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Long-Term Psychiatric and Medical Consequences of Anabolic-Androgenic Steroid Abuse:

A Looming Public Health Concern?

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Abstract

Background—The problem of anabolic-androgenic steroid (AAS) abuse has recently generated widespread public and media attention. Most AAS abusers, however, are not elite athletes like those portrayed in the media, and many are not competitive athletes at all. This larger but less visible population of ordinary AAS users began to emerge in about 1980. The senior members of this population are now entering middle age; they represent the leading wave of a new type of aging former substance abusers, with specific medical and psychiatric risks.

Methods—We reviewed the evolving literature on long-term psychiatric and medical consequences of AAS abuse.

Results—Long-term use of supraphysiologic doses of AAS may cause irreversible cardiovascular toxicity, especially atherosclerotic effects and cardiomyopathy. In other organ systems, evidence of persistent toxicity is more modest, and interestingly, there is little evidence for an increased risk of prostate cancer. High concentrations of AAS, comparable to those likely sustained by many AAS abusers, produce apoptotic effects on various cell types, including neuronal cells - raising the specter of possibly irreversible neuropsychiatric toxicity. Finally, AAS abuse appears to be associated with a range of potentially prolonged psychiatric effects, including dependence syndromes, mood syndromes, and progression to other forms of substance abuse. However, the prevalence and severity of these various effects remains poorly understood.

Conclusions—As the first large wave of former AAS users now moves into middle age, it will be important to obtain more systematic data on the long-term psychiatric and medical consequences of this form of substance abuse.

Keywords

anabolic steroids; androgens; substance abuse; male; adverse effects

1. Introduction

The anabolic-androgenic steroids (AAS) are a family of hormones that includes the natural male hormone testosterone, together with its many synthetic relatives (Pope and Brower,

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2005), all of which exhibit both *anabolic* ("muscle building") and *androgenic* ("masculinizing") properties (Kopera, 1985; Sheffield-Moore and Urban, 2004). AAS should not be confused with other types of steroids such as *corticosteroids* (e.g., cortisone or prednisone), which have no anabolic effects and hence little abuse potential (Pope and Brower, 2005; Sheffield-Moore and Urban, 2004). When taken in supraphysiologic doses, AAS allow users to greatly increase muscle strength and athletic performance, often well beyond the limit attainable by natural means (Kouri et al., 1995). As a result, many elite competitive athletes have used AAS - and this phenomenon has recently generated much publicity, as evidenced by burgeoning media reports around the world (Ewing, 2008; Fainaru-Wada and Williams, 2006; Magnay, 2008; Swartz, 2007) and recent investigations by the United States Congress (110th United States Congress, 2005; Mitchell, 2007). The great majority of illicit AAS users, however, are not elite athletes; indeed many are not competitive athletes at all, but simply individuals who want to become more muscular (Buckley et al., 1988; Kanayama et al., 2001b; Parkinson and Evans, 2006).

This much larger population of ordinary AAS abusers started to grow in the late 1970s and early 1980s (as detailed below), but has remained less visible than most other populations of substance abusers, because AAS users rarely seek treatment (Pope and Brower, in press), rarely come to the attention of physicians in general (Dawson, 2001; Kutscher et al., 2002), and frequently distrust physicians (Pope et al., 2004). Field studies of these illicit users show that they commonly take two or more AAS simultaneously (a practice known as "stacking"), often ingesting a total AAS dose equivalent to 600-1000 mg of testosterone per week, and sometimes even 3000-5000 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). These latter doses are 50-100 times greater than the natural weekly production of testosterone by the normal male testis (Reyes-Fuentes and Veldhuis, 1993). Illicit users typically take AAS in repeated courses, or "cycles," each lasting several weeks to several months (Pope and Katz, 1988), sometimes adding up to several years of cumulative lifetime exposure (Kanayama et al., 2006; Kanayama et al., 2003b; Parkinson and Evans, 2006).

Over the last 20-30 years, illicit AAS use has grown into a widespread substance abuse problem in the United States (Buckley et al., 1988; Johnston et al., 2006; McCabe et al., 2007; Yesalis et al., 1993) and many other countries (Galduroz et al., 2005; Handelsman and Gupta, 1997; Melia et al., 1996; Nilsson et al., 2001; Pallesen et al., 2006; Rachon et al., 2006; Wanjek et al., 2007). Most individuals with current or past AAS use are young men (Brower, 2002; Kutscher et al., 2002; Pope and Brower, 2005), but some - especially those who first started AAS in the 1980s - are now reaching middle age. Although many of these older men no longer use AAS, accumulating evidence suggests that they may still be vulnerable to long-term psychiatric and medical effects from their former drug use. In this paper, we suggest that these effects may pose a growing public health concern, as large numbers of these men move into middle age and beyond. As a foundation for this discussion, we begin with a more detailed chronology of the AAS epidemic, illustrated in Figure 1, and explained in the following paragraphs.

2. The evolution of the problem

Testosterone was first isolated in the 1930's (David et al., 1935; Wettstein, 1935); synthetic derivatives of testosterone quickly followed, and both testosterone and other AAS were widely applied for medical and psychiatric purposes by the end of the following decade (Altschule and Tillotson, 1948; Gribetz et al., 1955). It was not until the 1950's, however, that athletes began to discover that AAS could greatly increase their muscularity. AAS were apparently first used by the Russians at the weightlifting championships in Vienna in 1954 (Wade, 1972), and quickly spread into competition bodybuilding, track and field events such as the

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shot put, and other sports where performance depended on muscle strength or speed of recovery during training (Fitzpatrick, 2002). Still, throughout the 1960's and even into the 1970's, AAS use was confined largely to the elite levels of sport. The efficacy of AAS remained a well-kept secret among athletes; sports physicians and medical texts were still widely proclaiming that AAS were ineffective for gaining muscle (Casner et al., 1971; Haupt and Rovere, 1984; Wade, 1972).

By the late 1970's competitive bodybuilding had gained in popularity. Fitness and bodybuilding magazines, usually with an AAS-using male model on the front cover, began to proliferate, and increasing numbers of young men became aware of the dramatic muscle gains that they could achieve with AAS (Pope et al., 2000a). Underground guides to the use of AAS began to appear, starting with Daniel Duchaine's *Original Underground Steroid Handbook* in 1981 (Duchaine, 1981). This book contained detailed information on how to obtain and use AAS, including instructions about how to self-administer injections; it quickly became a bible in the bodybuilding underground and appeared in successively larger revised editions in 1983 in 1989 (Duchaine, 1983, 1989). It was soon joined by other underground guides, such as Phillips' *anabolic reference guide*, which first appeared in 1985 (Phillips, 1985). Also in the 1980's, Western culture became increasingly focused on male muscularity, as demonstrated by recent studies from our laboratory and others (Pope et al., 2000a). For example, male bodies began to proliferate in women's magazine advertisements (Pope et al., 2001); the centerfold men in *Playgirl* magazine grew steadily more muscular (Leit et al., 2001); and even action toys, such as GI Joe, began to acquire the bodies of AAS users (Pope et al., 1999). In this climate, AAS use began to break out from the domain of elite athletics and into the general community.

By the late 1980's, epidemiologic studies began to document substantial rates of AAS use among American boys and young men. In a widely cited 1988 paper, Buckley and colleagues (Buckley et al., 1988) reported that 6.6% of 3403 male 12^{th}-grade students, surveyed by anonymous questionnaires, had used AAS at some time. Importantly, more than a third of these respondents reported that they had used AAS purely to enhance personal appearance or for "social" purposes, and not for athletic performance. In 1989, Johnson and colleagues reported AAS use in 11% of 853 male students in six Southern high schools (Johnson et al., 1989). Also in 1989, the Monitoring the Future Study added AAS to its annual anonymous questionnaires; in that year, 3.0% of 12^{th} grade students of both sexes reported lifetime AAS use (Johnston et al., 2006). Since a large majority of AAS users were boys (see Johnston et al., 2006, p. 243), lifetime AAS use for boys alone in this study was likely about 5%. In 1991, AAS were included for the first time on the National Household Survey (NHS) of drug use. This survey produced lower estimates of AAS use than the anonymous questionnaire studies, for reasons that we have discussed elsewhere (Kanayama et al., 2007). But even by this more conservative estimate, nearly a million American men had used AAS by 1991 (SAMHSA, 1991; Yesalis et al., 1993). In 1990, the United States Congress passed the Steroid Trafficking Act (One Hundred First Congress, 1990), acknowledging that AAS use had arisen as an important substance use problem in the United States. Also by the early 1990s, population studies began to document widespread AAS use among students in the United Kingdom (Williamson, 1993), South Africa (Schwellnus et al., 1992), and Scandinavia (Nilsson, 1995).

This chronology has important implications for assessing the long-term medical and psychiatric consequences of AAS use. Because AAS use was uncommon in the general population prior to the 1980's, until recently there have been relatively few men over the age of 45 who used AAS when they were younger. But this number will now grow rapidly; even using the conservative figures from the 1991 NHS, it would follow that about half a million American men with a lifetime history of AAS use will have passed the age of 45 by the year 2010. This estimate would be even higher - well over one million - if we were to extrapolate from the

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higher figures generated by anonymous surveys of American high school students in the 1980's (Buckley et al., 1988; Johnson et al., 1989; Johnston et al., 2006). This cohort of aging AAS users is the first of its kind - the leading wave of a new epidemiologic phenomenon. Although many of these older men have discontinued AAS use, and evolving literature suggests that they may be vulnerable to a range of psychiatric and medical effects that may persist long after last AAS exposure. These are briefly summarized in Table 1; we review the relevant literature in the following sections.

3. Specific long-term effects of AAS use

3.1. Cardiovascular effects

Supraphysiologic doses of AAS appear to produce a range of adverse cardiovascular effects, including hypertension (Kuipers et al., 1991; Lenders et al., 1988; Urhausen et al., 2004), cardiomyopathy (Ferenchick, 1991b; Stolt et al., 1999; Sullivan et al., 1999; Vogt et al., 2002), left ventricular hypertrophy (Payne et al., 2004; Urhausen et al., 2004), dyslipidemia (increased low-density lipoprotein and decreased high-density lipoprotein cholesterol, with potential acceleration of atherosclerosis) (Bonetti et al., 2007; Hartgens et al., 2004; Kasikcioglu et al., 2007; Kouri et al., 1996; Kuipers et al., 1991; Lajarin et al., 1996; Lenders et al., 1988), myocardial ischemia (Mewis et al., 1996), adverse effects on coagulation and platelet aggregation (Ferenchick et al., 1992; Ferenchick, 1991a; Ferenchick et al., 1995; McCarthy et al., 2000), and arrhythmias (D'Andrea et al., 2007). Some of these effects, such as hypertension, dyslipidemia, and coagulation abnormalities, remit after AAS use is discontinued, but effects such as atherosclerosis and cardiomyopathy are likely irreversible (Hartgens and Kuipers, 2004; Sullivan et al., 1998). These effects have been blamed for numerous premature deaths among athletes in their 20's and 30's known or believed to have used AAS - either from cardiac disease (Di Paolo et al., 2007; Dickerman et al., 1995; Ferenchick and Adelman, 1992; Fineschi et al., 2007; Fisher et al., 1996; Godon et al., 2000; Halvorsen et al., 2004; Hausmann et al., 1998; Kennedy, 1993; Kennedy et al., 1993; Kennedy and Lawrence, 1993; McNutt et al., 1988; Tischer et al., 2003) or cerebrovascular accidents (Kennedy et al., 1993; Kledal et al., 2000; Lisiewicz et al., 1999). Older former AAS users, who are now entering the age of increased risk for cardiovascular morbidity and mortality, might therefore be expected to display an increased rate of serious cardiovascular events.

At present, it is difficult to estimate the prevalence or severity of cardiovascular pathology in older AAS users, since there are few empirical studies. Parssinen and colleagues (Parssinen et al., 2000) compared the mortality of 62 male powerlifters who placed 1st-5th in Finnish championships during 1977-1982 (all likely to have used AAS) and 1094 male population controls. Eight (12.9%) of the powerlifters but only 34 (3.1%) of controls had died - a ratio of 4.6 (95% CI 2.04-10.45; $p = 0.0002$). Three of the 8 deaths among powerlifters were ascribed to myocardial infarction, and the authors speculate that these deaths may have been attributable to AAS use. Of course, it must be remembered that there was no direct evidence, either from self-report or body-fluid analysis, that these athletes had used AAS - but the excess mortality among powerlifters appears unlikely to be attributable to powerlifting itself, since weightlifters and power sports athletes studied before the AAS era showed survival curves similar to male controls (Parssinen and Seppala, 2002). Similarly, Thiblin and colleagues noted chronic cardiac changes in 12 of 34 medically investigated deaths of male AAS users (Thiblin et al., 2000) in 2 of these cases, the cardiac pathology was judged to have contributed to death.

In a cross-sectional study, Di Bello and colleagues (1999) performed videodensitometry measures on 10 weightlifters reporting AAS use (mean [SD] age 32.6 [5.3] years), together with age-matched groups of 10 non-AAS-using weightlifters and 10 non-athletic controls. The AAS users were required to be currently abstinent from AAS, but to have used at least 4 "cycles" within the past year; the authors state that "cycles" each lasted typically 10 weeks,

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with 4-6 weeks of abstinence in between. The AAS users exhibited marked and significant differences from both other groups on ultrasonic measures of myocardial texture such as the "cyclic variation index," with five of the 10 AAS users differing by more than two standard deviations from the mean for both non-AAS-using weightlifters and non-athletic controls on this measure. The authors speculate that these findings may reflect focal increases in myocardial collagen as a reparative mechanism against myocardial cellular damage in the AAS users - a potentially irreversible effect.

In another cross-sectional study of similar design, D'Andrea and colleagues compared 20 AAS-using bodybuilders (mean age 33.4 [2.2] years) with age-matched groups of 25 non-AAS-using bodybuilders and 25 non-athletic control men, using Doppler echocardiography, Doppler myocardial imaging, strain rate imaging, and an EKG treadmill test (D'Andrea et al., 2007). The AAS users, though studied a mean of several years after last AAS exposure, still exhibited impaired myocardial function; for example, the investigators found that middle intraventricular septum strain rates among AAS users were strongly associated with both the mean reported number of weeks of AAS use per year, and independently with mean reported weekly dose of AAS ($p < 0.001$ for both associations). Recent cross-sectional studies of similar design in France (Nottin et al., 2006: 6 AAS users, mean age 41 [6] years; 9 non-using weightlifters; 16 non-athletic controls) and Germany (Krieg et al., 2007: 14 users, mean age 36 [7] years; 11 non-using weightlifters; 15 non-athletic controls) have also reported significant differences in measures of myocardial function among AAS-using weightlifters versus comparison groups. Although the precise origin of these effects is uncertain, one possible mechanism is suggested by a recent study finding that AAS, in a dose-dependent manner, can induce apoptotic cell death in myocardial cells in a rat model (Zaugg et al., 2001).

3.2. Neuroendocrine effects

Long-term use of AAS suppresses the hypothalamic-pituitary-testicular (HPT) axis (Pope and Brower, 2005; Reyes-Fuentes and Veldhuis, 1993); thus when a "cycle" of AAS is stopped, male users will often become temporarily hypogonadal. Although HPT function usually recovers spontaneously within a few weeks to a few months, the authors have encountered several men where hypogonadism persisted for more than a year after discontinuing AAS, and several recent published reports have documented post-AAS hypogonadism of similar duration (Boyadjiev et al., 2000; Menon, 2003; van Breda et al., 2003). Persistent suppression of HPT function may have serious clinical consequences, including infertility (de la Torre Abril et al., 2005; Menon, 2003; Turek et al., 1995) and major depressive illness (Brower, 1997, 2002; Brower et al., 1989b; Malone and Dimeff, 1992; Malone et al., 1995; Pope and Katz, 1988, 1994). In addition, dysphoric feelings associated with hypogonadism may prompt some AAS users to resume taking AAS again and again, thus prolonging the problem of HPT suppression and leading to a syndrome of AAS dependence (Brower, 2002; Kashkin and Kleber, 1989).

Even in users who recover HPT function uneventfully, there are concerns about the effects of prolonged, markedly supraphysiologic levels of AAS on other tissues sensitive to androgens, such as the prostate. High doses of AAS may contribute to prostatic hypertrophy,(Jin et al., 1996; Wemyss-Holden et al., 1994), and two case reports, to our knowledge, have described prostate cancer among AAS users who were still in their 40s or early 50s (Larkin, 1991; Roberts and Essenhigh, 1986). However, both of these latter case reports appeared more than 15 years ago; the apparent absence of any similar reports since 1991 argues against an association of AAS use with prostatic neoplasia. This conclusion is congruent with recent endocrinological reports arguing that there is no adequate scientific basis for the long-held belief that testosterone stimulates prostate cancer to grow (Morgentaler, 2006, 2007). However, to our knowledge, no systematic studies have assessed the prevalence of prostate pathology in a population of AAS users as compared to age-matched control men.

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3.3. Other physiological effects

The long-term effects of supraphysiologic doses of AAS on other organ systems are incompletely understood, and most of the available literature consists either of animal studies or small case reports in humans. Use of 17-alpha alkylated AAS (which are orally active) is definitely, albeit rarely, associated with adverse hepatic effects, such as peliosis hepatis (Karasawa et al., 1979), intrahepatic cholestasis (Kafrouni et al., 2007; Sanchez-Osorio et al., 2008), hepatocellular adenomas or carcinomas (Bagia et al., 2000; Gorayski et al., 2008; Socas et al., 2005; Velazquez and Alter, 2004), hepatic angiosarcomas (Daneshmend and Bradfield, 1979; Falk et al., 1979) and spontaneous hepatic rupture (Patil et al., 2007). Adverse hepatic effects with non-17-alpha alkylated AAS, such as testosterone, appear to be extremely rare, but have been described (Carrasco et al., 1985). The risk of these hepatic effects is presumably greater with increasing duration of AAS exposure, as suggested for example by reports of hepatocellular adenomas developing after years of therapeutic AAS treatment for certain anemias (Nakao et al., 2000; Velazquez and Alter, 2004). However, AAS-induced hepatic pathology is often reversible upon discontinuation of AAS (Modlinski and Fields, 2006), and the overall prevalence of adverse hepatic effects among long-term illicit AAS users is likely low. For example, one large naturalistic study of 88 illicit AAS users (mean [SD] age 25.5 [7.0] years; mean lifetime AAS exposure 62.7 [67.2] weeks) found virtually no evidence of hepatic pathology on laboratory testing or physical examination (Pope and Katz, 1994). However, it is not clear whether these findings can be extrapolated to older populations.

Also disquieting are studies suggesting that supraphysiologic levels of AAS produce dose-dependent apoptotic cell death. For example, apoptosis of human endothelial cells has been demonstrated with supraphysiologic concentrations of several different AAS in vitro (D'Ascenzo et al., 2007). In a rat model, supraphysiologic levels of testosterone and stanozolol were found to induce apoptotic death of myocardial cells - prompting the authors to speculate that this mechanism might account for cardiac pathology in human AAS users (Zaugg et al., 2001). Recently, another study has found that supraphysiologic levels of testosterone can produce apoptosis in neuronal cells (Estrada et al., 2006). Although this study was in vitro, the levels of testosterone causing significant apoptosis were within the range that might plausibly be reached by illicit human AAS users, who may ingest doses equivalent to 50-100 times the level of endogenous testosterone production (Fudala et al., 2003; Parkinson and Evans, 2006; Parrott et al., 1994; Pope and Katz, 1988, 1994; Wilson-Fearon and Parrott, 1999). Thus, the authors suggest that their findings might have clinical significance in humans. To our knowledge, however, no studies have systematically assessed older long-term high-dose AAS users for signs of dementia or specific neuropsychological deficits.

3.4. Neuropsychiatric effects

Even if supraphysiologic AAS do not prove to have a clinically significant toxic effect on human neuronal cells, these drugs are known to be associated with a variety of psychiatric effects (Pope and Katz, 2003). Among illicit AAS users, it may be difficult to judge which of these psychiatric effects are attributable to AAS themselves, as opposed to underlying personality attributes of the user, or psychosocial factors surrounding AAS use (Bahrke and Yesalis, 1994; Bahrke et al., 1996; Midgley et al., 2001; Perry et al., 2003). Nevertheless, both experimental studies (Pope et al., 2000b; Su et al., 1993; Yates et al., 1999) and naturalistic field studies (Choi and Pope, 1994; Hall et al., 2005; Malone et al., 1995; Pagonis et al., 2006a; Pagonis et al., 2006b; Parrott et al., 1994; Pope and Katz, 1988, 1994; Wilson-Fearon and Parrott, 1999) have suggested that supraphysiologic doses of AAS can directly cause hypomanic or manic symptoms, sometimes associated with aggression and violence (Choi and Pope, 1994; Kouri et al., 1996; Pagonis et al., 2006b; Pope and Katz, 1990; Wilson-Fearon and Parrott, 1999). However, not all studies have documented such mood changes (Bahrke et al., 1992; Bhasin et al., 1996; Tricker et al., 1996); these psychological effects appear to be variable

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and idiosyncratic in both humans (Daly, 2001; Rubinow and Schmidt, 1996) and in rodent models of aggression (Clark and Henderson, 2003; Melloni et al., 1997), with some individuals exhibiting prominent symptoms and others none (Pope and Katz, 2003). Many field studies have also documented depressive symptoms associated with AAS use, especially during withdrawal from AAS at the end of a "cycle," possibly attributable to HPT suppression (Brower, 2002; Kashkin and Kleber, 1989; Malone and Dimeff, 1992; Malone et al., 1995; Pope and Katz, 1994). These studies have included several reports of suicides (Agren et al., 1999; Allnut and Chaimowitz, 1994; Brower et al., 1989a; Papazisis et al., 2007; Thiblin et al., 1999). Depressive symptoms, like hypomanic symptoms, appear to be idiosyncratic, with occasional individuals showing marked symptoms and others showing none (Schmidt et al., 2004).

Most of the above studies, however, describe short-term mood changes, measured in weeks or months, during or shortly after AAS use. It is less clear whether mood changes may persist longer. However, recent Scandinavian studies offer some cause for concern. Petersson and colleagues found that suicide was significantly more common among deceased former AAS users than among other types of substance users (Petersson et al., 2006). Also, in the study of older powerlifters by Parssinen et al., 3 of the 8 deaths were from suicide (Parssinen et al., 2000). Recently, a Swedish research group has presented preliminary results from a structured questionnaire mailed to 996 former Swedish elite male athletes who placed 1st though 10th in Swedish championships between 1960 and 1979 in wrestling, track and field (throwing events), power lifting, and Olympic lifting (Lindqvist et al., 2007). Among the 698 respondents, 683 answered the question about AAS, and of these, 143 (20.9%) reported prior AAS use. The former users were much more likely to report seeking treatment for psychiatric symptoms; for example, 19 (13.3%) of the AAS users had sought treatment for depression, as compared to 27 (5.0%) of nonusers ($p = 0.001$).

Of course, the above studies do not establish that AAS played a causal role in the development of long-term depression or other psychiatric symptoms - but there are several reasons to suspect that AAS users might be at increased risk for depression even into middle age. First, some individuals become dependent on AAS, repeatedly taking these drugs to prevent hypogonadal symptoms, and thus may continue to use AAS well into middle age. Second, even among those who discontinue AAS use in their 20s or 30s, HPT suppression and consequent hypogonadal symptoms may persist in some cases for prolonged periods. The prevalence of this phenomenon among AAS users, and its contribution to depressive symptoms, remains unknown. Third, AAS users may suffer from prominent body-image disorders, such as muscle dysmorphia, a form of body dysmorphic disorder in which individuals become preoccupied that they do not look sufficiently big and muscular (Cafri et al., 2005; Choi et al., 2002; Chung, 2003; Kanayama et al., 2006; Leit et al., 2002; Olivardia et al., 2000; Pope et al., 1997; Rhea et al., 2004). This syndrome, which is sometimes also called "reverse anorexia nervosa" (Cole et al., 2003; Kanayama et al., 2006; Pope et al., 1993), is associated with considerable psychiatric morbidity, and may be both a cause and a consequence of AAS use (Cole et al., 2003; Kanayama et al., 2006; Kanayama et al., 2003b; Kanayama et al., 2001b; Mangweth et al., 2001; Nilsson et al., 2001; Pope et al., 1993; Schwerin et al., 1996). Specifically, men with body-image concerns may be motivated to use AAS initially, and then paradoxically become increasingly concerned about their muscularity even as they are growing bigger on AAS. Muscularity becomes central to their self-esteem, and loss of muscularity triggers anxiety. This phenomenon frequently contributes to the syndrome of AAS dependence (Brower, 2002; Brower et al., 1990).

Also as a result of their body image concerns, AAS users may abuse a wide range of additional substances to gain muscle, lose fat, or otherwise affect body appearance. These substances, which we have elsewhere termed "body image drugs"(Kanayama et al., 2001b), include other hormones (such as human growth hormone, somatomedin-C, thyroid hormones, insulin, and

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human chorionic gonadotropin), beta agonists (clenbuterol), stimulants (amphetamine, ephedrine, pseudoephedrine), drugs for weight or fluid loss (diuretics, laxatives), drugs believed to stimulate testosterone or growth hormone secretion (clomiphene, cyclofenil, gamma hydroxybutyrate, levodopa, clonidine), and numerous other agents (erythropoietin, tamoxifen, danazol, yohimbine), including even industrial chemicals such as 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 wishing to use these substances can obtain detailed advice from comprehensive underground guides (Gallaway, 1997; Llewellyn, 2007; Roberts and Clapp, 2006) or from countless Internet websites, forums, and discussion groups 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). Many of these substances have been studied under legitimate medical conditions, but their effects when used illicitly, alone or in combination with AAS, are little studied.

Yet another potential long-term problem among AAS users is abuse of, or dependence upon classical illicit drugs (“street drugs”). For example, in a recent study from our group, 17 (35%) of 48 male AAS users met DSM-IV criteria for a lifetime history of abuse of or dependence upon an illicit drug, as compared to only 1 (2%) of 45 experienced non-AAS-using weightlifters recruited in an identical manner ($p < 0.001$) (Kanayama et al., 2003b). Among the various illicit drugs ingested by AAS users, opioids may represent a particular problem. Specifically, two reports have described illicit use of the opioid agonist-antagonist nalbuphine among AAS users (McBride et al., 1996; Wines et al., 1999); some of these nalbuphine users then progressed to dependence on classic opioid agonists. Another report (Arvary and Pope, 2000) found that 21 (9%) of 227 male heroin addicts at a treatment facility were apparently first introduced to opioids through their AAS use; 17 (81%) of the 21 men first purchased opioids from the same drug dealer who had sold them AAS, and 14 (67%) reported that they had used opioids to counteract depressive symptoms associated with AAS withdrawal. Another study of 223 consecutive men admitted to an inpatient substance abuse treatment facility suggested a similar link between AAS and opioids: among 88 men with a primary diagnosis of opioid dependence, 22 (25%) reported prior AAS use, as compared to only 7 (5%) of 135 men with other forms of substance dependence ($p < 0.001$). Interestingly, animal studies also suggest possible links between AAS and opioids; for example, hamsters will self-administer testosterone, sometimes even to the point of death (Wood, 2006), and several lines of evidence suggest that opioidergic mechanisms may be involved in this self-administration process (Peters and Wood, 2005). Thus, there may be a neurobiological basis for the progression from AAS use to opioid use in humans.

4. The prevalence of adverse effects in long-term AAS users

Little is known about the lifetime prevalence of the various medical and psychiatric consequences of AAS use described above. It might be speculated that publication bias exaggerates the apparent magnitude of AAS-associated pathology, in that rare cases of cardiac or hepatic toxicity, or of psychiatric effects such as violence or suicide, find their way into published case reports, while the great majority of long-term illicit AAS users are healthy. Indeed, some authors have suggested that political and moral forces have demonized AAS use, and that in this atmosphere, the dangers of AAS are being greatly exaggerated (Cohen et al., 2007; Collins, 2002). As recently as 2005, a well-known medical ethicist has referred to “steroid hysteria,” and questioned the evidence that “steroids cause life-threatening harms” (Fost, 2005). Certainly these arguments deserve consideration - but on the other hand, there are several reasons to suspect that we might be underestimating, rather than overestimating, the public health consequences of long-term AAS use.

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First, as discussed above, a majority of individuals with a lifetime history of AAS use have yet to pass middle age, and thus the long-term effects of AAS may not have had a chance to fully declare themselves. Imagine, for example, that widespread use of cigarettes began only in 1980, and that a majority of all cigarette smokers in 2008 were still under age 45. In this scenario, one might find scattered case reports of lung cancer among cigarette smokers, but the magnitude of the association between cigarettes and lung cancer would not yet be appreciated.

Of course, some AAS users in the population are well over age 45 - especially men who competed in bodybuilding competitions or Olympic events in the 1960s and 70s, such as the Swedish sample described above (Lindqvist et al., 2007). However our experience from interviews of numerous older weightlifters, together with published reports in the media, suggests that the doses of AAS used in the 1960s and 70s were typically much lower than those used today. It should also be remembered that most AAS users prior to 1980 were competitive athletes, presumably attempting to optimize their health and performance, and rarely using other illicit drugs for recreational purposes. For example, among the older athletes in the Swedish sample, more than 80% reported that they had never used any recreational illicit drugs in their lives. By comparison, most modern AAS users are not competitive athletes, and many use large amounts of other illicit recreational drugs (Kanayama et al., 2003b) and other potentially hazardous body-image drugs (Kanayama et al., 2001b; Parkinson and Evans, 2006). Thus with advancing age, the outcomes of these individuals may be quite different from the outcomes of older elite athletes.

Second, some individuals may develop adverse effects from long-term AAS use, but the etiologic role of AAS in these cases may go unrecognized, either because the clinician fails to elicit a history of AAS use, or because the patient fails to disclose it. AAS users are particularly reluctant to disclose their AAS use to doctors. In a study from our group (Pope et al., 2004), 20 (56%) of 36 AAS users reported that they had never disclosed their AAS use to any physician that they had seen.

Furthermore, clinicians are often much less familiar with AAS use than they are with other forms of substance abuse (Dawson, 2001; Kanayama et al., 2007; Kutscher et al., 2002), and hence they may fail to seek a history of AAS exposure in an individual exhibiting medical or psychiatric problems. Such a history is easily missed when evaluating men who are older and not visibly athletic. In one recent study of 223 men admitted to a general substance abuse treatment unit (Kanayama et al., 2003a), 29 (13%) reported a history of AAS use on a research screening interview, but in only four of these cases was this history noted in the physician's admission evaluation.

Nondisclosure may also compromise studies comparing AAS users to non-AAS-using weightlifters, because "non-user" groups are often contaminated with occult AAS users (Brower et al., 1991; Ferenchick, 1996; Kanayama et al., 2003b). Although urine testing can detect recent AAS use, individuals who have used AAS months or years earlier cannot be identified and excluded - and the inclusion of such individuals will lead to an underestimate of effect sizes.

Third, one must allow for the unknown number of AAS users who die prematurely - as suggested, for example, by the study of Parssinen and colleagues (Parssinen et al., 2000), which found more than four times as many deaths among former likely AAS users as in an age-matched male population. Our own anecdotal experience also suggests increased premature mortality among AAS users; we are personally familiar with several deaths (primarily by suicide or by unintentional overdose of opiates) among AAS users under age 40, and colleagues have described many others (Arvary, D., personal communication, January, 2008). Premature death could cause studies to underestimate the effects of AAS in cross-sectional samples of

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aging men, because dead individuals would of course have exited the available study population.

5. Conclusions

Accumulating evidence suggests that long-term use of supraphysiologic doses of AAS may have adverse effects on a number of organ systems, leading to both medical and psychiatric pathology. Importantly, accumulating evidence suggests that some of these effects may persist long after last AAS exposure. However, the frequency and severity of AAS-induced morbidity and mortality is still poorly understood, largely because these effects may not declare themselves until users enter middle or old age - and investigators have examined at most small samples of aging AAS users. But this situation is poised to change, as hundreds of thousands of former (and sometimes still current) illicit AAS users begin to pass the age of 45. As this wave of aging users approaches, it is imperative to initiate larger and more systematic studies of the long-term effects of AAS, so that we can better inform both the present and future generations.

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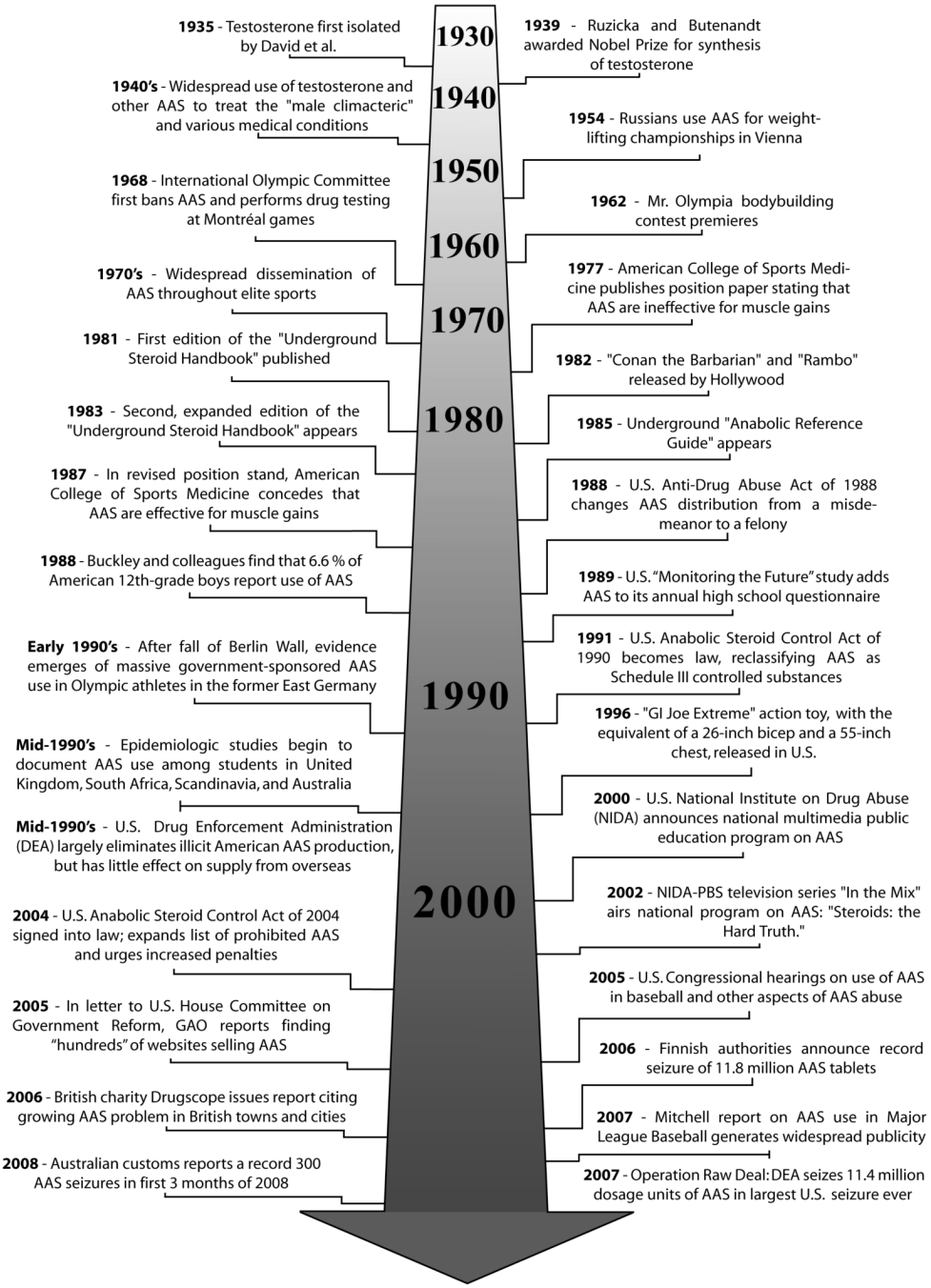

Figure 1.
Time points in the evolution of anabolic-androgenic steroid abuse. See text for further discussion and references.

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Table 1

Possible Long-Term Adverse Effects of Anabolic-Androgenic Steroid Abuse

Cardiovascular effects:	
Atherosclerosis	++
Cardiomyopathy	++
Other medical effects:	
Prolonged suppression of testicular function	+
Prostate cancer	-
Other cancers	+
Neuropsychiatric effects:	
Major mood disorders	++
AAS dependence	++
Progression to other forms of substance dependence	+
Neuropsychological deficits	+/-

++ Moderate evidence

+ Limited evidence

- Little or no evidence

+/- Speculative