Prescription and non-prescription medications permitted for performance enhancement

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INTRODUCTION

Performance-enhancing drugs, supplements, and other substances have been used in a variety of settings by both athletes and non-athletes for decades. Individuals take performance-enhancing drugs and substances for a variety of reasons, which include improving athletic performance, increasing alertness, and improving appearance. Although the focus of the news media is on competitive athletes caught using banned hormonal agents (eg, androgens, growth hormones) [1], many non-hormonal drugs and other substances for performance enhancement are used, some of which are banned but others of which are permitted and freely available.

There has been a massive increase in the use of supplements among athletes over the past few decades. Companies worldwide make a range of claims about the ergogenic benefit of many supplements. However, evidence suggests that only a small number have demonstrable benefits for athletes. It is unknown whether the common practice of combining supplements causes additive or interactive benefits or harms. Importantly, throughout the world, quality control for these substances is generally poor, and regulations pertaining to their manufacture and marketing are weak, making it difficult for athletes to determine which supplements are safe, effective, and legal.

This topic will review some of the most common prescription and non-prescription medications that are not banned by the World Anti-Doping Agency and are used by athletes for performance enhancement. Banned performance-enhancing drugs, including hormonal agents, and other

unbanned supplements are discussed separately. (See "Prohibited non-hormonal performance-enhancing drugs in sport" and "Use of androgens and other hormones by athletes" and "Nutritional and non-medication supplements permitted for performance enhancement".)

PRESCRIPTION MEDICATIONS

Psychiatric and neurologic medications — Antidepressants, anxiolytics, antipsychotics, and anticonvulsants can improve mood and decrease anxiety [2]. These medications are not prohibited by the World Anti-Doping Agency (WADA), although some have suggested that such drugs may give certain athletes an unfair advantage. We believe that, for athletes suffering from anxiety or depression, appropriate therapy with such medications should help to restore energy and motivation, allowing them to optimize their training, performance, and recovery; but these medications are unlikely to provide benefit beyond the athlete's normal baseline function. The use and adverse effects of specific psychiatric and anticonvulsant medications are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects" and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Generalized anxiety disorder in adults: Management".)

Selective serotonin reuptake inhibitors (SSRIs) are widely used to treat depression. While some have postulated that by improving the emotional state of healthy athletes, SSRIs might improve performance, evidence supporting this assumption is lacking. A few small studies involving healthy young men and trained male cyclists given fluoxetine reported no improvement in anaerobic power, endurance, maximum oxygen consumption (VO_2 max), or fatigue time when tested on cycle ergometers [3,4]. There are reports of serotonergic medications increasing perceptions of fatigue, both mentally and physically, among users, which would be detrimental to training and competing. Some SSRIs may induce insulin resistance and weight gain, which may be important to athletes with polycystic ovary syndrome or a family history of type 2 diabetes. Limited studies of serotonin/norepinephrine reuptake inhibitors have shown no benefit to athletes [5].

Phosphodiesterase-5 inhibitors — Phosphodiesterase-5 (PDE5) inhibitors are generally used to manage erectile dysfunction based on their vasodilatory effects. PDE5 inhibitors affect nitric oxide-related cardiovascular, endocrine, and metabolic pathways. They do not affect energy metabolism or mitochondrial biogenesis. PDE5 inhibitors have the potential to improve athletic performance via their cardiovascular and vasodilatory effects, which may improve oxygen

availability to exercising muscle. Abuse of these medications has been reported among athletes hoping to improve their exercise capacity [6].

Few data are available about the effect of PDE5 inhibitors on athletic performance in normoxic environments. Sildenafil was thought to increase exercise tolerance in healthy subjects during severe hypoxia both at sea level and high altitude [7], but a systematic review of 14 studies (210 total participants) found that while sildenafil reduces pulmonary arterial pressure it has no meaningful effect on athletic performance [8]. This did not change with alterations in the degree of hypoxia. PDE5 inhibitors have not been added to WADA's prohibited drug list. Potential adverse effects include headache, flushing, dyspepsia, hypotension, and blurring of vision(See "Treatment of male sexual dysfunction", section on 'Initial therapy: PDE5 inhibitors'.)

Angiotensin-converting enzyme inhibitors — Angiotensin-converting enzyme (ACE) inhibitors are routinely used in the treatment of hypertension, coronary artery disease, and heart failure. They are not included in the WADA list of prohibited substances.

Individuals with the "insertion" allele of the ACE gene appear to have higher maximum oxygen uptake and better response to endurance training compared with those with the "deletion" allele, and it has been reported that many elite athletes in a variety of endurance sports possess the insertion allele [9]. As the insertion allele was found to decrease ACE activity, similar to the effects of ACE inhibitors, some have postulated that lower ACE levels may allow athletes to respond better to training, thereby providing an advantage in endurance sporting events. This could be due to lower levels of angiotensin II or higher levels of bradykinin. Nevertheless, the available evidence that ACE inhibitors enhance athletic performance is scant and unconvincing.

Potential adverse effects of ACE inhibitors (and angiotensin receptor blockers [ARBs]) include cough, hypotension, hyperkalemia, renal insufficiency, and angioedema. A number of UpToDate topics discuss the therapeutic use and side effects of ACE inhibitors. (See "Renin-angiotensin system inhibition in the treatment of hypertension" and "Major side effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers".)

Telmisartan — Telmisartan is an ARB used primarily to treat hypertension. Telmisartan is not banned and has been removed from the WADA monitoring list.

Telmisartan has been used by endurance athletes, particularly cyclists, and is purported to improve endurance, increase fat-burning capacity, reduce lactic acid formation, and enhance recovery from exercise [10]. However, the drug's actual performance-enhancing effects remain the subject of debate, and evidence that it has ergogenic effects is lacking. Side effects from reduced blood pressure are of concern. (See "Renin-angiotensin system inhibition in the

treatment of hypertension" and "Major side effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers".)

NON-PRESCRIPTION MEDICATIONS

Analgesics — Some athletes take analgesics with the intention of improving performance [11]. Pain and discomfort can discourage athletes and may hinder training and performance. According to some observational studies, athletes of all ages and levels use analgesics (generally before training and competition) four times more often than the general population [12]. Acetaminophen (paracetamol) and nonsteroidal antiinflammatory drugs (NSAIDs) are among the medications used most often by athletes. Analgesics may provide ergogenic effects indirectly through the suppression of pain during exercise or possibly directly through effects on other physiologic pathways. These possible effects and the drugs' ready accessibility create the potential for misuse.

Acetaminophen (paracetamol) — Literature reviews cite studies reporting improvements in performance of both short- and long-duration exercise in athletes using paracetamol [11,13]. However, variations in research methodology make it difficult to determine whether any performance-enhancing effect is real. There is much speculation about the mechanism through which paracetamol exerts these purported ergogenic effects, but this remains unknown. Performance may improve through increased corticospinal excitability leading to greater force production or through antipyretic effects that reduce thermal heat load during exercise. A randomized trial involving 16 trained cyclists reported increased power and muscle activation during maximum cycling resistance among those given acetaminophen [14].

The dose taken by some athletes for analgesic and performance effects is 1.5 grams about one hour prior to competition or training. Side effects of paracetamol are well known, as are the potentially lethal effects of overdose. Exercise does not alter the medication's pharmacokinetics or risk profile. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation" and "Clinical manifestations and diagnosis of acetaminophen (paracetamol) poisoning in children and adolescents".)

NSAIDs — NSAIDs inhibit cyclooxygenase (COX)-1 and COX-2 enzyme activity both centrally and peripherally, limiting prostaglandin synthesis in order to reduce inflammation and pain. When used prior to training or competition, NSAIDs may allow athletes to withstand greater pain and reduce post-exercise inflammation, thereby enabling them to train harder and longer. Overall, there is as yet no conclusive evidence of a benefit from NSAIDs to reduce post-exercise inflammation or improve exercise capacity [11]. However, studies of the effects of NSAIDs on

performance are conflicting, with some reporting reductions in post-exercise muscle inflammation and soreness and others reporting no benefit. Representative studies include the following:

- A small randomized trial of older, untrained individuals (n = 36) reported that those given 1200 mg ibuprofen/day while performing strength training three days per week for 12 weeks demonstrated increased muscle hypertrophy and strength compared with those given placebo [15]. Of note, the group given acetaminophen experienced similar gains.

- A small randomized trial of young adults (n = 18) experienced with resistance training reported no benefit among those given 400 mg ibuprofen/day compared with those given placebo [16]. Notable differences between this trial and the first described above include participants with resistance training experience, assessment of a smaller upper extremity muscle (biceps), 6 weeks of training versus 12, and a smaller dose of ibuprofen.

- In two small trials, active males were given 400 mg of ibuprofen 60 minutes prior to completing either 60 three-second maximal voluntary contractions of the knee extensors or two three-minute all-out tests against fixed resistance on a cycle ergometer. Neuromuscular fatigue declined at a similar rate in all groups, suggesting that this dose of ibuprofen does not improve strength or performance [17].

Potential side effects caused by NSAIDs include peptic ulcer disease, gastric bleeding, acute kidney injury, and cardiovascular disease. Risk of complications increases if supratherapeutic doses are taken. In addition, the risk of bleeding in contact and collision sports may be increased due to the inhibitory effect of NSAIDs on platelet function, particularly with the injectable NSAID ketorolac.

Tramadol — Tramadol has been widely used among athletes, particularly cyclists, for its analgesic properties and possible performance benefits. A World Anti-Doping Agency (WADA) study in 2017 found that 4.4 percent of in-competition tests on cyclists detected tramadol. Among samples taken from participants in 35 Olympic sports, 68 percent of urine samples positive for tramadol were from cyclists. These findings led to a ban by the Union Cycliste Internationale (UCI), the international governing body for cycling.

There is no strong evidence that tramadol improves athletic performance. In a randomized trial of 16 trained cyclists given 100 mg of tramadol or placebo one hour prior to completing a 15-km time trial, no performance differences were noted between the two groups, including mean power output, perceived exertion and pain, and serum lactate [18]. A similar study reported increased performance during the first arm but could not replicate these results in the second arm with a different group of athletes [19].

Tramadol is a mu-opioid receptor agonist and also a serotonin and norepinephrine reuptake inhibitor. Stimulation of the mu receptor produces analgesia, while reduction in serotonin and norepinephrine reuptake reduces the brain's response to sensory stimulation. Tramadol remains on the WADA monitoring list.

Codeine — Codeine is a weak opioid that is not banned but remains on the WADA monitoring list. A small amount of codeine is converted to morphine after absorption.

Bemitil — Bemitil is included in a class of drugs called actoprotectors, which were developed in the 1970s by the Soviet Union for the military with the aim of improving physical and mental performance in combat and accelerating recovery following physical exertion. Bemitil is an imidazole derivative, 2-ethylsulfanyl-1H-benzimidazole hydrobromide, similar to purine bases in structure. It remains in the WADA monitoring program, where testing assesses the prevalence of this drug in and out of competition. There is little literature regarding the use of bemitil in sport and little research about its ergogenic effects. However, it is increasingly declared on doping control forms submitted by Russian and eastern European athletes [20].

Bemitil appears to amplify expression of RNA and proteins, especially the enzymes of gluconeogenesis and oxidative phosphorylation [21]. It is promoted as increasing mental and physical work capacity without an increase in oxygen consumption or heat production. It is purported to have anti-hypoxia, antioxidant, and immunomodulatory actions, and has reportedly allowed soldiers and rescue workers to perform in hypoxic and high-temperature environments.

The greatest effect of bemitil appears to be on individuals with low or moderate resistance to extreme conditions (eg, very high or very low temperatures, low oxygen environments), with little impact in those with high resistance. Thus, the benefit for highly trained athletes may be negligible.

Bemitil may cause nausea, irritability, reduced sleep quality, headache, and facial erythema. Its use is contraindicated if hypoglycemic or there is concurrent barbiturate intake. Bemitil is freely available on the internet and manufactured in Ukraine. It is not approved for therapeutic use in many Western countries.

BLOOD BUFFERS

Sodium bicarbonate and sodium citrate — Sodium bicarbonate and sodium citrate are alkaline substances (often referred to as "buffers") taken by some athletes to counteract the muscle fatigue experienced during high-intensity training or competition, which is thought to

result from the increasingly acidic milieu of exercising skeletal muscle [22]. This form of performance enhancement has been reported since the 1930s. In a 2007 survey of over 300 elite track and field athletes, alkalinizing agents such as sodium bicarbonate and sodium citrate were among the supplements listed [23]. However, buffers were used much less often than creatine, vitamins, and stimulants, probably due to the gastrointestinal (GI) side effects of these substances. Buffering agents are permitted by the World Anti-Doping Agency (WADA).

Anaerobic glycolysis is the primary means of energy production during exercise of near-maximal intensity lasting longer than 20 to 30 seconds. During such intense exercise, intracellular acidity increases. Lactate and hydrogen ions diffuse into the extracellular space once the maximum buffering capacity of the intracellular environment has been reached. The fatigue associated with high rates of anaerobic glycolysis is probably associated more closely with the high concentration of protons than the accumulation of lactate. Use of blood buffers is based on the theory that by increasing extracellular buffering capacity, muscular fatigue is delayed, as more of the excess protons can be cleared from the muscle.

Sodium bicarbonate has been reported to improve training efficiency [24-29]; however, the effect size is moderate and significantly less for trained athletes than recreational athletes [26,29]. The effect size is greater for a single bout of exercise than for repeated bouts. It is thought that athletes participating in activities lasting from one to seven minutes (eg, the 800 m run, 200 m swim, and rowing events) may benefit most from blood buffers [30]. There is weaker evidence of benefit for participants in sports requiring repeated sprints and endurance events that involve sustained exertion just below the lactate threshold (eg, cycling time trials, 5- to 10-km running races).

A meta-analysis of 25 randomized trials involving closed-end exercise tests lasting between 45 seconds and 8 minutes, including time trials or total work done in a given time, reported a small effect size but statistically significant performance benefit for bicarbonate compared with placebo [30]. A subsequent meta-analysis reported comparable results, with the maximum benefit found for exercise with durations between 30 seconds and ten minutes [29]. A systematic review of 35 randomized trials performed to assess the effectiveness of bicarbonate based on the duration of exercise emphasized the large heterogeneity among studies, making it difficult to compare and interpret results [31]. In 11 of the 20 studies involving an exercise test shorter than four minutes, bicarbonate provided some benefit, but only 6 of 15 studies involving an exercise test four minutes or longer reported a benefit.

Sodium bicarbonate does not appear to increase strength [28].

The traditional protocol for blood buffers is to ingest 0.3 g/kg of sodium bicarbonate (approximately 4 to 5 teaspoons of bicarbonate powder) two to two and a half hours before athletic training in split doses. Sodium citrate is taken in doses of 0.3 to 0.5 g/kg but probably has less efficacy as a buffering agent [24].

Investigators have studied alternative strategies for using sodium bicarbonate, including slowing the administration, altering the form of the bicarbonate, and ingesting it with different fluids or foods [24]. The best alkalotic response with the fewest GI side effects was achieved using bicarbonate capsules taken slowly, over 120 to 150 minutes before the beginning of the event. A fluid and a carbohydrate-rich meal taken at the same time improved tolerance. A serial loading protocol has been suggested by some [32]. This involves ingesting 500 mg/kg each day, taken in four divided doses for six consecutive days. The alkalotic benefit was seen during the ingestion period and for one to two days afterward.

Significant alteration of body pH can have significant adverse effects, depending particularly on the rate of change from normal acid-base levels. However, such concerns as they relate to buffering for sport are more theoretical than real, as the body is highly adept at rapidly metabolizing alkalizing agents to achieve a normal acid-base balance. In contrast, GI side effects from using buffers are relatively common. These may include nausea, abdominal pain, diarrhea, and vomiting. Hence, many athletes avoid using buffers immediately prior to and during competition.

ADDITIONAL RESOURCES

Several National Anti-Doping Organizations (NADOs) have developed a website to provide information about medicines and supplements to athletes and others. At this stage, NADOs from the United States, Canada, Australia, Japan, Switzerland, New Zealand, and the United Kingdom are directly linked, and the websites for many other countries are available. General information about supplements, including whether their use is proscribed generally or for competition, is provided, but there is no detailed information about particular compounds.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Performance-enhancing substances".)

SUMMARY AND RECOMMENDATIONS

- Clinicians involved in the care of competitive athletes should be aware of doping regulations, particularly as some banned drugs may be taken for medical purposes (eg, diuretics, 5-alpha-reductase inhibitors). The World Anti-Doping Agency (WADA) maintains a list of prohibited substances, which includes stimulants, recreational drugs (eg, opioids, cannabinoids), beta-agonists, diuretics, and other prescription medications. The list can be found on the WADA website. The contents of the list are revised annually, and it is important that sports medicine clinicians, competitive athletes, and anyone involved in the care of athletes keep current with its contents. (See "Prohibited non-hormonal performance-enhancing drugs in sport".)

- A wide range of non-hormonal, proven and purportedly performance-enhancing medications are taken by recreational and elite athletes. These include antidepressants, anxiolytics, antihypertensives, analgesics, stimulants, blood buffers, and others. Medications commonly used for performance enhancement are reviewed in detail in the text. Controlled studies pertaining to the purported benefits of these supplements are often limited, but relevant evidence is reviewed. For many substances, benefit is unproven or minimal. (See 'Prescription medications' above and 'Non-prescription medications' above.)

- The practice of combining several supplements is common, but studies to assess the benefits and harms of using such combinations are difficult to design and interpret, and few have been performed. Many multicomponent supplements pose a risk to athletes from the declared or undeclared banned substances they often contain.

- In many countries, the sports supplement industry is poorly regulated, and supplements are sometimes a source of doping violations due to inadvertent contamination or intentional addition of additives not included on the label. Supplements are generally not tested for contamination or accurate labeling, and they frequently contain unlisted substances.

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