www.medscape.com

Male Central Hypogonadism Secondary to Exogenous Androgens

A Review of the Drugs and Protocols Highlighted by the Online Community of Users for Prevention and/or Mitigation of Adverse Effects

Stamatios Karavolos; Michael Reynolds; Nikoletta Panagiotopoulou; Kevin McEleny; Michael Scally; Richard Quinton
Clin Endocrinol. 2015;82(5):624-632.

Abstract and Introduction

Abstract

Androgen- or anabolic steroid-induced hypogonadism (ASIH) is no longer confined to professional athletes; its prevalence amongst young men and teenagers using androgens and/or anabolic steroids (AASs) is rising fast, and those affected can experience significant symptoms. Clinicians are increasingly encountering demanding, well-informed men affected by ASIH, yet lacking authoritative information on the subject may struggle to project a credible message. In this article, we overview the methods and drugs that men use in an attempt to counteract ASIH (with a view to either preventing its onset, or reversing it once it has developed) and summarize the scientific evidence underpinning these. The main channel for obtaining these drugs is the Internet, where they can be readily sourced without a valid prescription. An Internet search using relevant terms revealed a huge number of websites providing advice on how to buy and use products to counteract ASIH. Drugs arising repeatedly in our search included human chorionic gonadotrophin (hCG), selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). The quality and accuracy of the online information was variable, but review of medical literature also highlighted a lack of scientific data to guide clinical practice. It is important for clinicians to be aware of the AAS user's self-treatment strategies with regard to ASIH side-effect mitigation. By ensuring that they are well-informed, clinicians are more likely to retain the credibility and trust of AAS users, who will in turn likely be more open to engage with appropriate management.

Introduction

Use of performance-enhancing drug is an important aspect of endocrinology that is often overlooked. Anabolic androgenic steroids (AASs) are amongst the most common and serious form of drug used for performance enhancement in sport and bodybuilding[1] and increasingly also for enhancement of physical appearance ('get that sculpted body and six-pack abdomen'). Inappropriate prescribing of native testosterone (T) may also be on the increase and potentially carries the same risk of anabolic steroid-induced hypogonadism (ASIH).[2] The lifetime prevalence of AAS use in men is estimated to be between 3·0 and 4·2%, but is rapidly increasing, with even USA high school students well-represented amongst users.[3] However, clinicians are often unaware just how ubiquitous AAS use has become[4,5] and, due to their knowledge base, may anyway be uncomfortable addressing the issue; indeed, some authors report that over 50% of AAS users are reluctant to disclose their AAS use to clinicians.[6] Moreover, mainstream academic endocrinology rather lost credibility with the 'performance-enhancement community' in the 1980s and 1990s, by persisting overlong in (a) doubting whether further enhancement of athletic performance could be achieved through raising serum T levels above the physiological reference range and (b) questioning whether any therapeutic separation of androgenic and anabolic actions was achievable, due to the single androgen receptor.[6]

AASs are a family of hormones including T, the primary male sex hormone and its derivatives. '*Anabolic*' refers to the muscle-building properties of these drugs and '*androgenic'* refers to their promotion of male sex characteristics. The anabolic effects represent the principal motivation for the illicit use of AAS, with users attempting to minimize or mitigate the unwanted side effects (principally ASIH and gynaecomastia) arising from the androgenic properties. Although all genomic AAS actions are ultimately transduced by ligand binding to the androgen receptor, selectivity of signalling towards anabolic vs androgenic pathways is mediated by an interacting web of molecular chaperones, co-activators/-repressors and transcription factors.[7,8] Indeed, many users take T alongside nandrolone ('stacking'), specifically because of the latter's perceived inadequate androgenicity in respect of supporting sexual function. AASs can be taken orally, transdermally or by intramuscular injection, the latter being the most popular mode of administration amongst illicit users.

There is an acute dose-dependent suppression of endogenous gonadotropin-driven androgen secretion with exogenous AAS.[9] However, ASIH refers to the phenomenon of hypogonadotrophic hypogonadism persisting

even after discontinuation of the exogenous AAS product. It was first described by Boje in 1939,[10] who suggested that AAS might enhance athletic performance but could also have potential health-related side effects. It is biochemically indistinguishable from organic hypogonadotrophic hypogonadism and results from chronic sex steroid-mediated feedback-inhibition of the hypothalamus–pituitary–testicular axis. Although a near-universal consequence of AAS use, its duration and severity are highly variable, reflecting dose, duration and type of prior AAS exposure.[11] A retrospective study of 15 ex-AAS users (the mean time off steroids was 43 months; range 1 to 10 years) found 13 of 15 to be in the lower 20 percentage of the normal reference range for testosterone and 2 of 15 below the normal range.[12] Thus, prolonged, severe ASIH is relatively uncommon amongst former AAS users. In some centres, approximately one-fifth of men seeking treatment for hypogonadism have reported the earlier use of AAS.[13] It is hypothesized (although by no means proven) that addictive behaviour might contribute to users' continuing their regimens even when side effects occur, partly due to psychological dependence and partly through fear of losing muscle mass.[11,14–16]

AAS users are thus necessarily motivated to counteract or reverse the unwanted side effects of exogenous androgens, frequently seeking information on the use of steroidal and nonsteroidal ancillary drugs for this purpose: a therapeutic manoeuvre that users also define as within the category of 'stacking' (*i.e*. taking more than one agent simultaneously). The most easily accessible source for obtaining such information is the Internet,[14,17,18] wherein we identified numerous websites and forums allowing AAS users around the world to anonymously offer and solicit advice, share drug sources and personal outcomes, and collaborate on dosing schedules. Indeed, many AAS users attending our endocrinology and male infertility clinics will already be 'stacking' and may simply be attempting to have these ancillary agents prescribed; others will just want professional information about their use and effectiveness.

These drugs are steroid, or glycoprotein hormones that should only be available on medical prescription, and yet the typical source of information and procurement for AAS users regarding these substances is the Internet.[14,18–21] Commonly used agents include human chorionic gonadotrophin (hCG), selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). The off-label illicit use of these medications is concerning, as so little is known about their long-term effects and drug interactions in the context of AAS use.[1] Clinicians should be aware of the methods exogenous androgen users use in an attempt to mitigate the features of ASIH, particularly loss of endogenous testosterone secretion, but also reduced testicle size and infertility secondary to reduced sperm count.

In this paper, we review the beliefs of AAS users, the current best scientific evidence related to these beliefs and the current best scientific evidence for treatment of ASIH. We identified Internet sites and forums offering information on the use of these products and reviewed the methods and drugs advised therein for the self-medication. We then examined the evidence-based medical information currently available to support or refute this advice.

Methods

We used Google, the most popular online search engine (Search Engine Watch, 2012), along with the search terms listed in to identify Internet sites related to methods and substances used to counteract the symptoms of hypogonadism secondary to exogenous steroid use. We performed searches using those terms and noted the number of websites containing each search term. This does not reveal whether the websites actually focus on that content, but rather whether the search term appeared somewhere on the sites. This strategy provided a rough indicator of the prevalence or dominance of the search term in the literature and how popular is the online usage.

Table 1. Number of links generated by relevant terms using the Google search engine, as of 31st January 2014

Search term	Number of sites
Anabolic androgenic steroids	340 000
Hypogonadotrophic hypogonadism	670 000
Steroids testicular atrophy	932
Steroids testicular shrinkages	1320
Steroids male infertility	352 000
'Buy Clomiphene online'	266 000

Steroids human chorionic gonadotrophin	296 000
Steroids and aromatase inhibitors	240 000
(O)estrogen blockers	126 000

We selected the top twenty links generated by our search () and navigated through them to obtained details of (i) the methods and substances advised to counteract the side effect of hypogonadism and (ii) the quality of medical information and advice provided online with regard to the use of these methods. Best results were yielded by utilizing the terminology the AAS users commonly use, such as 'postcycle therapy', 'stacking' or 'steroid recovery'. We included nonmedical terms in our search to identify sites and results which were not just from the medical and research communities. We then navigated through links within the top 20 websites to gain more understanding. We found that a vast amount of information appears on private websites and online discussion groups and forums. Many of these websites provide information on how to use these substances but also links and advice on how to obtain them online.

Table 2. Websites evaluated for information on the substances used to counteract ASIH

No.	Website	URL	Server location	Language	Type of website
1	Anabolic Steroids - Steroid.com Forums	http://forums.steroid.com/pct-post-cycle-therapy/403869-post-cycle-recovery-clomid-nolvadex-pregnyl.html	USA	English	Forum, e-magazine
2	UK muscle bodybuilding community	http://www.uk-muscle.co.uk/steroid-testosterone-information/24947-pct-clomid-when-how-much-etc.html	Netherlands	English	Forum
3	Elite Fitness	http://www.elitefitness.com/forum/anabolic-steroids/recovery-steroid-cycle-isnt-just-pct-746147.html	Canada	English	Store, Forum, e-magazine
4	T-nation	http://www.t-nation.com/	Europe	English	Store, Forum, e-magazine
5	Steroidal.com	http://www.steroidal.com/	UK	English	Store, Forum
6	Predator Nutrition	http://www.predatornutrition.com	UK	English	Store-supplements
7	AFboard.com	http://www.afboard.com/	USA	English	Store-supplements e-magazine, Forum
8	Iron Magazine	http://www.ironmagazine.com/2013/clomid-post-cycle-recovery/	Panama	English	Forum, e-magazine, store-supplements
9	Bluelight	http://www.bluelight.org	Netherlands	English	Forum
10	Muscle steroids	http://muscle-steroids.com	France	English	Store
11	Bodybuilding.com	http://www.bodybuilding.com	Europe	English	Store, Forum, e-magazine
12	Muscle-gear	http://www.muscle-gear.net	Luxembourg	English	Store
13	Juiced Muscle	http://juicedmuscle.com	Ukraine	English	Forum, Blog
14	The iron den	http://www.theironden.com	Netherlands	English	Forum
15	Blackstone Labs	http://store.blackstonelabs.co/	Panama	English	Store,

					Forum
16	Steroids and image enhancing drugs: SIEDs	http://siedsinfo.co.uk/	UK	English	Public health resource
17	Rxcart	http://rxcart-uk.com	Russia	English	Store
18	Anabolics2buy UK	http://www.anabolics2buyuk.com	Russia	English	Store
19	Ana Sci	http://www.anasci.org	USA	English	Forum
20	Ergo Log	http://www.ergo-log.com	Netherlands	English	Blog

Results

Information Available on the Internet

We found that online discussions and advertisements concerning agents that can be used to combat the side effect of hypogonadism are very common. There was a mixture of information available from online communities (forums), AAS user blogs and from websites attempting to sell products such as anabolic steroids and substances directly related to hypogonadal recovery. Roughly one-third of the Internet sites we reviewed also offered to sell these drugs without prescription. Information was also available from official public health websites, such as the Welsh government funded and image-enhancing drugs website (SIEDSinfo.co.uk). The later provided risk reduction advice by providing information on safe injection practices.

Information on forums consisted of anecdotal reports and advice from unverifiable sources (some claiming to be medically qualified). These sources referenced mainstream scientific papers and abstracts on the issues discussed. However, there were clear flaws to this superficially 'evidence-based approach'. The papers quoted were of only limited generalizability to AAS users, ASIH, or to the argument proposed by the 'expert'. Equally most users were unable or unwilling to progress beyond subscription pay-walls, leaving them to draw conclusions from the abstracts or the 'expert opinion' alone.

Sites directly attempting to sell products to consumers could be broken into two groups, those purportedly selling medications and those selling supplements. Websites recommending the use of medications provided a balanced view with reference to current evidence with citations to peer-reviewed articles in the medical literature. Links to 'Frequently Asked Questions' for specific drugs (e.g. clomid) were available in some websites (e.g. steroidology.com), with information including the mechanism of action, instructions on how to use the drugs in relation to a 'steroid cycle', costs in the UK and USA and options to purchase online. Comparison of the efficacy of some drugs was also available in some websites (e.g. nolva *vs* clomid). We found that the use of these medications was positively discussed on forums.

Supplements advocated ranged from transparent preparations such as milk thistle to blends with a multitude of ingredients, such as vitamins (notably vitamin D), minerals (most often zinc), amino acids, herbal extracts and synthesized compounds such as L-carnitine. These supplements were mostly derided as ineffective on forum discussions.

The rationale behind the different tactics used was the quick restoration of the hypothalamus–pituitary–testicular axis and return of the endogenous steroid production to normal, whilst minimizing 'time lost' to AAS use and/or muscle mass augmentation and avoiding other symptoms of low testosterone in men, namely erectile problems, loss of libido and low mood. Fertility concerns were typically secondary; indeed, plenty of users reported getting their partners pregnant whilst using AASs and most users ignored potentially sustained effects on numbers and quality of sperm.[22] Discussions often lead to misunderstanding the pathophysiology of spermatogenesis and its impairment, leaving users to believe that return to normal serum testosterone levels translated to normal spermatogenesis. In most discussions, men seemed to equate regaining endogenous steroid production to normal fertility, ignoring long-term effects on quality of sperm, such as poor morphology and motility, which might potentially be irreversible.[22]

Purported Methods for Avoiding ASIH

Steroid Cycling. A common method suggested by the websites was the use of steroid 'cycles'. This involves alternating active periods of AAS use with respite intervals. The aim of cycling was to minimize AAS-associated side effects, by facilitating recuperation of the hypothalamus–pituitary–testicular axis, restoring endogenous

testosterone production and, hopefully, reversing ASIH during the drug-free interval. Cycling was also suggested to avoid detection during competition in drug-free athletic events. AAS users typically use steroids in cycles of 6–12 weeks, with varying periods of no use.

Nonandrogenic Drugs. Users often combine different preparations of AASs with nonandrogenic drugs (hCG, SERMs or AIs) to counteract the negative side effects of AASs, a method referred to as 'stacking'. In addition to stacking, users will often use substances during the respite intervals, commonly referred to as 'postcycle therapy' (e.g. gonadotrophins), with the aim to restore the hypothalamus–pituitary–testicular axis and testicular function quicker than might have occurred naturally, if at all.

Certain drugs cropped up as being suggested for treatment either during the steroid cycle or postcycle. These included hCG, SERMs, such as clomiphene, toremifene, tamoxifen and raloxifene, and the various AIs (anastrozole, letrozole and exemestane). Other agents were mentioned less often and with controversy, for example mesterolone and FSH-based products, principally human menopausal gonadotrophin (hMG), but also r-hFSH. Drug recommendations partially depended on reported 'off-label' availability.

hCG was advocated for use in two ways. A group of users suggested hCG injections during the steroid cycle to try and maintain testicular volume and function that exogenous amounts of steroids would normally suppress. Others advocated waiting till one's body contained low amounts of AAS and then starting hCG. This could be up to several weeks from the last steroid injection, given the slow half-life of many esterified steroids (although for an oral steroid cycle, this washout period will often be considerably less).

A common theme was that users felt hCG reversed primary gonadal failure (i.e. the atrophy) but perpetuated the hypothalamic failure as it prompted testosterone production, but did not alleviate the underlying secondary failure (low FSH/LH); thus, hCG regimes tended to be recommended for shorter periods than other drugs. Users also differed on dosing schedules. Some argued for 250 IU every other day whilst using AAS, whereas others suggested hCG after stopping AAS and using 2500 IU every other day for a week. Hundreds of more variations were suggested, mainly lower steady doses for longer periods or 'pulsing' the doses, that is high but infrequent doses. Partly, this was down to users perceived differences on effectiveness but also a common fear was that hCG would desensitize Leydig cells to producing testosterone in response to LH, if large amounts of hCG was used, an effect that has been shown in rat studies,[23] often quoted in these websites.

SERMs and AIs stimulate pituitary gonadotrophin secretion, and hence testicular T secretion, by inhibiting negative feedback at the hypothalamus. This is because oestrogen (E_2) is the dominant moiety for sex steroid feedback-inhibition of gonadotrophin secretion even in men. It is generated by aromatization from T, both locally (*e.g.* breast bud) and systemically (principally in adipose tissue), but the testicular E_2/T secretory ratio also rises with supraphysiological LH levels (as seen in Klinefelter's), or with hCG-overstimulation. Testosterone and other aromatizable AASs are metabolized in part to E_2 and other oestrogen agonists. Indeed, men using high doses of AAS can achieve circulating E_2 levels within the normal range for women reproductive age.[24]

Clomiphene users suggested its use primarily as postcycle therapy after a steroid cycle to block the negative feedback of E_2 on FSH/LH production, thus restoring hypothalamus–pituitary–testicular axis function. Dosing was often advocated for several weeks up to a month, with doses normally between 25 and 150 mg daily. Almost universally, users suggested not medicating until serum androgen levels were dropping close to normal. One user indicated differing schedules with age, with those over 35 requiring longer dosing schedules, quoting that 'at least 50% of the older men do not fully recover with normal Clomid treatment'.

Tamoxifen use was mainly advocated to prevent gynaecomastia, rather than hypogonadism. Users sometimes reported side effects such as blurred vision, dizziness, headaches and reduced libido, although others claimed that ocular side effects were a myth, quoting papers in support.[25] Some users also suggested using tamoxifen in combination with or just after stopping cycles of hCG injections, with the aim of extending the post-hCG rise in serum T through blockade of E_2-mediated negative feedback.

Less commonly, raloxifene was suggested as an equivalent to tamoxifen, but it seemed less well known and available on the websites. Toremifene, a newer drug, is licensed for the treatment of hormone-dependent metastatic breast cancer in postmenopausal women.[26] It was advocated similarly to clomiphene and tamoxifen, as a stimulator of FSH/LH production, with users suggesting greater potency than clomiphene a website where a purported doctor posts paper abstracts linked but not always directly relevant to the issue of ASIH.[27]

Anastrozole, letrozole and exemestane were the typically mentioned AI choices on the websites. AIs were popular with those who suffered side effects from SERMs, or who reported difficulty sourcing alternatives. On occasion users expressed a dislike for AIs because they reduce E_2 levels to a point where the users report 'aching joints' that they ascribed to E_2-mediated 'lack of lubrication'. Users seemed to draw support from this form of anecdotal reports and menopausal women reporting similar joint problems.

Physiological Effects of Exogenous Testosterone and AAS

Testosterone in supraphysiological blood concentrations increases lean muscle mass, burns fat and increases strength in healthy eugonadal men.[15] This effect is linearly related to blood T levels.[28] Similar effects are seen with synthetic androgens,[7] although serum levels cannot routinely be measured, nor mapped in relation to a physiological male normal range.

The use of exogenous AASs causes hypogonadotrophic hypogonadism by exerting negative feedback both on hypothalamic GnRH release and directly on LH and FSH secretion by pituitary gonadotrophs. At the pituitary level, feedback-inhibition by T is largely mediated by E_2, following local aromatization. The overall results are testicular atrophy and impaired spermatogenesis with resultant infertility.[29] Normal spermatogenesis is associated with intratesticular T levels some 30-fold higher than serum T levels. Exogenous administration cannot deliver anything remotely approaching this requisite T concentration within the seminiferous tubules; indeed, it will tend to markedly reduce it by suppressing endogenous LH-mediated T secretion.[30]

The duration of suppression and the resultant central hypogonadism varies between individuals. This is due to factors including the use of multiple drugs, the dose and duration of use. Most AAS users will recover normal HPG function within a few weeks to months, even after prolonged cycles of supraphysiological doses of AAS.[31] However, some users demonstrate prolonged hypogonadism, occasionally persisting more than a year after stopping AAS, although some of these will have persistent low-level spermatogenesis.[32–35] Younger men may recover faster and more completely from ASIH following cessation of AAS use as compared to older men.[36] The symptoms of testosterone deficiency in ASIH typically manifest 'postcycle', when the supraphysiological androgen levels drop. For this reason, AAS users seek the use of ancillary drugs such as hCG, SERMs and AIs in an attempt to hasten the recovery of the hypothalamus–pituitary–testicular axis and T production. SERMS and AIs may also be taken with the primary aim of avoiding AAS- or hCG-induced gynaecomastia.

The pathophysiology of ASIH is likely to be more complex than that of a simple T excess effect, because AAS users are likely to be taking a 'cocktail' of high-dose synthetic androgens and ancillary drugs by a combination of administration routes, as has been revealed by our Internet search. On top of the endocrine disruption that these may cause, they may also contribute to a degree of primary testicular failure through a direct toxic effect, as suggested by animal studies.[37–39]

Effective Treatment of ASIH

hCG is a naturally occurring glycoprotein normally produced by the human placenta. It is available in purified or recombinant forms and is licensed for use in the treatment of female infertility.[26,40] hCG binds to the LH receptor and, having a much longer effective plasma half-life, is a useful analogue of LH to stimulate testosterone secretion by Leydig cells. In men, hCG acts directly on Leydig cells to increase both intratesticular and serum T levels.[41–43] Clinical indications for hCG use in men are for the treatment of T deficiency and/or induction of spermatogenesis in gonadotrophin-deficient adults (typically with concomitant FSH therapy in the latter role) and in treating hypogonadotrophic pubertal delay.[44] There are no other proven uses of hCG for men in routine clinical practice. As discussed above, we found that AAS users misused hCG in two settings: (i) by men with sustained suppression of their hypothalamus–pituitary–testicular axis from prolonged use of high-dose AAS use, in an attempt to increase endogenous testicular T secretion and (ii) by AAS users seeking to avoid detection of exogenous androgens by stimulating endogenous testosterone production. In reality, this merely prolongs suppression of the hypothalamus–pituitary–testicular axis, which is the root cause of the reduction in testicular size and serum T levels.

In a small case series of 13 azoospermic men with acquired gonadotrophin deficiency, hCG in combination with FSH was successful in stimulating and maintaining spermatogenesis in hypogonadotrophic, hypogonadal men.[45] Low-dose hCG with testosterone supplementation has also been shown to be effective in maintaining spermatogenesis, although whether this can translate to successful pregnancies is uncertain.[46] In the context of AAS use, hCG has been shown to be effective in accelerating testicular production of testosterone and reversing azoospermia, but evidence is only available from case reports.[47–49]

SERMs such as clomiphene, tamoxifen and raloxifene stimulate pituitary gonadotropin and, consequently, T secretion by blocking E_2 receptors in pituitary gonadotrophs. They have long been used off-label for the treatment of male infertility and gynaecomastia.[50–55] In men, there are no valid clinical indications for the use of SERMs, except in the exceptionally rare case of male breast cancer (unlicensed indication), and there are thus only limited number of studies on their therapeutic use. The use of clomiphene to treat subfertile men was first reported in 1966.[56] Since then, there have been reports of clomiphene use 'off-label' for the treatment of different forms of sperm abnormalities, including unexplained couple infertility, with variable results.[57–59] Much better results, in respect of improvement in T levels and semen, have been reported where clomiphene was targeted in men with nonsyndromic hypogonadotrophic hypogonadism,[60] with similar findings reported for other SERMs.[61] However, individual SERMs vary in their biological effects in men. For instance, standard doses of raloxifene promote a smaller degree of gonadotropin-driven T secretion (E_2-antagonist-effect) in men than equivalent doses of tamoxifen, but also induce less inhibition of growth hormone (GH)-mediated IGF1 secretion (E_2-agonist-effect).[62] Despite promising data, enclomiphene (the trans-isomer of clomiphene citrate) has not yet obtained regulatory approval in the USA for the desired indication of obesity-related hypogonadotrophic hypogonadism.[63]

Recent meta-analyses do suggest that empiric treatment with clomiphene or tamoxifen for idiopathic male infertility may improve sperm concentration and motility and increase spontaneous pregnancy rates,[64,65] but optimal dosing schedules for the treatment of such patients have not been established, and there are reports of high-dose clomiphene being associated with a decline in spermatogenesis in some men.[66] Based on current published data, there is insufficient evidence to suggest that clomiphene is effective for the treatment of idiopathic male infertility. With regard to treatment of ASIH, we could only find two case reports of the successful clomiphene-induced restoration of FSH, LH and free T levels in men.[67,68] It is therefore difficult to draw any conclusions from these data.

AIs such as anastrozole block the conversion of androgens to oestrogens, conversely leading to increasing serum T levels in a similar fashion to anti-oestrogens. They are licensed for use in the treatment of breast cancer and can be used in men for the prevention of gynaecomastia associated with raised E_2 levels.[40] AIs have been used to treat men with idiopathic infertility and hypogonadism related to obesity, with mixed results.[69–72] These studies did not demonstrate any significant negative effects on sperm production; however, the primary concern associated with the prolonged use of AIs in men is oestrogen deficiency that can lead to osteopenia or osteoporosis. On the other hand, inhibition of E_2 synthesis tends to impair GH pulsatility, but promote GH-mediated IGF1 synthesis.[73] Overall, strong evidence on the effectiveness of AIs to treat ASIH is currently lacking.

Discussion

We analysed 20 websites offering advice on the use or selling ancillary medications to counteract the side effects of ASIH. We are not aware of any other study that has examined these online practices in the past. Our study illustrates the degree of information available on the Internet that extends beyond that covered in the current medical literature. We found that many sites conveyed controversial prodrug messages, often appearing to be based upon personal experience and nonrelevant available scientific literature. The authors of these websites sometimes accused the medical profession of biased motives.

The treatment of ASIH and subsequent subfertility remains inadequately studied, and many clinicians have limited experience with regard to managing men with ASIH. AAS users appear to be well aware of this and may thus tend to give less weighting to clinician recommendations than those of 'online expert users'.

hCG, SERMs and AIs are amongst the drugs commonly used to counteract the side effects of ASIH. Although some of these are certainly effective in the context of congenital (or pituitary lesion-related) hypogonadotrophic hypogonadism,[74] the extent to which data from medical treatments can be compared and extrapolated to ASIH is uncertain. This is because the pathophysiology of ASIH may be more complex, representing a combination of the endocrine disruption and direct testicular toxicity related to the supraphysiological doses or multiple drug combinations used by users.[75]

We recommend that, based on currently available evidence, if fertility is desired, the logical first-line management is to cease using AAS along with any other potentially 'culprit' agents (*e.g.* marijuana, opioids, methamphetamine, cocaine), with serial semen analysis. Studies of exogenous androgen–progestagen

combinations examining their potential role in male contraception have shown that the typical probability of recovery of spermatogenesis to 20 million/ml was 67% within 6 months, 90% within 12 months, 96% within 16 months and 100% within 24 months,[76] so the timelines and outcomes for men with ASIH may not be dissimilar.

However, what if the period of biochemical recovery from ASIH is prolonged and associated with relationship-endangering features, and/or the partner's age militates against a prolonged watch-and-wait strategy in respect of fertility? A judgemental approach imputing patient 'fault' may not be hugely effective, whereas involvement of community-based addiction teams can be invaluable (*e.g.* http://goodhealth-manchester.nhs.uk/mphds/drugs/drugs-team.html).

If spontaneous reversal of hypogonadism does not occur with expectant management within a reasonable timeframe as discussed above, then use of hCG ± hMG, SERMs or AIs is potentially effective alternatives.[75] However, robust evidence on their effectiveness and safety is currently lacking, and there is no consensus on the actual regimes that are effective in treating ASIH or in shortening the recovery interval, which is highly variable between individual patients. More research is needed in this area in the form of therapeutic trials to assess the effectiveness of ASIH treatments. In the meantime, by ensuring that they are well-informed and have a good understanding of what supplements their patients use, clinicians will be more likely to retain the credibility and trust of AAH users, who will in turn be more open to engaging with lifestyle modification. We would also like to caution physicians against prescribing agents with significant resale value within the index community without first involving their local community drugs team.

Conclusion

Widespread misperception that AAS use is safe with manageable adverse effects has contributed to their growing use. When evaluating hypogonadism and infertility, it is important for clinicians to inquire about AAS use because it is more prevalent than is generally thought and AAS users are often reluctant to disclose this to their clinicians.

The long-term adverse consequences of AAS use needs further investigation. Some studies suggest a potential benefit of adjuvant medications in the treatment of ASIH but quality data on the effect and safety of these medications are lacking. The limitations of the present literature with regards to the pathophysiology and treatment of ASIH necessitates more research that will facilitate the reach of consensus on the treatment of ASIH and resultant male infertility.

References

1. Adverse Health Consequences of Performance-Enhancing Drugs. (2014) An Endocrine Society Scientific Statement. *Endocrine Reviews*, 35, 341–375.
2. Gan, E.H., Pattman, S., Pearce, S.H.S. *et al.* (2013) A UK epidemic of testosterone prescribing, 2001–2010. *Clinical Endocrinology (Oxford)*, 79, 564–570.
3. de Souza, G.L. & Hallak, J. (2011) Anabolic steroids and male infertility: a comprehensive review. *BJU International*, 108, 1860–1865.
4. Kutscher, E.C., Lund, B.C. & Perry, P.J. (2002) Anabolic steroids: a review for the clinician. *Sports Medicine (Auckland, N. Z.)*, 32, 285–296.
5. Dawson, R.T. (2001) Drugs in sport - the role of the physician. *Journal of Endocrinology*, 170, 55–61.
6. Pope, H.G., Kanayama, G., Ionescu-Pioggia, M. *et al.* (2004) Anabolic steroid users' attitudes towards physicians. *Addiction*, 99, 1189–1194.
7. Hartgens, F. & Kuipers, H. (2004) Effects of androgenic-anabolic steroids in athletes. *Sports Medicine (Auckland, N. Z.)*, 34, 513–554.
8. Kuhn, C.M. (2002) Anabolic steroids. *Recent Progress in Hormone Research*, 57, 411–434.
9. Singh, G.K., Turner, L., Desai, R. *et al.* (2014) harmacokineticpharmacodynamic study of subcutaneous injection of depot nandrolone decanoate using dried blood spots sampling coupled with ultrapressure liquid chromatography tandem mass spectrometry assays. *Journal of Clinical Endocrinology and*

Metabolism, 99, 2592–2598.

10. Boje, O. (1939) *Doping.* Bulletin of the Health Organisation of the League of Nations, 8.
11. Kanayama, G., Brower, K.J., Wood, R.I. *et al.* (2010) Treatment of anabolic–androgenic steroid dependence: emerging evidence and its implications. *Drug and Alcohol Dependence*, 109, 6–13.
12. Urhausen, A., Torsten, A. & Wilfried, K. (2003) Reversibility of the effects on blood cells, lipids, liver function and hormones in former anabolic-androgenic steroid abusers. *Journal of Steroid Biochemistry and Molecular Biology*, 84, 369–375.
13. Coward, R.M., Rajanahally, S., Kovac, J.R. *et al.* (2013) Anabolic steroid induced hypogonadism in young men. *Journal of Urology*, 190, 2200–2205.
14. Cohen, J., Collins, R., Darkes, J. *et al.* (2007) A league of their own: demographics, motivations and patterns of use of 1,955 male adult non-medical anabolic steroid users in the United States. *Journal of the International Society of Sports Nutrition*, 4, 12.
15. Tan, R.S. & Scally, M.C. (2009) Anabolic steroid-induced hypogonadism–towards a unified hypothesis of anabolic steroid action. *Medical Hypotheses*, 72, 723–728.
16. Kalivas, P.W. & Volkow, N.D. (2005) The neural basis of addiction: a pathology of motivation and choice. *American Journal of Psychiatry*, 162, 1403–1413.
17. Kanayama, G. & Pope, H.G.J. (2012) Illicit use of androgens and other hormones: recent advances. *Current Opinion in Endocrinology, Diabetes and Obesity*, 19, 211–219. doi:10.1097/MED.0b013e3283524008.
18. Parkinson, A.B. & Evans, N.A. (2006) Anabolic androgenic steroids: a survey of 500 users. *Medicine & Science in Sports & Exercise*, 38, 644–651.
19. Ip, E.J., Barnett, M.J., Tenerowicz, M.J. *et al.* (2011) The Anabolic 500 survey: characteristics of male users versus nonusers of anabolic-androgenic steroids for strength training. *Pharmacotherapy*, 31, 757–766.
20. Perry, P.J., Lund, B.C., Deninger, M.J. *et al.* (2005) Anabolic steroid use in weightlifters and bodybuilders: an internet survey of drug utilization. *Clinical Journal of Sport Medicine*, 15, 326–330.
21. Pirola, I., Cappelli, C., Delbarba, A. *et al.* Anabolic steroids purchased on the Internet as a cause of prolonged hypogonadotrophic hypogonadism. *Fertility and Sterility*, 94, 2331.e1–2331.e3.
22. Fronczak, C.M., Kim, E.D. & Barqawi, A.B. (2012) The insults of illicit drug use on male fertility. *Journal of Andrology*, 33, 515–528.
23. Cigorraga, S.B., Dufau, M.L. & Catt, K.J. (1978) Regulation of luteinizing hormone receptors and steroidogenesis in gonadotropin-desensitized leydig cells. *Journal of Biological Chemistry*, 253, 4297–4304.
24. Wilson, J.D. (1988) Androgen abuse by athletes. *Endocrine Reviews*, 9, 181–199.
25. Lazzaroni, F., Scorolli, L., Pizzoleo, C.F. *et al.* (1998) Tamoxifen retinopathy: does it really exist? *Graefe's Archive for Clinical and Experimental Ophthalmology*, 236, 669–673.
26. *British National Formulary 67*. 2014.
27. Farmakiotis, D., Farmakis, C., Rousso, D. *et al.* (2007) The beneficial effects of toremifene administration on the hypothalamic-pituitary-testicular axis and sperm parameters in men with idiopathic oligozoospermia. *Fertility and Sterility*, 88, 847–853.
28. Bhasin, S., Woodhouse, L., Casaburi, R. *et al.* (2001) Testosterone dose-response relationships in healthy young men. *American Journal of Physiology. Endocrinology and Metabolism*, 281, E1172–E1181.
29. Karavolos, S., Stewart, J., Evbuomwan, I. *et al*. (2013) Assessment of the infertile male. *The Obstetrician and Gynaecologist*, 15, 1–9.

30. Turner, T.T., Jones, C.E., Howards, S.S. *et al*. On the Androgen Microenvironment of Maturing Spermatozoa. (1984) *Endocrinology*, 115, 1925–1932.

31. Knuth, U.A., Maniera, H. & Nieschlag, E. (1989) Anabolic steroids and semen parameters in bodybuilders. *Fertility and Sterility*, 52, 1041–1047.

32. Jarow, J.P. & Lipshultz, L.I. (1990) Anabolic steroid-induced hypogonadotrophic hypogonadism. *American Journal of Sports Medicine*, 18, 429–431.

33. Boyadjiev, N.P., Georgieva, K.N., Massaldjieva, R.I. *et al.* (2000) Reversible hypogonadism and azoospermia as a result of anabolic-androgenic steroid use in a bodybuilder with personality disorder. A case report. *Journal of Sports Medicine and Physical Fitness*, 40, 271–274.

34. Gazvani, M.R., Buckett, W., Luckas, M.J. *et al.* (1997) Conservative management of azoospermia following steroid abuse. *Human Reproduction*, 12, 1706–1708.

35. van Breda, E., Keizer, H.A., Kuipers, H. *et al.* (2003) Androgenic anabolic steroid use and severe hypothalamic-pituitary dysfunction: a case study. *International Journal of Sports Medicine*, 24, 195–196.

36. Moretti, E., Collodel, G., La Marca, A. *et al.* (2007) Structural sperm and aneuploidies studies in a case of spermatogenesis recovery after the use of androgenic anabolic steroids. *Journal of Assisted Reproduction and Genetics*, 24, 195–198.

37. Boettcher, M., Kosmehl, T. & Braunbeck, T. (2011) Low-dose effects and biphasic effect profiles: is trenbolone a genotoxicant? *Mutation Research*, 723, 152–157.

38. Chainy, G.B., Samantaray, S. & Samanta, L. (1997) Testosterone-induced changes in testicular antioxidant system. *Andrologia*, 29, 343–349.

39. Karila, T., Hovatta, O. & Seppala, T. (2004) Concomitant abuse of anabolic androgenic steroids and human chorionic gonadotrophin impairs spermatogenesis in power athletes. *International Journal of Sports Medicine*, 25, 257–263.

40. Plourde, P.V., Reiter, E.O., Jou, H.C. *et al.* (2004) Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism*, 89, 4428–4433.

41. Padron, R.S., Wischusen, J., Hudson, B. *et al.* (1980) Prolonged biphasic response of plasma testosterone to single intramuscular injections of human chorionic gonadotropin. *Journal of Clinical Endocrinology and Metabolism*, 50, 1100–1104.

42. Ulloa-Aguirre, A., Mendez, J.P., Diaz-Sanchez, V. *et al.* (1985) Self-priming effect of luteinizing hormone-human chorionic gonadotropin (hCG) upon the biphasic testicular response to exogenous hCG. I. Serum testosterone profile. *Journal of Clinical Endocrinology and Metabolism*, 61, 926–932.

43. Trinchard-Lugan, I., Khan, A., Porchet, H.C. *et al.* (2002) Pharmacokinetics and pharmacodynamics of recombinant human chorionic gonadotrophin in healthy male and female volunteers. *Reproductive Biomedicine Online*, 4, 106–115.

44. Liu, P.Y., Gebski, V.J., Turner, L. *et al.* (2002) Predicting pregnancy and spermatogenesis by survival analysis during gonadotrophin treatment of gonadotrophin-deficient infertile men. *Human Reproduction*, 17, 625–633.

45. Depenbusch, M., von Eckardstein, S., Simoni, M. *et al.* (2002) Maintenance of spermatogenesis in hypogonadotrophic hypogonadal men with human chorionic gonadotropin alone. *European Journal of Endocrinology*, 147, 617–624.

46. Hsieh, T.C., Pastuszak, A.W., Hwang, K. *et al.* (2013) Concomitant intramuscular human chorionic gonadotropin preserves spermatogenesis in men undergoing testosterone replacement therapy. *Journal of Urology*, 189, 647–650.

47. Turek, P.J., Williams, R.H., Gilbaugh, J.H. *et al.* (1995) The reversibility of anabolic steroid-induced

azoospermia. *Journal of Urology*, 153, 1628–1630.

48. Repcekova, D. & Mikulaj, L. (1977) Plasma testosterone response to HCG in normal men without and after administration of anabolic drug. *Endokrinologie*, 69, 115–118.

49. Menon, D.K. (2003) Successful treatment of anabolic steroid-induced azoospermia with human chorionic gonadotropin and human menopausal gonadotropin. *Fertility and Sterility*, 79 (Suppl 3), 1659–1661.

50. Tenover, J.S., Dahl, K.D., Hsueh, A.J. *et al.* (1987) Serum bioactive and immunoreactive follicle-stimulating hormone levels and the response to clomiphene in healthy young and elderly men. *Journal of Clinical Endocrinology and Metabolism*, 64, 1103–1108.

51. Guay, A.T., Bansal, S. & Heatley, G.J. (1995) Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. *Journal of Clinical Endocrinology and Metabolism*, 80, 3546–3552.

52. Parker, L.N., Gray, D.R., Lai, M.K. *et al.* (1986) Treatment of gynecomastia with tamoxifen: a double-blind crossover study. *Metabolism*, 35, 705–708.

53. Maier, U. & Hienert, G. (1988) Tamoxifen and testolactone in therapy of oligozoospermia: results of a randomized study. *European Urology*, 14, 447–449.

54. Krause, W., Holland-Moritz, H. & Schramm, P. (1992) Treatment of idiopathic oligozoospermia with tamoxifen–a randomized controlled study. *International Journal of Andrology*, 15, 14–18.

55. Duschek, E.J., Gooren, L.J. & Netelenbos, C. (2004) Effects of raloxifene on gonadotrophins, sex hormones, bone turnover and lipids in healthy elderly men. *European Journal of Endocrinology*, 150, 539–546.

56. Mellinger, R.C. & Thompson, R.J. (1966) The effect of clomiphene citrate in male infertility. *Fertility and Sterility*, 17, 94–103.

57. Micic, S. & Dotlic, R. (1985) Evaluation of sperm parameters in clinical trial with clomiphene citrate of oligospermic men. *Journal of Urology*, 133, 221–222.

58. Paulson, D.F. (1977) Clomiphene citrate in the management of male hypofertility: predictors for treatment selection. *Fertility and Sterility*, 28, 1226–1229.

59. Check, J.H., Chase, J.S., Nowroozi, K. *et al.* (1989) Empirical therapy of the male with clomiphene in couples with unexplained infertility. *International Journal of Fertility*, 34, 120–122.

60. Whitten, S.J., Nangia, A.K. & Kolettis, P.N. (2006) Select patients with hypogonadotrophic hypogonadism may respond to treatment with clomiphene citrate. *Fertility and Sterility*, 86, 1664–1668.

61. Tsourdi, E., Kourtis, A., Farmakiotis, D. *et al.* (2009) The effect of selective estrogen receptor modulator administration on the hypothalamic-pituitary-testicular axis in men with idiopathic oligozoospermia. *Fertility and Sterility*, 91 (4 Suppl), 1427–1430.

62. Birzniece, V., Sata, A., Sutanto, S. *et al.* (2010) Neuroendocrine regulation of growth hormone and androgen axes by selective estrogen receptor modulators in healthy men. *Journal of Clinical Endocrinology and Metabolism*, 95, 5443–5448.

63. Hill, S., Arutchelvam, V. & Quinton, R. (2009) Enclomiphene, an estrogen receptor antagonist for the treatment of testosterone deficiency in men. *IDrugs*, 12, 109–119.

64. Chua, M.E., Escusa, K.G., Luna, S. *et al.* (2013) Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. *Andrology*, 1, 749–757.

65. Willets, A.E., Corbo, J.M., Brown, J.N. (2013) Clomiphene for the treatment of male infertility. *Reproductive Sciences*, 20, 739–744.

66. Ross, L.S., Kandel, G.L., Prinz, L.M. *et al.* (1980) Clomiphene treatment of the idiopathic hypofertile male: high-dose, alternate-day therapy. *Fertility and Sterility*, 33, 618–623.

67. Bickelman, C., Ferries, L. & Eaton, R.P. (1995) Impotence related to anabolic steroid use in a body builder. Response to clomiphene citrate. *Western Journal of Medicine*, 162, 158–160.

68. Tan, R.S. & Vasudevan, D. (2003) Use of clomiphene citrate to reverse premature andropause secondary to steroid abuse. *Fertility and Sterility*, 79, 203–205.

69. Moss, J.L., Crosnoe, L.E. & Kim, E.D. (2013) Effect of rejuvenation hormones on spermatogenesis. *Fertility and Sterility*, 99, 1814–1820.

70. Raman, J.D. & Schlegel, P.N. (2002) Aromatase inhibitors for male infertility. *Journal of Urology*, 167 (2 Pt 1), 624–629.

71. Clark, R.V. & Sherins, R.J. (1989) Treatment of men with idiopathic oligozoospermic infertility using the aromatase inhibitor, testolactone. Results of a double-blinded, randomized, placebocontrolled trial with crossover. *Journal of Andrology*, 10, 240–247.

72. Saylam, B., Efesoy, O. & Cayan, S. (2011) The effect of aromatase inhibitor letrozole on body mass index, serum hormones, and sperm parameters in infertile men. *Fertility and Sterility*, 95, 809–811.

73. Veldhuis, J.D., Mielke, K.L., Cosma, M. *et al.* (2009) Aromatase and 5-alpha-reductase inhibition during an exogenous testosterone clamp unveils selective sex steroid modulation of somatostatin and growth hormone secretagogue actions in healthy older men. *Journal of Clinical Endocrinology and Metabolism*, 94, 973–981.

74. Kim, E.D., Crosnoe, L., Bar-Chama, N. *et al.* (2013) The treatment of hypogonadism in men of reproductive age. *Fertility and Sterility*, 99, 718–724.

75. Rahnema, C.D., Lipshultz, L.I., Crosnoe, L.E. *et al.* (2014) Anabolic steroid-induced hypogonadism: diagnosis and treatment. *Fertility and Sterility*, 101, 1271–1279.

76. Liu, P.Y., Swerdloff, R.S., Christenson, P.D. *et al.* (2006) Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. *Lancet*, 367, 1412–1420

Clin Endocrinol. 2015;82(5):624-632.