PM R XXX (2017) 1-11
www.pmrjournal.org

Narrative Review

Analgesics and Sport Performance: Beyond the Pain-Modulating Effects

Darias Holgado, MD, James Hopker, PhD, Daniel Sanabria, PhD, Mikel Zabala, PhD

Abstract

Analgesics are used widely 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. Although the pharmacologic 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. Nonsteroidal anti-inflammatory drugs affect both central and peripheral body systems, but investigation on their ergogenic effect on muscle strength development has provided equivocal results. The therapeutic use of glucocorticoids is indubitable, but clear evidence exists for a performance-enhancing effect after short-term oral administration. Based on 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 of opioids such as tramadol on sporting performance.

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" often are 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 pharmacologic analgesics substances before training and competition up to 4-fold more than their age-matched general population [2]. The general term analgesic covers a variety of different pharmacologic substances, including nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics (such as paracetamol and others), weak opioids (for example, tramadol, codeine, or morphine [3]) and orally administered or injected glucocorticosteroids [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 analgesics [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 versus 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 postexercise use of analgesics to accelerate recovery, there is potential for their prophylactic use as a potential performance-enhancing intervention. In comparison with 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, because analgesics exert a pharmacologic action on key physiological systems related to exercise performance, a theoretical rationale exists whereby these drugs could provide a significant ergogenic effect.

1934-1482/$ - see front matter
http://dx.doi.org/10.1016/j.pmrj.2017.07.068

Materials and Methods

The aim of this work 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 in which researchers investigated the use of analgesics in sport for all period of time up to September 2016. The following key words were used in different combinations: "analgesics," "paracetamol," "acetaminophen," "painkillers," "NSAID," "nonsteroidal 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 also were 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). After a review of retrieved articles, we determined that 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 understood completely. Paracetamol may exert its action via the cyclooxygenase (COX) pathway [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 and transient receptor potential cation channel 1 [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 also might inhibit pain sensation by decreasing the activation of higher brain structures (eg, 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 determined fully, 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 [19-23]. Mauger et al [23] found that 1.5 g of paracetamol ingestion increased cycling power output and reduced the time required to complete a 16.1-km cycling time trial (26 minutes, 15 seconds ± 1 minute, 36 seconds), compared with a placebo condition (26 minutes, 45 seconds, ± 2 minutes, 2 seconds) in trained cyclists. The authors hypothesized that paracetamol may exert its effect by reducing perceived pain and rating of perceived exertion, although no differences were observed between conditions in their study. More recently, the influence of 1.5 g of paracetamol ingestion on exercise performance was examined during a series of "all-out" Wingate sprints [21]. Results demonstrated a 5% improvement in mean power output in the paracetamol (391 ± 74 W) compared with the placebo (372 ± 90 W) condition. Collectively, these studies suggest that, both short- [21] and long-duration [23] exercise performance can be improved by paracetamol ingestion.

An alternative explanation as to why paracetamol might improve exercise performance is via an increased corticospinal excitability and thus greater force output from the muscular system [18,24]. Mauger and Hopker [24] demonstrated that ingestion of paracetamol significantly increased the motor-evoked potential and motor-evoked area of the right first dorsal interossei muscle after transcranial magnetic stimulation of the motor cortex. However, more research is required to verify the pharmacologic effects of paracetamol on corticospinal 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 30°C and 50% relative humidity at an exercise intensity corresponding to the 70% VO_{2max} after ingestion of a single 500-mg dose of paracetamol or a placebo. They found a smaller increase in core temperature after 20 minutes' running after the ingestion of paracetamol but no difference between conditions at exhaustion, or in terms of the exercise time-to-exhaustion performance. In a similar study, Mauger et al [20] examined the influence of paracetamol on cycling time to exhaustion in 30°C and 50% relative humidity at 70% maximal oxygen consumption (VO_{2max}). The authors measured core temperature, skin temperature, body temperature, and thermal sensation. Results demonstrated an increased time to exhaustion in the paracetamol compared with placebo condition (23 ± 15 minutes versus 19 ± 13 minutes). The authors concluded that the antipyretic effect of paracetamol was a useful mechanism to enhance performance by reducing core temperature, skin temperature, body temperature, and thermal sensation during exercise in the heat, in the absence of a precooling mechanism at rest.

Table 1
Summary of research articles on the effect of paracetamol on exercise performance

Study	Sample Size	Subjects	Treatment	Protocol	Main Outcome
Coombs et al [19]	9	Active men 25 ± 4 y; VO_{2peak}: 3.87 ± 0.60 L/min	20 mg/kg of their total body weight of paracetamol or placebo 60 min before	60 min on an upright cycle ergometer at 8 W/kg of heat production at 34.5 ± 0.1°C, 52 ± 1% relative humidity	No changes in perceptual responses No changes in thermometry No changes in sweeting No changes in heart rate
Mauger et al [20]	11	Recreationally but untrained male adults, 21 ± 1 y; VO_{2max}: 44 ± 6 mL min/kg/min	20 mg/kg/ lean body mass of paracetamol or a placebo 45 min before	Time to exhaustion at 70% VO_{2max} 30°C and 50% relative humidity	Increased time to exhaustion Reduced core, skin, and body temperature and thermal sensation
Foster et al [21]	9	Recreationally male, 21 ± 2 y; VO_{2max}: 47 ± 6 ml/kg/min	3x 500-mg paracetamol or placebo 30 min before	8 × 30 s sprints separated by a rest interval of 2 min	Higher mean power output Lower power decrement
Burtscher et al [22]	7	Well-trained sport students 25.9 y; VO_{2max}: 67.3 mL/min/kg	Paracetamol (500 mg) or placebo 2 h before	Time to exhaustion at 70% VO_{2max} 30°C and 50% relative humidity	Less increment in heat core temperature at 20 min but there were not differences at the end of time to exhaustion
Mauger et al [23]	13	Competitive male cyclists, 26 ± 9 y; VO_{2max}: 65.5 mL/kg/min	3× 500-mg paracetamol or a Placebo 45 min before	10-mile time trial	Reduced time trial time and increased average power

VO_{2peak} = peak oxygen volume; VO_{2max} = maximal oxygen consumption.

However, Coombs et al [19] 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 methodologic 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 [19] could separate the effects of the exercise on thermoregulatory responses from those attributable to the pharmacologic action of the paracetamol. Thus, instead of paracetamol exerting a performance enhancing antipyretic effect, the findings of Mauger et al [20] 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 and 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 core temperature 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 (ie, plasma concentration, clearance, and half-life) and do not change during exercise compared with rest [25]. Paracetamol intake has not been associated with serious adverse events among most users [11], although some frequently reported mild-to-moderate side effects of short-term administration within the therapeutic dose (maximum of 3 g daily) include nausea, vomiting, diarrhea, and abdominal pain. Liver failure has been reported after an overdose of paracetamol (>10 g) [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].

Nonsteroidal 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) [30-35]. NSAIDs appear to have both central and peripheral affects by inhibiting COX activity [15]. Two COX enzymes have been identified in skeletal muscle (COX-1 and COX-2) [36]. Through COX inhibition, NSAIDs limit prostaglandin synthesis both centrally and

Table 2
Summary of research articles on the effect of NSAIDs on exercise performance

Study	Sample Size	Subjects	Treatment	Protocol	Main Outcome
Semark et al [30]	25	Rugby and field hockey players	Flurbiprofen patch (40 mg) 12 h before and every 12 h	3 × 30-m maximal sprints and a series of drop jumps to induce muscle soreness. At 12, 24, 48, and 72 h they repeated 3 × 30-m sprints	No differences in acceleration and time in sprints
Baldwin et al [31]	15	Untrained (10 male; 5 female), 60 ± 2 y	Naproxen sodium (220 mg) or placebo 3 times a day (every 8 h) for 10 d, after an eccentric exercise, separated by 3-wk washout	Unilateral quadriceps concentric 1RM tests and eccentric exercise on a knee extension machine	Greater loss of strength for placebo than NSAID for the 1RM
Krentz et al [32]	18	Resistance-trained (12 male, 6 female) 24.1 ± 0.6 y	Ibuprofen (2× 200 mg tablets per day) immediately after training the biceps of one arm and placebo after training the other arm the next day	Resistance training 5 d/wk for 6 wk	No effect on muscle strength
Hudson et al [33]	15	College-aged men, 22.0 ± 1.3 y	Caffeine (6—6.4 mg/kg body weight), aspirin (10—10.4 mg/kg/ body weight), or placebo with 500 mL of water 1 h before	4-12RM of Leg extension and arm curl with 3-min rest between set and 5 min between exercise	Higher RPE for aspirin than for caffeine
Trappe et al [34]	36	Elderly subjects; placebo (67 ± 2 y; n = 12) acetaminophen (64 ± 1 y, n = 11) ibuprofen (64 ± 1 y; n = 13)	3 doses/d (8 AM, 2 PM, 8 PM) of 3 placebo pills; paracetamol: 2 × 1500 mg, 1 × 1000 mg, total 4000 mg; or ibuprofen: 3 × 400 mg/dose, total 1200 mg	Resistance training 3 d/wk for 12 wk on an isotonic knee extension device	Increased quadriceps muscle strength by a greater amount in the drug groups compared with the placebo group
Correa et al [35]	12	Male subjects experienced in strength training, 22.83 ± 3.24 y	Ibuprofen tablet (1.2 g) or placebo 1 h before training	Six sets of bench press and squat at 65% of the 1RM reaching the highest number of repetitions as possible until exhaustion	No performance differences No changes in total training volume

NSAIDs = nonsteroidal anti-inflammatory drugs; 1RM = one repetition maximum; RPE = rating of perceived exertion.

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 [37]. As a consequence of COX inhibition, NSAIDs assist in alleviating the swelling and pain of inflammation [38].

Burian and Geisslinger [14] suggest that NSAIDs normalize 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 anti-hyperalgesic, rather than analgesic. From a sport performance perspective, if athletes were to use NSAIDs prophylactically, they may be able to tolerate greater exercise-induced pain levels or reduce postexercise inflammation, providing the potential for greater training volume/intensity than could have been sustained naturally. Indeed, there is some evidence, generated with the use of indirect markers of inflammation, such as creatine kinase concentration or muscle soreness, that postexercise inflammation is reduced after ingestion of NSAID compared with placebo [39]. However, other studies have failed to find an influence of ingestion of NSAID on muscle inflammatory cell concentrations [40].

Trappe et al [34] 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/d of ibuprofen (400 mg/dose, 1200 mg total), paracetamol (1500 mg, 1500 mg, 1000 mg, 4000 mg total), or placebo, 3 d/wk over a 12-week period. All 3 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 previously, 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 greater tolerance of exercise-induced pain levels, thus allowing them to complete more work per training session.

Baldwin et al [31] recruited a group of elderly healthy, but nonresistance-trained individuals and asked them to ingest sodium naproxen (220 mg) or placebo (sucrose) 3 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 ($-32 \pm 9\%$) than for NSAIDs ($-6 \pm 8\%$) treatment, with similar findings for maximal isometric force ($-24 \pm 4\%$ versus $-12 \pm 7\%$). Muscle soreness was also perceived to be lower in a visual analog scale after the 3 days of NSAIDs. The authors concluded that sodium naproxen attenuated the loss of muscle function after eccentric exercise by inhibiting the COX and subsequently reducing prostaglandin synthesis, which also may have attenuated the inflammatory response.

Contrary to the findings of Trappe et al [34], Krentz et al [32] reported no additional benefits of strength training with NSAIDs. These authors 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 d/wk, 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. Ingestion of ibuprofen 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 [34] and Krentz et al [32] are unclear. However, differences in the study population (67 versus 24 years), NSAID dose (1200 mg/d versus 400 mg/d), muscle group trained (quadriceps versus biceps), the duration of the protocol (12 versus 6 weeks), and training experience of participants (untrained versus experienced), may all have contributed to the conflicting results.

The effect of NSAIDs on resistance exercise performance also has been studied with an acute dosage study methodology, with ibuprofen, flurbiprofen, and aspirin all demonstrating no effect on exercise-induced pain or exercise performance [30,33,35]. Reasons for these negative findings are unclear, but it could be plausible that the muscle soreness experienced after 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 before resistance training to reduce postexercise 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 failure, 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 also has 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 [52-60] summaries the current available evidence of the effect of glucocorticoids on exercise performance. In 2 separate studies, Arlettaz et al [52] and Le Panse et al [58] investigated the effects of 7 days of prednisolone administration (oral dose 60 mg/d and 50 mg/d, 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 minutes versus placebo: 46.1 ± 3.3 minutes; Le Panse et al, prednisolone: 66.4 ± 8.4 minutes versus prednisolone: 47.9 ± 6.7 minutes). Both sets of authors also found that adrenocorticotrophic

Table 3
Summary of research articles on the effect of glucocorticoids on exercise performance

Study	Sample Size	Subjects	Treatment	Protocol	Main Outcome
Arlettaz et al [52]	10	Male recreational-trained, 20.2 ± 0.5 y; VO_{2max}: 56.0 ± 1.3 mL/kg/min	1 wk of prednisolone (60 mg) or placebo at home 07:00-08:00 AM separated by 3-wk wash-out	Time to exhaustion at 70%-75% VO_{2max}	Longer time to exhaustion time
Arlettaz et al [53]	14	Male recreational athletes, 25.2 (2.8) y; VO_{2max} = 56.4 (1) mL/kg/min	Prednisolone (30 mg) or placebo 3 h before	Time to exhaustion at 70%-75% VO_{2max}	No significant changes in time to exhaustion time
Arlettaz et al [54]	9	Male recreational trained, 22.7 ± 1.7 y; VO_{2peak}: 57.9 ± 0.8 mL/kg/min	Prednisolone (20 mg) or placebo, 2 h before	1 h at 60% VO_{2max}	Increased total energy expenditure high VO_2
Arlettaz et al [55]	7	Male active cyclist, 23.3 ± 1.1 y; VO_{2peak} 59.4 ± 3.4 mL/kg/min	Prednisolone (20 mg), prednisolone + salbutamol (4 mg) or placebo, 3 h before	Time to exhaustion at 80%-85% VO_{2max}	No significant changes in time to exhaustion time
Collomp et al [56]	8	Male recreational athletes, 21.3 (0.5); VO_{2peak}: 54.0 ± 1.3 mL/kg/min	1-wk prednisolone (60 mg) or placebo at 07:00—08:00 AM daily at home	Four cycling trials at 70%—75% VO_{2peak} consumption until exhaustion just before and after either oral placebo or prednisolone treatment coupled with standardized physical training (2 h/d)	Training associated with glucocorticoid treatment improved endurance performance
Kuipers et al [57]	28	Well-trained, male endurance athletes in cycling and rowing, glucocorticoid: 24 (6) y, n = 14; placebo group, 24 (8) y, n = 14	28 d, 2 puffs twice daily (in the morning and evening) of either budesonide (200 mg) or placebo	Maximal graded test after 2 and 4 wk	No significant differences in maximal power output
Le Panse et al [58]	9	Recreational female athletes, 20.4 ± 0.2; VO_{2max}: 43.8 ± 1.6 mL/kg/min	1 wk of prednisone (50 mg) or placebo and separated by a 4-wk wash-out	Time to exhaustion at 70%-75% VO_{2max}	Longer time to exhaustion
Casuso et al [59]	17	Healthy subjects, 25.2 ± 2.5 y	Dexamethasone (2 mg) or placebo between 07:00 and 09:00 AM and between 5:00 and 9:00 PM for 5 consecutive days	3 × 30-m sprint separated by 2 min, maximal voluntary contraction test and shuttle test	Increased total running distance in shuttle
Zorgati et al [60]	10	Physically active men 20.6 ± 0.9 y	1 wk of prednisone (60 mg) or placebo or at home, between 7:00 and 8:00 AM, separated by 4-wk drug-free washout period	3 × 30-s hopping bouts on their dominant leg, with 5-min recoveries between bouts. 1 hopping bout until exhaustion	No improvements nor in force during the hop neither in time to exhaustion

VO_{2max} = maximal oxygen consumption; VO_{2peak} = peak oxygen volume.

hormone, dehydroepiandrosterone, growth hormone, and prolactin values were significantly decreased after the time-to-exhaustion test under the short-term prednisolone treatment. Insulin and glucose were significantly greater during the whole experiment, and lactate concentration increased significantly after 10 minutes of exercise until 10 minutes 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 [61]. A reduction in serotonin activity has been shown to inhibit descending motor neurons and thus motor output from the locomotor muscles [61]. 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 [53]. Likewise, an increase in energy store mobilization has been demonstrated as a result of the change in hormonal balance after prednisolone ingestion [62].

Collomp et al [56] recruited a group of 8 male recreational cyclists to perform 4 cycling trials at 70%-75% peak oxygen volume until exhaustion before and after either oral prednisolone treatment or placebo, coupled with a standardized period of physical training (2 h/d). Training associated with glucocorticoid treatment resulted in an 80% improvement in time-to-exhaustion performance after 1 week, as well as decreases in adrenocorticotrophic hormone, dehydroepiandrosterone, prolactin, growth hormone, and thyroid-stimulating hormone, free testosterone, and increase in blood glucose concentration. Similarly, Casuso et al [59] assessed muscle function after 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 [63] and corticospinal excitability [60].

In contrast to the aforementioned findings, Kuipers et al [57] 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 between treatments, and Zorgati et al [60] 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 versus inhaled). As well as the route of administration, the mode (systematic versus acute) may modify the effects. An acute dose of prednisolone (20 mg) did not influence performance in time-to-exhaustion performance at either 70%-75% VO_{2max} [54] or at 80%-85% VO_{2max} [55].

In conclusion, the mechanisms by which short-term administration of glucocorticoids are able to improve exercise performance is not completely understood [52,56,58,64]. However, single, acute doses do not appear to have the same performance-enhancing effect as systematic short-term administration, despite having 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 of producing 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 after 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 the World Anti-Doping Agency (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 via 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 4 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 greater pain tolerance than the other teams, even though they were given a placebo substance before competition.

The results of the study by Benedetti et al suggest 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 antidoping authorities, as this practice would be considered entirely legal under antidoping legislation, as morphine is only prohibited in-competition. Codeine is another opioid pain-reliever, similar to morphine, but it currently is not banned. Indeed, after 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 Vicoprofen (Knoll Pharmaceutical Co, Mt Olive, NJ), which 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 Vicoprofen in comparison with ibuprofen and placebo. In addition, VanHeest et al [79] found participants who ingested Vicoprofen 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 after 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 procycling peloton [82]. Moreover, it has been suggested that the use of tramadol alone or in combination with other medications may lead to suboptimal 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.

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 synchronizes antidoping policies in all sports and in all countries).

Table 4
Current World Antidoping Agency status and their potential ergogenic effects

Analgesic	Status	Potential Ergogenic Effect
Paracetamol	Allowed	Increasing pain tolerance Increasing corticospinal excitability Reducing thermal stress
Nonsteroidal anti-inflammatory drug	Allowed	Reducing exercise-induced muscle damage Increasing pain tolerance
Glucocorticoids	Banned in competition	Inducing hormonal and metabolic changes Enhancing excitatory muscle afferents
Opioids	Tramadol and codeine are monitored Morphine is banned	Increasing pain tolerance

Table 4 summarizes the current status of these analgesics and their potential ergogenic effects.

Because of 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 because of its ergogenic effect [21,23,24]. Similarly, the use of NSAIDs currently is not 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 because of the degree of variation in the methodologies of the current research literature. As a consequence of the potentially damaging side effects outlined herein, 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 therapeutic use exception during training. However, there currently is not enough evidence to support this suggestion, and it is 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] to detect potential patterns of abuse, whereas the use of morphine currently is prohibited.

Conclusions

The pharmacologic 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 among 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 EA, Burgess WM. The psychological and physiological responses of sedentary individuals to prescribed and preferred intensity exercise. Br J Health Psychol 2006;11:39-53.
2. Alaranta A, Alaranta H, Heliövaara M, et al. Ample use of physician-prescribed medications in Finnish elite athletes. Int J Sports Med 2006;27:919-925.
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;238:125-132.
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;38:133-140.
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;45:91-94.
6. Taioli E. Use of permitted drugs in Italian professional soccer players. Br J Sports Med 2007;41:439-441.
7. Tsitsimpikou C, Jamurtas A, Fitch K, et al. Medication use by athletes during the Athens 2004 Paralympic Games. Br J Sports Med 2009;43:1062-1066.
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.
9. Bastian B, Jetten J, Hornsey MJ, et al. The positive consequences of pain: A biopsychosocial approach. Pers Soc Psychol Rev 2014;18:256-279.
10. Anderson BJ. Paracetamol (acetaminophen): Mechanisms of action. Paediatr Anaesth 2008;18:915-921.
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;28:204-210.
12. Hinz B, Brune K. Antipyretic analgesics: Nonsteroidal antiinflammatory drugs, selective cox-2 inhibitors, paracetamol and pyrazolinones. Handb Exp Pharmacol 2007;177:65-93.
13. Aminoshariae A, Khan A. Acetaminophen: Old drug, new issues. J Endod 2015;41:588-593.
14. Burian M, Geisslinger G. COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites. Pharmacol Ther 2005;107:139-154.
15. Ziltener JL, Leal S, Fournier PE. Non-steroidal anti-inflammatory drugs for athletes: An update. Ann Phys Rehabil Med 2010;53:278-288.
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.
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;531:280-281.
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;9:3853-3862.
19. Coombs GB, Cramer MN, Ravanelli NM, et al. Acute acetaminophen ingestion does not alter core temperature or sweating during exercise in hot-humid conditions. Scand J Med Sci Sports 2015;25:96-103.

20. Mauger AR, Taylor L, Harding C, et al. Acute acetaminophen (paracetamol) ingestion improves time to exhaustion during exercise in the heat. Exp Physiol 2014;99:164-171.
21. Foster J, Taylor L, Chrismas BCR, et al. The influence of acetaminophen on repeated sprint cycling performance. Eur J Appl Physiol 2014;114:41-48.
22. Burtscher M, Gatterer H, Philippe M, et al. Effects of a single low-dose acetaminophen on body temperature and running performance in the heat: A pilot project. Int J Physiol Pathophysiol Pharmacol 2013;5:190-193.
23. Mauger AR, Jones AM, Williams CA. Influence of acetaminophen on performance during time trial cycling. J Appl Physiol 2010;108:98-104.
24. Mauger AR, Hopker JG. The effect of acetaminophen ingestion on cortico-spinal excitability. Can J Physiol Pharmacol 2013;91:187-189.
25. Lenz TL, Lenz NJ, Faulkner MA. Potential interactions between exercise and drug therapy. Sport Med 2004;34:293-306.
26. Nourjah P, Ahmad SR, Karwoski C, et al. Estimates of acetaminophen (paracetomal)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf 2006;15:398-405.
27. Etminan M, Sadatsafavi M, Jafari S, et al. Acetaminophen use and the risk of asthma in children and adults: A systematic review and metaanalysis. Chest J 2009;136:1316-1323.
28. Bertolini A, Ferrari A, Ottani A, et al. Paracetamol: New vistas of an old drug. CNS Drug Rev 2006;12:250-275.
29. Schoenfeld DBJ. The use of nonsteroidal anti-inflammatory drugs for exercise-induced muscle damage. Sport Med 2012;42:1017-1028.
30. 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.
31. Baldwin AC, Stevenson SW, Dudley GA. Nonsteroidal anti-inflammatory therapy after eccentric exercise in healthy older individuals. J Gerontol Ser A Biol Sci Med Sci 2001;56:510-513.
32. 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;33:470-475.
33. Hudson GM, Green JM, Bishop PA, et al. Effects of caffeine and aspirin on light resistance training performance, perceived exertion, and pain perception. J Strength Cond Res 2008;22:1950-1957.
34. 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-R662.
35. 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;19:116-119.
36. 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-R2248.
37. Warden SJ. Cyclo-oxygenase-2 inhibitors: Beneficial or detrimental for athletes with acute musculoskeletal injuries? Sports Med 2005;35:271-283.
38. Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med 1998;104:2S-8S.
39. 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;17:53-59.
40. Peterson JM, Trappe TA, Mylona E, et al. Ibuprofen and acetaminophen: Effect on muscle inflammation after eccentric exercise. Med Sci Sport Exerc 2003;35:892-896.
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;38:618-622.
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.
43. Sawyer GA, Anderson BC, Raukar NP, et al. Intramuscular ketorolac injections in the athlete. Sports Health 2012;4:319-327.
44. Bauer KA, Gerson W, Wright C IV, 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;22:510-518.
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;21:441-443.
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;52:3137-3142.
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;25:544-553.
48. Cohen DB, Kawamura S, Ehteshami JR, et al. Indomethacin and celecoxib impair rotator cuff tendon-to-bone healing. Am J Sports Med 2006;34:362-369.
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;107:1600-1611.
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.
51. Duclos M. Evidence on ergogenic action of glucocorticoids as a doping agent risk. Phys Sport 2010;38:121-127.
52. Arlettaz A, Portier H, Lecoq AM, et al. Effects of short-term prednisolone intake during submaximal exercise. Med Sci Sports Exerc 2007;39:1672-1678.
53. Arlettaz A, Portier H, Lecoq AM, et al. Effects of acute prednisolone intake on substrate utilization during submaximal exercise. Int J Sports Med 2008;29:21-26.
54. Arlettaz A, Collomp K, Portier H, et al. Effects of acute prednisolone administration on exercise endurance and metabolism. Br J Sports Med 2008;42:250-254.
55. Arlettaz A, Collomp K, Portier H, et al. Effects of acute prednisolone intake during intense submaximal exercise. Int J Sports Med 2006;27:673-679.
56. 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;42:983-988.
57. 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;42:868-871.
58. 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;107:437-443.
59. Casuso RA, Melskens L, Bruhn T, et al. Glucocorticoids improve high-intensity exercise performance in humans. Eur J Appl Physiol 2014;114:419-424.
60. 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;86:10-15.
61. Meeusen R, Watson P, Hasegawa H, et al. Central fatigue: The serotonin hypothesis and beyond. Sport Med 2006;36:881-909.
62. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. Diabetes Metab Rev 1988;4:17-30.
63. Hall ED. Glucocorticoid effects on serotonergic and noradrenergic facilitation of spinal monosynaptic transmission. Psychiatry Res 1980;2:241-250.
64. 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.
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;157:142-148.
66. Wolkowitz OM, Burke H, Epel ES, et al. Glucocorticoids. Mood, memory, and mechanisms. Ann N Y Acad Sci 2009;1179:19-40.

67. Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis 2009;68:1119-1124.
68. Chatham WW, Kimberly RP. Treatment of lupus with corticosteroids. Lupus 2001;10:140-147.
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;112:122-126.
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;147:447-458.
71. Berridge CW, Schmeichel BE, España RA. Noradrenergic modulation of wakefulness/arousal. Sleep Med Rev 2012;16:187-197.
72. Schug SA. The role of tramadol in current treatment strategies for musculoskeletal pain. Ther Clin Risk Manag 2007;3:717-723.
73. Benson D. Tramadol abuse in the cycling peloton. Cyclingnews.com. 20013. Available at http://www.cyclingnews.com/news/tramadol-abuse-in-the-cycling-peloton. Accessed April 23, 2015.
74. Lipp J. Possible mechanisms of morphine analgesia. Clin Neuropharmacol 1991;14:131-147.
75. Benedetti F, Pollo A, Colloca L. Opioid-mediated placebo responses boost pain endurance and physical performance: Is it doping in sport competitions? J Neurosci 2007;27:11934-11939.
76. Sindrup SH, Brøsen K. The pharmacogenetics of codeine hypoalgesia. Pharmacogenetics 1995;5:335-346.
77. Brunton TL. On the use of codeine to relieve pain in abdominal disease. Br Med J 1888;1:1213-1214.
78. Kraemer WJ, Gómez A, Ratamess N, et al. Effects of VICOPROFEN and ibuprofen on anaerobic performance after muscle damage. J Sport Rehabil 2002;11:104-119.
79. VanHeest J, Stoppani J, Scheett TP, et al. Effects of ibuprofen and Vicoprofen® on physical performance after exercise-induced muscle damage. J Sport Rehabil 2002;11:224-234.
80. Langley PC, Patkar AD, Boswell KA, et al. Adverse event profile of tramadol in recent clinical studies of chronic osteoarthritis pain. Curr Med Res Opin 2010;26:239-251.
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;9:469-473.
82. WADA proposes Tramadol remains a monitored rather than a banned substance in 2015 | CyclingTips. Available at https://cyclingtips.com/2014/05/wada-proposes-tramadol-remains-a-monitored-rather-than-a-banned-substance-in-2015/. Accessed September 18, 2015.
83. Martinez-Silvestrini JA. Prescribing Medications for Pain and Inflammation. Edinburgh: W.B. Saunders; 2007.
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;37:260-265.
85. Orchard JW. Why glucocorticoids should be removed from the World Antidoping Agency's list of banned products. Br J Sports Med 2008;42:944-945.
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. Available at https://wada-main-prod.s3.amazonaws.com/resources/files/wada-2017-monitoring-program-en.pdf. Accessed March 30, 2016.

Disclosure

D.H. Department of Physical Education and Sport, Faculty of Sport Sciences, Carretera de Alfacar s/n 18011 Granada, Spain; and Mind, Brain, and Behavior Research Center, University of Granada, Granada, Spain. Address correspondence to D.H.; e-mail: dariashn@ugr.es
Disclosure: nothing to disclose

J.H. Endurance Research Group, School of Sport and Exercise Sciences, University of Kent, Kent, United Kingdom
Disclosure: nothing to disclose

D.S. Mind, Brain, and Behavior Research Center and Department of Experimental Psychology, University of Granada, Granada, Spain
Disclosure: nothing to disclose

M.Z. Faculty of Sport Sciences, University of Granada, Granada, Spain
Disclosure: nothing to disclose

This project was supported from by grants from the Spanish Ministerio de Economía, Industria y Competitividad (PSI2016-75956-P) to D.S. and M.Z. and by a predoctoral grant from the Spanish "Ministerio de Educación, Cultura y Deporte" (FPU14/06229) to D.H.

Submitted for publication February 23, 2017; accepted July 25, 2017.