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

Harrison G. Pope, Jr. Ruth I. Wood, Alan Rogol, Fred Nyberg, Larry Bowers, and Shalender Bhasin

McLean Hospital (H.G.P.), Harvard Medical School, Belmont, Massachusetts 02478; University of Southern California (R.I.W.), Los Angeles, California 90089; University of Virginia (A.R.), Charlottesville, Virginia 22904; Department of Pharmaceutical Biosciences, (F.N.), Upsala University, SE-751 24, Upsala, Sweden; United States Anti-Doping Agency (L.B.), Colorado Springs, Colorado 80919; and Brigham and Women's Hospital (S.B.), Harvard Medical School, Boston, Massachusetts 02115

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 additional 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)**

I. Introduction
II. Definitions
III. The Process of Data Gathering and Synthesis
IV. Factors Contributing to the Limited Appreciation of the Adverse Effects of PEDs
V. A History of PED Use
VI. Epidemiology of PED Use
  A. Age of onset
  B. Prevalence of use
  C. The types and patterns of PED use
  D. Association of PED use with other high-risk behaviors
VII. Adverse Health Effects of PEDs
  A. Androgenic-anabolic steroids
  B. Human GH
  C. Insulin
  D. Erythropoiesis-stimulating agents
VIII. The Interactive Effects of Performance-enhancing Drugs and Sports Injury
IX. Gene Doping
X. Gaps in Our Knowledge

I. Introduction

The Endocrine Society's Scientific Statement Task Force (SSTF) deemed the medical consequences of performance-enhancing drug (PED) use an important topic for a

ISSN Print 0163-769X ISSN Online 1945-7189
Printed in U.S.A.
Copyright © 2014 by the Endocrine Society
Received June 27, 2013. Accepted December 9, 2013.
First Published Online December 17, 2013

Abbreviations: AAS, androgenic-anabolic steroid; CIR, $^{13}C/^{12}C$ ratio; CNS, central nervous system; ESA, erythropoiesis-stimulating agent; GABA, γ-aminobutyric acid; hGH, human GH; HPT, hypothalamic-pituitary-testicular; MRSA, methicillin-resistant *Staphylococcus aureus*; PED, performance-enhancing drug; P-III-NP, N-terminal propeptide of procollagen type III; rhGH, recombinant hGH; SARM, selective androgen receptor modulator; SSTF, Scientific Statement Task Force; T/E, testosterone to epitestosterone; VO_{2max}, maximal oxygen uptake; WADA, World Anti-Doping Agency.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 look leaner 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 corepressor proteins, 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 5 α-reductase enzyme (6, 7, 10, 11). These landmark discoveries have reinstated 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-

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

ment. 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 (eg, 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

Figure 1.

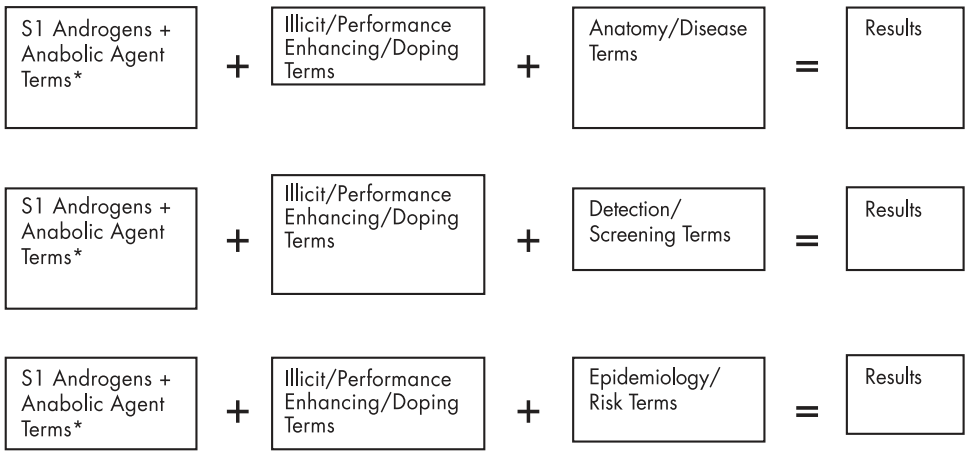


Figure 1. An example of the combined search sets researchers used for each category of PEDs.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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).

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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-norandrostenediol, 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.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

Figure 2.

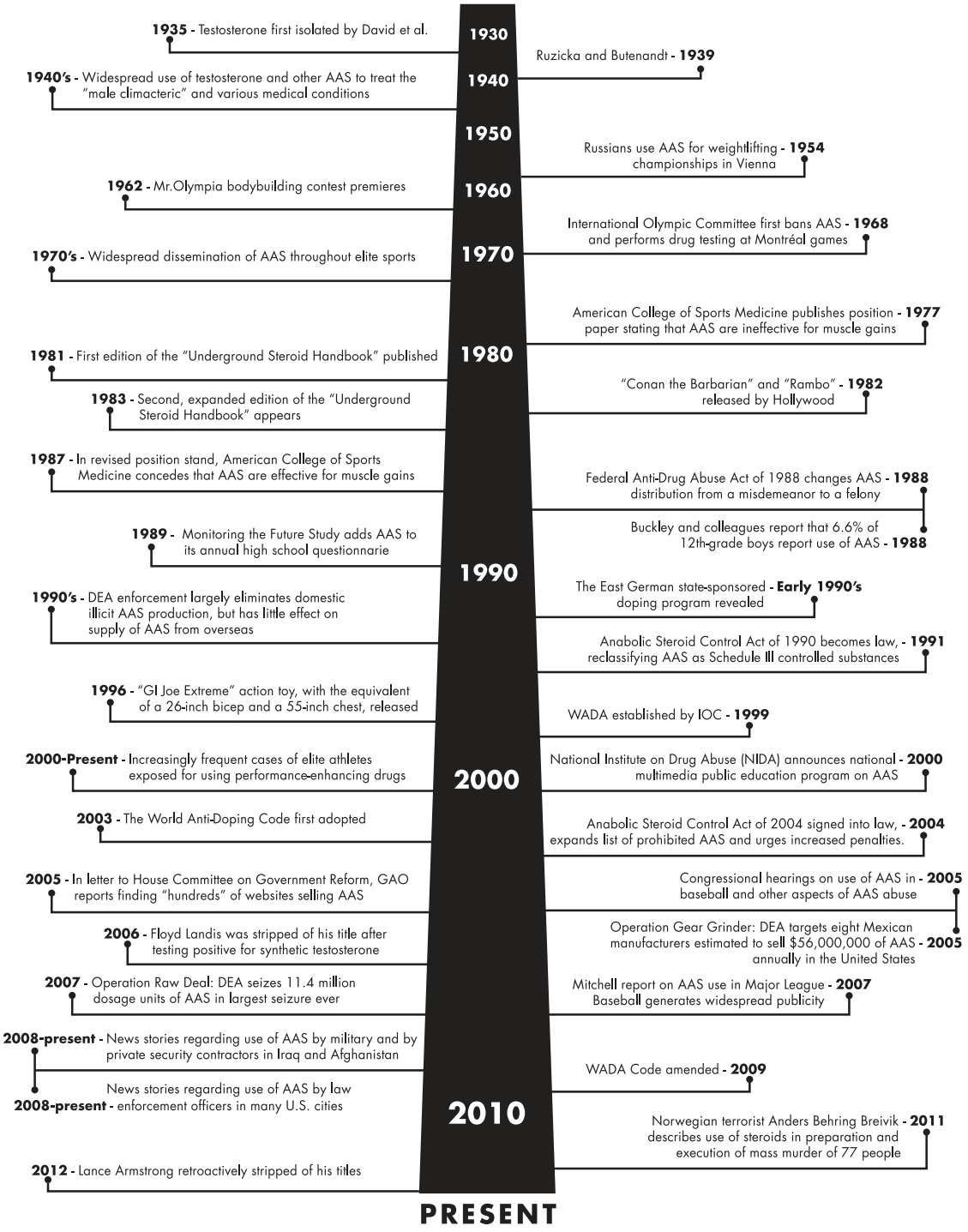


Figure 2. An historical timeline of the evolution of image- and PED use.

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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

Figure 3.

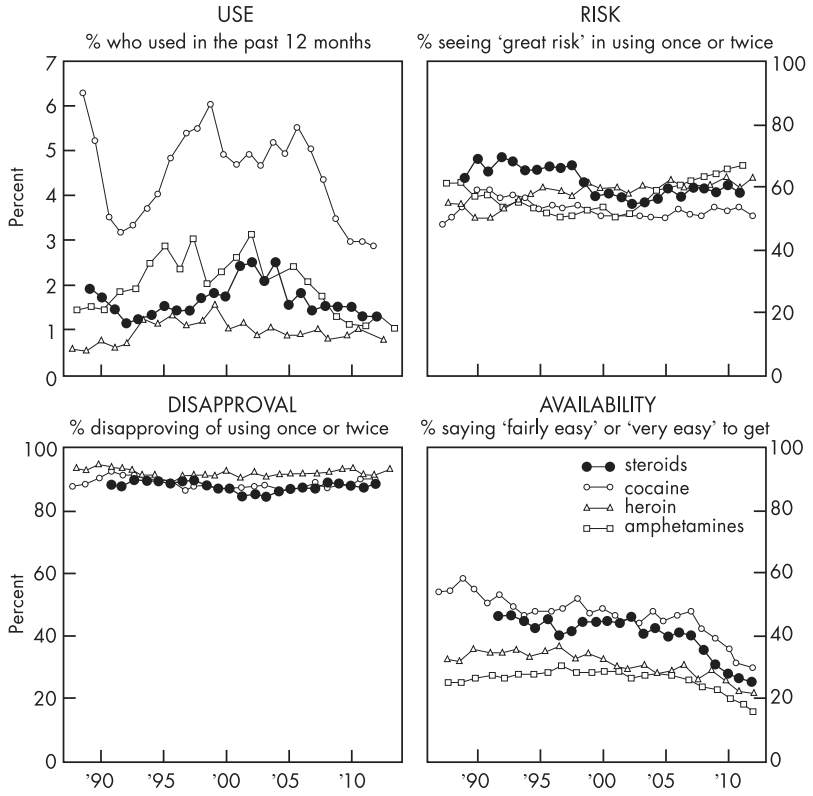


Figure 3. The estimates of the prevalence of AASs, cocaine, heroin, and amphetamine use among 12th-grade students from the Monitoring the Future study. The Monitoring the Future survey question states, "Steroids, or anabolic steroids, are sometimes prescribed by doctors to treat certain conditions. Some athletes, and others, have used them to try to increase muscle development. On how many occasions (if any) have you taken steroids on your own—that is, without a doctor telling you to take them?" The limitations of these data include the potential for false positives from a respondent's lack of understanding of the question as well as the potential underestimation of the problem because AAS users do not begin using steroids until they reach their early 20s.

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).

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 muscularity, 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 AASs 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 rewarding 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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

Figure 4.

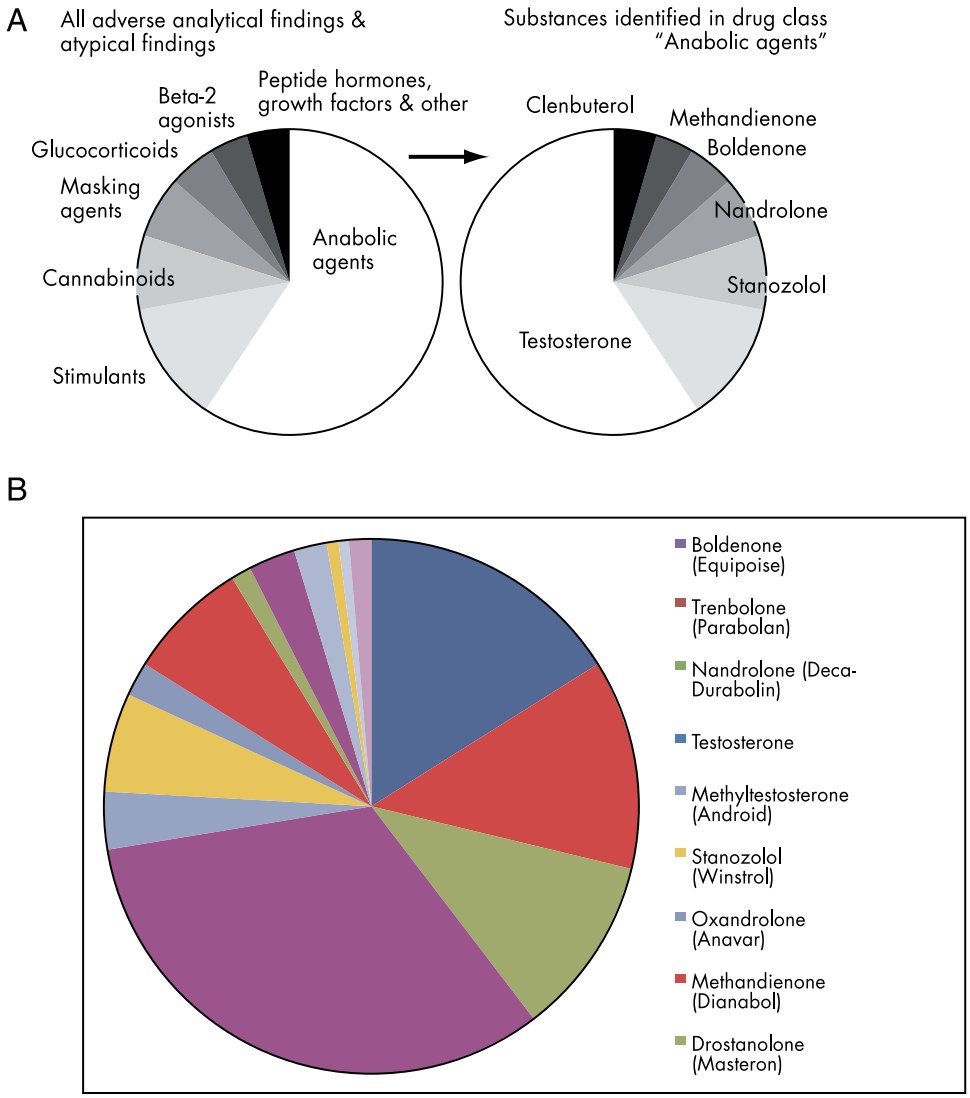


Figure 4. The types of PEDs used by competitive athletes based on the WADA's 2011 testing data (A) and by nonathlete weightlifters from a recently published study by Dr Pope (B). A, The types of PEDs used by competitive athletes based on WADA's 2011 testing data. B, The types of PEDs used by nonathlete weighlifters. Because WADA tests only athletes participating in certain competitive sports events, the data in A do not provide information about the frequency of use of various PEDs by nonathlete weightlifters. The distribution of AAS use by nonathlete weightlifters shown in B differs substantially from that among athletes tested by WADA in A. Although testosterone, stanazolol, and nandrolone were the AASs most frequently found in WADA's tests of athletes, testosterone, boldenone, trenbolone, and nandrolone were the AAS most frequently found in nonathlete weightlifters (19).

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-

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 training 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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

Figure 5.

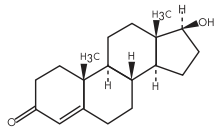
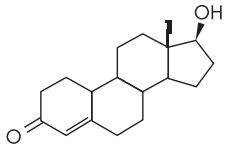
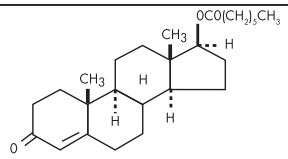
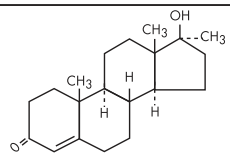
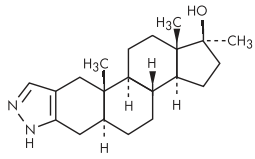
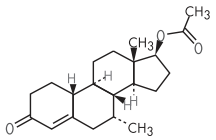
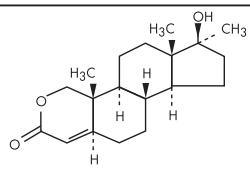
Molecule	Structure	Structural Features And Structure-Activity Relationship	Comments
Testosterone		A testosterone molecule is characterized by a 3-keto group, methyl groups in 19 and 21 positions, a 17-beta-hydroxyl group, and a double bond between carbons 4 and 5 in the A ring.	Testosterone and its esters are the AASs athletes and non-athlete weightlifters most widely use.
19-nortestosterone (Nandrolone)		The removal of the 19-methyl group increases the anabolic activity relative to androgenic activity.	Nandrolone is popular as a training drug, and accounts for a large number of positive tests.
Testosterone enanthate		Esterification of the17β-hydroxyl group renders the molecule more hydrophobic; its duration of action is extended when the molecule is injected in an oil suspension.	Testosterone esters, cypionate and enathate are used in therapy and also used widely by non-athlete weightlifters and athletes.
17-alpha methyl testosterone		17-alpha alkyl substitutions retard first-pass presystemic metabolism and render it possible to administer these compounds orally.	Orally administered 17-α-alkylated androgens are hepatotoxic.
Stanozolol		17-alpha methyl substitution renders the molecule resistant to presystemic metabolism and makes it orally active; A ring modifications prevent its aromatization.	This is also a commonly used AAS that can be taken orally or parenterally. When administered orally, it can be hepatotoxic.
7-alpha-methyl 19 nortestosterone		7-alpha alkyl substitutions increase anabolic activity.	Because of its high anabolic to androgenic activity ratio, and relative sparing of the prostate, it's being explored for clinical use in replacement theraphy and in male contraceptive regimens.
Oxandrolone		17-alpha alkyl substitutions retard first-pass presystemic metabolism and make it orally active. Because of A ring modification, it does not undergo aromatization.	This is an orally active compound used clinically as an anabolic drug. Because of 17-alpha alkyl substitution, it can be hepatotoxic.

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.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

curve to the left, thereby facilitating oxygen unloading from oxyhemoglobin (HbO_2) (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-

Table 1. Adverse Events Associated With Anabolic-Androgenic Steroid Use[a]

Organ System/Effect	Severity
Cardiovascular	
Dyslipidemia, atherosclerotic disease	++
Cardiomyopathy	++
Cardiac conduction abnormalities	+
Coagulation abnormalities	+
Polycythemia	+
Hypertension	+
Neuroendocrine (males)	
HPT suppression, hypogonadism from AAS withdrawal	++
Gynecomastia	+
Prostatic hypertrophy	+/−
Prostate cancer	+/−
Virilizing effects	
Neuroendocrine (females)	++
Neuropsychiatric	
Major mood disorders: mania, hypomania, depression	++
Aggression, violence	+
AAS dependence	++
Neuronal apoptosis, cognitive deficits	+/−
Hepatic	
Inflammatory and cholestatic effects	+
Peliosis hepatis (rare)	+
Neoplasms (rare)	+
Musculoskeletal	
Premature epiphyseal closure (in adolescents, rare)	+
Tendon rupture	+
Kidney	
Renal failure secondary to rhabdomyolysis	+
Focal segmental glomerulosclerosis	+
Neoplasms (rare)	+/−
Immune	+/−
Immunosuppressive effects	
Dermatologic	
Acne	+
Striae	+

[a] Severity is scored as follows: ++, well-recognized and probably of serious concern; +, well-recognized but either less common or causing less serious morbidity; +/−, possible risks whose relation to AAS use remains poorly understood.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 17-α-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 nonusers 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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 $(5HT)_{1B}$ or $5HT_2$ 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 seems to be a competitive and dominant behavior. Studies have used experimental animal models to better understand the relationship between and 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 AASs 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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 σ-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. AASs 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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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.

h. 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 glomerulonephritis 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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 consistent with doping to 4:1. In the early 1990s, intraindividual biologic variability of the T/E ratio began to be used in combination with population ranges to detect doping (354). Sottas et al (355) reported a predictive model that compared the T/E ratio and other steroid concentrations with previous results from individual athletes.

Genetic differences in testosterone metabolism can alter the T/E ratio and result in a false-negative test (356). 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).

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 [VO_{2max}]), 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 chorionic somatomammotropin

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 posttranslationally 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 VO_{2max} 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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

Table 2. Adverse Events Associated With rhGH Use[a]

Organ System/Effect	Severity
Cardiovascular	
Cardiomyopathy	++
Heart failure	+
Hypertension	+
Metabolic: diabetes	++
Dermatologic	
Excessive seating	+
Coarsening of skin	+
Musculoskeletal	
Acral enlargement	+
Carpal tunnel syndrome	+
Osteoarthritis	+
Other: increased risk of cancers	+/−

[a] Severity is scored as follows: ++, well-recognized and probably of serious concern; +, well-recognized but either less common or causing less serious morbidity; +/−, possible risks whose relation to AAS use remains poorly understood.

times (usually for many years). GH excess in patients with acromegaly is characterized by acral enlargement, excessive sweating, hypertension, congestive heart failure, cardiomyopathy, sleep apnea, arthropathy, carpal tunnel syndrome, increased insulin resistance, neuropathy, diabetes, and increased mortality (376). Retrospective analyses of patients with acromegaly have suggested increased frequency of benign and malignant neoplasms (377–380).Thyroid nodules and cancers, colonic polyps and cancers, and endometrial and cervical cancers are the most frequently reported neoplasms in patients with acromegaly (377–380).

3. Detection

Two tests have been developed for the detection of rhGH: a direct method that measures variants of GH produced by the pituitary gland (381) and a biomarkers method based on the GH-induced release of IGF-1 and the N-terminal propeptide of procollagen type III (P-III-NP) (382, 383). In the variants or isoforms test, one immunoassay detects primarily pituitary isoforms of GH including the 22-kDa isoform, oligomers of the 22-kDa isoform, and some other isoforms. The second immunoassay primarily detects the monomeric 22-kDa GH found in rhGH preparations. When a subject receives GH, it increases the concentration measured by the second assay and suppresses the pituitary forms, decreasing the concentration. The result is a dramatic increase in the ratio of the 2 assays (recombinant/pituitary). The main limitation of any direct GH test is the short serum half-life of GH, which limits the detection window to less than 24 hours.

The biomarkers test is based on a score calculated from the age of the athlete, the IGF-1 concentration, and the P-III-NP concentration (384). By combining the 2 tests, one can correctly classify subjects who had received GH 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-

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

ferentiation of these cells. The burst-forming units (erythroid [BFU-E]), proerthyroblasts, 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 (VO_{2max}) 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 chemiluminiscence (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 glycoform 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 chemiluminiscence. The method separates the erythropoietin glycoforms on the basis of their hydrodynamic volume. Chemiluminiscence 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 Use[a]

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.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 adenovirus-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-δ, α-actinin 3, cytosolic phosphoenolpyruvate 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

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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 nonathlete weightlifters. 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

Gaps in Our Knowledge: Unmet Need	Recommendation
There is a lack of prospective, systematically gathered data on the long-term adverse health effects of PED use.	Establish prospective observational cohort studies (registries) to determine the long-term health effects of PED use.
There is a lack of reliable and current epidemiological data on the frequency of PED use among the general population.	Establish epidemiologic surveys to determine the prevalence of PED use in the general population.
The mechanisms by which PEDs exert their adverse health effects remain poorly understood.	Perform human and animal studies to determine the mechanisms by which PEDs exert their adverse effects on the health of users.
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.	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.

The mechanisms by which PEDs exert their adverse health effects also remain unclear and need further investigation. Animal models may be particularly useful in studying the mechanistic pathways that contribute to the adverse effects of PEDs. An understanding of these mechanistic pathways may unveil targets for therapeutic intervention.

AAS withdrawal is another issue that needs further investigation. When AAS users stop taking steroids, they often experience distressing symptoms associated with a suppressed HPT axis. There are no data from intervention trials of therapeutic modalities (eg, estrogen receptor antagonists, aromatase inhibitors, and opiate antagonists) to

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

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.

Acknowledgments

Dr Jag H. Khalsa, chief of the Medical Consequences Branch, National Institute on Drug Abuse (NIDA), served as a member of the expert panel that was assembled by The Endocrine Society. Because Dr Khalsa is the program officer on a National Institutes of Health (NIH) grant held by one of the coauthors, he requested that his name be removed from the author list and added to the Acknowledgments, citing this conflict of interest by NIDA's policies. The authors gratefully acknowledge the expert literature search assistance from medical librarians Andrea Horne Denton, MILS (Master of Information and Library Science), Karen Knight, MSLS (Master of Science and Library Science), and Kelly Near, MSN (Master of Science in Nursing), WHNP-BC (Women's Health Nurse Practitioner – Board Certified), MLS (Master of Library Science) from the University of Virginia Claude Moore Health Sciences Library.

Address requests for reprints to: Shalender Bhasin, MD; Director, Research Program in Men's Health: Aging and Metabolism; Director, Boston Claude D. Pepper Older Americans Independence Center, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115.

The preparation of this Scientific Statement was supported entirely by the Endocrine Society. The following grants are also acknowledged from the National Institutes of Health (NIH): 5RO1AG037193-08 and 2UO1AG014369 (to S.B.), DA029613 (to R.I.W.), and NIDA DA-029141 (to H.G.P.).

Disclosure Summary: The authors have no conflicts in relation to this research. S.B. has received research grants from the NIH, AbbVie, Regeneron, and Eli Lilly and Company for other research not directly related to this project. H.G.P. has received grant support from NIDA and testified in cases related to AAS use. R.W.'s research has been supported by an RO1 grant from NIDA. F.N. has received grant support from the Swedish Research Council and has provided expert testimony on the action of AASs in a Swedish court. L.B. is an employee of the United States Anti-Doping Agency. A.R. reports no conflict. The authors received no remuneration for their contributions to the preparation of the manuscript.

References

1. **Pope HG Jr, Kanayama G, Hudson JI.** Risk factors for illicit anabolic-androgenic steroid use in male weightlifters: a cross-sectional cohort study. *Biol Psychiatry*. 2012;71:254–261.
2. **Parkinson AB, Evans NA.** Anabolic androgenic steroids: a survey of 500 users. *Med Sci Sports Exerc*. 2006;38(4):644–651.
3. **Wilson JD.** Androgen abuse by athletes. *Endocr Rev*. 1988;9(2):181–199.
4. **Handelsman DJ.** Commentary: androgens and "anabolic steroids": the one-headed janus. *Endocrinology*. 2011;152(5):1752–1754.
5. **Miner JN, Chang W, Chapman MS, et al.** An orally active selective androgen receptor modulator is efficacious on bone, muscle, and sex function with reduced impact on prostate. *Endocrinology*. 2007;148(1):363–373.
6. **Schmidt A, Kimmel DB, Bai C, et al.** Discovery of the selective androgen receptor modulator MK-0773 using a rational development strategy based on differential transcriptional requirements for androgenic anabolism versus reproductive physiology. *J Biol Chem*. 2010;285(22):17054–17064.
7. **Schmidt A, Harada S, Kimmel DB, et al.** Identification of anabolic selective androgen receptor modulators with reduced activities in reproductive tissues and sebaceous glands. *J Biol Chem*. 2009;284(52):36367–36376.
8. **Narayanan R, Mohler ML, Bohl CE, Miller DD, Dalton JT.** Selective androgen receptor modulators in preclinical and clinical development. *Nucl Recept Signal*. 2008;6:e010.
9. **Narayanan R, Coss CC, Yepuru M, Kearbey JD, Miller DD, Dalton JT.** Steroidal androgens and nonsteroidal, tissue-selective androgen receptor modulator, S-22, regulate androgen receptor function through distinct genomic and nongenomic signaling pathways. *Mol Endocrinol*. 2008;22(11):2448–2465.
10. **Jasuja R, Costello JC, Singh R, et al.** Combined administration of testosterone plus an ornithine decarboxylase inhibitor as a selective prostate-sparing anabolic therapy. *Aging Cell*. 2014;13(2):303–310.
11. **Gao W, Dalton JT.** Ockham's razor and selective androgen receptor modulators (SARMs): are we overlooking the role of 5α-reductase? *Mol Interv*. 2007;7(1):10–13.
12. **Bhasin S, Jasuja R.** Selective androgen receptor modulators as function promoting therapies. *Curr Opin Clin Nutr Metab Care*. 2009;12(3):232–240.
13. **Bhasin S, Calof OM, Storer TW, Lee ML, Mazer NA, Jasuja R, Montori VM, Gao W, Dalton JT.** Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. *Nat Clin Pract Endocrinol Metab*. 2006;2(3):146–159.
14. **Brennan BP, Kanayama G, Hudson JI, Pope HG Jr.** Human growth hormone abuse in male weightlifters. *Am J Addict*. 2011;20(1):9–13.
15. **Ip EJ, Barnett MJ, Tenerowicz MJ, Perry PJ.** Weightlifting's risky new trend: a case series of 41 insulin users. *Curr Sports Med Rep*. 2012;11(4):176–179.
16. The 2013 list of prohibited substances and methods. World Anti-Doping Agency website. http://www.wada-ama.org/en/World-Anti-Doping-Program/Sports-and-Anti-Doping-Organizations/International-Standards/Prohibited-List/. Accessed January 30, 2013.
17. The world anti-doping code. World-Anti-Doping Agency website. http://www.wada-ama.org/en/world-anti-doping-program/sports-and-anti-doping-organizations/the-code. Accessed January 30, 2013.
18. **Kanayama G, Hudson JI, Pope HG Jr.** Long-term psychiatric and medical consequences of anabolic-androgenic steroid abuse: a looming public health concern? *Drug Alcohol Depend*. 2008;98(1–2):1–12.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

19. **Pope HG, Kanayama G, Athey A, Ryan E, Hudson JI, Baggish A.** The lifetime prevalence of anabolic-androgenic steroid use and dependence in Americans: current best estimates [published online September 20, 2013]. *Am J Addict*. doi:10.1111/j.1521-0391.2013.12118.x.
20. **Pope HG, Kanayama G.** Can you tell if your patient is using anabolic steroids? *Curr Psychiatry Primary Care*. 2005;1:28–34.
21. **Pope HG, Kanayama G, Ionescu-Pioggia M, Hudson JI.** Anabolic steroid users' attitudes towards physicians. *Addiction*. 2004;99(9):1189–1194.
22. **Dawson R.** Drugs in sport: the role of the physician. *J Endocrinol*. 2001;170:55–61.
23. **Kutscher EC, Lund BC, Perry PJ.** Anabolic steroids: a review for the clinician. *Sports Med*. 2002;32(5):285–296.
24. **Pope HG, Kanayama G.** Treatment of anabolic-androgenic steroid related disorders. In: Galanter M, Kleber H, Brady K, eds. *The American Psychiatric Publishing Textbook of Substance Abuse Treatment*. 5th ed. Washington, DC: American Psychiatric Association; in press.
25. Drug Abuse Warning Network (DAWN). Substance Abuse and Mental Health Services Administration website. http://www.samhsa.gov/data/DAWN.aspx. Accessed March 14, 2013.
26. **Mitchell GJ.** Report to the Commissioner of Baseball of an independent investigation into the illegal use of steroids and other performance-enhancing substances by players in Major League Baseball. Office of the Commissioner of Baseball; 2007.
27. **Yesalis CE, Bahrke MS.** Anabolic-androgenic steroids. Current issues. *Sports Med*. 1995;19(5):326–340.
28. **Brown-Séquard C.** Des effets produits chez l'homme par des injections souscutanées d'un liquide retiré des testicules frais de cobaye et de chien. *C R Séance Soc Biol*. 1889:415–422, 429–431.
29. **Kahn A.** Regaining lost youth: the controversial and colorful beginnings of hormone replacement therapy in aging. *J Gerontol A Biol Sci Med Sci*. 2005;60(2):142–147.
30. **Freeman ER, Bloom DA, McGuire EJ.** A brief history of testosterone. *J Urol*. 2001;165(2):371–373.
31. **Boje O.** Doping. *Bulletin of Health Organization of the League of Nations*. 1939;8:439–469.
32. **Wade N.** Anabolic steroids: doctors denounce them, but athletes aren't listening. *Science*. 1972;176:1399–1403.
33. **Bahrke MS, Yesalis CE.** Abuse of anabolic androgenic steroids and related substances in sport and exercise. *Curr Opin Pharmacol*. 2004;4(6):614–620.
34. **Franke WW, Berendonk B.** Hormonal doping and androgenization of athletes: a secret program of the German Democratic Republic government. *Clin Chem*. 1997;43(7):1262–1279.
35. **Catlin DH, Sekera MH, Ahrens BD, Starcevic B, Chang YC, Hatton CK.** Tetrahydrogestrinone: discovery, synthesis, and detection in urine. *Rapid Commun Mass Spectrom*. 2004;18(12):1245–1249.
36. **Jasuja R, Catlin DH, Miller A, et al.** Tetrahydrogestrinone is an androgenic steroid that stimulates androgen receptor-mediated, myogenic differentiation in C3H10T1/2 multipotent mesenchymal cells and promotes muscle accretion in orchidectomized male rats. *Endocrinology*. 2005;146(10):4472–4478.
37. **Sekera MH, Ahrens BD, Chang YC, Starcevic B, Georgakopoulos C, Catlin DH.** Another designer steroid: discovery, synthesis, and detection of 'madol' in urine. *Rapid Commun Mass Spectrom*. 2005;19(6):781–784.
38. **Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE.** Monitoring the Future national results on drug use: overview of key findings, 2012. Monitoring the Future website. http://www.monitoringthefuture.org/data/12data/pr12t1.pdf. Accessed March 12, 2013.
39. **Cohen J, Collins R, Darkes J, Gwartney D.** A league of their own: demographics, motivations and patterns of use of 1,955 male adult non-medical anabolic steroid users in the United States. *J Int Soc Sports Nutr*. 2007;4:12.
40. **Carter A, Flueck M.** A polymerase chain reaction-based methodology to detect gene doping. *Eur J Appl Physiol*. 2012;112(4):1527–1536.
41. **Kanayama G, Boynes M, Hudson JI, Field AE, Pope HG, Jr.** Anabolic steroid abuse among teenage girls: an illusory problem? *Drug Alcohol Depend*. 2007;88(2–3):156–162.
42. **Brower KJ, Eliopulos GA, Blow FC, Catlin DH, Beresford TP.** Evidence for physical and psychological dependence on anabolic androgenic steroids in eight weight lifters. *Am J Psychiatry*. 1990;147(4):510–512.
43. **Copeland J, Peters R, Dillon P.** Anabolic-androgenic steroid use disorders among a sample of Australian competitive and recreational users. *Drug Alcohol Depend*. 2000;60(1):91–96.
44. **Gridley DW, Hanrahan SJ.** Anabolic-androgenic steroid use among male gymnasium participants: knowledge and motives. *Sports Health*. 1994;12:11–14.
45. **Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope HG.** Anabolic-androgenic steroid dependence: an emerging disorder *Addiction*. 2009;104(12):1966–1978.
46. **Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope HG Jr.** Issues for DSM-V: clarifying the diagnostic criteria for anabolic-androgenic steroid dependence. *Am J Psychiatry*. 2009;166(6):642–645.
47. **Malone DA Jr, Dimeff RJ, Lombardo JA, Sample RH.** Psychiatric effects and psychoactive substance use in anabolic-androgenic steroid users. *Clin J Sport Med*. 1995;5(1):25–31.
48. **Midgley SJ, Heather N, Davies JB.** Dependence-producing potential of anabolic-androgenic steroids. *Addict Res*. 1999;7:539–550.
49. **Perry PJ, Lund BC, Deninger MJ, Kutscher EC, Schneider J.** Anabolic steroid use in weightlifters and bodybuilders: an internet survey of drug utilization. *Clin J Sport Med*. 2005;15(5):326–330.
50. **Ip EJ, Lu DH, Barnett MJ, Tenerowicz MJ, Vo JC, Perry PJ.** Psychological and physical impact of anabolic-androgenic steroid dependence. *Pharmacotherapy*. 2012;32:910–919.
51. **Pope HG Jr, Katz DL.** Psychiatric and medical effects of anabolic-androgenic steroid use. A controlled study of 160 athletes. *Arch Gen Psychiatry*. 1994;51(5):375–382.
52. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2010. HIV Surveillance Supplemental Report, Volume 17, Number 3 (Part A). Centers for Disease Control and Prevention website. http://www.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

cdc.gov/hiv/library/reports/surveillance/. Accessed January 5, 2014.
53. National diabetes statistics, 2011. U.S. Department of Health and Human Services website. http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.aspx?control=Pubs. Accessed March 14, 2013.
54. **Hakansson A, Mickelsson K, Wallin C, Berglund M.** Anabolic androgenic steroids in the general population: user characteristics and associations with substance use. *Eur Addict Res*. 2012;18(2):83–90.
55. Doping in Sweden: an inventory of its spread, consequences, and interventions. Trans. Semantx AB. Stockholm: Strömberg. Swedish National Institute of Public Health.
56. **Mattila VM, Parkkari J, Laakso L, Pihlajamäki H, Rimpela A.** Use of dietary supplements and anabolic-androgenic steroids among Finnish adolescents in 1991–2005. *Eur J Public Health*. 2010;20(3):306–311.
57. **Leifman H, Rehman C.** Prevalence of doping among gymnasium clients in Stockholm County [in Swedish]. Stockholm, Sweden: Stockholm förebyggare alcohol- och drogproblem (STAD); 2008.
58. **Pallesen S, Jøsendal O, Johnsen BH, Larsen S, Molde H.** Anabolic steroid use in high school students. *Subst Use Misuse*. 2006;41(13):1705–1717.
59. **Nilsson S, Spak F, Marklund B, Baigi A, Allebeck P.** Attitudes and behaviors with regards to androgenic anabolic steroids among male adolescents in a county of Sweden. *Subst Use Misuse*. 2004;39(8):1183–1197.
60. **Galduróz JC, Noto AR, Nappo SA, Carlini EA.** Household survey on drug abuse in Brazil: study involving the 107 major cities of the country–2001. *Addict Behav*. 2005;30(3):545–556.
61. **Galduróz JCF, Noto AR, Fonseca AM, Carlini EA.** Levantamento Nacional Sobre o Consumo de Drogas Psicotrópicas entre Estudantes do Ensino Fundamental e Médio da Rede Pública de Ensino nas 27 Capitais Brasileiras—2004. São Paulo, Brazil: Centro Brasileiro de Informações sobre Drogas Psicotrópicas. http://www.cebrid.epm.br/levantamento_brasil2/index.htm. Accessed January 5, 2014.
62. **Dunn M, White V.** The epidemiology of anabolic-androgenic steroid use among Australian secondary school students. *J Sci Med Sport*. 2011;14(1):10–14.
63. **Baker JS, Graham MR, Davies B.** Steroid and prescription medicine abuse in the health and fitness community: A regional study. *Eur J Intern Med*. 2006;17(7):479–484.
64. **Australian Institute of Health and Welfare.** *2010 National Drug Strategy Household Survey Report*. Canberra, Australia: Australian Institute of Health and Welfare; 2011.
65. **Smith K, Flatley J, eds.** *Drug use declared: Findings from the 2010/11 British Crime Survey – England and Wales*. London: British Home Office. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147938/drugs-misuse-dec-1112-pdf.pdf. Accessed January 5, 2014.
66. **Wanjek B, Rosendahl J, Strauss B, Gabriel HH.** Doping, drugs and drug abuse among adolescents in the State of Thuringia (Germany): prevalence, knowledge and attitudes. *Int J Sports Med*. 2007;28(4):346–353.
67. **Racho D, Pokrywka L, Suchecka-Racho K.** Prevalence and risk factors of anabolic-androgenic steroids (AAS) abuse among adolescents and young adults in Poland. *Soz Praventivmed*. 2006;51(6):392–398.
68. **Kokkevi A, Fotiou A, Chileva A, Nociar A, Miller P.** Daily exercise and anabolic steroids use in adolescents: a cross-national European study. *Subst Use Misuse*. 2008;43(14):2053–2065.
69. **Kanayama G, Hudson JI, Pope HG Jr.** Culture, psychosomatics and substance abuse: the example of body image drugs. *Psychother Psychosom*. 2012;81(2):73–78.
70. **Yang CF, Gray P, Pope HG Jr.** Male body image in Taiwan versus the West: Yanggang Zhiqi meets the Adonis complex. *Am J Psychiatry*. 2005;162(2):263–269.
71. **Skarberg K, Nyberg F, Engstrom I.** Multisubstance use as a feature of addiction to anabolic-androgenic steroids. *Eur Addict Res*. 2009;15(2):99–106.
72. **Arvary D, Pope HG Jr.** Anabolic-androgenic steroids as a gateway to opioid dependence. *N Engl J Med*. 2000;342(20):1532.
73. **Thiblin I, Lindquist O, Rajs J.** Cause and manner of death among users of anabolic androgenic steroids. *J Forensic Sci*. 2000;45(1):16–23.
74. **Wines JD, Jr., Gruber AJ, Pope HG, Jr., Lukas SE.** Nalbuphine hydrochloride dependence in anabolic steroid users. *Am J Addict*. 1999;8(2):161–164.
75. **Kanayama G, Cohane GH, Weiss RD, Pope HG.** Past anabolic-androgenic steroid use among men admitted for substance abuse treatment: an underrecognized problem? *J Clin Psychiatry*. 2003;64(2):156–160.
76. **Tennant F, Black DL, Voy RO.** Anabolic steroid dependence with opioid-type features. *N Engl J Med*. 1988;319(9):578.
77. **Kanayama G, Pope HG Jr.** Illicit use of androgens and other hormones: recent advances. *Curr Opin Endocrinol Diabetes Obes*. 2012;19(3):211–219.
78. **Dodge T, Hoagland MF.** The use of anabolic androgenic steroids and polypharmacy: a review of the literature. *Drug Alcohol Depend*. 2011;114(2–3):100–109.
79. **Kanayama G, Kean J, Hudson JI, Pope HG.** Cognitive deficits in long-term anabolic-androgenic steroid users. *Drug Alcohol Depend*. 2013;130(1–3):208–214.
80. **Pope HG, Kean J, Nash A, et al.** A diagnostic interview module for anabolic-androgenic steroid dependence: preliminary evidence of reliability and validity. *Exp Clin Psychopharmacol*. 2010;18:203–213.
81. **Cicero TJ, O'Connor LH.** Abuse liability of anabolic steroids and their possible role in the abuse of alcohol, morphine, and other substances. *NIDA Res Monogr*. 1990;102:1–28.
82. **Johansson P, Lindqvist A, Nyberg F, Fahlke C.** Anabolic androgenic steroids affects alcohol intake, defensive behaviors and brain opioid peptides in the rat. *Pharmacol Biochem Behav*. 2000;67(2):271–279.
83. **Kindlundh AM, Lindblom J, Bergström L, Wikberg JE, Nyberg F.** The anabolic-androgenic steroid nandrolone decanoate affects the density of dopamine receptors in the male rat brain. *Eur J Neurosci*. 2001;13(2):291–296.
84. **Le Grevès P, Zhou Q, Huang W, Nyberg F.** Effect of combined treatment with nandrolone and cocaine on the NMDA receptor gene expression in the rat nucleus accumbens and periaqueductal gray. *Acta Psychiatr Scand Suppl*. 2002;412:129–132.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

85. **Steensland P, Hallberg M, Kindlundh A, Fahlke C, Nyberg F.** Amphetamine-induced aggression is enhanced in rats pre-treated with the anabolic androgenic steroid nandrolone decanoate. *Steroids*. 2005;70(3):199–204.
86. **Hildebrandt T, Lai JK, Langenbucher JW, Schneider M, Yehuda R, Pfaff DW.** The diagnostic dilemma of pathological appearance and performance enhancing drug use. *Drug Alcohol Depend*. 2011;114(1):1–11.
87. **Kanayama G, Hudson JI, Pope HG.** Illicit anabolic-androgenic steroid use. *Horm Behav*. 2010;58(1):111–121. PMCID 2883629.
88. **Summers J.** *Steroids 101*. Aurora, CO: Anabolics.com Inc.; 2003.
89. **Midgley SJ, Heather N, Best D, Henderson D, McCarthy S, Davies JB.** Risk behaviours for HIV and hepatitis infection among anabolic-androgenic steroid users. *AIDS Care*. 2000;12(2):163–170.
90. **Larance B, Degenhardt L, Copeland J, Dillon P.** Injecting risk behaviour and related harm among men who use performance- and image-enhancing drugs. *Drug Alcohol Rev*. 2008;27(6):679–686.
91. **Aitken C, Delalande C, Stanton K.** Pumping iron, risking infection? Exposure to hepatitis C, hepatitis B and HIV among anabolic-androgenic steroid injectors in Victoria, Australia. *Drug Alcohol Depend*. 2002;65(3):303–308.
92. **Rich JD, Dickinson BP, Feller A, Pugatch D, Mylonakis E.** The infectious complications of anabolic-androgenic steroid injection. *Int J Sports Med*. 1999;20(8):563–566.
93. **Bolding G, Sherr L, Elford J.** Use of anabolic steroids and associated health risks among gay men attending London gyms. *Addiction*. 2002;97(2):195–203.
94. **Hoffman JR, Kraemer WJ, Bhasin S, et al.** Position stand on androgen and human growth hormone use. *J Strength Cond Res*. 2009;23(5 Suppl):S1–S59.
95. **Bhasin S, Storer TW, Berman N, et al.** The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med*. 1996;335(1):1–7.
96. **Bhasin S, Storer TW, Javanbakht M, et al.** Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA*. 2000; 283(6):763–770.
97. **Bhasin S, Woodhouse L, Casaburi R, et al.** Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab*. 2001;281(6):E1172–E1181.
98. **Sinha-Hikim I, Artaza J, Woodhouse L, et al.** Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. *Am J Physiol Endocrinol Metab*. 2002;283(1):E154–E164.
99. **Sinha-Hikim I, Roth SM, Lee MI, Bhasin S.** Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy, young men. *Am J Physiol Endocrinol Metab*. 2003;285(1):E197–E205.
100. **Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF, Bhasin S.** Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology*. 2003;144(11):5081–5088.
101. **Singh R, Artaza JN, Taylor WE, et al.** Testosterone inhibits adipogenic differentiation in 3T3-L1 cells: nuclear translocation of androgen receptor complex with β-catenin and T-cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription factors. *Endocrinology*. 2006;147(1):141–154.
102. **Braga M, Bhasin S, Jasuja R, Pervin S, Singh R.** Testosterone inhibits transforming growth factor-β signaling during myogenic differentiation and proliferation of mouse satellite cells: potential role of follistatin in mediating testosterone action. *Mol Cell Endocrinol*. 2012;350(1):39–52.
103. **Serra C, Bhasin S, Tangherlini F, et al.** The role of GH and IGF-I in mediating anabolic effects of testosterone on androgen-responsive muscle. *Endocrinology*. 2011;152(1): 193–206.
104. **Storer TW, Magliano L, Woodhouse L, et al.** Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. *J Clin Endocrinol Metab*. 2003;88(4):1478–1485.
105. **Bhasin S, Travison TG, Storer TW, et al.** Effect of testosterone supplementation with and without a dual 5α-reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. *JAMA*. 2012;307(9):931–939.
106. **Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S.** Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab*. 2008;93(3):914–919.
107. **Gupta V, Bhasin S, Guo W, et al.** Effects of dihydrotestosterone on differentiation and proliferation of human mesenchymal stem cells and preadipocytes. *Mol Cell Endocrinol*. 2008;296(1–2):32–40.
108. **Singh R, Bhasin S, Braga M, et al.** Regulation of myogenic differentiation by androgens: cross talk between androgen receptor/β-catenin and follistatin/transforming growth factor-β signaling pathways. *Endocrinology*. 2009; 150(3):1259–1268.
109. **Leslie M, Forger NG, Breedlove SM.** Sexual dimorphism and androgen effects on spinal motoneurons innervating the rat flexor digitorum brevis. *Brain Res*. 1991;561(2): 269–273.
110. **Blanco CE, Popper P, Micevych P.** Anabolic-androgenic steroid induced alterations in choline acetyltransferase messenger RNA levels of spinal cord motoneurons in the male rat. *Neuroscience*. 1997;78(3):873–882.
111. **Clark BM, Schofield RS.** Dilated cardiomyopathy and acute liver injury associated with combined use of ephedra, γ-hydroxybutyrate, and anabolic steroids. *Pharmacotherapy*. 2005;25(5):756–761.
112. **Vogt AM, Geyer H, Jahn L, Schänzer W, Kübler W.** Cardiomyopathy associated with uncontrolled self medication of anabolic steroids [in German]. *Z Kardiol*. 2002;91(4): 357–362.
113. **Ferenchick GS.** Association of steroid abuse with cardiomyopathy in athletes. *Am J Med*. 1991;91(5):562.
114. **Schollert PV, Bendixen PM.** Dilated cardiomyopathy in a user of anabolic steroids [in Danish]. *Ugeskr Laeger*. 1993; 155(16):1217–1218.
115. **Ahlgrim C, Guglin M.** Anabolics and cardiomyopathy in a bodybuilder: case report and literature review. *J Card Fail*. 2009;15(6):496–500.
116. **Bispo M, Valente A, Maldonado R, et al.** Anabolic steroid-induced cardiomyopathy underlying acute liver failure in a

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

young bodybuilder. *World J Gastroenterol*. 2009;15(23):2920–2922.
117. **Halvorsen S, Thorsby PM, Haug E.** Acute myocardial infarction in a young man who had been using androgenic anabolic steroids [in Norwegian]. *Tidsskr Nor Laegeforen*. 2004;124(2):170–172.
118. **Fineschi V, Baroldi G, Monciotti F, Paglicci Reattelli L, Turillazzi E.** Anabolic steroid abuse and cardiac sudden death: a pathologic study. *Arch Pathol Lab Med*. 2001;125(2):253–255.
119. **Godon P, Bonnefoy E, Guerard S, et al.** Myocardial infarction and anabolic steroid use. A case report [in French]. *Arch Mal Coeur Vaiss*. 2000;93(7):879–883.
120. **Varriale P, Mirzai-tehrane M, Sedighi A.** Acute myocardial infarction associated with anabolic steroids in a young HIV-infected patient. *Pharmacotherapy*. 1999;19(7):881–884.
121. **Fisher M, Appleby M, Rittoo D, Cotter L.** Myocardial infarction with extensive intracoronary thrombus induced by anabolic steroids. *Br J Clin Pract*. 1996;50(4):222–223.
122. **Kennedy C.** Myocardial infarction in association with misuse of anabolic steroids. *Ulster Med J*. 1993;62(2):174–176.
123. **Kennedy MC, Lawrence C.** Anabolic steroid abuse and cardiac death. *Med J Aust*. 1993;158(5):346–348.
124. **Ferenchick GS, Adelman S.** Myocardial infarction associated with anabolic steroid use in a previously healthy 37-year-old weight lifter. *Am Heart J*. 1992;124(2):507–508.
125. **McNutt RA, Ferenchick GS, Kirlin PC, Hamlin NJ.** Acute myocardial infarction in a 22-year-old world class weight lifter using anabolic steroids. *Am J Cardiol*. 1988;62(1):164.
126. **Huie MJ.** An acute myocardial infarction occurring in an anabolic steroid user. *Med Sci Sports Exerc*. 1994;26(4):408–413.
127. **Appleby M, Fisher M, Martin M.** Myocardial infarction, hyperkalaemia and ventricular tachycardia in a young male body-builder. *Int J Cardiol*. 1994;44(2):171–174.
128. **Lisiewicz J, Fijalkowski P, Sankowski J.** Ischemic cerebral stroke and anabolic steroids (case report) [in Polish]. *Neurol Neurochir Pol*. 1999;32(Suppl 6):137–139.
129. **Shimada Y, Yoritaka A, Tanaka Y, et al.** Cerebral infarction in a young man using high-dose anabolic steroids. *J Stroke Cerebrovasc Dis*. 2012;21(8):906.e9–911.e9.
130. **Kennedy MC, Corrigan AB, Pilbeam ST.** Myocardial infarction and cerebral haemorrhage in a young body builder taking anabolic steroids. *Aust N Z J Med*. 1993;23(6):713.
131. **Lau DH, Stiles MK, John B, Shashidhar, Young GD, Sanders P.** Atrial fibrillation and anabolic steroid abuse. *Int J Cardiol*. 2007;117(2):e86–e87.
132. **Furlanello F, Bentivegna S, Cappato R, De Ambroggi L.** Arrhythmogenic effects of illicit drugs in athletes. *Ital Heart J*. 2003;4(12):829–837.
133. **Mewis C, Spyridopoulos I, Kühlkamp V, Seipel L.** Manifestation of severe coronary heart disease after anabolic drug abuse. *Clin Cardiol*. 1996;19(2):153–155.
134. **Sullivan ML, Martinez CM, Gallagher EJ.** Atrial fibrillation and anabolic steroids. *J Emerg Med*. 1999;17(5):851–857.
135. **Tischer KH, Heyny-von Haussen R, Mall G, Doenecke P.** Coronary thrombosis and ectasia of coronary arteries after long-term use of anabolic steroids [in German]. *Z Kardiol*. 2003;92(4):326–331.
136. **Ment J, Ludman PF.** Coronary thrombus in a 23 year old anabolic steroid user. *Heart*. 2002;88(4):342.
137. **McCarthy K, Tang AT, Dalrymple-Hay MJ, Haw MP.** Ventricular thrombosis and systemic embolism in bodybuilders: etiology and management. *Ann Thorac Surg*. 2000;70(2):658–660.
138. **Ferenchick G, Schwartz D, Ball M, Schwartz K.** Androgenic-anabolic steroid abuse and platelet aggregation: a pilot study in weight lifters. *Am J Med Sci*. 1992;303(2):78–82.
139. **Ferenchick GS.** Anabolic/androgenic steroid abuse and thrombosis: is there a connection? *Med Hypotheses*. 1991;35(1):27–31.
140. **Krieg A, Scharhag J, Albers T, Kindermann W, Urhausen A.** Cardiac tissue Doppler in steroid users. *Int J Sports Med*. 2007;28(8):638–643.
141. **Vanberg P, Atar D.** Androgenic anabolic steroid abuse and the cardiovascular system. *Handb Exp Pharmacol*. 2010;195:411–457.
142. **Nascimento JH, Medei E.** Cardiac effects of anabolic steroids: hypertrophy, ischemia and electrical remodelling as potential triggers of sudden death. *Mine Rev Med Chem*. 2011;11(5):425–429.
143. **Achar S, Rostamian A, Narayan SM.** Cardiac and metabolic effects of anabolic-androgenic steroid abuse on lipids, blood pressure, left ventricular dimensions, and rhythm. *Am J Cardiol*. 2010;106(6):893–901.
144. **Angell PJ, Chester N, Sculthorpe N, Whyte G, George K, Somauroo J.** Performance enhancing drug abuse and cardiovascular risk in athletes: implications for the clinician. *Br J Sports Med*. 2012;46(Suppl 1):i78–i84.
145. **Far HR, Ågren G, Thiblin I.** Cardiac hypertrophy in deceased users of anabolic androgenic steroids: an investigation of autopsy findings. *Cardiovasc Pathol*. 2012;21(4):312–316.
146. **Montisci M, El Mazloum R, Cecchetto G, et al.** Anabolic androgenic steroids abuse and cardiac death in athletes: morphological and toxicological findings in four fatal cases. *Forensic Sci Int*. 2012;217:e13–e18.
147. **Sculthorpe N, Grace F, Jones P, Davies B.** Evidence of altered cardiac electrophysiology following prolonged androgenic anabolic steroid use. *Cardiovasc Toxicol*. 2010;10(4):239–243.
148. **Maior AS, Carvalho AR, Marques-Neto SR, Menezes P, Soares PP, Nascimento JH.** Cardiac autonomic dysfunction in anabolic steroid users. *Scand J Med Sci Sports*. 2013;23(5):548–555.
149. **Maior AS, Menezes P, Pedrosa RC, Carvalho DP, Soares PP, Nascimento JH.** Abnormal cardiac repolarization in anabolic androgenic steroid users carrying out submaximal exercise testing. *Clin Exp Pharmacol Physiol*. 2010;37(12):1129–1133.
150. **Medei E, Marocolo M, Rodrigues Dde C, et al.** Chronic treatment with anabolic steroids induces ventricular repolarization disturbances: cellular, ionic and molecular mechanism. *J Mol Cell Cardiol*. 2010;49(2):165–175.
151. **Montisci R, Cecchetto G, Ruscazio M, et al.** Early myocardial dysfunction after chronic use of anabolic androgenic steroids: combined pulsed-wave tissue Doppler im-

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

aging and ultrasonic integrated backscatter cyclic variations analysis. *J Am Soc Echocardiogr*. 2010;23(5):516–522.
152. **Baggish AL, Weiner RB, Kanayama G, et al.** Long-term anabolic-androgenic steroid use is associated with left ventricular dysfunction. *Circulation*. 2010;3:472–476.
153. **Hassan NA, Salem MF, Sayed MA.** Doping and effects of anabolic androgenic steroids on the heart: histological, ultrastructural, and echocardiographic assessment in strength athletes. *Hum Exp Toxicol*. 2009;28(5):273–283.
154. **D'Andrea A, Caso P, Salerno G, et al.** Left ventricular early myocardial dysfunction after chronic misuse of anabolic androgenic steroids: a Doppler myocardial and strain imaging analysis. *Br J Sports Med*. 2007;41(3):149–155.
155. **Nottin S, Nguyen LD, Terbah M, Obert P.** Cardiovascular effects of androgenic anabolic steroids in male bodybuilders determined by tissue Doppler imaging. *Am J Cardiol*. 2006;97(6):912–915.
156. **Kasikcioglu E, Oflaz H, Umman B, Bugra Z.** Androgenic anabolic steroids also impair right ventricular function. *Int J Cardiol*. 2009;134(1):123–125.
157. **Nyberg F, Hallberg M.** Interactions between opioids and anabolic androgenic steroids: implications for the development of addictive behavior. *Int Rev Neurobiol*. 2012;102:189–206.
158. **Luijkx T, Velthuis BK, Backx FJ, et al.** Anabolic androgenic steroid use is associated with ventricular dysfunction on cardiac MRI in strength trained athletes. *Int J Cardiol*. 2013;167(3):664–668.
159. **Kasikcioglu E, Oflaz H, Arslan A, et al.** Aortic elastic properties in athletes using anabolic-androgenic steroids. *Int J Cardiol*. 2007;114(1):132–134.
160. **Rothman R, Weiner R, Pope H Jr, et al.** Anabolic androgenic steroid induced myocardial toxicity: an evolving problem in an ageing population. *BMJ Case Rep*. 2011;pii:bcr0520114280.
161. **Riezzo I, De Carlo D, Neri M, Nieddu A, Turillazzi E, Fineschi V.** Heart disease induced by AAS abuse, using experimental mice/rats models and the role of exercise-induced cardiotoxicity. *Mine Rev Med Chem*. 2011;11(5):409–424.
162. **Hartgens F, Rietjens G, Keizer HA, Kuipers H, Wolffenbuttel BH.** Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a). *Br J Sports Med*. 2004;38(3):253–259.
163. **Grundy SM, Cleeman JI, Merz CN, et al.** Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110(2):227–239.
164. **Thompson PD, Cullinane EM, Sady SP, et al.** Contrasting effects of testosterone and stanozolol on serum lipoprotein levels. *JAMA*. 1989;261(8):1165–1168.
165. **Fontana K, Oliveira HC, Leonardo MB, Mandarim-de-Lacerda CA, da Cruz-Höfling MA.** Adverse effect of the anabolic-androgenic steroid mesterolone on cardiac remodelling and lipoprotein profile is attenuated by aerobicz exercise training. *Int J Exp Pathol*. 2008;89(5):358–366.
166. **Santora LJ, Marin J, Vangrow J, Met al.** Coronary calcification in body builders using anabolic steroids. *Prev Cardiol*. 2006;9(4):198–201.
167. **Pärssinen M, Kujala U, Vartiainen E, Sarna S, Seppala T.** Increased premature mortality of competitive powerlifters suspected to have used anabolic agents. *Int J Sports Med*. 2000;21(3):225–227.
168. **Pope HG, Katz DL.** Psychiatric effects of exogenous anabolic-androgenic steroids. In: Wolkowitz OM, Rothschild AJ, eds. *Psychoneuroendocrinology: The Scientific Basis of Clinical Practice*. Washington, DC: American Psychiatric Press; 2003:331–358.
169. **Hall RC, Hall RC, Chapman MJ.** Psychiatric complications of anabolic steroid abuse. *Psychosomatics*. 2005;46(4):285–290.
170. **Talih F, Fattal O, Malone D Jr.** Anabolic steroid abuse: psychiatric and physical costs. *Cleve Clin J Med*. 2007;74(5):341–344, 346, 349–352.
171. **Parrott AC, Choi PY, Davies M.** Anabolic steroid use by amateur athletes: effects upon psychological mood states. *J Sports Med Phys Fitness*. 1994;34(3):292–298.
172. **Pope HG Jr, Katz DL.** Affective and psychotic symptoms associated with anabolic steroid use. *Am J Psychiatry*. 1988;145(4):487–490.
173. **Cooper CJ, Noakes TD, Dunne T, Lambert MI, Rochford K.** A high prevalence of abnormal personality traits in chronic users of anabolic-androgenic steroids. *Br J Sports Med*. 1996;30(3):246–250.
174. **Bahrke MS, Wright JE, Strauss RH, Catlin DH.** Psychological moods and subjectively perceived behavioral and somatic changes accompanying anabolic-androgenic steroid use. *Am J Sports Med*. 1992;20(6):717–724.
175. **Choi PY, Pope HG Jr.** Violence toward women and illicit androgenic-anabolic steroid use. *Ann Clin Psychiatry*. 1994;6(1):21–25.
176. **Midgley SJ, Heather N, Davies JB.** Levels of aggression among a group of anabolic-androgenic steroid users. *Med Sci Law*. 2001;41(4):309–314.
177. **Moss H, Panzak G, Tarter R.** Personality, mood, and psychiatric symptoms among anabolic steroid users. *Am J Addict*. 1992;1:315–324.
178. **Perry PJ, Andersen KH, Yates WR.** Illicit anabolic steroid use in athletes. A case series analysis. *Am J Sports Med*. 1990;18(4):422–428.
179. **Perry PJ, Kutscher EC, Lund BC, Yates WR, Holman TL, Demers L.** Measures of aggression and mood changes in male weightlifters with and without androgenic anabolic steroid use. *J Forensic Sci*. 2003;48(3):646–651.
180. **Yates WR, Perry P, Murray S.** Aggression and hostility in anabolic steroid users. *Biol Psychiatry*. 1992;31(12):1232–1234.
181. **Choi PY, Parrott AC, Cowan D.** High-dose anabolic steroids in strength athletes: effects upon hostility and aggression. *Hum Psychopharmacol*. 1990;5:349–356.
182. **Fudala PJ, Weinrieb RM, Calarco JS, Kampman KM, Boardman C.** An evaluation of anabolic-androgenic steroid abusers over a period of 1 year: seven case studies. *Ann Clin Psychiatry*. 2003;15(2):121–130.
183. **Pagonis TA, Angelopoulos NV, Koukoulis GN, Hadjichristodoulou CS.** Psychiatric side effects induced by supraphysiological doses of combinations of anabolic steroids correlate to the severity of abuse. *Eur Psychiatry*. 2006;21(8):551–562.
184. **Pagonis TA, Angelopoulos NV, Koukoulis GN, Hadji-**

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

christodoulou CS, Toli PN. Psychiatric and hostility factors related to use of anabolic steroids in monozygotic twins. *Eur Psychiatry*. 2006;21(8):563–569.
185. **Wilson-Fearon C, Parrott AC.** Multiple drug use and dietary restraint in a Mr. Universe competitor: psychobiological effects. *Percept Mot Skills*. 1999;88(2):579–580.
186. **Pope HG, Brower KJ.** Anabolic-androgenic steroid-related disorders. In: Sadock B, Sadock V, eds. *Comprehensive Textbook of Psychiatry*. 9th ed. Philadelphia, PA: Lippincott Williams, Wilkins; 2009:1419–1431.
187. **Rubinow DR, Schmidt PJ.** Androgens, brain, and behavior. *Am J Psychiatry*. 1996;153(8):974–984.
188. **Daly RC, Su TP, Schmidt PJ, Pagliaro M, Pickar D, Rubinow DR.** Neuroendocrine and behavioral effects of high-dose anabolic steroid administration in male normal volunteers. *Psychoneuroendocrinology*. 2003;28(3):317–331.
189. **Schmidt PJ, Berlin KL, Danaceau MA, et al.** The effects of pharmacologically induced hypogonadism on mood in healthy men. *Arch Gen Psychiatry*. 2004;61(10):997–1004.
190. **Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN.** One year follow-up study of the association between chemical castration, sex hormones, β-amyloid, memory and depression in men. *Psychoneuroendocrinology*. 2004;29(8):1071–1081.
191. **Bahrke MS, Yesalis CE 3rd.** Weight training. A potential confounding factor in examining the psychological and behavioural effects of anabolic-androgenic steroids. *Sports Med*. 1994;18(5):309–318.
192. **Bahrke MS, Yesalis CE 3rd, Wright JE.** Psychological and behavioural effects of endogenous testosterone and anabolic-androgenic steroids. An update. *Sports Med*. 1996;22(6):367–390.
193. **Björkqvist K, Nygren T, Björklund AC, Björkqvist SE.** Testosterone intake and aggressiveness: real effect or anticipation? *Aggressive Behavior*. 1994;20(1):17–26.
194. **Riem K, Hursey K.** Using anabolic-androgenic steroids to enhance physique and performance: effects on moods and behavior *Clin Psychol Rev*. 1995;15:235–256.
195. **Pope HG Jr, Kouri EM, Hudson JI.** Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. *Arch Gen Psychiatry*. 2000;57(2):133–140; discussion 155–136.
196. **Clark AS, Henderson LP.** Behavioral and physiological responses to anabolic-androgenic steroids. *Neurosci Biobehav Rev*. 2003;27(5):413–436.
197. **Melloni RH Jr, Connor DF, Hang PT, Harrison RJ, Ferris CF.** Anabolic-androgenic steroid exposure during adolescence and aggressive behavior in golden hamsters. *Physiol Behav*. 1997;61(3):359–364.
198. **DeLeon KR, Grimes JM, Melloni RH Jr.** Repeated anabolic-androgenic steroid treatment during adolescence increases vasopressin V(1A) receptor binding in Syrian hamsters: correlation with offensive aggression. *Horm Behav*. 2002;42(2):182–191.
199. **Conacher GN, Workman DG.** Violent crime possibly associated with anabolic steroid use. *Am J Psychiatry*. 1989;146(5):679.
200. **Pope HG Jr, Katz DL.** Homicide and near-homicide by anabolic steroid users. *J Clin Psychiatry*. 1990;51(1):28–31.
201. **Pope HG Jr, Kouri EM, Powell KF, Campbell C, Katz DL.** Anabolic-androgenic steroid use among 133 prisoners. *Compr Psychiatry*. 1996;37(5):322–327.
202. **Dalby JT.** Brief anabolic steroid use and sustained behavioral reaction. *Am J Psychiatry*. 1992;149(2):271–272.
203. **Schulte HM, Hall MJ, Boyer M.** Domestic violence associated with anabolic steroid abuse. *Am J Psychiatry*. 1993;150(2):348.
204. **Stanley A, Ward M.** Anabolic steroids–the drugs that give and take away manhood. A case with an unusual physical sign. *Med Sci Law*. 1994;34(1):82–83.
205. **Thiblin I, Kristiansson M, Rajs J.** Anabolic androgenic steroids and behavioural patterns among violent offenders. *J Forensic Psychiatry*. 1997;8:299–310.
206. **Thiblin I, Pärlklo T.** Anabolic androgenic steroids and violence. *Acta Psychiatr Scand Suppl*. 2002;412:125–128.
207. **Thiblin I, Petersson A.** Pharmacoepidemiology of anabolic androgenic steroids: a review. *Fundam Clin Pharmacol*. 2005;19(1):27–44.
208. **Klötz F, Petersson A, Isacson D, Thiblin I.** Violent crime and substance abuse: A medico-legal comparison between deceased users of anabolic androgenic steroids and abusers of illicit drugs. *Forensic Sci Int*. 2007;173(1):57–63.
209. **Klötz F, Petersson A, Hoffman O, Thiblin I.** The significance of anabolic androgenic steroids in a Swedish prison population. *Compr Psychiatry*. 2010;51(3):312–318.
210. **Lundholm L, Käll K, Wallin S, Thiblin I.** Use of anabolic androgenic steroids in substance abusers arrested for crime. *Drug Alcohol Depend*. 2010;111(3):222–226.
211. **Friedl KE, Dettori JR, Hannan CJ Jr, Patience TH, Plymate SR.** Comparison of the effects of high dose testosterone and 19-nortestosterone to a replacement dose of testosterone on strength and body composition in normal men. *J Steroid Biochem Mol Biol*. 1991;40(4–6):607–612.
212. **Friedl KE, Jones RE, Hannan CJ Jr, Plymate SR.** The administration of pharmacological doses of testosterone or 19-nortestosterone to normal men is not associated with increased insulin secretion or impaired glucose tolerance. *J Clin Endocrinol Metab*. 1989;68(5):971–975.
213. **Hannan CJ Jr, Friedl KE, Zold A, Kettler TM, Plymate SR.** Psychological and serum homovanillic acid changes in men administered androgenic steroids. *Psychoneuroendocrinology*. 1991;16(4):335–343.
214. **Matsumoto AM.** Effects of chronic testosterone administration in normal men: safety and efficacy of high dosage testosterone and parallel dose-dependent suppression of luteinizing hormone, follicle-stimulating hormone, and sperm production. *J Clin Endocrinol Metab*. 1990;70(1):282–287.
215. **Forbes GB, Porta CR, Herr BE, Griggs RC.** Sequence of changes in body composition induced by testosterone and reversal of changes after drug is stopped. *JAMA*. 1992;267(3):397–399.
216. **Bagatell CJ, Heiman JR, Matsumoto AM, Rivier JE, Bremner WJ.** Metabolic and behavioral effects of high-dose, exogenous testosterone in healthy men. *J Clin Endocrinol Metab*. 1994;79(2):561–567.
217. **Ip EJ, Barnett MJ, Tenerowicz MJ, Perry PJ.** The Anabolic 500 survey: characteristics of male users versus nonusers of

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

anabolic-androgenic steroids for strength training. *Pharmacotherapy*. 2011;31(8):757–766.
218. **Su TP, Pagliaro M, Schmidt PJ, Pickar D, Wolkowitz O, Rubinow DR.** Neuropsychiatric effects of anabolic steroids in male normal volunteers. *JAMA*. 1993;269(21):2760–2764.
219. **Tricker R, Casaburi R, Storer TW, et al.** The effects of supraphysiological doses of testosterone on angry behavior in healthy eugonadal men–a clinical research center study. *J Clin Endocrinol Metab*. 1996;81(10):3754–3758.
220. **Yates WR, Perry PJ, MacIndoe J, Holman T, Ellingrod V.** Psychosexual effects of three doses of testosterone cycling in normal men. *Biol psychiatry*. 1999;45(3):254–260.
221. **Kouri EM, Lukas SE, Pope HG Jr, Oliva PS.** Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate. *Drug Alcohol Depend*. 1995;40(1):73–79.
222. **Maldonado R, Blendy JA, Tzavara E, et al.** Reduction of morphine abstinence in mice with a mutation in the gene encoding CREB. *Science*. 1996;273(5275):657–659.
223. Guidance for industry. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. U.S. Food and Drug Administration website. http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf. Accessed July 11, 2013.
224. **Oberlander JG, Henderson LP.** The Sturm und Drang of anabolic steroid use: angst, anxiety, and aggression. *Trends Neurosci*. 2012;35(6):382–392.
225. **Rejeski WJ, Brubaker PH, Herb RA, Kaplan JR, Koritnik D.** Anabolic steroids and aggressive behavior in cynomolgus monkeys. *J Behav Med*. 1988;11(1):95–105.
226. **Lumia AR, Thorner KM, McGinnis MY.** Effects of chronically high doses of the anabolic androgenic steroid, testosterone, on intermale aggression and sexual behavior in male rats. *Physiol Behav*. 1994;55(2):331–335.
227. **Grimes JM, Ricci LA, Melloni RH Jr.** Glutamic acid decarboxylase (GAD65) immunoreactivity in brains of aggressive, adolescent anabolic steroid-treated hamsters. *Horm Behav*. 2003;44(3):271–280.
228. **Steensland P, Blakely G, Nyberg F, Fahlke C, Pohorecky LA.** Anabolic androgenic steroid affects social aggression and fear-related behaviors in male pair-housed rats. *Horm Behav*. 2005;48(2):216–224.
229. **Fischer SG, Ricci LA, Melloni RH Jr.** Repeated anabolic/androgenic steroid exposure during adolescence alters phosphate-activated glutaminase and glutamate receptor 1 (GluR1) subunit immunoreactivity in Hamster brain: correlation with offensive aggression. *Behav Brain Res*. 2007;180(1):77–85.
230. **Carrillo M, Ricci LA, Melloni RH.** Glutamate and the aggression neural circuit in adolescent anabolic steroid-treated Syrian hamsters (*Mesocricetus auratus*). *Behav Neurosci*. 2011;125(5):753–763.
231. **Breuer ME, McGinnis MY, Lumia AR, Possidente BP.** Aggression in male rats receiving anabolic androgenic steroids: effects of social and environmental provocation. *Horm Behav*. 2001;40(3):409–418.
232. **McGinnis MY, Lumia AR, Breuer ME, Possidente B.** Physical provocation potentiates aggression in male rats receiving anabolic androgenic steroids. *Horm Behav*. 2002;41(1):101–110.
233. **Hallberg M, Johansson P, Kindlundh AM, Nyberg F.** Anabolic-androgenic steroids affect the content of substance P and substance P(1–7) in the rat brain. *Peptides*. 2000;21(6):845–852.
234. **Le Grevès P, Huang W, Johansson P, Thörnwall M, Zhou Q, Nyberg F.** Effects of an anabolic-androgenic steroid on the regulation of the NMDA receptor NR1, NR2A and NR2B subunit mRNAs in brain regions of the male rat. *Neurosci Lett*. 1997;226(1):61–64.
235. **Henderson LP, Penatti CA, Jones BL, Yang P, Clark AS.** Anabolic androgenic steroids and forebrain GABAergic transmission. *Neuroscience*. 2006;138(3):793–799.
236. **Kindlundh AM, Lindblom J, Bergström L, Nyberg F.** The anabolic-androgenic steroid nandrolone induces alterations in the density of serotonergic 5HT1B and 5HT2 receptors in the male rat brain. *Neuroscience*. 2003;119(1):113–120.
237. **Keleta YB, Lumia AR, Anderson GM, McGinnis MY.** Behavioral effects of pubertal anabolic androgenic steroid exposure in male rats with low serotonin. *Brain Res*. 2007;1132(1):129–138.
238. **Kindlundh AM, Hagekull B, Isacson DG, Nyberg F.** Adolescent use of anabolic-androgenic steroids and relations to self-reports of social, personality and health aspects. *Eur J Public Health*. 2001;11(3):322–328.
239. **Schwartzer JJ, Melloni RH Jr.** Anterior hypothalamic dopamine D2 receptors modulate adolescent anabolic/androgenic steroid-induced offensive aggression in the Syrian hamster. *Behav Pharmacol*. 2010;21(4):314–322.
240. **Lindqvist AS, Johansson-Steensland P, Nyberg F, Fahlke C.** Anabolic androgenic steroid affects competitive behaviour, behavioural response to ethanol and brain serotonin levels. *Behav Brain Res*. 2002;133(1):21–29.
241. **Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope HG.** Treatment of anabolic-androgenic steroid dependence: emerging evidence and its implications. *Drug Alcohol Depend*. 2010;109:6–13.
242. **Pope HG Jr, Gruber AJ, Choi P, Olivardia R, Phillips KA.** Muscle dysmorphia. An underrecognized form of body dysmorphic disorder. *Psychosomatics*. 1997;38(6):548–557.
243. **Kanayama G, Pope HG Jr.** Gods, men, and muscle dysmorphia. *Harvard Rev Psychiatry*. 2011;19:95–98.
244. **Cole JC, Smith R, Halford JC, Wagstaff GF.** A preliminary investigation into the relationship between anabolic-androgenic steroid use and the symptoms of reverse anorexia in both current and ex-users. *Psychopharmacology*. 2003;166(4):424–429.
245. **Pope HG Jr, Katz DL, Hudson JI.** Anorexia nervosa and "reverse anorexia" among 108 male bodybuilders. *Compr Psychiatry*. 1993;34(6):406–409.
246. **Association AP.** *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
247. **Kanayama G, Barry S, Hudson JI, Pope HG Jr.** Body image and attitudes toward male roles in anabolic-androgenic steroid users. *Am J Psychiatry*. 2006;163(4):697–703.
248. **Chung B.** Muscle dysmorphia in weightlifters. *Br J Sports Med*. 2003;37(3):280–281.
249. **Olivardia R, Pope HG Jr, Hudson JI.** Muscle dysmorphia

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

in male weightlifters: a case-control study. *Am J Psychiatry*. 2000;157(8):1291–1296.
250. **Hildebrandt T, Alfano L, Langenbucher JW.** Body image disturbance in 1000 male appearance and performance enhancing drug users. *J Psychiatr Res*. 2010;44(13):841–846.
251. **Pope CG, Pope HG, Menard W, Fay C, Olivardia R, Phillips KA.** Clinical features of muscle dysmorphia among males with body dysmorphic disorder. *Body Image*. 2005;2(4):395–400.
252. **Rohman L.** The relationship between anabolic androgenic steroids and muscle dysmorphia: a review. *Eat Disord*. 2009;17(3):187–199.
253. **Kashkin KB, Kleber HD.** Hooked on hormones? An anabolic steroid addiction hypothesis. *JAMA*. 1989;262(22):3166–3170.
254. **Tan RS, Scally MC.** Anabolic steroid-induced hypogonadism–towards a unified hypothesis of anabolic steroid action. *Med Hypotheses*. 2009;72(6):723–728.
255. **Llewellyn W.** *Anabolics*. 10th ed. Jupiter, FL: Molecular Nutrition; 2011.
256. **Pinna G, Agis-Balboa RC, Pibiri F, Nelson M, Guidotti A, Costa E.** Neurosteroid biosynthesis regulates sexually dimorphic fear and aggressive behavior in mice. *Neurochem Res*. 2008;33(10):1990–2007.
257. **Elfverson M, Johansson T, Zhou Q, Le Grevès P, Nyberg F.** Chronic administration of the anabolic androgenic steroid nandrolone alters neurosteroid action at the sigma-1 receptor but not at the sigma-2 or NMDA receptors. *Neuropharmacology*. 2011;61(7):1172–1181.
258. **Skuza G.** Pharmacology of sigma (σ) receptor ligands from a behavioral perspective. *Curr Pharm Des*. 2012;18(7):863–874.
259. **Johansson T, Elfverson M, Zhou Q, Nyberg F.** Allosteric modulation of the NMDA receptor by neurosteroids in rat brain and the impact of long term morphine administration. *Biochem Biophys Res Commun*. 2010;401(4):504–508.
260. **Arnedo MT, Salvador A, Martinez-Sanchis S, Gonzalez-Bono E.** Rewarding properties of testosterone in intact male mice: a pilot study. *Pharmacol Biochem Behav*. 2000;65(2):327–332.
261. **Arnedo MT, Salvador A, Martínez-Sanchís S, Pellicer O.** Similar rewarding effects of testosterone in mice rated as short and long attack latency individuals. *Addict Biol*. 2002;7:373–379.
262. **Alexander GM, Packard MG, Hines M.** Testosterone has rewarding affective properties in male rats: implications for the biological basis of sexual motivation. *Behav Neurosci*. 1994;108(2):424–428.
263. **Wood RI.** Anabolic-androgenic steroid dependence? Insights from animals and humans. *Front Neuroendocrinol*. 2008;29(4):490–506; PMC 2585375.
264. **Zaugg M, JAMAli NZ, Lucchinetti E, Xu W, Alam M, Shafiq SA, Siddiqui MA.** Anabolic-androgenic steroids induce apoptotic cell death in adult rat ventricular myocytes. *Journal of cellular physiology*. 2001;187(1):90–95.
265. **Abu-Shakra S, Alhalabi MS, Nachtman FC, Schemidt RA, Brusilow WS.** Anabolic steroids induce injury and apoptosis of differentiated skeletal muscle. *J Neurosci Res*. 1997;47(2):186–197.
266. **D'Ascenzo S, Millimaggi D, Di Massimo C, et al.** Detrimental effects of anabolic steroids on human endothelial cells. *Toxicol Lett*. 2007;169(2):129–136.
267. **Fanton L, Belhani D, Vaillant F, et al.** Heart lesions associated with anabolic steroid abuse: Comparison of postmortem findings in athletes and norethandrolone-induced lesions in rabbits. *Exp Toxicol Pathol*. 2009;61:317–323.
268. **Vicencio JM, Estrada M, Galvis D, et al.** Anabolic androgenic steroids and intracellular calcium signaling: a mini review on mechanisms and physiological implications. *Mine Rev Med Chem*. 2011;11(5):390–398.
269. **Janjic MM, Stojkov NJ, Andric SA, Kostic TS.** Anabolic-androgenic steroids induce apoptosis and NOS2 (nitric-oxide synthase 2) in adult rat Leydig cells following in vivo exposure. *Reprod Toxicol*. 2012;34(4):686–693.
270. **Estrada M, Varshney A, Ehrlich BE.** Elevated testosterone induces apoptosis in neuronal cells. *J Biol Chem*. 2006;281(35):25492–25501.
271. **Caraci F, Pistarà V, Corsaro A, et al.** Neurotoxic properties of the anabolic androgenic steroids nandrolone and methandrostenolone in primary neuronal cultures. *J Neurosci Res*. 2011;89(4):592–600.
272. **Cunningham RL, Giuffrida A, Roberts JL.** Androgens induce dopaminergic neurotoxicity via caspase-3-dependent activation of protein kinase Cδ. *Endocrinology*. 2009;150(12):5539–5548.
273. **Pieretti S, Mastriota M, Tucci P, et al.** Brain nerve growth factor unbalance induced by anabolic androgenic steroids in rats. *Med Sci Sports Exerc*. 2013;45(1):29–35.
274. **Reyes-Fuentes A, Veldhuis JD.** Neuroendocrine physiology of the normal male gonadal axis. *Endocrinol Metab Clin North Am*. 1993;22(1):93–124.
275. **Gårevik N, Strahm E, Garle M, et al.** Long term perturbation of endocrine parameters and cholesterol metabolism after discontinued abuse of anabolic androgenic steroids. *J Steroid Biochem Mol Biol*. 2011;127:295–300.
276. **van Breda E, Keizer HA, Kuipers H, Wolffenbuttel BH.** Androgenic anabolic steroid use and severe hypothalamic-pituitary dysfunction: a case study. *Int J Sports Med*. 2003;24(3):195–196.
277. **Menon DK.** Successful treatment of anabolic steroid-induced azoospermia with human chorionic gonadotropin and human menopausal gonadotropin. *Fertil Steril*. 2003;79(Suppl 3):1659–1661.
278. **de Souza GL, Hallak J.** Anabolic steroids and male infertility: a comprehensive review. *BJU Int*. 2011;108:1860–1865.
279. **Boregowda K, Joels L, Stephens JW, Price DE.** Persistent primary hypogonadism associated with anabolic steroid abuse. *Fertil Steril*. 2011;96(1):e7–e8.
280. **Tan RS, Vasudevan D.** Use of clomiphene citrate to reverse premature andropause secondary to steroid abuse. *Fertil Steril*. 2003;79(1):203–205.
281. **Guay AT, Jacobson J, Perez JB, Hodge MB, Velasquez E.** Clomiphene increases free testosterone levels in men with both secondary hypogonadism and erectile dysfunction: who does and does not benefit? *Int J Impot Res*. 2003;15(3):156–165.
282. **Takayanagi A, Kobayashi K, Hashimoto K, et al.** Case of androgenic anabolic steroid abuse caused hypogonado-

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

tropic hypogonadism [in Japanese]. *Nihon Hinyokika Gakkai Zasshi*. 2008;99(7):729–732.
283. **Crampin AC, Lamagni TL, Hope VD, Newham JA, Lewis KM, Parry JV, Gill ON.** The risk of infection with HIV and hepatitis B in individuals who inject steroids in England and Wales. *Epidemiol Infect*. 1998;121(2):381–386.
284. **Sklarek HM, Mantovani RP, Erens E, Heisler D, Niederman MS, Fein AM.** AIDS in a bodybuilder using anabolic steroids. *N Engl J Med*. 1984;311(26):1701.
285. **Scott MJ, Scott MJ Jr.** HIV infection associated with injections of anabolic steroids. *JAMA*. 1989;262(2):207–208.
286. **Henrion R, Mandelbrot L, Delfieu D.** HIV contamination after injections of anabolic steroids [in French]. *Presse Med*. 1992;21(5):218.
287. **Rich JD, Dickinson BP, Merriman NA, Flanigan TP.** Hepatitis C virus infection related to anabolic-androgenic steroid injection in a recreational weight lifter. *Am J Gastroenterol*. 1998;93(9):1598.
288. **Nemechek PM.** Anabolic steroid users–another potential risk group for HIV infection. *N Engl J Med*. 1991;325(5):357.
289. **Bolding G, Sherr L, Maguire M, Elford J.** HIV risk behaviours among gay men who use anabolic steroids. *Addiction*. 1999;94(12):1829–1835.
290. **Nemechek PM, Polsky B, Gottlieb MS.** Treatment guidelines for HIV-associated wasting. *Mayo Clin Proc*. 2000;75(4):386–394.
291. **Isacsson G, Garle M, Ljung EB, Asgård U, Bergman U.** Anabolic steroids and violent crime–an epidemiological study at a jail in Stockholm, Sweden. *Compr Psychiatry*. 1998;39(4):203–205.
292. **Lood Y, Eklund A, Garle M, Ahlner J.** Anabolic androgenic steroids in police cases in Sweden 1999–2009. *Forensic Sci Int*. 2012;219(1–3):199–204.
293. **Baillargeon J, Black SA, Leach CT, et al.** The infectious disease profile of Texas prison inmates. *Prev Med*. 2004;38(5):607–612.
294. **Hennessey KA, Kim AA, Griffin V, Collins NT, Weinbaum CM, Sabin K.** Prevalence of infection with hepatitis B and C viruses and co-infection with HIV in three jails: a case for viral hepatitis prevention in jails in the United States. *J Urban Health*. 2009;86(1):93–105.
295. **MacDougall DS.** HIV/AIDS behind bars. *J Int Assoc Physicians AIDS Care*. 1998;4(4):8–13.
296. **Mahon N.** New York inmates' HIV risk behaviors: the implications for prevention policy and programs. *Am J Public Health*. 1996;86(9):1211–1215.
297. **Rothon DA, Mathias RG, Schechter MT.** Prevalence of HIV infection in provincial prisons in British Columbia. *CMAJ*. 1994;151(6):781–787.
298. **Centers for Disease Control and Prevention (CDC).** Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants – Colorado, Indiana, Pennsylvania, and Los Angeles County, 2000–2003. *MMWR*. 2003;52:793–795.
299. **Lloyd-Smith E, Hull MW, Tyndall MW, et al.** Community-associated methicillin-resistant *Staphylococcus aureus* is prevalent in wounds of community-based injection drug users. *Epidemiol Infect*. 2010;138(5):713–720.
300. **Evans NA.** Local complications of self administered anabolic steroid injections. *Br J Sports Med*. 1997;31(4):349–350.
301. **Rich JD, Dickinson BP, Flanigan TP, Valone SE.** Abscess related to anabolic-androgenic steroid injection. *Med Sci Sports Exerc*. 1999;31(2):207–209.
302. **Palacios A, Campfield LA, McClure RD, Steiner B, Swerdloff RS.** Effect of testosterone enanthate on hematopoiesis in normal men. *Fertil Steril*. 1983;40(1):100–104.
303. **Maggio M, Snyder PJ, Ceda GP, et al.** Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. *Andrology*. 2013;1(1):24–28.
304. **Bachman E, Travison TG, Basaria S, et al.** Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point [published online October 24, 2013]. *J Gerontol A Biol Sci Med Sci*. doi:10.1093/gerona/glt154.
305. **Bachman E, Feng R, Travison T, et al.** Testosterone suppresses hepcidin in men: a potential mechanism for testosterone-induced erythrocytosis. *J Clin Endocrinol Metab*. 2010;95(10):4743–4747.
306. **Guo W, Bachman E, Li M, et al.** Testosterone administration inhibits hepcidin transcription and is associated with increased iron incorporation into red blood cells. *Aging Cell*. 2013;12(2):280–291.
307. **Pertusi R, Dickerman RD, McConathy WJ.** Evaluation of aminotransferase elevations in a bodybuilder using anabolic steroids: hepatitis or rhabdomyolysis? *J Am Osteopath Assoc*. 2001;101(7):391–394.
308. **Daniels JM, van Westerloo DJ, de Hon OM, Frissen PH.** Rhabdomyolysis in a bodybuilder using steroids [in Dutch]. *Ned Tijdschr Geneeskd*. 2006;150(19):1077–1080.
309. **Hageloch W, Appell HJ, Weicker H.** Rhabdomyolysis in a bodybuilder using anabolic steroids [in German]. *Sportverletz Sportschaden*. 1988;2(3):122–125.
310. **Adamson R, Rambaran C, D'Cruz DP.** Anabolic steroid-induced rhabdomyolysis. *Hosp Med*. 2005;66(6):362.
311. **Braseth NR, Allison EJ Jr, Gough JE.** Exertional rhabdomyolysis in a body builder abusing anabolic androgenic steroids. *Eur J Emerg Med*. 2001;8(2):155–157.
312. **Winnett G, Cranfield L, Almond M.** Apparent renal disease due to elevated creatinine levels associated with the use of boldenone. *Nephrol Dial Transplant*. 2011;26(2):744–747.
313. **Herlitz LC, Markowitz GS, Farris AB, et al.** Development of focal segmental glomerulosclerosis after anabolic steroid abuse. *J Am Soc Nephrol*. 2010;21:163–172.
314. **Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM.** Liver damage from long-term methyltestosterone. *Lancet*. 1977;2(8032):262–263.
315. **Karasawa T, Shikata T, Smith RD.** Peliosis hepatis. Report of nine cases. *Acta Pathol Jpn*. 1979;29(3):457–469.
316. **Schumacher J, Müller G, Klotz KF.** Large hepatic hematoma and intraabdominal hemorrhage associated with abuse of anabolic steroids. *N Engl J Med*. 1999;340(14):1123–1124.
317. **Daneshmend TK, Bradfield JW.** Hepatic angiosarcoma associated with androgenic-anabolic steroids. *Lancet*. 1979;2(8154):1249.
318. **Falk H, Thomas LB, Popper H, Ishak KG.** Hepatic angio-

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

sarcoma associated with androgenic-anabolic steroids. *Lancet*. 1979;2(8152):1120–1123.
319. **Bagia S, Hewitt PM, Morris DL.** Anabolic steroid-induced hepatic adenomas with spontaneous haemorrhage in a bodybuilder. *Aust N Z J Surg*. 2000;70(9):686–687.
320. **Nakao A, Sakagami K, Nakata Y, et al.** Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. *J Gastroenterol*. 2000; 35(7):557–562.
321. **Velazquez I, Alter BP.** Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol*. 2004;77(3):257–267.
322. **Gorayski P, Thompson CH, Subhash HS, Thomas AC.** Hepatocellular carcinoma associated with recreational anabolic steroid use. *Br J Sports Med*. 2008;42(1):74–75; discussion 75.
323. **Carrasco D, Prieto M, Pallardó L, et al.** Multiple hepatic adenomas after long-term therapy with testosterone enanthate. Review of the literature. *J Hepatol*. 1985;1(6):573–578.
324. **Modlinski R, Fields KB.** The effect of anabolic steroids on the gastrointestinal system, kidneys, and adrenal glands. *Curr Sports Med Rep*. 2006;5(2):104–109.
325. **Neri M, Bello S, Bonsignore A, et al.** Anabolic androgenic steroids abuse and liver toxicity. *Mine Rev Med Chem*. 2011;11(5):430–437.
326. **Pettersson J, Hindorf U, Persson P, et al.** Muscular exercise can cause highly pathological liver function tests in healthy men. *Br J Clin Pharmacol*. 2008;65(2):253–259.
327. **Dickerman RD, Pertusi RM, Zachariah NY, Dufour DR, McConathy WJ.** Anabolic steroid-induced hepatotoxicity: is it overstated? *Clin J Sport Med*. 1999;9(1):34–39.
328. **Nikolopoulos DD, Spiliopoulou C, Theocharis SE.** Doping and musculoskeletal system: short-term and long-lasting effects of doping agents. *Fundam Clin Pharmacol*. 2011;25(5):535–563.
329. **Horn S, Gregory P, Guskiewicz KM.** Self-reported anabolic-androgenic steroids use and musculoskeletal injuries: findings from the center for the study of retired athletes health survey of retired NFL players. *Am J Phys Med Rehab*. 2009;88(3):192–200.
330. **Laseter JT, Russell JA.** Anabolic steroid-induced tendon pathology: a review of the literature. *Med Sci Sports Exerc*. 1991;23(1):1–3.
331. **Stannard JP, Bucknell AL.** Rupture of the triceps tendon associated with steroid injections. *Am J Sports Med*. 1993; 21(3):482–485.
332. **Visuri T, Lindholm H.** Bilateral distal biceps tendon avulsions with use of anabolic steroids. *Med Sci Sports Exerc*. 1994;26(8):941–944.
333. **David HG, Green JT, Grant AJ, Wilson CA.** Simultaneous bilateral quadriceps rupture: a complication of anabolic steroid abuse. *J Bone Joint Surg*. 1995;77(1):159–160.
334. **Lambert MI, St Clair Gibson A, Noakes TD.** Rupture of the triceps tendon associated with steroid injections. *Am J Sports Med*. 1995;23(6):778.
335. **Liow RY, Tavares S.** Bilateral rupture of the quadriceps tendon associated with anabolic steroids. *Br J Sports Med*. 1995;29(2):77–79.
336. **Sollender JL, Rayan GM, Barden GA.** Triceps tendon rupture in weight lifters. *J Shoulder Elbow Surg*. 1998;7(2): 151–153.
337. **Cope MR, Ali A, Bayliss NC.** Biceps rupture in body builders: three case reports of rupture of the long head of the biceps at the tendon-labrum junction. *J Shoulder Elbow Surg*. 2004;13(5):580–582.
338. **Evans NA, Bowrey DJ, Newman GR.** Ultrastructural analysis of ruptured tendon from anabolic steroid users. *Injury*. 1998;29(10):769–773.
339. **Michna H.** Organisation of collagen fibrils in tendon: changes induced by an anabolic steroid. I. Functional and ultrastructural studies. *Virchows Archiv*. 1986;52(1):75–86.
340. **Wood TO, Cooke PH, Goodship AE.** The effect of exercise and anabolic steroids on the mechanical properties and crimp morphology of the rat tendon. *Am J Sports Med*. 1988;16(2):153–158.
341. **Inhofe PD, Grana WA, Egle D, Min KW, Tomasek J.** The effects of anabolic steroids on rat tendon. An ultrastructural, biomechanical, and biochemical analysis. *Am J Sports Med*. 1995;23(2):227–232.
342. **Brenu EW, McNaughton L, Marshall-Gradisnik SM.** Is there a potential immune dysfunction with anabolic androgenic steroid use?: A review. *Mine Rev Med Chem*. 2011;11(5):438–445.
343. **Vougiouklakis T, Mitselou A, Batistatou A, Boumba V, Charalabopoulos K.** First case of fatal pulmonary peliosis without any other organ involvement in a young testosterone abusing male. *Forensic Sci Int*. 2009;186(1–3):e13–16.
344. **Kraus SL, Emmert S, Schön MP, Haenssle HA.** The dark side of beauty: acne fulminans induced by anabolic steroids in a male bodybuilder. *Arch Dermatol*. 2012;148(10): 1210–1212.
345. **Froehner M, Fischer R, Leike S, Hakenberg OW, Noack B, Wirth MP.** Intratesticular leiomyosarcoma in a young man after high dose doping with Oral-Turinabol: a case report. *Cancer*. 1999;86(8):1571–1575.
346. **Martorana G, Concetti S, Manferrari F, Creti S.** Anabolic steroid abuse and renal cell carcinoma. *J Urol*. 1999; 162(6):2089.
347. **Bryden AA, Rothwell PJ, O'Reilly PH.** Anabolic steroid abuse and renal-cell carcinoma. *Lancet*. 1995;346(8985): 1306–1307.
348. **Roberts JT, Essenhigh DM.** Adenocarcinoma of prostate in 40-year-old body-builder. *Lancet*. 1986;2(8509):742.
349. **Larkin GL.** Carcinoma of the prostate. *N Engl J Med*. 1991;324(26):1892.
350. **Wiesing U.** Should performance-enhancing drugs in sport be legalized under medical supervision? *Sports Med*. 2011; 41(2):167–176.
351. **Shuster S, Devine JW.** The banning of sportsmen and women who fail drug tests is unjustifiable. *J R Coll Physicians Edinb*. 2013;43(1):39–43.
352. **Savulescu J, Foddy B, Clayton M.** Why we should allow performance enhancing drugs in sport. *Br J Sports Med*. 2004;38(6):666–670.
353. **Donike M, Barwald KR, Klostermann K, Schanzer W, Zimmermann J.** The detection of exogenous testosterone. In: Liesen H, Rost R, eds. *Sport: Leistung Gesundheit*. Cologne, Germany: Deutscher Arzte; 1982;293–298.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

354. **Baenziger J, Bowers LD.** Variability of T/E ratios in athletes. In: Donike M, Geyer H, Gotzmann A, Mareck-Engelke U, Rauth S, eds. *Recent Advances in Doping Analysis*. Vol 2. Köln, Germany: Sport und Buch Strauss; 1994: 41–52.
355. **Sottas PE, Baume N, Saudan C, Schweizer C, Kamber M, Saugy M.** Bayesian detection of abnormal values in longitudinal biomarkers with an application to T/E ratio. *Biostatistics*. 2007;8(2):285–296.
356. **Chen EY, Liao YC, Smith DH, Barrera-Saldaña HA, Gelinas RE, Seeburg PH.** The human growth hormone locus: nucleotide sequence, biology, and evolution. *Genomics*. 1989;4(4):479–497.
357. **Schulze JJ, Lundmark J, Garle M, Skilving I, Ekström L, Rane A.** Doping test results dependent on genotype of uridine diphospho-glucuronosyl transferase 2B17, the major enzyme for testosterone glucuronidation. *J Clin Endocrinol Metab*. 2008;93(7):2500–2506.
358. **Anielski P, Simmchen J, Wassill L, Ganghofner D, Thieme D.** Epidemiological investigation of the UGT2B17 polymorphism in doping control urine samples and its correlation to T/E ratios. *Drug Test Anal*. 2011;3(10):645–651.
359. **Xue Y, Sun D, Daly A, et al.** Adaptive evolution of UGT2B17 copy-number variation. *Am J Hum Genet*. 2008;83(3):337–346.
360. **Becchi M, Aguilera R, Farizon Y, Flament MM, Casabianca H, James P.** Gas chromatography/combustion/isotope-ratio mass spectrometry analysis of urinary steroids to detect misuse of testosterone in sport. *Rapid Communications in Mass Spectrometry*. 1994;8(4):304–308.
361. **Kicman AT.** Pharmacology of anabolic steroids. *Br J Pharmacol*. 2008;154(3):502–521.
362. **Kicman AT.** Biochemical and physiological aspects of endogenous androgens. *Handb Exp Pharmacol*. 2010;195: 25–64.
363. **Schänzer W.** Metabolism of anabolic androgenic steroids. *Clin Chem*. 1996;42(7):1001–1020.
364. **Horning S, Hoehn M, Muenster H, Geyer H, Schänzer W.** GC/HRMS-ION TRAP screening and confirmation of anabolic steroids. Paper presented at 16th Cologne Workshop on Dope Analysis; March 15–20, 1998; Cologne, Germany.
365. **Thevis M, Makarov AA, Horning S, Schänzer W.** Mass spectrometry of stanozolol and its analogues using electrospray ionization and collision-induced dissociation with quadrupole-linear ion trap and linear ion trap-orbitrap hybrid mass analyzers. *Rapid Commun Mass Spectrom*. 2005;19(22):3369–3378.
366. **Geyer H, Parr MK, Koehler K, Mareck U, Schänzer W, Thevis M.** Nutritional supplements cross-contaminated and faked with doping substances. *J Mass Spectrom*. 2008; 43(7):892–902.
367. **Carroll PV, Christ ER, Bengtsson BA, et al.** Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *J Clin Endocrinol Metab*. 1998;83(2):382–395.
368. **Baumann GP.** Growth hormone doping in sports: a critical review of use and detection strategies. *Endocr Rev*. 2012; 33(2):155–186.
369. **Baumann G.** Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. *Endocr Rev*. 1991;12(4):424–449.
370. **Liu H, Bravata DM, Olkin I, et al.** Systematic review: the effects of growth hormone on athletic performance. *Ann Intern Med*. 2008;148(10):747–758.
371. **Rennie MJ.** Claims for the anabolic effects of growth hormone: a case of the emperor's new clothes? *Br J Sports Med*. 2003;37(2):100–105.
372. **Birzniece V, Nelson AE, Ho KK.** Growth hormone and physical performance. *Trends Endocrinol Metab*. 2011; 22(5):171–178.
373. **Pipe A.** Growth hormone temporarily improves sprint capacity in recreational athletes. *Clin J Sport Med*. 2011; 21(4):369–370.
374. **Meinhardt U, Nelson AE, Hansen JL, et al.** The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. *Ann Intern Med*. 2010;152(9):568–577.
375. **Woodhouse LJ, Asa SL, Thomas SG, Ezzat S.** Measures of submaximal aerobic performance evaluate and predict functional response to growth hormone (GH) treatment in GH-deficient adults. *J Clin Endocrinol Metab*. 1999; 84(12):4570–4577.
376. **Wass JA, Trainer PJ, Korbonits M.** Acromegaly. In: Wass J, Stewart P, eds. *Oxford Textbook of Endocrinology and Diabetes*. 2nd ed. Oxford, UK: Oxford Press; 2011;197–209.
377. **Dutta P, Bhansali A, Vaiphei K, et al.** Colonic neoplasia in acromegaly: increased proliferation or deceased apoptosis? *Pituitary*. 2012;15(2):166–173.
378. **Jenkins PJ, Fairclough PD, Richards T, et al.** Acromegaly, colonic polyps and carcinoma. *Clin Endocrinol (Oxf)*. 1997;47(1):17–22.
379. **Jenkins PJ, Frajese V, Jones AM, et al.** Insulin-like growth factor I and the development of colorectal neoplasia in acromegaly. *J Clin Endocrinol Metab*. 2000;85(9):3218–3221.
380. **Tita P, Ambrosio MR, Scollo C, et al.** High prevalence of differentiated thyroid carcinoma in acromegaly. *Clin Endocrinol (Oxf)*. 2005;63(2):161–167.
381. **Bidlingmaier M, Suhr J, Ernst A, et al.** High-sensitivity chemiluminescence immunoassays for detection of growth hormone doping in sports. *Clin Chem*. 2009;55(3):445–453.
382. **Wallace JD, Cuneo RC, Bidlingmaier M, et al.** Changes in non-22-kilodalton (kDa) isoforms of growth hormone (GH) after administration of 22-kDa recombinant human GH in trained adult males. *J Clin Endocrinol Metab*. 2001; 86(4):1731–1737.
383. **Erotokritou-Mulligan I, Guha N, Stow M, et al.** The development of decision limits for the implementation of the GH-2000 detection methodology using current commercial insulin-like growth factor-I and amino-terminal propeptide of type III collagen assays. *Growth Horm IGF Res*. 2012;22(2):53–58.
384. **Wallace JD, Cuneo RC, Lundberg PA, et al.** Responses of markers of bone and collagen turnover to exercise, growth hormone (GH) administration, and GH withdrawal in trained adult males. *J Clin Endocrinol Metab*. 2000;85(1): 124–133.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022

385. **Azzazy HM, Mansour MM, Christenson RH.** Gene doping: of mice and men. *Clin Biochem*. 2009;42(6):435–441.
386. **Biolo G, Declan Fleming RY, Wolfe RR.** Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. *J Clin Invest*. 1995;95(2):811–819.
387. **Elliott S.** Erythropoiesis-stimulating agents and other methods to enhance oxygen transport. *Br J Pharmacol*. 2008;154(3):529–541.
388. **Erslev AJ.** Erythropoietin. *N Engl J Med*. 1991;324(19):1339–1344.
389. **Fisher LM.** Stamina-building drug linked to athletes. *New York Times*. May 19, 1991. http://www.nytimes.com/1991/05/19/us/stamina-building-drug-linked-to-athletes-deaths.html. Accessed January 30, 2013.
390. **Lasne F, de Ceaurriz J.** Recombinant erythropoietin in urine. *Nature*. 2000;405(6787):635.
391. **Lasne F, Martin L, Crepin N, de Ceaurriz J.** Detection of isoelectric profiles of erythropoietin in urine: differentiation of natural and administered recombinant hormones. *Anal Biochem*. 2002;311(2):119–126.
392. **Takeuchi M, Kobata A.** Structures and functional roles of the sugar chains of human erythropoietins. *Glycobiology*. 1991;1(4):337–346.
393. **Reichel C, Kulovics R, Jordan V, Watzinger M, Geisendorfer T.** SDS-PAGE of recombinant and endogenous erythropoietins: benefits and limitations of the method for application in doping control. *Drug Test Anal*. 2009;1(1):43–50.
394. **Morkeberg J, Sharpe K, Karstoft K, Ashenden MJ.** Detection of microdoses of rhEPO with the MAIIA test [published online January 24, 2013]. *Scand J Med Sci Sports*. doi:10.1111/sms.12049.
395. **Lönnberg M, Drevin M, Carlsson J.** Ultra-sensitive immunochromatographic assay for quantitative determination of erythropoietin. *J Immunol Methods*. 2008;339(2):236–244.
396. **Schumacher YO, Saugy M, Pottgiesser T, Robinson N.** Detection of EPO doping and blood doping: the haematological module of the Athlete Biological Passport. *Drug Test Anal*. 2012;4(11):846–853.
397. **Zorzoli M, Rossi F.** Case studies on ESA-doping as revealed by the Biological Passport. *Drug Test Anal*. 2012;4(11):854–858.
398. **Monfort N, Ventura R, Platen P, et al.** Plasticizers excreted in urine: indication of autologous blood transfusion in sports. *Transfusion*. 2012;52(3):647–657.
399. **Segura J, Monfort N, Ventura R.** Detection methods for autologous blood doping. *Drug Test Anal*. 2012;4(11):876–881.
400. **DeKosky ST, Ikonomovic MD, Gandy S.** Traumatic brain injury–football, warfare, and long-term effects. *N Engl J Med*. 2010;363(14):1293–1296.
401. Steroid test results. Army Substance Abuse Program. Washington, DC: U.S. Army; 2012:3.
402. **Nuñez J.** Sex and steroid hormones in early brain injury. *Rev Endocr Metab Disord*. 2012;13(3):173–186.
403. **Vagnerova K, Koerner IP, Hurn PD.** Gender and the injured brain. *Anesth Analg*. 2008;107(1):201–214.
404. **van der Gronde T, de Hon O, Haisma HJ, Pieters T.** Gene doping: an overview and current implications for athletes. *Br J Sports Med*. 2013;47(11):670–678.
405. **Sweeney HL.** Gene doping. *Sci Am*. 2004;291(1):62–69.
406. **Kay MA.** State-of-the-art gene-based therapies: the road ahead. *Nat Rev Genet*. 2011;12(5):316–328.
407. **Mingozzi F, High KA.** Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges. *Nat Rev Genet*. 2011;12(5):341–355.
408. **Sheridan C.** Gene therapy finds its niche. *Nat Biotechnol*. 2011;29(2):121–128.
409. **Carpentier AC, Frisch F, Labbé SM, et al.** Effect of alipogene tiparvovec (AAV1-LPL(S447X)) on postprandial chylomicron metabolism in lipoprotein lipase-deficient patients. *J Clin Endocrinol Metab*. 2012;97(5):1635–1644.
410. **Tian G, Liu J, Sui J.** A patient with huge hepatocellular carcinoma who had a complete clinical response to p53 gene combined with chemotherapy and transcatheter arterial chemoembolization. *Anticancer Drugs*. 2009;20(5):403–407.
411. **Svensson EC, Black HB, Dugger DL, et al.** Long-term erythropoietin expression in rodents and non-human primates following intramuscular injection of a replication-defective adenoviral vector. *Hum Gene Ther*. 1997;8(15):1797–1806.
412. **Binley K, Askham Z, Iqball S, et al.** Long-term reversal of chronic anemia using a hypoxia-regulated erythropoietin gene therapy. *Blood*. 2002;100(7):2406–2413.
413. **Puskovic V, Wolfe D, Wechuck J, et al.** HSV-mediated delivery of erythropoietin restores dopaminergic function in MPTP-treated mice. *Mol Ther*. 2006;14(5):710–715.
414. **Musarò A, McCullagh K, Paul A, et al.** Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nat Genet*. 2001;27(2):195–200.
415. **Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R.** Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. *Endocr Rev*. 2009;30(6):586–623.
416. **Lee SJ.** Regulation of muscle mass by myostatin. *Annu Rev Cell Dev Biol*. 2004;20:61–86.
417. **Schuelke M, Wagner KR, Stolz LE, et al.** Myostatin mutation associated with gross muscle hypertrophy in a child. *N Engl J Med*. 2004;350(26):2682–2688.
418. **Vogel G.** Mighty mice: inspiration for rogue athletes? *Science*. 2004;305(5684):633.
419. **Lee SJ.** Sprinting without myostatin: a genetic determinant of athletic prowess. *Trends Genet*. 2007;23(10):475–477.
420. **Moser DA, Neuberger EW, Simon P.** A quick one-tube nested PCR-protocol for EPO transgene detection. *Drug Test Anal*. 2012;4(11):870–875.
421. **Neuberger EW, Jurkiewicz M, Moser DA, Simon P.** Detection of EPO gene doping in blood. *Drug Test Anal*. 2012;4(11):859–869.

Downloaded from https://academic.oup.com/edrv/article/35/3/341/2354633 by guest on 20 August 2022