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Illicit anabolic–androgenic steroid use

Gen Kanayama, James I. Hudson, Harrison G. Pope Jr. *

Biological Psychiatry Laboratory, McLean Hospital, Belmont, and Harvard Medical School, Boston, MA, USA

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ABSTRACT

The anabolic–androgenic steroids (AAS) are a family of hormones that includes testosterone and its derivatives. These substances have been used by elite athletes since the 1950s, but they did not become widespread drugs of abuse in the general population until the 1980s. Thus, knowledge of the medical and behavioral effects of illicit AAS use is still evolving. Surveys suggest that many millions of boys and men, primarily in Western countries, have abused AAS to enhance athletic performance or personal appearance. AAS use among girls and women is much less common. Taken in supraphysiologic doses, AAS show various long-term adverse medical effects, especially cardiovascular toxicity. Behavioral effects of AAS include hypomanic or manic symptoms, sometimes accompanied by aggression or violence, which usually occur while taking AAS, and depressive symptoms occurring during AAS withdrawal. However, these symptoms are idiosyncratic and afflict only a minority of illicit users; the mechanism of these idiosyncratic responses remains unclear. AAS users may also ingest a range of other illicit drugs, including both "body image" drugs to enhance physical appearance or performance, and classical drugs of abuse. In particular, AAS users appear particularly prone to opioid use. There may well be a biological basis for this association, since both human and animal data suggest that AAS and opioids may share similar brain mechanisms. Finally, AAS may cause a dependence syndrome in a substantial minority of users. AAS dependence may pose a growing public health problem in future years but remains little studied.

Introduction

The anabolic–androgenic steroids (AAS) are a family of hormones that includes the natural male hormone testosterone, together with numerous closely related chemical relatives (Pope and Brower, 2009). All AAS possess both anabolic (muscle building) and androgenic (masculinizing) properties, and they affect a wide range of physiological systems. As a result, the AAS have become the subject of a vast literature of medical and behavioral studies in humans and animals, too large to cover here in its entirety. Therefore this review will concentrate primarily on the illicit use of supraphysiologic doses of AAS by humans. We begin with a short history of the development of AAS and the evolution of illicit AAS use over the last several decades. We also discuss current knowledge regarding the prevalence of AAS abuse in both men and women in various countries. We then briefly review the growing literature on the adverse medical effects of illicit supraphysiologic AAS use, followed by a more detailed review of the behavioral effects of these drugs. Finally, we discuss the associations between AAS abuse and other drugs of abuse, together with the related issue of AAS dependence.

History

AAS as therapeutic agents

In 1889, the renowned investigator Brown-Séquard injected himself with an extract that he had prepared from the testicles of dogs and guinea pigs (Brown-Séquard, 1889). He thought that he felt a boost of vitality — but in fact, his preparation probably lacked genuine biological activity (Katz and Pope, 1989). Several more decades passed before testosterone was first isolated and characterized in Germany in the 1930s (David et al., 1935; Wettstein, 1935). In the following years, numerous testosterone derivatives were synthesized, creating the family of hormones that we now call AAS (Kopera, 1985). The behavioral effects of these agents were quickly acknowledged; indeed, by the early 1940s, it is said that Hitler gave AAS to his troops to make them more aggressive in battle, although definitive evidence of this has never been obtained (Wade, 1972).

Also by the late 1930s and early 1940s, testosterone and its relatives were widely prescribed to treat depression in psychiatric patients and were hailed as a possible cure for the "male climacteric" (Altschule and Tillotson, 1948; Barahal, 1938; Danziger et al., 1944; Davidoff and Goodstone, 1942; Guirdham, 1940; Zeifert, 1942). By the 1950s, however, with widespread use of electroconvulsive therapy and the introduction of tricyclic antidepressants and monoamine oxidase inhibitors, AAS largely disappeared from psychiatric practice (Kanayama et al., 2007a), save for a few small trials in depressed men

* Corresponding author. McLean Hospital, Belmont, MA 02478, USA. Fax: +1 617 855 3585.
E-mail address: hpope@mclean.harvard.edu (H.G. Pope).

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in the 1980s (Itil et al., 1984; Vogel et al., 1978, 1985). Throughout these decades, AAS continued to be prescribed largely for the treatment of male hypogonadism, together with a handful of other specialized medical indications (Basaria et al., 2001; Gribetz et al., 1955; Nakao et al., 2000; Pavlatos et al., 2001; Velazquez and Alter, 2004).

The last 10 years, however, have witnessed a new surge of interest in the possible therapeutic effects of testosterone in men with depression and related symptoms. This trend was stimulated partly by placebo-controlled studies suggesting that testosterone was effective for both the wasting syndrome and for associated depression and fatigue in HIV-positive men (Grinspoon et al., 2000; Rabkin et al., 2000). Although a larger more recent study failed to show a difference between testosterone and placebo on behavioral measures in HIV-positive men (Rabkin et al., 2004), androgens continue to be widely used in this population. Also in the last 10 years, a series of studies has investigated testosterone as a possible antidepressant treatment, administered either as a monotherapy (Perry et al., 2002; Seidman et al., 2001, 2009) or as an augmentation strategy (Orengo et al., 2005; Pope et al., 2003; Seidman et al., 2005; Seidman and Rabkin, 1998). We have reviewed this literature in detail elsewhere (Kanayama et al., 2007a). Briefly, the various studies have produced mixed results, perhaps attributable to differences in study populations (hypogonadal vs. eugonadal men, men with major depressive disorder vs. dysthymic disorder) and drug administration (transdermal vs. intramuscular testosterone). Thus it is still premature to conclude that testosterone or other AAS are truly efficacious in major depressive illness, even though it is certainly accepted that these hormones may improve energy, libido, and mood in some hypogonadal men receiving replacement therapy (Wang et al., 1996, 2000).

AAS as drugs of abuse

Soon after the introduction of AAS as possible therapeutic agents, athletes discovered that these drugs could allow them to gain high levels of muscle mass, often far beyond that obtainable by natural means (Fitzpatrick, 2002). AAS quickly began to spread through the elite athletic community, and by 1954, the Russian team was found to be using AAS at the Vienna weightlifting championships (Wade, 1972). By the 1960s, AAS became banned drugs in the Olympics. Still, the public and much of the medical community remained unfamiliar with these substances. Indeed for many years, well into the 1970s and even 1980s, many laboratory studies still claimed that AAS were not effective for gaining muscle mass (Casner et al., 1971; Crist et al., 1983; Golding et al., 1974; O'Shea and Winkler, 1970), and the American College Of Sports Medicine issued a position paper as late as 1977 claiming that AAS were ineffective for muscle gains (Kanayama et al., 2008). It was eventually recognized that the modest doses of AAS administered in laboratory studies did not approach those abused by actual athletes (Haupt and Rovere, 1984), and by 1987, the American College of Sports Medicine retracted its claim and conceded that AAS were indeed effective (Kanayama et al., 2008). The failure of the medical community to recognize the efficacy of AAS for such a long period has represented an embarrassment even to this day; this failure has likely contributed to the scorn that some AAS users express towards physicians and other professionals (Dawson, 2001; Pope et al., 2000a, 2004).

Throughout the 1970s, AAS remained largely in the domain of elite athletes and competitive bodybuilders, and most of these individuals were careful not to divulge their secret to the general public. By about 1980, however, AAS began to break out of the elite athletic community and onto the street. This progression was fueled in part by the appearance of a series of underground guides, beginning with Duchaine's "Underground Steroid Handbook," which first appeared in 1981 (Duchaine, 1981) and then appeared in progressively larger revised editions over the next decade (Duchaine, 1983, 1988). Similar guides, such as Phillips' Anabolic Reference Guide soon followed (Phillips, 1985, 1991), offering detailed advice on what AAS to use, together with comments on recommended doses, side effects, and tips on how to self-inject the drugs. As this information became increasingly accessible, hundreds of thousands of young American men began to use AAS, which were still readily available as prescription drugs with minimal federal enforcement until 1991 (One Hundred First United States Congress, 1990).

The spread of illicit AAS use was also fueled in the 1980s by an increasing Western cultural emphasis on male body image and muscularity — a trend that we have described in detail previously (Pope et al., 2000a). Briefly, recent decades have seen a growing flood of muscular male images in Western movies, television dramas, magazines, comic strips, and advertising, all seeming to convey the message that muscularity is a measure of masculinity (Leit et al., 2002, 2001; Pope et al., 2001). Even children's action toys, such as GI Joe in the United States and Action Man in British Commonwealth countries, have shown a steady increase in muscularity, growing from ordinary looking male bodies in the 1960s to markedly muscular bodies by the 1980s and 1990s (Pope et al., 1999). As young men in Western cultures sought to emulate the male images that they saw around them, AAS use gained in its appeal. This trend has continued to the present (see Fig. 1); despite increasing legislative (One Hundred Eighth United States Congress, 2004; One Hundred First United States Congress, 1990; United States Drug Enforcement Administration, 2007) and educational (National Institutes on Drug Abuse, 2000) attempts to control AAS use, AAS continue to pour into the United States and other Western countries, often purchased over the Internet from countries where AAS are still legally available or minimally enforced (Kanayama et al., 2008; United States Drug Enforcement Administration, 2007).

The magnitude of the problem

The prevalence of AAS use in boys and men

By the late 1980s and early 1990s, surveys of American teenage students first began to inquire about AAS; these early studies reported that 3% and 11% of male high school students acknowledged having used AAS at some time (Buckley et al., 1988; Johnson et al., 1989; Johnston et al., 2006). Studies of the prevalence of AAS use in other countries first began to appear some years later, but by the end of the 1990s, epidemiologic evidence of illicit AAS use had begun to appear in British Commonwealth countries (Handelsman and Gupta, 1997; Melia et al., 1996; Williamson, 1993), Scandinavian countries (Nilsson et al., 2001), and elsewhere. This evidence has mounted in the most recent decades, with numerous more recent studies documenting substantial levels of AAS use in the United States (Centers for Disease Control and Prevention (CDC), 2008; Field et al., 2005; Johnston et al., 2006; McCabe et al., 2007), Europe (Kokkevi et al., 2008; Pallesen et al., 2006; Rachon et al., 2006; Wanjek et al., 2007), and Brazil (Galduroz et al., 2005). These studies have produced a wide range of prevalence estimates and are subject to various methodological limitations (see below), but they generally suggest that at least 3% of young men in most Western countries, and possibly well over 3% in many instances, have used AAS at some time in their lives. By contrast, Asian countries show little evidence of illicit AAS use, possibly because they lack the cultural emphasis on muscularity seen in the West, as we have explained elsewhere (Yang et al., 2005, 2009).

AAS use in girls and women

Girls and women rarely use AAS, since they rarely desire to become extremely muscular, and are also subject to the masculinizing effects

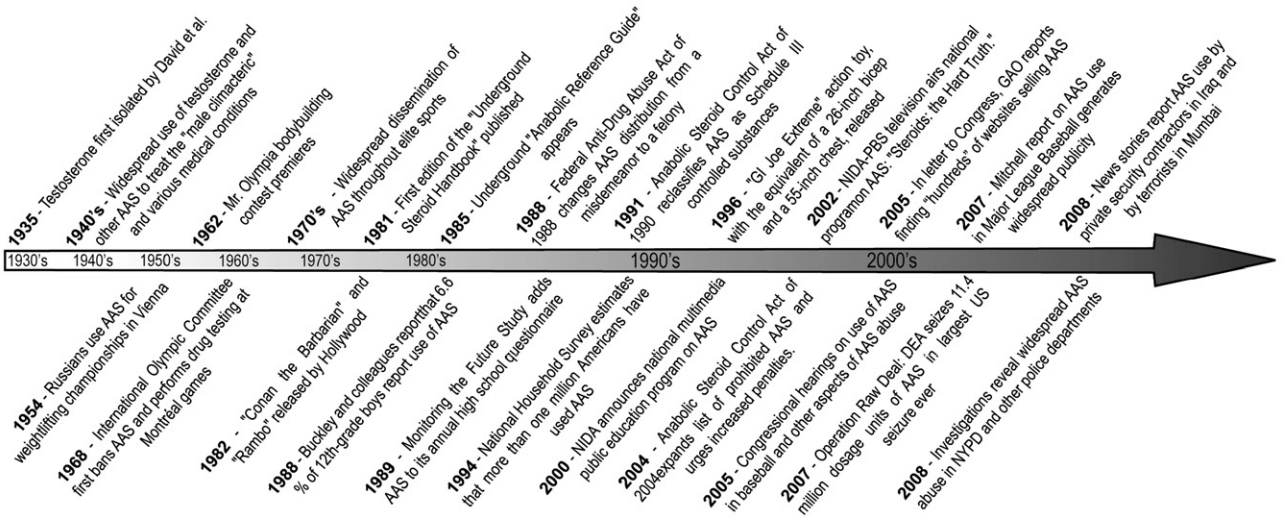

Fig. 1. Some time points in the evolution of illicit AAS use (adapted from Kanayama et al., 2008).

of AAS, such as beard growth, deepening of the voice, and masculinization of secondary sexual characteristics. Indeed, we are aware of only one study in the last 20 years that has recruited and personally evaluated a dedicated group of female AAS users (Gruber and Pope, 2000), and even this study managed to recruit only 25 female AAS users over a span of 2 years.

Surprisingly, some anonymous surveys of AAS use have reported a high prevalence in girls as young as their early teens (Centers for Disease Control and Prevention (CDC), 2004; Faigenbaum et al., 1998; Irving et al., 2002). However, as we have explained in a recent review (Kanayama et al., 2007b), these estimates may be greatly inflated by false-positive responses, because anonymous questionnaires often asked generically about use of "steroids," without clarifying that anabolic–androgenic steroids should not be confused with corticosteroids or with over-the-counter sports supplements. Thus many respondents – both girls and boys – likely responded that they had used "steroids" when in fact they had never used actual illicit AAS.

Even allowing for these sources of error in surveys of teenage students, it should be remembered that the lifetime prevalence of AAS use rises substantially after the teenage years, because a majority of AAS users first initiate these drugs in their 20s (Kanayama et al., 2009a, 2003b). Thus, the lifetime prevalence of AAS use among men who have reached their late 20s or early 30s is likely several times as great as the prevalence among teenagers (Kanayama et al., 2007b).

Finally, it should be noted that since illicit AAS abuse did not become widespread until the 1980s, the first large wave of former (or sometimes still current) AAS users, who first ingested AAS as youths during that decade, is only now reaching middle age (Kanayama et al., 2008). It follows that certain long-term adverse medical effects of illicit supraphysiologic AAS use, such as AAS-induced cardiovascular disease, may have yet to fully declare themselves in the population. Suppose by analogy that cigarette smoking did not become widespread in the general population until the 1980s and that the first generation of heavy cigarette smokers was only reaching middle age today. If this were the case, we might perhaps see some scattered reports or small case series of emphysema or lung cancer in cigarette smokers, but we would not yet appreciate the full magnitude of the association between cigarette smoking and these outcomes. It seems possible that a similar scenario may unfold with AAS, as increasing numbers of aging AAS users begin to enter the age of risk for possible long-term AAS-induced complications.

Adverse medical effects of AAS

Cardiac effects

Although this review focuses primarily on behavioral features of illicit AAS use, it is important to note in passing that these drugs may produce various adverse medical effects, especially on the heart – as suggested by the growing number of anecdotal reports of death attributable to apparent cardiac problems among AAS users as young as their 20s and 30s (Kanayama et al., 2008). The prevalence and underlying mechanisms of AAS-induced cardiovascular toxicity remain poorly understood, but it appears that AAS may perhaps be directly toxic to cardiac tissue, resulting in a cardiomyopathy characterized by impaired systolic and diastolic function (D'Andrea et al., 2007; Kasikcioglu et al., 2009; Krieg et al., 2007; Nottin et al., 2006; Weiner et al., in press). Second, AAS use increases low-density lipoprotein cholesterol and decreases high-density lipoprotein cholesterol (Glazer, 1991; Hartgens et al., 2004; Kouri et al., 1996; Lenders et al., 1988; Thompson et al., 1989), and these lipid abnormalities represent a major risk factor for coronary heart disease (Grundy et al., 2004). Direct evidence of AAS-induced atherosclerosis still remains limited (Parssinen and Seppala, 2002; Santora et al., 2006), but we would speculate that this evidence may start to increase as a result of the demographic trends discussed above, with greater numbers of long-term AAS users beginning to enter the age of risk.

Other medical effects

Orally active AAS may sometimes also cause hepatotoxicity, including hepatic neoplasms (Bagia et al., 2000; Gorayski et al., 2008; Kafrouni et al., 2007; Sanchez-Osorio et al., 2008; Socas et al., 2005; Velazquez and Alter, 2004). Possible AAS effects on the prostate effects include hypertrophy (Jin et al., 1996; Wemyss-Holden et al., 1994) and perhaps an increased risk of prostate cancer (Larkin, 1991; Roberts and Essenhigh, 1986) — although the latter association has recently been questioned (Morgentaler, 2006, 2007). Occasional adverse renal, immunologic, and musculoskeletal effects have also been reported (Bryden et al., 1995; Maravelias et al., 2005; Martorana et al., 1999; Modlinski and Fields, 2006).

Neuroendocrine effects

Exogenous AAS suppress the hypothalamic–pituitary–testicular (HPT) axis in males (Pope and Brower, 2005; Reyes-Fuentes and

Veldhuis, 1993). Thus when AAS abusers discontinue use of these drugs – especially if they stop AAS abruptly after a prolonged period of use – they become hypogonadal. Usually, HPT function recovers within weeks to months, but several reports have described hypogonadism persisting for more than a year after AAS were discontinued (Boyadjiev et al., 2000; Menon, 2003; van Breda et al., 2003). AAS-induced hypogonadism can lead to impaired sexual functioning (Brower, 2002; Pope and Brower, 2009) and infertility (de la Torre Abril et al., 2005; Menon, 2003; Turek et al., 1995). Also, as discussed below, hypogonadism may sometimes cause major depressive episodes (Brower, 1997, 2002; Brower et al., 1989b; Malone and Dimeff, 1992; Malone et al., 1995; Pope and Katz, 1988, 1994). AAS users experiencing sexual dysfunction or depression after stopping AAS may be strongly tempted to quickly resume AAS to relieve these symptoms, thus contributing to AAS dependence syndromes (Brower, 2002; Kashkin and Kleber, 1989).

Behavioral effects of AAS

Field studies

Mood disorders

For some 30 years, naturalistic studies have described psychiatric symptoms associated with illicit AAS use. These began with early anecdotal reports of psychosis (Annitto and Layman, 1980), hypomania (Freinhar and Alvarez, 1985), and major depression (Brower et al., 1989a; Tennant et al., 1988) in individual AAS users. In the late 1980s, our group published the first large psychiatric study of illicit AAS users, reporting interview data from 41 users recruited in the field (Pope and Katz, 1987, 1988). This study documented manic or hypomanic symptoms in some users during AAS exposure, sometimes associated with mild psychotic symptoms such as grandiose or paranoid delusions. Several men also reported major depressive episodes during AAS withdrawal. Of note, these effects appeared to be quite idiosyncratic, with a majority of users describing minimal psychiatric effects, while a minority reported prominent and even severe effects.

Since the early 1990s, many additional field studies have appeared, examining a variety of AAS-using populations using various methodologies. We have summarized these studies in several recent reviews (Kanayama et al., 2008; Pope and Brower, 2009; Pope and Katz, 2003), as have other authors (Hall et al., 2005; Hartgens and Kuipers, 2004; Talih et al., 2007; Trenton and Currier, 2005). Some of these field studies represented individual case reports or small case series of AAS abusers interviewed by various investigators (Allnutt and Chaimowitz, 1994; Brower et al., 1990; Cooper and Noakes, 1994; Elofson and Elofson, 1990; Malone and Dimeff, 1992; Papazisis et al., 2007; Stanley and Ward, 1994). Other studies, including our 1988 study described above, were retrospective comparisons of AAS users on-drug vs. off-drug (Cooper et al., 1996; Parrott et al., 1994; Pope and Katz, 1988). Many other reports, using personal interviews or psychological rating scales, compared AAS users with nonusers (usually non-AAS-using weightlifters) (Bahrke et al., 1992; Choi and Pope, 1994; Cooper et al., 1996; Lefavi et al., 1990; Malone et al., 1995; Midgley et al., 2001; Moss et al., 1992; Perry et al., 1990, 2003; Pope and Katz, 1994; Yates et al., 1992). Finally, several studies have described longitudinal assessments of users before, during and after AAS use (Choi et al., 1990; Fudala et al., 2003; Pagonis et al., 2006a; Wilson-Fearon and Parrott, 1999), including even a longitudinal assessment of two pairs of monozygotic twins where one used AAS and the other did not (Pagonis et al., 2006b). We are also aware of two other reports of monozygotic twins discordant for AAS use. In one twin pair, the AAS user shot a woman in the spine while he was on a course of AAS (Pope and Katz, 1990); the AAS user in the other twin pair committed suicide while using AAS (Thiblin et al., 1999b). In both twin pairs, the non-AAS-using twin showed no lifetime history of any significant psychopathology.

The consensus of the above field studies is that some AAS users exhibit hypomanic or manic symptoms during AAS exposure, occasionally (albeit rarely) accompanied by psychotic symptoms. Some studies have also reported users showing depressive symptoms, occasionally associated with suicidality, usually during AAS withdrawal. However, it is impossible to estimate the prevalence of these syndromes in the overall population of illicit AAS users, because there is such wide variation among the various studies. Some studies report relatively frequent and often severe pathology (Pope and Katz, 1988; Thiblin et al., 1999b), whereas others find little or even none (Bahrke et al., 1992). These differences may be partially attributable to differences in the doses of AAS used, with more frequent symptoms in studies that included large numbers of high-dose AAS users (particularly those ingesting the equivalent of more than 1000 mg of testosterone per week; see discussions in Pope and Brower, 2009; Pope and Katz, 2003). Differences in methods of selection and evaluation of participants also likely contributed to differences in the findings.

Aggression and violence

A growing literature of field studies has also documented cases of aggressive or violent behavior associated with AAS use. For example, several reports have described men with little or no apparent history of violence or criminal behavior prior to AAS use who committed murder or attempted murder while using AAS (Choi et al., 1990; Conacher and Workman, 1989; Pope and Katz, 1990; Pope et al., 1996). Other cases did not involve frank attempts at murder but seem to demonstrate violence or criminality on AAS that appeared entirely uncharacteristic of the individual's premorbid personality (Dalby, 1992; Schulte et al., 1993; Stanley and Ward, 1994). In one larger study, Choi and Pope (1994) assessed 23 AAS users and 14 nonusers regarding their relationships with wives or girlfriends. The users reported significantly more aggression and violence towards these women when using AAS than when not using AAS. However, the AAS users off-drug did not differ significantly from nonusers on measures of aggression. Thiblin and colleagues (1997) described 14 violent offenders who were evaluated for current or past AAS use. In several cases, this violence was "characterized by minimal provocation, great intensity and long duration." For example, one individual on AAS stabbed a victim 30 times all over his body, but could offer no reason for his anger. Subsequently, this same group (Thiblin and Parlklo, 2002) described five additional young men who exhibited violent criminal behavior when using AAS; four of these showed no apparent history of conduct disorder prior to AAS exposure. Another recent review (Hall et al., 2005) reports six cases of AAS-induced violence seen by the authors, including three homicides and three violent assaults. These men were described as experiencing psychotic symptoms, with "stereotypic qualities of irritability, aggressiveness, and grandiosity." The authors report that all six men returned to a normal mental status within 2 months of stopping AAS.

Of course it is impossible to be certain that AAS played a causal role in the various cases above, but it is impressive that most of the individuals described did not display similar behavior in the absence of AAS exposure — suggesting that AAS was indeed a causal factor. It is also notable that many of the cases seemed to exhibit stereotypic qualities of aggression or violence grossly disproportionate to the circumstances, often accompanied by an element of paranoia or grandiosity, again suggesting that these were not chance phenomena, but reflected an actual biological effect of the AAS themselves.

Recent Swedish forensic studies offer some further indirect support for these impressions. For example, a study of prisoners (excluding cases referred from substance abuse centers) found that those testing positive for AAS were significantly more likely than AAS-negative men to have been convicted of a weapons offense (Klotz et

al., 2006). Another study found that deceased AAS users were significantly more likely to have died from homicide or suicide than a comparison group of deceased amphetamine or heroin users (Petersson et al., 2006).

Laboratory studies

Throughout all of the above observations, the question remains open as to whether AAS represented a causal factor in the behaviors or syndromes observed. For example, premorbid personality traits of individuals who are disposed to use AAS might contribute strongly to such behaviors (Fudala et al., 2003; Midgley et al., 2001; Perry et al., 2003). Similarly, expectational factors or psychosocial effects of the "gym culture" might perhaps account for such effects (Bahrke and Yesalis, 1994; Bahrke et al., 1996; Björkqvist et al., 1994; Riem and Hursey, 1995). The only definitive way to resolve this question would be to conduct a blinded study administering high doses of AAS vs. placebo to normal volunteers. Of course, it would be unethical to conduct a study using large doses of multiple AAS simultaneously (a common practice among illicit users, referred to by these users as "stacking"), and thus laboratory studies can never fully mimic natural conditions. However, several blinded laboratory studies have attempted to assess the psychiatric effects of AAS at more modest doses.

Most of these latter studies have assessed AAS-induced psychological effects in doses of ≤300 mg of testosterone or equivalent per week (Bagatell et al., 1994; Björkqvist et al., 1994; Forbes et al., 1992; Friedl et al., 1991, 1989; Hannan et al., 1991; Matsumoto, 1990). These studies have generally found few psychological changes, prompting some investigators to doubt whether AAS actually produced biologically-mediated psychiatric effects at all (Bagatell et al., 1994; Björkqvist et al., 1994). However, although 300 mg of testosterone per week is four to six times the natural male production of testosterone (Reyes-Fuentes and Veldhuis, 1993), this dose is still far lower than that used by most illicit AAS users, who may sometimes ingest doses equivalent to 1000–5000 mg per week (Fudala et al., 2003; Parkinson and Evans, 2006; Parrott et al., 1994; Pope and Katz, 1988, 1994; Wilson-Fearon and Parrott, 1999). Thus it is inappropriate to extrapolate from these laboratory studies to the effects that might be seen in the field.

Four recent laboratory studies have administered doses of ≥500 mg per week of AAS to normal volunteers, and thus come somewhat closer to approximating illicit doses (Bhasin et al., 1996; Pope et al., 2000b; Su et al., 1993; Tricker et al., 1996; Yates et al., 1999). These combined studies evaluated 109 men at this dosage level; five (4.6%) of these men developed hypomanic or manic syndromes during blinded AAS administration, whereas none showed such syndromes on placebo. However, the 4.6% figure likely underestimates the true prevalence of such syndromes among illicit AAS users, because illicit users may reach far higher doses than those administered in the laboratory, as just mentioned. Also, laboratory studies typically screen volunteers to exclude individuals with existing psychopathology or substance use, but illicit AAS users do not screen themselves with such care.

Conclusions

The evidence of the above laboratory studies, combined with the extensive experience of field studies, strongly suggests that high doses of AAS may indeed produce psychiatric effects and that these effects cannot be fully explained by psychosocial factors. However, it is also clear that these effects are quite unpredictable and idiosyncratic: most illicit users, including even those ingesting high doses, exhibit little or no psychopathology, whereas a few demonstrate striking mood changes, aggression, and even violence in association with AAS use. This same idiosyncratic pattern has also been documented in animals; for example, most hamsters administered AAS display aggressiveness, but some show little behavioral change (Clark and Henderson, 2003; DeLeon et al., 2002; Melloni et al., 1997). In humans, there also appears to be an idiosyncratic association of depression with hypogonadism following AAS withdrawal. For example, in one laboratory study of pharmacologically induced hypogonadism, most men showed little or no depression, while a few showed marked depressive symptoms (Schmidt et al., 2004). Although the nonuniform nature of AAS psychological effects, both at physiologic doses (Kanayama et al., 2007a; Rubinow and Schmidt, 1996) and at supraphysiologic doses (Pope and Brower, 2009), has long been acknowledged, its mechanism is still unclear. Preliminary findings in animals (Clark and Henderson, 2003; DeLeon et al., 2002; Fischer et al., 2007; Grimes and Melloni, 2006) and humans (Daly, 2001; Daly et al., 2003, 2001) have implicated a variety of possible associations with brain neurochemistry and hormonal levels, with several studies suggesting that serotonergic effects may play a key role.

AAS and other forms of illicit drug use

Body image drugs

Illicit AAS users often use a wide range of other drugs, and these may cause additional psychiatric and medical effects. First, users often ingest other "body image drugs" to gain muscle, lose fat, and counteract the side effects of AAS or other body image drugs that they are taking (Kanayama et al., 2001b). These drugs include other hormones (human growth hormone, insulin-like growth factor-1 [IGF-1], thyroid hormones, human chorionic gonadotropin, and insulin), stimulants (amphetamine, ephedrine, pseudoephedrine, and especially the beta agonist clenbuterol), drugs supposed to stimulate testosterone or growth hormone secretion (clomiphene, gamma hydroxybutyrate, levodopa), drugs for weight or fluid loss (diuretics, laxatives), and numerous other agents (erythropoietin, tamoxifen, danazol, yohimbine, 2,4-dinitrophenol), (Clark and Schofield, 2005; Gruber and Pope, 2000; Juhn, 2003; Kanayama et al., 2001a; Kuipers and Hartgens, 1997; Parkinson and Evans, 2006; Wilson-Fearon and Parrott, 1999). Individuals wanting to utilize these substances can obtain detailed guidance on dosage, administration, and availability from numerous comprehensive underground guides (Gallaway, 1997; Llewellyn, 2009; Roberts and Clapp, 2006) or from various Internet websites and forums devoted to AAS and other body image drugs (for some examples, see a list of representative sites at http://www.dmoz.org/Sports/Strength_Sports/Bodybuilding/Supplements/Anabolic_Steroids). Although many of the above substances have been studied over the years at ordinary doses in medical studies, their effects in illicit non-medical usage, alone or in combination with AAS, are poorly understood.

Classical drugs of abuse

Second, illicit AAS users frequently use classical drugs of abuse in addition to AAS (Arvary and Pope, 2000; Bahrke et al., 2000; Buckley et al., 1988; DuRant et al., 1993; Johnson et al., 1989; Johnston et al., 2006; Kanayama et al., 2009b, 2003a, 2003b; Kindlundh et al., 2001, 1999; Middleman et al., 1995; Wines et al., 1999; Yesalis et al., 1997, 1993). Again, it is difficult to estimate the overall prevalence of classical substance abuse in illicit AAS users, because no single field study or survey study is likely to have captured an entirely random sample of the overall AAS-using population. Two recent American studies are representative. In a large survey of college students (McCabe et al., 2007), 77% of self-reported lifetime AAS users acknowledged 12-month illicit or nonmedical use of at least one other drug, as compared to 32% of nonusers. The adjusted odds ratio (95% confidence interval) for reported 12-month marijuana use in the AAS users versus nonusers was 2.9 (1.7, 5.0); for other drug categories

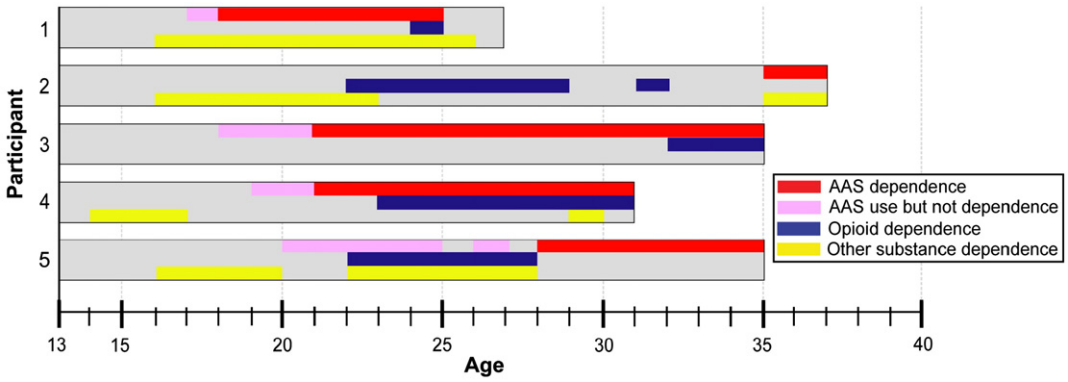

Fig. 2. Examples of lifetime course of AAS use and other substance abuse in five men with a history of AAS dependence (adapted from Kanayama et al., 2009b).

the odds ratios were even higher, ranging from 6.1 (ecstasy) to 13.0 (cocaine). AAS users were also significantly more likely to report 12-month alcohol dependence (OR 3.1; 95% conference interval: 1.7, 5.7). Similar findings emerge a recent study from our group, interviewing weightlifters recruited by advertisements in gymnasiums and supplement stores (Kanayama et al., 2009b). In this study we did not disclose our interest in AAS during the recruitment process in order to minimize possible selection bias. In a comparison of 72 non-AAS-using weightlifters and 62 AAS users (20 of whom were judged to have AAS dependence; see discussion below), we did not find a higher prevalence of lifetime alcohol dependence in AAS users (13 [21%] of users versus 12 [17%] nonusers), but we did find a higher prevalence of nonalcohol substance dependence (40 [65%] users versus 32 [44%] nonusers). This difference was driven largely by the strikingly higher prevalence of opioid abuse and dependence in the AAS users; only 5 (7%) of the nonusers reported a lifetime history of opioid abuse and dependence, versus 8 (19%) of the nondependent AAS users and 10 (50%) of the dependent AAS users.

Opioids

The above study is one of several suggesting a particularly close relationship between illicit AAS use and opiate use. For example, two reports have described AAS users who illicitly used the opioid agonist–antagonist nalbuphine (McBride et al., 1996; Wines et al., 1999); some of these nalbuphine users went on to develop dependence on classic opioid agonists such as morphine or heroin. Another study (Arvary and Pope, 2000), evaluating 227 consecutive male heroin addicts admitted to a treatment facility, concluded that 21 (9%) of them were first introduced to opioids through AAS use. In another study from our group examining consecutive men admitted to an inpatient substance abuse unit, 22 of 88 (25%) men with a primary diagnosis of opioid dependence reported prior AAS use. By comparison, among 135 men with other forms of substance dependence, only seven (5%) reported having ever used AAS ($p<0.001$) (Kanayama et al., 2003a). Interestingly, animal studies also suggest possible links between AAS and opioids; for example, rats and mice will choose to spend time in environments where they have previously received AAS (Alexander et al., 1994; Arnedo et al., 2000). Also, hamsters will self-administer testosterone, sometimes even to the point of death (Wood, 2006), and opioidergic mechanisms appear to be involved in this self-administration process (Peters and Wood, 2005). Thus, there may well be a biological basis for the association of AAS use and opioid use in humans.

We have reviewed elsewhere the mechanisms that might account for an association between AAS and opioids (Kanayama et al., 2010). Briefly, a human literature dating back to the 1980s has speculated that AAS might potentiate central endogenous opioid activity (Kashkin and Kleber, 1989), as suggested for example by the observation that naloxone precipitated opioid-like withdrawal symptoms in an individual with AAS dependence (Tennant et al., 1988), or that AAS appeared to reduce the threshold for overdose of opioids (Thiblin et al., 2000). Numerous animal studies also suggest that AAS can potentiate central opioid systems (for reviews, see Kanayama et al., 2010; Wood, 2008). Overall, it seems likely that AAS act as partial opioid agonists, although they undoubtedly act through several other nonopioid neurotransmitter systems, including serotonin (Daly et al., 2001; Kurling et al., 2005; Lindqvist et al., 2002; Ricci et al., 2006; Schwartzer et al., 2009a; Tamaki et al., 2003; Thiblin et al., 1999a), norepinephrine (Tamaki et al., 2003), dopamine (Birgner et al., 2008; Frye, 2007; Kindlundh et al., 2004; Ricci et al., 2009; Schroeder and Packard, 2000; Schwartzer et al., 2009b; Wood, 2004), and gamma-amino-butyric acid (Frye, 2007; Henderson, 2007; Schwartzer et al., 2009b).

In animal studies, AAS may also influence the effects of other drugs of abuse, including alcohol (Johansson et al., 2000; Lindqvist et al., 2002), cannabis (Celerier et al., 2006), and stimulant drugs (Kurling et al., 2008). The implications of these findings for human AAS use remain unclear; certainly illicit AAS users ingest all of these latter substances, but their association with illicit AAS use does not appear as striking as with opioids. Also unclear is the direction of causality in such cases; our group has speculated that AAS use might act as a gateway to opioid dependence (Arvary and Pope, 2000; Kanayama et al., 2003a), but more recent data suggest that opioid use may arise before, during, or after AAS use, raising the possibility that both forms of substance abuse may arise from a common diathesis (Kanayama et al., 2009b; see Fig. 2).

AAS dependence

A growing literature, which we have recently reviewed (Kanayama et al., 2010), has also documented that AAS can cause a dependence syndrome. Briefly, individual case reports of AAS dependence have appeared as far back as the late 1980s, describing men who developed chronic and maladaptive AAS use despite adverse medical or psychosocial effects (Brower et al., 1989a, 1990; Hays et al., 1990; Tennant et al., 1988). Over the last 20 years, eight field studies of AAS users (Brower et al., 1991; Copeland et al., 2000; Gridley and Hanrahan, 1994; Kanayama et al., 2009b; Malone et al., 1995; Midgley et al., 1999; Perry et al., 2005; Pope and Katz, 1994) have diagnosed AAS dependence using *DSM-III-R* (American Psychiatric Association, 1987) or *DSM-IV* criteria (American Psychiatric Association, 1994) for substance dependence. In these studies collectively, 197 of 653 (30.1%) AAS users met these criteria (Table 1) — suggesting that dependence is a frequent outcome of AAS use.

AAS dependence shares many features with classical substance dependence. For example, like many classical drugs, AAS can stimulate self-administration in animal models, as just mentioned. AAS also produce a characteristic withdrawal syndrome. AAS

Table 1
Individuals meeting *DSM* criteria for substance dependence in eight field studies of AAS users.

Study	Location	Instrument	Criteria	AAS users[a]	AAS dependence, *n* (%)[a]
Brower et al. (1991)	USA	Questionnaire	DSM-III-R	49 M	28 (57)
Gridley and Hanrahan (1994)	Australia	Questionnaire	DSM-IV	21 M	12 (57)
Pope and Katz (1994)	USA	SCID[b]	DSM-III-R	88 M	22 (25)
Malone et al. (1995)	USA	SCID[b]	DSM-III-R	71 M, 6 F	10 M, 1 F (14% overall)
Midgley et al. (1999)	England	Semi-structured interview	DSM-III-R	50 M	13 (26)
Copeland et al. (2000)	Australia	Semi-structured interview	DSM-IV	94 M, 6 F	21 M, 2 F (23% overall)
Perry et al. (2005)	USA	Internet survey	DSM-IV	206 M	68 (33)
Kanayama et al. (2009b)	USA	Semi-structured interview	DSM-IV[c]	62 M	20 (32)
Total				641 M, 12 F	194 M, 3 F (30% overall)

[a] Gender distribution obtained from published papers and from P.J. Perry, personal communication, October 2008, and D.A. Malone, personal communication, January 2009.
[b] Structured clinical interview for DSM-III-R.
[c] Modified DSM-IV criteria adapted for diagnosing AAS dependence (see Kanayama et al., 2009a).

withdrawal is mediated partly by hypogonadism due to suppression of testicular function, and it also likely shares various mechanisms with other endocrine withdrawal syndromes and with the mechanisms of withdrawal from other drugs of abuse — including changes in opioid peptide systems, the mesolimbic dopaminergic system, and other central pathways (Hochberg et al., 2003). In psychosocial terms, AAS dependence may also resemble classical substance dependence in that AAS use and the surrounding culture of the gym may become a dominant feature of the individual's life, often to the exclusion of desirable social and occupational opportunities. However, AAS dependence differs from most classical substance dependence in that AAS use produces little, if any immediate intoxication or "high." Thus, the standard DSM-IV substance dependence criteria, which were crafted primarily for intoxicating drugs, do not apply quite as easily to AAS dependence. To rectify this problem, we have recently proposed and published slightly modified DSM-IV criteria for the specific case of AAS dependence (Table 2) (Kanayama et al., 2009a). Of note, AAS are the only class of substances regulated by the United States Drug Enforcement Administration under Schedules II or III (United States Drug Enforcement Administration, 2002) that is not yet acknowledged in DSM-IV as causing a dependence syndrome.

AAS dependence represents one of the least-explored aspects of illicit AAS use, and it remains unclear why a large minority of AAS users goes on to develop dependence syndromes. One possible risk factor for AAS dependence may be the presence of body image disorders such as "muscle dysmorphia" (Pope et al., 1997), in which individuals develop excessive preoccupation with their muscularity. Muscle dysmorphia appears to be associated with illicit AAS abuse (Cafri et al., 2005; Cole et al., 2003; Kanayama et al., 2006, 2009b, 2003b; Olivardia et al., 2000; Pope et al., 2005), but some preliminary data suggest that muscle dysmorphia in and of itself may be insufficient to catalyze the progression from initial AAS use to subsequent AAS dependence (Kanayama et al., 2010). Another possible risk factor may be a biological susceptibility to dysphoric effects from hypogonadism during AAS withdrawal. As noted above, certain individuals develop marked depressive symptoms in response to pharmacologically induced hypogonadism, even though most do not (Schmidt et al., 2004). Possibly such depression-prone individuals are particularly prone to resuming AAS use to blunt the withdrawal effects after stopping a previous course of AAS. A third possibility, as we have discussed elsewhere (Kanayama et al., 2010; Kanayama et al., 2009b), is that individuals with underlying personality disorders or traits, especially conduct disorder or antisocial personality disorder, may be particularly vulnerable to developing AAS dependence. For example, it has been speculated that the combination of antisocial traits, together with associated cognitive deficits in risk-taking and decision making, may collectively mark an endophenotype (Gottesman and Gould, 2003) that plays a causal role in the development of substance dependence (Verdejo-Garcia et al., 2008).

At present, these hypotheses remain speculative, because so little is known about AAS dependence. Indeed, AAS dependence is arguably the only major form of worldwide substance dependence that remains almost completely unstudied. Given the medical and psychiatric correlates of chronic AAS use discussed above, together with the growing numbers of chronic AAS users now entering middle age, it will be critical to better understand risk factors for AAS dependence, the mechanisms by which dependence establishes itself, and the public health consequences of chronic illicit AAS use.

Table 2
DSM substance dependence criteria interpreted for diagnosing AAS dependence (from Kanayama et al., 2009a).

A maladaptive pattern of AAS use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:
(1) Tolerance, as defined by either of the following:
  (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect; for AAS this progression to markedly larger doses may be related to dissatisfaction with the previous level of desired effect (e.g., level of muscle mass)
  (b) markedly diminished effect with continued use of the same amount of the substance (e.g., failure to maintain the same level of lean muscle mass on a given dose of AAS)
(2) Withdrawal, as manifested by either of the following:
  (a) a characteristic withdrawal syndrome, characterized for AAS by two or more of the following features: depressed mood, prominent fatigue, insomnia or hypersomnia, decreased appetite, and loss of libido
  (b) AAS are used to relieve or avoid withdrawal symptoms.
(3) The substance is often taken in larger amounts or over a longer period than was intended. For AAS, this may be manifested by repeatedly resuming courses of AAS use after a shorter "off" period than the individual had originally planned, or by eliminating "off" periods entirely.
(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use. For AAS, this may be manifested by unsuccessful attempts to reduce or stop AAS use because of prominent anxiety about losing perceived muscular size.
(5) A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects. For AAS, this may be manifested by extensive time spent participating in muscle-related activities surrounding AAS use (e.g., time spent in weight training, attending to diet and supplement use, and associating with other AAS users) in addition to actual time spent obtaining and administering AAS.
(6) Important social, occupational, or recreational activities are given up or reduced because of substance use. For AAS, this may be manifested by giving up important outside activities because of an extreme preoccupation with maintaining a supraphysiologic AAS-induced level of muscularity (e.g., the individual relinquishes outside activities for fear that these activities will cause him to miss workouts, violate dietary restrictions, or compromise his ability to use of AAS).
(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. For AAS, this includes medical problems such as gynecomastia, sexual dysfunction, hypertension, dyslipidemia, and cardiomyopathy; or psychological problems such as dysphoric mood swings, severe irritability, or increased aggressiveness.

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