38 Correa CS, Cadore EL, Baroni BM, *et al.* Effects of Prophylactic Anti-Inflammatory Non-Steroidal Ibuprofen on Performance in a Session of Strength Training. *Rev Bras Med Do Esporte* 2013;**19**:116–9.

39 Semark a, Noakes TD, St Clair Gibson a, *et al.* The effect of a prophylactic dose of flurbiprofen on muscle soreness and sprinting performance in trained subjects. *J Sports Sci* 1999;**17**:197–203. doi:10.1080/026404199366091

40 Hudson GM, Green JM, Bishop P a, *et al.* Effects of caffeine and aspirin on light resistance training performance, perceived exertion, and pain perception. *J Strength Cond Res* 2008;**22**:1950–7. doi:10.1519/JSC.0b013e31818219cb

41 Wharam PC, Speedy DB, Noakes TD, *et al.* NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc* 2006;**38**:618–22. doi:10.1249/01.mss.0000210209.40694.09

42 Küster M, Renner B, Oppel P, *et al.* Consumption of analgesics before a marathon and the incidence of cardiovascular, gastrointestinal and renal problems: a cohort study. *BMJ Open* 2013;**3**:e002090-. doi:10.1136/bmjopen-2012-002090

43 Sawyer G a, Anderson BC, Raukar NP, *et al.* Intramuscular ketorolac injections in the athlete. *Sports Health* 2012;**4**:319–27. doi:10.1177/1941738112439686

44 Bauer KA, Gerson W, Wright IV C, *et al.* Platelet function following administration of a novel formulation of intravenous diclofenac sodium versus active comparators: A randomized, single dose, crossover study in healthy male volunteers. *J Clin Anesth* 2010;**22**:510–8. doi:10.1016/j.jclinane.2009.12.011

45 Singer AJ, Mynster CJ, McMahon BJ. The effect of IM ketorolac tromethamine on bleeding time: A prospective, interventional, controlled study. *Am J Emerg Med*

2003;**21**:441–3. doi:10.1016/S0735-6757(03)00100-1

46 Reijman M, Bierma-Zeinstra SMA, Pols HAP, *et al.* Is there an association between the use of different types of nonsteroidal antiinflammatory drugs and radiologic progression of osteoarthritis? The Rotterdam Study. *Arthritis Rheum* 2005;**52**:3137–42. doi:10.1002/art.21357

47 Slatyer MA, Hensley MJ, Lopert R. A randomized controlled trial of piroxicam in the management of acute ankle sprain in Australian Regular Army recruits. The Kapooka Ankle Sprain Study. *Am J Sports Med* 1997;**25**:544–53. doi:10.1177/036354659702500419

48 Cohen DB, Kawamura S, Ehteshami JR, *et al.* Indomethacin and celecoxib impair rotator cuff tendon-to-bone healing. *Am J Sports Med* 2006;**34**:362–9. doi:10.1177/0363546505280428

49 Mikkelsen UR, Langberg H, Helmark IC, *et al.* Local NSAID infusion inhibits satellite cell proliferation in human skeletal muscle after eccentric exercise. *J Appl Physiol* 2009;**107**:1600–11. doi:10.1152/japplphysiol.00707.2009

50 Morin C, Fardet L. Systemic glucocorticoid therapy: risk factors for reported adverse events and beliefs about the drug. A cross-sectional online survey of 820 patients. *Clin Rheumatol* 2015;:1–8. doi:10.1007/s10067-015-2953-7

51 Duclos M. Evidence on ergogenic action of glucocorticoids as a doping agent risk. *Phys Sport* 2010;**38**:121–7. doi:10.3810/psm.2010.10.1817

52 Arlettaz A, Portier H, Lecoq AM, *et al.* Effects of short-term prednisolone intake during submaximal exercise. *Med Sci Sports Exerc* 2007;**39**:1672–8. doi:10.1249/mss.0b013e3180dc992c

53 Le Panse B, Thomasson R, Jollin L, *et al.* Short-term glucocorticoid intake improves

exercise endurance in healthy recreationally trained women. *Eur J Appl Physiol* 2009;**107**:437–43. doi:10.1007/s00421-009-1149-8

54 Meeusen R, Watson P, Hasegawa H, *et al.* Central fatigue: The serotonin hypothesis and beyond. *Sport Med* 2006;**36**:881–909. doi:10.2165/00007256-200636100-00006

55 Arlettaz A, Portier H, Lecoq AM, *et al.* Effects of acute prednisolone intake on substrate utilization during submaximal exercise. *Int J Sports Med* 2008;**29**:21–6. doi:10.1055/s-2007-964994

56 McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. *Diabetes Metab Rev* 1988;**4**:17–30.

57 Collomp K, Arlettaz a, Portier H, *et al.* Short-term glucocorticoid intake combined with intense training on performance and hormonal responses. *Br J Sports Med* 2008;**42**:983–8. doi:10.1136/bjsm.2007.043083

58 Casuso RA, Melskens L, Bruhn T, *et al.* Glucocorticoids improve high-intensity exercise performance in humans. *Eur J Appl Physiol* 2014;**114**:419–24. doi:10.1007/s00421-013-2784-7

59 Hall ED. Glucocorticoid effects on serotonergic and noradrenergic facilitation of spinal monosynaptic transmission. *Psychiatry Res* 1980;**2**:241–50.

60 Baudry S, Lanfranco F, Merletti R, *et al.* Effects of short-term dexamethasone administration on corticospinal excitability. *Med Sci Sports Exerc* 2014;**46**:695–701. doi:10.1249/MSS.0000000000000162

61 Kuipers H, Van't Hullenaar G a C, Pluim BM, *et al.* Four weeks' corticosteroid inhalation does not augment maximal power output in endurance athletes. *Br J Sports Med* 2008;**42**:868–71. doi:10.1136/bjsm.2007.042572

62 Zorgati H, Prieur F, Vergniaud T, *et al.* Ergogenic and metabolic effects of oral glucocorticoid intake during repeated bouts of high-intensity exercise. *Steroids* 2014;**86**:10–5. doi:10.1016/j.steroids.2014.04.008

63 Arlettaz A, Collomp K, Portier H, *et al.* Effects of acute prednisolone administration on exercise endurance and metabolism. *Br J Sports Med* 2008;**42**:250–4. doi:10.1136/bjsm.2007.040667

64 Arlettaz A, Collomp K, Portier H, *et al.* Effects of acute prednisolone intake during intense submaximal exercise. *Int J Sports Med* 2006;**27**:673–9. doi:10.1055/s-2005-872826

65 Fardet L, Flahault a., Kettaneh a., *et al.* Corticosteroid-induced clinical adverse events: Frequency, risk factors and patient's opinion. *Br J Dermatol* 2007;**157**:142–8. doi:10.1111/j.1365-2133.2007.07950.x

66 Wolkowitz OM, Burke H, Epel ES, *et al.* Glucocorticoids. Mood, memory, and mechanisms. *Ann N Y Acad Sci* 2009;**1179**:19–40. doi:10.1111/j.1749-6632.2009.04980.x

67 Huscher D, Thiele K, Gromnica-Ihle E, *et al.* Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 2009;**68**:1119–24. doi:10.1136/ard.2008.092163

68 Chatham WW, Kimberly RP. Treatment of lupus with corticosteroids. *Lupus* 2001;**10**:140–7. doi:10.1191/096120301675075008

69 Ueda N, Chihara M, Kawaguchi S, *et al.* Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. *J Pediatr* 1988;**112**:122–6. doi:10.1016/S0022-3476(88)80136-7

70 Liu X-Y, Liu Z-C, Sun Y-G, *et al.* Unidirectional cross-activation of GRPR by MOR1D uncouples itch and analgesia induced by opioids. *Cell* 2011;**147**:447–58.

549 doi:10.1016/j.cell.2011.08.043

550 71 Berridge CW, Schmeichel BE, España R a. Noradrenergic modulation of
551 wakefulness/arousal. *Sleep Med Rev* 2012;**16**:187–97. doi:10.1016/j.smrv.2011.12.003

552 72 Schug SA. The role of tramadol in current treatment strategies for musculoskeletal pain.
553 *Ther Clin Risk Manag* 2007;**3**:717–23.

554 73 Benson D. Tramadol abuse in the cycling peloton. Cyclingnews.com.
555 20013.http://www.cyclingnews.com/news/tramadol-abuse-in-the-cycling-peloton
556 (accessed 23 Apr2015).

557 74 Lipp J. Possible mechanisms of morphine analgesia. *Clin Neuropharmacol*
558 1991;**14**:131–47.http://www.ncbi.nlm.nih.gov/pubmed/21426916

559 75 Benedetti F, Pollo A, Colloca L. Opioid-Mediated Placebo Responses Boost Pain
560 Endurance and Physical Performance: Is It Doping in Sport Competitions? *J Neurosci*
561 2007;**27**:11934–9. doi:10.1523/JNEUROSCI.3330-07.2007

562 76 Sindrup SH, Brøsen K. The pharmacogenetics of codeine hypoalgesia.
563 Pharmacogenetics. 1995;**5**:335–46. doi:10.1097/00008571-199512000-00001

564 77 Brunton TL. On the Use of Codeine to Relieve Pain in Abdominal Disease. *BMJ*
565 1888;**1**.http://www.bmj.com/content/1/1432/1213 (accessed 4 Jul2017).

566 78 Kraemer, WJ, Gómez A, Ratamess N, *et al.* Effects of VICOPROFEN and ibuprofen on
567 anaerobic performance after muscle damage. *J Sport Rehabil* 2002;**11**:104–119
568 16p.https://proxy.library.upenn.edu/login?url=http://search.ebscohost.com/login.aspx?dir
569 ect=true&db=cin20&AN=106976832&site=ehost-live

570 79 VanHeest J, Stoppani J, TP S, *et al.* Effects of ibuprofen and VICOPROFEN on physical
571 performance after exercise-induced muscle damage. *J Sport Rehabil* 2002;**11**:224–234

11p.https://proxy.library.upenn.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=106796136&site=ehost-live

80 Langley PC, Patkar AD, Boswell K a, *et al.* Adverse event profile of tramadol in recent clinical studies of chronic osteoarthritis pain. *Curr Med Res Opin* 2010;**26**:239–51. doi:10.1185/03007990903426787

81 Perez-Lloret S, Videla AJ, Richaudeau A, *et al.* A Multi-Step Pathway Connecting Short Sleep Duration to Daytime Somnolence, Reduced Attention, and Poor Academic Performance: An Exploratory Cross-Sectional Study in Teenagers. *J Clin Sleep Med* 2013;**9**:469–73. doi:10.5664/jcsm.2668

82 WADA proposes Tramadol remains a monitored rather than a banned substance in 2015 | CyclingTips.

83 Martinez-Silvestrini JA. *Prescribing Medications for Pain and Inflammation*. Edinburgh: : W.B. Saunders 2007. doi:10.1016/B978-1-4160-2443-9.50018-0

84 Tscholl P, Feddermann N, Junge A, *et al.* The use and abuse of painkillers in international soccer: data from 6 FIFA tournaments for female and youth players. *Am J Sports Med* 2009;**37**:260–5. doi:10.1177/0363546508324307

85 Orchard JW. Why glucocorticoids should be removed from the World Antidoping Agency's list of banned products. *Br J Sports Med* 2008;**42**:944–5. doi:10.1136/bjsm.2008.053371

86 Pigozzi F, Di Gianfrancesco A, Zorzoli M, *et al.* Why glucocorticosteroids should remain in the list of prohibited substances: A sports medicine viewpoint. *Int J Immunopathol Pharmacol* 2012;**25**:19–24.

87 WADA. The 2017 Monitoring Program. World Anti-Doping Agency. 2016.https://wada-main-prod.s3.amazonaws.com/resources/files/wada-2017-monitoring-program-en.pdf

596