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## 1 **Abstract**

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

## 16 **Keywords**

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

## 18 **Introduction**

19 There is little doubt that when exercise is performed above certain intensities, or over a prolonged period  
20 of time, it causes feeling of pain and discomfort. Sayings such as ‘no pain, no gain’ are often heard in  
21 relation to both training and competition settings across a variety of different sports. Indeed, these  
22 feelings of exercise-induced pain have been shown to have a negative effect on training and performance  
23 [1]. As a consequence, there has been a trend for athletes from all levels and ages to use pharmacological  
24 analgesics substances prior to training and competition up to 4-fold more than their age-matched general  
25 population [2]. The general term analgesic covers a variety of different pharmacological substances,  
26 including non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesic (such as paracetamol

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

32 The aforementioned negative association between pain and exercise capacity increases the likelihood of  
33 analgesic use as a method to increase the level of performance during competition [5,9]. Furthermore, the  
34 trends for more frequent use of analgesics in-competition vs. out-competition, use of more than one drug  
35 at the same time, and administration of these medications at supratherapeutic dosages, all suggest athletes  
36 may be using these analgesics as ergogenic aids [4,5]. Therefore, in contrast to the post-exercise use of  
37 analgesics to accelerate recovery, there is potential for their prophylactic use as a potential performance  
38 enhancing intervention. In comparison to what is known about the use of analgesics for treating sporting  
39 injury [10,11], much less is known about their effects on exercise related physiology and performance  
40 [12–14]. However, as analgesics exert a pharmacological action on key physiological systems related to  
41 exercise performance, a theoretical rationale exists whereby these drugs could provide a significant  
42 ergogenic effect.

## 43 **Material and methods**

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

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

## 57 **Results**

### 58 **Paracetamol (Acetaminophen)**

#### 59 **Summary of the evidence on performance**

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

71 Even though the exact mechanism of action is yet to be fully determined, some researchers have  
72 attempted to use paracetamol's analgesic effects as a method to reduce pain induced by exercise. The  
73 current available research is summarized in Table 1. Mauger et al. [19] found that 1.5g paracetamol  
74 ingestion increased cycling power output, and reduced the time required to complete a 16.1 km cycling  
75 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  
76 cyclists. The authors hypothesized that paracetamol may exert its effect by reducing perceived pain and  
77 rating of perceived exertion (RPE), although no differences were observed between conditions in their  
78 study. More recently, the influence of 1.5g paracetamol ingestion on exercise performance was examined  
79 during a series of "all-out" Wingate sprints [20]. Results demonstrated a 5% improvement in mean power  
80 output in the paracetamol (391 ± 74 W) compared to the placebo (372 ± 90 W) condition. Collectively,  
81 these studies suggest that, both short [20] and long duration [19] exercise performance can be improved

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

89 Paracetamol also has a notable antipyretic effect, and has the potential to enhance exercise performance  
90 via a reduction in thermal stress of exercise in hot conditions [12]. Burtcher et al. [22], recruited 7  
91 runners to perform a running time-to-exhaustion test in 30°C and 50% relative humidity at an exercise  
92 intensity corresponding to the 70%  $\text{VO}_{2\text{max}}$  following ingestion of a single 500mg dose of paracetamol or  
93 a placebo. They found a smaller increase in core temperature after 20 min running following paracetamol  
94 ingestion, but no difference between conditions at exhaustion, or in terms of the exercise time-to-  
95 exhaustion performance. In a similar study, Mauger et al. [23] examined the influence of paracetamol on  
96 cycling time-to-exhaustion in 30 °C and 50% relative humidity at 70%  $\text{VO}_{2\text{max}}$ . The authors measured  
97 core temperature ( $T_{\text{core}}$ ), skin temperature ( $T_{\text{skin}}$ ), body temperature ( $T_{\text{body}}$ ) and thermal sensation. Results  
98 demonstrated an increased time-to-exhaustion in the paracetamol compared with placebo condition ( $23 \pm$   
99  $15$  min vs.  $19 \pm 13$  min). The authors concluded that the antipyretic effect of paracetamol was a useful  
100 mechanism to enhance performance by reducing  $T_{\text{core}}$ ,  $T_{\text{skin}}$ ,  $T_{\text{body}}$  and thermal sensation during exercise in  
101 the heat, in the absence of a pre-cooling mechanism at rest. However, Coombs et al. [24] failed to find  
102 any effect of paracetamol on thermoregulatory control or perceptual responses during exercise at a fixed  
103 rate of metabolic heat production in hot-humid condition. Interestingly their methodological design  
104 afforded a fixed level of heat production between participants over a standardized exercise duration,  
105 something not done by either of the aforementioned studies. Therefore, Coombs et al.<sup>22</sup> could separate the  
106 effects of the exercise on thermoregulatory responses from those attributable to the pharmacological  
107 action of the paracetamol. Thus, instead of paracetamol exerting a performance enhancing antipyretic  
108 effect, the findings of Mauger et al. [23] could be attributable to its aforementioned analgesic properties.

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

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

## 115 **Side effects**

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

## 124 **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

### 125 **Summary of the evidence on performance**

126 Research on NSAIDs in sport has primarily focused on their effects on exercise-induced muscle damage  
127 and soreness [29]. In contrast, there are limited studies that investigate the effects of NSAIDs on sport  
128 performance (Table 2). NSAIDs appear to have both central and peripheral effects by inhibiting  
129 cyclooxygenase oxidase (COX) activity [15]. Two COX enzymes have been identified in skeletal muscle  
130 (COX-1 and COX-2) [30]. Through COX inhibition, NSAIDs limit prostaglandin synthesis both centrally  
131 and peripherally, and subsequently mask its nociceptive effect [14]. New NSAIDs allow the selective  
132 inhibition of the COX-2 enzyme, which seems to more effectively counteract inflammatory reactions  
133 [31]. As a consequence of COX inhibition, NSAIDs assist in alleviating the swelling and pain of  
134 inflammation [32].

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

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

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

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

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

167 days/week, for 6 weeks. Participants were required to ingest ibuprofen (two 200 mg tablets per day)  
168 immediately after training the biceps of one arm, and placebo after training the other arm the next day.  
169 ibuprofen ingestion was shown to have no effect on either 1RM strength or daily muscle soreness  
170 compared with placebo. The reasons for the divergent findings of Trappe et al. [35] and Krentz et al. [37]  
171 are unclear. However, differences in the study population (67 vs. 24 years), NSAID dose (1200mg/day vs  
172 400mg/day), muscle group trained (quadriceps vs. biceps), the duration of the protocol (12 vs. 6 weeks),  
173 and training experience of participants (untrained vs. experienced), may all have contributed to the  
174 conflicting results.

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

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

## 188 **Side effects**

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



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

## 201 **Glucocorticoids**

### 202 **Summary of the Evidence on performance**

203 Glucocorticoids remain one of the most controversial analgesics used in sport. Their therapeutic use in the  
204 treatment of pain and inflammation seems unquestionable [50], but they also have a powerful effect  
205 related to exercise performance at both central and peripheral levels. As a consequence glucocorticoids  
206 have the potential to be used as ergogenic aids [51]. Table 3 summarizes the current available evidence of  
207 the effect of glucocorticoids on exercise performance. In two separate studies, Arlettaz et al. [52] and Le  
208 Panse et al. [53] investigated the effects of 7 days of prednisolone administration (oral dose 60mg/day  
209 and 50mg/day, respectively) on exercise performance during submaximal exercise (time to exhaustion at  
210 70-75%  $VO_{2max}$ ). Both studies found an improvement in time-to-exhaustion compared with a placebo  
211 condition (Arlettaz et al., prednisolone:  $74.5 \pm 9.5$  min vs. placebo:  $46.1 \pm 3.3$  min; Le Panse et al.,  
212 prednisolone:  $66.4 \pm 8.4$  min vs. prednisolone:  $47.9 \pm 6.7$  min). Both sets of authors also found that  
213 adrenocorticotrophic hormone (ACTH), dehydroepiandrosterone (DHEA), growth hormone (GH) and  
214 prolactin (PRL) values were significantly decreased following the time-to-exhaustion test under the short-  
215 term prednisolone treatment. Insulin and glucose were significantly higher during the whole experiment,  
216 and lactate concentration increased significantly after 10 min exercise until 10 min of recovery under  
217 prednisolone treatment. Therefore, alterations in hormonal and metabolic parameters during exercise  
218 indicate that short-term glucocorticoid treatment induced both central and peripheral effects. Indeed, it is  
219 possible that prednisolone exerted a central effect by inducing alteration in either brain serotonin or  
220 dopaminergic activity at the onset of fatigue [54]. A reduction in serotonin activity has been shown to  
221 inhibit descending motor neurons and thus motor output from the locomotor muscles [54]. Peripherally,  
222 glucocorticoids increase fat oxidation and lower carbohydrate oxidation during submaximal exercise,

223 with a significant increase in energy expenditure possibly due to a reduction in respiratory exchange ratio  
224 [55]. Likewise, an increase in energy store mobilization has been demonstrated as a result of the change  
225 in hormonal balance after prednisolone ingestion [56].

226 Collomp et al. [57] recruited a group of 8 male recreational cyclists to perform four cycling trials at 70–  
227 75%  $VO_{2peak}$  until exhaustion before and after either oral prednisolone treatment or placebo, coupled with  
228 a standardised period of physical training (2 hours/day). Training associated with glucocorticoid  
229 treatment resulted in an 80% improvement in time-to-exhaustion performance after 1 week, as well as  
230 decreases in ACTH, DHEA, PRL, GH, TSH, free testosterone; and increment in blood glucose  
231 concentration. Similarly, Casuso et al. [58] assessed muscle function following a 5-day ingestion period  
232 (twice/day) of either 2 mg of dexamethasone or placebo, but in a one-legged kicking exercise, and whole  
233 body exercise performance, using 20-m shuttle run and 30 m sprint tests. One-leg kicking exercise time-  
234 to-exhaustion was longer and total running distance in the 20-m shuttle run test was improved. A possible  
235 explanation for these improvements in muscle function might be enhanced monosynaptic transmission  
236 between excitatory muscle afferents and spinal motor neurons [59], and corticospinal excitability [60].

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

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

## 250 **Side effects**

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

## 260 **Opioids**

### 261 **Summary of the evidence on performance**

#### 262 **Tramadol**

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

#### 275 **Morphine and codeine**

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

### 302 **Side effects**

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

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

### 313 **World Anti-Doping Agency (WADA) status**

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

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

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

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

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

## 339 **Conclusions**

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

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