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Common symptoms associated with usage and cessation of anabolic androgenic steroids in men

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Anabolic-androgenic steroid (AAS) have widespread and growing illicit use as image and performance enhancing drugs (IPED), predominantly in young men. Users trying to stop AAS are prone to distressing withdrawal symptoms which may trigger relapse in use. It is important to develop therapies to support AAS withdrawal. The illicit nature of AAS use has impeded the robust characterisation of its clinical withdrawal syndrome within any single study. Therefore, we conducted a systematic review summarising the available clinical studies describing symptoms associated with non-medically indicated AAS use, and AAS withdrawal. Reported clinical features of AAS withdrawal include headache, fatigue, myalgia, restlessness, insomnia, low mood and libido, anorexia, suicidal ideation, body image dissatisfaction, and steroid cravings; novel therapies for AAS withdrawal would need evaluation against these symptoms.

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Abbreviations

AAS	anabolic-androgenic steroids
BDI	Beck Depression Inventory
BPRS	Brief Psychiatric Rating Scale
DHT	dihydrotestosterone
DSM	Diagnostic and Statistical Manual of Mental Disorders
HAM-D	Hamilton Anxiety Depression Scale
IIEF	International Index on Erectile Function
IPED	image and performance enhancing drugs
MAI	methandrostenolone
MT	methyltestosterone
ND	nandrolone decanoate
SCL-90	Symptom Checklist-90
T	testosterone
TC	testosterone cypionate
TE	testosterone enanthate
TP	testosterone propionate
TU	testosterone undecanoate
VAS	Visual Analogue Rating Scale

Introduction

Anabolic-androgenic steroids (AAS) is an umbrella term for drugs designed to increase the bodily effects of testosterone directly or indirectly. AAS include testosterone (T) itself, its metabolite dihydrotestosterone (DHT), and synthetic derivatives such as 19-nortestosterone (nandrolone), methyltestosterone (MT), ehtyltestosterone, ethynyltestosterone (ethisterone) and vinyltestosterone [1]. However, drugs increasing endogenous T secretion such as human chorionic gonadotrophin (hCG) and selective oestrogen receptor modulators (SERM) may also be considered as AAS. T is used therapeutically for the treatment of male hypogonadism, and other AAS have been used to treat cachexia associated with chronic diseases such as human immunodeficiency syndrome, cancer, burns, renal and hepatic failure, and anaemia associated with leukaemia or kidney failure [2]. However, AAS now have widespread illegal use as image and performance enhancing drugs (IPED), predominantly in young men [3]; this has been fueled by a large 'black-market' of online availability, and online message boards and websites promoting and advising on AAS use [4]. AAS have damaging health consequences. Men who try stopping AAS experience distressing withdrawal which often triggers relapse in use [5]. There are currently no treatments proven to alleviate AAS withdrawal symptoms to support long-term cessation in users. To test future AAS withdrawal therapies, it is important to design and validate symptom scores of AAS withdrawal. The illicit nature of AAS use has impeded the robust description of its clinical withdrawal syndrome within a single study. Therefore, we conducted a systematic review summarising the available clinical studies describing symptoms associated with non-medically indicated AAS use, and AAS withdrawal.

Methods

Search and selection

A search of the electronic databases EMBASE, MEDLINE and PubMed, was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement during October 2021 (Fig. 1). All studies identified using search terms up from inception until October 2021 were considered for inclusion to the study. Database was searched using the following terms- 'androgen' OR 'androgens' OR 'anabolic steroid' OR 'anabolic steroids' OR 'androgenic-anabolic steroid',

OR 'androgenic-anabolic steroids' OR 'testosterone' OR 'performance enhancing drugs' OR 'doping sports' AND 'withdrawal OR 'withdrawal symptoms' OR 'dependency' OR 'addiction' OR 'Substance abuse*' OR 'hypogonadism' OR 'libido' Or 'subfertility' OR 'infertility' OR 'effect' AND 'male*' OR 'males' OR 'men' OR 'man' OR 'weightlifter' OR 'weightlifters OR 'bodybuilder' OR 'athlete' OR 'athletes' were used. The following studies were excluded: non-English language; non-human species; female participants; steroids with predominantly non-androgenic activity and prescribed AAS (i.e. for a medical

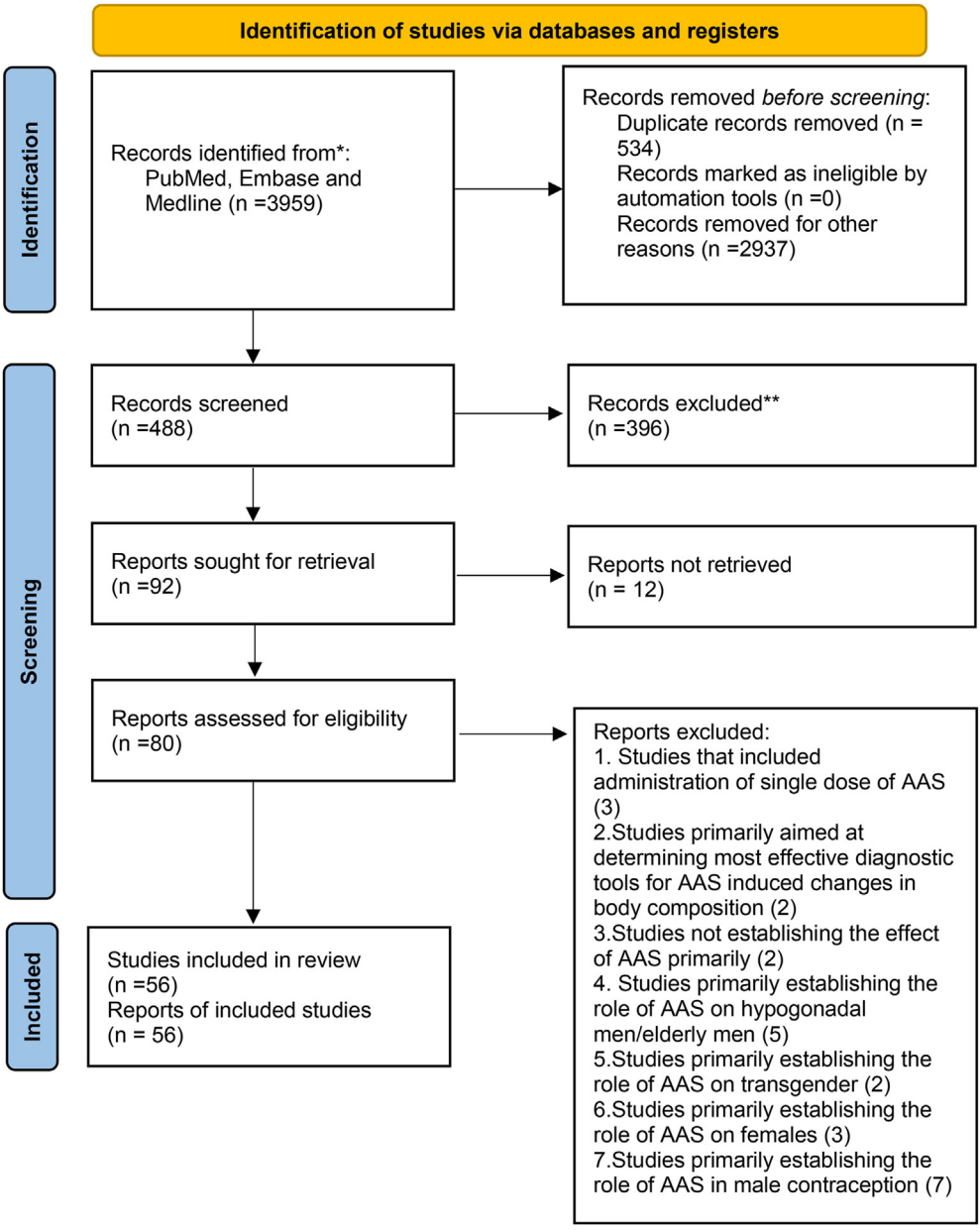

Fig. 1. PRISMA chart.

indication). Randomised controlled studies, clinical trials, prospective, observational studies such as case reports and clinical structured interviews were all included. Meta-analysis and systematic reviews were excluded. This study was not registered on an open database, due to likely low chance of parallel study conduct prior to publication.

Data extraction

Study titles and abstracts were initially screened before full-text review was completed in duplicate by two study investigators (AK, HI). Discrepancies were addressed by consensus and discussion with AS. A total of 56 studies fulfilled the criteria for inclusion to this systematic review (Fig. 1). Data identified for all studies were: authors, date of publication; number of participants, age of participants, study design, intervention, route of administration, dosage and preparation, duration of treatment, outcomes investigated and findings (Table 1).

Results

Endocrine symptoms of AAS use

It is well-known that long-term AAS suppresses testicular function by suppressing hypothalamic gonadotrophin releasing hormone (GnRH) and pituitary gonadotrophins. AAS use is therefore an iatrogenic cause of hypogonadotropic hypogonadism. Former AAS users commonly present to endocrine clinics with features of hypogonadism such as low libido and erectile dysfunction [6]. However, it is unclear whether symptoms of hypogonadism during AAS withdrawal differ from symptoms associated with other forms of hypogonadism. In a case series of weightlifters, smaller testicular size, lower levels of serum testosterone, and lower IIEF-15 scores (indicative of erectile dysfunction) were observed in AAS users versus non-users [6]. A further study using structured clinical interviews in athletes has noted a higher frequency of gynecomastia and lower testicular volume in AAS users vs. non-users [7].

Recovery of the male reproductive axis following exogenous testosterone administration has been studied extensively, owing to efforts to create a male contraceptive [8]. However, these studies do not explain the apparently long delay in reproductive recovery that clinicians observe in some patients. A systematic review and metanalysis concluded that AAS users had significantly lower levels of serum LH, FSH, SHBG and semen parameters compared with non-users [9]. Furthermore, two case series have been published recently providing an insight to potential timescale of recovery following AAS in men. An Australian cross-sectional study of bodybuilders, including current, past and never-users of AAS, observed that the mean time for recovery of LH was about 10.7 months [10]. However, it took much longer for serum FSH (mean 19.6 months) and sperm output (mean 14.1 months) to recover following cessation of AAS. In contrast, a Dutch prospective study of 100 amateur athletes observed much quicker recovery of reproductive function from AAS [11]. Specifically, 3 months after stopping AAS, mean serum total testosterone was non-significantly lower than at baseline. Furthermore, 1 year after stopping AAS, most participants had reference range levels of serum testosterone levels (89%) and total sperm count (66%). It is interesting to consider why the Dutch study suggested that recovery from AAS may be quicker when compared with the Australian study. Eighty percent of the Dutch athletes used hormones such as selective oestrogen receptor modulators (SERM) for between 2 and 4 weeks directly following AAS cessation; this practice is termed, post-cycle therapy (PCT), recommended by members of the online AAS community to lessen withdrawal symptoms. PCT data was collected but not reported in the Australian study, other than stating it had no significant association with reproductive recovery [10]. SERM work by reducing negative, oestrogenic feedback on GnRH and gonadotrophin secretion. It is intriguing to speculate whether differences in SERM use might have caused discrepancies in reported recovery times following AAS use. Furthermore, usage and past usage of AAS was determined by self-reporting, so future corroboration with serum or urine detection would be important to determine to what extent concealed AAS use (in self-reporting past users) might have skewed results of either study.

There is currently no consensus approach or clinical guideline for managing hypogonadism following AAS cessation. Many clinicians make the logical assumption that recovery from hypogonadism is inevitable, so provide reassurance while recommend monitoring for biochemical recovery

(of serum testosterone); unfortunately, some former AAS users do not engage with this approach, since it does not directly address the hypogonadal symptoms they are experiencing, which may be accompanied by any other troubling symptoms discussed later in this article. Further studies are needed to investigate the effectiveness and acceptability of 'watchful waiting' monitoring approaches to past AAS users and determine when/if there exists a threshold of time beyond which former AAS users should be treated simply as men with long-term hypogonadism (prescribed therapeutic testosterone). Such decisions are clearly controversial, so would benefit from a multidisciplinary, evidence-based approach engaging both clinicians, (past) AAS users, and policy makers.

Neuropsychiatric symptoms of AAS use

AAS have powerful effects on the limbic system of brain [12]. Several qualitative studies have been conducted investigating the neuropsychiatric symptoms reported by male AAS users; however, there remains a lack of large-scale, population data studying the proportion of male AAS users, and the severity of symptoms experienced by men during AAS use. This section will summarise the qualitative studies found to date. A structured clinical interview of athletes (88 AAS users and 68 AAS non-users) was conducted to identify psychiatric illnesses associated with AAS use [7]. The authors observed a significantly higher prevalence of major mood disorders such as hypomania, mania and major depressive disorder presenting with irritability, aggression, delusions, low mood, and suicidal tendencies amongst athletes who were AAS-misusers in comparison with athletes who never misused steroids. The authors also observed "reverse anorexia" wherein steroid users perceived themselves to be fragile and weak although they were well-built and muscular. Another study conducted structured interviews on 41 bodybuilders and football players who were AAS-users. Twelve percent of participants had psychotic symptoms including auditory hallucinations, delusions of grandiosity, persecution, and reference and 22% an affective syndrome disorder presenting with impulsivity, euphoria, sleep disturbances and low mood [13]. Another study reported a higher incidence of hypomania amongst current AAS users when compared with non-users [14]. Several other studies have reported similar findings to the studies discussed above [15–18]. The tragic social burden of AAS use is illustrated in a case report of a 20-year-old bodybuilder misusing 1,120 mg of methandrostenolone (MAI) and 150 mg of nandrolone decanoate (ND) per month for a period of 10 months, who developed acutely aggressive and violent behaviour [19]. AAS increases the risk of other addictive substance use. For instance, increased rates of heroin use have been reported in AAS users fulfilling the DSM-IV criteria for dependence [20].

Therapeutic testosterone is not associated with neuropsychiatric illness. It is interesting to consider to the threshold of exogenous androgen exposure required to induce adverse neuropsychiatric effects characteristic of AAS in men. Su TP et al. [21] conducted a double-blinded randomised controlled trial on 20 men aged 18–42 years with no prior history of AAS use. The participants were sequentially administered each of the following drugs for 3 days - low dose MT (40 mg/day), high dose MT (240 mg/day), and placebo. Clinical symptoms were investigated using several validated symptom scales. During high-dose MT exposure, participants exhibited a significant increase in euphoria, energy, sexual arousal, irritability, violent feelings, mood swings, confusion, distractibility, and forgetfulness in comparison with baseline ratings. Additionally, a significant increase in somatisation, anxiety and hostility was noted in this group when compared with baseline scores. During low-dose MT exposure, similar neuropsychiatric complications were observed, but less severe than during high dose MT [21]. In contrast, another study reported reductions in tension, fatigue, and anger in men receiving weekly I.M. injections 200 mg testosterone-enanthate (TE) versus 200 mg sodium chloride for 8 weeks [22]. Taking results of these two studies together, it is possible that the neuropsychiatric effects of exogenous testosterone are dependent on the potency (and possibly duration) of exposure. Further studies are needed to clarify the precise relationships among exogenous testosterone exposure, pre-morbid psychological burden, and adverse behavioural changes during AAS use in men.

Effects of AAS on musculature and strength

AAS increase muscle mass with associated reductions in fat mass. In 1996, Bhasin et al. [23] conducted a trial on 43 men randomly allocated to receive either TE or placebo with or without exercise for

a period of 10 weeks. Arm and leg strength were assessed using exercises such as bench press and squatting respectively. It was observed that T administered in supraphysiological doses alongside muscle strengthening activities, lead to an increase in muscle mass and fat free mass in healthy men identified by an MRI scan. In contrast, a trial conducted by Van GD at al [24] to determine the effect of AAS on body composition and performance enhancement amongst males revealed no significant effects on strength or body composition. Participants were assigned to randomly receive either 100 mg of 19-nor-4-androstene-3,17-dione and 56 mg of 19-nor-4-androstene-3,17-diol or placebo. The parameters measured included waist, arm and thigh circumference and determination of strength with dumbbell bench press [24]. This trial however used lower doses of testosterone and thus the outcomes cannot be directly compared with other studies of similar type. In another trial, by Hartgens F et al. [25], strength was investigated after administration of multiple AAS drugs. This RCT included 15 volunteers who were given ND for a total of 12 weeks along with another parallel study of 12 participants who self-administered a combination of AAS drugs at supra-therapeutic doses with 7 other individuals as controls. It was observed that muscle strength increased in individuals on polydrug administration. Muscle fibre size of the deltoid was studied using percutaneous needle biopsy. Results showed that although ND did not affect muscle fibre size, polydrug regimens had a significant impact on the increase in muscle fibre size [25]. In conclusion, AAS have dramatic effects on physical appearance. There is limited evidence suggesting that AAS may increase muscle strength, but the results are surprisingly equivocal. One possible explanation is that AAS may shorten the recovery time from hard exercise, allowing more strenuous exercise in users to increase muscle bulk.

Other symptoms of AAS use

AAS have well-described adverse effects on the cardiovascular system including dyslipidaemia, hypertension, and cardiac dysfunction which may lead to adverse cardiovascular events [10,26]. However, it is rare for men to experience cardiovascular symptoms related to AAS use. A rare clinical presentation associated with AAS use is described by Robert A et al. [27]; a 22-year-old professional weightlifter using intramuscular and oral steroids for a period of 6 weeks presented with acute chest pain and electrocardiogram demonstrated myocardial ischemia. Despite the well-known effects of AAS on the cardiovascular system, we cannot find evidence that AAS use commonly causes symptoms of cardiovascular disease. Current AAS users have increased left ventricular interventricular septum thickness and posterior wall thickness; but such changes are not seen in past users [10]. Furthermore, functional (global myocardial strain) echocardiographic parameters are worsened during AAS use but appear to reverse following cessation. These data are important since current or recent past AAS users should be counselled that potential, full reversibility of cardiac damage is a key advantage of stopping their addiction.

AAS may cause various forms of short-term hepatic injury including cholestasis and peliosis hepatis, and hepatocyte proliferation on liver biopsy [28]. Benign hepatic adenomata have also been described in a report of two patients, with adenoma size shrinking with long-term AAS discontinuation [29]. There is a lack of large-scale data on the delayed effects of AAS in men. However hepatocellular, renal cell and prostate carcinoma has also been described in AAS users [30–32], although causality cannot be inferred. Truncal acne is a common side effect of AAS [10]. The clinical effects of AAS exposure are summarised in Fig. 2.

Symptoms associated with AAS withdrawal

The clinical features of AAS withdrawal are understudied, and most studies lack objective validation of self-reported drug cessation using toxicology screening. Nevertheless, Brower KJ [33] classified withdrawal from AAS in two distinctive phases, acute and chronic. The acute phase includes sympathetic activation leading to somatic symptoms of headache, tremors, palpitations, and nausea. This phase manifests within 1–2 days of AAS withdrawal, following which the chronic phase develops which comprises of symptomologies including, hypogonadism with fatigue, myalgia, lower libido because of testosterone deficiency. Furthermore, psychiatric symptoms involving intense fear, depressive disorder, cravings, dysmorphia, and insomnia can also develop [33]. AAS withdrawal

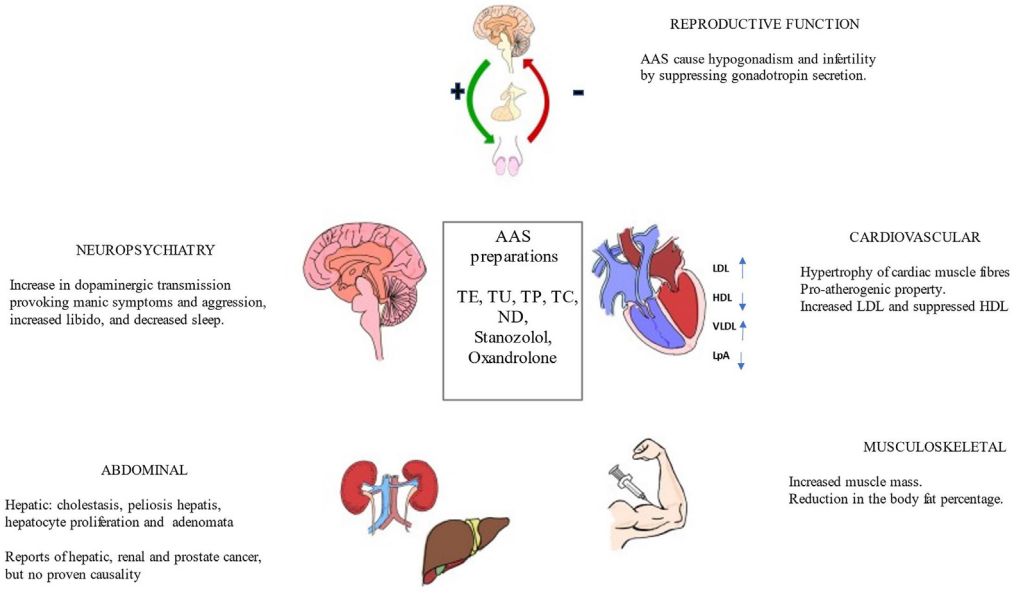

Fig. 2. A schematic diagram representing effects of anabolic androgenic steroids on various body systems AAS-Anabolic androgenic steroids; TE-Testosterone enanthate; TP-Testosterone propionate; TC-Testosterone Cypionate; ND- Nandrolone Decanoate; LH-Luteinizing hormone; FSH- Follicle Stimulating hormone; LDL-low density lipoprotein cholesterol; HDL-High density lipoprotein; VLDL- Very low-density lipoprotein; Lp(a)- Lipoprotein.

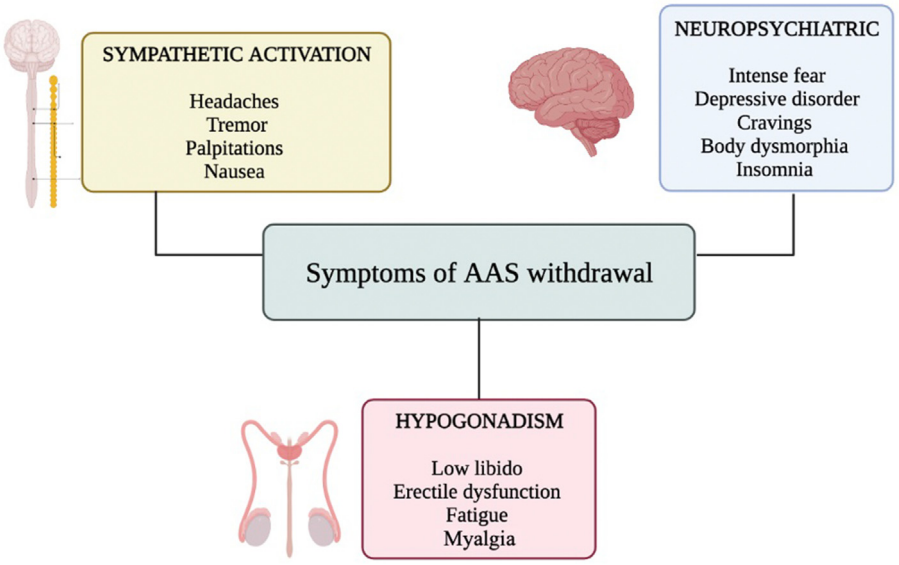

Fig. 3. Symptoms associated with withdrawal from anabolic androgenic steroid use. Symptoms divided into those due to sympathetic activation, hypogonadism, and other neuropsychiatric symptoms. AAS = anabolic androgenic steroids.

symptoms are summarised in Fig. 3. A study of structured interviews in bodybuilders and football players found that 3 months post-cessation of AAS, 5/41 subjects developed major depression in accordance with DSM III-R [13]. These observations are strengthened by a study by Malone et al. [14], who assessed the psychiatric outcomes of participants in 3 categories: current users with a recent history of AAS abuse and a positive urine test for AAS; past users with a definite history of AAS abuse and negative urine test for AAS; and finally, non-users with a negative history of AAS abuse and a negative urine test; like the previous study, an increased frequency of major depressive disorder was reported among past users.

Symptoms of AAS withdrawal are a core feature of AAS dependency in users. An anonymous questionnaire of male weightlifters fulfilling the DSM-III R criteria for dependency while taking AAS [18], revealed that depressed mood, anorexia, fatigability, akathisia, decreased sex drive, insomnia, suicidal tendencies, body image dissatisfaction, abuse liability, and headache were reported during withdrawal. These findings were subsequently supported by another study by the same authors [15]. However, it is important to consider that AAS cessation may also ameliorate some distressing psychiatric features of AAS use. This is illustrated by observing that mood disorders have been reported to be more common in current AAS users when compared those who had recently stopped AAS (within 3 months post-cessation) [7]. Studies are required to elucidate the predictors of withdrawal symptoms; however, likely risk factors are prior psychiatric illness, potency of androgen exposure, duration of AAS, and doses of AAS use.

Conclusion

Our review reveals growing but limited clinical evidence exploring the clinical features of AAS withdrawal. Acute features of sympathetic overactivation (headache, tremors, palpitations, and nausea) are followed by chronic symptoms which may be broadly classified into neuropsychiatric and reproductive-endocrine. Low mood, suicidal thoughts and body image dissatisfaction are described during AAS withdrawal. Furthermore, hypogonadism during AAS withdrawal is associated with low libido, erectile dysfunction, and fatigue. However, a much broader evidence-base is required, exploring the effects of specific AAS drug classes on different user demographics. In particular, there exists a paucity of data on female AAS use. Endocrinologists are currently restricted to treating frustrated past AAS users with biochemical monitoring for expectant reproductive recovery while psychiatrists are faced with the devasting presentations of illness provoked by AAS in users. Further studies are needed to provide evidence for novel interventions which may encourage cessation, reduce the distressing features of withdrawal, and discourage relapse in AAS users.

Practice points

- AAS misuse is common and under reported.
- Chronic AAS use may cause dependency and its cessation may cause acute and chronic withdrawal symptoms, primarily with neuropsychiatric manifestations.
- The illicit nature of AAS use has impeded the robust description of its clinical withdrawal syndrome.
- PCT drugs such as SERM and hCG are commonly administered (illicitly) by users to lessen withdrawal symptoms in the first few weeks after AAS cessation; however, there is neither data on their reproductive nor symptomatic effects. It is plausible that a gradual reduction in testicular stimulation may avoid withdrawal symptoms, like with stopping glucocorticoid treatment

Research agenda

- Underlying pathophysiology of AAS withdrawal syndrome is not completely understood. Further studies are required to investigate short-, medium- and long-term features of AAS withdrawal and their underlying pathophysiological mechanisms.
- It is important to explore strategies to ensure long term AAS withdrawal to prevent relapse of AAS misuse. Future prospective studies to determine novel treatments to alleviate AAS withdrawal symptoms
- It remains unclear whether full endocrine recovery from AAS is inevitable; this will not be possible without validation of self-reporting of drug cessation with objective testing
- PCT drugs such as SERMs and hCG stimulate testicular function; but it is not known whether these affect chances of reproductive recovery from AAS.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.beem.2022.101691.

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