Adverse Health Consequences of Performance-Enhancing Drugs: An Endocrine Society Scientific Statement


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Despite the high prevalence of performance-enhancing drug (PED) use, media attention has focused almost entirely on PED use by elite athletes to illicitly gain a competitive advantage in sports, and not on the health risks of PEDs. There is a widespread misperception that PED use is safe or that adverse effects are manageable. In reality, the vast majority of PED users are not athletes but rather nonathlete weightlifters, and the adverse health effects of PED use are greatly underappreciated. This scientific statement synthesizes available information on the medical consequences of PED use, identifies gaps in knowledge, and aims to focus the attention of the medical community and policymakers on PED use as an important public health problem. PED users frequently consume highly supraphysiologic doses of PEDs, combine them with other PEDs and/or other classical drugs of abuse, and display associated risk factors. PED use has been linked to an increased risk of death and a wide variety of cardiovascular, psychiatric, metabolic, endocrine, neurologic, infectious, hepatic, renal, and musculoskeletal disorders. Because randomized trials cannot ethically duplicate the large doses of PEDs and the many factors associated with PED use, we need observational studies to collect valid outcome data on the health risks associated with PEDs. In addition, we need studies regarding the prevalence of PED use, the mechanisms by which PEDs exert their adverse health effects, and the interactive effects of PEDs with sports injuries and other high-risk behaviors. We also need randomized trials to assess therapeutic interventions for treating the adverse effects of PEDs, such as the anabolic-androgen steroid withdrawal syndrome. Finally, we need to raise public awareness of the serious health consequences of PEDs. (Endocrine Reviews 35:341–375, 2014)
scientific statement. Despite the high prevalence of PED use in the United States and in many other countries, most media attention regarding PED use has focused on elite athletes and the illicit competitive advantage they gain from PEDs. Neither the medical community nor policymakers appreciate that most PED users are not competitive athletes, but rather nonathlete weightlifters (sometimes referred to as recreational bodybuilders) (1, 2). Indeed, many nonathlete weightlifters are not focused on performance per se, but are primarily focused on personal appearance, in that they simply want to lookleaner and more muscular. Therefore, more strictly, these agents might be referred to as performance-enhancing and body-image-enhancing drugs, although we will use the abbreviation PED for the sake of brevity throughout this manuscript. Moreover, there is widespread misperception that PED use is safe or that the adverse effects are manageable, when in fact the adverse health effects of PED use remain understudied and underappreciated. Similarly, at a national policy level, the limited resources allocated to this problem focus primarily on the detection and deterrence of athletes using PEDs to gain a competitive advantage, and not on the health concerns associated with PED use by both athletes and nonathlete weightlifters. With at least 3 million PED users in the U.S. alone, PED use ranks ahead of type 1 diabetes and HIV infection in prevalence, and yet the resources allocated to address PED use as a public health problem are negligible in comparison with these diseases. This scientific statement aims to synthesize the available information on the medical consequences of PED use among nonathlete weightlifters, identify gaps in our knowledge, and focus the attention of the medical community and policymakers on PED use among nonathlete weightlifters as an important public health problem. Clearly, this issue deserves substantially greater investigation of its prevalence, medical consequences, mechanisms, prevention, and treatment than it has received to date. Because androgenic-anabolic steroids (AASs) are the most frequently used class of PEDs among athletes and nonathlete weightlifters, this review has devoted greater space and attention to the health consequences of AAS.

II. Definitions

PEDs are pharmacologic agents that athletes and nonathlete weightlifters use to enhance performance. The term doping refers to the use of PEDs in competitive sports. For the purpose of this statement, we define nonathlete weightlifters as individuals whose goal is to become leaner and more muscular, often simply for personal appearance, and not to participate in formal sports competitions. There are several categories of PEDs that are currently popular among nonathlete weightlifters and athletes. Lean mass builders, the most frequently used PEDs, are generally promyogenic (anabolic) drugs that increase muscle mass or reduce fat mass. By far the most prevalent illicit drugs in this category are AASs, which are the primary focus of this report. Among nonathlete weightlifters, the use of AASs represents a higher proportion of overall PED use than that of all other categories of PEDs combined.

Historically, the term AAS reflected the view that androgenic and anabolic effects of androgens could be dissociated and that, in comparison with testosterone, some androgens were more anabolic than androgenic. In the 1980s, Dr Jean D. Wilson (3), citing the singularity of the androgen receptor, suggested that androgenic and anabolic activity of androgens could not be dissociated. Therefore, he and others have argued that the term AAS is a misnomer and should be abandoned (4).

However, a large body of data emerged in the late 1990s that revealed that the selectivity of androgen receptor signaling could be mediated at multiple levels of the steroid hormone interactome that encompasses (in addition to the androgen receptor) an interacting web of chaperone proteins, a repertoire of 300 or so coactivators and corepressors, elements of the chromatin, effector proteins, and transcription factors that bind specific regions of the androgen-responsive genes (5–9). Although the precise molecular mechanisms that mediate tissue-selective actions of selective androgen receptor modulators (SARMs) are not fully characterized, a growing body of evidence suggests that ligand specificity can be imparted by the recruitment of a specific repertoire of tissue-specific coactivators and corepressors, the variations in the level of expression of the coregulator proteins in different tissues, the regulation of chromatin remodeling, differential activation of signaling pathways in the prostate vs the skeletal muscle, and differential susceptibility to the action of the steroid 5α-reductase enzyme (6, 7, 10, 11). These landmark discoveries have re-instated the view that multiple levels of the androgen receptor interactome contribute to tissue-specific actions of the androgen receptor ligands, and can be targeted to achieve the desired tissue specificity. Indeed, a number of SARMs have achieved relative differentiation of androgenic and anabolic activity, being preferentially more potent in the muscle than in the prostate (5–9, 12, 13). Several publications have described the mechanistic basis of tissue specificity (5–13). This growing body of literature suggests that despite the singularity of the androgen receptor protein, tissue selectivity of ligand action can be achieved. Therefore, we decided to use the term AAS for this state-
Another reason for retaining the use of the term AAS is that this term is widely used and understood by the media, lay public, and policymakers.

In addition to AASs, nonathlete weightlifters and athletes also use human GH (hGH) and IGF-1 because these PEDs have recently become available on the black market at reduced cost (14). Similarly, some nonathlete weightlifters use the hormone insulin for its potential anabolic effects (15). Finally, some nonathlete weightlifters use clenbuterol, a β-adrenergic agonist that is thought to possess possible anabolic properties. Clenbuterol and other illegal stimulants, such as amphetamine, and some hormones, such as thyroid hormones, also have thermogenic (fat-burning) properties that make them popular among nonathlete weightlifters.

Competitive athletes tend to use several other categories of PEDs in addition to AASs. For example, some competitive bodybuilders use diuretics (e.g., furosemide and thiazides) to improve muscle definition onstage. Some boxers or wrestlers use diuretics to reduce body weight so they can compete in a lower weight class. Diuretics may also dilute the urine, which can reduce the concentration of the PED below the limit of detection. Blood boosters (erythropoietins, other erythropoiesis-stimulating agents [ESAs], and transfusions) increase endurance in events such as cycling, long-distance running, and skiing. Athletes also may combine AASs and erythropoietins to train harder and recover faster. Masking drugs reduce the ability to detect a banned substance. For instance, epitestosterone can mask the detection of testosterone use. And tranquilizers (benzodiazepines and opiates) reduce anxiety in events that require steady nerves (such as archery), and opiates can mask pain during competition.

The World Anti-Doping Agency (WADA), an international agency that oversees the implementation of the antidoping policies in all sports worldwide, maintains a list of substances (drugs, supplements, etc.) that are banned from use in all sports at all times, banned from use during competition, or banned in specific sports (16). WADA’s Anti-Doping Program is based on the WADA Code, a universal document that contains comprehensive guidelines for best practices in international and national antidoping programs (17). WADA also publishes the doping violation thresholds for banned substances.

### III. The Process of Data Gathering and Synthesis

The SSTF selected the chair (S.B.) of the statement development group. The chair selected a 6-member expert panel (approved by The Endocrine Society) with expertise in the use and health consequences of PEDs. The expert panel conducted its deliberations regarding the scientific statement content through multiple teleconferences, written correspondence, and a face-to-face meeting. All panelists volunteered their time to prepare this Scientific Statement without any financial remuneration.

Three librarians associated with the writing team created search sets for the major categories and topics that the writing group prepared. These search sets included the WADA prohibited substances (divided into each substance subgroup), illicit/performance enhancing/doping terms, anatomy/organ/disease terms, detection/screening terms, and epidemiology/risk terms.

Figure 1 provides an example of how these sets were combined for each category of PEDs. We used these terms...
to search the PubMed database for articles written in English or translated into English. We supplemented this by searching the bibliographies of major review articles published in these content areas. We also added to the reference list any additional references that were known to the members of the writing group but did not appear in this search. The expert panel reviewed and synthesized evidence in their areas of expertise and prepared the Scientific Statement. The SSTF, the Advocacy and Public Outreach Core Committee, and the Council of The Endocrine Society reviewed the Scientific Statement. We incorporated their comments into the final version.

The expert panel recognizes that randomized trials of PED use in the doses that athletes and nonathletes typically use them (which may range up to several thousand milligrams of testosterone or its equivalent per week) will never be possible because of ethical concerns. Even if it were possible to conduct randomized trials of PEDs, they would be constrained by the inability to replicate the high-risk behaviors, the multiplicity of PED and accessory drug use, and the psychologic, genetic, and behavioral attributes of actual PED users. No systematic prospective observational studies of PED users exist. Thus, most of the evidence about the medical consequences of PED use has emerged from case-control studies, case reports, and retrospective surveys and, as such, is generally not of high quality. Therefore, studies of PEDs in animal models provide important comparisons with the human data.

IV. Factors Contributing to the Limited Appreciation of the Adverse Effects of PEDs

Given the high prevalence of PED use, and in particular the high prevalence of AAS use (the largest category of illicit PEDs), one might ask why their adverse effects are not better understood and why policymakers have not allocated more resources to investigate and mitigate the public health impact of PEDs. Several factors may explain why the issue of PED use and its adverse health effects has remained neglected.

First, public attention is focused almost entirely on PED use among elite athletes, with an emphasis on how these drugs enable athletes to illicitly gain a competitive advantage. Hence, there appears to be a widespread misconception that PED use is primarily a phenomenon among a small group of highly competitive elite athletes. This misperception has distracted attention from the health risks associated with PED use and the fact that PED use is not limited to elite athletes but involves a much larger group of nonathlete weightlifters. And although testing is a major preoccupation in athletics, it is virtually nonexistent elsewhere, in part because of the high cost of PED testing.

Second, researchers cannot ethically conduct controlled studies of the long-term adverse effects of PEDs in normal volunteers, especially when using supraphysiologic doses. Therefore, most of our knowledge comes from studies of PED users in the field (supplemented with studies in animals). These uncontrolled human studies are subject to inherent methodologic limitations including selection bias (eg, individuals experiencing adverse effects may be more likely or less likely to present for study than those without such effects), information bias (eg, individuals are retrospectively reporting use of illicit drugs of uncertain potency and authenticity, often used years before the time of index evaluation), and confounding variables (eg, PED users frequently consume a wide range of other PEDs, frequently use classical drugs of abuse, and may also display additional risk factors for diseases that are associated with weightlifting [diet, use of needles, and other aspects of their lifestyle]).

Third, because widespread illicit PED use did not appear in the general population until the 1980s and 1990s, the great majority of the world’s PED users are still under the age of 50 today (18). As such, this relatively young population has not reached the age of risk for a range of diseases, such as cardiovascular problems, that typically arise later in life. This likely explains why, to date, only occasional case reports have highlighted acute medical events and deaths associated with PEDs. And it’s likely that some of the long-term effects of PEDs will only now start to become visible as the older members of the PED-using population reach the age of risk for these phenomena. Therefore, current observations likely underestimate the full magnitude of medical consequences of PEDs that will become evident over the next 2 or 3 decades.

Fourth, PED use in the general population is usually covert. PED use typically begins after the teenage years and therefore evades scrutiny of parents or high school teachers. Consequently, national surveys focusing on teenagers, such as high school students, will underestimate the total number of individuals who ultimately use PEDs, because the great majority of such individuals initiate use after their teenage years (19). Also, it has been our observation that people are less apt to disclose PED use than other forms of drug use, perhaps because doing so would acknowledge that their physical prowess is largely due to chemical enhancement (20, 21).

Fifth, PED users often do not trust physicians; in one study, 56% of AAS users reported that they had never disclosed their AAS use to any physician (21). Thus, physicians are often unaware of the prevalence of PED use (22–24).
Sixth, PED use rarely brings individuals to emergency rooms, because the most widely used class of PEDs, AASs, rarely precipitate a medical emergency comparable to an overdose of alcohol or heroin. Thus, surveillance techniques such as the Drug Abuse Warning Network (25) do not capture AAS users. Collectively, these many factors may conspire to keep nonathletic AAS use out of view, and thus obscure the magnitude of this public health problem.

V. A History of PED Use

A recent report on the use of illegal PEDs in professional baseball by Senator George Mitchell acknowledged the widespread use of PEDs by athletes in the United States, further emphasizing the fact that PED use is far more prevalent in the United States and the world than most are willing to acknowledge (26).

The use of PEDs in sports is not a new phenomenon; documentation exists of a variety of potions, plants, and animal extracts that early Olympic athletes used to improve performance in ancient Greece. Other reports have reviewed this history in detail. Figure 2 provides a brief timeline of the evolution of PED use from its beginnings in modern professional sports to its much wider use by the general population.

Long before the isolation and synthesis of testosterone in the 1930s, Brown-Séquard and later Zoth and Pregl recognized that testicular extracts could improve physical and mental energy, as well as muscle strength (27–30). Shortly after the successful synthesis of testosterone, Boje (31) suggested that sex hormones might enhance physical performance. The Germans allegedly administered AASs to soldiers going into combat (32). The Germans also allegedly gave athletes testosterone in preparation for the 1936 Berlin Olympics (32). However, the most cited example of systematic use of AASs in elite sports is that of the Soviet weightlifting team in the 1952 and 1956 Olympics. Dr John Ziegler, a physician associated with the U.S. weightlifting team, learned about the use of AASs by the Russian team at the weightlifting championships in Vienna in 1954 (32, 33) and experimented with testosterone on himself and other weightlifters in the York Barbell Club in New York (33). AAS use, which had been exclusive to strength-intensive sports, spread gradually to other sports and to nonathlete weightlifting over the ensuing decades (32, 33).

In particular, Ben Johnson’s positive test for stanozolol at the Seoul Olympic Games in 1988 brought widespread public attention to AASs. The most egregious example of state-sponsored doping was uncovered in the former German Democratic Republic after the fall of the Communist government in 1990 (34); classified documents revealed a comprehensive secret state program to improve national athletic performance using PEDs with the complicity of the state and the sports medicine physicians. Recently, the relentless glare of media limelight surrounding the detection of PED use by elite athletes such as Lyle Alzado, Mark Maguire, Barry Bonds, Floyd Landis, Marion Jones, and Lance Armstrong has added to the allure of PEDs and contributed to the widely held misperception that PED use is largely limited to elite athletes and is therefore not a widespread public health problem.

Although officials have banned PEDs from Olympic competition since 1967, and the International Olympic Committee has prohibited AAS use since 1975, it was not until 1991 that the U.S. Congress designated AASs as Schedule III controlled substances. In 2004, the Anabolic Steroid Control Act amended the Controlled Substances Act and expanded its definition of anabolic steroids. The new definition, which does not require proof of muscle growth, identified 59 specific substances (including their salts, esters, and ethers) as anabolic steroids and listed them as Schedule III controlled substances.

Most of the PEDs that athletes and nonathlete weightlifters used before the 1990s were pharmacologic agents approved for medicinal or veterinary use. By the 1990s, various androgen precursors became available over the counter as unregulated nutritional supplements. Androgen precursors are either inactive or weak androgens that the body converts into potent androgens. These include naturally occurring precursors to testosterone such as 4-androstenediol, 5-androstenediol, 4-androstenedione, and dehydroepiandrosterone as well as precursors to synthetic AASs, including 4-norandrostenedione, 4-norandrostenol, and 5-norandrostenediol, which the body converts to nandrolone. The widespread, unregulated sale of dietary supplements on the Internet has greatly increased the number of anabolic steroids available. Of even greater concern is the introduction of synthetic anabolic steroids such as 17-desmethylstanozolol, methylclostebol, and methyltrienolone into the market as dietary supplements. Androsterones such as 4-androstenediol, 5-androstenediol, 4-androstenedione, and dehydroepiandrosterone as well as precursors to synthetic AASs, including 4-norandrostenedione, 4-norandrostenol, and 5-norandrostenediol, which the body converts to nandrolone. The widespread, unregulated sale of dietary supplements on the Internet has greatly increased the number of anabolic steroids available. Of even greater concern is the introduction of synthetic anabolic steroids such as 17-desmethylstanozolol, methylclostebol, and methyltrienolone into the market as dietary supplements. A partial list of steroids contained in dietary supplements can be found at www.supplement411.org. The Steroid Control Act of 2004 banned most of these substances. However, we are now seeing novel synthetic designer androgens, such as tetrahydrogestrinone (35, 36) and madol (37). Because these designer steroids have not undergone toxicologic or safety testing in humans or animals, they potentially pose an even more serious health risk than the more traditionally used AASs, which have received some level of animal or human testing.
VI. Epidemiology of PED Use

A. Age of onset

Although it is widely believed that AAS use is common among teenagers, the great majority of AAS use begins after the teenage years (Figure 3). Data on high school drug use from the University of Michigan’s Monitoring the Future study provides valuable information concerning the youngest AAS users (38). As shown in Figure 3, some 2% of American high school students report having used AAS in the past 12 months. Although the annual prevalence figures may well be inflated as a result of false-positive
responses to the steroid question, the data suggest that AAS use may have declined since the year 2000 when the media widely publicized adverse Congressional comments regarding PED abuse. However, we cannot exclude the possibility that this might not reflect a true decline in AAS use, but rather a decline in false-positive responses as students became better informed about AAS and hence less likely to misinterpret the steroid question on the survey.

We have found 9 studies from the United States, Australia, and the United Kingdom since the year 2000 that provide at least some data on age of onset of AAS use. These included 6 studies that evaluated AAS users in person and 3 Internet surveys of AAS users (19).

In the largest Internet study, only 1 of 1955 male AAS users (0.05%) reported starting AAS use before age 15, and only 6% started before age 18 (39). In 5 other studies, collectively evaluating 801 AAS users, only 12 (1.5%) started before age 16, and 199 (24.8%) started before age 20. Notably, the median age of onset across all studies consistently fell into the narrow range of 22 to 24 years. However, the actual median age of onset is probably higher, because at the time of recruitment, many study candidates had not completed the age range of risk for starting AAS use.

B. Prevalence of use

Although AAS use is widespread in Western countries, the United States appears to have the largest absolute number of AAS users. This is not surprising because the United States is the most populous country with substantial AAS use, and likely the first country in which AAS use began to spread from elite athletics to the general population (18).

A recent study (19) based on data from American surveys of school and youth populations used mathematical models to generate estimates of the lifetime prevalence of AAS use in the United States (this value should technically be called the cumulative incidence, although the term lifetime prevalence is generally used in studies of substance abuse and other psychiatric disorders). Important to note, this study took into account the fact that anonymous surveys of American high school students almost always overestimate the prevalence of AAS use because students erroneously answer that they have used steroids when in fact they have used corticosteroids, rather than actual AASs, or have used over-the-counter supplements that the students incorrectly believe are steroids (41). After adjusting for this source of bias and applying the mathematical models, the analysis produced an estimate that 2.9 to 4.0 Americans have used an AAS at some time in their lives.

The AAS users at greatest risk for adverse effects are likely those who develop AAS dependence and accumulate many years of AAS exposure. Therefore, this same study sought to estimate the number of Americans who had experienced AAS dependence. To do so, the investigators combined the data from 10 studies that collectively diagnosed AAS dependence in 1248 AAS users; we also included a recently published paper that tabulates these studies (19, 42–51).
Applying a random-effects model to these 10 studies, the analysis yielded an estimate that 32.5% (95% confidence interval, 25.4%–39.7%) of AAS users develop AAS dependence. Applying this proportion to the above estimates of the overall American AAS-using population, it follows that in the United States alone, about 1 million men have experienced AAS dependence at some time. As noted in the analysis, virtually all of these AAS-dependent individuals are likely to be male, because only 2 of the 363 cases of AAS dependence found in the 10 pooled studies described above were female. Thus, the lifetime prevalence of AAS dependence in American men is likely in the same general range as that of HIV infection or of type 1 diabetes, both of which afflict fewer than 1 million American men (52, 53).

The use of PEDs is not limited to the United States. High rates have been consistently documented in Scandinavia (54–59), Brazil (60, 61), and British Commonwealth countries (62–65) and more recently in continental Europe (66–68). By contrast, AAS use is rare in East Asian countries such as China, Korea, and Japan, perhaps because these cultures place less emphasis on male masculinity, as explained in recent reports (69, 70).

C. The types and patterns of PED use

AASs are the most commonly used PEDs, with testosterone, boldenone, and trenbolone being the most frequently detected drugs among illicit PED users in the United States (Figure 4). Although boldenone is a veterinary steroid not approved for human use, this fact has not diminished its popularity among illicit AAS users. In the small subgroup of PED users who are elite athletes, WADA most commonly detects testosterone, stanozolol, and nandrolone, and the highest prevalence of positive tests occur in bodybuilding, power lifting, weightlifting, boxing, and kickboxing.

PED users often combine multiple drugs, including classical drugs of abuse such as opiates (71–75). Most AAS users engage in high-intensity exercise to maximize anabolic gains. The combined use of AAS and opiates enables the user to continue training despite muscle and joint pain. Inevitably, some individuals develop opioid dependence. In particular, nalbuphine hydrochloride (Nubain) is popular among weightlifters (74) and is associated with other substance abuse. Arvary and Pope (72) have suggested that AAS could act as a gateway drug to opioid dependence. In another study of 223 men entering a drug treatment program, AAS use was considerably higher (25%) among opioid users compared with men using other drugs (5%) (75). In yet another recent study, 50% of dependent AAS users met Diagnostic and Statistical Manual of Mental Disorders-IV criteria for a lifetime history of opioid abuse or dependence as compared with 8 nondependent AAS users (19%) and 5 nonusers (7%) (45). In 1 case report of a man with AAS dependence, naloxone precipitated symptoms suggestive of opiate withdrawal, even though the man denied using opiates (76). AASs may also interact with heroin in accidental drug overdoses (73).

Recent studies increasingly suggest that the use of AAs and other PEDs often occurs in conjunction with use of multiple classical drugs of abuse (77, 78). PED users are increasingly encountered in needle-exchange programs, where they may sometimes represent most of the clientele (79, 80).

AAS use has also been linked to alcohol use in humans (81) and rats (82). Chronic AAS use may make rats susceptible for alcohol intake. Steroid-induced alterations in opioid peptides in the brain reward system may explain the increased sensitivity to alcohol (82). Other studies have observed an imbalance in dopaminergic pathways in the nucleus accumbens, a brain area involved in reward, leading to speculation that the alterations in the actual peptidergic and monoaminergic systems promote the reward effects of ethanol, thereby increasing alcohol intake (83). Additional studies have reported increased sensitivity to cocaine (84) and amphetamine (85) in rats exposed to high doses of AAS. Thus, AASs may induce effects on the brain reward system that may render individuals susceptible to other drugs of abuse.

Athletes and nonathlete weightlifters that use AASs commonly combine different steroids (stacking) in cycles of increasing and decreasing concentrations (pyramiding). Most stacks will include both androgens and nonsteroidal drugs. The latter are typically chosen to provide further anabolic effects (hGH, IGF-1, and insulin), to counteract negative side effects of AAS (aromatase inhibitors and estrogen receptor antagonists), to enhance fat and water loss (diuretics, thyroid hormones, and β2-adrenergic receptor agonists), to reactivate endogenous testosterone production at the end of a cycle (gonadotropins), and to reduce the risk of detection (diuretics and probenecid) (86, 87).

Side effects of these nonsteroidal drugs include headache, nausea, nervousness, diarrhea, perspiration, hot flushes, and bone pain (88). Athletes may add epitestosterone to normalize their testosterone to epitestosterone (T/E) ratios, thus avoiding testosterone-use detection. Researchers have not adequately investigated interactions of AAS with nonsteroidal drugs.

D. Association of PED use with other high-risk behaviors

Athletes and nonathlete weightlifters that use PEDs often engage in other high-risk health behaviors. In addition
to the risks associated with concomitant use of other drugs such as alcohol and opiates with AASs (77), users of high doses of AAS may be more susceptible to rage, antisocial and violent behaviors, and suicidality. Sharing of needles and other paraphernalia and unprotected sex may increase the risk of infections such as hepatitis and HIV (89–93). The use of PEDs, especially in conjunction with analgesics or stimulants, may allow athletes to engage in extremely high-intensity exercise, increasing the risk of musculoskeletal injuries.

VII. Adverse Health Effects of PEDs

Because AASs, hGH, insulin, and erythropoietins are the most frequently used PEDs, we address the medical consequences of their use in detail below.

A. Androgenic-anabolic steroid

1. Clinical pharmacology

An androgen is a sex hormone that promotes the development and maintenance of the male sex characteris-
tics; testosterone is the principal secreted androgen in men. Androgens have both androgenic (masculinizing) effects (development of male secondary sex characteristics, including hair growth) and anabolic effects (increase in skeletal muscle mass and strength). For decades, pharmaceutical companies have attempted to develop androgens that have preferential anabolic activity and reduced or no androgenic activity; these compounds have been referred to as anabolic steroids. Although some steroidal compounds available to date are preferentially anabolic, most generally have both androgenic and anabolic effects. Therefore, for the sake of uniformity and accuracy, we have used the term AAS to describe these compounds that are structurally related to testosterone, bind to androgen receptor, and exert masculinizing as well as anabolic effects to varying degrees. The literature uses a number of terms (anabolic steroids, androgenic steroids, and androgens) to describe these androgen derivatives.

Testosterone remains popular, both among elite athletes and nonathlete weightlifters, because of its low price, relatively ready access, and the challenges in distinguishing exogenous from endogenous sources of testosterone. Numerous AASs have been synthesized by structural modifications of the testosterone molecule (12, 94). These structural modifications may alter the relative anabolic or androgenic activity, the binding affinity for the androgen receptor, coactivator recruitment, metabolic clearance, susceptibility to presystemic metabolism, and aromatization (12, 94).

Testosterone is metabolized rapidly in the body; however, esterification of the 17β-hydroxyl group renders the molecule more hydrophobic. When these esters of testosterone (such as testosterone enanthate and cypionate) are administered in an oily suspension, they are released very slowly into the aqueous plasma because of their hydrophobicity. This extends their duration of action. These esters are readily de-esterified to testosterone in the body.

Investigations of the structure-activity relationships (Figure 5) have established that removal of the 19-methyl group increases the anabolic activity; thus, 19-nortestosterone (nandrolone) is a potent AAS and a very popular drug that accounts for a large number of positive tests (94). 7α-Alkyl substitutions of the 19-nortestosterone molecule may further increase the anabolic to androgenic activity. 17α-Alkyl substitutions render the molecule resistant to degradation; thus, 17α-alkylated androgens can be administered orally. Stanozolol is a 17α-alkylated androgen that can be taken orally or by injection. Orally administered 17α-alkylated androgens are hepatotoxic. Stanozolol is also nonaromatizable. Other substitutions in the steroid A ring may alter the susceptibility of the steroid molecule to aromatization. A number of nonsteroidal SARMs, which display tissue-specific activation of androgen signaling, are in development (8, 13). Although the U.S. Food and Drug Administration has not approved these novel nonsteroidal SARMs for clinical use, some of them are already being sold illicitly on the Internet.

Athletes and nonathlete weightlifters take AASs orally, transdermally, or by im injection; however, the most popular mode is the im route. Oral preparations have a short half-life and are taken daily, whereas injectable androgens are typically used weekly or biweekly. A number of transdermal testosterone preparations have become available recently, but it is difficult to deliver large amounts of testosterone using the transdermal formulations. Users may supplement their program of injections and pills with topical gels to provide a constant low-level testosterone supply.

The mechanisms by which AASs improve athletic performance are not fully understood. Testosterone administration increases skeletal muscle mass (95–97) by inducing the hypertrophy of both type 1 and 2 fibers (98); testosterone does not change the absolute number or the relative proportion of type 1 and 2 fibers (98). Testosterone administration increases the number of muscle progenitor cells (satellite cells), which contribute to muscle fiber hypertrophy (99). Testosterone promotes myogenic differentiation of muscle progenitor cells (100, 101). Upon binding to its cognate androgen receptor, the liganded androgen receptor associates with β-catenin and other proteins, and the complex translocates into the nucleus where it binds transcription factor-4 and activates a number of Wnt target genes, including follistatin (100–102). Follistatin blocks the effects of a number of TGF-β family members, including myostatin and activins, and plays an essential role in mediating testosterone’s effects on myogenic differentiation (102). Most of the anabolic effects of testosterone appear to be mediated through androgen receptor signaling. Testosterone stimulates circulating GH and IGF-1, although circulating GH is not essential for mediating testosterone’s effects on muscle mass (103). However, im IGF-1 receptor signaling plays an important role in mediating the effects of testosterone on myogenesis (104). The conversion of testosterone to dihydrotestosterone by steroid 5α-reductase is not essential for mediating its effects on the muscle (105).

Testosterone increases maximal voluntary strength and leg power but does not increase specific force (104). Testosterone also promotes mitochondrial biogenesis and quality control and increases net oxygen delivery to the tissue by increasing red cell mass and tissue capillarity. Testosterone also increases the circulating levels of 2,3-biphosphoglycerate, which shifts the oxygen-hemoglobin
Figure 5. Structure-activity relationships of steroidal androgens. AAS compounds are derivatives of testosterone. Structural modifications of the testosterone molecule based on rational structure-activity relationships have yielded numerous derivatives that differ in their affinity for the androgen receptor, coactivator recruitment, susceptibility to presystemic metabolism, aromatization, metabolism and duration of action, and anabolic to androgenic activity. Novel orally active nonsteroidal SARMs are being developed for their clinical applications in sarcopenia associated with aging and chronic illnesses, although these compounds have not yet been approved for any indication. These oral nonsteroidal SARMs are not widely abused by nonathlete weightlifters because of their relative inaccessibility.

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<th>Molecule</th>
<th>Structure</th>
<th>Structural Features And Structure-Activity Relationship</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td><img src="image" alt="Testosterone Structure" /></td>
<td>A testosterone molecule is characterized by a 3-keto group, methyl groups in 19 and 21 positions, a 17beta-hydroxyl group, and a double bond between carbons 4 and 5 in the A ring.</td>
<td>Testosterone and its esters are the AASs of choice for athletes and non-athlete weightlifters.</td>
</tr>
<tr>
<td>19-nortestosterone</td>
<td><img src="image" alt="19-nortestosterone Structure" /></td>
<td>The removal of the 19-methyl group increases the anabolic activity relative to androgenic activity.</td>
<td>Nandrolone is popular as a training drug and accounts for a large number of positive tests.</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td><img src="image" alt="Testosterone Enanthate Structure" /></td>
<td>Esterification of the 17beta-hydroxyl group renders the molecule more hydrophobic. Its duration of action is extended when the molecule is injected in an oil suspension.</td>
<td>Testosterone esters, cyano esters, and ethyl acetate are used in therapy and also used widely by non-athlete weightlifters and athletes.</td>
</tr>
<tr>
<td>17-alpha methyl testosterone</td>
<td><img src="image" alt="17-alpha Methyl Testosterone Structure" /></td>
<td>17-alpha alkyl substitutions render the molecule resistant to presystemic metabolism and render it possible to administer these compounds orally.</td>
<td>Orally administered 17alpha-alkylated androgens are hepatotoxic.</td>
</tr>
<tr>
<td>Stanozolol</td>
<td><img src="image" alt="Stanozolol Structure" /></td>
<td>17-alpha methyl substitution renders the molecule resistant to presystemic metabolism and makes it orally active. A ring modifications prevent its aromatization.</td>
<td>This is also a commonly used AAS that can be taken orally or parenterally. When administered orally, it can be hepatotoxic.</td>
</tr>
<tr>
<td>7-alpha-methyl 19-nortestosterone</td>
<td><img src="image" alt="7-alpha Methyl 19-nortestosterone Structure" /></td>
<td>7-alpha alkyl substitutions increase anabolic activity.</td>
<td>Because of its high anabolic to androgenic activity ratio, and relative sparing of the prostate, it’s being explored for clinical use in replacement therapy and in male contraceptive regimens.</td>
</tr>
<tr>
<td>Oxandrolone</td>
<td><img src="image" alt="Oxandrolone Structure" /></td>
<td>17-alpha alkyl substitutions render the molecule resistant to presystemic metabolism and make it orally active. Because of A ring modification, it does not undergo aromatization.</td>
<td>This is an orally active compound used clinically as an anabolic drug. Because of 17-alpha alkyl substitution, it can be hepatotoxic.</td>
</tr>
</tbody>
</table>
curve to the left, thereby facilitating oxygen unloading from oxyhemoglobin (HbO₂) (106–108). The observations that testosterone improves neuromuscular transmission and upregulates acetyl cholinesterase expression in the frog hind limb model (109, 110) have led to speculation that testosterone may reduce reaction time, which may contribute to improved performance in sprint events or in sports requiring a high level of hand-eye coordination, such as baseball.

Testosterone administration may also affect mood and motivation, which may indirectly affect athletic performance.

2. Adverse effects

Adverse effects of AASs on several organ systems have begun to emerge. Of particular concern are cardiovascular effects, hematologic effects, psychiatric and neuropsychologic effects, and hormonal and metabolic effects (Table 1). There are also a variety of apparently less frequent effects on various other bodily tissues.

a. Cardiovascular effects. For decades, individual case reports or small case series have described a variety of cardiovascular effects, including cardiomyopathy (111–116), myocardial infarction (117–127), cerebrovascular accidents (128–130), conduction abnormalities (131–134), and coagulation abnormalities (121, 135–139), in known or suspected AAS users. Several recent reviews have summarized these reports (115, 140–144). More recently, larger controlled studies, using a variety of methodologies, have supported these findings. In a recent postmortem pathologic study, comparing 87 deceased men testing positive for AAS with 173 control men (145), AAS users exhibited significantly greater cardiac mass even after adjusting for body mass, age, and history of trauma. Another pathologic study (146) found ventricular hypertrophy, associated with fibrosis and myocytolysis, after cardiac death in 4 AAS users. Recent conduction studies have demonstrated decreased cardiac electrical stability (147), abnormal tonic cardiac autonomic regulation (148), and ventricular repolarization abnormalities in AAS users (149); the last finding has also been demonstrated in rats that received AAS (150). Perhaps most importantly, numerous recent controlled studies (using echocardiography [140, 151–157] or cardiac magnetic resonance imaging [158] to compare AAS users with non-AAS-using athletes and/or nonathletes) have demonstrated cardiomyopathy in AAS users, characterized by decreased ventricular ejection fractions and reduced diastolic tissue velocities. One study also found decreased aortic elasticity in AAS users (159). These changes may be profound but may be at least partially reversible after AAS abstinence (160). However, loss of tissue elasticity appears likely due at least in part to increased fibrotic content resulting from direct AAS-induced cellular injury (146, 161) and hence may be irreversible.

In addition to their direct effects on cardiac tissue, AAS cause dyslipidemia, characterized by decreased high-den-
sity lipoprotein cholesterol (HDL-C) and increased low-density lipoprotein cholesterol (LDL-C)—an established risk profile for atherosclerotic disease (162, 163). This effect is particularly associated with orally administered 17α-alkylated AAS (162, 164, 165). One imaging study of 14 professional weightlifters with long-term AAS exposure found coronary-artery calcium scores much higher than expected for men of comparable age (166). Atherosclerotic coronary disease may contribute to many of the cases of myocardial or cerebral infarction reported in young men with known or suspected AAS use (141, 143, 162, 167).

b. Psychiatric effects in humans. Numerous field studies have described psychiatric symptoms associated with illicit AAS use, including major mood disorders (87, 168–170). These psychological studies have included interview studies assessing psychiatric history in AAS users, on-drug vs off-drug (51, 171–173); comparisons of AAS users vs non-users using interviews or psychological rating scales (47, 51, 174–180); and/or longitudinal assessments of AAS users over intervals of AAS use vs intervals of nonexposure (181–185). In general, these field studies have suggested that some AAS users exhibit hypomanic or manic symptoms during AAS exposure (characterized by irritability, aggressiveness, exaggerated self-confidence, hyperactivity, reckless behavior, and occasional psychotic symptoms) and depressive symptoms during AAS withdrawal (characterized by depressed mood, loss of interest in usual activities, hypersomnia, anorexia, loss of libido, and occasional suicidality). However, these psychiatric effects appear to be idiosyncratic, with a majority of users displaying few such symptoms and only a small minority showing severe or disabling symptoms. Tentative evidence suggests that mood disorders are more common in individuals using higher doses of AAS, especially at levels equivalent to more than 1000 mg of testosterone per week (168, 186). However, there are no clear predictors of AAS-induced psychiatric effects, and it appears that there are wide variations in individual sensitivity to both androgen excess (187, 188) and androgen withdrawal or deprivation (189, 190). Certainly, psychosocial factors account for many of the differences in psychiatric vulnerability observed among AAS users (191–194). However, these factors alone cannot fully explain the variation among AAS users, because a similar variation has been observed with blinded administration of supraphysiologic doses of AAS to normal volunteers (87, 195) and also in the behavior of laboratory animals that were given AAS (196–198).

Occasional field observations have also documented strikingly aggressive or violent behavior in some AAS users who had no history of such behaviors. These have included cases of previously normal individuals committing murder or attempted murder (181, 199–201) or displaying other uncharacteristically aggressive behavior while using AASs (169, 202–204). Although the causal relationships between AAS use and aggressive behaviors may vary, and AASs are not necessarily the proximal trigger to violence (205–210), the phenomenon of AAS-induced aggression is sufficiently established that it likely meets the American Daubert standard for admissibility as legal testimony (179) (ie, it may be regarded by the court as a phenomenon that is testable, subject to peer review and publication, and generally accepted in the relevant scientific community).

Although our discussion has involved primarily field studies of illicit AAS users, some controlled laboratory studies have also examined the psychiatric effects of AAS. However, a majority of these studies have used a maximum dose of only 300 mg of testosterone enanthate or equivalent per week (193, 211–216), a dose much lower than generally self-administered by illicit users, who typically use at least 500 mg per week (2, 49, 51, 168, 217) and often well over 1000 mg per week (2, 79, 168, 171, 172, 182, 185). Thus, it is inappropriate to use these low-dose laboratory studies to gauge the experience of illicit users. However, there have now been 4 additional laboratory studies that have assessed psychiatric symptoms in individuals receiving the equivalent of at least 500 mg of testosterone per week (95, 195, 218–220). Of 109 men treated under blinded conditions in these studies, 5 (4.6%) displayed hypomanic or manic syndromes on AAS vs none on placebo. These latter studies offer clear evidence for a biologically mediated psychiatric effect of supraphysiologic doses of AAS, although they still likely underestimate the prevalence of such effects among illicit users, who may ingest much higher doses. Also, in human subjects, studies have reported increased aggressive responsiveness to provocation (221).

c. Behavioral effects in preclinical models. Animal studies have provided important insights into the specific neurochemical changes and the mechanisms underlying the various behaviors associated with AAS use. Many of the central nervous system (CNS) effects and behaviors observed in humans in association with AAS use at high doses are related to brain circuits that function similarly in other mammalian species. Indeed, several studies carried out in animal models confirm that changes in defensive and offensive aggression, dominant behavior, anxiety, and sensitivity to other abused drugs often mimic what has been observed in human subjects abusing AASs. For example, AAS has been shown to increase the expression of opioid...
tolerance in mice (222). Although it is difficult to precisely scale androgen doses from rodents to humans, when adjusted according to body surface area using the U.S. Federal Drug Administration guidelines (223), the doses tested in animal studies (up to 7.5 mg/kg) appear to fall within the range of human AAS use.

The effect of AAS on aggressive behavior has been studied extensively in many laboratories. A recent article reviewing the impact of AAS exposure on brain circuits crucial for the expression of anxiety and aggressive behavior compared these effects in relation to different classes of AAS; the study examined potential signaling mechanisms as well as aspects of their action in relation to age and sex (224). The study revealed that these steroids induce profound effects on aggression as well as the signaling molecules and receptors in pathways related to aggression.

The administration of testosterone propionate has been shown to significantly increase aggressive behavior in cynomolgus monkeys (225); similar observations were later recorded in rodents. The type of aggression, which we record in our experimental animal models, is characterized as defensive aggression, measured by means of specific approaches to provoke the animals. Chronic exposure to testosterone has also been shown to increase male aggressive response patterns without altering the male sexual behavior or body weight (226). Additional studies have confirmed that high doses of AASs could elicit aggressive behavior in both rats and hamsters (82, 227–230). However, different steroids may exhibit different potency in this regard (231, 232). Furthermore, AASs can induce both offensive (229) and defensive behaviors (82, 228), and various strains of rats exhibited different responses to provocation (82, 228).

A variety of signaling pathways are involved in mediating the effects of AASs on aggressive behaviors observed in rodents. The brain pathways associated with aggression include neural circuits that use signaling by excitatory amino acid systems and monoaminergic and peptidergic neurotransmitters. The changes within each neurotransmitter system within different neural circuits are specific for the type of AAS used. The key brain regions involved in aggressive behavior include the anterior hypothalamus, periaqueductal gray, and amygdaloid nuclei (particularly the central and medial amygdala). For instance, a tachykinin (substance P) pathway originating in the central amygdala and innervating the hypothalamus and the periaqueductal gray is activated in rats chronically treated with supraphysiologic doses of AAS (233), whereas an enkephalinergic pathway was downregulated. All these events were consistent with increased sensitivity toward provocation (82, 233). AAS exert additional effects on the glutamate system, also known to be involved in aggressive behavior (230, 234).

Another amino acid of interest with respect to aggressive behavior is γ-aminobutyric acid (GABA). AASs elicit both acute modulation of GABA(A) receptor-mediated currents and chronic regulation of the expression of the GABA(A) receptor and forebrain GABAergic transmission (235).

The serotonergic system also may have an important function in the control of the aggressive dominance induced by AAS (236). The serotonergic 5-hydroxytryptamine (5HT), or 5HT₂ receptors may play a role in the mediation of emotional states and behavioral changes that we see among human AAS users (237).

A role of dopaminergic pathways in AAS-induced aggression has also been suggested. AAS exposure affects dopamine receptors in brain areas included in the functional anatomy of aggression (238, 239).

A typical feature seen in individuals taking steroids appears to be a competitive and dominant behavior. Studies have used experimental animal models to better understand the relationship between AAS use and competitive behavior under various conditions. For instance, researchers have studied competition and locomotor activity response to a sedative dose of ethanol after AAS exposure in rats (240). The rats treated with AAS exhibited enhanced dominant behavior in the competition test compared with controls. Ethanol did not affect the AAS groups’ locomotor activity, whereas the controls showed decreased locomotor activity. Also, AAS animals had significantly lower levels of serotonin in basal forebrain and dorsal striatum compared with controls. These results have led to the hypothesis that AAS use may constitute a risk factor for disinhibitory behavior, partly by affecting the serotonergic system. An additional study on dominant behavior assessed pair-housed male rats for dominance status based on their behavior and alterations in body weights (228). Throughout the study, the rats had limited social interactions on a daily basis. After 1 week, rats received nandrolone or placebo, and their behavior was observed over 2 months. Dominant AAS-treated rats spent more time on highly aggressive behaviors than the dominant placebo-treated rats. In addition, the probability for highly aggressive behaviors was maintained for the AAS-treated rats throughout the study, whereas it was decreased for the placebo-treated rats. These observations are similar to the relatively long-term behavioral changes we see in humans after AAS use.

d. Dependence in humans. As noted above, it appears that about 30% of AAS users may develop AAS dependence, which in some instances may be part of a larger pattern of

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dependence on PEDs, involving additional agents such as hGH and CNS stimulants (14, 86).

Unlike most dependence-inducing drugs, which typically deliver an immediate reward of intoxication, AASs produce few intoxicating effects and are instead taken primarily for the delayed reward of increased muscle mass and decreased body fat. Despite these differences, AAS dependence may nevertheless become a chronic and potentially dangerous disorder. One group has suggested that AAS dependence may develop via any or all of 3 different pathways, namely a body image pathway, a neuroendocrine pathway, and a hedonic pathway (241).

The body image pathway refers to the observation that many individuals initiate AAS use because they exhibit symptoms of muscle dysmorphia, a form of body dysmorphic disorder where individuals develop severe preoccupations that they are not adequately muscular (242–246).

Muscle dysmorphia appears closely associated with AAS use (247–252). Individuals with such concerns often become extremely anxious if they stop AAS use and lose even a little muscular size (45, 80, 241). Thus, they often quickly resume AAS, which contributes to the AAS dependence syndrome.

Neuroendocrine factors also contribute to AAS dependence (253). Because exogenous AAS suppresses hypothalamic-pituitary-testicular (HPT) function (254), users will gradually develop suppressed testosterone levels and may become hypogonadal upon discontinuation of AAS use. Although illicit AAS users employ various techniques to minimize hypogonadism associated with AAS withdrawal (eg, self-administration of clomiphene and/or human chorionic gonadotropin at the end of a cycle of AAS use) (255), many will display profound hypogonadism for weeks or months after discontinuing use. The associated symptoms of fatigue, loss of libido, and depression may prompt some users to quickly resume using AAS to treat these dysphoric symptoms.

e. Dependence in preclinical models. Finally, animal studies have provided strong support for a third, hedonic pathway to AAS dependence, likely mediated by nongenomic pathways via membrane receptors rather than by the classical genomic effects of AASs. Reports that AAS abusers often experience mental effects within 15 to 20 minutes of AAS administration also favor the nongenomic effects through membrane receptors rather than the classical androgen receptor-mediated genomic effects. In fact, studies have reported steroid binding sites on both GABA and the N-methyl-D-aspartate neurons (256). Studies have also reported interaction of AAS with GABA receptors (257). The function of these receptors remains poorly understood, although there is some overlap with the opioid system (257, 258). These sites are recognized by neurosteroids produced endogenously in the brain. AAS also may interact with enzymes involved in neurosteroid metabolism, thereby modulating the action of these neurosteroids, which are known to produce effects on various behaviors (256, 259).

Rats and mice display conditioned place preference to testosterone (260–262), and male hamsters will self-administer testosterone to the point of death (263). AASs enhance β-endorphin in the ventral tegmental area and may thereby activate the brain reward system. Interestingly, the opioid antagonist naltrexone can block testosterone self-administration in hamsters (263). These observations, combined with others, suggest that opioidergic mechanisms may be involved in the hedonic pathway to AAS dependence (157, 263).

f. Neurotoxicity. Recent evidence suggests that supraphysiologic levels of testosterone and other AASs exhibit apoptotic effects in a variety of cell types (161, 264–269), including human neuronal cells (270). Two subsequent studies have now also demonstrated neurotoxic effects of supraphysiologic AAS in mammalian neuronal cells (271, 272). A recent animal study found spatial memory deficits, as assessed by the Morris water maze, in rats after supraphysiologic AAS exposure (273). Collectively, these findings raise the ominous possibility that long-term users of high-dose AAS might develop potentially irreversible cognitive deficits (270, 271). In a pilot study exploring this possibility among 31 AAS user and 13 nonuser weightlifters, one group of investigators found significant deficits in visuospatial memory among AAS users as opposed to nonusers; and within the AAS-users group, these deficits were significantly associated with a total lifetime burden of AAS exposure (79). Thus, the possibility of AAS-induced neurotoxicity clearly demands further study.

g. Neuroendocrine effects. As mentioned above, AASs suppress HPT function (254, 274). When individuals stop taking AASs after a lengthy course of use (ie, several months or longer), HPT activity may be suppressed for months (275), or years (276, 277); and some individuals may never regain normal testosterone levels. Furthermore, AAS may also produce direct toxic effects on the testis (278), which may be irreversible, so that some AAS users will continue to display primary hypogonadism even after hypothalamic and pituitary functions have returned to normal (279). Several case reports have described successful treatment of AAS-induced hypogonadism with clomiphene (280, 281), human chorionic gonadotropin (277), and/or human menopausal gonadotropin (277). However, case reports also have described failure with these
interventions (279, 282). To date, we are not aware of any systematic treatment studies in AAS-induced hypogonadism. The suppression of pituitary LH and FSH secretion by AAS can be associated with suppression of spermatogenesis and infertility in men and menstrual irregularity and infertility in women.

b. Infectious complications. In addition to the direct adverse effects of AAS, illicit users are vulnerable to infectious complications associated with use of contaminated needles, contaminated products obtained on the black market, or other risks associated with weightlifting and AAS use. Although needle-sharing appears uncommon in modern American AAS users (91, 217, 283), one recent Internet survey found that 65 of 500 AAS users (13%) reported unsafe needle practices, including needle sharing, needle reuse, and sharing of multiple-dose vials. Moreover, respondents to Internet surveys are likely better educated and more affluent than the population of AAS users as a whole (39, 87), so that Internet surveys likely underestimate the prevalence of unsafe practices in the global population of AAS users. Thus, it is not surprising that the literature has documented various infectious complications of AAS use, including the blood-borne pathogens, HIV, hepatitis B, and hepatitis C, as well as skin and soft tissue infections, most notably due to community-acquired methicillin-resistant Staphylococcus aureus (MRSA). The first report of HIV infection in an AAS user surfaced nearly 30 years ago (284), and subsequent reports in both the United States (285) and Europe (286) have documented additional cases. AAS users have also contracted hepatitis B and C (92, 287). The greatest risk for transmission of HIV and other diseases in AAS users appears to arise from needle sharing and other unsafe needle practices (90, 288). This is likely because of the frequent use of injectable preparations, such as testosterone and nandrolone, among long-term illicit AAS users.

However, unsafe needle practices represent only one possible risk factor for HIV and other infections in AAS users. For example, a study of homosexual men in London gyms found that current AAS users were significantly more likely than never-users to report unprotected anal intercourse with partners of unknown serostatus, even in analyses adjusting for potential confounders (289). Given that AASs are widely used by homosexual men, both illicitly (93) and as prescribed treatments for the wasting syndrome associated with HIV infection (290), there is a clear opportunity for the spread of HIV both through needles and sexual practices. AAS users are also likely to have spent time in prison (1, 201, 209, 210, 291, 292), and prisoners, in turn, are well-documented to display an elevated risk for hepatitis and HIV (293–297).

Studies have linked community-acquired MRSA colonization and soft tissue infection with competitive sports participants (298). Additional research has linked injection of drugs with community-acquired MRSA infection (299). Studies have also reported soft tissue abscesses related to anabolic-steroid injections (300, 301).

i. Effects on other organ systems. AAS use is associated with dose-related increases in hemoglobin and hematocrit, and polycythemia is a frequent adverse event of AAS use (106, 302–306). Androgens stimulate erythropoiesis by increasing sensitivity to erythropoietin, suppressing hepcidin transcription, and increasing iron availability for erythropoiesis (304–306).

Muscular AAS users engaged in heavy weightlifting can display rhabdomyolysis (307), sometimes with massive elevations of serum creatine kinase levels (308–311), leading to myoglobinemia, myoglobinuria, elevated creatinine levels, decreased glomerular filtration rate (312), and the occasional progression to acute renal failure (51, 308). Notably, one recent case series has documented 10 cases of focal segmental glomerulosclerosis among frequent AAS users (313).

AASs may occasionally cause hepatotoxicity, with consequences including peliosis hepatis (an accumulation of blood-filled cysts in the liver) (314–316), and various types of hepatic tumors (316–322). Virtually all AAS-associated hepatotoxic effects are associated with orally active 17α-alkylated AASs (321, 323–325). The frequency of AAS-induced hepatotoxicity is likely overestimated, however, because rhabdomyolysis from heavy workouts can increase transaminases (307, 326), and this finding may be erroneously interpreted as evidence of abnormal liver function (327).

AASs may cause adverse musculoskeletal effects (328, 329), especially tendon rupture (329–337), attributable both to the disproportionate strength of hypertrophied muscles (338) and to possible deleterious effects of AAS on the architecture of the tendons themselves (339–341). AASs may affect the immune system (342), the lungs (343), and possibly other organ systems (18) and might cause acne (344), although knowledge in these areas remains limited. Notably, there is little evidence of an association between AAS use and cancer, with the exception of rare reports of hepatic cancers (322), intratesticular leiomyosarcoma (345), and renal cell carcinoma (346, 347). Conspicuous by their absence are reports of prostate cancer in AAS users. To date, there is no clear evidence that androgen administration causes prostate cancer; we are aware of only 2 case reports of prostate cancer in bodybuilders, both published more than 20 years ago (348, 349). However, the possibility remains that high doses of
AAS administered during the peripubertal period may exert long-term epigenetic effects and may increase the risk of prostate-related events later in life. Given that older AAS users (who started AAS use in their peripubertal years in the 1980s) are just now entering the fifth decade of their life, we may have more evidence regarding AAS use and prostate cancer in the coming years.

3. Detection

Given the mounting evidence of adverse effects related to PED use, there is strong justification for the need to improve methods for detecting illicit PED use and eliminating abuse by both athletes and nonathletes, despite occasional arguments by some authors that PEDs be explicitly allowed in athletic competitions (350–352).

Some of the adverse effects seen in patients who use AASs may include infertility, gynecomastia, sexual dysfunction, hair loss, acne, muscular appearance, and testicular atrophy. Some indicators that might suggest AAS use are increased hemoglobin and hematocrit; suppressed LH, FSH, and testosterone levels; low high-density lipoprotein cholesterol, and low sperm density. Mass spectrometry-based tests (available in many commercial laboratories) can detect AASs in urine. Testosterone abuse is more difficult to detect, but high testosterone, in association with suppressed LH and FSH levels, should raise suspicion of testosterone abuse. A T/E ratio of more than 4 can confirm testosterone abuse, although it is rarely necessary to check testosterone levels in the clinical setting. Often direct questioning will result in an admission by a patient that he or she is using AASs.

In 1982, Donike and coworkers (353) first reported a method for detecting testosterone abuse. They based their method on the fact that exogenously administered testosterone is predominantly excreted in the urine as the glucuronide conjugate. By determining the T/E ratio, they eliminated the influence of urine density variations. The mode of the population distribution of T/E ratios is about 1:1, and early research suggested that ratios above 6:1 were linked to doping. WADA has decreased the ratio of more than 3%. The use of the CIR in conjunction with the steroid profile results can provide a definitive answer about whether the athlete used a pharmaceutical testosterone product or not.

A test based on gas chromatography/combustion/isotope ratio mass spectrometry can detect the difference in $^{13}$C/$^{12}$C ratios (CIRs) in endogenous and exogenous testosterone (360). The CIRs for androsterone, etiocholanolone, 5α- and 5β-androstanediol, and testosterone are documented. As an internal reference, tests use an endogenous steroid either upstream of the steroid of interest or from another steroid pathway, such as pregnanediol. The difference between the CIRs of the 2 steroids should be less than 3%. The use of the CIR in conjunction with the steroid profile results can provide a definitive answer about whether the athlete used a pharmaceutical testosterone product or not.

The detection of synthetic anabolic steroids by gas chromatography/mass spectrometry began in the mid 1980s (361–363). Use of either magnetic sector or orbitrap mass spectrometers in the high mass resolution mode significantly decreased limits of detection and lengthened the detection window (364). The emergence of liquid chromatography/tandem mass spectrometry as a routine testing tool has allowed researchers to analyze a number of additional compounds, such as stanozolol (365), tetrahydrogestrinone (35), and clenbuterol (366), with much greater sensitivity.

B. Human GH

Human GH is a metabolic hormone in adults with fused epiphyses of the long bones. Those with hGH deficiency experience a loss of its anabolic and lipolytic activities, which is characterized by decreased lean body mass and increased fat mass with abdominal obesity, loss of bone mineral density, diminution of muscle strength and aerobic capacity (maximal oxygen uptake [$\text{VO}_{2\text{max}}$]), and reduced physical performance and quality of life, usually noted as diminished well-being. Most of these findings of hGH deficiency are reversed by recombinant hGH (rhGH) replacement, although restoration may take months to a few years and might not be complete (367). In addition to rhGH, GH-releasing peptides, ghrelin mimetics, and other growth factors are now available on the Internet, although we do not have data on the prevalence of their use.

1. Clinical pharmacology

The GH gene cluster on chromosome 17q24.2 contains 5 GH-related genes consisting of 2 GH genes (GH-N and GH-V) and 3 related choric gonadotropin (2B17) (the major enzyme for testosterone glucuronidation) with significantly lower T/E ratios (357). Because of the high frequency of this polymorphism among East Asian populations, the likelihood of a false-negative test is higher in these populations than in Caucasian populations. Additionally, studies have shown variations in UGT2B17 copy number, which may affect T/E ratios among populations from Africa, Europe, and East Asia (358, 359).

Studies have linked deletion polymorphisms of uridine diphospho-glucurosyl transferase 2B17 (UGT2B17) (the major enzyme for testosterone glucuronidation) with significantly lower T/E ratios (357). Because of the high frequency of this polymorphism among East Asian populations, the likelihood of a false-negative test is higher in these populations than in Caucasian populations. Additionally, studies have shown variations in UGT2B17 copy number, which may affect T/E ratios among populations from Africa, Europe, and East Asia (358, 359).

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genes, also known as placental lactogen genes (368). The pituitary GH-secreting cells express the GH-N gene, whereas the placenta expresses GH-V and chorionic somatomammotropin genes (368). The rhGH produced for therapeutic purpose is a 191-amino-acid, 22 129 molecular weight, single-chain polypeptide, which is similar to the product of the native GH-N gene, which makes detection of GH doping challenging (356, 369). The predominant circulating form of GH secreted by the pituitary is the 22K form often referred to as the 22K-GH (368). Alternate splicing of the GH-N gene yields another GH isoform, the 20K-GH variant, whose structure is similar to that of the 22K-GH except for the deletion of the residues 32 to 46. Additionally, studies have described several post-translationally modified monomeric GH isoforms and oligomeric series of at least up to pentameric GH (355, 360).

Thus, in healthy adults, circulating endogenously produced GH exists in multiple isoforms, including 22K, 20K, and other oligomeric and acidic GH isoforms; this heterogeneity of isoforms distinguishes endogenous GH production from exogenously derived GH, which yields only a single 22K isoform (368, 369).

In GH-deficient adults, replacement therapy with rhGH improves fat and protein metabolism, leading to a partial reversal of these abnormalities but not complete restoration to normal (367). The metabolic actions of hGH also interact with those of insulin (and perhaps IGF-1) to control fat. hGH enhances lipolysis and fatty acid oxidation as well as carbohydrate and protein metabolism during both the fasted and fed states. In the fasted state, GH secretion increases and it partitions metabolic fuels from fat by stimulating lipolysis and fatty acid oxidation to provide energy to protect from catabolism. At the whole-body level, GH suppresses glucose oxidation and utilization while at the same time enhancing hepatic glucose oxidation. GH also antagonizes insulin action, promotes protein anabolism and the acquisition of lean body mass, and reduces urea synthesis, blood urea concentration, and urinary urea excretion. In adults with GH deficiency, rhGH replacement restores muscle strength toward normal over several years, but even after 3 years, the muscle strength in these persons is well below that of healthy controls. Impaired exercise capacity in GH-deficient individuals, as measured by the VO2max method, increased virtually to the level in healthy controls after rhGH replacement.

In healthy adults, hGH regulates all of the activities mentioned above (protein anabolic effects), spares protein oxidation, increases lean body mass (extracellular water and body cell mass), and decreases fat mass (367). Despite these changes in body composition, there is little evidence that hGH in supraphysiologic doses affects physical performance (368, 370, 371). A systematic review of randomized trials concluded that although GH increases lean body mass, it may not improve strength (370). The systematic review seemed to indicate that hGH may in fact decrease exercise capacity and may be associated with adverse events (370). Birzniece and colleagues (372) summarized the data, noting that the scientific literature does not support claims that hGH administration enhances physical performance, but there is some evidence regarding the effects of hGH on some athletic performance outcomes, such as anaerobic capacity. Only a few studies have shown positive effects on athletic performance (373–375). The first was a study of abstinent anabolic steroid-dependent competitive athletes who were likely in a mild catabolic state (373). The second was a study of recreational athletes who received a combination of a modest dose of rhGH and moderately supraphysiologic doses of testosterone in a controlled trial (374). This study showed that rhGH administration was associated with improvement in sprint capacity in those receiving the combination of drugs, but the increases in sprint capacity were not sustained 6 weeks after discontinuation of the drug (374). Although results might show only a small decrease in time to complete the sprint event, these seemingly minor differences may be crucial in elite athletic competitions. The anabolic effects observed with the doses of rhGH use in randomized trials may not fully reflect those that might be associated with the massive doses and combinations used in the real world. Furthermore, PED users typically take cocktails of PEDs often in high doses, and thus few statements can be made implicating the effect of one or another pure agent, especially at low doses. However, the lack of experimental evidence does not necessarily diminish the allure of hGH for athletes. The expectation that supraphysiologic levels of hGH (or IGF-1) might increase an individual’s athletic performance is enough to encourage use. Even if the administration of rhGH does not increase athletic performance, some elite athletes may take it to purportedly recover more rapidly (eg, from soft tissue damage) and allow for more vigorous training.

2. Adverse effects

There are no systematic studies of the adverse effects of GH use. Therefore, most of the information is anecdotal, and these reports are often confounded by concurrent use of other PEDs, especially AASs. The likely adverse effects include edema, excessive sweating, myalgias and arthralgias, carpal tunnel syndrome, and diabetes (Table 2). Much of the information about potential adverse effects of rhGH use in supraphysiologic doses has been inferred from the studies of patients with acromegaly, a disease of excessive GH production with elevated GH levels at all
from normal subjects for a period of at least 7 to 10 days. We can measure the concentration of IGF-1 by immunoassay and, more recently, by liquid chromatography tandem mass spectrometry. The P-III-NP is measured by immunoassay and can stay elevated for several weeks even after discontinuation of rhGH use (385).

C. Insulin

Insulin is purportedly a PED, but most information on illicit insulin use is anecdotal. Athletes and nonathletes often use it after heavy workouts to enhance recovery. It is popular because it is cheap and available. The ingestion of glucose is vital to this type of doping, given the glucose-lowering action of insulin, especially in those with normal tissue insulin sensitivity. The rationale of injecting insulin as a PED relates to its mediation of increases in the transport of glucose and amino acids into skeletal muscle and its effects on muscle fibers. By infusing insulin along with stable isotopes of glucose and amino acids into human muscle (quadriceps), Biolo and coworkers (386) were able to demonstrate an approximately 70% increase in the fractional synthetic rate of muscle protein. They also reported a decrease in the concentrations of the essential amino acids, implicating incorporation into the muscle fiber. There was little effect on protein breakdown. The investigators concluded that insulin promoted muscle anabolism primarily by stimulating protein synthesis independently of any effect on the transmembrane transport of glucose or amino acids.

Insulin use also accelerates lipogenesis, inhibiting the release of free fatty acids (a muscle fuel); this is especially significant for endurance athletes. However, athletes can gain additional weight (adipose tissue as well), which could be detrimental to performance in many sports, especially those separated into weight classes.

D. Erythropoiesis-stimulating agents

1. Clinical pharmacology

a. Erythropoietins. Erythropoietin is a glycoprotein hormone that regulates red cell production. It is produced by the peritubular interstitial fibroblasts of the kidney and the perisinusoidal cells in the liver. In adults, the kidneys are the dominant source of circulating erythropoietin, although the liver is an important contributor to erythropoietin production in the fetal and perinatal period.

Erythropoietin stimulates erythropoiesis by binding to specific receptors on the surface of red cell progenitors, activating the Janus kinase 2 signaling pathway, and promoting the survival of these progenitors. Erythropoietin receptors are expressed maximally on colony-forming units (erythroid [CFU-E] cells) and regulate further dif-
ferentiation of these cells. The burst-forming units (erythroidine [BFU-E]), proerythroblasts, and basophilic erythroblasts also express erythropoietin receptors. In addition to its effects on erythropoiesis, erythropoietin also plays a role in wound healing, angiogenesis, and the brain’s response to hypoxic injury.

Recombinant erythropoietins are effective in treating anemia associated with chronic kidney disease, myelodysplasia, cancer, and chemotherapy. ESAs include the recombinant erythropoietins and other agents that stimulate erythropoiesis.

ESA use is most prevalent in endurance sports, such as distance running, cycling, race-walking, cross-country skiing, biathlons, and triathlons (387). ESAs increase net oxygen delivery to the muscle by increasing red cell mass (VO2max) and thereby improving endurance. ESA use in cycling started around 1990 and became widespread by 1998. A number of elite cyclists in the Tour de France, including Floyd Landis and Lance Armstrong, have admitted to using PEDs including erythropoietin. A number of antidoping activists, Greg LeMond, Sandro Donati, etc, have documented the widespread use of ESAs in professional cycling.

2. Adverse effects

Erythropoietins increase red cell mass and plasma viscosity and thereby augment the risk of thrombosis, cardiovascular events, and stroke (Table 3). Although there has been considerable media speculation that erythropoietin could have been implicated in the deaths of as many as 18 European professional bicycle racers between 1987 and 1991, there is no forensic documentation from verifiable sources substantiating this claim (388, 389). Meta-analyses of randomized trials in patients with cancer and in those with end-stage renal disease have revealed an increased risk of mortality, thromboembolic events, cardiovascular events (including myocardial infarction and stroke), and hypertension.

3. Detection

Since the 2000 Olympics, WADA has used a combination of biochemical and hematologic tests to detect recombinant erythropoietin. The biochemical tests on urine are based on the differences in the electrophoretic mobility of recombinant erythropoietin and endogenous human erythropoietin, reflecting differences in glycosylation patterns and the isoelectric point. An isoelectric focusing method separates the isoforms of erythropoietin, which are detected using double immunoblotting chemiluminescence (390, 391). The test is quite sensitive and can detect about 10 pg/mL of erythropoietin in the urine. The isoelectric point for each erythropoietin isoform is determined by the presence of charged groups on the carbohydrate moieties. The carbohydrate of recombinant erythropoietin, expressed from Chinese hamster ovary or baby hamster kidney cells, is different from that expressed in human kidney cells (392).

Reichel et al (393) has reported a n SDS-PAGE method for detecting erythropoietin that also uses double immunoblotting chemiluminescence. The method separates the erythropoietin glycoforms on the basis of their hydrodynamic volume. Chemiluminescence produces a single broad band; the position of the band is relatively sensitive to the carbohydrate content of the erythropoietin (392).

Recent studies have reported that a membrane-assisted isoform immunoassay test has excellent sensitivity (394, 395). Because this test is performed on a membrane support, we can use either antibodies or lectins that separate various glycoforms in conjunction with the immune detection to assess whether the erythropoietin is native or recombinant.

However, the test may be negative if the sample is collected after 3 or 4 days of erythropoietin use, especially after administration of low doses. New models that also incorporate the measurement of hemoglobin, erythropoietin levels, and soluble transferrin receptor levels provide greater sensitivity, especially in users who may have taken small or moderate doses of recombinant erythropoietin several days or weeks before the test. Direct detection of blood transfusions and ESAs (erythropoietin, novel erythropoiesis stimulating protein darbepoetin alpha, and continuous erythropoietin receptor activator) is often difficult. Therefore, there’s a growing trend toward monitoring biomarkers of erythropoiesis (hemoglobin, hematocrit, and reticulocytes) over time (for an individual athlete) and analyzing these data using analytical models to identify patterns suggestive of doping (396). This type of monitoring is referred to as the Athlete Biological Passport. With this information, athletes can either be sanctioned directly based on their profile or targeted with conventional doping tests. Both the International Cycling Union and other federations that have implemented the Passport to target athletes for the presence of ESAs have

| Table 3. Adverse Events Associated With Erythropoietin Usea |
|-----------------|-----------------|
| Adverse Event | Severity |
| Thromboembolic events | ++ |
| Increased risk of stroke | ++ |
| Increased risk of cardiovascular events | + |
| Hypertension | + |
| Increased risk of death | +++ |

Severity is scored as follows: +, mild to moderate; ++, potentially severe and life-threatening; ++++, very severe.
reported a reduction of blood doping among their athletes (397).

Studies are also exploring the excretion of plasticizers as indicators of autologous blood transfusion (398, 399).

VIII. The Interactive Effects of PEDs and Sports Injury

PEDs have potential not only for direct medical consequences but also for exacerbating other conditions. As previously stated, PEDs, especially when used in combination with other analgesics such as opiates and nonsteroidal anti-inflammatory drugs, may allow the athletes to engage in extremely intensive training exercises even in the face of previous injury, thus greatly increasing the risk of musculoskeletal injury.

Another concern relates to the possible interaction of AASs with CNS injuries, including traumatic brain injury and posttraumatic stress disorder. In recent years, clinical, scientific, and public attention has focused on the chronic neurologic and behavioral effects of head injuries in football players and soldiers (400). These may represent the accumulated effects of repeated mild head trauma (in football players) or the lasting response to blast exposure (in soldiers). Unfortunately, we lack substantial clinical or basic science evidence to address this issue. Although the armed forces monitor blast injuries, they do not routinely test troops for AAS use (401). Conversely, sports federations may test players for AAS but lack comparable data on concussive injuries.

Basic science has also largely overlooked the potential interaction of AASs and traumatic brain injury. For many neurologic conditions, estrogen is neuroprotective in females (402). This is particularly true for response to hypoxic-ischemic brain damage, as occurs with stroke. Whether testosterone at physiologic levels reduces or exacerbates neuronal injury in males remains unresolved (403). One emerging hypothesis is that endogenous androgens may be harmful during the acute phase of ischemic brain injury but can have beneficial effects during recovery. Even so, it is unclear how this may translate to the elevated levels of androgens characteristic of AAS use. Under these circumstances, the cellular targets and mechanisms of action may be substantially different from the effects at normal physiologic levels.

IX. Gene Doping

Gene doping refers to the use of nucleic acid sequences (delivered either as naked DNA or through viral vectors) and/or normal or genetically modified cells to enhance sports performance (385, 404, 405). Gene doping has not been detected in any sports event to date, although many experts have predicted that gene doping will become a reality in the near future (385, 404–408). Currently, it remains a theoretical but plausible threat in competitive sports, but because of its complexity and expense, gene doping is unlikely to be easily accessible to nonathlete weightlifters or to become a major public health problem in the near future.

The conceptual and technological framework of gene therapy in humans has largely been developed in hereditary diseases and some types of cancer (409, 410). The methods used to deliver genetic material include the naked DNA, viral vectors, and genetically modified stem cells. Viral vectors are the most frequently used approach for delivery of genetic material (385, 404–407). Applying antisense RNA sequences or inhibitory RNAs, blocking splicing recognition sequences, or using exon skipping can also modify gene expression. The approved gene therapies include alipogene tiparvovec for the treatment of lipoprotein lipase deficiency and recombinant human adeno-virus-p53 to inhibit cancer cell growth (409, 410). Gene therapy has also shown promise in SCID-X1, Leber’s congenital amaurosis, and some forms of muscular dystrophies. Despite its enormous promise, the progress in the gene therapy field has lagged substantially behind the early expectations because of technological and safety issues.

A number of genes have been considered as candidates for doping, including erythropoietin, IGF-1, hGH, follistatin, myostatin, androgen receptor, peroxisome proliferator-activated receptor-γ, α-actinin 3, cytosolic phospho-enolpyruvate carboxykinase, vascular endothelial growth factor, fibroblast growth factor, and endorphin and encephalin (385, 404, 405). In early trials in rhesus macaques, gene therapy with the erythropoietin gene was associated with the development of severe polycythemia, hyperviscosity, and autoimmunity (411–413). Subsequent studies have reported long-term regulated expression of erythropoietin in mice and macaques (411–413). Transgenic mice with lifelong hyperexpression of IGF-1 exhibit larger muscle mass but have substantially shortened lifespan (414, 415). Studies have explored a number of strategies to inhibit myostatin, including the expression of myostatin propeptide, which blocks myostatin action; the expression of follistatin, which inhibits the action of myostatin and other TGFβ family members; or the hyperexpression of a modified myostatin gene, which lacks a cleavage site in the myostatin protein, resulting in reduced production of active myostatin protein (416–419).

In addition to the methodologic problems that have limited the success of gene therapy to date (such as limited...
expression of the recombinant protein and gene silencing), many safety issues remain to be resolved (385, 404–408). These safety concerns include immune reactions to the vector proteins or to the recombinant protein itself; the viral vector integrating with host genome in an unpredictable manner; the viral vector integrating with tumor suppressor genes, which could increase the risk of cancers; the unregulated hyperexpression of the recombinant protein (eg, IGF-1), which could pose serious health problems, especially as users get older; and the genetic material transfecting the germ cells and transmitting to the offspring. Currently, there are no WADA-approved methods for the detection of gene doping. However, researchers are developing novel technologies to detect gene doping based on structural differences in the transgene or differences in the posttranslational modifications of the recombinant proteins (40, 421, 422).

X. Gaps in Our Knowledge

The long-term adverse consequences of PED use remain inadequately studied (Table 4). Uncontrolled studies, retrospective reviews, and case reports indicate that PED use is associated with serious health consequences including the increased risk of death as well as the risk of cardiovascular, psychiatric, metabolic, endocrine, neurologic, infectious, hepatic, renal, and musculoskeletal disorders. To date, no systematic prospective studies of the medical consequences of PED use exist. Widespread misperception that PEDs are safe or associated with manageable adverse effects has contributed to their growing use and to a substantial neglect of PED use as a serious public health problem. Therefore, long-term observational studies to determine the health risks associated with PED use are a public health imperative. Randomized trials would be both unethical and inappropriate for studying the adverse health effects of PEDs, because such trials cannot be ethically designed with safety as a primary endpoint. Furthermore, such hypothetical trials could not duplicate the highly supraphysiologic doses of PEDs or long durations of PED exposure experienced by illicit users, nor could such trials recreate the lifestyle factors and other high-risk behaviors associated with PED use. Thus, an observational study design, implemented by establishing a registry, may not only provide better evidence than randomized trials but may be the only feasible method of collecting scientifically meaningful and valid outcome data for this form of illicit substance use. There is an urgent need to establish such long-term prospective studies and registries.

PED use appears to be far more prevalent than is generally believed and is widespread among nonathletes. Therefore, epidemiologic surveys to determine the prevalence of PED use and the evolving patterns of PED use in the general adult population are an equally important priority.

Table 4. The Gaps in Our Knowledge and the Recommendations of the Panel

<table>
<thead>
<tr>
<th>Gaps in Our Knowledge: Unmet Need</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a lack of prospective, systematically gathered data on the long-term adverse health effects of PED use.</td>
<td>Establish prospective observational cohort studies (registries) to determine the long-term health effects of PED use.</td>
</tr>
<tr>
<td>There is a lack of reliable and current epidemiological data on the frequency of PED use among the general population.</td>
<td>Establish epidemiologic surveys to determine the prevalence of PED use in the general population. Perform human and animal studies to determine the mechanisms by which PEDs exert their adverse effects on the health of users.</td>
</tr>
<tr>
<td>The mechanisms by which PEDs exert their adverse health effects remain poorly understood.</td>
<td>Conduct randomized trials of various therapeutic strategies (such as estrogen receptor antagonists, aromatase inhibitors, or opiate antagonists) to treat AAS withdrawal syndrome and to treat the complications of PED use.</td>
</tr>
<tr>
<td>There are no randomized trials of therapies to treat or prevent the complications of PED use, especially strategies to treat AAS withdrawal syndrome, which is an important contributor to AAS dependence and continued use.</td>
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</table>
mitigate the AAS withdrawal syndrome and facilitate recovery of the HPT axis. Therefore, therapeutic trials to treat the AAS withdrawal syndrome are equally important.

We also need to further investigate the interactive effects of PEDs with sports injuries and other high-risk behaviors as well as innovative approaches to enhance public awareness of the serious health consequences of PEDs.

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