Prohibited non-hormonal performance-enhancing drugs in sport

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INTRODUCTION

Athletes continue to use a wide range of substances and methods to improve their performance. Banned substances and methods are included in the World Anti-Doping Agency WADA prohibited list. This list is updated every January and is freely available on the WADA website.

Prohibited non-hormonal performance enhancing drugs and some other prohibited methods for performance enhancement are reviewed here. Hormonal performance-enhancing drugs and other illicit methods of performance enhancement are reviewed separately. (See "Use of androgens and other hormones by athletes".)

WORLD ANTI-DOPING AGENCY AND PROHIBITED SUBSTANCES USED FOR PERFORMANCE ENHANCEMENT

Non-hormonal drugs used illicitly to improve sports performance are included in a comprehensive list maintained by the World Anti-Doping Agency (WADA). This list is updated every January and is freely available on the WADA website. Thus, it is important when reading this topic or any source of information about these substances to ensure that it correlates with the latest version of the WADA prohibited substance list.

In the past decade, the WADA list of banned performance-enhancing substances has grown to over 192 drugs and methods. In addition to androgens and other hormones, the WADA prohibited list includes stimulants, recreational drugs such as narcotics and cannabinoids, beta agonists, diuretics, and other prescription medications. In 2011, section S0 was added to the WADA list to include substances that have yet to be approved for human use, are still in clinical development, or have been discontinued (S0). In 2021, WADA introduced a new category to the prohibited list, "Substances of Abuse." Athletes found using substances in this category may be required to seek appropriate treatment, as well as serve a period of sanction. Helpful resources for information about supplements include: Informed Sport website, Australian Institute of Sport website, and the US Anti-Doping Agency website.

When prescribing medications or advising about supplements, clinicians should check that none of the contents are banned by WADA or any relevant national anti-doping organizations. In the United States, United Kingdom, Japan, Canada, Switzerland, and Australia, medications can be checked on Globaldro.com. This website also provides the email contact details for many national anti-doping organizations. (See "Vitamin intake and disease prevention" and "Overview of herbal medicine and dietary supplements".)

In addition to WADA and government agencies, other national sporting organizations (eg, National Collegiate Athletic Association in the United States) and governing bodies for particular sports (eg, Union Cycliste Internationale [UCI]) may ban substances **not** included on the WADA list. Thus, it is important for clinicians involved in the care or management of athletes to keep current with the restrictions and guidelines maintained by all such organizations relevant to their athletes.

BANNED NON-HORMONAL PERFORMANCE-ENHANCING DRUGS

Stimulants: Overview of their effects — Stimulants can enhance both physical and cognitive performance among athletes through a range of effects, including the following [1-4]:

- Improving endurance and anaerobic performance
- Diminishing feelings of fatigue
- Accelerating reaction time
- Improving concentration and working memory
- Increasing alertness
- Decreasing appetite and accelerating weight loss

Studies consistently have failed to confirm the purported ergogenic effect of stimulants.

Examples of stimulants used by athletes include: amphetamine, D-methamphetamine, ephedrine, caffeine, methylphenidate, pseudoephedrine, dimethylamylamine (DMAA), cocaine, fenfluramine, pemoline, selegiline, sibutramine, strychnine, and modafinil [2,4-6]. The majority act upon the adrenergic, dopaminergic, or serotonergic systems, and some upon multiple systems [4,7-11]. Therapeutic use of particular stimulants may be genuine in some cases (eg, pseudoephedrine), but this can be hard to validate objectively. An increasing number of athletes are prescribed a form of stimulant to treat attention deficit hyperactivity disorder (ADHD), and this requires a therapeutic use exemption. (See 'Stimulants (banned)' below and 'Therapeutic use exemptions' below.)

The potential adverse short and long-term effects from stimulant use are numerous and possibly dangerous. The presentation and management of acute intoxication and chronic dependence on stimulants are reviewed separately, while the use of particular stimulants for performance enhancement is discussed below. (See "Acute amphetamine and synthetic cathinone ("bath salt") intoxication" and "Methamphetamine: Acute intoxication" and "Stimulant use disorder: Psychosocial management" and "Stimulant use disorder: Treatment overview" and "Methamphetamine use disorder: Epidemiology, clinical features, and diagnosis" and "Cocaine: Acute intoxication" and "Cocaine use disorder: Epidemiology, clinical features, and diagnosis" and "Benefits and risks of caffeine and caffeinated beverages".)

Complications from stimulant use range from the relatively mild, such as nausea, insomnia, anxiety, tremor, and panic attacks, to the more concerning, such as agitation, hypertension, and tachycardia, to the potentially life-threatening, such as myocardial infarction and stroke [1,2,4,6,12]. Higher doses may lead to aggressive behavior and psychosis. Particularly during activity, stimulant use predisposes to extra exertion, which can lead to heatstroke and rhabdomyolysis [2]. Methylphenidate has been shown to increase core temperature even at rest [2]. One case-control study reported an association between stimulant use and sudden unexplained death in children 7 to 19 years of age [13]. Modafinil may cause Stevens-Johnson syndrome [4]. (See "Exertional heat illness in adolescents and adults: Epidemiology, thermoregulation, risk factors, and diagnosis" and "Rhabdomyolysis: Clinical manifestations and diagnosis" and "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis".)

Stimulants (banned) — Stimulants are banned in sporting events only "in-competition" according to section S6 of the World Anti-Doping Agency (WADA) prohibited list, where "in-competition" is described as the period just before midnight (11:59 PM) on the day before a competition in which the athlete is scheduled to participate until the end of the competition and

the sample collection process. However, in rare cases, a given sporting body may define such a period differently.

There are exceptions to this proscription for some drugs in some circumstance (described below). Otherwise, all stimulants on the WADA list are banned, and substances with a similar chemical structure or similar biologic effect are also banned. In some cases, urinary cutoffs have been set, in which case a substance may be legal in small therapeutic doses.

Stimulants commonly used for performance enhancement include:

- **Amphetamines** – Amphetamines are used by athletes to increase alertness and concentration [4]. Although amphetamine, methamphetamine, and cocaine are primarily drugs of abuse, amphetamine salts (eg, dextroamphetamine) are used for legitimate treatment of some conditions (eg, attention deficit hyperactivity disorder, or ADHD). Some substances in this class are designated as substances of abuse and may be subject to different sanctions (eg, cocaine). (See "Acute amphetamine and synthetic cathinone ("bath salt") intoxication" and "Cocaine use disorder: Epidemiology, clinical features, and diagnosis" and "Methamphetamine use disorder: Epidemiology, clinical features, and diagnosis" and "Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents", section on 'Amphetamines'.)

- Methylphenidate – Methylphenidate (also known as Ritalin, Methylin, Concerta, Focalin, and Metadate) is used to treat ADHD, but illicit use is widespread among athletes and the general population to improve alertness [14]. Among United States professional baseball players, the number of therapeutic use exemptions for the use of stimulants to treat ADHD increased almost fourfold, from 28 athletes to 103 in 2007, after these stimulants were banned in 2006 [2,15]. (See "Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents", section on 'Stimulants' and "Attention deficit hyperactivity disorder in adults: Treatment overview".)

- **Ephedra** – Ephedra alkaloids are derived from the herb Ephedra sinica (or Ma huang), and supplements are made using the stem of the plant. Ephedra is commonly used by athletes to promote alertness, endurance, and strength, although no studies have demonstrated a significant athletic benefit [16]. The alkaloids in ephedra have been identified as ephedrine, pseudoephedrine, and phenylpropanolamine. Supplements containing ephedra may be purchased over the counter, and ephedra is included in some cough medicines, decongestants, and diet agents. Adverse effects may be significant, with one sporting fatality in 2003 attributed to the supplement. WADA prohibits urinary concentrations greater than 10 mcg/mL of ephedrine or methylephedrine. Ephedra is

reviewed in greater detail separately. (See "Overview of herbal medicine and dietary supplements", section on 'Adverse effects'.)

- Ephedrine – Ephedrine is heavily used among athletes to improve alertness and to accelerate weight loss, and can be obtained with relative ease on the Internet. According to a 2007 review article, ephedrine use among track and field athletes may be over 50 percent [17]. Among respondents to a 2004 survey of United States college hockey players, 38 percent reported using ephedrine, while 46 percent reported using pseudoephedrine [18]. Survey results from nearly 900 male and female college athletes and non-athletes published in 2008 reported that just over 6 percent of male athletes and 4.5 percent of female athletes used ephedrine, but the surveys did not include pseudoephedrine [19]. According to the 2016 WADA prohibited list, ephedrine may be used in small doses. Urinary cut off levels are listed below. (See 'Urine concentration thresholds for selected stimulants' below.)

  The US Food and Drug Administration (FDA) banned ephedrine for use as a diet aid due to the increased risk of heart attack and stroke [2]. It remains a common remedy in Chinese medicine. (See "Overview of herbal medicine and dietary supplements", section on 'Adverse effects' and "Obesity in adults: Drug therapy", section on 'Adverse effects' and "Obesity in adults: Drug therapy".)

- **Dimethylamylamine (methylhexanamine)** – DMAA (1,3-dimethylamylamine) is an amphetamine derivative widely used in sports supplements sold in the United States [6]. Because of health concerns, in 2011 the United States military removed supplements containing DMAA from military exchanges [20], and Health Canada classified DMAA as a drug subject to regulation and removed approval of any DMAA-containing products [21]. In 2013 the US FDA made the manufacture and sale of methylhexanamine illegal due to toxicity and side effects. However, DMAA continues to be found as an unacknowledged additive in many sports supplements, particularly those purchased over the Internet, and hence is the cause of many inadvertent violations of anti-doping rules.

  DMAA has numerous other names, such as dimethylpentylamine, pentylamine, geranamine, forthane, and 2-amino-4-methylhexane. Not all these names are included on the WADA prohibited list, creating more confusion. Some supplements label this ingredient as geranium oil or geranium root extract, but analysis has shown that the substance is not a natural ingredient of geranium plants. A health warning on the United States National Center for Biotechnology Information website states that "DMAA, especially when used in combination with caffeine, can be a health risk elevating blood

pressure and leading to cardiovascular problems ranging from shortness of breath to heart attack."

- **MDMA (ecstasy)** – While not a performance-enhancing drug (PED) per se, MDMA may give a perception of enhanced energy that some athletes may believe to be helpful. In addition, some MDMA users may feel a sense of well-being, mental stimulation, and reduced anxiety [22].

  MDMA (3,4 methylenedioxymethamphetamine) is an illicit drug with potentially serious side effects, which may include severe hypertension, hyperthermia, delirium, psychomotor agitation, and profound hyponatremia. Acute MDMA intoxication and its management are discussed separately. MDMA is further classified by WADA as a substance of abuse. (See "MDMA (ecstasy) intoxication".)

- **Oxilofrine (methylsynephrine)** – Oxilofrine is a sympathomimetic agent used by athletes as a "fat burner," as well as for improved alertness and mental focus. Oxilofrine increases inotropic cardiac activity [11]. Although oxilofrine has never been approved for use by the US FDA as either a dietary supplement or pharmaceutical, and is not widely used in the United Kingdom, it has been identified as a contaminant in a variety of supplements, and two well-known sprinters tested positive for this substance in 2013 [23].

  In one study, oxilofrine was identified in 14 different supplements available for over-the-counter purchase in the United States [23]. The drug's potentially harmful cardiac effects are similar to ephedrine, and there are reports of tachycardia, vomiting, and agitation [23]. It is easily available on the Internet and can be disguised in medications such as methylsynephrine or "Acacia rigidula," often in dosages that far exceed therapeutic recommendations. Oxilofrine is approved for use in some countries where it is given during anesthesia and for treatment of orthostatic hypotension.

- **Sibutramine** – Sibutramine is a combined serotonin and norepinephrine reuptake inhibitor that acts by increasing thermogenesis and making the user feel fuller after a meal. It is used as a weight-loss supplement and has been shown to be more effective than placebo in obese populations when combined with diet and exercise interventions [24]. Its use in sport was suspended in 2010 in Europe due to associations with an increased risk of cardiovascular events such as hypertension, myocardial infarction, and stroke. Sibutramine has been detected in weight loss products, and in some cases was not included in the list of ingredients. Contamination of such weight loss products has resulted in inadvertent doping offences since 2006.

Stimulants (monitored)

- A number of stimulants included in the 2016 WADA monitoring program are not yet prohibited. However, the status of these agents may change, and we suggest that readers check the WADA list each January to determine whether any of these drugs have subsequently been banned. These stimulants include:

  - Bupropion – While not technically a stimulant, bupropion is structurally similar to amphetamine and does possess some stimulatory properties. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion'.)

  - Caffeine – Caffeine was on the prohibited list from 1980 to 2003 but is now on the monitoring list. Athletes may use caffeine in their diet at any desired dosage. Caffeine is discussed in detail separately. (See "Benefits and risks of caffeine and caffeinated beverages" and "Cardiovascular effects of caffeine and caffeinated beverages" and "Nutritional and non-medication supplements permitted for performance enhancement", section on 'Caffeine'.)

  - **Nicotine** – Nicotine may act like a stimulant by reducing anxiety, elevating mood, enhancing weight loss and satiety, and improving attention [3,4]. Chronic use through smoking increases the risk of cardiovascular disease, chronic obstructive lung disease, and several types of cancer. Nicotine is not prohibited in most sporting events, obviating the need for testing. (See "Cardiovascular effects of nicotine" and "Cardiovascular risk of smoking and benefits of smoking cessation" and "Cigarette smoking and other possible risk factors for lung cancer".)

  - Phenylephrine

  - **Phenylpropanolamine**

  - **Pipradrol**

  - **Synephrine**

Urine concentration thresholds for selected stimulants

- The stimulants listed below may be used in normal therapeutic doses, provided that urine concentration thresholds do not exceed those listed:

  - **Cathine** – Prohibited when the urine concentration is greater than 5 micrograms per milliliter (mcg/mL).

- Ephedrine and **methylephedrine** – Prohibited when the urine concentration of either is greater than 10 mcg/mL.

- Epinephrine **(adrenaline**) – Not prohibited for local administration (eg, nasal, ophthalmologic, or co-administration with local anesthetic). Prohibited when the urine concentration is greater than 10 mcg/mL.

- Pseudoephedrine – Prohibited when the urine concentration is greater than 150 mcg/mL.

Recreational drugs — In addition to the stimulants discussed above, other recreational drugs used for performance enhancement include opioids, alcohol, and cannabinoids. Opioids and cannabinoids are banned by WADA during competition (ie, "in-competition") only for all sports. Testing for these drugs is reviewed separately. (See "Testing for drugs of abuse (DOAs)".)

Some sporting organizations perform independent, out-of-competition testing for recreational drugs. Sanctions vary by sport but may range from mandatory rehabilitation to suspension or bans from competition. Under the new "Substances of Abuse" section of the WADA prohibited list, this process occurs as a part of management for positive tests involving a substance of abuse.

Nicotine is not currently banned and is discussed briefly with the other monitored stimulants. (See 'Stimulants (monitored)' above.)

Opioids — Opioids have been used to increase an athlete's pain threshold during competition [25]. In rare circumstances, a retrospective therapeutic use exemption (TUE) may be necessary for appropriate administration of an opioid following an injury or illness. Application for a TUE should be made as soon as possible after the event. (See 'Therapeutic use exemptions' below.)

Adverse effects include dependence, nausea and vomiting, constipation, impaired coordination, decreased concentration, and fatigue. Many opioids are detectable using standard urine drug screens. Opioids are considered a substance of abuse in some circumstances. Codeine, tramadol, and hydrocodone remain on the WADA monitoring list. (See "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment" and "Acute opioid intoxication in adults" and "Testing for drugs of abuse (DOAs)".)

Tramadol — The potential ergogenic effects of tramadol are not well studied, and the medication is not banned by WADA. However, the Union Cycliste Internationale (UCI) has banned tramadol because it is misused by many cyclists and can cause lightheadedness, drowsiness, and physical dependency. In the 2017 WADA drug-monitoring program, 900

samples surpassed the threshold set for tramadol (0.7 percent of the sample total), and cyclists comprised 61 percent (548 samples) [26]. Between 2013 and 2017, the Madrid Doping Control Laboratory tested 9851 anonymous in-competition samples obtained from athletes competing at national (Spain) and international events for tramadol and identified 135 samples (1.4 percent of all samples) above the reporting threshold, of which 65.2 percent were from cyclists, 8.1 percent from triathletes, and 5.9 percent from rowers [27].

Alcohol — Alcohol is occasionally used to reduce performance anxiety during athletic events. Previously, alcohol was banned in some sports, such as archery, air sports (aerobatics, hang-gliding), automobile and motorcycle racing, and power boating, but it has been removed from prohibited substance lists. Alcohol can be quantified by blood testing. (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment" and "Cardiovascular benefits and risks of moderate alcohol consumption".)

Cannabinoids — Cannabinoids include marijuana and hashish (a resin). The active ingredient is tetrahydrocannabinol (THC), which can also be found in synthetic form, delta 9-tetrahydrocannabinol. All natural and synthetic cannabinoids are prohibited. The latter includes mimetics of cannabinoids, such as Spice, JWB-18, JWB073, and HU-210. Cannabidiol is not banned.

A survey of French university students found increased cannabinoid use for "sliding sports," including windsurfing, skiing, snowboarding, surfing, and sailing [28]. The physical effects of cannabinoids on sports performance are not well-known, but they can reduce anxiety.

Adverse effects of cannabinoids include reduced alertness, impaired short-term memory, and psychomotor retardation [28,29]. These substances may cause dysphoria, increased anxiety, paranoia, and psychosis [29]. Given the long excretion profile for cannabinoids and the potential for "passive inhalation," WADA sets the acceptable limit for free and conjugated urinary carboxy-THC at 15 mcg/L [29]. This group of compounds is tested "in-competition" in all sports. (See "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment" and "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects" and "Cannabis (marijuana): Acute intoxication" and "Synthetic cannabinoids: Acute intoxication".)

Beta blockers — The effects of beta blockers (ie, beta adrenergic antagonists) include a decrease in heart rate, reduction of hand tremor, and temporary relief of anxiety, and thus they are used by athletes in sports such as archery or billiards where these effects confer a benefit [5,30]. Beta blockers are of little use, and may be counterproductive, in endurance sports as they reduce maximum heart rate and increase stroke volume (via increased filling time for a

given intensity of activity), reduce gluconeogenesis in skeletal muscle, and restrict muscle blood flow [31]. Beta blockers are banned in-competition for specific sports, such as archery, automobile racing, billiards, darts, golf, shooting, and some ski and snowboard disciplines [30]. In addition, they are prohibited out of competition for archery and shooting. Beta blockers can be detected by gas chromatography mass spectrometry.

Beta blockers are used routinely in the treatment of heart disease, including heart failure and coronary artery disease. The athlete who requires therapy with a beta blocker must obtain a therapeutic use exemption, including a clear explanation as to why alternate therapies cannot be used. (See "Acute myocardial infarction: Role of beta blocker therapy" and 'Therapeutic use exemptions' below and "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Beta blocker'.)

Adverse effects of beta blockers with short-term use include bradycardia, increased airway resistance, and decreased endurance due to reduced maximum workload [30]. (See "Major side effects of beta blockers".)

Beta agonists

Inhaled — Inhaled beta agonists (ie, beta 2 adrenergic agonist) are commonly used to treat asthma. The purported performance-enhancing effects of beta agonists on non-asthmatic athletes are debated [5,32]. Although beta agonists cause bronchodilation, it is unlikely that this improves performance in athletes without asthma. A meta-analysis of 26 randomized trials involving 403 healthy, non-asthmatic athletes reported no significant effects from inhaled beta 2 agonists on endurance, strength, or sprint performance [33]. A similar meta-analysis of 47 randomized trials involving 607 non-asthmatic participants, but limited to assessments of aerobic performance, also found no significant effect on performance [34]. There is anecdotal evidence of benefit in swimmers who use these inhaled medications prior to a race [30]. Albuterol (salbutamol) is the beta agonist used most often for athletic performance [35]. (See "Beta agonists in asthma: Acute administration and prophylactic use".)

All beta agonists are banned in sport, both in and out of competition; however, salbutamol, formoterol, vilanterol, and salmeterol are permitted when used by inhalation at therapeutic doses. Urine concentration thresholds for these substances are used for testing. Inhaled terbutaline, fenoterol, and tulobuterol are banned and require a therapeutic use exemption (TUE) and pulmonary function testing as proof that the athlete has asthma. Terbutaline's actions are similar to salbutamol and a TUE is typically only granted when the athlete can demonstrate that they have been using the medication successfully for many years. Vilanterol and tulobuterol are longer-acting beta agonists. (See 'Therapeutic use exemptions' below.)

High urine concentrations of a beta agonist, defined as greater than 1000 ng/mL of salbutamol or 40 ng/mL of formoterol, may constitute a positive test ("Adverse Analytical Finding") for a PED, as such large doses are not deemed to be therapeutic (whilst unproven, high doses are considered to be anabolic). The athlete must then prove that the high urinary concentrations resulted from hospitalization for severe acute asthma or some other therapeutic use [36]. A maximal dosage of 1600 mcg of albuterol or 54 mcg of formoterol over 24 hours is approved for management of acute asthma exacerbations. An athlete may take a maximum of 25 mg of vilanterol over 24 hours.

Experts suggest that any athlete who experiences a severe asthma exacerbation requiring treatment with high doses of a beta agonist obtain a retrospective TUE as soon as is practically possible. If an athlete is found to have a urine concentration of one of these substances above the threshold, they must undergo a controlled pharmacokinetic study to demonstrate that the abnormal result was the consequence of a therapeutic inhaled dose; however, at this stage, there is no standard test that is performed. There are anecdotes of athletes "stacking" a variety of legal beta agonists, purportedly for their anabolic effects, but evidence supporting the ergogenic effect of this strategy is lacking.

Oral — Clenbuterol is a long-acting, oral beta agonist that has been used for many years in animal farming as a "repartitioning agent" to increase lean muscle mass due to its direct anabolic effects [37]. Clenbuterol and similar drugs increase skeletal muscle, inhibit breakdown of protein, and decrease body fat [30,37]. There has been some concern that clenbuterol-contaminated food could result in positive drug testing [38].

Clenbuterol continues to be used for agriculture, particularly in Mexico and China. Therefore, most international and national governing sporting bodies use a threshold concentration for clenbuterol if the athlete can prove they were in one of those countries and ate significant quantities of red meat. Zilpaterol, another oral beta agonist used in some countries to promote livestock growth, appears to have similar pharmacologic properties but is less potent. Little research has been performed on its anabolic properties in humans, but in horses, it has been shown to cause some negative effects, including muscle tremors, renal damage, and tachycardia [39].

In the authors' experience, clenbuterol has been used by athletes in power sports (eg, Olympic weightlifting), sports with weight categories (eg, wrestling), and bodybuilding. It was first identified as a doping agent in the 1992 summer Olympic Games when two American field athletes tested positive. In 1991, a study of bodybuilding athletes reported that the substance was present in a number of urine samples [40]. A prominent cyclist has been banned for using clenbuterol. Athletes usually cycle clenbuterol in two day on-off cycles for three weeks [41], then

go off the drug for 10 to 12 weeks [42], as receptors rapidly deregulate. It is often used in combination with anabolic steroids.

Potential adverse effects of oral beta agonists include tachycardia, arrhythmias, hypokalemia, increased plasma glucose, and muscle tremor [30,35]. Oral beta agonists can be detected by gas or liquid chromatography mass spectrometry or tandem mass spectrometry. In the WADA banned substances list, these drugs are classified as "other anabolic agents."

Hormone and metabolic modulators — In the 2021 WADA list of prohibited substances, this group (S4 on the list) was reorganized to clarify terminology and reflect the common underlying mechanism, which involves binding to estrogen receptors and blocking estrogen action. The reorganization did not result in the addition or removal of any substances; all remain banned. The non-hormonal drugs are discussed here, while the hormonal agents are discussed separately. (See "Use of androgens and other hormones by athletes".)

- **Aromatase inhibitors** – This group includes aromatase inhibitors (eg, anastrozole, Letrozole, testolactone, formestane, exemestane).
- **Anti-estrogenic substances (anti-estrogens and selective estrogen receptor modulators [SERMS])** – This group includes anti-estrogenic substances such as clomiphene and SERMS such as tamoxifen, raloxifene, and toremifene.
- **Agents preventing activin receptor IIB activation** – This group contains myostatin inhibitors and other substances that affect the activin A and IIB receptors.

Myostatin inhibitors — Myostatin, a myokine produced by myocytes, is a powerful negative regulator of muscle growth. Some researchers have proposed that inhibition of the myostatin pathway may improve functional outcomes in patients with muscular disorders. Of these, there are:

- Agents reducing or ablating myostatin expression.
- Myostatin-binding proteins – Follistatin is a powerful inhibitor of myostatin, first isolated from ovarian tissue. It has been shown to increase muscle mass and strength in animal models [43]. Follistatin also suppresses FSH, and thus may have negative effects on the hypothalamic-pituitary-gonadal axis.
- Myostatin-neutralizing antibodies – Domagrozumab, landogrozumab, and stamulumab are antibodies that bind myostatin to impair its function.

Activin A-neutralizing antibodies

- Anti-activin receptor IIB antibodies – BYM338, or bimagrumab, a monoclonal antibody that binds activin type II receptors in skeletal muscle, is being studied in clinical trials involving several muscular diseases, particularly involving sarcopenia and muscle weakness. This antibody blocks the myostatin-induced signaling cascade. BYM338, or Bimagrumab, a monoclonal antibody that binds activin type II receptors in skeletal muscle, is being studied in clinical trials involving several muscular diseases.

- Activin receptor IIB competitors (eg, Decoy activin receptors [eg, ACE-031])

Metabolic modulators

- **Meldonium** (mildronate) was developed in the 1970s to increase growth in animals. The drug is a carnitine analogue that inhibits formation of L-carnitine, which ultimately reduces fatty acid transport into mitochondria [44]. With less fatty acid available to serve as the substrate for energy production, more carbohydrate is used. Meldonium is usually prescribed for patients with ischemic heart disease, as it reduces oxygen consumption through enhanced glycolysis during ischemia. The reduction in oxygen consumption may translate into improved performance and recovery for endurance athletes. Mildronate was added to the WADA list of banned substances in 2016 after monitoring revealed widespread use during athletic competition [45]. Meldonium was detected in 8.7 percent of the urine samples tested at the 2015 Baku European games [46]. Since the introduction of the ban in January 2016, several high profile athletes have been sanctioned for using meldonium. As meldonium accumulates in some tissues, it can sometimes be detected as long as five months after use [47].

- **Trimetazidine** inhibits the beta-oxidation of free fatty acids, thereby increasing the use of carbohydrate as a substrate for energy production, which requires less oxygen. This may improve performance among endurance athletes. The proscription of trimetazidine has been expanded from in-competition to all sports activity.

- **Activators of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor delta (PPAR-delta) –** Examples of these substances include:

  - **AICAR** (5-aminoimidazole-4-carboxamide ribonucleotide) is an intermediary in the generation of inosine monophosphate. It is an analog of adenosine monophosphate (AMP) that is capable of stimulating AMP dependent protein kinase (AMPK) activity, which stimulates glucose uptake by skeletal muscle cells. AICAR is said to have performance benefits, such as accelerating weight loss and boosting oxygen availability. It is banned by WADA. It has been used to treat myocardial ischemia and

used in clinical trials since the 1980s, but limited testing has been performed in humans. Some cyclists may have used this compound during the 2009 Tour De France.

- **GW1516** (Endurobol) has not been approved for human use, and is said to modulate the gene PPAR-delta, which when stimulated causes increased production of slow twitch muscle fibers in mice. A number of elite cyclists were banned from sport in 2013 for using this drug. Preclinical trials were abandoned when high doses were linked to increased cancer rates in animals, and WADA has warned athletes of possible serious side effects. The drug continues to be available for purchase on the Internet and is an ingredient or contaminant in some online supplements. Websites continue to promote its benefits and safety, despite evidence to the contrary.

- **Insulin and insulin mimetics** (see "Use of androgens and other hormones by athletes", section on 'Other hormones')

Hypoxia-inducible factors (HIFs) activating agents — HIFs are a group of substances banned by WADA and described as peptide hormones, growth factors, and related substances (S2 in the WADA prohibited list). HIFs are transcription factors that mediate the cellular response to hypoxia, which develops in muscles during high intensity exercise. HIFs determine the genetic response to hypoxia, including regulation of erythropoietin production, the metabolic pathways used for energy production, angiogenesis, and iron supply. Autologous HIFs are quickly metabolized in the absence of hypoxia. HIF stabilizers may extend the activity of HIFs, resulting in higher levels of erythropoietin and increased capacity for oxygen transport. HIFs may increase the number of capillaries in skeletal muscles, thereby increasing carbohydrate metabolism and further improving oxygen carrying capacity.

HIFs are orally bioavailable small molecules developed as anti-anemia therapies. Most are experimental and the subject of clinical trials. They include the following substances:

- HIF activating agents include cobalt, FG 4592 (roxadustat), IOX2, and daprodustat (GSK1278863). These agents can be detected by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-EIT-MS/MS). Cobalt salt likely stimulates erythropoietin production more than other HIF stabilizers [48]. Cobalt is an essential base element, but in large amounts can cause end-organ damage, including cardiomyopathy and thyroid disease.

- HIF stimulators (eg, argon, xenon) may stimulate hypoxia inducible transcription factors in animals. However, the results of preclinical trials have been varied and inconsistent. No human data is available. HIF stimulators are expensive and impractical in athletes, as large

amounts are needed and the substances must be inhaled via specialized respirators during the activity [49].

Drugs that improve oxygen delivery — A number of drugs are available that increase oxygen delivery. Drugs that mimic the action of 2,3 bisphosphoglycerate (2,3-BPG, previously called 2,3-diphosphoglycerate or 2,3-DPG) shift the oxygen dissociation curve to the right (figure 1), which allows more oxygen delivery to tissues, such as skeletal muscle. (See "Structure and function of normal hemoglobins", section on '2,3-bisphosphoglycerate'.)

Allosteric modulators improve oxygen delivery to hypoxic tissues by decreasing the oxygen affinity of hemoglobin, which would be useful during athletic endeavors, particularly endurance events. RSR-13 (efaproxiral), an allosteric modulator of hemoglobin, has been shown to increase maximum oxygen consumption (VO2 max) in dogs, but it has a half-life of 3 to 6 hours and is easily detectable in urine tests within 36 hours of use. The drug has significant side effects when used for cancer treatment, including headache, nausea, mucosal irritation allergic reactions, and renal dysfunction.

Other agents that affect erythropoiesis include GATA inhibitors (eg, K-11706) and transforming growth factor beta (TGF-B) signaling inhibitors (eg, luspatercept, sotatercept).

Erythropoietin-based constructs — While not true hormones, these synthetic substances are created by modifying the erythropoietin (EPO) molecule. Methoxy polyethylene glycol-epoetin beta, marketed as Mircera, is a long-acting EPO receptor activator used for patients with anemia from kidney disease. None of these compounds has proven performance-enhancing effects in humans. Other erythropoietins (eg, carbamylated EPO [CEPO], Asialo-EPO) and agents affecting erythropoiesis are hormonal substances and discussed separately. (See "Use of androgens and other hormones by athletes", section on 'Other hormones'.)

AGENTS USED TO PREVENT DETECTION OF BANNED SUBSTANCES

Masking agents are used to conceal the presence of a prohibited substance in urine or other biologic samples. Substances that have been used as masking agents include diuretics, probenecid, desmopressin, and plasma expanders (eg, intravenous albumin, dextran, hydroxyethyl starch, and mannitol). All masking agents are banned by the World Anti-Doping Agency (WADA).

Diuretics — Diuretics are generally used in the treatment of hypertension and heart failure, and include thiazides (eg, hydrochlorothiazide), loop diuretics (eg, furosemide), acetazolamide, amiloride, and spironolactone. All classes of diuretics are banned under WADA regulations.

Pamabrom, a drug that includes the weak diuretic bromotheophylline, is sold over the counter and used to treat premenstrual symptoms. It is not banned by WADA.

While diuretics do not enhance performance, athletes may use them to increase urine output in order to dilute banned drugs or their metabolites in the urine. This technique is typically used for drugs with urine concentration cut-offs. In addition, diuretics are used to reduce the fluid retention that can accompany use of androgenic anabolic steroids. Diuretics are best detected by gas or liquid chromatography mass spectrometry or tandem mass spectrometry methods.

Potential adverse effects from diuretics may result from dehydration (eg, lightheadedness, hypotension, muscle cramps), or electrolyte disturbances (eg, hypokalemia, or possibly hyperkalemia from potassium-sparing diuretics). The relative hyperthermia and dehydration that sometimes accompany exercise may potentiate these effects. Diuretic use and side effects are discussed in greater detail separately. (See "Mechanism of action of diuretics" and "Loop diuretics: Dosing and major side effects" and "Thiazides versus loop diuretics in the treatment of hypertension" and "Use of diuretics in patients with heart failure" and "Diuretics and calcium balance" and "Diuretic-induced hyponatremia".)

Desmopressin — Desmopressin is a synthetic analogue of vasopressin (antidiuretic hormone) that causes increased water reabsorption in the renal collecting ducts. Desmopressin was added to the WADA list of prohibited substances in 2011 when a study demonstrated substantial hemodilution in athletes, and reductions in plasma concentrations of hemoglobin and other blood parameters [50]. Desmopressin has been used to mask use of rhuEPO and to modify the hematologic factors used in the WADA Athlete Biological Passport (ABP) program. (See "Arginine vasopressin deficiency (central diabetes insipidus): Treatment", section on 'Desmopressin'.)

Probenecid — Probenecid is an inhibitor of particular transport mechanisms in the renal tubules, and thus blocks excretion of a number of drugs, including anabolic steroids and their metabolites. This results in more dilute urine with a lower concentration of the prohibited drugs. Athletes may use probenecid to prevent exceeding thresholds for drugs with a urine concentration cut-off. However, in some cases, athletes are prescribed probenecid in combination with antibiotics for legitimate therapeutic reasons but may still be subject to sanctions for using a banned substance.

Plasma expanders — Plasma expanders are high molecular weight, biologically inert substances typically used in transfusions or as a blood substitute. Examples include mannitol, dextran, albumin, and hydroxyethyl starch (HES). These agents have also been used to improve hydration and to mask the use of banned drugs by athletes. When administered, plasma

expanders do not readily leave the circulation, and hence exert an osmotic effect pulling fluid into the blood vessels and increasing blood volume. In this way, they may dilute hematologic measurements, such as the hematocrit, important in the ABP, and mask the administration of erythropoietin or erythropoietin-like substances. Many are included in the WADA prohibited substance list. (See "Use of androgens and other hormones by athletes", section on 'Erythropoietin'.)

HES, a synthetic polymer derived from amylopectin, persists in the plasma for 17 to 24 weeks and causes plasma volume expansion for up to 24 hours. Side effects include an increased tendency for blood coagulation. Rapid screening tests for HES and dextran are available. Urinary cut-off thresholds for mannitol are used to distinguish doping from normal dietary intake. Albumin, an endogenous protein, can be administered intravenously, after extraction from whole blood. Some drugs bind to albumin, reducing their excretion rate. (See "Complications of mannitol therapy" and "Plasma derivatives and recombinant DNA-produced coagulation factors", section on 'Albumin'.)

Glycerol — Glycerol was removed from the WADA banned substances list in 2019 after research found its ergogenic effects to be minimal. Its use as a volume expander is discussed separately. (See "Nutritional and non-medication supplements permitted for performance enhancement", section on 'Glycerol'.)

Other agents — Although previously designated a masking agent, epi-testosterone is now classified as an anabolic agent. When co-administered with testosterone, it can normalize the urine testosterone/epitestosterone ratio, which is used to help detect abuse of exogenous testosterone and like hormones. (See "Use of androgens and other hormones by athletes", section on 'Androgens'.)

Alpha reductase inhibitors were removed from the masking agent category and the banned list in 2009.

TESTING FOR BANNED NON-HORMONAL PERFORMANCE-ENHANCING DRUGS

Recognition and the athlete-clinician relationship — Athletes using prohibited non-hormonal performance-enhancing drugs (NHPEDs) are unlikely to tell their physicians spontaneously. This makes detection difficult and reinforces the importance of a good therapeutic alliance between clinician and athlete when obtaining a medical history. Clinicians should help to educate athletes about the potential harms of supplements marketed as

performance enhancers, which may be sold online, through magazines, or at health fitness stores; as well as the risk of inadvertent doping from contamination.

It is best not to accuse athletes of drug use. Detection of non-hormonal performance enhancement use is possible when there is patient-clinician trust and supporting symptoms and signs. It can often be confirmed with urine testing or blood testing.

When an athlete presents with symptoms and signs consistent with the use of performance-enhancing drugs (PEDs), it is important to take a thorough history and perform a standard physical examination (see 'Symptoms and signs' below). Then the clinician should discuss the possible diagnoses with the athlete, and the likely causative or contributing factors, including the possible role of PEDs. It is appropriate at this stage to ask the athlete if they have been using any such substance.

In other circumstances, a third party may raise concerns about a particular athlete or group of athletes that a clinician helps to care for or is involved with in some way. In such cases, it may be possible to mention to a particular athlete that someone has raised questions about PEDs and to ask if they are aware of such activity. It is important to be honest and frank but not accusatory. There may be situations, such as when there is a risk of significant morbidity or death, or where there is evidence of widespread misuse among a group of athletes or teams that may be sanctioned by sporting officials, where it is appropriate for information to be given to drug enforcement agencies on an anonymous basis. Most anti-doping agencies have a process for the public to provide anonymous information regarding anti-doping violations. However, medical practitioners must be careful not to breach patient-doctor confidentiality laws and guidelines.

Symptoms and signs — When PED use is suspected, the clinician should look for presenting symptoms that seem unusual or do not make sense. Initial symptoms and signs may include any of the following:

- Sudden onset of sleep problems without other explanation
- Relatively acute changes in mood, energy, or body weight
- Psychomotor retardation, dysphoria, hypervigilance
- Palpitations, jitteriness
- Blood pressure and heart rate elevation not attributable to other causes
- Unexplained or unusual medical conditions not attributable to other causes
- Other physical changes (eg, acne, rapid increase in muscle bulk, menstrual dysfunction)
- Hypokalemia in a fit, otherwise healthy athlete

Competitive athletes may be more susceptible to pressure or the temptation to use non-hormonal PEDs at particular times, such as early during the preseason, during the height of the competitive season, or when recovering from an injury. During the pre-season, athletes may take PEDs to increase muscle mass and tolerate higher loads of training, and they may believe they are less likely to be tested at this time. The pressure to return to play after an acute injury can lead players to use non-hormonal performance enhancing drugs, particularly in team sports.

Athlete biological passport — The purpose of the athlete biological passport (ABP) is to monitor selected athlete variables (referred to as biomarkers of doping) over time that indirectly reveal the effects of doping. This approach stands in contrast to traditional detection methods based on direct testing for the presence of illicit substances in urine or blood. Each sporting body assesses the physiologic demands of its discipline to determine which module(s) is most applicable.

The ABP has two active modules:

- Hematological Module − Introduced in 2009, the hematological module is used to help identify illicit interventions to enhance oxygen transport, use of erythropoiesis-stimulating agents (ESAs), and any form of blood transfusion or manipulation. Blood tests are used to follow relevant biomarkers.

- Steroidal Module − Introduced in 2014, the steroidal module is used to help identify endogenous anabolic androgenic steroids administered exogenously, and other anabolic agents, such as selective androgen receptor modulators (SARMS). Urine tests are used to follow relevant biomarkers.

Following collection of appropriate samples, the athlete must complete the ABP doping control form, which includes question about the following items:

- Whether the athlete trained at an altitude above 1500 m during the two weeks prior to the test (information includes location, duration of stay, and altitude).

- Whether the athlete used a hypoxia tent or any other type of altitude simulation during the two weeks prior to the test (information includes the exact device and how it was used).

- Confirmation that the athlete had not participated in training or competition in the two hours prior to sample collection.

In addition to the hematological and steroidal modules, WADA is developing an endocrine module to help detect the use of growth factors. Over the longer term, WADA wishes to develop a large panel of doping biomarkers to improve monitoring. The ABP is not intended to replace traditional testing but serves as an important complement making anti-doping programs more effective.

The ABP involves a series of mandatory protocols relating to sample collection, analysis, and legal considerations that ensure scientific quality and legal standing and enable mutual recognition and data sharing among anti-doping organizations. The Athlete Passport Management Unit (APMU) is responsible for the administration of the ABP, and ideally it works alongside WADA accredited laboratories. The APMUs are established by WADA or a regional anti-doping organization. They liaise with an expert panel, which reviews test results, interprets the longitudinal data, suggests follow-up testing, and provides an opinion on atypical passport findings to the relevant International Sporting Federation.

Urine testing — Athletes undergoing urine testing only must complete a doping notification form with the doping control officer. On the form, they must note any medication or supplement that they have taken in the last seven days and confirm that they accept the testing protocol. Testing protocols may vary at individual sites, but the standard method of testing in athletes is a split sample urine test and high performance liquid chromatography analysis. A split sample involves dividing the initial urine collection into two separate containers, labeled "A" and "B" samples. The samples are then sent to the certified testing laboratory, following a strict chain of custody protocols. The "A" sample is run first, and, if positive for a banned drug, the athlete is notified of the positive test and informed that the "B" sample will be run to confirm the result. The athlete and a representative are permitted to be present at the running of the "B" sample, unless they waive their right to have the B sample tested. A brief description of the immunoassays and other methods used to detect the presence of drugs, particularly common drugs of abuse, is provided separately; a table summarizing common urine drug testing assays follows (table 1). (See "Testing for drugs of abuse (DOAs)", section on 'Specific drug assays: Methods and capabilities'.)

If a positive test is confirmed by the "B" sample, the results are turned over to a medical review officer or panel for appropriate follow-up. If the initial "A" test is negative, the "B" sample is not tested. If authorities suspect that PEDs may have been used but current tests are inadequate for detection, in some jurisdictions urine samples may be stored and frozen for up to 10 years and then reassessed using newly developed tests. In the past several years, many athletes have received sanctions for using performance-enhancing substances when the drugs were detected in stored urine, which was subsequently tested with more accurate methods.

The length of time a banned substance remains in the body and detectable depends on a number of clinical variables, including the half-life of the drug, other medications being taken (eg, diuretics and other masking agents), and other specific pharmacodynamic and pharmacokinetic factors. (See 'Agents used to prevent detection of banned substances' above.)

Blood testing — Blood testing is used to detect prohibited substances and other methods of performance enhancement (eg, enhancement of oxygen transport - including use of erythropoiesis-stimulating agents (ESAs), hemoglobin oxygen carriers (HBOCs), and any form of blood transfusion or manipulation). It is also used for long-term monitoring of an athlete's biological variables, in accordance with the Athlete Biological Passport (ABP) Guidelines.

The equipment used for blood collection and post-collection processing differs depending on the type of analysis required. The blood sample collection kit includes a sterile needle, syringe and the relevant vacutainers in a sealed bag. Whole blood or plasma is used for tests to detect blood transfusions, HBOCs and ESAs and is collected in two 3 mL EDTA tubes (A and B samples). For detection of growth hormone, along with ESAs and HBOCs, two 5 mL tubes (A and B samples) with a polymeric serum separator gel and an activated clotting factor is required. For the ABP, one EDTA tube of whole blood is required.

As per WADA protocol, athletes choose a sample kit randomly from a number of kits (usually three) made available by the doping control officer to ensure freedom of choice and reduce the possibility of kit manipulation. The athlete ensures that seals are intact and without signs of tampering. No more than three attempts to insert a needle into an athlete's vein may be attempted. Tamperproof collection bottles are filled, labeled, prepared, and then stored or transported using standard protocols. Following blood collection not intended for the ABP, doping control forms are completed, including the following information:

- Any medications or supplements the athlete has taken in the previous seven days.
- Whether the athlete has received any blood transfusions in the previous three months and if so, an explanation of why it was necessary.

Blood samples must be carefully stored after collection and maintained at temperatures between 2 and 12°C.

Future developments for testing — The Sports Medicine Research and Testing Laboratory in Salt Lake City (Utah, United States) has developed a blot testing technique for many substances assessed currently using blood samples. It is due to be tested in competition shortly. At present, IGF-1, growth hormone, erythropoietin, and biological passport parameters can be tested in this way.

The 2021 WADA regulations for banned substances include increased reporting thresholds for certain drugs that are currently banned in competition but not out of competition. Given that laboratories can now detect minute quantities of many substances, more violations at competitions are occurring from trace amounts of banned substances detected in the urine. At these low concentrations, the drugs have no ergogenic effect and are most likely residual from the substance being taken prior to competition.

THERAPEUTIC USE EXEMPTIONS

Definition and criteria for exemption — On occasion, an athlete will require a "therapeutic use exemption" (TUE) in order to use a prohibited substance for treatment of a medical condition. Exemptions are granted only when there is no unfair advantage to be gained by the athlete from taking the prohibited substance or using the prohibited method. In most cases, exemption involves a specific medical condition that must be treated with a particular medication, or group of medications, and no viable alternative treatment is available. Examples of possible TUEs include stimulants for treatment of ADHD and testosterone for treatment of hypogonadism following treatment for testicular cancer.

General information and guidelines for TUEs, including explanations of the roles of different organizations (eg, national anti-doping organizations [NADOs], International Federations [IFs], International Testing Agency, and major event organizers [MEOs]) are available at the WADA website.

Information for physicians who are completing TUE applications for specific medical conditions is available through the WADA (www.wada-ama.org). It is important that the requirements are followed precisely to ensure that the athlete is given a timely approval to use an otherwise banned medication.

The criteria for a TUE as defined by WADA are as follows:

- The prohibited substance or method is needed to treat an acute or chronic medical condition, such that the athlete would suffer a significant impairment to their health if the substance or method were withheld.
- The therapeutic use of the prohibited substance or method is highly unlikely to produce any additional enhancement of performance beyond what might be anticipated by a return to the athlete's normal state of health post-treatment.
- There is no reasonable therapeutic alternative to the prohibited substance or method.

Several points should be noted regarding treatment alternatives:

- Only valid and referenced medications are considered as alternatives. This means the medication must be registered in the athlete's country of residence, prescribed by an appropriately qualified clinician, and compelling evidence of medical necessity provided to the appropriate authority. It is important to include all necessary documentation from medical specialists.

- The definition of what constitutes a "valid and referenced" medication may vary from one country to another. These differences should be taken into account. As an example, a medication may be registered in one country and not in another, or approval by a government authority may be pending.

- There may be instances when it is not appropriate to use alternatives to the medication containing the prohibited substance. This may occur in a medical emergency or in a situation where the medical condition is serious and treatment must be administered quickly. This may occur when for example glucocorticoids are needed to treat severe asthma or a malignancy. In such cases, a physician must provide an explanation of why the medication is needed.

- A TUE will not be issued to an athlete for treatment of a condition that stems directly from use of a prohibited substance. As an example, an athlete would not be permitted to use an androgenic steroid in order to treat an aromatizing or androgenizing side-effect from having used such an agent in the past.

For elite athletes included in the registered testing pool for their sport, or participating on their national team or at a national championship, TUEs must be issued prospectively so the athlete can begin taking the medication after the appropriate authority has given approval. Such an athlete applies to their respective NADO, IF, or MEO, using the TUE application form available for download at the NADOs website. If the athlete commences use of the prohibited substance or method prior to approval from the relevant NADO, they do so at their own risk, and may be subject to an anti-doping violation in the event the TUE is denied. (See 'Application process' below.)

Retrospective exemption — One exception to the standard TUE criteria and process is the granting of a retrospective TUE. Application for a retrospective TUEs is made after treatment is given for a medical emergency or some other urgent situation. Examples might include treatment with opioids for pain relief following severe trauma, or treatment with diuretics for pulmonary edema.

The process of applying for a retrospective TUE should begin as soon as possible and supporting documentation from the hospital or treating authority must be included.

In exceptional circumstances, a retroactive TUE may be granted. Examples of such circumstances include cases when there was not sufficient time or opportunity to submit the necessary documentation or for the TUE committee to consider the application prior to sample collection.

Application process — The body to which the athlete submits their application depends on whether the athlete is in the international federation registered testing pool, or planning to compete at the international level, or in the national federation registered testing pool, or subject to testing at the national level. The process of applying for a TUE at the National or International level is as follows:

- The athlete obtains a Therapeutic Use Exemption application form (freely available online from national anti-doping organizations or WADA).
- The athlete completes their section of the form.
- The athlete asks the treating physician to complete the medical details requested on the form. This includes the diagnosis and an explanation of why a permitted medication cannot be used. The form requires: "a comprehensive medical history and the results of all relevant examinations, laboratory investigations and imaging studies. Copies of the original reports or letters should be included when possible. Evidence should be as objective as possible in the clinical circumstances. In the case of non-demonstrable conditions, independent supporting medical opinion will assist this application."

  Supporting documentation for a TUE must be thorough, reliable and relevant. In almost all cases, letters from medical specialists must accompany the application, along with pathology reports, respiratory function tests, or any other relevant tests and documents. If the application is incomplete, it cannot be approved and must be resubmitted.
- Note, the TUE Physician Guidelines can be accessed by entering the search term "Medical Information" in the WADA website. The guidelines address the diagnosis and treatment of a number of medical conditions commonly affecting athletes, and requiring treatment with prohibited substances.
- The physician must include the generic name of the medication, the route of administration, the dosage, frequency of use, and duration of treatment.

- The physician and athlete must sign a declaration confirming that the information provided is true, and that the submitted forms will be handled according to appropriate confidentiality legislation.

- The athlete submits their TUE application to the TUE committee appointed by the IF or NADO via WADA's Anti-Doping Administration and Management System (ADAMS), or in paper format using the appropriate TUE form. In the latter case, the NADO then enters the information into ADAMS.

- If an athlete has a TUE issued by the NADO but plans to compete at an International level, the TUE and approval from the NADO must be submitted to and recognized by the International Federation.

In summary, the process for an athlete who wishes to obtain a TUE is as follows:

- A national level athlete applies to their NADO.
- An international level athlete applies to the relevant international federation.
- For any athlete competing at major event (eg, Olympic Games), the MEO may require the athlete to obtain a TUE for their event. Usually, a TUE obtained from the international federation will suffice, as long as it complies with international standards.

Submission deadlines — Applications for TUEs must be submitted as early as possible.

- For substances prohibited in-competition, the athlete should apply for a TUE at least 30 days prior to the next competition, unless it is an emergency or exceptional situation.

- For substances prohibited at all times, the TUE application must be submitted as soon as the medical condition requiring the use of the prohibited substance or method is diagnosed, or as soon as the athlete becomes subject to the anti-doping rules.

If an application is approved, the TUE committee sets a start and end date for each approved medication. When approval expires, if the athlete needs to continue treatment, they must reapply for a further TUE well in advance of the expiration of the previous TUE to allow time for submission and approval of the new application (ideally, about four to six weeks).

MEOs, such as the Olympic Games or the Pan American Games, have their own TUE requirements for prohibited substances or methods, and these are granted only for the duration of the event. Generally, these TUEs must meet the International Standard for Therapeutic Use Exemptions (ISTUE). TUEs already granted by an IF or NADO that meet the ISTUE must be approved by the MEO. If the TUE application is deemed not to meet the

international standard, the athlete must be notified promptly. The athlete is given the opportunity to appeal to an independent body appointed by the MEO.

BANNED METHODS OF NON-PHARMACOLOGIC PERFORMANCE ENHANCEMENT

There are a number of prohibited methods used for performance enhancement during sport that do not involve taking drugs. Blood transfusion is among the most common. The World Anti-Doping Agency (WADA) regulations (section M1) specifically ban the manipulation of blood and blood components, including the following actions:

- Administration or reintroduction of any quantity of autologous, allogeneic (homologous), or heterologous blood or red blood cell products of any origin into the circulatory system.
- Artificial means for enhancing the uptake, transport, or delivery of oxygen. Including, but not limited to: perfluorochemicals, efaproxiral (RSR13), and modified hemoglobin products (eg, hemoglobin-based blood substitutes and microencapsulated hemoglobin products). Supplemental oxygen is **not** proscribed.
- Any form of intravascular manipulation of the blood or blood components by physical or chemical means.

Blood transfusions — Blood transfusions can be autologous (using one's own blood) or allogenic (ie, homologous; using blood from a different person) [51]. In sports requiring endurance, blood transfusions can be used to increase the number of erythrocytes and oxygen carrying capacity of the blood to improve performance and speed recovery. Blood transfusions prior to athletic competitions to enhance performance are prohibited by the WADA [5,51]. Platelet-rich plasma and other platelet-derived preparations contain growth factors and are used to treat injury, but they are not prohibited by WADA, as no specific performance-enhancing effect has been demonstrated. (See "Overview of the management of overuse (persistent) tendinopathy", section on 'Autologous blood and platelet-rich plasma injection' and "Investigational approaches to the management of osteoarthritis", section on 'Platelet-rich plasma'.)

Potential adverse effects from blood transfusions include sudden fluctuations in blood pressure, stimulation of atherosclerosis, oxidative damage to organs, impaired blood cell function, blood-borne infections, and iron deposition in organs [52]. (See "Indications and hemoglobin thresholds for red blood cell transfusion in the adult", section on 'Risks and complications of transfusion'.)

Autologous blood transfusions cannot be detected by direct testing. Homologous transfusions can be detected through surface antigen patterns using flow cytometry, which is highly sensitive and able to detect rare antigenically distinct cells in an athlete's sample. As the life of a red blood cell is three to four months, detection can be made up to several weeks after a transfusion [51,52].

As the ability to test for exogenous erythropoietin has improved, the use of blood transfusions has increased in sport. The athlete biological passport (ABP) is designed to detect sudden or unusual increases in an athlete's hemoglobin, hematocrit, and other indices of red blood cells. (See "Use of androgens and other hormones by athletes", section on 'Erythropoietin' and 'Athlete biological passport' above.)

Artificial oxygen carriers — Artificial oxygen carriers, such as hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbons, bind and deliver oxygen to tissues such as skeletal muscle. They have been used in select situations involving acute blood loss such as trauma and cardiac surgery. These compounds have a short half-life, so need to be given intravenously at the time of need. All such compounds are banned under WADA regulations because of the possibility of performance enhancement. HBOCs and synthetic hemoglobin impart a red color to the urine, making detection straightforward in most cases.

Free hemoglobin is toxic, particularly to the kidneys, and thus several techniques have been developed to prevent such injury. These techniques, including polymerization, cross-linking, conjugation, and encapsulation, have led to the development of compounds referred to as HBOCs. First generation HBOCs were reported to cause vasoconstriction, which impairs oxygen release to tissues [52,53]. Third generation HBOCs involve enclosing the contents of erythrocytes (hemoglobin and particular enzymes) within artificial erythrocytes (liposomes or biodegradable nanocapsules) or modifying them using complex conjugations. These newer HBOCs appear to be highly effective oxygen donors and may cause less vasoconstriction [53,54].

Reported effects of third generation HBOCs include increased concentrations of erythropoietin, serum iron, and serum ferritin [54,55], and improved exercise capacity compared with autologous transfusion in untrained healthy males [56]. Complications from HBOCs may include gastrointestinal dysfunction, renal toxicity, hypertension, and platelet dysfunction. Reactive oxygen radicals, a byproduct of the increased amounts of oxygen formed from HBOCs, may cause the tissue damage noted in clinical trials [55]. Significant safety concerns were raised in phase II and III clinical trials of some HBOCs and this has slowed development [57]. However, there remain a number of compounds being studied in clinical trials [53]. Several reports describe possession and administration of HBOCs among professional cyclists [54].

Emulsions of perfluorocarbon dissolve high concentrations of oxygen and thus can serve as effective oxygen providers to oxygen-deprived tissues. These are synthetic organic, highly fluorinated compounds, and the amount of oxygen dissolved in the emulsions correlates directly with the partial pressure of oxygen. Thus, perfluorocarbons require an environment with a high oxygen concentration to be effective, which is not easily achievable during athletic competition. Perfluorocarbons may cause back pain, fatigue, transient fevers, and clotting dysfunction [52]. There are no published reports of athletes using PFCs, and no studies have been performed on the possible ergogenic effect of PFCs during exercise.

Whether PFCs and HBOCs improve athletic performance remains a subject of debate. Neither responds to endogenous 2,3 DPG (2,3 BPG) and therefore both are probably less effective at improving oxygenation than transfusions of red blood cells. In addition, HBOCs may cause vasoconstriction, which would limit oxygen delivery to tissues, and may even impair performance [52]. Serum testing using an electrophoretic method is fast, effective, and sensitive, and is used as a screening test for anti-doping samples [58].

Intravenous fluid — The WADA list of prohibited methods (section M2) includes intravenous infusions, which may be used to offset dehydration during endurance events. Intravenous infusions or injections of more than 100 mL of fluid per 12-hour period, except for those legitimately received in the course of medical treatment, a surgical procedure, or diagnostic investigation, are not permitted. This rule was changed in 2019 due to the number of inadvertent violations occurring as a result of iron and other supplement infusions.

Gene doping and cell doping — "Gene doping" is the application of gene therapy techniques to enhance athletic performance [59,60]. In 2001, WADA declared that the "non-therapeutic use of cells, genes, genetic elements, or the modulation of genetic expression, having the capacity to enhance athletic performance, is prohibited."

Thus, neither of the following actions is permitted:

- Use of nucleic acids or nucleic acid analogues that may alter genomic sequences and/or alter gene expression (including gene editing, gene silencing, and gene transfer technologies) with the potential to enhance sport performance
- Use of normal or genetically modified cells with the potential to enhance sport performance

Candidate genes have been identified that increase the oxygen carrying capacity of the blood through increased production of erythropoietin, vascular endothelial factor, and other angiogenic factors, and that increase strength through stimulation of type I and type II muscle

fibers, insulin-like growth factor (IGF) I, and myostatin [59,61-65]. Using laboratory methods, gene doping has been demonstrated to improve endurance, strength, and tissue repair in animal models [59,61,62]. Gene transfer in mouse muscle has been shown to counteract age-related muscle atrophy [66], and to enhance the effects of training on muscle hypertrophy [67]. Inactivation of the myostatin gene resulted in marked muscle hypertrophy in mice [68].

To date, there is no evidence of gene doping by human athletes. However, WADA is sufficiently concerned to include gene doping in its official list of banned methods [59,61,69]. The potential for performance enhancement and extension of an athlete's career through improved healing capacity, along with the inherent difficulty in detection [70,71], increase the risk for this form of abuse. The potentially serious risks to the health of the athlete, and possibly others (eg, exposure to viral gene vectors), and the unfair advantage gained by cheaters, justify the need for close monitoring and an aggressive education campaign. Examples of possible health risks include inadequately regulated increases in erythropoietin expression that may cause significant polycythemia, and increases in IGF-1 or growth hormone that could stimulate production of malignant cells [72].

Although the prospects for gene doping are theoretical at present, improvements in genetic technology should be monitored closely and further research aimed at detecting genetic manipulation is warranted [60]. Monitoring may involve identifying specific substances (consistent with current methods for detection), but also patterns of changes that may occur as a response to genetic modification.

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: Androgens and other banned substances in athletes".)

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 physicians, competitive athletes, and anyone involved in the care of athletes keep current with its contents, along with any additional restrictions enforced by other organizations for governing bodies relevant to the athletes under their care. (See 'World anti-doping agency and prohibited substances used for performance enhancement' above.)

- Androgens and growth hormone are among the most commonly used performance-enhancing substances and these are discussed separately. Multiple non-hormonal drugs and other illicit methods are used for performance enhancement, including stimulants, recreational drugs, nutritional supplements, beta agonists, beta antagonists, and other prescription medications. (See 'Banned non-hormonal performance-enhancing drugs' above and "Use of androgens and other hormones by athletes".)

- A number of agents are used to prevent detection of banned performance-enhancing substances. These include diuretics, desmopressin, probenecid, and plasma expanders. (See 'Agents used to prevent detection of banned substances' above.)

- Methods for detecting banned performance-enhancing drugs (PEDs) include the history and physical examination, the athlete biological passport (ABP), and urine and drug testing. (See 'Testing for banned non-hormonal performance-enhancing drugs' above.)

- Waivers called "Therapeutic Use Exemptions" may be granted to some athletes who need to use a particular banned medication for a legitimate medical purpose. The criteria and application process for obtaining such a waiver are described in the text. (See 'Therapeutic use exemptions' above.)

- Non-pharmacologic performance enhancement methods include blood transfusion, hypoxia induction techniques, and gene doping. (See 'Banned methods of non-pharmacologic performance enhancement' above.)

Topic 15454 Version 46.0

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