

Behavioural Manifestations of Anabolic Steroid Use

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Contents

Abstract	571
1. Scope of Steroid Use	572
1.1 Prevalence of Use	572
1.2 Patterns of Use	573
2. Physiological Impact of Steroid Use	574
2.1 Physical Symptoms	574
2.2 Laboratory Abnormalities Associated with Use	576
3. Psychiatric Impact of Steroid Use	576
3.1 Evidence from Prospective Studies	576
3.2 Evidence from Naturalistic Studies and Case Reports	579
3.2.1 Aggression and Violence	579
3.2.2 Predominant Mood Symptoms	586
3.2.3 Psychosis	587
3.2.4 Dependence and Withdrawal	588
3.2.5 Other Psychiatric Co-morbidities	589
4. Management of Steroid Abuse	590
4.1 Acute Care	590
4.2 Long-Term Care	591
5. Conclusion	592

Abstract

The use of anabolic androgenic steroids (AAS) for gains in strength and muscle mass is relatively common among certain subpopulations, including athletes, bodybuilders, adolescents and young adults.

Adverse physical effects associated with steroid abuse are well documented, but more recently, increased attention has been given to the adverse psychiatric effects of these compounds. Steroids may be used in oral, 17 α -alkylated, or intramuscular, 17 β -esterified, preparations. Commonly, steroid users employ these agents at levels 10- to 100-fold in excess of therapeutic doses and use multiple steroids simultaneously, a practice known as 'stacking'. Significant psychiatric symptoms including aggression and violence, mania, and less frequently psychosis and suicide have been associated with steroid abuse. Long-term steroid abusers may develop symptoms of dependence and withdrawal on discontinuation of AAS.

Treatment of AAS abusers should address both acute physical and behavioural symptoms as well as long-term abstinence and recovery. To date, limited information is available regarding specific pharmacological treatments for individuals

recovering from steroid abuse. This paper reviews the published literature concerning the recognition and treatment of behavioural manifestations of AAS abuse.

Anabolic androgenic steroids (AAS) were initially synthesised in the late 1930s as a treatment for hypogonadism.^[1] While a small number of bodybuilders began to use AAS shortly thereafter, the first systematic abuse of AAS to gain muscle mass is attributed to Soviet weightlifting teams of the early 1950s.^[2] Subsequently, AAS use infiltrated professional and amateur athletics and bodybuilding. Recently, there has been a great deal of controversy concerning the use of AAS and steroid precursors in major league baseball.^[3] Although AAS can enhance athletic performance, the adverse physical effects induced by these substances are well documented.

More recently, the negative psychiatric effects of AAS use have received attention. Numerous instances of violence and aggression related to AAS use by athletes and bodybuilders have been reported in the popular press.^[4-9] While a causal link has not yet been established, it is clear that in some cases AAS abusers without prior psychiatric or criminal histories have become acutely agitated and violent. High doses of AAS have also been associated with manic-like affective symptoms (euphoria, increased energy, sexual arousal and mood swings), cognitive symptoms (impaired attention, memory and orientation) and less commonly with psychosis.^[1] This review addresses diagnosis and management of untoward behaviours caused by AAS use as described in the available literature. Pertinent articles were identified through MEDLINE searches, and supplemented by papers listed in the reference sections of these papers. Additional relevant articles were located in the popular press.

1. Scope of Steroid Use

1.1 Prevalence of Use

Since AAS are generally obtained illicitly, it is difficult to determine the true prevalence of AAS use. The 1991 National Household Survey on Drug Abuse (NHSDA)^[10] estimated that there are >1 mil-

lion current or former steroid users in the US, including 300 000 individuals who reported using steroids in the previous year. According to this survey, the lifetime prevalence of steroid use was 0.9% for males and 0.1% for females.^[10] Yesalis^[2] reported on a variety of single-state and multistate studies, published between 1975 and 1991, that described the results of self-report surveys or urine screening. Several studies that examined AAS use among adolescents and young adults reported a fairly wide range in the prevalence of steroid use from one population to another. The highest total incidence of steroid use (5.7%) was reported in a study of 1775 11th graders at six schools in Arkansas, and the lowest total incidence (0.7%) was reported among 1393 students at ten schools in Arizona (grade levels unknown). Among male students, reports of incidence were highly divergent, ranging from 1.1% in a survey of 190 9th–12th grade athletes at six schools in Oregon, to 18% in a study of 200 9th–12th grade students at one school in Florida. The incidence of steroid use was more consistent among females, ranging from 0% in the Florida survey to 2.5% in a survey of 2113 9th–12th graders at one school in Illinois.^[2]

At least three national surveys have characterised the prevalence of AAS use in US adolescents: the Youth Risk Behavior Surveillance System (YRBSS); Monitoring the Future (MTF); and the NHSDA. None of the three surveys displayed significant changes in terms of lifetime steroid use between the early and mid-1990s. The YRBSS, which was conducted in 1991, 1993 and 1995, indicated that lifetime steroid use ranged from 2.2% to 3.7% among 9th–12th grade students ($n = 10\,904$ – $16\,267$). The MTF survey, performed between 1991 and 1996, estimated that lifetime steroid use ranged from 1.9% to 2.4% among 12th grade students ($n = 2275$ – 2716). The NHSDA estimated that lifetime steroid use ranged from 0.2% to 0.7% among 12- to 17-year-olds in the years 1991–1994 ($n = 4678$ – 8005). Analysis of sex-specific data indicated some statistically significant changes in ster-

oid use in both genders, although these changes were not consistent from one study to another and no clear trends emerged.^[10]

More recent complete data from the 2002 MTF survey and preliminary reports from the 2004 MTF survey indicate that steroid use among high school students continues to be relatively common, particularly among males.^[11] Based on samples of 12 000–15 000 students per grade, annual prevalence rates were 1.8%, 3.2% and 3.8% for males in grades 8, 10 and 12, respectively, and 1.2%, 1.2% and 1.3% among females in grades 8, 10 and 12, respectively. After remaining relatively stable between 1991 and 1997, the overall annual prevalence of steroid use in 8th and 10th graders increased from 1.2% to 1.7% between 1998 and 1999. Among 12th graders, a gradual increase in use was seen between 1992 and 1999, reaching 1.7% in 2000, with another significant increase to 2.5% in 2001. Annual prevalence rates for each of the grade levels remained stable between 2001 and 2002. The percentage of 12th graders who associated a 'great risk' (physically or otherwise) with using steroids once or twice was 57.1% in 2002, marking the lowest level since this statistic began being monitored in 1989. Disapproval associated with steroid use remains quite high, having never been reported at a level <80%. There was significant disapproval in 2001, but no significant change in 2004.^[11] These data seem to indicate that in the early years of the 21st century, perceived risk and disapproval of use of steroids have decreased in conjunction with increased use.

The use of AAS by children and adolescents has been associated with other concurrent high-risk behaviours. In 1993, Yesalis et al.^[12] reported that 80% of 12- to 17-year-olds who had used steroids at least once in their lives had committed acts of violence or crimes against property within the past year, a rate more than twice that of those who had never used steroids. Adolescents who used AAS at least once were also more than twice as likely to use other illicit drugs compared with those who never abused AAS. This study did not specify whether these behaviours were demonstrated during periods of AAS use or were characteristics that actually promoted AAS use.^[12] Middleman et al.^[13] reported on the results of the Massachusetts Youth Risk Behavior questionnaire, which examined associations be-

tween various health risks and problem behaviours in a population of 3054 students from 45 high schools. The frequency of steroid use was associated with all risk factors assessed, including driving after drinking alcohol, carrying a weapon and physical fighting. These results suggest that steroid use is part of a 'risk behaviour syndrome' rather than an isolated behaviour, making a cause-and-effect relationship between steroid use and untoward behaviour less clear.

A lesser known subgroup of steroid users is females who have been victims of sexual assault. In a study of 75 female weightlifters,^[14] ten (13%) reported that they were raped as teenagers or adults, and nine (90%) of these said they had greatly increased their weightlifting activities after being assaulted. Of the ten rape victims, seven (70%) used steroids and/or clenbuterol (a β -agonist with anabolic properties) to gain muscle mass and strength after the assault. Among the other 65 women surveyed, 22 (34%) reported use of these anabolic substances.^[14]

In addition to the widespread use of illicit steroids, the use of over-the-counter (OTC) performance-enhancing agents, particularly those containing ephedrine or adrenal hormones such as androstenedione, is believed to be an under-recognised substance abuse problem. Kanayama et al.^[15] surveyed 511 individuals entering five different Massachusetts, USA gymnasiums. Among the men surveyed, 18% reported the use of androstenedione or other adrenal hormones, 25% reported ephedrine use and 5% reported anabolic steroid use. In women, the rates were 3%, 13% and 0%, respectively. Extrapolating these figures to the US population, the authors estimated that 1.5 million gymnasium clients have used adrenal hormones and 2.8 million have used ephedrine.^[15]

1.2 Patterns of Use

Many steroid users initially take oral 17α alkyl derivatives of testosterone such as ethylestrenol, fluoxymesterone, methyltestosterone, oxandrolone, oxymetholone and stanozolol. Habitual AAS users often progress to injectable 17β -esterified agents such as nandrolone decanoate, nandrolone phenpropionate, testosterone cypionate, testosterone enanthate and testosterone propionate. Many regular

Table I. Substances commonly used in conjunction with steroids^[18,19]

Treatment of adverse effects	Enhancement of effect	Masking use
Estrogen antagonists	Human chorionic gonadotrophin	Diuretics
Human chorionic gonadotrophin	Growth hormone	Probenecid
Ketoconazole shampoo	Stimulants	Epitestosterone
Analgesics	Amino acids	Etacrynic acid
Oral hypoglycaemics	Diuretics	(etacrinic acid)
	Dehydrating agents	
	Alprostadil	
	Erythropoietin	
	Aminoglutethimide	

steroid abusers use these compounds in doses 10- to 100-fold in excess of therapeutic levels. In many cases, multiple AAS are used simultaneously, a practice known as 'stacking', which may be done to produce a synergistic effect by exploiting different androgen receptors or merely to achieve a higher overall dose. AAS are generally used in 4–12 week 'cycles' followed by a similar period of abstinence in order to maximise the desired effects and limit adverse effects.^[16] A technique called 'plateauing' is sometimes used to avoid developing tolerance to a particular agent. This may involve staggering drugs, overlapping drugs, or discontinuing one agent and introducing another.^[2] Many AAS users 'pyramid' these agents to achieve a maximal dose at the middle or end of a 12-week cycle. The serious steroid user may ultimately add supplemental agents to the regimen to prevent adverse effects of AAS. Antiestrogen agents are used to prevent gynaecomastia and human chorionic gonadotrophin is used to decrease testicular atrophy. Table I lists common coingestants in AAS users.^[17]

AAS are available in the US only by prescription. Thus, steroids are generally obtained illicitly and veterinary preparations or illegally synthesised compounds are consumed. In many cases, AAS users do not know what compound they are using. In a naturalistic study of 37 male AAS users, the types of steroids used according to self-reports varied substantially from those detected through urine testing. Only 41% of 25 individuals reporting the use of testosterone tested positive for this compound. Conversely, only one subject reported using methyltestosterone, while six (16%) tested positive for this compound.^[20]

Steroid supplements are available without prescription in the US. Recently, 'prohormones', i.e. precursors of testosterone or related hormones, have been marketed as OTC dietary substances; as such, they do not require US FDA approval. One type of prohormone, androstenedione, has already been banned by the National Football League and the International Olympic Committee, among other organisations.^[21,22] Another commonly abused prohormone is dehydroepiandrosterone (DHEA [prasterone]), which manufacturers claim has a broad range of therapeutic effects including metabolising fat, building muscle mass, strengthening the immune system and preventing Parkinson's disease. None of these effects has been assessed adequately in randomised, placebo-controlled studies. DHEA is naturally produced in brain tissue as well as by the adrenal gland, with circulating levels declining with age.^[23,24] Decreased levels of DHEA(S), the sulphated metabolite of DHEA, and/or decreased ratios of DHEA to cortisol are sometimes evident in patients with depression, postpartum depression, anxiety, anorexia nervosa, psychosocial stress and functional limitations.^[23,24] Patients with schizophrenia are also thought to have low endogenous DHEA levels at certain times of the day,^[25] although the metabolite DHEA(S) may be elevated.^[23,26]

2. Physiological Impact of Steroid Use

2.1 Physical Symptoms

Aside from obvious increases in muscle mass, symptoms and signs in various organ systems may be indicative of steroid use. Pertinent aspects of the physical examination should include: vital signs; height, weight and body mass index; skin; head, eyes, ears, nose and throat; chest; abdomen; genitourinary system; musculoskeletal system; and the extremities, because abnormalities in any of these areas may be indicative of steroid use (see table II). Review of these systems should address complaints commonly associated with AAS abuse such as headaches, dizziness, muscle spasms, urinary frequency and menstrual abnormalities.^[18]

Cosmetic abnormalities, such as acne and gynaecomastia, although not requiring emergency treatment, may serve as an indicator of steroid use.

Observation of these symptoms in the early stages of steroid use might facilitate the prevention of more serious, potentially fatal conditions that have been associated with these substances.

Myocardial infarction (MI) and sudden cardiac death have been associated with steroid use in humans.^[18,27-34] In many cases, MI occurred in the absence of significant medical histories or known risk factors.^[28-30,33,34] The steroid regimens used by these individuals were often reported incompletely or omitted, and duration of steroid use at the time of cardiac event was highly variable, ranging from several months to several years.^[29] Other substances concurrently used by bodybuilders may also increase the risk of MI. For example, one individual, in addition to AAS, was regularly taking amphetamines, Frumil®¹ (furosemide [frusemide] and amiloride) and potassium supplements to reduce body fluid and increase muscle definition.^[32] Some of the pathological characteristics identified in cases of MI associated with AAS include cardiac hypertrophy (particularly of the left ventricle),^[18,29,33] myocardial fibrosis,^[29] infarct necrosis,^[34] thrombotic coronary arteries^[27,28] and coronary artery spasm.^[31] AAS have been associated with coronary artery vasospasm in the absence of both atherosclerosis and thrombosis.^[29] Thus far, there is no definitive evidence to suggest that MI is associated with steroid use in a dose-related fashion.

There are several theories as to how AAS use may induce MI. AAS are believed to counteract exercise-induced functional adaptations of the heart and alter the reserve capacities of the left ventricle.^[35] Compared with individuals not taking steroids at all or those who have stopped using steroids, current steroid users have been reported to have left ventricular hypertrophy, increased interventricular septal thickness, and decreased maximum oxygen uptake (VO_{2max}).^[29,33,36] Power lifters who take AAS may be at an increased risk of atherosclerosis secondary to increased levels of low-density lipoprotein (LDL) cholesterol and decreased levels of high-density lipoprotein (HDL).^[18,31,37,38] It has also been suggested that elevated total cholesterol may increase the coronary artery response of AAS users to circulating catecholamines.^[29] Hypertension has

been associated with steroid use in some cases,^[39] although this finding has been contradicted in other studies.^[40,41] AAS may facilitate thrombosis by altering vascular reactivity, enhancing platelet aggregation and increasing the concentration and activity of particular procoagulant factor proteins.

Other potentially serious pathologies have been associated with steroid abuse. AAS are known to cause complications in the endocrine and genitourinary systems. Abnormalities in tests of liver function have been associated with steroid use, particularly with oral 17 α -alkylated steroids.^[18] Increased levels of liver enzymes may result in jaundice in some patients. A rare condition known as peliosis hepatis, in which blood-filled liver cysts develop, has been associated with AAS use.^[42,43] Steroid users are also at an increased risk for infectious

Table II. Abnormalities that may be seen on physical examination of anabolic androgenic steroid users^[16,18,19]

Abnormalities
Vital signs and physical dimensions
High blood pressure
Rapid weight gain with increase in lean body mass
Skin
Acne
Needle marks in large muscle groups
Male pattern baldness
Hirsutism (females)
Jaundice
Head, eyes, ears, nose, throat
Icteric eyes
Deepened voice (females)
Chest
Gynaecomastia (males)
Atrophied breasts (females)
Abdominal
Right upper quadrant tenderness
Hepatomegaly
Genitourinary
Testicular atrophy
Prostatic hypertrophy (males)
Clitoral hypertrophy (females)
Musculoskeletal
Muscular hypertrophy
Disproportionate development of the upper torso
Extremities
Oedema

¹ The use of trade names is for product identification purposes only and does not imply endorsement.

disease as they often use nonsterile injection techniques and share needles. As a result, steroid users may be susceptible to viral infections such as HIV and hepatitis B and C.^[19]

2.2 Laboratory Abnormalities Associated with Use

When steroid abuse is suspected, laboratory testing can be used to confirm the suspicion. Many major urinary metabolites of AAS can be identified by gas chromatography/mass spectrometry with extreme sensitivity, i.e. at concentrations in the order of 1–10 µg/L in the urine.^[44] The development of high-resolution mass spectrometry has provided an even more sensitive option for steroid detection and is useful in screening for long-lasting metabolites such as those of stanozolol and methandienone.^[45]

The average male produces 6–10 mg/day of testosterone, of which only 1% is excreted unchanged in the urine.^[46] In AAS abusers, endogenous testosterone is suppressed by feedback inhibition on gonadotropins. However, individuals who administer exogenous testosterone will usually have high urine testosterone levels. Determination of exogenous testosterone use is made by evaluating the ratio of urine testosterone (T) to epitestosterone (E), a normal testosterone metabolite. The T : E ratio (median ratio for male non-users 1 : 1) increases after testosterone administration, and a T : E ratio of 6 : 1 is considered to be indicative of exogenous testosterone use.^[44,45] Although some individuals may have naturally increased testosterone levels, it is highly unlikely that an individual who did not use an exogenous source of testosterone would have a T : E ratio greater than 15 : 1.^[45]

If the use of exogenous testosterone cannot be determined definitely from a T : E ratio derived from a urine screen, various ancillary tests can be employed, although documented experience with these tests is limited. The ketoconazole challenge test involves collecting urine before and after an oral dose of ketoconazole, which inhibits the synthesis of testosterone. In a normal male, ketoconazole will decrease urinary T as well as the T : E ratio. If the T : E ratio is increased after ketoconazole administration, an exogenous source of testosterone is likely. Another approach involves comparing levels of testosterone precursors to testosterone. If exogenous

testosterone is being used, precursors are likely to be suppressed and the ratio will be high. A variety of less invasive approaches to steroid testing are being examined, including variations on the standard T/E analysis involving precursors of T and E, and measurement of the carbon isotope ratio in testosterone. Carbon isotope ratio testing is based on the hypothesis that the ratio of C¹³ : C¹² is different in synthetic testosterone compared with endogenous testosterone.^[45]

In addition to testing for steroids, it may be useful to examine for the presence of other illicit substances. Steroid users may abuse other substances to self-medicate psychomotor agitation associated with steroid use or the depression associated with withdrawal.^[47] Other laboratory tests may also reveal abnormalities indicative of steroid use and may be useful for alerting the patient to abnormalities that have the potential to cause serious health problems. Specific tests that may be useful for suspected steroid users, and common abnormalities that may be detected as a result, are detailed in table III.^[18]

3. Psychiatric Impact of Steroid Use

Low doses of AAS generally do not cause significant psychiatric symptoms. Psychiatric manifestations are more common with the grossly elevated doses seen in abuse and may include depression, insomnia, mood instability, mania, psychosis, delirium, aggression and suicidal and homicidal ideation or behaviour.^[1-10] As discussed below, AAS have been implicated as a cause or exacerbating factor in a multitude of psychiatric symptoms. As a minimum, psychiatric assessment in suspected AAS abusers should evaluate the following elements: attention; behaviour; mood; affect; thought process; thought content; and hallucinations (see table IV). Particular attention should also be paid to abuse of other substances and to suicidal and/or homicidal thoughts or plans. Because mood changes may begin to occur within the first week of use, acute behavioural disturbances may precede changes in body habitus.^[17]

3.1 Evidence from Prospective Studies

Few well designed prospective studies have evaluated the psychiatric effects of high-dose AAS use.

Table III. Laboratory tests relevant to anabolic androgenic steroid (AAS) users^[12,18,35]

Laboratory test	Associated abnormalities	Notes
Liver function tests	Elevations in: bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT	Elevations in ALT and AST can occur with extensive weightlifting in the absence of AAS use
Muscle enzymes	Elevations in CPK	CPK levels can be elevated in non-AAS using weightlifters as well, but the increases are more pronounced in AAS users. AAS users also show abnormal elevations prior to exercise
Cholesterol profile	Decreased HDL cholesterol Increased LDL cholesterol Possible increase in total cholesterol Elevated triglyceride levels	
Haematocrit and haemoglobin	Elevations in haematocrit and haemoglobin	Elevations may occur because of the erythropoietic effect of AAS
Electrolytes	Elevations in: nitrogen, sodium, potassium, phosphorus, calcium	Androgens promote retention of nitrogen, sodium, potassium and phosphorus, and decrease urinary excretion of calcium
Endocrine tests of the pituitary-gonadal axis	Decreased serum levels of: LH, FSH, testosterone (for AAS other than testosterone) Increased serum levels of: testosterone (when testosterone is used), estradiol (if testosterone esters are used)	
Thyroid function tests	Decreased serum levels of total T ₄ Increased resin uptake of T ₃ and T ₄	AAS use may result in decreased levels of thyroxine-binding globulin causing decreased total serum T ₄ levels and increased resin uptake of T ₃ and T ₄
Semen analysis	Sperm count and motility may be decreased, sperm morphology may be abnormal	
Cardiac function tests	ECG may indicate LVH	LVH may be seen in athletes who do not use AAS. However, LVH in AAS users may be associated with impaired diastolic functioning. ECG may have utility in screening for myocardial infarction in AAS users

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **CPK** = creatine phosphokinase; **FSH** = follicle-stimulating hormone; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **LH** = luteinising hormone; **LVH** = left ventricular hypertrophy; **T₃** = triiodothyronine; **T₄** = thyroxine.

In a randomised, placebo-controlled, crossover trial, Pope et al.^[48] explored the development of manic and aggressive symptoms in 56 normal men treated with intramuscular testosterone cypionate treatment at doses titrated to 600 mg/wk. Participants were recruited from colleges and one gymnasium in Massachusetts, USA and were aged between 20 and 50 years. Participants of three different classifications were chosen: (i) men who did not lift weights regularly and had never used AAS; (ii) men who lifted weights regularly (at least three times per week for at least 2 years and who had never used AAS); and (iii) men who had formerly used AAS illicitly. Individuals with recent histories of substance abuse, those with current or previous mental illness, those with clinically significant medical conditions, and recent users of AAS were excluded. Participants were randomised to receive either testosterone cypionate or placebo for 6 weeks, followed by a

6-week washout period, then 6 weeks of the opposite treatment, followed by another 6-week washout. At weekly visits, participants were screened with a variety of psychiatric scales including the Young Mania Rating Scale (YMRS), the Hamilton Depression Rating Scale (HDRS), the Aggression Questionnaire of Buss and Perry^[49] and the Symptom Checklist-90-R. Patients also self-monitored symptoms between visits using a 17-item daily diary that recorded symptoms of mania and depression. On average, participants' scores on the YMRS increased significantly after testosterone treatment. This effect was not uniform, with most patients showing minimal changes and a few showing marked symptoms. In the second year of this study, 27 participants were evaluated according to the Point Subtraction Aggression Paradigm.^[50] Aggression scores on this measure increased dramatically with testosterone use, although again the effect was

Table IV. Psychiatric assessment of potential anabolic androgenic steroid users^[16,18]

Domain	Symptoms
Attention	Reduced attention, distractibility
Behaviour	Psychomotor agitation or retardation
Mood	Euphoria, irritability, depression, marked anxiety
Affect	Lability with abrupt shifts in mood
Thought process	Slowed with depressive states, rapid or disorganised with manic states
Thought content	Suicidal or homicidal thoughts, grandiose or persecutory thoughts that may progress to delusions
Hallucinations	Generally auditory or visual

not uniform. Structured self-evaluation in daily diaries, which included 17 items assessing manic and depressive symptoms, also indicated a significant increase in aggression. Only one of four subscales on the Aggression Questionnaire, verbal hostility, increased significantly among evaluable patients. On the Symptom Checklist-90 (SCL-90)-R, only the phobic anxiety subscale showed a significant increase with testosterone treatment. The authors concluded that testosterone cypionate led to elevated aggression and mania in a small subgroup of patients. However, they also speculated that the low rates of manic and aggressive symptoms observed in this study may have been partially due to exclusion of subjects with premorbid psychiatric diagnoses or illicit drug use. Furthermore, only one type of AAS was used in this study, whereas steroid abusers often stack multiple substances. This protocol did, however, expose subjects to higher levels of steroids than are commonly used in clinical studies, although still lower than those generally used by bodybuilders. Moreover, the alternating 6-week treatment/wash-out design used may have mimicked the cycles used by bodybuilders.^[48]

A 12-day, inpatient, double-blind, placebo-controlled, crossover study evaluated the effects of methyltestosterone in 20 healthy male volunteers aged 18–42 years.^[51] No participants in this study were conditioned athletes, none had previous exposure to AAS, and all were judged to be free of medical and psychiatric illness. Participants completed four 3-day drug treatment phases: baseline (placebo); low-dose methyltestosterone (40 mg/day); high-dose methyltestosterone (240 mg/day); and withdrawal (placebo). The assessment measures

used were a visual analogue self-rating scale (VAS) that measured a variety of mood, behavioural and cognitive symptoms, the Beck Depression Inventory (BDI), and the Spielberger State Trait Anxiety Inventory State Form,^[52] all of which were conducted three times daily. In addition, 15 subjects completed the SCL-90 at the end of each of the four drug treatment phases. When participants taking high-dose methyltestosterone were compared with those at baseline, significant increases in distractibility, level of energy, irritability and sexual arousal were seen. In the low-dose state, almost all symptoms were intermediate between baseline and high-dose treatment. Significant increases were also seen in the Brief Psychiatric Rating Scale, HDRS and BDI when participants taking high-dose methyltestosterone were compared with baseline. Furthermore, as measured by the SCL-90, hostility, anxiety and somatisation were significantly greater with high-dose treatment compared with baseline, while depression, anxiety, somatisation and obsessive compulsion were significantly higher with low-dose treatment compared with baseline. Although no subjects displayed psychotic symptoms, three met DSM-III-R^[53] criteria for an affective disorder during AAS use. As in other studies, individual responses to steroids were highly variable. Nonetheless, this study indicated that mood changes may occur within days of initiating AAS use.^[51]

Another double-blind, placebo-controlled study examined the behavioural effects associated with use of testosterone enanthate.^[54] The study subjects were 43 healthy, non-obese men aged 19–40 years, with no significant medical, substance abuse or psychiatric history; all had previous experience with weightlifting, but none was currently involved in competitive sports. Subjects were randomised into one of four study groups: (i) placebo (sesame oil 3mL intramuscular) and no exercise; (ii) testosterone (testosterone enanthate 600mg intramuscular) and no exercise; (iii) placebo and exercise; or (iv) testosterone and exercise. Subjects were monitored throughout a 30-week study period that included 4 weeks in the control condition (placebo), 10 weeks of treatment (placebo or testosterone enanthate) and 16 weeks of recovery (placebo). Using the Multi-Dimensional Anger Inventory,^[55] Mood Inventory^[54] and Observer Mood Inventory,^[54] the authors

found that testosterone enanthate treatment did not cause a significant increase in angry behaviour relative to placebo, although doses of AAS administered in this study did not approach those used by many steroid abusers.^[54]

Another randomised, controlled, double-blind trial conducted by Yates et al.^[56] examined the psychosexual effects of testosterone cypionate. The study enrolled 42 healthy men (of whom 31 completed the study) aged 21–40 years. Subjects with diagnosed psychiatric disorders, elevated baseline aggressiveness or personality disorder traits, previous AAS use, active substance abuse, and those with previous criminal justice involvement were excluded. Subjects were given 2 weeks of placebo injections, then randomised to 14 weekly administrations of testosterone cypionate at doses of either 100, 250 or 500mg, followed by 12 weeks of placebo injections to simulate the withdrawal phase.^[56] As with other studies, the doses of steroids used in this study, although elevated, did not approach those used by AAS abusers. Subjects were rated on the following measures: Buss-Durkee Hostility Inventory,^[57,58] Sexual Interest and Orgasm Frequency Ratings,^[56] Brief Psychiatric Rating Scale,^[59] Modified Mania Rating Scale,^[60] or the HDRS.^[61] No dose-dependent effects were seen on any measure.^[56] However, one subject, randomised to receive 500mg of testosterone, discontinued participation at week 13 as a result of adverse psychological effects, believed to be related to the substance. The subject described significant irritability, early insomnia, and difficulties with concentration, as well as palpitations and a gnawing sensation in his abdomen. He almost fulfilled criteria for a DSM-IV^[62] diagnosis of mania and required treatment with alprazolam 0.5mg three times daily. The subject returned to baseline functioning approximately 2 weeks after the last testosterone injection. This study did not support the idea of a dose-dependent relationship between steroids and adverse psychiatric effects, but was consistent with the idea that steroid use may be related idiosyncratically to the onset of psychiatric symptoms.^[56]

The few available controlled studies of the psychiatric and behavioural effects of supratherapeutic steroid use appear to indicate that adverse behavioural responses to AAS use vary in accordance with as yet undefined patient subgroups.

These studies were successful in standardising various factors such as type of drug, dose and exercise levels, and in excluding patients with premorbid psychiatric disorders and/or substance abuse. Thus, at least to some extent, these studies evaluated the effects of steroids in isolation. As a result, they did not explore the effects of a multitude of issues that occur in regular practice, such as use of steroids at extremely supratherapeutic doses, stacking of multiple steroids simultaneously, the presence of pre-existing psychiatric disorders and the effects of other high-risk behaviours that may accompany steroid use.

3.2 Evidence from Naturalistic Studies and Case Reports

In the field, use of steroids has been associated with a variety of psychiatric symptoms.^[63] Below, various naturalistic studies and case reports are described according to symptom clusters. These distinctions have been made for clarity, although it is understood that these symptoms generally do not occur in isolation. Case reports in which abused substances were identified by name and dose are included in table V. In contrast to the aforementioned studies, these reports of drugs and doses are often unknown, the reports of adverse effects are not rigorously assessed, pre-existing disorders may be present, and a multitude of other complicating factors may exist. Despite these methodological weaknesses, these reports represent true-to-life conditions of steroid abuse.

3.2.1 Aggression and Violence

Agitation is perhaps the most common adverse psychiatric effect associated with steroid use, which is not surprising, as aggressive behaviour is often a desired effect of AAS use. Based on data from the 1991 NHSDA, AAS use is highly correlated with aggressive behaviour and crimes against property. Cooper and Noakes^[76] observed 12 bodybuilders who used non-therapeutic doses and combinations of AAS in their natural environment. These subjects displayed adverse personality changes and increases in antisocial behaviours including violence, joblessness and tendency towards dangerous or illegal activities. None of these effects was seen in the non-AAS control group.^[76] Parrott et al.^[63] compared on-

Table V. Reported cases of psychiatric symptoms associated with anabolic steroid (AAS) and steroid precursor use^[64-75]

Age (y)	Drug (dosage)	Onset	Symptoms	Substance abuse/premorbid psychiatric symptoms	Treatment	Outcomes
31	DHEA ^[70] (300–500 mg/d)	Began using DHEA 2mo prior to hospital admission	Irritability, decreased sleep	Sporadic alcohol use associated with difficulty controlling anger. Given a diagnosis of bipolar disorder 3y earlier, but no clear history of mania	VA 500mg bid	After hospitalisation for chemical dependency treatment, enrolled in outpatient treatment and reported abstinence from DHEA and other substances. VA appeared to be helpful in mediating the acute behavioural crisis
51	DHEA ^[69] (50 mg/d)	Symptoms began 2wk after initiating DHEA, hospitalised involuntarily after 4mo	Psychomotor acceleration, insomnia, irritability and grandiosity	No substance abuse reported. No psychiatric history, but baseline mood status may have been mildly hypomanic	HAL 10 mg/d, VAL 1500 mg/d	Patient's symptoms resolved completely over the course of several weeks; 4mo after hospitalisation the patient remained asymptomatic on VAL monotherapy
68	DHEA ^[68] (200–300 mg/d)	Admitted to an inpatient psychiatric unit 6mo after beginning DHEA. Onset of symptoms occurred 3mo prior to hospitalisation	Agitation, delusions, decreased sleep, pressured speech, grandiose thoughts, decreased appetite	Consumed alcohol daily; previously up to 24 beers/d, at time of admission 2 beers/d. Otherwise no reported psychiatric symptoms	VAL 500mg bid	After several days showed improvement in thought process, speech less pressured, sleep improved. Was discharged for follow-up care with primary care provider
22	MTA ^[71] (15 mg/d)	Developed symptoms after completing two 8-wk courses	Paranoid delusions, depressive symptoms	No previous significant psychopathology. Substance abuse not reported	AP (drug/dose unspecified)	Was able to discontinue AP within several weeks. Remained asymptomatic 2y post-discharge
40	MTT ^[71] (10mg bid, prescribed)	Developed symptoms within 2wk of starting AAS	Delusions of reference, visual and auditory hallucinations, met DSM-III ^[53] criteria for major depression	No previous significant psychopathology. Substance abuse not reported	AP (drug/dose unspecified)	Was able to discontinue AP within several weeks. Remained asymptomatic 2y post-discharge

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Table V. Contd

Age (y)	Drug (dosage)	Onset	Symptoms	Substance abuse/premorbid psychiatric symptoms	Treatment	Outcomes
21	NAN ^[66] (300 mg/wk)	Began AAS use 10wk prior to presentation for psychiatric care	Agitation, temper tantrums, racing thoughts, grandiose ideas, insomnia	No psychiatric or substance abuse history. Was reported to have premorbid narcissistic personality traits	Psychotherapy	Patient left therapy after three sessions, outcome unknown
27	OXA ^[67] (6mg orally bid)	Symptoms began within 2d of initiating AAS use	Irritability, hyperactivity, hyperphagia, hypersexuality	Patient had a tendency towards periodic depressions without vegetative symptoms alternating with hyperactivity and increased libido	None	All symptoms abated within 3–4d; 1wk later the patient resumed using OXA and the symptoms reappeared. Patient refused subsequent follow-up
20	MTA ^[75] (1120–4800 mg/mo) NAN (150–720 mg/mo)	Used steroids for a total of 10mo. Symptoms of agitation developed 7d after finishing a course of AAS	Interpersonal sensitivity, social isolation, anger and hostility, tendencies to extroversion and low self-control	No reported substance abuse history. Suspected that symptoms of borderline personality disorder may have been present prior to steroid use	DAZ, inpatient admission	Acute agitation resolved during admission and the patient was discharged. Borderline personality traits remained on assessment 10mo after discontinuation, suggesting that these may not have been associated with steroid use
23	MTA ^[73] (75mg qod) MTE (150mg qod) OXA (20 mg/d) OXM (100 mg/d)	Used the described regimen for 2mo prior to evaluation. In all, had a 3-y history of steroid use	Presented after discontinuation experiencing withdrawal symptoms, depression and fatigue	Psychiatric or substance abuse history not reported	NAL 0.2mg CLO (dose unspecified)	Initial challenge with NAL exacerbated withdrawal symptoms. Symptoms resolved over the course of 5d of CLO treatment. Patient resumed steroid use 7d after beginning treatment

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Table V. Contd

Age (y)	Drug (dosage)	Onset	Symptoms	Substance abuse/premorbid psychiatric symptoms	Treatment	Outcomes
24	MTA ^[64] last 4mo of 12th cycle (50 mg/d) OXA (25 mg/d) STAN (10 mg/d) TCY (intermittent injections) BOL (intermittent injections)	Began steroid use 4y prior to attempting murder. Took 12 courses 6wk–16mo in duration. In 12th cycle increased dose and stacked for first time	Irritability, racing thoughts, decreased attention span, reckless behaviour, attempted murder of his ex-fiancée	No psychiatric or substance abuse history	Patient was incarcerated with no psychiatric treatment	Following incarceration and discontinuation of steroids, patient developed major depression, which resolved after 4mo, apparently untreated
32	MTA ^[65] (30 mg/d) Unspecified agent Unknown	Psychiatric symptoms began approximately 2mo after starting AAS. Committed second degree murder 3mo after onset of AAS	Irritability, sleeplessness, increased alcohol consumption	Intoxicated at time of murder. No significant psychiatric history, but had displayed violence previously while intoxicated	None reported	Results of a mental status examination conducted 6mo after the crime unremarkable
23	OXM ^[64] During last 9wk of 2nd cycle (250 mg/d) TCY (800 mg/wk) MTA (unspecified)	Committed murder 2y after initiating steroid use, after increasing doses in last 9wk of second cycle	Met criteria for a manic episode: decreased sleep, irritability, explosive temper, reckless behaviour, grandiosity	No psychiatric history. Occasional alcohol and cocaine use	Patient was incarcerated with no psychiatric treatment	After arrest and incarceration, patient returned to his premorbid mild-mannered personality. After 19mo in prison, he remained asymptomatic

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Table V. Contd

Age (y)	Drug (dosage)	Onset	Symptoms	Substance abuse/premorbid psychiatric symptoms	Treatment	Outcomes
26	MTE ^[66] (300 mg/wk) TCY (300 mg/wk)	Presented to psychiatric clinic 6mo after starting AAS	Agitation, homicidal ideations, hostility, paranoia, racing thoughts, insomnia	No psychiatric or substance abuse history. Stressors, particularly a gunshot to the abdomen the patient sustained, may have contributed	Psychotherapy AD (drug/dose unspecified)	Most symptoms remitted with discontinuation of AAS. Symptoms of major depression developed within 4wk of cessation and were treated with an AD. Patient remained symptom free 1y post-hospitalisation
32	TCY ^[64] During fifth cycle (300 mg/wk) MTA (30 mg/d max.) MTE (unknown)	Shot a woman in the spine during fifth 6-wk cycle of AAS when there was a large increase in dose and number of AAS taken	Met criteria for a manic episode: irritability, grandiosity, paranoid suspicions, delusions of reference	No psychiatric or substance abuse history	Patient was incarcerated with no psychiatric treatment	Developed depression with abrupt withdrawal of steroids, resolved after 1mo. Displayed no further psychiatric symptoms 3y after the incident
20	TCY ^[74] (200mg q3d) TP (100mg q3d)	Patient had been using steroids for 2y. Experienced agitation and aggression during fourth 6-mo cycle. Presented to psychiatric emergency services 2mo after discontinuation due to increased depressive symptoms and suicidal ideation	Depressive symptoms included: insomnia, loss of appetite, marked weight loss, diminished motivation, suicidal ideation	No psychiatric history. Experimented with LSD and marijuana 4y prior, but reported only moderate alcohol use since	DMI (250 mg/d) Li (dose unspecified) HAL (dose unspecified) FLU (dose unspecified) ECT	DMI alone and in combination with lithium was ineffective. After the first trial of DMI failed the patient was hospitalised. HAL was used intermittently for depersonalisation with success. FLU was attempted for 8wk and was ineffective. ECT proved to be effective in reducing depressive symptoms. After seven effective treatments the patient was discharged on DMI

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Table V. Cont'd

Age (y)	Drug (dosage)	Onset	Symptoms	Substance abuse/premorbid psychiatric symptoms	Treatment	Outcomes
24	TCY ^[72] (200mg q3d) NAN (100mg q3d) OXA (25 mg/d) MTA (40 mg/d) BOL (30–45 mg/d)	Patient had been using steroids for 1y and had been using this regimen for 9mo when admitted to a hospital	During use: depression and periodic angry outbursts. On attempted discontinuation: depressive symptoms, decreased energy, and headaches	No psychiatric history or history of treatment for substance abuse	Inpatient chemical dependency program	Patient signed out of the chemical dependency programme on the 5th day against medical advice

AD = antidepressant; **AP** = antipsychotic; **bid** = twice daily; **BOL** = bolasterone; **CLO** = clonidine; **DAZ** = diazepam; **DHEA** = dehydroepiandrosterone; **DMI** = desipramine; **ECT** = electroconvulsive therapy; **FLU** = fluoxetine; **HAL** = haloperidol; **LI** = lithium; **LSD** = lysergic acid diethylamide; **MTA** = methandrostolone; **MTE** = methenolone; **MTT** = methyltestosterone; **NAL** = naloxone; **NAN** = nandrolone decanoate; **OXA** = oxandrolone; **OXM** = oxymetholone; **q3d** = every 3 days; **qod** = every other day; **STAN** = stanozolol; **TCY** = testosterone cypionate; **TP** = testosterone propionate; **VA** = valproic acid; **VAL** = valproate semisodium.

steroid and off-steroid psychological states in 21 amateur athletes using the Buss-Durke Inventory and a feeling state questionnaire. All subjects were using high doses of AAS in 6- to 14-week cycles. On average, subjects reported significantly elevated feelings of aggression, aggression towards objects, verbal aggression and aggression during training during on-steroid periods. Conversely, these individuals did not report increased aggression towards other people, which may or may not have reflected a reporting bias.^[63]

In a study of 75 female athletes, 25 reported steroid use.^[77] Of these, 13 (52%) reported irritability and 10 (40%) reported behaviour perceived as aggressive. However, none of these women reported irritability at a level consistent with a diagnosis of irritable mood, based on standardised criteria for psychosomatic research outlined by Fava et al.^[78] Furthermore, the presence of these symptoms was not compared with that in non-users, and individuals with premorbid psychiatric syndromes were not included in this analysis.^[77]

In another study, Pope et al.^[79] performed forensic evaluations of prisoners at a corrections facility in Massachusetts, USA. It is standard procedure for all men who present to the facility to undergo psychological evaluation by the prison's Corrections Department of Mental Health. A consecutive sample of 133 subjects (age range 17–57 years) was obtained from prisoners presenting for this evaluation, after approximately half declined participation. Of these 133, two were believed to have used steroids, based on greatly elevated fat-free mass index. The authors had used this formula, which is based on weight, percentage body fat and height, in a previous study and had consistently found that non-users rarely exceed a certain threshold of FFMI. However, both subjects in this study with significantly elevated fat-free mass index denied steroid use at interview. While the reliability of fat-free mass index as a method of determining steroid use has not been rigorously established, the utility of urine testing would have been limited in this study in which the emphasis was on prior steroid use. An additional seven participants (5%) in this study admitted to significant steroid use; of these, four reported little or no psychiatric change and three described clear changes in mood and levels of irritability in associa-

tion with steroid use. One of these three men attributed previous criminal activity to steroid use; he had taken two cycles of steroids involving the equivalent of 1000–1500 mg/week of testosterone several years earlier. The other two attributed their current incarcerations (for drug trafficking and shooting a man, respectively) to steroid use. One of these individuals had used multiple steroids continuously for 6 years, the other had been using prescribed replacement testosterone, in excess of recommended doses, for an unspecified period of time.^[79]

AAS use has been temporally associated with violent crimes in some cases. Pope and Katz^[64] described three cases of homicide or near-homicide by AAS users. These individuals had been using steroids in cycles for 2–4 years prior to exhibiting violent behaviour. All three had completed previous cycles (4, 1 and 11 cycles, respectively) without ill effects, but had experienced adverse effects with stacking and/or increased doses. The abused substances included: case 1) methandrostenolone (30 mg/day), testosterone cypionate (300 mg/week) and methenolone (unknown dose); case 2) methandrostenolone (30 mg/day), oxymetholone (250 mg/day) and testosterone cypionate (800 mg/week); and case 3) methandrostenolone (50 mg/day), oxandrolone (25 mg/day) and stanozolol (10 mg/day), with intermittent injections of testosterone cypionate and bolasterone. These patients displayed symptoms including severe irritability, grandiosity, paranoid suspicions, decreased sleep, explosive temper and reckless behaviour. Two of the three AAS abusers met DSM-III-R^[53] criteria for a manic episode. None of the three had a history of pathological behaviour, although one admitted to occasional cocaine use. Upon discontinuation of AAS, two of these individuals experienced symptoms of withdrawal and depression, but all three ultimately returned to their baseline personalities.^[64]

Another case report described an AAS user who committed murder 3 months after beginning a regimen of methandrostenolone 30 mg/day combined with an unidentified intramuscular agent. Although this individual did not have a criminal or psychiatric history, he had displayed previous episodes of mild drunken violence and was intoxicated at the time of the murder.^[65] Another case report described an individual who took at least nine AAS cycles, 1–4

weeks in duration, over the course of 2 years, starting at the age of 14 years. This individual apparently used testosterone as well as several other orally active AAS of uncertain identity. While using steroids, he began to display violent and aggressive behaviour, including breaking into a school and three incidents of assault and battery. He also unsuccessfully attempted murder on one occasion and committed murder in a separate incident. He did not have a history of aggressive behaviour, but throughout his childhood had displayed symptoms of depression and social phobia. This individual was described by Pope et al.^[79] as the index case for their aforementioned study of steroid use among prisoners.

One form of steroid-associated aggression that has not been examined extensively, but may be of particular concern, is domestic violence. Choi and Pope^[80] have compared violence and verbal aggression towards women by 24 males during periods of steroid use relative to the same men during periods of non-use and another 14 males who had never used steroids. Relative to periods of non-use, steroid users reported significantly more fights, verbal aggression and violence towards their domestic partners while using steroids. The behaviour of steroid users during off-drug periods did not differ substantially from non-users. These results support anecdotal evidence that women who are domestic partners of steroid users may be at an increased risk of verbal or physical aggression.^[80]

In addition to the reported association between steroid abuse and violence towards others, steroid abuse has also been associated with suicide. Thiblin et al.^[81,82] have described 11 medicolegally investigated suicides among male users of AAS aged 21–39 years in Sweden. Among these patients, six were judged definitively to be current users at the time of suicide. Detailed information was available for three of the six known current users, whose duration of use ranged from 2.5 to 15 years. All three of these patients had premorbid psychiatric histories involving depression and/or polysubstance abuse, as well as traits consistent with personality disorders. One of these individuals attempted suicide twice prior to beginning steroid use. The three patients for whom detailed information was available all displayed acute mental status changes while

taking steroids, including increased energy, mood swings, depression, diminished impulse control, increased irritability and increased libido. The mental status descriptions of these individuals at the time of suicide were: major depression in partial remission with excitement; excitement with rapid mood changes; and major depression with pronounced anxiety. Thiblin et al.^[81,82] characterised suicides committed during steroid use as having an impulsive character consistent with concurrent depression and lack of impulse control.

Based on the available evidence, it appears that violent behaviour is associated with steroid use in only a small subpopulation of AAS users. It is possible that a larger percentage of AAS users experience subacute increases in agitation and aggressive behaviour that may not come to medical or legal attention. Furthermore, the cases presented seem to describe individuals who had previously taken multiple cycles of steroids and experienced a dramatic increase in violent behaviour upon increasing doses or stacking multiple drugs. Although there is no evidence to indicate a direct dose-dependent effect of AAS use on aggressive behaviour, an increased pharmacological burden seems to lower the threshold for violent behaviour in certain vulnerable individuals.

3.2.2 Predominant Mood Symptoms

In a naturalistic study described previously, Pope and Katz^[20] compared 88 athletes who were current or former steroid users with 68 non-users using the Structured Clinical Interview for DSM-III-R^[53] (SCID). For steroid users, the SCID was completed twice to capture 'on-steroid' and 'off-steroid' periods of the subject's life through retrospective reports. Among the steroid users, 23% reported one or more major mood syndromes (major depression [13%], hypomanic episode [10%] and manic episode [5%]) during periods of steroid use. Steroid users displayed mood disorders significantly more frequently during periods of steroid use than when not using steroids, and significantly more frequently than non-users. The four steroid users that displayed manic symptoms were believed to be taking AAS >1000 mg/week.

A naturalistic study examined the association between steroid use and affective symptoms in sub-

jects recruited from gymnasiums in Boston, MA, USA and Los Angeles, CA, USA.^[83] Subjects ranged in age from 17 to 51 years and included 39 men and two women. These subjects generally had unremarkable psychiatric histories, although six (14.6%) reported prior alcohol abuse or dependence and 13 (31.7%) reported other prior substance abuse or dependence, most often involving cannabis or cocaine. The subjects included in this study had completed between 1 and 30 cycles over the course of 8–240 weeks prior to enrolment. Most were using steroids in doses 10- to 100-fold greater than those used for therapeutic purposes. Of the 41 AAS users, five (12.2%) met DSM-III^[53] criteria for a manic episode during steroid exposure. Eight others (19.5%) only just failed to meet the criteria for a diagnosis of manic episodes. Conversely, none of these subjects met the criteria for manic episodes during periods of non-use. These patients displayed common symptoms of mania such as euphoria and grandiosity. Of the 13 participants with manic symptoms, ten were stacking when they experienced these symptoms; the other three were taking either methandrostenolone or oxandrolone exclusively. Nine subjects (22%) met the criteria for either a full manic or depressive syndrome during steroid exposure, whereas only two (4.9%) met these criteria in the absence of steroid exposure.^[83]

Another naturalistic study examined the effects of steroids on women aged 18–65 years who had competed in at least one bodybuilding competition or who had weight trained at least 5 days a week for 2 years.^[77] Information on medical and psychiatric symptoms was obtained from retrospective reports. Fourteen of 25 current or former steroid users reported hypomanic symptoms during AAS use, although none met the full DSM-IV^[62] criteria for a mood disorder. Reported symptoms included euphoria, overconfidence or expansive mood (56%), poor judgement (36%) and increased libido (24%). Moreover, ten of these women described depressive symptoms after discontinuing AAS, nine of whom had displayed hypomanic symptoms while taking steroids. It is unclear what proportion of non-users displayed symptoms of hypomania and depression; however, there was no reported difference between groups in the prevalence of any individual or class of DSM-IV^[62] disorders.^[77]

These findings are supported by case reports of two patients in whom AAS use was linked with affective symptoms.^[66,67] One patient presented with agitation, racing thoughts, insomnia and grandiose ideas. At the time, he had been taking nandrolone decanoate (300 mg/week) for 10 weeks. This patient did not have a psychiatric or substance abuse history, although collateral reports suggested he had narcissistic personality features.^[66] The other case report described an individual who developed symptoms of irritability, hyperactivity, hyperphagia and hypersexuality 2 days after starting a regimen of oxandrolone 6mg twice daily. On discontinuation, these symptoms abated within 3–4 days. However, a week later the patient began a regimen of oxymetholone and he developed a similar hypomanic picture. The patient did not have a history of psychiatric illness or substance abuse, but was reported to have a premorbid 'cyclothymic disposition'.^[67] These reports anecdotally support the notion that AAS use may be associated with rapid mood changes in some individuals.^[66]

Other case reports have associated the AAS precursor DHEA with mania in three men aged 31, 51 and 68 years.^[68–70] Clinical presentation included agitation, decreased sleep, decreased appetite, pressured speech, delusional thinking and, in one case, suicidal and homicidal threats. These individuals had been taking DHEA 50–500 mg/day for 2–6 months prior to hospitalisation for manic symptoms. The onset of symptoms likely occurred substantially earlier, beginning within 2 weeks of initiation of DHEA treatment in one patient. However, at least two of these three individuals displayed potential underlying risk factors for a psychiatric syndrome, including excessive alcohol consumption in one patient and suspected underlying bipolar disorder in another.^[68–70]

3.2.3 Psychosis

Although less common than aggression, violence and mood symptoms, psychosis has also been reported in AAS users. In the aforementioned naturalistic study by Pope et al.,^[20] 3 of 88 steroid users developed psychotic symptoms. All these individuals were believed to be taking AAS at a dosage >1000 mg/week; however, the specific agents taken were not specified. Although the duration of steroid

use for these three individuals was also not specifically reported, there was a large variation in the length of steroid use among people in the study, ranging from 2 to 336 weeks. None of these individuals displayed psychotic symptoms while not taking steroids and no non-users in the study displayed any psychotic symptoms. A subsequent study of 41 bodybuilders and football players who used steroids found that five subjects (12.2%) met DSM-III-R^[53] criteria for psychotic symptoms during periods of steroid exposure, including auditory hallucinations, paranoid delusions, grandiose delusions and delusions of reference.^[83] Four other subjects reported mild or equivocal psychotic symptoms during steroid exposure, such as paranoia and referential thinking. None of the nine subjects experienced these symptoms in the absence of steroid exposure. All the users who experienced psychotic symptoms were stacking between two and four steroids, at least one of which was an orally activated 17-alkylated steroid, but specific doses were not reported.^[83]

Pope and Katz^[71] provided further description of two of the aforementioned cases, in which psychotic symptoms emerged in association with steroid use. One man developed symptoms of depression together with delusions of reference and visual and auditory hallucinations 2 weeks after beginning a regimen of methyltestosterone 10mg twice daily prescribed for impotence. In the other case, a 22-year-old bodybuilder developed paranoid delusions after taking two 8-week courses of methandrostenolone 15 mg/day. Both of these patients required hospitalisation, during which they responded well to conventional antipsychotics. Both patients were able to discontinue antipsychotics permanently after several weeks of treatment. Another case report described a 17-year-old weightlifter, with no prior psychiatric history, who was diagnosed with paranoid-type schizophrenia approximately 6 months after beginning a regimen of methandienone (dose unspecified).^[84] The patient's symptoms initially resolved with haloperidol 0.5mg three times daily, but returned 1 year later when he decided to discontinue haloperidol and continue to abuse steroids. The patient was again treated pharmacologically and remained asymptomatic approximately 2 years later on treatment with mesoridazine 25mg at bedtime and having discontinued steroids.^[84]

3.2.4 Dependence and Withdrawal

There has been speculation that the use of AAS may lead to a dependence syndrome in certain users and associated withdrawal symptoms on attempted discontinuation. Malone et al.^[85] reported on a sample of 164 subjects classified as current steroid users, past steroid users or non-users, and found that 12.9% of current users and 15.2% of past users displayed psychological dependence on AAS. In Pope's series of 88 steroid users, approximately 25% appeared to show a syndrome of dependence, although formal diagnostic criteria were not employed.^[20] In one study of steroid dependence among 49 male AAS-abusing weightlifters, 94% displayed at least one symptom of dependence and 28 AAS users were classified as dependent, defined as displaying at least three DSM-III-R^[53] criteria for dependence.^[86] The most commonly cited DSM-III-R^[53] symptoms were withdrawal symptoms (84%), more substance taken than intended (51%), large amount of time expended on substance-related activity (40%) and continued AAS use despite problems caused or worsened by use (37%). Dependent users took larger doses of AAS, completed more cycles and displayed more aggressive symptoms than non-users.^[86] Another survey indicated that seven of eight steroid users admitted they used steroids despite adverse consequences (e.g. nervousness, irritability and depression), all eight reported symptoms of dependence, and six met DSM-III-R^[53] criteria for dependence.^[87] Brower et al.^[72] described a steroid abuser who displayed at least six DSM-III-R^[53] criteria for dependence: taking steroids longer than initially intended; attempting unsuccessfully to reduce steroid use; continuing steroid use despite emotional and marital problems; developing tolerance leading to supratherapeutic administration; displaying withdrawal symptoms of fatigue, psychomotor retardation and headaches; and using steroids to avoid withdrawal symptoms. This individual had been using steroids for approximately 1 year and at the time of admission was using five different steroids in addition to human chorionic gonadotrophin.

A biphasic model of steroid dependence has been described that includes a brief hyperadrenergic state, followed by a prolonged period of depression and craving. To date, the acute hyperadrenergic state,

which has been likened to opioid withdrawal, has not been well characterised and has been reported only infrequently.^[73,88] It is estimated to begin approximately 1–2 days after discontinuation of steroids and last for about 1 week.^[89] The hyperadrenergic phase was initially described in a patient who had been abusing steroids for 3 years. In the 2 months immediately prior to the case report, he had injected methandrostenolone 75mg and methenolone 150mg every other day, and orally ingested oxandrolone 20mg and oxymetholone 100mg daily.^[73] The patient was treated with an opioid antagonist, naloxone 0.2mg subcutaneously, and within 15 minutes developed nausea, chills, headache, dizziness and an increase in diaphoresis, piloerection, pulse rate and blood pressure that persisted for 4 hours. He was managed successfully with clonidine and became asymptomatic after 5 days. However, on the seventh day, the patient complained of depression, fatigue and steroid craving and stated that he intended to resume using steroids. As the symptoms displayed by this patient were consistent with opioid dependence, it was hypothesised that steroid abuse may produce a similar syndrome.^[73] However, a recent trial in which rhesus monkeys were exposed to high doses of testosterone cypionate did not support this hypothesis.^[90]

The second phase of the steroid dependence/withdrawal model, involving depression and craving, has been better characterised and more consistently reported.^[89] Symptoms that commonly occur on discontinuation of AAS use include fatigue, muscle and joint pain, decreased libido, insomnia, anorexia, dissatisfaction with body image, desire to take more steroids, headaches and depression.^[86,87,89] In a study of steroid use among female athletes, 10 of 25 steroid users (40%) reported depression associated with discontinuation of AAS.^[77] It has been suggested that depression associated with AAS discontinuation may represent the manifestation of an underlying depressive syndrome as opposed to a true steroid withdrawal syndrome. In Pope's report on 41 steroid users, five (12.2%) met DSM-III-R^[53] diagnostic criteria for major depression following discontinuation of steroids, only one of whom had a history of depression prior to use.^[83] Another case series described four patients who experienced depressive symptoms lasting as long as

several years following discontinuation of steroid use, although none had premorbid depressive symptoms.^[91] A case report described an individual who experienced profound depression 2 months after discontinuing steroid use for four 6-month cycles (testosterone cypionate 200mg every 3 days and testosterone propionate 100mg every 3 days).^[74] Symptoms included insomnia, loss of appetite, marked weight loss, diminished motivation and suicidal ideation. The duration of depressive symptoms described in many of these cases extends far beyond the probable boundaries of a clear withdrawal syndrome. The potential for prolonged depressive symptoms on discontinuation of steroids presents a serious concern for treatment providers, particularly when these symptoms include suicidal ideation.

In the study by Brower et al.,^[86] 4% of 49 subjects experienced suicidal ideation in conjunction with discontinuation of steroids. Moreover, completed suicide has also been temporally associated with discontinuation of steroid use.^[81,82] Thiblin et al.^[81,82] implied that circumstances leading to suicide occurring after steroid discontinuation may differ from those associated with suicide during current steroid use. Whereas suicides during current steroid use tend to be impulsive in nature, suicides during withdrawal may be more likely to be premeditated in association with severe depression. One individual described by Thiblin et al.^[81,82] committed suicide 6 weeks after terminating a 6-year stint of steroid use. This patient was not believed to have had a substance abuse history, but did have a history of depression and avoidant personality disorder with narcissistic features. Another case of suicide occurred 6 months after discontinuation of steroid use in an individual who had used steroids for 3 years. The patient did not have a significant psychiatric history, but did display irritability and aggression in association with steroid use. It is not yet certain whether suicides and other adverse outcomes associated with steroid discontinuation are characteristics of a withdrawal syndrome or manifestations of underlying psychiatric disorders and personality traits.

3.2.5 Other Psychiatric Co-morbidities

Porcerelli and Sandler^[92] evaluated the prevalence of narcissistic personality traits among ster-

oid-abusing weightlifters. The Narcissistic Personality Inventory^[93] and clinical ratings were performed on 16 weightlifters who had used AAS in the past year and 20 weightlifters who had not. Steroid users displayed significantly higher scores on dimensions of pathological narcissism and significantly lower scores on clinical ratings of empathy. Elevated scores on exhibitionism, entitlement and exploitative factors suggested that weightlifters who use AAS display more maladaptive and pathological aspects of narcissism.^[92] A case report described a steroid abuser who was diagnosed with borderline personality disorder characterised by interpersonal sensitivity, anger and hostility.^[75] This patient had been using methandrostenolone (mean oral dose 1120 mg/month) and nandrolone decanoate (mean oral dose 150 mg/month) for 10 months. Symptoms of hostility and aggression associated with AAS exposure prompted this individual's entry into treatment, but it was suggested that he may have had an underlying personality disorder prior to beginning steroid use. In general, it is debatable whether certain maladaptive personality characteristics lead to steroid abuse or whether steroid abuse amplifies maladaptive personality characteristics.

Another less common symptom complex sometimes associated with AAS is referred to as 'reverse anorexia'. This is a type of body dysmorphic disorder characterised by a fear of being too small and weak, even when one is of muscular stature. In one study, 108 men were interviewed (55 steroid users, 53 non-users) to determine the prevalence of anorexia and reverse anorexia.^[94] For the purposes of this study, the diagnostic criteria were: (i) that the subject exhibited a persistent and unrealistic belief that he looked too small or too weak; and (ii) that this belief concretely affected his daily activities. Among the 108 subjects, three (2.8%) reported a past history of anorexia nervosa, which occurs at a rate of 0.2% in American men. Two of these three individuals and seven others reported a history of reverse anorexia; all nine of these subjects were steroid users. Four of these nine patients reported reverse anorexia only after steroid use. Five of the nine patients also reported hypomania (4) or mania (1).^[94]

It has recently been suggested that steroid abuse may be linked to subsequent opioid abuse.^[95-98] Sus-

picion of this association was triggered by reports of abuse of the opioid nalbuphine hydrochloride by AAS users.^[97,98] One study, conducted at an inpatient substance abuse treatment facility, indicated that of 227 men admitted for dependence on heroin or other opioids in 1999, 21 (9.3%) had a history of AAS use.^[95] Of these 21 men, 17 (81%) first purchased opioids from the same dealer who sold them AAS, 14 (67%) were encouraged to use opioids by a fellow bodybuilder, 18 (86%) claimed that they first used opioids to counteract insomnia and irritability induced by AAS, and 14 (67%) had used opioids to counteract depression associated with withdrawal from AAS. The authors reported that in the 1–11 months during which the patients were followed after discharge, 17 (81%) relapsed into opioid use and two (10%) committed suicide.^[95] Another study involved 223 male substance abusers admitted to an inpatient substance abuse treatment unit.^[96] Significantly more men, 22 of 88 (25%), who listed opioids as their drug of choice reported AAS use, compared with seven of 135 (5%) whose drug of choice was something other than opioids. Among the 22 former steroid users who listed opioids as their drug of choice, six (27%) indicated that they first learned about opioids from fellow bodybuilders and subsequently first obtained opioids from the same person who sold them AAS. This was also the case for another individual being treated for opioid dependence whose drug of choice was cocaine. In the remaining 16 of 22 former AAS users who listed opioids as their drug of choice, past AAS use was believed to be unrelated to subsequent opioid dependence.^[96] While there are insufficient data to indicate that steroid use is a gateway for opioid dependence, these two reports offer some support for this hypothesis. As suggested by Kanayama et al.,^[96] it is also possible that certain psychological characteristics predispose individuals to abuse both AAS and opioids.

4. Management of Steroid Abuse

4.1 Acute Care

Active steroid users may require acute treatment for symptoms of agitation, possibly related to substance-induced psychosis or mania. However, there

are no well established guidelines for treatment. Clinicians should consider a similar course as that used for the management of other forms of substance-induced agitation. As with other behavioural emergencies, the least invasive interventions should be attempted first.^[99] Clinicians should initially attempt to calm the patient verbally. Steroid abusers may be difficult to address because of the denial frequently associated with substance abuse. Moreover, the negative effects of steroid use may not be readily apparent to the patient, further intensifying feelings of denial and combativeness.^[18] Providing a calm treatment environment is important, and refraining from challenging the patient about AAS use is crucial until the potential for violence is established. When appropriate, partners should be screened for domestic violence.

If medication is required for agitation in association with mania or psychosis, oral preparations should be offered first with parenteral drugs as a secondary choice. As a last resort, physical restraints may be necessary. Anecdotal evidence has indicated that haloperidol has been effective in treating steroid-induced agitation and may be the best option if intramuscular medication is required.^[84] Haloperidol can be given in a dose of 1–10mg orally or intramuscularly, and a repeat dose may be administered after approximately 1 hour if necessary.^[99] Recently, intramuscular ziprasidone mesylate has become available in several countries, and use of this atypical antipsychotic may supplant haloperidol in the near future. If a patient is willing to accept oral medication, atypical antipsychotics may be effective, although their use has not been reported for steroid-induced agitation. Benzodiazepines may represent another potential therapeutic option for steroid-induced agitation. Benzodiazepines such as lorazepam (0.5–2mg, orally or intramuscular) have been used effectively in psychotic agitation associated with other substances, although use with AAS has not been reported.^[99] Valproate semisodium may be useful in patients demonstrating manic symptoms, with loading strategies sometimes being appropriate in the emergency setting.^[68–70]

If a steroid-abusing patient presents with symptoms consistent with the aforementioned opioid-like withdrawal syndrome, it may be appropriate to initiate treatment with clonidine. Clonidine is initially

given at a dose of 0.1mg every 4–6 hours, then increased daily by 0.1–0.2mg to a maximum of 1.2 mg/day.^[89] Because of potentially serious adverse effects, including hypotension associated with clonidine, patients should be monitored closely. Moreover, this treatment should be reserved only for patients presenting with clear symptoms of opioid withdrawal, which is not generally reported with steroid use.^[89]

4.2 Long-Term Care

Once the patient has been stabilised, the emphasis should be placed on initiating appropriate treatment. Initial treatment should be focused on the management of withdrawal symptoms to improve the chances of longer-term abstinence.^[18] Patients should receive early education about the symptoms they may experience during withdrawal to make these events less frightening if they occur. Pharmacotherapy for AAS withdrawal is symptom-focused and largely supportive. In particular, NSAIDs may be useful for the headaches and muscle pains commonly associated with withdrawal.^[18,100] If NSAIDs are used, liver function testing is important since NSAIDs may elevate levels of certain liver enzymes such as alanine aminotransferase and aspartate aminotransferase, which may already be elevated in AAS abusers.^[89]

Depression associated with steroid discontinuation may improve with antidepressant therapy, particularly in the presence of co-morbid major depression, panic disorder or another condition that would indicate the use of these medications. One case series described four individuals who experienced resolution of depressive symptoms associated with steroid discontinuation within 6 weeks of starting fluoxetine 20 mg/day.^[91] None of these patients had a premorbid history of depression and all remained symptom free for the period they were followed (3–24 months). Fluoxetine was not tapered abruptly in any of the four patients; two continued treatment for 1 year and 16 months respectively, one was lost to follow-up after 3 months, and the fourth was tapered successfully after 2 years of treatment.^[91]

Although fluoxetine was the first antidepressant to be studied for the treatment of steroid withdrawal, there is no reason to believe that any one antidepressant is superior to another. However, it may be

advisable to avoid the use of TCAs because of their narrow therapeutic range and their potential to exacerbate cardiac problems caused by steroids. As in the treatment of depression, SSRIs are likely to be the treatment of choice. Antidepressants can be prescribed at standard doses and their duration of use based on responsiveness of symptoms, coexisting disorders and potential for relapse.^[89] A case report described a patient who did not respond to treatment with fluoxetine or desipramine, alone or in combination with lithium, but who was managed successfully with ECT.^[74]

In addition to treating withdrawal symptoms supportively, the other potential target of pharmacotherapy is the hypothalamic-pituitary-gonadal (HPG) axis. Serum testosterone levels tend to decrease substantially with discontinuation of steroids. In one controlled crossover study ($n = 5$), testosterone levels remained significantly decreased (mean 10 nmol/L) from pre-use levels (mean 22 nmol/L) for up to 38 weeks after the conclusion of 26 weeks of steroid use (variable doses of methandienone, nandrolone phenylpropionate, stanozolol and testosterone).^[101] In a case report, subnormal serum testosterone levels persisted for at least 5 months following AAS discontinuation.^[75] However, regular monitoring of serum testosterone levels after steroid discontinuation has not been reported extensively in the literature. It has been suggested that using a tapering course of medically prescribed steroids might be beneficial for preventing some of the withdrawal symptoms of steroid abuse.^[102] However, because of the risks associated with prescribing an abused substance to a high-risk patient, close supervision would be essential if this were to be attempted. An alternative would be to administer intramuscular injections of testosterone esters, starting at a high therapeutic dose and tapering over 1- to 2-week intervals. This intervention could be performed in the physician's office and would therefore not be reliant on appropriate use of prescribed medication by the steroid abuser. If such a treatment course were initiated, a prolonged taper of more than 2 months should be avoided as this could result in prolonged AAS dependence. Furthermore, continued use of testosterone esters, although likely to provide symptomatic relief, would likely delay the return of the HPG axis to normal functioning.^[89]

Human chorionic gonadotrophin may be a more promising treatment for AAS withdrawal. It stimulates the testes and should not cause further suppression of the HPG axis. Furthermore, human chorionic gonadotrophin is approved for the treatment of hypogonadotropic hypogonadism, which is essentially what occurs following discontinuation of steroid use. It has been reported that, during withdrawal, a single 50IU dose of human chorionic gonadotrophin can double serum testosterone within 3–4 days.^[89] This regimen can be continued for 4–6 weeks or until serum luteinising hormone levels return to normal.

Antiestrogen agents such as clomiphene may be useful in reducing elevated estradiol levels and restoring a more favourable testosterone-to-estradiol ratio in individuals discontinuing the use of steroids. Brower et al.^[89] described the strategy of prescribing clomiphene 50mg twice a day for 10–14 days, which can be repeated if indicated by symptomatic response and serial measurements of serum testosterone and luteinising hormone. This is an off-label use of clomiphene, which is currently approved only for the treatment of female infertility. In addition, discretion should be exercised in the prescription of both clomiphene and human chorionic gonadotrophin, since steroid abusers commonly self-prescribe these medications to limit adverse effects associated with AAS.^[89]

The choice of treatment setting for an AAS abuser should be taken with the treatment goals of detoxification and rehabilitation in mind, as these are part of the overall process of recovery from substance abuse.^[100] Detoxification may take place on an inpatient or outpatient basis depending on the condition of the patient. If the patient is actively suicidal, acutely psychotic or has severe physical problems, hospitalisation is generally indicated.^[100] Most patients will be suitable for outpatient treatment, for which psychotherapy is generally the cornerstone. Direct clinical assessment and consultation are more likely to produce a positive outcome than passive education. Patients may benefit most from a therapist who is knowledgeable about the effects of steroid use and withdrawal. In any case, supportive therapy is always necessary during AAS detoxification because of the high risk of relapse and suicide during withdrawal.^[18] Recommendations for psy-

chotherapeutic treatment of AAS users are discussed more completely elsewhere.^[47,89]

Long-term rehabilitation, on an inpatient or outpatient basis, may be necessary following detoxification for patients dependent on steroids and those experiencing other adverse effects of steroid use.^[18] Steroid users are generally avid bodybuilders, and thus some effort should be made to address this component of their lifestyle directly. As such, patients may benefit from referral to a nutritional consultant or physiologist who can assist them in developing realistic training goals and establishing a safe and effective fitness regimen.^[18,47,89]

5. Conclusion

Various psychiatric manifestations including agitation, mania and psychosis have been associated with AAS use. While there does not appear to be a direct relationship between AAS usage and psychiatric symptoms, certain vulnerable individuals may display relatively severe symptoms. When psychiatric symptoms do manifest in conjunction with AAS use, onset tends to be associated with increased doses or stacking. Because mood changes may be evident as early as a few days after the initiation of steroid use, muscular body habitus may not alert clinicians to steroid use.

For the patient who presents to psychiatric emergency services with steroid-induced psychiatric symptoms, the first priority is management of any acute behavioural disturbances. In the absence of specific treatment guidelines for steroid-induced intoxication, the best option may be to follow treatment recommendations for other forms of substance-induced agitation. Haloperidol has shown anecdotal efficacy in treating steroid-induced agitation related to psychosis and mania. However, although the use of oral or parenteral atypical antipsychotic agents in the treatment of behavioural disturbances associated with steroid use has not been reported, this should also be considered. Atypical agents have shown equivalent efficacy and reduced adverse effects relative to traditional antipsychotics, such as haloperidol, in the acute treatment of psychotic agitation.^[103] Anecdotal evidence suggests that valproate semisodium may be effective in managing mania associated with steroid use, although the available literature also suggests that AAS-induced

manic symptoms may be self-limited. Any decision to initiate mood stabilisers should be guided by the degree of symptomatology and the availability of supportive aftercare. In the absence of a pre-existing psychotic or mood disorder, aggressive tapering of psychotropic medications should be considered. Finally, benzodiazepines, such as lorazepam, have been widely used in the treatment of substance-induced agitation and may represent another pharmacological option for agitation associated with steroid use.

After managing acute symptoms, clinicians should also initiate definitive ongoing treatment for patients recovering from AAS abuse. AAS discontinuation is essential in conjunction with appropriate management of withdrawal symptoms. Prescription of an antidepressant may be appropriate for a patient who is experiencing major depression in conjunction with withdrawal from steroid use, and NSAIDs may be used to treat headaches and muscle pain associated with withdrawal. Additional treatments depend on the specific symptomatology.

One crucial task is to arrange the appropriate level of care for a patient attempting to recover from AAS abuse. Although outpatient services are generally appropriate, acute psychosis, physical problems or suicidal ideations may necessitate hospitalisation. For both inpatients and outpatients, psychotherapy is essential for successful detoxification and rehabilitation. Recovery from steroid abuse, as with other substances, may be a prolonged process that requires a strong therapeutic alliance. However, successful recovery is vital given the multitude of adverse physical and psychiatric effects that can result from AAS use.

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