Nutritional and non-medication supplements permitted for performance enhancement

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Literature review current through: **Oct 2023.**
This topic last updated: **May 16, 2023.**

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 in the sports community over the past few decades. Companies worldwide make a range of claims about the ergogenic benefit of many of these supplements. However, research suggests that only a small number have demonstrable benefits for athletes. The additive, interactive, and potentially harmful effects from the common practice among athletes of combining multiple supplements remains largely unknown. 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 nutritional and non-medication supplements that are **not** banned and are used by athletes for performance enhancement. Banned performance-enhancing drugs, including hormonal agents, permitted performance-enhancing medications, and supplements commonly marketed to the general public are discussed separately. (See "Prohibited non-hormonal performance-enhancing drugs in sport" and "Use of androgens and other hormones by athletes" and "Prescription and non-prescription medications permitted for performance enhancement" and "High-risk dietary supplements: Patient evaluation and counseling".)

NUTRITIONAL SUPPLEMENTS

Use of supplements and contamination — Many substances are designated or marketed as nutritional supplements, including vitamins, minerals, herbs, extracts, amino acids, metabolites, or any combination of these and other substances [2-5]. As testing for performance-enhancing drugs has expanded to nearly all levels of competition, athletes have begun to use more over-the-counter nutritional supplements, assuming they are legal, safe, and beneficial. A survey of athletes participating in the 2004 Athens Olympic Games found that over 47 percent reported use of nutritional supplements [6]. However, in many countries, the sports supplement industry is poorly regulated, and supplements are sometimes a source of doping violations. This is due to either inadvertent contamination or the intentional addition of additives not included on the label that provide the beneficial effects touted by the manufacturer. Supplements are generally not tested for contamination or accurate labeling, and they frequently contain unlisted substances. (See "High-risk dietary supplements: Patient evaluation and counseling".)

There is an international movement encouraging larger supplement manufacturers to submit products for testing. Some countries, including Australia, and international organizations (eg, Informed-Sport) are working with supplement companies to have them submit their supplements for testing, with the incentive of being given a "safe in sport" label acknowledging that their product has been found to be free of contaminants.

Large manufacturers of conventional supplements, such as protein powders, usually follow reasonable quality-control practices. Supplements obtained via the internet from small, unregulated companies can be contaminated or mislabeled. In one case series, a number of healthy individuals were found to be taking dietary supplements laced with steroids, and they presented for medical care with complaints including nausea, anorexia, jaundice, severe pruritus, and kidney failure [7].

Supplements promoting increased muscle mass are more likely to contain anabolic contaminants, such as nandrolone, stanozolol, and oxandrolone. Prohormones, peptide hormones, and releasing factors have also been found in supplements. These include growth hormone-releasing peptides (eg, GHRP6, GHRP2), hexarelin (a synthetic growth hormone agonist), and growth hormone secretogogues, such as ghrelin. All such substances are banned by the World Anti-Doping Agency (WADA). In a 2004 study, 634 supplements from 215 suppliers in 13 countries were analyzed, and 14.8 percent were found to be contaminated with hormones or prohormones, most commonly anabolic androgenic steroid hormones and prohormones [8].

Some supplements have been contaminated with selective androgen receptor modulators (eg, ostarine, LGD-4033), which act on androgen receptors and exert anabolic effects on muscle and bone. These substances are banned by WADA. Stimulants such as methylhexanamine, ephedrine, and sibutramine have been found in supplements, particularly pre-workout powders, energy boosters, and fat burners [9]. Clenbuterol has been detected in a small number of cases of alleged doping violations involving a supplement promoted for weight loss. Clenbuterol was not included on the label. Higenamine, a beta-2 agonist, is a stimulant that has been detected in many supplements. Labeling of these supplements often includes the name of the plant from which higenamine is derived (eg, *Nandina domestica*, *Tinospora crispa*, *Aconitum japonicum*) or the chemical name (eg, norcoclaurine), rather than the common name, making it difficult to determine whether the supplement is safe.

A number of common supplements are discussed below. Some have proven ergogenic benefits, whilst there is limited (if any) evidence for the performance-enhancing effects of others. Helpful resources for information about supplements include: Informed Sport website, Australian Institute of Sport website, and the US Anti-Doping Agency website. (See "Vitamin intake and disease prevention" and "Overview of herbal medicine and dietary supplements".)

Creatine

Overview and biology — Creatine is likely the most popular nutritional supplement used for performance enhancement [10-12]. It is not prohibited by WADA and has been shown to be effective at improving training and performance of short-duration, high-intensity exercise. Creatine is available in a wide range of commercial products, primarily as a powder [10].

Creatine is a naturally occurring substance derived from three amino acids (methionine, glycine, and arginine). Approximately 95 percent is stored in skeletal muscle, with the remainder being located in the brain, testes, and kidneys. Of the creatine in muscle, approximately 65 percent is in the form of phosphocreatine. Phosphocreatine is a source of phosphate for the rapid resynthesis of adenosine triphosphate (ATP), which muscles rely on for energy during short–duration, high-intensity exercise. Creatine supplementation increases the rate of phosphocreatine resynthesis during recovery between such bouts, thereby enhancing recovery and performance [10,13]. In addition, creatine may have direct cellular effects via upregulation of genes and increased activity of enzymes involved in protein synthesis and other activities with anabolic effects [14].

Effectiveness — Multiple studies have reported improvement in the performance of repeated bouts of 6- to 30-second maximal exercise (eg, sprint, heavy weightlifting) with short recovery periods (20 seconds to 5 minutes) following creatine supplementation. In a meta-analysis of seven trials of young men (<36 years old), creatine supplementation combined with resistance training increased the maximal lifting weight for the bench press and squat [15]. There was no effect in women or older men, and performance of other types of muscular effort did not improve. The lack of improvement reported in women may be due to the use of lower doses, stemming from concerns about weight gain.

According to a review of creatine and its effects, short- and long-term supplementation in female athletes improves strength and power, as well as anaerobic and aerobic exercise measures, with minimal effect on body composition parameters [16]. Subsequent randomized trials have confirmed that creatine increases maximum power output [17,18]. A meta-analysis of 12 trials in patients with muscular dystrophies found a similar increase in muscle strength among those taking creatine compared with placebo [19].

Results suggesting that creatine enhances performance in endurance sports are inconsistent, and further investigation is required, particularly in sports that require high-intensity bursts (eg, road cycling) where supplementation may be useful [20]. A systematic review of 13 controlled trials involving trained endurance athletes found no evidence of benefit [21]. Theoretically, creatine supplementation may be useful for sports that involve short intervals of high-intensity effort followed by brief recovery periods, such as American football, rugby, racquet sports, and other team sports.

A review of studies of creatine use among adolescent athletes noted relatively heavy use in the United States and the absence of reports of adverse effects [22]. The authors concluded that creatine appears well tolerated and effective in adolescents, while noting the paucity of rigorous, well-designed studies assessing either safety or effectiveness in this age group.

Dosing and formulations — Acute loading over a five-day period is probably less beneficial than chronic loading over a 28-day period. Rapid loading is achieved by taking 20 to 25 g (0.3 g/kg per day) in four divided doses for five days (eg, 5 g four times per day for five days) [23]. Chronic loading involves consuming 3 g per day over 28 days. Elevated muscle creatine stores are maintained by continued supplementation using doses of 2 to 3 g per day [23]. Doses do not differ for power athletes, sprinters, and other athletes.

Of note, creatine is sold in several formulations other than the recommended creatine monohydrate supplement. These formulations include ethyl ester, nitrate, and phosphate, are usually more expensive, may contain impurities, and may have no added ergogenic benefit. When supplementation ceases, it takes four to five weeks for muscle creatine concentrations to return to pre-supplementation levels.

Side effects — Reported side effects of acute creatine ingestion include weight gain (from increased water retention), reduced joint mobility, and muscle cramping, although the evidence for this last purported side-effect is not strong [24,25]. Nausea, gastrointestinal (GI) upset, and headaches have been reported anecdotally but are not consistent findings in well-designed studies. Up to 30 percent of individuals do not respond to creatine supplementation and will not significantly increase muscle creatine stores.

Effects on kidney function — Although some have claimed that creatine can adversely affect kidney function, limited published evidence and wide experience with this supplement suggest that this is not true in patients with normal baseline renal function [26,27]. In fact, creatine may be beneficial when exercising in hot, humid conditions, as the increased body water appears to aid thermoregulation, reduce heart rate, and reduce sweating [2]. The potential long-term consequences of creatine supplementation are unknown, and the American College of Sports Medicine (ACSM) recommends it be used only by physically mature, well-developed athletes. For this reason, it is not recommended for adolescent athletes.

Serum creatinine concentrations may become slightly elevated in athletes with normal renal function who take creatine supplements [28-31]. Primarily, such increases occur because creatinine is a normal byproduct of creatine metabolism, and they do not reflect kidney dysfunction or injury. In some cases, increases may stem from direct absorption of creatinine present in the supplement [32]. Particular formulations of creatine may lead to relatively larger increases in serum creatinine. Creatine ethyl ester (CEE) appears to cause larger increases than creatine monohydrate, for example [28,30,33]. Creatinine concentrations return to normal when supplementation is ceased.

Protein and amino acids — Proteins and their amino acid constituents have been promoted widely as muscle-building agents. Common types and their use for sports performance are discussed below.

Branched-chain amino acids — The branched-chain amino acids (BCAAs), leucine, valine, and isoleucine, are the most abundant amino acids in muscle [34]. They cannot be synthesized in the body, but large amounts are found in red meat and dairy products. Vegetarians can obtain sufficient amounts if they eat an adequate amount and appropriate mix of legumes, nuts, grains, and seeds daily. BCAAs are oxidized in the muscle during exercise.

Manufacturers of BCAA supplements claim they reduce fatigue, improve endurance, provide fuel for working muscle, and reduce muscle protein breakdown and soreness from exercise. Nevertheless, although BCAAs are widely used by athletes, there is no high-quality evidence of their efficacy, particularly when compared with eating a diet rich in meat, which is less expensive. A chicken breast is said to contain the equivalent of seven average BCAA tablets.

Laboratory studies have found that the rate of oxidation of BCAAs is too low for the process to make a significant contribution to energy production [35]. There is limited scientific evidence (much of it in vitro) that BCAAs may accelerate the repair of muscle damage after exercise.

Adequate amino acids are needed for muscle protein synthesis following resistance exercise, but no studies have examined the effects of BCAA supplementation on protein synthesis in this setting [36]. In addition, no studies have found any change in muscle function as a result of BCAA supplementation. Several studies have reported reductions in muscle soreness after both acute and chronic supplementation, but this is probably most prominent in untrained individuals [34].

5-hydroxytryptophan has been implicated in the development of fatigue in athletes. Increased plasma levels of BCAA during exercise may reduce transport of tryptophan into the brain, and this might reduce the synthesis of 5-hydroxytryptophan [37]. A small observational study reported that BCAA supplementation during prolonged exercise improved cognitive function and reduced perceived exertion levels [38].

Suggested doses for BCAA supplementation are approximately 2 to 4 g per hour during exercise and the immediate recovery period. They are best consumed as a drink.

Glutathione, glutamate, and glutamine — Glutathione is an important intracellular antioxidant that helps to modulate reactive oxygen species. Glutathione also plays an important role in cellular signaling and transcription processes, including some involved in the adaptations of skeletal muscle to athletic training. Based on these functions, some researchers have proposed that increasing glutathione concentrations via supplementation or increased synthesis may enhance athletic performance. Glutathione is synthesized from glutamate, cysteine, and glycine. However, there is no convincing, high-quality evidence that supplementation with glutathione or with its amino acid precursors improves athletic performance [39,40]. Therefore, we do not advocate such supplementation outside of well-conducted research trials.

Individuals with low baseline, pre-exercise glutathione concentrations are more likely to sustain increased oxidative stress and impaired physical performance compared with those with higher baseline concentrations; preliminary research suggests that high baseline concentrations may buffer the effects of reactive oxygen species following such exercise [41,42]. Nevertheless, little research has explored directly the effect of glutathione supplementation on exercise performance. In a randomized trial, 75 males with experience performing resistance exercise were given placebo, 2g/day of L-citrulline, or 200mg/day of glutathione and 2g/day of L-citrulline [40]. After eight weeks of supervised resistance training, no significant differences in strength, lean muscle mass, or blood chemistries were noted among groups.

Glutathione concentrations decrease with age, and reduced serum concentrations are associated with poor health. Thus, supplementation is popular among some patients with chronic medical conditions, such as HIV, type 2 diabetes mellitus, and cancer; but there is no high-quality evidence of benefit.

Gastric enzymes likely limit the action of glutathione. To circumvent these enzyme effects, glutathione is taken orally in liposomes, parenterally, transdermally, or in nebulized form. Substances such as curcumin, selenium, vitamins C and E, and N-acetylcysteine may boost endogenous production of glutathione. Foods high in glutathione include garlic, broccoli, asparagus, avocado, and spinach.

The side effects of glutathione supplementation are largely unknown. Gastric cramping, nausea, abdominal bloating, and allergic reactions have been reported. Chronic supplementation has been linked to low serum zinc concentrations. Inhaled glutathione has been reported to trigger asthma attacks. The US Food and Drug Administration (FDA) has warned that glutathione powders used to prepare injectable forms may contain large amounts of endotoxins that may cause myalgia, arthralgia, nausea, vomiting, and hypotension.

Glutamine and glutamate — Glutamine is an abundant, nonessential amino acid, an important precursor of glutathione production, and plays a role in acid-base regulation. Glutamine, which is converted to glutamate during normal metabolism, is purported to have anabolic and immune effects of benefit to athletes. Normal dietary intake is approximately 3 to 6 g per day. During intense athletic training, glutamine stores are depleted, and this has been associated with the depressed immune function seen in some endurance athletes [39]. Nevertheless, there is little evidence that glutamine supplementation stimulates protein synthesis, reduces protein breakdown or muscle soreness, or improves immune function. Observational evidence suggests that glutamine supplementation may reduce the incidence of upper respiratory tract infections among endurance athletes training intensively [43]. The authors of one literature review suggest that chronic oral administration of free L-glutamate or the dipeptide can attenuate the inflammation induced by intense exercise, but find that the effects on muscle recovery remain unclear [44]. Glutamine supplementation has few side effects and is well tolerated by most.

Cysteine and cystine — Cysteine, like glycine and glutamate, is a precursor of the tripeptide glutathione; synthesis of glutathione depends upon the concentration of cysteine, as the other two amino acids are usually plentiful in the body. Glutathione is an important antioxidant. (See 'Glutathione, glutamate, and glutamine' above.)

Theoretically, supplementation with cysteine may improve performance by delaying fatigue, but few studies have been performed to test this concept [45]. Administration of the cysteine-donor N-acetyl cysteine in humans increases blood and muscle glutathione concentrations [46]. In a small observational study, 30 days of supplementation with N-Acetyl cysteine improved exercise performance (time trial, maximum oxygen consumption [VO2 max], Wingate test), but these improvements only occurred in individuals with low pre-study glutathione concentrations [47].

Potential side effects, including nausea, diarrhea, and bloating, may occur with large oral doses. The results of one small controlled study using a combination of cystine, a dipeptide of cysteine, and theanine for supplementation in runners suggest that this combination may improve immune response after intense exercise [48]. Further research is needed to determine whether cystine or cysteine supplementation is useful.

Arginine — Some researchers claim that arginine improves immune function, increases release of insulin and growth hormone, increases tissue creatine levels, and generally improves performance. Nevertheless, there is no evidence that arginine supplementation improves athletic performance, despite its addition to a number of supplements marketed to bodybuilders and weight lifters.

Arginine infusions at high doses stimulate marked increases in pituitary growth hormone secretion [49] and insulin secretion [34]. However, most oral supplements contain much smaller amounts of arginine (1 to 2 g per day), and no effect on growth hormone or insulin secretion has been demonstrated in well-designed studies [50]. Large doses of arginine may cause significant GI side effects, and relatively large amounts are needed to increase hormone secretion. By contrast, 60 minutes of moderate-intensity physical activity causes greater endogenous secretion of growth hormone than a tolerable oral dose of arginine [51].

Citrulline — There is no high-quality evidence that citrulline supplementation improves athletic performance. Nevertheless, it is included in a large number of commercially available supplements. Citrulline is a nonessential amino acid found in protein-rich foods and is used by the body to synthesize arginine, which is important in nitric oxide (NO) metabolism.

Few well-designed studies investigating the use of citrulline as an ergogenic aid have been performed. In a systematic review of controlled studies involving 137 athletes, citrulline was associated with a slight increase in the number of repetitions performed to failure for given strength exercises [52]. The ergogenic effect was slightly greater for lower extremity exercises, but the overall effect was not as large as that reported for other comparable supplements, such as caffeine, bicarbonate, and creatine. (See 'Caffeine' below and "Prescription and non-prescription medications permitted for performance enhancement", section on 'Blood buffers' and 'Creatine' above.)

A controlled study of 17 healthy young men and women reported a slight reduction in the time to exhaustion during treadmill testing among those given citrulline supplementation [53]. Another small trial reported reductions in markers of oxidative damage after intense cycling among those given citrulline [54].

Colostrum — Colostrum is a mammalian lactation product made in the 24 to 72 hours after giving birth. It is rich in growth factors, immune cells, and antimicrobial factors. The results of studies of the performance-enhancing qualities of colostrum supplementation are inconsistent. Colostrum supplements are made from bovine colostrum and are available as liquids, capsules, tablets, or powder.

Some believe that the growth factors in colostrum provide ergogenic effects. The insulin-like growth factor-1 (IGF-1) found in colostrum is thought by some to increase strength. However, while some studies of long-term colostrum supplementation (eight weeks of 10 to 60 g per day) have reported increased vertical jump, peak sprint cycle power, and endurance performance, other studies of similar design have failed to show benefit [55].

Improved immunity is another purported benefit of colostrum [56-58]. In a secondary analysis of small randomized trials, athletes taking a colostrum supplement experienced fewer upper respiratory tract infections [56]. A small observational study of cyclists reported less immune suppression after intensive exercise among those taking colostrum [57].

A study carried out in a laboratory accredited by the International Olympic Committee of subjects taking 60 g per day of colostrum (125 mcg per day IGF-1) over four weeks reported no positive doping tests [59].

Dietary antioxidants — Antioxidants are taken by some athletes with the intention of improving immune function and reducing muscle damage and fatigue caused by training [60]. Antioxidants are purported by some to counteract the negative consequences of reactive oxygen species (free radicals) produced during high-intensity physical activity. However, antioxidant supplementation has not consistently been found to reduce muscle damage or muscle soreness in acute exercise and does not appear to have an ergogenic effect on athletic performance, although some studies show reduced oxidative stress [61,62]. In addition, there is some evidence suggesting that chronic intake of antioxidants may impair training adaptations.

Antioxidant processes and the metabolism surrounding oxidative stress associated with exercise are complex. Oxidative stress has both beneficial (eg, cellular signaling, transcription) and deleterious (eg, muscle damage, inflammation) metabolic effects, and individuals exhibit wide variations in oxidative stress following eccentric exercise. Supplementation with any antioxidant must balance the potential benefits of reducing the harmful physiologic and performance effects of oxidative stress with the potential harms of blunting adaptive pathways. This balance is as yet unknown. As an example, in a small randomized trial, subjects pre-treated with N-acetyl cysteine and vitamin C sustained greater increases in serum markers of cellular damage following injury induced by eccentric exercise compared with those given placebo [63]. In a small observational study, competitors in full and half ironman races who consumed antioxidant supplements had higher serum concentrations of markers of oxidative stress [64].

Common antioxidants taken by athletes include beetroot juice and other substances thought to increase nitric oxide production, such as quercetin, resveratrol, vitamins E and C, and N-acetylcysteine. Glutathione supplementation is also taken in part for its antioxidant effects. Tart cherry juice is becoming popular among endurance athletes.

Nitrates — NO plays a number of metabolic roles, including some involving skeletal muscle function [65]. Preliminary evidence suggests that nitrate supplementation designed to increase the bioavailability of NO may reduce fatigue during exercise and may improve performance in short-duration exercise (<15 minutes). NO plays important roles in vasodilatation, platelet aggregation, immune function, mitochondrial function, and hormone regulation, particularly around glucose and calcium homeostasis.

During physical activity, NO production increases in skeletal muscle. It is thought that NO contributes to the therapeutic effects of exercise and increases glucose uptake by skeletal muscles during exercise independent of any increase in muscle blood flow [66]. NO is produced via oxidation of the amino acid L-arginine and involves the enzyme NO synthase. In addition, NO can be produced by a process not reliant on oxygen, and possibly in acidic conditions, involving the modification of nitrate into nitrite. Given the relative hypoxia and acidic milieu of some tissues during exercise, this mechanism may be important for athletes.

Nitrate is present in vegetables. Approximately 25 percent of nitrate is converted into nitrite via oral bacteria, and a portion of nitrate intake is converted to NO by the acidic stomach environment. Dietary nitrate produces peak serum concentrations in one to two hours, while nitrite and NO concentrations peak at 2.5 hours. Levels return to baseline at 24 hours. Given the importance of oral bacteria in the metabolic processes, those taking supplements should avoid antibacterial mouthwashes and chewing gums.

A meta-analysis of 80 randomized, placebo-controlled trials involving 1179 men and 156 women found that nitrate supplementation improves performance among younger, healthy, non-elite endurance athletes; but the effect size was small overall and varied widely among study populations, suggesting that additional factors may be at play [67]. The outcome in the large majority of trials was the time required to cover a set distance, but measures of exercise efficiency were also used. As an example, a randomized trial involving nine male athletes reported that supplementation with 0.1 mmol/kg per day of dietary nitrate improved exercise efficiency, as demonstrated by lower oxygen demand during submaximal work on a cycle ergometer, compared with placebo (ie, sodium chloride supplementation) [68]. A similar trial involving beetroot juice, a naturally occurring rich source of nitrates, reported comparable findings about oxygen demand from submaximal exercise and extended time to exhaustion during high-intensity exercise [69]. These findings have been confirmed in studies of running, walking, cycling, and resistance training [70-72].

Benefit from nitrate supplementation has **not** been found consistently in high-level athletes. The authors of the aforementioned meta-analysis found that ergogenic benefits demonstrated in other populations were "not observed in well-trained endurance athletes" [67]. As an example, in a study of female speed skaters, no difference in performance was noted among athletes given low-dose (1 mmol nitrate) versus high-dose (6.5 mmol nitrate) supplementation [73]. Possibly, higher doses are needed in such athletes.

Nitrate supplementation may be of benefit to athletes competing in higher-intensity events lasting four to eight minutes (eg, sprint cycling, rowing, swimming), particularly less fit athletes [60]. Benefit has also been reported in some team sport participants [74]. Overall, available evidence suggests a small improvement in time to exhaustion and a small improvement in performance, and that these effects are greater in recreational athletes [75]. The improvement has been estimated at approximately 3 percent in non-elite male athletes [67].

The dosing needed acutely to improve performance in highly trained athletes is thought to be between 5.1 and 25 mmol (approximately 1.5 to 6 beetroot juice shots) per day, consumed two and a half hours prior to competition, but chronic supplementation for the few days prior to a completion appears to give better results. There is no consistency in supplementation doses or protocols, subject selection, or sports and exercise protocols in studies to date [60,66,68-71,74]. According to a comprehensive review, the reduced oxygen cost of submaximal exercise can be maintained for at least 15 days if supplementation is continued at a dose of 6 mmol per day

[76]. Further research is needed to determine appropriate dosing protocols for training and competition, the true benefits of NO-containing products, particularly in women, and for which sports these purported benefits are most useful.

Note that **nitrite** salts can be toxic, causing methemoglobinemia. There is one report on an internet forum of an athlete confusing nitrate supplementation with nitrite salts and subsequently developing methemoglobinemia. Nitrite reacts rapidly with hemoglobin, converting it to the ferric form (Fe3+ methemoglobin) rather than the usual ferrous (Fe2+) form. The ferric form of hemoglobin binds oxygen but does not release it readily to tissues, causing ischemia. The lethal dose (LD_{50}) for oral nitrite (100 to 200 mg/kg) is comparable to that of cyanide. Organic nitrates and nitrites (eg, nitroglycerin and amyl nitrite) can be fatal at too high a dose. High doses of inorganic nitrates are probably safe, as the body can only convert these slowly to nitrite. However, some experts urge caution [77], suggesting that athletes refrain from using nitrate and nitrite salts as dietary supplements, as confusion among the available types could lead to a large unintentional intake that could be life threatening. (See "Methemoglobinemia".)

Although these warnings are important to keep in mind, natural sources of nitrate, such as whole vegetables or vegetable juices, appear to hold little risk. At recommended doses, the use of natural products such as beetroot juice seldom causes side effects, and such effects are typically mild. Side effects may include mild GI upset and altered color of urine and stool. Long-term studies on the effects of NO supplement use have not been performed. If nitrate-containing supplements are used, athletes should ensure that they are using only the inorganic form of nitrate.

Tart cherry juice — Montmorency (or tart) cherries contain anthocyanins, flavonoids (including quercetin), flavonols, procyanidins, and phenolic acids. Limited evidence suggests that tart cherries produce antiinflammatory and antioxidant effects and may reduce muscle soreness and improve recovery. These effects may improve performance in endurance sports.

Tart cherry juice can be obtained in bottle or sachet concentrates, as a gel, and in a dried form. Many suggest that the equivalent of 45 to 60 tart cherries be taken twice daily between five and seven days prior to an endurance race, during extended periods of endurance training, and within 30 minutes of completing an intense training session. Montmorency cherries contain melatonin and hence may have positive effects on sleep when used as a supplement [78].

Studies of tart cherry juice supplementation by athletes are preliminary but report encouraging results. In a controlled study of 20 recreational marathon runners, those given tart cherry juice rather than placebo for five days prior to the day of the race and continuing for two days afterward demonstrated faster recovery of baseline isometric muscle strength and reduced levels of inflammatory markers [79]. A randomized trial of 16 trained cyclists noted improved performance, enhanced muscle oxygenation, and reductions in some markers of inflammation among those given tart cherry juice [80]. Other studies have reported reduced muscle pain after long-distance running [81], improved recovery of isometric muscle strength after an intensive, leg-based workout [82], and improved strength and reduced pain following eccentric resistance training of the elbow flexors [83]. Well-controlled studies of the effect of tart cherry on athletic performance are needed to confirm these preliminary findings.

Quercetin — Quercetin is a flavonoid that may provide some benefit during exercise lasting more than 100 minutes, but there is little information about its effect on other types of athletic performance, and more research is needed [60]. Quercetin is reported to possess antioxidant, antiinflammatory, and immune regulatory effects [84-86]. It is found in red onion, dill, apples, and capers.

Several meta-analyses have looked at studies assessing the benefit of quercetin supplementation on sport performance. One found minimal benefit [87], while another reported a small improvement in power output, primarily in untrained individuals [88]. The results of a few small studies suggest that acute supplementation with quercetin may improve neuromuscular performance during and after resistance training [89], attenuate muscle soreness following eccentric exercise [90], and reduce inflammation after exhaustive swimming [91].

A dose of 1 g per day may improve performance during endurance exercise [60]. However, few studies have assessed potential adverse effects in humans using this suggested daily dose, which is significantly higher than typical dietary intake. Animal studies suggest a potential risk of tumor promotion in estrogen-dependent tumors and of exacerbating kidney injury. Potentially harmful interactions with statins, cyclosporine, and fexofenadine have been reported.

Resveratrol — Resveratrol is a naturally occurring antioxidant, a non-flavonoid phenol, found in red wine, mulberries, peanuts, rhubarb, and grapes. A range of claims about its health benefits have been made, including prevention of ischemic heart disease and peripheral vascular disease, and improved tolerance of stress [92,93]. Animal studies report improved motor skills, higher maximum oxygen consumption, and increases in oxidative muscle fiber. Studies in humans are needed to determine whether ergogenic benefits accrue. There is no widely accepted dose.

Beta-alanine and carnosine — Carnosine is a dipeptide consisting of beta-alanine and histidine that is important in acid-base regulation in skeletal muscle, acting as an intracellular buffer for approximately 10 percent of the proton buffering that occurs in muscles during high-intensity exercise. In addition, carnosine may protect against oxidative damage and participate in glycation. It may also increase the efficiency of excitation-contraction coupling during muscle fiber contraction.

Carnosine is found in large amounts in type II muscle. Synthesis is limited by the availability of beta-alanine, which can be increased by eating white meat (eg, poultry breast) or taking a supplement. Increasing muscle carnosine via supplementation with beta-alanine most likely improves athletic performance by directly increasing muscular exercise capacity [94,95]. According to a 2015 position paper from The International Society of Sports Nutrition, four weeks of supplementation with beta-alanine significantly increases muscle carnosine concentrations, providing an effective intracellular pH buffer [95]. As with sodium bicarbonate, the buffering effect from carnosine is likely to benefit athletes involved in high-intensity activity lasting from 30 seconds to 10 minutes; there is no proof of benefit for activities of shorter duration [94].

A meta-analysis of 40 studies of long-term beta-alanine supplementation in 1461 participants involving a wide range of exercise outcome measures reported a small but statistically significant effect size of 0.18 (95% CI 0.08-0.28) [94]. Of note, the beneficial effect on exercise-to-exhaustion was greater than that on performance-based tests, such as time trials, and the effect on trained individuals was less than for non-trained persons. Nevertheless, the authors believe that trained athletes in appropriate sports (eg, 4 km cycling, 2 km rowing, middle-distance running, and 100, 200, 400, and 800 m swimming) can benefit from supplementation. Sports involving both whole-body exercise and isolated limb exercise benefited equally. The meta-analysis found that both continuous exercise protocols and those involving repeated bouts of high-intensity work improved with supplementation. However, testing was not sport-specific, so questions remain about the effectiveness of beta-alanine for individual sports involving intermittent bursts of high-intensity work over a prolonged period. Another review of the literature concluded that the benefit of beta-alanine is likely sport specific and that there appears to be a slight added benefit when it is given in combination with sodium bicarbonate [96].

The typical loading dose among the included studies was 4 to 6 g of beta-alanine per day, ingested in divided doses every three to four hours for at least two to four weeks, or two doses of 2.4 g for 10 weeks, followed by a maintenance dose of 2 g per day.

Long-term supplementation with both beta-alanine and sodium bicarbonate, aimed at increasing both intra- and extracellular buffering capacity, appears to provide greater benefits than beta-alanine supplementation alone, according to limited data [94]. (See "Prescription and non-prescription medications permitted for performance enhancement", section on 'Blood buffers'.)

Beta-alanine appears to be widely used, particularly among athletes participating in strength-related sports, middle- to long-distance running, and rowing. At the stated doses, beta-alanine has been shown to improve exercise performance in time trials one to four minutes in duration. Upon stopping supplementation, muscle carnosine slowly decreases back to baseline concentrations over 15 or more weeks [97].

With single doses exceeding 800 mg of beta-alanine, many athletes experience pruritus and paresthesias, most likely from direct stimulation of cutaneous nerves, but the supplement appears to be safe in healthy populations at recommended doses. Side effects do not occur if a slow-release formulation of beta-alanine is ingested or if the amount is taken in divided doses, suggesting that the effects are due to a rapid increase in the plasma concentration after ingestion of a powder formulation.

Carnitine — Carnitine is found in skeletal and cardiac muscle and is ingested mainly through meat, fish, poultry, and some dairy. Vegetarians have lower muscle carnitine stores. During intense exercise, carnitine plays a role in the metabolism of carbohydrates and the oxidation of long-chain fatty acids [98]. It has been postulated that carnitine supplementation may enhance performance by sparing glycogen at lower exercise intensities, along with improving the efficiency of the citric acid (Krebs) cycle at higher intensities. Several well-controlled studies in both moderately and highly trained athletes have demonstrated no improvement in these parameters, and no increase in muscle carnitine levels following oral supplementation of 2 to 6 g per day taken for between five days and four months [99,100]. However, two small trials performed by the same research group report that oral carnitine taken with large amounts of carbohydrate for several months leads to increases in muscle carnitine, sparing of muscle glycogen, improved exercise tolerance, and increased use of body fat stores for energy [101,102]. The findings of a few studies suggest that carnitine exerts its effect by enhancing blood flow and oxygen supply to muscle, thereby helping to alleviate muscle damage during exercise [103].

Despite limited evidence of benefit, L-carnitine is a common ingredient in fat-loss supplements. Further research is needed to determine the benefits of carnitine supplements for athletic performance and body composition. If the benefits are genuine, long-term supplementation in association with large amounts of carbohydrate may be necessary, and this would not suit all athletes.

Hydroxymethyl butyrate — Hydroxymethyl butyrate (HMB) is a fatty acid formed as a breakdown product of leucine. In humans, up to 1 g per day is produced from normal metabolism, with some used for the synthesis of cholesterol but up to 40 percent excreted unchanged in the urine. HMB was initially used to increase muscle and reduce fat in animals. During the 1990s, use increased among athletes due to claims that it increased lean muscle mass, reduced muscle soreness, and improved aerobic capacity. HMB is also said to have an anticatabolic effects and reduce muscle breakdown. However, available evidence suggests that any ergogenic effect from HMG supplementation in athletes is probably trivial. We suggest that athletes focus on appropriate nutrition to improve protein synthesis, rather than strategies intended to reduce protein breakdown. Doses of 6 g per day are common for HMB supplementation, and there appear to be minimal side effects [104].

According to a 2003 meta-analysis of studies of dietary supplements for mass and strength gain, HMB and creatine were the only dietary supplements shown to augment lean muscle mass and increase strength when used with resistance training [105]. However, a subsequent meta-analysis of nine studies involving 394 subjects concluded that HMB caused no significant change in strength or body composition in trained male power athletes [106].

Phosphate — Phosphate is the second most abundant mineral in the body after calcium. Both are vital to bone and dental health, while phosphate plays a critical role in energy metabolism.

Multiple claims have been made about phosphate supplementation and performance enhancement. Several studies report improvements in maximal oxygen consumption, anabolic threshold, and simulated race performances with oral supplementation of 3 to 4 g per day taken over three to six days [107]. However, other studies found no benefit. These disparate results may be due to the different forms of phosphate used for supplementation, which can include potassium phosphate, calcium phosphate, and mixed buffer supplements containing sodium phosphate. Purported ergogenic benefit is thought to be from increased levels of 2,3 diphosphoglycerate (2,3 DPG) in red blood cells, which shifts the oxygen dissociation curve to the right, thereby increasing the availability of oxygen to muscle tissues. Phosphate supplementation may also increase the availability of phosphate for ATP production and pH buffering capacity.

Typically, 3 to 5 g per day of sodium phosphate is taken for three to six days prior to competition. Supplementation may benefit participants in high-intensity athletic events of two to eight minutes duration, endurance events, and possibly intermittent high-intensity sports.

Short-term side effects typically involve GI problems (eg, vomiting, diarrhea), so a trial of supplementation should be performed during training rather than competition.

Care should be taken when using phosphate supplementation, as a number of drug interactions (see Lexicomp drug interactions program) have been reported, including with antacids, anticonvulsants, glucocorticoids, cardiac glycosides, nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin-converting-enzyme (ACE) inhibitors, and tricyclic antidepressants.

Consumption of large amounts of phosphate may have unfavorable effects on bone health, renal function, and the cardiovascular system. As increasing amounts of phosphate are ingested, the body's requirement for calcium increases concomitantly. It appears that an imbalance in the calcium to phosphate ratio in favor of phosphate can produce a range of biochemical changes causing increased bone resorption, higher parathyroid hormone (PTH) concentrations, and increased urinary calcium resulting in reduced bone mineral density [108]. Animal studies report a risk of increased PTH concentrations and bone loss with prolonged phosphate supplementation [109], and there are reports of hypercalcemic hyperparathyroidism in susceptible persons [110].

In animal studies, high phosphorus intake is associated with both renal and vascular calcification as well as albuminuria [111]. In addition, observational studies suggest that high serum phosphorus concentrations are associated with an increased risk of cardiovascular complications [112]. However, most human studies are observational, and further research is required to accurately define the potential adverse outcomes of phosphate supplementation.

Betaine — Betaine (trimethylglycine) is a component of whole grains, spinach, shrimp, and sugar beets, and can be metabolized from dietary choline. Betaine is a methyl derivative of glycine that acts as a methyl donor in the transmethylation of homocysteine to form methionine. The average daily intake is between 100 to 400 mg, but amounts up to 9 to 15 g per day appear to be safe [113]. Betaine is used in animal feed, particularly for pigs and poultry, to increase muscle and decrease fat, but similar effects have not been demonstrated in humans. Betaine is found in pre- and post-workout dietary supplements.

While a few studies report that betaine contributes to increased muscle power and endurance, the evidence overall is inconsistent, and further research is needed [114,115]. A systematic review of studies on the effects of betaine supplementation on muscle strength and power was not conclusive [116]. Of the seven "excellent quality" studies included, five were unable to demonstrate any change in these parameters while two reported substantial increases in strength and power measures. Betaine supplementation may need to be combined with structured resistance training to provide benefit [117,118]. In a small randomized trial of young, novice female strength trainees, betaine supplementation led to statistically significant reductions in body fat but not increases in strength when compared with placebo [119].

The results of individual studies of the physiological effects of betaine are contradictory. As examples, in two small randomized trials performed in trained men, betaine supplementation led to improvements in force and power production and in muscular endurance [114,115]. However, a follow-up study using an identical supplementation protocol failed to demonstrate such increases [120]. Body composition and bench press work capacity improved after six weeks of training with betaine supplementation when compared with placebo, but no improvements in strength or power were found.

A number of potential mechanisms for betaine's role in increasing lean body mass have been proposed, including stimulation of lipolysis and inhibition of lipogenesis via gene expression, stimulation of growth hormone secretion, increased creatine synthesis, increased protein synthesis via intracellular hyper-hydration, and psychological effects, such as attenuating sensations of fatigue [121]. According to a small observational study of trained men, betaine supplementation appears to enhance the anabolic endocrine signaling environment when combined with exercise [122]. Research has not supported theories that increased phosphocreatine stores [117] or endothelial NO production are responsible for betaine's ergogenic actions [123-125].

STIMULANTS

Stimulants are considered both physical and cognitive performance enhancers. Beneficial effects for sport may include improvements in energy level, endurance, anaerobic performance, reaction time, concentration, and alertness. Relatively common potential adverse effects include headache, nausea, insomnia, anxiety, tremor, agitation, panic attacks, hypertension, and tachycardia. In extreme cases, stimulants may contribute to myocardial ischemia, stroke, psychosis, heatstroke, or rhabdomyolysis. While many stimulants (eg, methylhexanamine, amphetamine, oxilofrine) are banned by the World Anti-Doping Agency (WADA), a number are permitted, and some are only monitored (eg, phenylephrine, synephrine, caffeine, bupropion). With the exception of caffeine, which is discussed below, all stimulants and their use for performance enhancement, including urine concentration thresholds for particular agents, are discussed separately.

Caffeine — Caffeine was included on the prohibited list from 1980 to 2003, and a urine concentration threshold was used to determine violations, but as of 2016, caffeine is included on the WADA monitoring list. Athletes may ingest caffeine as part of their diet or as a supplement.

Caffeine appears to improve exercise capacity during prolonged submaximal exercise (>90 minutes), sustained high-intensity training (20 to 60 minutes), and even short-duration, high-intensity exercise (one to five minutes) [126,127]. In addition, acute caffeine supplementation increases movement velocity during resistance exercise at low, moderate and high loads; and in both the upper and lower body, according to a meta-analysis of 12 randomized trials involving 151 participants [128]. The increase manifests for both peak and mean velocity, suggesting that caffeine is beneficial for weightlifting, throwing and jumping sports, and other activities that rely on powerful movement.

Caffeine supplementation is therefore likely to have performance benefits for a wide range of sports, ranging from extended endurance events to field and court sports involving short bursts of activity [127,129]. Research has demonstrated improved reaction times and delayed fatigue in simulated taekwondo competition [130] and improved performance in tennis [131]. The effects of caffeine on high-intensity, single-event sports such as Olympic weightlifting, high or long jumping, sprinting, and throwing (eg, discus, javelin) are not known, although there may be benefit during multiple attempts [132].

Traditionally, caffeine was taken as a single dose of 6 mg/kg body weight one hour before exercise, but smaller doses (1 to 3 mg/kg body weight) have been shown to have an ergogenic effect. No specific dose for eliciting an ergogenic effect during endurance exercise has been defined, but it is thought to be no more than 200 mg total. Some studies suggest there may be benefit from consuming small amounts of caffeine (1 mg/kg) both before and throughout exercise [133]. Habitual, dietary consumption of caffeine (eg, daily coffee) does not appear to diminish its ergogenic effects when taken as a supplement to improve athletic performance according to a systematic review of 60 studies [134].

The form in which caffeine is taken does not appear to alter its effects. Coffee, tea, and cola drinks provide approximately 50 to 150 mg caffeine, but products such as caffeine tablets, energy drinks, and pre-workout supplements can contain much higher amounts. The caffeine content of a large number of common beverages and foods is included in the following table (table 1). Of note, the actual caffeine content of supplements and beverages can vary substantially from what is stated on packaging and from batch to batch [135-138]. (See "High-risk dietary supplements: Patient evaluation and counseling", section on 'Sports supplements'.)

Caffeine's mechanism of action remains unclear, and there is significant variation in individual athlete's responses, which may be due in part to variation in the genes affecting metabolism

[139]. Caffeine is rapidly absorbed (approximately 99 percent is absorbed within 45 minutes), and peak blood concentrations are seen within about one hour of ingestion, with these levels maintained for three to four hours. When consumed in beverages, caffeine is absorbed rapidly from the gastrointestinal (GI) tract and distributed throughout body water. The most rapid absorption occurs by chewing gum or using preparations containing caffeine that allow the compound to be absorbed directly via the oral mucosa [140]. Oral contraceptive use can double the half-life of caffeine via its effects on hepatic microsomal enzyme systems.

Caffeine has a complex range of actions, including:

- Stimulation of adrenaline release
- Increased cardiac muscle inotropy
- Increased skeletal muscle contractility
- Decreased perceived effort and fatigue
- Sparing glycogen and mobilizing fat (although this effect appears to be short lived and inconsistent) [126]

The weight of opinion favors the most important effects being a perception of reduction of effort or pain and the direct effect on muscle action [141].

Caffeine is considered safe, and in many cultures, high daily caffeine intake is the norm. Moderate, daily caffeine intake does not appear to cause dehydration, as was once thought [142,143]. In a systematic review of 12 studies involving 205 endurance athletes, caffeine did not cause a significant increase in core body temperature when taken as a supplement immediately prior to exercise in hot and moderately humid conditions [144]. After repeated use, tolerance can develop for some of caffeine's effects, such as its stimulant properties, but the lipolytic actions are not affected.

The effects of caffeine supplementation are variable. Non-responders exist, as do individuals who are more sensitive to caffeine's effects and who may experience irritability, tremor, sleep impairment, and tachycardia even at low doses. Rarely, individuals experience exaggerated side effects such as nervousness and anxiety that impair performance, and they should avoid use. Caffeine withdrawal can cause fatigue and headaches, which may be deleterious to the competing athlete. (See "Benefits and risks of caffeine and caffeinated beverages", section on 'Athletic performance enhancement' and "Benefits and risks of caffeine and caffeinated beverages", section on 'Alertness'.)

Caffeine is used widely among athletes in many sports (eg, distance running, cross-country ski racing) and among military personnel to increase alertness and for other purposes. Among elite distance runners (who drink cooled coffee or diluted soft drink), there is anecdotal evidence that caffeine improves performance near the 20 mile/30 km mark in marathons, possibly due to the glycogen sparing effect, which has increased its popularity for endurance events, including running and cycling.

Guarana — Guarana (*Paullinia cupana*), a native Amazonian climbing plant from the maple family, contains high levels of guaranine. The chemical guaranine is identical to the chemical caffeine derived from other sources (caffeine is so-called because it was first discovered in the coffee plant; caffeine comprises 1 to 2 percent of a coffee bean, but 3 to 8 percent of a guarana seed). Thus, in comparable amounts, guarana seeds contain approximately twice the amount of caffeine as coffee beans. However, the effects of ingested guarana seeds are not just due to guaranine, as guarana contains other xanthine alkaloids, such as theophylline and theobromine. Guarana is often found in energy drinks, energy "shots," and herbal teas.

Guarana is freely available and commonly included in energy drinks and energy supplements, which are widely used as a weight loss supplement and for their stimulant effects. While guarana may have ergogenic benefits, controlled research to determine its effects on athletes is lacking.

ENERGY BEVERAGES

The consumption of beverages explicitly for sport began with drinks developed to replace the electrolytes and carbohydrates lost during intense physical activity. The original drinks are known as "sports drinks" and contain a low percentage carbohydrate solution and a mixture of electrolytes to allow maximal, rapid absorption in the stomach. The newer generation of beverages, so-called "energy drinks," include a wide variety of stimulants and other additives, including caffeine, taurine, glucuronolactone, B vitamins, antioxidants, trace minerals, guarana, *Ginkgo biloba*, ginseng, L-carnitine, and sucrose [145]. Of note, some of these additives may interact with prescription medicines, so care should be taken investigate potential adverse interactions before consuming these drinks. Any purported benefit from energy drinks is most likely due to caffeine, which is discussed separately. (See 'Caffeine' above.)

The amount of caffeine in an energy drink ranges from approximately 50 to 500 mg per can or bottle. Energy beverages should not be used for the purposes of athletic hydration or rehydration. The higher carbohydrate content results in slower absorption from the stomach and may cause nausea, bloating, cramping, diarrhea, or vomiting. Caffeine may act as a diuretic, resulting in increased urine output during and after exercise. For the same reasons, athletes who are dehydrated should not consume energy drinks.

Consumption of energy beverages, or energy drinks, is widespread and growing. It is reported that 31 percent of 12- to 17-year-olds consume energy drinks regularly, with 5 percent of high school students and up to 6 percent of college students consuming one per day [146]. Young men appear to be the primary market. Active United States military personnel consume large amounts of energy drinks to assist with alertness and reduce fatigue. According to a 2010 survey of United States troops in Afghanistan, 44.8 percent of respondents drank at least one energy drink per day, and 13.9 percent reported drinking three or more per day [147].

The recommended daily dose of energy beverages is no more than 500 mL, although this depends upon the ingredients. However, sports drink enthusiasts routinely drink much more, sometimes combining them with other supplements or alcohol, which can be particularly dangerous [148]. The effects of energy beverages vary widely depending on the ingredients and amounts consumed. As an example, caffeine content varies from 50 to 500 mg per can or bottle (table 1) [149]. Opinions among experts differ about the effectiveness and safety of combining energy drinks with exercise to increase body fat loss [148]. We feel that potential risks outweigh benefits.

Potential adverse effects of energy beverages may be due to caffeine or other stimulants or ingredients, and may include elevated blood pressure, arrhythmias, seizures, sleeplessness, and mood changes. The consumption of energy drinks, alone and in combination with alcohol or other drugs, is associated with increased visits to the emergency department [150]. The risk of dental caries is often overlooked by those drinking large quantities of sugar-containing energy drinks. Some drinks contain up to 8 teaspoons of sugar, which can contribute to weight gain, hypertension, and diabetes.

In children and adolescents, the use of energy sports drinks is more likely to cause caffeine intoxication due to a lack of tolerance. Multiple reports found on the website of the US Food and Drug Administration (FDA) describe cases of acute myocardial infarction, convulsions, cardiac arrest, anaphylaxis, spontaneous abortion, arrhythmias, renal and liver impairment, and psychiatric disorders associated with heavy consumption of energy drinks. Massive overuse of these beverages by United States military in Afghanistan has caused insomnia (<4 hours sleep per night) and sleep disruption due to stress and illness, with some soldiers falling asleep while on duty [147]. There has been litigation against Monster Energy by people who claim to have developed renal or cardiac issues due to high consumption.

PLASMA EXPANDERS AND HYDRATION AIDS

Glycerol — In 2016, glycerol was added to the WADA banned substances list but was removed in 2019 after research found its ergogenic effects to be negligible. Glycerol is a 3-carbon sugar alcohol found in dietary fats and other foods. Some food manufacturers add it to processed foods and drinks as an emulsifier, sweetener, and thickener. As with other plasma expanders, glycerol causes fluid retention and temporary expansion of body fluid levels and hence may act as a masking agent against the detection of erythropoietin and its analogues, anabolic steroids, and other banned substances with urinary thresholds.

Hydration with glycerol may benefit individuals who are active for prolonged periods in hot environments (eg, firefighters, military personnel, endurance athletes) [151]. The typical dosing range is 1 to 1.5 g of glycerol per kg of body weight mixed with 25 to 35 mL/kg body weight of fluid [152]. Approximately 600 to 1000 mL of fluid expansion may be expected over an oral fluid bolus alone, primarily by reducing urinary output. The results of one animal study suggest there is additional benefit if a carbohydrate-electrolyte solution is used instead of water [153]. A meta-analysis of studies of glycerol versus water hyperhydration in endurance athletes concluded that glycerol hyperhydration improves fluid balance and endurance performance compared with water–based approaches [154]. Hyperhydration with glycerol before exercise in a hot environment can help to reduce fluid deficits and to prevent the diuresis that occurs with aggressive standard hydration practices, which are common in weight-restricted sports after weigh in. Side effects can be significant and may include nausea, vomiting, and headache.

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, 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

- **Banned substances** – 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 physicians, competitive athletes, and anyone involved in the care of athletes keep current with its contents. (See "Prohibited non-hormonal performance-enhancing drugs in sport".)

- **Types of non-medication supplements** – A wide range of non-hormonal performance-enhancing substances, not including medications, are taken by recreational and elite athletes. These include stimulants, nutritional supplements, and energy drinks. Common nutritional supplements taken explicitly to improve performance include creatine, protein and amino acids, antioxidants, beta-alanine, carnosine, carnitine, and hydroxymethyl butyrate. Each supplement type is discussed in the text. Controlled studies pertaining to the purported benefits of these supplements are often limited, but relevant evidence is reviewed above. The additive, interactive, and potentially harmful effects from the common practice among athletes of combining multiple performance-enhancing supplements remain largely unknown. For many substances, benefit is unproven or minimal. (See 'Stimulants' above and 'Creatine' above and 'Nutritional supplements' above.)

- **Poor quality control** – Throughout the world, quality control for performance-enhancing 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. Supplements are sometimes a source of doping violations due to inadvertent contamination or intentional addition of additives not included on the label. Both single and multicomponent supplements are generally not tested for contamination or accurate labeling, and they frequently contain unlisted substances. Several national anti-doping organizations have developed a website to provide information about medicines and supplements to athletes and others.

Topic 120019 Version 25.0

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