

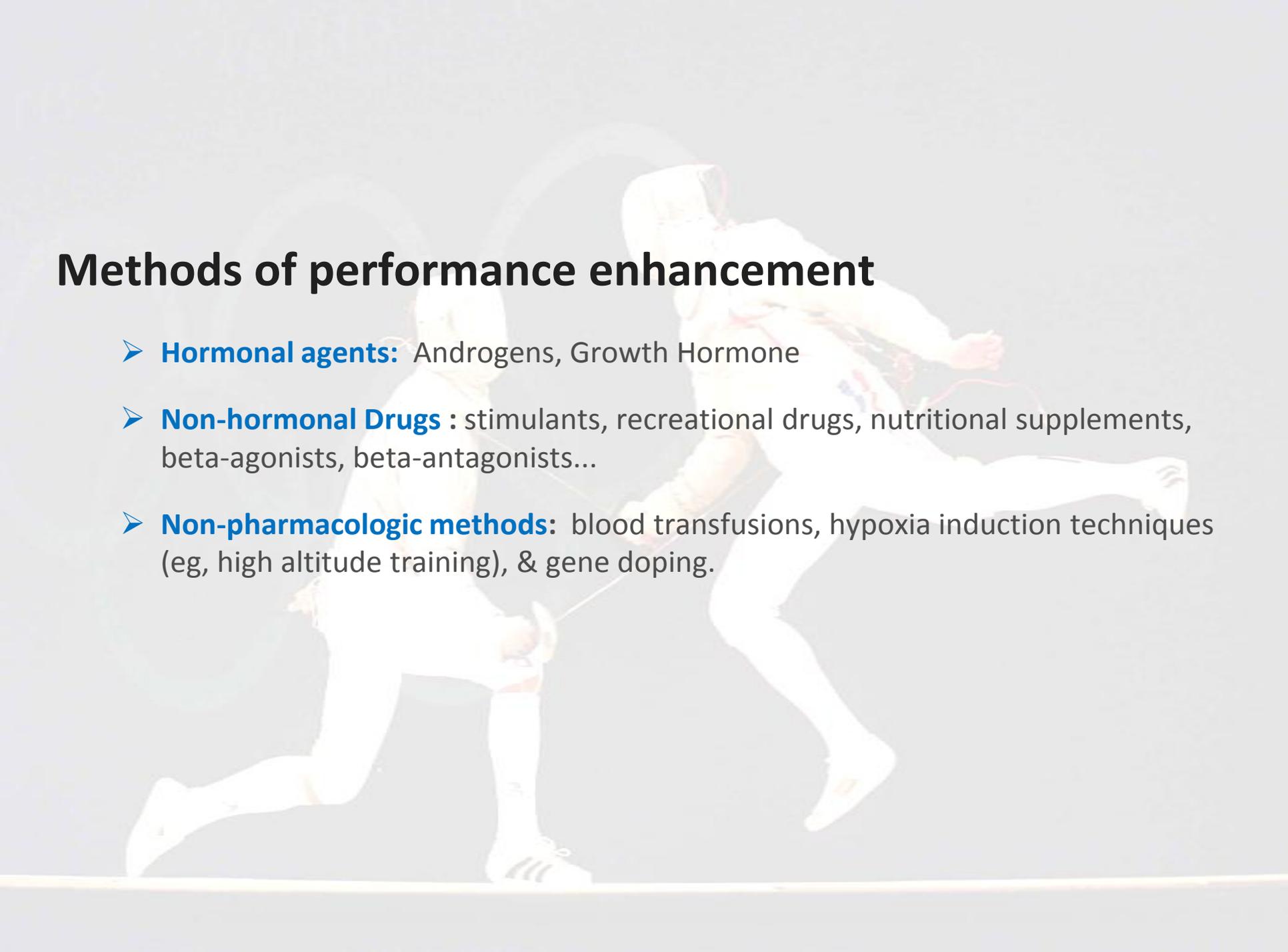
# **Drug Abuse in Sport**

**Dr Mohammad Taraz**

# Introduction

- ❖ **Hormonal medications** have been used for many years to improve athletic performance.
- ❖ The use of androgens has spread from competitive sports to leisure & fitness sports.
- ❖ Bodybuilders & non-athletes use androgens as a strategy to increase muscle mass & physical attractiveness.
- ❖ Performance-enhancing drugs have been used in a variety of settings by both athletes & non-athletes. Individuals are taking performance-enhancing drugs not only to improve athletic performance, **but also to increase alertness or improve appearance.**

# Methods of performance enhancement

The background of the slide features a faded image of two fencers in white protective gear, including masks and jackets, engaged in a foil match. They are in a dynamic, lunging position on a dark fencing strip.

- **Hormonal agents:** Androgens, Growth Hormone
- **Non-hormonal Drugs :** stimulants, recreational drugs, nutritional supplements, beta-agonists, beta-antagonists...
- **Non-pharmacologic methods:** blood transfusions, hypoxia induction techniques (eg, high altitude training), & gene doping.

# Patterns of use

- ❖ Users often obtain the drugs from sources other than clinicians. Some will use drugs intended for veterinary purposes.
- ❖ Athletes often take performance-enhancing drugs in various patterns, including in escalating doses ("pyramiding"), consecutively ("stacking"), simultaneously, intermittently, or cyclically, in an attempt to increase the overall effect on performance & the latter to avoid detection.
- ❖ Users may attempt to counter a side effect of one medication with another medication. As examples, an athlete might take hCG to counteract the reduction in testicular size resulting from high-dose androgen use, take an aromatase inhibitor to counteract gynecomastia from high doses of hCG, or take a 5-alpha reductase inhibitor to prevent balding & acne that occur with exogenous androgens.
- ❖ Athletes discontinue the medications periodically to avoid side effects & detection just before a competition.
- ❖ Rather than asking a clinician, users may seek information about performance-enhancing drugs from athletes, trainers, magazines, underground publications, & the internet.

# Banned drugs

- ❖ In the past decade, the list of drugs banned by the **World Anti-Doping Agency (WADA)** has grown to over 100.
- ❖ The 2011 WADA list includes androgens, “peptide hormones, growth factors & related substances,” hormone antagonists & modulators, diuretics & other masking agents, stimulants, narcotics, cannabinoids, alcohol, glucocorticoids, beta-agonists, & beta-blockers.
- ❖ It also includes different prohibited methods of enhancement including oxygen transfer, chemical & physical manipulation, & gene doping.

# Androgens

## ❖ Types of androgens :

- ❖ Virtually all androgens produced for **human or veterinary purposes** have been taken by athletes.
- ❖ These include **testosterone esters**, which are usually taken by injection, the **17-alpha-alkylated androgens**, which are usually taken orally, & **androgen precursors**.

## ➤ Exogenous testosterone

- The testosterone esters include the **enanthate & cypionate**, which are also used for hormone replacement.

## ➤ Synthetic androgens

- Synthetic steroidal androgens, **eg, oral stanozolol or parenteral nandrolone**, were originally developed to have a greater anabolic to androgenic effect than testosterone.
- They were therefore given the name "**anabolic steroids**," which persists today. However, whether these compounds have a higher ratio of anabolic to androgenic activity than testosterone in humans is **uncertain**.
- **Nevertheless, no compound has yet been found to have a greater anabolic effect than androgenic effect in humans, & therefore they will all be referred to here simply as androgens.**

## ➤ Androgen precursors

- The androgen precursors include **androstenedione & dehydroepiandrosterone (DHEA)**.
- Androstenedione is widely used & promoted in bodybuilding magazines. Until 2004, products containing **androstenedione (“andro”) were available as OTC nutritional supplements**. As of **January 2005**, these substances may not be sold without a prescription.
- **Androstenedione does not appear to have an anabolic effect like testosterone, & its effect on serum androgens is variable.**
- DHEA is also available as a **"nutritional supplement"** & is widely touted in body building magazines as an agent that will increase muscle strength. **It is not androgenic itself, but is converted to testosterone**. However, in three trials of administration of DHEA to normal young men, the serum concentration of DHEA increased, **but that of testosterone did not**.

# Selective androgen receptor modulators (SARMs)

- ❖ SARMs are **nonsteroidal, orally active molecules** developed to bind better to androgen receptors in certain tissues, such as muscle & bone, than to those in genital tissue with the goal of improving muscle weakness, osteoporosis, & other conditions **with less risk of worsening prostate diseases in men or causing virilization in women.**
- ❖ **Although none of these compounds have been approved for use in humans in any country,** a doping laboratory in Germany obtained a vial of the SARM Andarine via the Internet, **indicating that at least one of these compounds is available for abuse.**

## Other forms of androgen stimulation

- ❖ Another approach to increasing endogenous testosterone concentrations is by taking **exogenous hCG, antiestrogens such as tamoxifen or raloxifene, or aromatase inhibitors.**
- ❖ These drugs result in an increase in serum testosterone concentrations, & all are banned by the WADA.



- ❖ Exogenous hCG, which binds to the LH receptor & stimulates the Leydig cells of the testes to secrete testosterone, has also been used by athletes. hCG leads to production of endogenous testosterone in the normal ratio to epitestosterone, making its use more difficult to distinguish from normal secretion. LH has a very short half-life & is not likely to be abused.
- ❖ Side effects of hCG include edema & gynecomastia.

# Efficacy of Androgens

- ❖ It seems intuitive that androgens **increase muscle mass & muscle strength**, given the obvious differences between men & women.
- ❖ Administration of **supraphysiologic doses of exogenous testosterone** to healthy young men has been shown to increase their muscle strength.
- ❖ However, there is **no evidence that androstenedione increases muscle strength**, & **the evidence for an effect of DHEA is conflicting**.

# Side effects

## ❖ Reproductive:

- All androgens suppress gonadotropin secretion & therefore in men suppress endogenous testicular function, both testosterone & sperm production. Spermatogenesis & fertility are greatly diminished by exogenous androgens. The sperm count usually returns to normal within 4 months after discontinuation, but may take more than a year.
- Testicular size may decrease if androgen administration continues for many years. Gonadotropin & testosterone secretion remain suppressed for a few months after androgens are discontinued.
- Gynecomastia occurs because testosterone is converted to estradiol via the action of the aromatase enzyme complex, so that high doses of testosterone result in high serum estradiol concentrations. Androgens that have been 5 alpha-reduced, such as dihydrotestosterone, & synthetic androgens in which the A ring has been modified, cannot be aromatized & therefore cannot be converted to estrogens & do not cause gynecomastia.
- In women, side effects of androgens include acne, hirsutism, temporal hair recession in a male pattern, clitoromegaly, & deepening of the voice, which is irreversible. Although not well studied, many women also develop oligomenorrhea or amenorrhea.

## ❖ Cardiac:

- ❖ The effect of high doses of androgens on cardiac function is uncertain. Several case reports describe sudden death in young athletes who had no previously known heart disease but who were taking androgens; cardiac hypertrophy or myocarditis were found at autopsy. It is not possible to establish causality in these sporadic cases.
- ❖ There are also reports of left ventricular hypertrophy in body builders & power lifters, but most of these studies have not been randomized or controlled for degree of exercise, which itself can affect the degree of cardiac hypertrophy. In one randomized, placebo-controlled trial, eight body builders treated with nandrolone decanoate showed no difference in several echocardiographic parameters at the end of eight weeks from those treated with placebo, but this study was limited by the small numbers of subjects & short duration.

## ❖ Lipids:

- ❖ Although physiologic doses of testosterone have no consistent effects on serum lipid concentrations, pharmacologic doses of androgens, especially 17-alpha-alkylated androgens administered orally, decrease serum HDL & increase LDL concentrations.
- ❖ In a study of normal men aged 30 to 56 years given androstenedione (300 mg/day for 28 days), serum HDL cholesterol concentrations decreased by 15 percent, a change that, in the general population, would predict an increase in risk of coronary heart disease.

## ❖ Hemostasis:

- ❖ Androgen administration is associated with activation of the hemostatic system, as illustrated in a study of 49 weight lifters in whom androgen use was ascertained by history & urine testing.
- ❖ The confirmed steroid users had a higher percentage of abnormally high thrombin–antithrombin complexes in plasma than nonusers (16 versus 6 percent,  $p = 0.01$ ), higher plasma concentrations of prothrombin fragment 1 (44 versus 24 percent,  $p < 0.001$ ), antithrombin III (22 versus 6 percent,  $p = 0.005$ ), & protein S (19 versus 0 percent), & lower plasma concentrations of tissue plasminogen activator & its inhibitor. The importance of hemostatic system activation with regard to risk of thrombosis is unclear.

## ❖ Neuropsychiatric:

- Many psychological abnormalities have been described, both in the medical literature & anecdotally, in men taking high doses of androgens. One hundred sixty men recruited from gyms responded to a questionnaire about androgen use & psychiatric symptoms. Psychiatric symptoms, including major mood disorders & aggressive behavior, were more common in the men who had taken androgens than in those who had never taken androgens, & among the former the symptoms were more common when they were taking androgens.
- Several studies describe an association between nonmedical use of androgens & risky or even criminal behavior. Such as cigarette smoking, other illicit drug use, drinking & driving.
- Women who use anabolic steroids have described both hypomanic & depressive symptoms. In addition, some women report rigid dietary practices (referred to as “eating disorder, bodybuilder type”), nontraditional gender roles, & dissatisfaction/preoccupation with their bodies (referred to as “muscle dysphoria”).

## ❖ Erythrocytosis :

- Testosterone stimulates erythropoiesis, & in men made hypogonadal by administration of a GnRH agonist, increases hemoglobin & hematocrit in a dose-dependent manner.
- Erythrocytosis is a well-recognized side effect of treatment of hypogonadism with physiologic doses of testosterone. Erythrocytosis, sometimes to a severe degree, has also been reported in association with administration of pharmacologic doses of androgens, but only in case reports.

## ❖ **Hepatotoxicity:**

- Hepatic side effects occur only with oral 17-alpha-alkylated androgens & include high serum concentrations of liver enzymes, cholestatic jaundice, & peliosis hepatitis, characterized by blood-filled hepatic cysts. Hepatomas have also been reported, but the number of cases is few & causality is uncertain.

## ❖ **Prostate**

- Because the prostate is a testosterone-dependent gland, there is concern that the high doses of androgens that athletes take might increase the risk of BPH & prostate cancer. A meta-analysis of replacement doses of testosterone in hypogonadal men did not show such increased risks, but the risk in athletes who take large doses of androgens has not been reported.

## ❖ **Tendon rupture**

- Rupture of tendons (such as the triceps or biceps tendon) has been reported in weight lifters who use androgens.

# Detection of use

## ❖ Testosterone :

### ❖ The WADA utilizes two main methods for detecting testosterone:

- Testosterone/epitestosterone ratio – Testosterone taken exogenously cannot be distinguished from that produced endogenously by the usual methods for measuring testosterone radioimmunoassay & tandem mass spectroscopy, so other methods must be used. The conventional method is to determine the urinary ratio of testosterone glucuronide to its endogenous epimer, epitestosterone glucuronide (T/E ratio). Normally the ratio is 1 to 3:1, but subjects taking exogenous testosterone, which suppresses the production of both testosterone & epitestosterone & replaces it only with testosterone, have higher ratios, usually >6:1. However, a T/E ratio of >4:1 is considered evidence of doping by the WADA.

One limitation of the T/E ratio is that athletes can mask testosterone use by taking gonadotropins or epitestosterone, which can reduce the T/E ratio.

- The method currently considered most accurate is determination of the ratio of carbon 13 ( $^{13}\text{C}$ ) to carbon 12 ( $^{12}\text{C}$ ) in urinary metabolites of testosterone using isotope ratio mass spectrometry. The rationale is that pharmacologic testosterone preparations are synthesized from plant sterols, which have a lower ratio of  $^{13}\text{C}$  to  $^{12}\text{C}$  than do endogenous testosterones. This method will show a low  $^{13}\text{C}$  to  $^{12}\text{C}$  ratio even if an athlete takes epitestosterone in an attempt to mask taking testosterone.
- ❖ Thus, suspicion for exogenous testosterone use should be high in an athlete with a normal or elevated testosterone:epitestosterone ratio & low  $^{13}\text{C}$  to  $^{12}\text{C}$  ratio. These tests are offered by official testing bodies but not clinically.

## ❖ Other androgens

- Androgens other than testosterone can be detected by gas chromatography & mass spectrometry if the athlete is still taking the compound(s) at the time of testing. These tests are usually performed at commercial laboratories.
- Androgens other than testosterone also cause a high T/E ratio since androgens suppress endogenous testosterone production.
- SARMs can be detected in urine. This detection can be accomplished through solid-phase extraction followed by liquid chromatography-tandem mass spectrometry utilizing electrospray ionization.

## ❖ hCG :

- hCG can be detected by immunoextraction of urine & mass spectrometry. The proposed male cutoff is 5 IU/L. Because hCG is elevated in patients with testicular cancer, it may be a false positive for doping in this condition. There are privacy implications when testing urinary hCG in women, as the test is also used to detect pregnancy. LH use can be determined by urine immunoassay.

# Avoiding detection

- ❖ Athletes are continually finding ways to avoid detection. The most common way is to discontinue the drug before testing will occur.
- ❖ Screening tests can also be manipulated by urine substitutes, urine dilution, refusing to provide samples of urine or blood, & placing substances in the urethra to mask the samples. As an example, athletes may concomitantly take diuretics & increase fluid intake to dilute urine. Some substances have protease activity, & there should be a high level of suspicion in the absence of urinary proteins in a sample.
- ❖ Other indicators of sample tampering include urine at room temperature from a newly-obtained sample or specific gravity out of the range of normal. If the screening tests detect abnormal results, typically more advanced techniques such as liquid chromatography & mass spectrometry are used to confirm the results.

# Therapeutic use exemption

- ❖ The World & the US Anti-Doping Agencies allow athletes to compete if they are taking a banned medication because they need it medically.
- ❖ In this situation, they grant a Therapeutic Use Exemption (TUE) after reviewing a TUE form completed by the athlete's clinician.
- ❖ The clinician must state that the athlete would experience a significant health problem if he did not take the prohibited medication, the medication would not produce significant enhancement of performance, & there is no reasonable therapeutic alternative.
- ❖ An example is an athlete who takes testosterone because he has had bilateral orchiectomy for testicular cancer.

# Estrogen Blockade

- ❖ Estrogen blockade with drugs that block estrogen action or synthesis is another strategy for raising serum testosterone levels in men. They are also sometimes coadministered with androgens to prevent gynecomastia.
- ❖ Drugs in this category include:
- ❖ **Antiestrogens** — Antiestrogens bind to & block the estrogen receptor. The original antiestrogens included the nonsteroidal drugs [clomiphene](#) & [tamoxifen](#). These drugs are also referred to as selective estrogen receptor modulators (SERMs); they have estrogen agonist properties in some tissues & estrogen antagonist properties in others.

# Aromatase inhibitors

- ❖ Aromatase inhibitors are steroidal or nonsteroidal agents that block the conversion of androgens to estrogen. Examples include androstenedione analogs such as testolactone, & the nonsteroidal agents [letrozole](#) & [anastrozole](#).
- ❖ They are used to reduce the development of gynecomastia & to attempt to elevate the serum testosterone concentration. Modest elevations of serum testosterone are seen with aromatase inhibitor use in men, but an effect on muscle strength has not been demonstrated. There are sensitive assays available to detect aromatase inhibitors & antiestrogens. These can be detected in urine by gas chromatography/mass spectrometry.

# GROWTH HORMONE

- ❖ Growth hormone, like androgens, has been linked to many prominent athletes in sports including baseball, swimming, & cycling.
- ❖ **Physical effects**
  - Athletes take recombinant human growth hormone because of its demonstrated effects on body composition (more muscle, less fat).
  - In the largest study to date in recreational athletes, men were randomly assigned to receive placebo, growth hormone (2 mg/day SC), testosterone (250 mg/week IM), or combined treatments, while women were randomly assigned to receive either placebo or growth hormone (2 mg/day). In both men & women, growth hormone significantly reduced fat mass, increased lean body mass through an increase in extracellular water, & improved sprint capacity, but not strength, power, or endurance. The improvement in sprint capacity was greater when growth hormone was coadministered with testosterone to men. The effects of growth hormone disappeared after 6 weeks of being discontinued. The clinical significance of the increase in one physical performance parameter but not others in spite of supraphysiologic doses of both drugs is uncertain.

- ❖ Growth hormone would be expected to cause acromegaly if given in high doses long enough, but no such cases have been reported. Another potential concern is cancer, as epidemiologic data suggest an association between serum concentrations of insulin-like growth factor I (IGF-I) & cancer risk.
  
- ❖ A review of studies in which growth hormone was administered to normal men & women showed an increased incidence of soft tissue edema compared with those not treated.
  
- ❖ **Adverse effects**
- ❖ Growth hormone can cause insulin resistance, hyperglycemia, diabetes, sodium retention, hypertension, cardiomegaly, premature epiphyseal closure, myopathy, carpal tunnel syndrome, & swelling of the hands.

## ❖ **Detection methods:**

- ❖ Detection of growth hormone can occur only through the blood because less than 0.1 percent is excreted through urine. Two methods have been proposed to detect use of growth hormone by athletes:
  - Markers of growth hormone action, such as IGF-I & N-terminal extension peptide of procollagen type III (P-III-P)
  - **Growth hormone isoforms** — The pituitary gland normally secretes a variety of growth hormone isoforms, including a 20 kDa form & a 22 kDa form in monomers & dimers. However, recombinant human growth hormone (rhGH) consists only of the 22 kDa monomer. Immunoassays have been developed that can recognize either the 22 kDa form selectively or all of the isoforms nonselectively. Since administration of rhGH suppresses endogenous growth hormone secretion, an elevated ratio of the selective 22 kDa assay to growth hormone measured by the nonselective assay indicates administration of exogenous rhGH.

# Growth factors: IGF-I & insulin

- ❖ The rates of insulin-like growth factor (IGF-I) & insulin use for performance enhancement is lower than growth hormone.
- ❖ Insulin-like growth factor-I (IGF-I) should have similar effects to growth hormone, but this has not been studied. Athletes have also begun to use insulin, in particular, short-acting insulins, because of their anabolic effects on muscle.
- ❖ Insulin & IGF-I may lead to hypoglycemia. In one survey of 20 men who were recruited from gyms & admitted to using androgens, five reported that they also used insulin. They reported ingesting large amounts of sugar after insulin injection to avoid hypoglycemia. Serum concentrations of IGF-I may be associated with an increased risk of prostate cancer.
- ❖ IGF-I can only be detected through blood. However no commercial screen tests are available at this time. Detection of insulins can be done in the urine with use of antibody/antigen reactions & liquid chromatography/mass spectrometry. However, it is often difficult to distinguish between human insulin, insulin analogs, & porcine insulin.

# Nonhormonal Performance Enhancing Drugs

## ❖ Stimulants:

- ❖ Stimulants include amphetamine, D-methamphetamine, ephedrine, caffeine, [methylphenidate](#), [pseudoephedrine](#), dimethylamylamine (DMAA), cocaine, fenfluramine, pemoline, [selegiline](#), sibutramine, strychnine, & [modafinil](#).
- ❖ Stimulants are banned in sporting events only In-Competition (within 12 hours in which an athlete is scheduled to participate in a sporting event & through the duration of the event itself).
- ❖ Stimulants are known to be both physical & cognitive performance enhancers. Stimulants decrease appetite, increase energy, improve endurance, increase anaerobic performance, decrease feelings of fatigue, improve reaction time, increase concentration, improve working memory, increase alertness, & can lead to weight loss.

# **Nonhormonal Performance Enhancing Drugs**

# Amphetamine

- ❖ Amphetamine was first made in 1887, later used by the military in World War II to increase energy, & is currently used to increase alertness & concentration. Although amphetamine, methamphetamine, & cocaine can be drugs of abuse, amphetamine salts (eg, dextroamphetamine) are typically used for treatment, particularly for ADHD.
- ❖ Methylphenidate — Methylphenidate (Ritalin) is widely used as a cognition enhancer by patients with ADHD. It is also used illegally without a prescription by the general population.
- ❖ Ephedrine — Ephedrine was marketed as a dietary supplement, but was banned by the US FDA due to risk of heart attack & stroke. It is still commonly used today for medicinal purposes in Chinese medicine.

# Caffeine

- ❖ Caffeinated products are often used to improve athletic performance, as well as increase alertness in non-sporting events. Moderate amounts of caffeine (~ 3 mg/kg body mass) can have performance benefits in a variety of sports (eg, endurance events, racquet sports, swimming, running). Caffeine has urinary thresholds set by the International Olympic Committee (IOC) & National Collegiate Athletic Association (NCAA).
- ❖ **Dimethylamylamine — DMAA** (1,3-dimethylamylamine) is an amphetamine derivative that is widely used in sports supplements sold in the United States [6]. Because of health concerns, in 2011 the US military removed supplements containing DMAA from military exchanges [13], & Health Canada classified DMAA as a drug subject to regulation with no approved products [14].

- ❖ Adverse effects include headache, nausea, insomnia, anxiety, tremor, agitation, panic attacks, hypertension, tachycardia, & in some instances myocardial infarction & stroke. Higher doses may lead to aggressive behavior & psychosis. They also predispose users to extra exertion which can lead to heatstroke & rhabdomyolysis [3]. [Methylphenidate](#) has been shown to increase core temperature even at rest. One case-control study found an association between stimulant use & sudden unexplained death in children 7 to 19 years of age. [Modafinil](#) may also lead to Stevens-Johnson syndrome.

- ❖ **Narcotics** — Opiates have been used for increased pain threshold in athletics. Adverse effects include dependence, nausea, vomiting, constipation, loss of coordination, decreased concentration, & fatigue. Many opiates are detectable with standard urine drug screens.
- ❖ **Alcohol** — Alcohol is occasionally used to reduce anxiety for performance in athletic events & is banned in some sports, such as archery, karate, & motorcycling. Alcohol can be quantified by blood testing.

# Cannabinoids

- ❖ Cannabinoids include marijuana & hashish. The active ingredient is tetrahydrocannabinol (THC). A study of French university students found increased cannabinoid use for 'sliding sports,' including windsurfing, skiing, snowboarding, surfing, & sailing. The physical effects of cannabinoids in sports performance are not well-known, but they can reduce anxiety.
- ❖ Adverse effects of cannabinoids include reduced alertness, impaired short-term memory, & psychomotor retardation. It can cause dysphoria, increased anxiety, paranoia, & psychosis, particularly during its first use. Urine testing can detect cannabinoid metabolites. Based on gas-chromatography/mass spectrometry measurements, WADA sets the acceptable limits of free & conjugated carboxy-THC at 15 mcg/L.

# Nutritional supplements

- ❖ As the testing for performance-enhancing drugs has expanded to virtually all levels of competition, athletes have turned to over-the-counter nutritional or dietary supplements, assuming they are legal & safe. This is not always the case. One case series reported healthy patients taking dietary supplements laced with steroids who presented with nausea, anorexia, jaundice, severe pruritis, & kidney failure.
- ❖ Nutritional supplements in general are not seen as performance-enhancing drugs by the public, & are largely unregulated. Some concerns with these products include their lack of testing, contamination with banned substances, & banned products being used under different names. These supplements are a potential source for doping violations. At the 2004 Athens Olympic Games over 47 percent of athletes reported use of nutritional supplements.
- ❖ There are innumerable substances labeled as nutritional supplements, including vitamins, minerals, herbs, extracts, amino acids, metabolites, or any combination of these & other substances.

# Creatine

- ❖ Creatine is one example of a nutritional supplement contained in several commercial products specifically advertised for performance enhancement in sports.
- ❖ Creatine is currently not on the WADA list of banned substances & is the most popular nutritional supplement for performance enhancement. In one high school in the US, creatine was used by 9 % of male & 2 % of female athletes.
- ❖ At a university in the US, 48 % of male & 4 % of female athletes reported long-term use of creatine supplements.

- ❖ Creatine increases energy through ATP production in skeletal muscle during anaerobic exercise, & particularly enhances performance in short-duration, high-intensity exercise. However, no studies suggest that creatine enhances performance in endurance sports.
- ❖ In a meta-analysis of seven trials of young men (<36 years old), creatine supplements combined with resistance training increased the maximal lifting weight for bench press & squat. There was no effect in women or older men, & performance of other types of muscular effort did not improve.
- ❖ Subsequent randomized trials have confirmed that creatine increases maximum power output. Another meta-analysis of 12 trials in patients with muscular dystrophies found a similar increase in muscle strength compared to placebo. There are no studies investigating the long-term benefits & risks of creatine supplementation.
- ❖ Side effects of creatine include weight gain & acute interstitial nephritis, with more rapid progression of chronic renal disease.

# Energy beverages

- ❖ The consumption of beverages for athletic events began with sports drinks developed to replace electrolytes & carbohydrates lost during physical activity. Beverages evolved to include a variety of stimulants & other additives such as caffeine, taurine, glucuronolactone, B vitamins, antioxidants, trace minerals, guarana, ginkgo biloba, ginseng, L-carnitine, & sucrose, among others.
- ❖ The energy beverage industry is expanding rapidly, with hundreds of brands currently available. The recommended daily dose of energy beverages is no more than 500 mL, or one can. However, sports enthusiasts routinely drink much more and/or combine with alcohol consumption, which can be particularly dangerous. The effects of energy beverages vary based on the individual beverage components & doses.

# Beta agonists

- ❖ Beta agonists increase airway responsiveness. It is unlikely that they lead to improvement in most athletic events in individuals without asthma; however, there is anecdotal evidence of benefits in swimmers who use these agents prior to a race. All beta agonists are prohibited by the WADA except salbutamol, formoterol, & salmeterol by inhalation.
- ❖ High levels of even inhaled beta agonists detected in the urine may constitute a positive test, & the use of these drugs in athletics requires a therapeutic exemption along with pulmonary function testing. Albuterol is the most commonly used beta agonist for athletic performance.

# Beta blockers

- ❖ Beta blockers are banned in sports where there is benefit to having a decreased heart rate & increased steadiness. They are prohibited in specific sports such as archery, billiards, boules, gymnastics, & shooting.
- ❖ Physical effects of beta blockers on performance include a decrease in heart rate, a reduction of hand tremor, & temporary relief of anxiety.
- ❖ Despite the lack of evidence of efficacy, some practitioners prescribe beta-blockers for performance in speeches (eg, [propranolol](#) 20 mg taken 20 to 30 minutes prior to the event) & other noncompetitive sporting events (eg, dancing).
- ❖ Adverse effects of beta blockers with short-term use include bradycardia, increased airway resistance, & decreased endurance due to reduced maximum workload.

# Diuretics & other masking agents

- ❖ Diuretics can be used to quickly decrease body mass in sports where there are weight categories (eg, wrestling, boxing) or to alter normal urinary excretion of performance-enhancing drugs.
- ❖ Adverse effects include dizziness, lightheadedness, muscle cramps, rash, gout, hypotension, renal insufficiency, & electrolyte imbalances (eg, hypokalemia, metabolic alkalosis); potassium sparing diuretics (eg, amiloride, spironolactone) can cause hyperkalemia, & spironolactone can also cause gynecomastia.
- ❖ Diuretics are best detected by gas or liquid chromatography mass spectrometry or tandem mass spectrometry methods.

# Phosphodiesterase 5 inhibitors

- ❖ Phosphodiesterase 5 inhibitors are generally used to enhance erectile performance based on their vasodilatory effects via nitric oxide.
- ❖ Athletes also use phosphodiesterase 5 inhibitors for presumed effects of increased oxygenation & exercise capacity. However, there are little data available that have evaluated the effect of phosphodiesterase 5 inhibitors on athletic performance. They are not on the WADA prohibited list. Adverse effects include headache, flushing, dyspepsia, hypotension, & blurring of vision.



# **Non-pharmacologic Performance Enhancement**

# Blood transfusions

- ❖ Blood transfusions can be autologous or homologous.
- ❖ Blood transfusions can increase the number of erythrocytes & oxygen carrying capacity in the blood. Blood transfusions prior to athletic competitions have been used to enhance performance, but are currently prohibited by the WADA. Platelet-rich plasma & other platelet-derived preparations contain growth factors but they are not prohibited by WADA.
- ❖ Blood transfusions can lead to sudden changes in blood pressure, promote atherosclerosis, cause oxidative damage to organs, impair blood cell functions, lead to blood-borne infections, & lead to iron deposition in organs.

# Hypoxia induction

- ❖ The induction of hypoxia leads to a natural response of endogenous erythropoietin production, hemoglobin elevation, & oxygen-carrying capacity. High altitude training & sleeping in negative pressure tents create a hypoxia effect to subsequently improve oxygen-carrying capacity.
- ❖ Although there is physiologic benefit to training at high elevation, the ability to train vigorously is reduced due to low oxygen tension at high altitude. A high-low method of sleeping at high altitude & training at low altitude appears to be better at improving endurance performance than either method alone.
- ❖ Adverse effects include pulmonary & cerebral edema associated with high altitude illness. High altitude illness can be prevented with slow acclimatization. High altitude training is not currently prohibited by antidoping agencies.

# Gene doping

- ❖ “Gene doping” is the application of gene therapy techniques to enhance athletic performance. The history of doping in sports clearly demonstrates some athletes will do anything, & risk everything, to gain a competitive advantage.
- ❖ Candidate genes have been identified that effect erythropoietin production, the development of type I & type II muscle fibers, insulin-like growth factor I, & myostatin (a negative regulator of muscle growth), & gene doping has been demonstrated to impact endurance, strength, & tissue repair in animal models. As an example, gene therapy has been used to promote erythropoietin production to treat anemia, which makes it a potential target for abuse.

**END**