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Title: Physical, Psychological and Biochemical Recovery from Anabolic Steroid-Induced Hypogonadism: A Scoping Review

Short Title: Recovery from Anabolic Steroidal Hypogonadism

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Abstract

Hypogonadism can result following anabolic steroid abuse. The duration and degree of recovery from anabolic steroid-induced hypogonadism (ASIH) is immensely variable, and there is a paucity of prospective controlled data characterising the trajectory of natural recovery following cessation. This poses difficulties for users trying to stop androgen abuse, and clinicians wanting to assist them.

The objective of this paper was to synthesise evidence on the physical, psychological, and biochemical patterns of ASIH recovery. We present the pathophysiology of ASIH through a literature review of hypothalamic-pituitary-testosterone axis recovery in supraphysiological testosterone exposure. This is followed by a scoping review of relevant observational and interventional studies published on PubMed and finally, a conclusion that is an easy reference for clinicians helping patients that are recovering from AAS abuse.

Results indicate that ASIH recovery depends on age and degree of androgen abuse, with physical changes like testicular atrophy expected to have near full recovery over months to years; spermatogenesis expected to achieve full recover over months to year/s; libido returning to baseline over several months (typically less potent than during AAS use); and recovery from gynaecomastia being unlikely. For psychological recovery, data is insufficient and conflicting, indicating a transient withdrawal period which may be followed by persisting longer-term milder symptoms. For biochemical recovery, near complete recovery of testosterone is seen over months, and complete gonadotropin recovery is expected over 3-6 months. Further prospective studies are indicated to more closely describe patterns of recovery.

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Introduction

Anabolic-androgenic steroid (AAS) use is illegal if not prescribed by a medical practitioner (1). Androgens are abused predominantly by young males trying to improve sporting performance or to increase muscle mass and decrease body fat (2). After a period of AAS abuse, cessation may result in anabolic steroid-induced hypogonadism (ASIH), a state of dysfunction that may involve a suppressed hypothalamic-pituitary-testicular (HPT) axis accompanied by physical, psychological, and biochemical changes. Clinical management to assist patients and the complications that ensue from androgen abuse is complex (2).

In this paper, we present an overview of the pathophysiology of ASIH, and a scoping review to explore what is known about the recovery from ASIH following cessation of AAS.

The estimated prevalence of AAS abuse is 3.3% of the global population, making it likely that doctors are seeing patients who abuse androgens. Often, clinicians are unaware that they are encountering these patients in clinical practice, given that abuse of AAS is often kept secret from health practitioners even if presenting with complications of androgen abuse such as infertility or gynaecomastia (1). Disclosure is typically only made on specific questioning by health professionals. Although this behaviour of secrecy is similar to that seen with drug addiction, in contrast to those abusing classical drugs, most AAS users do extensive research beforehand and have considerable forethought in their patterns of use (1).

Sequelae arising from AAS abuse are wide ranging, encompassing direct biological effects of the androgen such as thromboembolic disease, to indirect sequelae including infection of injection sites (3). In terms of the sequelae and management of ASIH, there are a wide range of recovery patterns of the HPT axis seen in AAS abuse (2, 4), which have been detailed recently by de Ronde and Smit (2). They range from spontaneous recovery, to needing

medical assistance using Selective Estrogen Receptor Modulators (SERMs) that stimulate gonadotropins, LH and FSH and or Human Chorionic Gonadotropin (HCG) which stimulates testicular function, to cases of permanent non-recovery of the HPT axis requiring physiological testosterone replacement therapy (5).

The severity of ASIH depends on the type, combination, timeframe, and dosages of AAS being abused, which can vary considerably between abusers (6). Up to 90% may combine various forms of AAS, otherwise known as 'stacking', believed to achieve optimal results whilst minimising side effects (7). Stacked regimes may achieve supraphysiological testosterone levels that are beyond the detection limit of commercially available assays. Users of AAS often utilise several 'cycles' of stacked testosterone regimens, including intervals between cycles that are free of AAS use. During these times, they often add in medications to help recovery, forming a post-cycle treatment (PCT) with the rationale of minimising unwanted side effects of AAS abuse (Table 2). The stacking and cycling of these anabolic steroids make the pharmacodynamics difficult to predict compared to medical testosterone replacement therapy, which is given as single androgenic agent in a fixed dose to maintain serum testosterone in the physiological range.

Given the dangers of AAS abuse, advocating abstinence alone is frequently insufficient as the symptoms of withdrawal or hypogonadism that ensues can be challenging. Furthermore, some patients do not wish to cease use which means that a harm minimisation approach should be considered in reducing adverse events summarised by de Ronde and Smit (2). If patients can be persuaded to cease AAS abuse, there is considerable variability in terms of recovery of the Hypothalamic-Pituitary-Testosterone Axis (HPT).

Our objective in this scoping review was to illustrate the breadth of recovery patterns observed, and to synthesise the evidence on recovery patterns observed in existing studies

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to assist clinicians advising patients who wish to cease AAS abuse on what is to be expected. We first examine the pathophysiology of HPT axis recovery in supraphysiological testosterone exposure in a literature review, and then present a scoping review of cross-sectional and prospective studies (cohort and randomised trials) that examine the recovery of hypogonadism, categorising outcomes into physical recovery, psychological recovery and biochemical recovery.

Pathophysiology of ASIH

AAS abuse can have numerous potential sequelae, as summarised in Table 2. Most symptoms of ASIH can be understood through prolonged feedback inhibition (if not long-term suppression) of Gonadotropin Releasing Hormone (GnRH) and therefore Leutinising Hormone (LH) and Follicle Stimulating Hormone (FSH). The degree and duration of suppression of GnRH varies depending on several factors, as explored below with the mechanism of pathophysiology coming from animal studies due to paucity of human studies.

The process of inhibition of GnRH by androgens is via androgen and estrogen receptors (8), which are not actually found in GnRH neurons but rather in neurons located in the arcuate nucleus and preoptic area the hypothalamus (9). These neurons are known as kisspeptin neurons and it is kisspeptin neurons in the arcuate nucleus (often referred to as KNDy neurons, as they contain the neuropeptides Kisspeptin, Neurokinin B and Dynorphin A (10)) that project to GnRH neurons and tightly regulate the tonic/pulsatile release of GnRH in both males and females (11).

Neurokinin B serves as an autoregulatory stimulatory signal for KNDy neurons while dynorphin A serves as an autoregulatory inhibitory signal (12). Both culminate in a pulsatile release of kisspeptin from the KNDy neurons. Kisspeptin then serves to generate GnRH pulses in GnRH neurons (see Figure 1). In ASIH, the feedback inhibition of GnRH is believed to occur in KNDy cells as seen in animal models that use supraphysiological doses suppressing neurokinin, increasing Dynorphin A, and decreasing Kisspeptin (13).

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The suppression of gonadotropins is dose dependent, and is also dependent on the type of androgen used. In other words, the feedback inhibition of androgens is not absolute, (switching 'on or off'), but that of degree. This can be shown in standard testosterone replacement therapy for hypogonadal men, for example, where testosterone replacement from 8nmol/L to 14nmol/L results in LH decreasing by 40%; testosterone replacement to 19nmol/L results in LH decreasing by 60%; and testosterone replacement to 27nmol/L results in LH decreasing by 80% (14). Different androgen also exert different degrees of suppression of the HPT axis. Dihydrotestosterone (DHT) for example, a non-aromatisable testosterone, shows dose-dependent lowering of LH in animal models (15), but not to the same extent as testosterone (16). Taken together, this suggests that abusers of AAS that often go 10-100 times above physiologic endogenous serum testosterone levels using multiple androgens (Table 1) will have significant variation in their HPT axis suppression. To date, these have not been specifically quantified in clinical studies, given (among other factors) the unreliability of what is acquired on the black market and of recall.

Another reason for the variation seen in recovery from ASIH is that KNDy neurons receive input from the hormonal milleu of the organism from leptin (17), CRH, cortisol (18) and prolactin (19), as well as being subject to higher neuronal regulation, such as the first order metabolic neurons POMC and NPY/AgRP as well as neurons from the suprachiasmatic region (20). This suggests that individual factors and co-morbidities, as well as other factors such as concurrent anti-depressant use and psychological stress disorders (21) as well as adiposity (22) are highly relevant. Age is also an important variable, with the HPT axis known to recover more rapidly in younger than older men, although the mechanisms remain unknown (23).

Lastly, cessation of AAS abuse is commonly associated with burdensome psychological disorders, especially anxiety and depression. (24) Whether these disorders predate and contribute to the abuse of AAS, or whether AAS abuse brings out or leads to anxiety and depression, is unclear. ASIH may cause psychological disturbances by directly and indirectly mediating several brain regions, primarily the amygdala, the hippocampus, and the bed nucleus of the striae terminalis (25). For example, the degree of amygdala activation in relation to fear has been found to have a positive correlation with testosterone levels in men (26). Furthermore, KNDy neuropeptides play an important role in regulating mood; for instance, in male mice hypogonadal from absent kisspeptin signalling (via transgenic kisspeptin receptor deletion) demonstrate anxiety-related behaviours independent of circulating levels of androgen replacement (27). This may explain the persistent mood disturbance when ceasing androgen abuse despite adequate testosterone replacement therapy.

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Scoping Review of Recovery from ASIH

To review the current evidence regarding recovery from ASIH, PubMed was searched from inception to 26th April 2022. The following search strategy (returning 811 results) was used on Title/Abstract: ("Anabolic Steroids" OR Androgen* OR "Anabolic steroid-induced hypogonadism") AND (Abuse* OR Recover* OR Cessation OR Former OR Previous) AND (Hypogonad* OR Reproduc* OR Testic* OR Sperm* OR Fertility).

Eligibility criteria included studies of human subjects who had taken (or were taking) AAS, in which physical, psychological, or biochemical measurements were taken following AAS cessation. Male contraceptive trials of testosterone were also included, as these serve as simplistic models of AAS misuse. Excluded studies were those that were case studies or series; studies that were not in the English language; or studies of animal models. Articles were first assessed on title/abstract basis, with all potentially relevant articles assessed in full. In addition, the reference lists of all included articles were scanned for other relevant articles.

All included studies are summarised in Table 3. Studies described considerable variability in the substances abused, the amount abused, the length of abuse, and the duration of follow-up after cessation. As such, a meta-analysis was not feasible. Many studies were limited, with small sample sizes meaning that not all differences reached statistical significance. Only one study assessed different usage patterns (stacking, cyclical, continuous etc), finding this factor to have no impact on the recovery of any parameter (4).

To aid interpretability of results, the physical, psychological, and biochemical changes measured across these studies will be reviewed in turn. A broad summary table of conclusions is provided at the end of this paper (Table 4).

Physical Changes

Testicular volume

For many individuals, testicular volume is not fully reversible after AAS cessation. Amongst AAS abusers, Smit et al found mean testicular volume to be a mean 0.7ml lower than baseline 3 months after AAS cessation, although most individuals recovered to their baseline at 9 months (28). Prospective trials investigating testosterone's contraceptive potential have found that mean testicular volume, compared to individuals' pre-use baseline, remains 15% lower (3mL reduction in testicular volume) 18 weeks after cessation of testosterone enanthate (29), but only 4% lower (1.5mL reduction in total testicular volume) 12 months after cessation of testosterone undecanoate (with only 28% of these subjects having a smaller total testis volume than their baseline) (30). Over longer time periods however, testicular volume may recover fully with men treated with testosterone for idiopathic tall stature having no significant difference in testicular volume after a mean of 10.6 years compared to controls who had never used testosterone (31). However, data from male contraceptive cohorts may not be applicable to AAS abuse, as patterns of AAS abuse typically involve more complex regimes of testosterone involving supraphysiological doses.

In AAS abusers, the cross-sectional study by Rasmussen et al demonstrate a negative correlation between accumulated weeks of AAS abuse and testicular volume (32). The control group in this study had an average testicular volume measured by orchidometer of 22.3mL compared with a volume of 17.4mL of past abusers who had not used AAS for over 2 years. Current abusers in the study had the lowest volume of 12.2mL, as expected.

These findings are supported by a more recent case control study by Shankara-Narayana et al using ultrasound to measure testicular volume. In this study, those who had ceased use

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for a median 10.7 months had a reduction of 32% (9mL) compared with healthy controls (4). In terms of longest duration since AAS abuse and testicular volume change, another cross-sectional study by Kanayama et al supports a reduced testicular volume of 10% (2.3mL) up to a mean of 4.9 years of previous AAS abuse compared with controls (33).

Taken together, the evidence suggests that most testicular volume lost does recover after ceasing AAS use, but it may take years and often is not complete. A limitation of these studies is the use of orchidometry, with the exceptions of Shankara-Narayana et al and Lemcke et al, which measured testicular volume with ultrasonography (4, 31).

Gynaecomastia

Gynaecomastia is a consequence of increased estradiol from aromatisation of excessively high levels of testosterone, as well as imbalance of the estrogen-to-testosterone ratio after AAS abuse. To avoid this outcome, tamoxifen or other estrogen receptor blockers are often used concomitant with AAS. Unfortunately, tamoxifen use in males can be associated with side effects of nausea, loss of libido, and mood deterioration, as well as an increased risk of thromboembolism (34).

Gynaecomastia “in the past” is reported by two-thirds of former AAS abusers (35), and is known to persist after AAS cessation. Compared to controls who had never used AAS, former AAS abusers who had ceased use for at least 1-4 weeks (having used up to 28 cycles over their lifetime) were significantly more likely to have gynaecomastia on physical examination (31% vs 3%) (36). Moreover, former AAS abusers who had ceased use for a mean 10.7 months reported gynaecomastia at greater rates than controls (23% vs 0%), but this difference did not reach statistical significance (4). Beyond this timeframe, evidence is lacking.

Libido / Erectile dysfunction

Using psychometric questionnaires, a cross-sectional study of former AAS abusers who had ceased use for at least 3 months found more had erectile dysfunction (27% vs 7%) or low libido (40% vs 10%) compared to controls (32). Similarly, another study of AAS abusers with a mean 6.9 years of abuse who had ceased use for a mean 4.9 years finding reduced sexual desire compared to controls (33).

This is however not universal. There were studies that found no differences in libido amongst former AAS abusers (29, 37, 38) but most of these measured libido and erectile dysfunction via self-reported history rather than psychometric questionnaires.

A prospective controlled study of 3-monthy testosterone undecanoate versus placebo amongst eugonadal men with insulin resistance found that sexual satisfaction (in terms of erectile function and sexual desire) was increased in the testosterone-supplemented group compared with controls. Once testosterone use was ceased, sexual satisfaction returned to baseline control levels beyond 18 weeks (39). Although not a study of AAS abuse, this study does support anecdotal reports of lower libido and erectile function after AAS cessation, but suggests that this reduction is merely a return to baseline.

However, some individuals have lower libido and erectile function during AAS abuse, depending on the type of androgen used. If the androgen is non-aromatisable (resists aromatisation to oestrodiol despite a supraphysiological testosterone), this would lead to lowering of libido and erectile function as both testosterone and estradiol are needed for libido and erectile function (40). Examples of synthetic non-aromatisable androgens include Nandralone and stanazolol (Table 1). Stanzolol bears a 17a-alkyl substitution rendering it resistant to degradation and despite anabolic activity, involves reduced reproductive function (reported anecdotally and observed in animal studies) (41).

Spermatogenesis

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In interventional contraceptive studies of healthy young men, spermatogenesis recovers after cessation of testosterone. A meta-analysis of interventional contraceptive studies of testosterone found sperm concentration to recover to ≥20 x 10^6/mL at a mean 4.6 months (19 weeks) after cessation of testosterone. However, many took longer to recover, with 67% recovering by 6 months, 90% by 12 months, and 100% by 24 months. When sperm concentration recovered to individuals 'baseline values, sperm motility and morphology were significantly lower than pre-interventional values by 1.6% and 3.4% respectively. This suggests that sperm concentration may be the first parameter to recover, followed by sperm motility, then sperm morphology. However, findings could not be extrapolated beyond the maximum usage duration of 18 months, and only 60% of individuals were followed up long enough for sperm concentration to recover to pre-interventional values (42). In another interventional study, it was found that by 15 months of ceasing testosterone use, sperm concentration recovered to individuals 'pre-interventional values in 99.7% of cases (30).

A prospective study of AAS abusers found that 3 months after AAS cessation, individuals had lower semen volume (mean difference 0.4ml), sperm concentration (mean difference 10.4 x10^6/ml), sperm count (mean difference 57.1 x10^6/ml), and motile sperm count (mean difference 34.1 x10^6/ml) than baseline, with only sperm progressive motility recovering to baseline. However, 9 months after AAS cessation, all variables recovered to baseline, with the exception of semen volume (mean difference 0.4ml) and sperm count (mean difference 25 x10^6/ml) remaining lower than baseline (28).

In contrast, cross-sectional studies of those abusing multiple AAS substances have found signs of impaired spermatogenesis up to at least 7.5 months after AAS cessation (23). Former AAS abusers who had ceased use for at least 4 months were found to have

significantly lower sperm motility and morphology (but not concentration) than controls who had never used AAS (43), whereas sperm parameters amongst those who had ceased use for a median 11 months had recovered to those of controls (4). Regression analyses in the latter study found the duration of recovery to be positively associated with the duration of AAS abuse, with recovery time being a mean 10 months for sperm concentration and a mean 38 months for sperm motility (4). Encouragingly, a prospective controlled study following participants detected for abusing androgens in an antidoping program in Denmark showed that though fertility rate is significantly lower in the group of androgen users at baseline, catch up is achieved in the 2-3 years following (44).

Psychological changes

Former AAS abusers are at higher risk of psychopathology during the immediate period of AAS cessation as well as longer term. The earliest case control study performed in 2015 showed that following AAS abuse cessation, there is an increased risk of 29% of major depression compared with control of 5% (33). This was assessed by structured interview based on DSM-IV criteria and included suicidal ideation being observed. Following withdrawal, the rate of major depression equalised to rates of control but in a subsequent study by Rasmussen et al. a year later in 2016 showed that in the longer term, former AAS abusers still had significantly higher rates of depressive symptoms as measured by SF-36 questionnaire (24% vs 3%) and more severe fatigue than controls who had never used AAS (32).

Overall, former AAS abusers are significantly more likely to have had a psychiatric diagnosis (37% vs 12%) or experienced suicide ideation (13% vs 1%) (45), and significantly more likely to have experienced self-reported depression (13% vs 5%) or anxiety (13% vs 6%) than controls who had never used AAS (46). It is not clear however whether those who are prone

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to symptoms of depression and anxiety seek out AAS, or whether depression and anxiety is a consequence of AAS abuse. It would be reasonable to hypothesise that both are possible but the latter seems more significant contributing to the higher rates of psychopathology, given that former AAS abusers who had used cycles lasting more than 2 years were found to be significantly more likely to self-report having experienced anxiety (24.5% vs 6.7%) or any psychiatric illness (28.3% vs 12.4%) than former AAS abusers who had not used cycles lasting more than 2 years (46). In the absence of prospective studies, this remains a hypothesis.

There are however studies that show no differences in depression and anxiety between AAS past abusers and controls. In former AAS abusers ceasing use for at least 1-4 weeks, cross-sectional studies found no significant differences (according to a self-rated aggression scale) in aggression, mood or other psychopathology (except for lower self-rated affability) (47), and no significant differences in psychiatric diagnoses as per the Structured Clinical Interview for DSM-III-R (36). Similarly, a prospective laboratory study found no significant differences in psychopathology (as per the Brief Psychiatric Rating Scale, Hamilton Depression Rating Scale, Modified Mania Rating Scale, and Buss–Durkee Hostility Inventory) 12 weeks after cessation of testosterone cypionate compared to pre-interventional baseline, and no evidence for a dose-response relationship (38).

This apparent lack of differences could mean no psychological difference or psychological impact from past AAS abuse but this is to be interpreted with the following caveats. Firstly, recruitment bias is likely in these studies which were recruiting through advertisements in gyms which could exclude those that suffer from lethargy, anhedonia or individuals that prone to paranoia. Secondly, psychopathology was not measured consistently and methods used are hard to compare between studies which include psychometric questionnaires (38),

clinical history (33, 45, 46), or self-rating scales (47). Thirdly, differences may not have been detected due to the small sample sizes of studies (38).

In summary, psychological disturbances affect many former AAS abusers, but long term symptoms are mild in most cases. Evidence to indicate a specific timeframe for recovery and the predictors of recovery is lacking. Further studies that can quantify and take into account the bidirectional relationship between the psychopathology of AAS abuse and the effect of AAS abuse on psychopathology are needed.(24).

Biochemical changes

Testosterone

The recovery of serum testosterone levels after AAS cessation is variable and controversial. The first meta-analysis examining the changes to testosterone was published in 2017 by Christou et al (23). It showed that testosterone did not recover fully by 16 weeks, with a weighted mean difference in testosterone between abusers and non-abusers of 9.4nmol/L. This is supported by the case control study by Rasmussen et al in 2016 (not included in the meta-analysis), that showed that a longer duration of abstinence from AAS abuse up to 2 years still did not equalise the median testosterone level (32). The control group median was 18.8nmol/L, whilst the past AAS abusers group had a median of 14nmol/L. By contrast, Shankara-Narayana et al showed no statistically significant difference between mean testosterone levels of abusers and non-abusers with the average of 300 days of AAS cessation (4). However in Handelsman et al, following 2 years of blinded testosterone treatment, testosterone levels remained 11% lower than the placebo group after 1 year of follow-up (39).

In more controlled studies examining supraphysiological dosing of AAS use, results are similarly mixed. Testosterone levels are reported to recover to baseline anywhere between

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10 days (48), 14 days (49), 5 weeks (50), 8 weeks (38), 10-14 weeks (51), 12 weeks (28, 52, 53), 16 weeks (54), 18 weeks (29), or 12-15 months (30) after AAS cessation, which is in contrast to studies that show a persistent reduction in testosterone between 4.5 to 11 nmol/L lower than baseline anywhere between 7 days (55), 14 days (56), 12 weeks (57), and 13 weeks (58) after AAS cessation.

Factors such as the type/s of AAS used, the pattern and duration of usage make it difficult to pool these findings together into an overall conclusion. Pattern and duration of usage is difficult to quantify accurately in studies but where it is attempted, those with a cumulative lifetime dose of AAS exceeding the median as in Karila et al showed significantly lower serum testosterone 6 months after cessation (mean 6.1 vs 12.3 nmol/L) (59). Similarly, In Caminos-Torres et al, at 5 weeks after cessation of testosterone, the 50mg group had recovered to pre-interventional baseline, but the 200mg group was at a mean 6.1 nmol/L lower than baseline (50). However, this potential dose-response relationship was not universal, as in MacIndoe et al, where recovery of serum testosterone to pre-interventional baseline took 10 weeks in the 100 mg/week group, 14 weeks in the 250 mg/week group, but 10 weeks in the 500 mg/week group (51). This suggest that individual factors play a significant role (as outlined in the pathophysiology earlier; Figure 1), highlighting the need for prospective controlled studies.

Finally, it should be noted that studies that show former AAS abusers recover testosterone to the normal range often recover to only the lower limit of the reference interval. In Rasmussen et al, most AAS abusers had testosterone in the lower normal range (with only 3.3% below the lower reference range limit) (32), and all but 2 former AAS abusers in Urhausen et al had serum testosterone in the lower 20% of the normal reference range (35). Even case control studies that show no statistically-significant difference between past AAS

abusers and controls show that past abusers have a mean serum testosterone lower than controls (as in Shankara-Narayana et al.; 6.2ng/mL versus 8.7ng/mL respectively).

Taken together, testosterone recovery is expected but likely to be incomplete despite months or years of AAS cessation.

Gonadotropins

In most studies, FSH and LH recovered to baseline values (or were not significantly different to controls) 2-16 weeks after cessation (29, 49, 50, 53, 57, 58). However, a few studies described reduced gonadotropin levels when measured at 2 weeks (56, 60), 6 weeks (48), or 12 weeks (28, 52) after AAS cessation.

In Handelsman et al, following a 2-year blinded treatment with testosterone in hypogonadal men with diabetes, it took a median 33.9 weeks for individuals' FSH and LH to recovery to their own pre-treatment baselines (39). In Shankara-Narayana et al, the projected time taken for FSH and LH to recover was 19.6 and 10.7 months respectively (4). Like testosterone recovery, the degree of AAS abuse is also likely to impact on recovery of gonadotropin levels, with those having a cumulative lifetime dose of AAS exceeding the median in Karila et al demonstrating significantly lower FSH (mean 0.9 vs 2.9 IU/L) and LH (mean 1.5 vs 3.4 IU/L) than other study participants 6 months after cessation (59).

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Conclusion

Amongst those who abuse AAS, cessation often results in the wide-ranging sequelae of anabolic steroid-induced hypogonadism. These sequelae encompass physical, psychological, and biochemical changes, which in some cases may be irreversible. In this scoping review, we found that recovery from the sequelae of ASIH was immensely variable, depending on the type of AAS used ('stacking' if multiple); the dosages used; the duration of use; the patterns ('cycles') of use; and comorbid conditions.

Our scoping review demonstrated broad conclusions across some of the changes associated with ASIH, as summarised in Table 4. Recovery usually does occur in relation to gonadotropin levels while testosterone has near to complete recovery over the weeks to months of follow up depending on duration and dose of AAS abuse. Spermatogenesis is usually completely recovered over months to years with sperm concentration typically recovering first, followed by sperm motility, then sperm morphology, with fertility rates eventually normalising over years.

Similar to recovery of spermatogenesis, the recovery of testicular volume takes months to years; however, the volume difference is still present up to a year, be it minimal in reduction in AAS abusers. Gynaecomastia is more common in AAS abusers and can persist despite years of follow up, potentially warranting surgical intervention.

Owing to the paucity of data, the recovery patterns for libido and erectile dysfunction, and psychological changes remain less clear. There is an initial increase in depressive and anxious symptoms with recovery seen over months to years, however, some studies do not find any significant differences. The variability in duration of recovery and depth of symptoms ranging from mild to potential suicidality warrants further study in terms of

helping patients avoid these dire outcomes, and helping those that are willing to abstain from returning to AAS abuse.

The secrecy, stigma, and illegality associated with AAS abuse has long made recruitment for research a challenge prone to selection bias. Nonetheless, there is a need for controlled prospective studies and quantification of the abused regimes used rather than just considering the cohort homogenously. In the absence of these fine-grained studies, the evidence base for managing abusers of AAS will continue to be challenging.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figure 1: Reinitiation of GnRH pulse by KNDy neurons and its regulation

Schematic representation of the signalling pathway responsible for the generation of gonadotropin releasing hormone (GnRH) pulses. KNDy neurons (containing the neuropeptides kisspeptin, neurokinin B (NKB) and dynorphin (Dyn) in the arcuate nucleus (ARC) of the hypothalamus receive autoregulatory input from NKB and Dyn, forming a local circuit. Kisspeptin release is enhanced by NKB and reduced by Dyn and this net effect increases GnRH pulses. The resultant production of sex steroids will feedback to KNDy neurons to facilitate homeostatic regulation of GnRH pulses. Higher neuronal centres, such as the supra-chiasmatic nucleus as well as proopiomelanocortin (POMC) and neuropeptide Y (NPY) / Agouti-related protein (AgRP) feed into this circuitry. Peripheral hormones and potentially anabolic-androgenic steroids also regulate this system to govern fertility.

Table 1: Commonly abused Anabolic-Androgenic Steroids

Generic name	Trade names	Formula	Route	Half-life	Aromatisation	5α-reduction	A/A ratio
17 α alkyl derivatives							
Methandrostenolone / Metandienone	Dianabol, Anabol, Refovit	$C_{20}H_{28}O_2$	PO	3.2-4.5 hours	✓	✓	
17α-Methyltestosterone	Android, Testred, Methitest	$C_{20}H_{30}O_2$	PO	150 minutes	-	✓	
Oxandrolone	Anavar, Oxandrin, Vasorome	$C_{19}H_{30}O_2$	PO	9 hours	-	✓	10
Oxymetholone	Anadrol, Roboral, Anasteron, Anapolon	$C_{21}H_{32}O_3$	PO		-	✓	9
Stanozolol	Winstrol, Stromba, Winstrol V	$C_{21}H_{32}N_2O$	PO / IM	24 hours	-	✓	30
Danazol	Danocrine	$C_{22}H_{27}NO_2$	PO	24 hours			
Fluoxymesterone	Halotestin, Fluotestin, Ora-Testryl	$C_{20}H_{29}O_3$	PO	9.2 hours	-	✓	
17 β ester derivatives							
Testosterone	Testavan, Androforte 5, AndroGel, Testim, Fortigel, Testoderm, Androderm	$C_{19}H_{28}O_2$	Transdermal	10-100 minutes	✓	✓	1
	Testosus, Aquaviron, Univet Uni-test		IM				
Testosterone propionate	Testrex, Androgeston, Testogen	$C_{22}H_{32}O_3$	IM	4.5 days			
Testosterone enanthate	Delatestryl, Primotestone, Testinon	$C_{26}H_{40}O_3$	IM	7-9 days			
Testosterone cypionate	Depo-Testosterone, Durandro	$C_{27}H_{40}O_3$	IM	8 days			

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Testosterone undecanoate	Reandron, Andriol, Undestor, Nebido	$C_{30}H_{48}O_3$	PO / IM				
Testosterone propionate + phenylpropionate + isocaproate + decanoate	Sustanon 250			**			
Nandrolone* decanoate	Deca-Durabolin, Anabolin	$C_{28}H_{44}O_3$	IM	6-8 days	-	✓	
Nandrolone* phenylpropionate	Deca Rapide		IM		-	✓	10
Boldenone undecylenate	Equipoise, Ganadol, Equigon	$C_{30}H_{44}O_3$	IM	14 days	✓	✓	
Metenolone acetate	Primobolan	$C_{22}H_{32}O_3$	PO		-	✓	
Metenolone enanthate	Primobolan Depot, Delapromor	$C_{27}H_{42}O_3$	IM		-	✓	
Trenbolone acetate	Finaplix H, Finaplix S, Parabolan	$C_{20}H_{24}O_3$	PO, IM, pellets		-	✓	
Drostanolone propionate	Masteron	$C_{23}H_{36}O_3$	IM		-	-	

Abbreviations: A/A ratio, Anabolic/Androgenic ratio; PO, oral; IM, intramuscular injection.

Information sources: trade names (1), formula (1, 2), route (1), therapeutic dose (3), half-life (3, 4), aromatisation (5), 5α-reduction (5), anabolic/androgenic ratio (6).

#Where applied for a recognised therapeutic use.

*Or 19-nortestosterone.

**Takes 21 days for plasma testosterone to return to lower normal range in males (3).

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Table 2: Possible sequelae of AAS abuse

Physical	Psychological	Biochemical
Acne	Depression	Reduced testosterone
Alopecia	Increased anxiety	Increased haematocrit
Testicular atrophy	Psychosis	Erythrocytosis
Gynaecomastia*	Alcohol and drug addiction	Increased LDL and decreased HDL cholesterol
Tendon rupture	Cognitive deficit	PSA elevation
Premature epiphyseal closure	Aggression	Azoospermia
Arrythmias	Eating disorders	Hepatotoxicity
Left ventricular hypertrophy	Mania	Rhabdomyolysis and Focal Segmental Glomerulosclerosis
Decreased libido and erectile dysfunction	Anti-social behaviour	Infection

Abbreviations: LDL, low density lipoprotein; HDL, high density lipoprotein; PSA, prostate specific antigen.

*If aromatisable AAS are used (see Table 1).

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Table 3: Studies investigating recovery from ASIH following cessation of AAS^

Study and Design	Subjects	AAS used	Duration of use	Duration of follow-up after cessation	Parameters measured	Outcome at follow-up*
Analyses of previous studies						
Christou et al. 2017 **(1)** Meta-analysis	For T: 27 athletes (from 5 studies) For FSH & LH: 17 athletes (from 3 studies) For semen, numerous subjects from 8 studies	Variable	Variable	Variable	T, FSH, LH Sperm features	- For testosterone-based AAS, T significantly lower at 16 weeks by mean 9.4 nmol/L - FSH & LH not significantly different at 13-24 weeks - Sperm: persistent qualitative or quantitative differences in 7/8 studies at 8-30 weeks
Liu et al. 2006 **(2)** Meta-analysis	1,549 healthy eugonadal men aged 31.8 (6.1) years (from 30 studies)	Testosterone + (in 58% of subjects) progestogen Sensitivity analysis found no difference in recovery rate with +/- progestogen	9.45 (4) months (up to 18)	Variable	Sperm concentration, motility, and morphology	- Sperm recovery (to concentration ≥20 x 10^6/mL) occurred at a median of 4.6 months - 67% recovered within 6 months, 90% within 12 months, 96% within 16 months and 100% within 24 months - Upon recovery of sperm concentration to baseline, sperm motility 1.6% lower and sperm morphology 3.4% lower than individuals' baseline - Semen volume remained unchanged
Ly et al. 2005 **(3)** Secondary analysis	532 healthy fertile men aged 21-45 years (from 2 prospective studies)	Testosterone enanthate 200mg/week IM	Until azoospermic (up to 6 months)	Until sperm recovery to ≥20 x 10^6/mL	Sperm concentration	- Sperm concentration recovered to baseline by 18 weeks in 85% of cases
Interventional (including male contraception) studies						
Handelsman et al. 2022 **(4)** Randomised Controlled Trial	Men aged mean 60.1 years with impaired glucose tolerance or newly diagnosed type 2 diabetes mellitus, randomised to receive testosterone or placebo	Testosterone undecanoate 1000mg IM	2 years (dose at baseline, 6 weeks, then 3-monthly)	12 months	T, FSH, LH Psychosexual quality of life	- T consistently 11% lower in treatment group compared to placebo - FSH recovered to individuals' pre-treatment levels at median 33.9 weeks (95% CI 31.0–36.0) - LH recovered to individuals' pre-treatment levels at median 33.9 weeks (95% CI 31.1–36.0) - Psychosexual quality of life (measured with International Index of Erectile Function and

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						Psychosexual Diary Questionnaire) greater in treatment group until 18 weeks, after which no difference between groups
Garevik et al. 2016 **(5)** Prospective study	11 healthy Caucasian men aged 29-46 years, medically screened for illicit drug use	Nandrolone decanoate 150mg IM	Single dose	14 days	T, FSH, LH	- T 10.1 nmol/L lower - FSH 1.6 IU/L lower - LH 2.6 IU/L lower
Garevik et al. 2014 **(6)** Prospective study	25 healthy men aged 27-43 years, medically screened for illicit drug use and other health issues	Testosterone enanthate 500mg, then 250mg, then 125mg IM	Three doses 6-8 weeks apart	14 days (after each dose)	T, FSH, LH	- T increased at 14 days after 500 mg dose (by 39%), but only increased at 4 days after 250 mg and 125 mg doses (by 112% and 91% respectively) - FSH lower at 14 days after 500 mg, 250 mg, and 150 mg doses (by 94%, 83% and 38% respectively) - LH lower at 14 days after 500 mg, 250 mg, and 150 mg doses (by 92%, 78% and 35% respectively)
Gu et al. 2009 **(7)** Multicenter phase III contraceptive efficacy clinical trial	733 healthy Chinese men aged 20-45 years	Testosterone undecanoate 500mg/month	30 months	12-15 months	Total testicular volume T, FSH, LH Sperm concentration, morphology, and semen volume	- Total testicular volume lower by 1.5 mL - Sperm concentration recovered to baseline at median 26 weeks, entering normal reference ranges for 98% of subjects at 12 months (and for all but 2 subjects at 15 months) - No differences in other parameters
Wang et al. 2007 **(8)** Randomised Control Trial	18 Chinese men aged 27-48 years	Testosterone undecanoate 1000mg followed by 500mg 6-weekly IM	18 weeks	12 weeks	T, FSH, LH Sperm concentration, motility, and morphology	- All parameters recovered to baseline
Yates et al. 1999 **(9)** Randomised Control Trial	31 healthy men aged 21-40 years	Testosterone cypionate 100mg, 250mg, or 500mg/ week IM	14 weeks	12 weeks	Psychosexual (aggression, libido, mood, psychopathology) T	- No psychometric differences (for all doses) - T recovered to baseline by 8 weeks (for all doses)

MacIndoe et al. 1997 **(10)** Randomised Control Trial	31 men aged 18-40 years	Testosterone cypionate 100, 250, or 500mg/week IM	14 weeks	12 weeks	T, FSH, LH Sperm concentration and motility	- T recovered to baseline at 10 weeks (100 mg dose), 14 weeks (250 mg dose) or 10 weeks (500 mg dose) - HCG-stimulated T (taken 72 hours after administering HCG 1000IU IV to assess Leydig cell function) at 3 weeks not different to baseline for 20/21 subjects - FSH & LH (normal and 2 hours after stimulation with LHRH 100µg IV) detectable at 3-6 weeks (dose-response relationship, i.e. more time needed for higher doses) - Sperm parameters recovered to baseline at 24 weeks
Small et al. 1984 **(11)** Prospective study	9 healthy men aged 19-35 years	Stanozolol 10mg/day PO	2 weeks	2 weeks	T, LH, FSH	- All parameters recovered to baseline
Bijlsma et al. 1982 **(12)** Prospective study	11 men with rheumatoid arthritis[#] aged 44-62 years	Nandrolone decanoate 25mg/week for 6 weeks, then 50mg/week for 6 weeks IM	12 weeks	12 weeks	T, FSH, LH	- FSH lower by 3.28 IU/L - No differences in other parameters
Clerico et al. 1981 **(13)** Prospective study	9 male athletes aged 20-36 years, who were AAS-free for ≥50 days	Methandrostenolone 20-35mg/day	14 days	7 days	T, FSH, LH	- T lower by 4.5 nmol/L at day 7 - FSH & LH recovered to baseline at day 4
Remes et al. 1977 **(14)** Randomised Control Trial	12 male athletes aged 20-28 years, randomised into two experiments	Methandienone 5mg/day (phase I) → 10mg/day (phase II) PO DHEAS 20mg/day (phase I) → 40mg/day (phase II) PO	3-5 months per phase	6 weeks	T, FSH, LH	- T recovered to baseline at 10 days - FSH & LH recovered to baseline by 6 weeks, except for LH after DHEAS (26% lower at 6 weeks)
Caminos-Torres et al. 1977 **(15)** Prospective study	12 healthy men aged 20-27 years	Testosterone enanthate 50mg/week or 200mg/week IM	8 weeks	5 weeks	T FSH & LH (normal and GnRH-stimulated)	- T lower by 6.1 nmol/L in 200mg dose only - No differences in other parameters

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Mauss et al. 1975 **(16)** Prospective study	7 healthy men aged 20-27 years	Testosterone oenanthate 250mg/week IM	21 weeks	18 weeks	Libido, sexual frequency, hair growth, acne Testicular volume T, FSH, LH Sperm concentration, motility, and morphology	- T recovered to baseline at 18 weeks, FSH & LH at 10 weeks - Sperm motility recovered to baseline at 10 weeks, concentration and morphology at 14 weeks - Testicular volume at 18 weeks lower by 3mL - All other parameters recovered to baseline by 18 weeks
Observational studies: prospective						
Smit et al. 2021 **(17)** Prospective study	100 male amateur athletes aged 19–67, who intended to start androgen cycle in the next 2 weeks	Variable (number of AAS used: median 5, range 1–11) Median dose 901mg/week (range 250–3382)	Median 13 weeks (range 2–52 weeks)	Median 9.4 months (range 3.7–12.1)	T, FSH, LH Testicular volume Semen volume and sperm concentration, count, progressive motility, motile sperm count	- T recovered to baseline at 3 and 9 months - FSH lower at 3 months (mean 3.2 vs 3.9 IU/L), but recovered to baseline at 9 months - LH recovered to baseline at 3 and 9 months - Testicular volume lower at 3 months (mean 16.7 vs 17.4 ml), but recovered to baseline at 9 months - Semen volume lower at both 3 and 9 months (mean 2.7ml vs 3.1ml) - Sperm concentration lower at 3 months (mean 36.4 vs 46.8 $x10^6$/ml), but recovered to baseline at 9 months - Sperm count lower at both 3 and 9 months (mean 87.9 and 120 vs 145 $x10^6$/ml) - Sperm progressive motility recovered to baseline at 3 months - Motile sperm count lower at 3 months (43.1 vs 77.2 $x10^6$/ml), but recovered to baseline at 9 months
Windfeld-Mathiasen et al 2021 **(18)** Prospective study	545 males aged 26.2 (6.3) years attending fitness centers with positive AAS in urine sample, compared to age-matched controls from population registry	Variable	Unknown	Mean 7.3 years	Fertility rate	- Total fertility rate was 7% lower in former AAS abusers than controls, with this difference not being statistically significant (RR 0.93, 95% CI 0.84-1.03)

Garevik et al. 2011 **(19)** Prospective study	35 AAS-abusing men aged 26.4 (7.2) years, recruited through anti-doping hotline	Testosterone IM, Nandrolone IM	<5 weeks for testosterone	6 months	FSH, LH	- FSH 3.31 (1.5) IU/L at 6 months - LH 2.3 (1.9) IU/L at 6 months - Baseline measurements not available
Karila et al. 2004 **(20)** Prospective study	21 male power athletes aged 24-42 years, undergoing medical assessment to rule out chronic diseases and medication use 'Major users' are those with cumulative lifetime dose > median value	Variable 17-167mg/day	5.4-38.3 weeks	6 months	T, FSH, LH Sperm concentration and morphology	- Major users had lower T (mean 6.1 vs 12.3 nmol/L), FSH (mean 0.9 vs 2.9 IU/L) and LH (mean 1.5 vs 3.4 IU/L) than minor users - Sperm concentration mean 77 x 10^6/mL at 6 months, with only one subject azoospermic - Significant correlation (r=0.6) between hCG dose used and % morphologically abnormal sperm - Baseline measurements not available
Alen et al. 1987 **(21)** Prospective study	7 power athletes in training aged 24-34 years	Testosterone IM, Methandienone PO, Nandrolone IM, Stanozolol IM (variable doses)	12 weeks	13 weeks	T, LH, FSH	- All parameters recovered to baseline
Alen et al. 1985 **(22)** Prospective pilot study	5 power athletes aged 27 (5.5) years	Testosterone IM, Methandienone PO, Stanozolol IM, Nandrolone IM (variable doses)	26 weeks	12 weeks	T, FSH, LH	- T lower by 11 nmol/L - FSH & LH recovered to baseline
Ruokonen et al. 1985 **(23)** Prospective study	4 power athletes	Methandienone PO, Nandrolone IM, Stanozolol IM, Testosterone IM (variable doses)	26 weeks	16 weeks	T	- T recovered to baseline
Observational studies: cross-sectional						
Shankara-Narayana et al. 2020 **(24)** Cross-sectional	31 previous users aged 33 (2) years, compared with 21 healthy controls aged 32 (2) years	Variable Median 5 compounds used	Lifetime median 115 weeks	Median 42.9 weeks since cessation	Gynaecomastia, acne, temporal hair loss Testicular volume	- Testicular volume lower by 9mL - No differences in other parameters - Estimated time taken for previous users to reach mean of control groups: 14.1 months for sperm output, 10.4 months for sperm concentration, 37.6 months for

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	All were males regularly involved in recreational exercise (≥3 times/week)				Sperm output, concentration and motility T, FSH, LH	sperm motility, 19.6 months for FSH, 10.7 months for LH - Greater length of AAS abuse associated with slower recovery of sperm parameters - Usage pattern (stacking, cyclical vs continuous etc) had no effect on recovery of any parameter
Lindqvist Bagge et al. 2017 **(25)** Cross-sectional	143 male elite athletes reporting a history of AAS abuse, compared with 540 who reported none	Not stated	Not stated	30 years after ceasing their active sports career	Lifetime prevalence of physical/mental health issues where professional help was sought	- Higher prevalence of depression (13.3% vs 5%) and anxiety (13.3% vs 6.3%) in previous abusers - Lower prevalence of decreased libido (2.8% vs 9.3%) in previous abusers - Higher prevalence of anxiety (24.5% vs 6.7%) and any psychiatric illness (28.3% vs 12.4%) in previous users who had used cycles lasting ≥2 years than previous users who had not
Rasmussen et al. 2017 **(26)** and *Rasmussen et al. 2016* **(27)** Cross-sectional	33 previous users aged 34.8yrs (1.2) years, compared with 30 healthy controls aged 31.5 (1.2) years All were males in recreational strength training	Not stated Median 6 different compounds used	Lifetime mean 111.8 weeks	At least 3 months since cessation	Psychosexual features Testicular volume T, FSH, LH	- Higher prevalence of depressive symptoms (24.2% vs 3.3%), erectile dysfunction (27.3% vs 6.7%) and decreased libido (40.1% vs 9.7%) in previous users - More severe energy/fatigue (58.9 vs 73.5 on SF-36 questionnaire) in previous users - Testicular volume lower by 4.9mL in previous users - Negative correlation between testicular volume and accumulated weeks of use - T lower by 4.1 nmol/L in previous users - T in previous users mostly in the low normal range; only 3.3% below lower reference range
Kanayama et al. 2015 **(28)** Cross-sectional	19 previous users aged 42.7 (3.8) years, compared with 36 weightlifting controls aged 42.9 (5.8) years	Not stated	6.9 (4.5) years over lifetime	Mean 4.9 (6.6) years since cessation (range 0.25-21.2 years)	Psychosexual factors Testicular volume T, FSH, LH	- Testicular volume lower by 2.3 mL - T lower by 4.6 nmol/L - Reduced sexual desire amongst previous users - All other parameters not different - 29% of previous users reported experiencing major depression during AAS withdrawal
Graham 2006 **(29)** Cross-sectional	10 previous users aged 41.7 (3) years, compared with 10 bodybuilding controls aged 43.1 (4.6) years	Not stated	20.7 (2.8) years over lifetime	Single point in time, at least 3 months after cessation	T	- T not different between groups

Urhausen et al. 2003 **(30)** Cross-sectional	15 male bodybuilding/ powerlifting previous users	Variable	Mean 720mg/week for 26 weeks yearly, over 9 years	At least 12 months since cessation (median 24 months, mean 43 months)	Gynaecomastia T, LH, FSH	- 2/3 had experienced gynaecomastia "in the past" - Mean T normal, but 13/15 in lower 20% of reference range and 2/15 below lower limit of reference range - All other parameters in normal ranges
Lemcke et al. 2996 **(31)** Cross-sectional	47 men aged 21-30 years previously treated for idiopathic tall stature, compared with 123 healthy controls without idiopathic tall stature	Testosterone enanthate 250mg/week IM	12.1 (5.2) months	10.6 (2.5) years	Testicular volume Sperm count, concentration, progressive motility and morphology T, FSH, LH	- Testicular volume not different between groups - % sperm progressive motility lower by 5.1% in treated men - T lower by 4 nmol/L in treated men - No differences in other parameters
Bond et al. 1995 **(32)** Cross-sectional	16 previous users aged 24.4 (2.6) years, compared with 14 controls aged 23.5 (4.4) years, all of whom had lifted weights for ≥2 years	Variable	Previous cycles lasting 8-11 weeks	Single point in time, at least 1 week (for PO) or 1 month (for IM) after cessation	Psychological factors, aggression	- No differences, other than lower self-rated affability amongst previous users
Malone et al. 1995 **(33)** Cross-sectional	46 previous powerlifting/bodybuildin g users aged 27.5 years (including 3 females), compared with 87 controls aged 26.7 years (including 11 females)	Not stated	Lifetime mean 5.3 years	Not stated	Prevalence of psychiatric diagnoses (ever) Current recreational drug use/dependence	- Higher lifetime occurrence of psychiatric diagnoses (37% vs 11.5%) or suicide ideation (13% vs 1.2%) in previous users - No differences in recreational drug use
Pope & Katz 1994 **(34)** Cross-sectional	51 previous users aged 25.5 (7) years, compared to 68 controls aged 28.3 (10) years, all of whom had lifted weights for ≥2 years	Not stated	Variable (1-28 cycles over lifetime)	At least 1 week (PO) or 1 month (IM) since cessation	Gynaecomastia, acne, hair loss (physical examination)	- Testicular length lower by 3.4mm in previous users - Gynaecomastia more frequent (31% vs 3%) in previous users - No differences in prevalence of psychiatric diagnoses

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	All were weightlifting males				Testicular length (calipers) Psychiatric diagnoses	
O'Connor & Baldini 1990 **(35)** Cross-sectional	5 retired-powerlifter previous users aged 40 (1.2) years	Not stated, mean 233mg/week	3-4 cycles yearly, each lasting 9.8 (1.3) weeks	At least 5 years since cessation	T	- T in normal range: 12.5 (0.8) nmol/L
Knuth et al. 1989 **(36)** Cross-sectional	11 bodybuilding previous users, compared with 41 controls Aged 26.7 (0.7) years	Variable	Not stated	Single point in time, at least 4 months after cessation	Sperm concentration, motility and morphology T, FSH, LH	- Sperm motility and morphology lower in previous users - No differences in sperm concentration
Shephard et al. 1977 **(37)** Cross-sectional	4 bodybuilding previous users aged 23-52 years	Methandrostenolone 10-15mg/day	7-10 months	2 weeks – 7 months since cessation	Sexual function T, LH, FSH	- LH below normal range, FSH mixed - All other parameters in normal range

Abbreviations: AAS, Anabolic Androgenic Steroid; T, (serum) testosterone; FSH, Follicle Stimulating Hormone; LH, Luteinising Hormone; IM, intramuscular; PO, oral; CI, Confidence Interval; RR, Relative Risk.

Parameters reported as mean (SD) or a range (min – max) unless otherwise stated. Differences reported were all statistically significant. A parameter 'recovered' when it had no statsiticaily-significant difference to baseline.

^Subjects, parameters and outcomes not relevant to the research question (e.g. data on current AAS users) omitted.

*Unless otherwise stated, refers to measurement at the endpoint of the study, compared to baseline (i.e. individual levels before AAS use, or controls who had never used AAS).

#Rheumatoid arthritis treatment, comprising of non-steroidal anti-inflammatory drugs (8 subjects) or chloroquine (3 subjects) was continued throughout the study period.

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Table 4: Conclusions from scoping review

Change associated with ASIH	Recovery pattern after cessation of AAS
Physical changes	
Testicular atrophy	Near-complete recovery expected over months to years, with difference in volume in one year being minimal.
Gynaecomastia	Recovery is not likely.
Libido and erectile dysfunction	Recovery to baseline is expected over months, but 'baseline' is typically not as potent or active as during AAS abuse.
Spermatogenesis	Complete recovery in months likely.
Psychological changes	
Mood Disorder	Insufficient and conflicting data; depressive and anxious symptoms are common on cessation of AAS and improvement after initial withdrawal period is likely, but incomplete.
Quality of Life Measures	Insufficient and conflicting data, but symptoms like fatigue often remain, perhaps normalized over years but not as good as during AAS abuse.
Biochemical changes	
Testosterone	Near-complete recovery in 3 to 6 months is likely, but full recovery is uncertain.
Gonadotropins (FSH, LH)	Full recovery in 3 to 6 months is highly likely.

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