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REVIEW ARTICLE

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Designer steroids – over-the-counter supplements and their androgenic component: review of an increasing problem

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SUMMARY

Colloquially referred to by various misleading monikers ('pro-hormones', 'natural steroids', 'testosterone boosters', etc.) designer anabolic steroids have been popular now for over a decade as a way to achieve classic anabolic steroid-like results from products sold in the legal marketplace. Recent evidence suggests that anabolic steroid use may be the most common cause of hypogonadism in men of reproductive age. Despite recent regulatory efforts that have banned specific compounds, many anabolic-androgenic steroids (AAS) remain available in over-the-counter dietary supplements that are legally sold in the United States. Severe side effects including hepatotoxicity, cholestasis, renal failure, hypogonadism, gynecomastia, and infertility have been reported secondary to the use of these products. While some of these side effects may be reversible, more aggressive use may result in more permanent end-organ damage as has been previously described for the case of aggressive AAS users (Rahnema *et al.*, Fertil Steril, 2014). Designer AAS remain easily available for purchase in over-the-counter bodybuilding supplements and these products appear to be increasingly popular, despite the known health risks associated with their use. We conducted a systematic search to identify the designer steroids that are most commonly sold in dietary supplements as of April 2014 and review what is known regarding their potency and toxicity. We propose that the impact of AAS use on the reproductive and hormonal health of men is underestimated in the literature owing to previous studies' failure to account for designer steroid use. Lastly, we make clinical recommendations to help physicians steer patients away from potentially harmful supplements, and summarize key regulatory obstacles that have allowed potent androgens to remain unregulated in the legal marketplace.

INTRODUCTION

The modern perception of 'ideal' body image has arguably fueled the development and use of dietary supplements and 'body image drugs' such as anabolic-androgenic steroids (AAS) – use is widespread, no longer limited to bodybuilders or elite athletes (Rahnema *et al.*, 2014). Recent evidence suggests that illicit AAS use may be the most common cause of severe hypogonadism in younger men (Coward *et al.*, 2013). A recent meta-analysis of the epidemiology of AAS use included 187 published studies to obtain a global lifetime prevalence rate of 3.3% (Sagoe *et al.*, 2014). While these data confirms that AAS use is a widespread and important public health concern, such studies have historically focused exclusively on illicit androgens (mostly injectable) obtained on the black market. Since 2002, potent synthetic oral AAS have been detected in as many as 20% of legally sold sports nutrition products (Baume *et al.*, 2006; Geyer *et al.*, 2008; Rahnema *et al.*, 2014). With global sales of dietary supplements reaching tens of billions of dollars yearly (Geyer *et al.*, 2008), significant public consumption of these over-the-counter AAS can be inferred (Kanayama *et al.*, 2001).

While dietary supplement adulteration with a variety of drugs including controlled androgens, PDE5 inhibitors, and prescription diuretics remains an important problem (Cohen, 2012), a number of bona fide AAS are listed openly on product labels (Cavalcanti *et al.*, 2013). Despite this, many patients and physicians may be unaware that these products contain 'real' anabolic steroids that often come with side effects that are unique from their more thoroughly studied injectable pharmaceutical counterparts. Because of designer steroids, the impact of non-medical AAS exposure on the development of hypogonadism

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and infertility, especially in men of reproductive age, is likely underestimated by current published statistics (Kanayama *et al.*, 2001; Van Thuyne *et al.*, 2006; Brennan *et al.*, 2013; Sagoe *et al.*, 2014). Although there are a paucity of published data regarding the risks of designer steroids, there is a need for increased awareness among physicians regarding the nature and availability of these over-the-counter compounds. While we have previously reported on the complications of well-known anabolic steroids (Rahnema *et al.*, 2014), the purpose of this systematic review of the literature was to introduce and provide an overview of designer steroids, a relatively unknown segment of the anabolic steroid market.

MATERIALS AND METHODS

A comprehensive list of popular designer AAS was obtained from Internet blog postings on www.prohormonedb.com and www.totalflexblog.com. An exhaustive search of the Internet using the three most trafficked search engines in the United States (Google, Yahoo, and Bing) was conducted to identify Internet retailers selling these designer AAS. Search criteria included the names of each designer steroid as well as the terms 'prohormones', 'designer steroids', 'testosterone boosters', and 'legal steroids'. Products met initial inclusion criteria if they were legal for sale in the United States as of April 2014 and their advertised ingredient label included the chemical name of a known designer AAS.

A systematic PubMed search was then conducted from the time periods 1950–2014 using the chemical as well as generic names of the designer AAS identified from the Internet search. In addition, PubMed was searched for key terms, which included 'designer steroids', 'dietary supplements', 'AAS', and 'androgens'. We included specific designer steroids for review if associated literature in peer-reviewed journals existed (Table 1).

RESULTS

Definition

A 'designer steroid' is an AAS synthesized from a known parent steroid and chemically modified with the intent to circumvent controlled substances laws (Van Thuyne *et al.*, 2006; Kazlauskas,

Table 1 Currently unscheduled designer steroids

Generic name	References	Product label name(s)	Summary
Dimethazine	De Ruggieri *et al.* (1963) and Matscher *et al.* (1962)	• 2a,17a-dimethyl-5a-androstan-17b-ol-3,3′-azine • 2a,17a-dimethyl-5a-androstan-17b-ol-3-one-azine	• 17aa oral androgen with high potential for hepatotoxicity • Studied in humans in Italy for its anabolic effects • Chemically detected in dietary supplements
Methylepitiostanol	Okano *et al.* (2009), Kurachi *et al.* (1975) and Ueda *et al.* (1986)	• 2α,3α-epithio-17α-methyl-5α-androstan-17β-ol	• 17aa oral androgen with high potential for hepatotoxicity • Oral version of an androgen/antiestrogen previously used for breast cancer in Japan • Chemically detected in dietary supplements
Methoxygonadiene[a]	Edgren *et al.* (1966) and Buzby *et al.* (1966)	• 13β-ethyl-3-methoxy-gona-2,5(10)-dien-17-one	• Progestin related to levonorgesterel • Effects of oral consumption in humans unknown
Methylclostebol	Lootens *et al.* (2011)	• 4-chloro-17α-methyl-androst-4-en-17β-ol-3-one	• 17aa oral androgen with high potential for hepatotoxicity • Oral version of the pharmaceutical androgen clostebol • Chemically detected in dietary supplements • Minimal data on toxicity
Methylstenbolone[a]	Geldof *et al.* (2014) and Cavalcanti *et al.* (2013)	• 2,17a-dimethyl-17b-hydroxy-5a-androst-1-en-3-one	• 17aa oral androgen with high potential for hepatotoxicity • Oral version of the pharmaceutical androgen stenbolone • Chemically detected in dietary supplements
Mentabolan/Trestione	Campbell *et al.* (1963) and Segaloff (1963)	• 7a-methyl-estra-4-en-3,17-dione • 7a-methyl-19-norandrostenedione	• Closely related to MENT/Trestolone • May convert to MENT/Trestolone • Strong androgen

[a]These designer steroids are specifically listed in the WADA Prohibited List.

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2010; Lootens *et al.*, 2011). Designer steroids share a common mechanism of action with testosterone, acting at the androgen receptor (Diel *et al.*, 2007; Kazlauskas, 2010). Like all androgens, parameters by which designer steroids are characterized differ among compounds – aromatization and 5-alpha reduction are possible for some designer AAS, and all exhibit varying ratios of anabolic to androgenic activity. A vast number of designer steroids exist, many are novel compounds with no associated published research. We review six compounds that are currently sold over the counter or on the Internet and are not scheduled as controlled substances. These compounds are dimethazine, methylclostebol, mentabolan, methoxygonadiene, methylepitiostanol, and methylstenbolone. Table 1 summarizes our knowledge regarding these compounds and their consumption in humans.

Currently popular designer steroids

Dimethazine

'DMZ' was first studied in Italy in the 1960s for its potent anabolic effects employed for a variety of indications including gynecologic malignancy, osteoporosis, fibrocystic dysplasia, tuberculosis, and cachexia in children (Matscher *et al.*, 1962; De Ruggieri *et al.*, 1963). In animal studies, dimethazine was found to have a greater myotrophic effect than methyltestosterone, oxymetholone (Anadrol), and testosterone propionate (Matscher *et al.*, 1962; De Ruggieri *et al.*, 1963). Dimethazine first appeared as a labeled ingredient in dietary supplements in 2008. In 2009 the FDA charged one supplement manufacturer with the sale of unapproved drugs, including dimethazine, resulting in a fine of $125 000 (Criminal Investigations, 2011). In 2013 the FDA issued a press release warning consumers that dimethazine and the controlled AAS methasteron (Superdol) were detected in a vitamin B dietary supplement (Press Announcements, n.d.). Despite these actions, dimethazine continues to appear as a labeled ingredient (2a,17a-dimethyl-5a-androstan-17b-ol-3-one-azine) in dietary supplements and was identified on the label of 17 currently sold products by our Internet search method.

Methylclostebol

Clostebol (4-chloro-17β-hydroxyandrost-4-en-3-one) is the chlorinated derivative of testosterone (17β-hydroxyandrost-4-en-3-one). Clostebol is a Schedule III controlled substance used medically in topical ophthalmologic and dermatologic treatments. A 17-alpha-alkylated version of clostebol (methylclostebol) was determined by chemical analysis to be present in significant amounts in a nutritional supplement (Lootens *et al.*, 2011). We found methylclostebol to be a listed as an ingredient in four currently sold 'dietary supplements'. Common to many designer steroids products, the labeled ingredient (4-chloro-17α-methyl-androst-4-en-17β-ol-3-one) is written in a convoluted and outdated nomenclature, and could be more succinctly described as 4-chloro-17α-methyltestosterone (methylclostebol). As a 4-chlorinated derivative of testosterone, methylclostebol, like clostebol, is not a substrate for aromatase or 5-alpha reductase. Thus, it can be predicted that gynecomastia and virilization would be less common with this compound. Likely owing to its non-virilizing side effect profile, German athletes in the 1960s and 1970s used methylclostebol as an ergogenic, but this oral androgen has never been studied for medical use. In vivo animal assays found oral methylclostebol to be approximately half as anabolic and significantly less androgenic than testosterone (Vida, 1969).

Mentabolan

In the 1960s 7-alpha-alkylated derivatives of nandrolone were synthesized and shown to exhibit increased androgenic activity (Segaloff, 1963). One such compound was 7-alpha-methyl-19-nortestosterone (MENT). MENT, also known as Trestolone, is currently being evaluated as an experimental male contraceptive in studies supported by the Population Council (Nieschlag *et al.*, 2013). A related compound, 7a-methyl-19-nor-androstenedione (mentabolan, trestione) has recently emerged as a designer steroid and was identified as a labeled ingredient in two products from our systematic product search. The similarity in name to MENT (Trestolone) is warranted as 'trestione' is simply the 'dione' version of trestolone, just as androstenedione is to testosterone (Fig. 1). We know from early studies, that mentabolan along with trestolone exhibit increased androgenicity relative to other 19-nor androgens such as nandrolone (Deca Durabolin). Mentabolan by oral administration effectively suppressed gonadotropins while increasing the weight of the ventral prostate, seminal vesicles, and levator ani, more so than nandrolone albeit less so than trestolone or testosterone (Segaloff, 1963).

Methoxygonadiene

In the 1960s and 1970s organic chemist Herchel Smith and colleagues filed a series of patents leading to the development of some of the first synthetic oral contraceptives. One of these early experimental compounds was methoxygonadiene (18-methyl-19-nortestosterone) (Hughes & Smith, 1976). This compound was identified by our systematic search as a labeled ingredient in ten products with the chemical name 13β-ethyl-3-methoxy-gona-2,5(10)-dien-17-one. Related to the levonorgestrel family of progestins, methoxygonadiene is a potent anabolic by injection with an anabolic : androgenic ratio of approximately 54 : 27 vs. testosterone propionate and 90 : 625 vs. 19-nortestosterone (Edgren *et al.*, 1966). However, no data exist regarding the oral activity of methoxygonadiene in humans.

Methylepitiostanol

Commonly known as 'epistane', this compound is the 17-alpha-alkylated version of the known AAS epitiostanol (Fig. 1), an androgen developed in Japan for the treatment of breast cancer (Konishi *et al.*, 1988). Regarded as a steroidal antiestrogen as well as an androgen (Konishi *et al.*, 1988), epitiostanol inhibits the hypothalamic-pituitary-gonadal (HPG) axis (Kurachi *et al.*, 1975) and thus has the potential to cause ASIH (Rahnema *et al.*, 2014). As a 17-alpha-alykylated androgen, there is a potential for hepatotoxicity (Kazlauskas, 2010). Methylepithiostanol has been chemically detected in nutritional supplements and it is suspected that methlyepithiostanol may degrade into the controlled AAS desoxymethyltestosterone (Madol) while in some product containers (Okano *et al.*, 2009). We identified over 30 currently sold products listing methylepitiostanol (2α,3α-epithio-17α-methyl-5α-androstan-17β-ol) as an ingredient on their product label.

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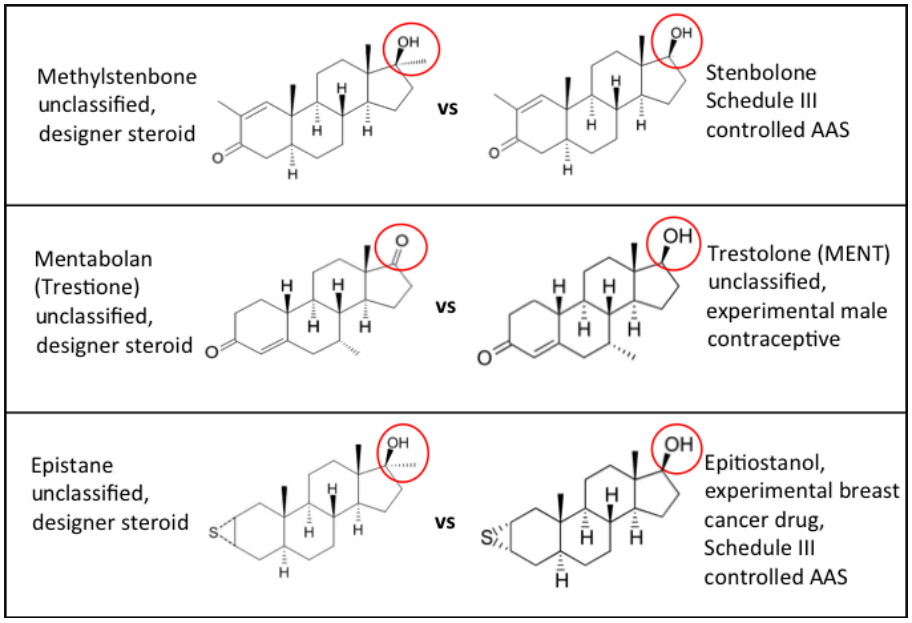
Figure 1 Structural similarities between known androgens and several designer steroids currently available over-the-counter.



Methylstenbolone

Commonly known as 'Ultradrol', this compound appears to be a popular new generation designer steroid and was recently detected in a nutritional supplement (Cavalcanti *et al.*, 2013). Methylstenbolone is the 17-alpha alkylated oral version of the controlled AAS stenbolone (Cavalcanti *et al.*, 2013). Early animal studies report oral methylstenbolone to be 660% as myotrophic and 124% as androgenic as orally administered methyltestosterone (Nutting *et al.*, 1966). Methylstenebolone has never been studied for medical use, however, as an androgen with activity at the HPG axis, it has the potential to cause ASIH and infertility. Our Internet search identified at least 20 distinct, legally sold products listing methylstenbolone (2,17a-dimethyl-17b-hydroxy-5a-androst-1-en-3-one) on their product label.

DISCUSSION

Chemical tricks to evade regulation

Most designer steroids are orally formulated with varying degrees of bioavailability. Some compounds are 17-alpha alkylated to improve the oral bioavailability of injectable pharmaceutical androgens, but this modification increases the toxicity of the androgen (Kazlauskas, 2010). The designer steroid methasteron (Superol) is an example of the hepatotoxicity associated with the consumption of 17-alpha alkylated steroids. This oral AAS, also known as methyldrostanolone, was sold over-the-counter until 2012 and is a methylated (17-alpha alkylated) version of the injectable steroid drostanolone (Masteron). Consumption of methasteron as a dietary supplement for bodybuilding has been reported to cause severe hepatotoxicity, cholestasis, and acute renal failure (Shah *et al.*, 2008; Nasr & Ahmad, 2009; Singh *et al.*, 2009). Chemists may employ methods to deliver potent androgens without technically selling controlled substances by using pro-drugs that are unclassified compounds in the bottle, but in vivo are metabolized to Schedule III Controlled AAS (Van Thuyne *et al.*, 2006; Lootens *et al.*, 2011). For example, compounds such as boldione (banned in 2010) and prostanozolol (banned in 2012) were designed as oral pro-drugs to boldenone (Equipoise) and stanozolol (Winstrol), respectively (Baume *et al.*, 2006; Geyer *et al.*, 2008; Kazlauskas, 2010).

Complications of designer steroid use

About 30% of classic AAS users develop dependence, and the ease of availability of designer steroids could potentially contribute to a dependence disorder (Kanayama *et al.*, 2001, 2009). Many designer steroids or their closely related parent compounds have been studied at some point for therapeutic or research purposes. As exogenous androgens, designer steroids have the potential to cause reversible adverse effects such as hypertension, secondary hypogonadism, infertility, as well as polycythemia and adverse shifts in lipoprotein subfractions. Evidence exists that some designer steroid compounds may cause more permanent adverse effects including hepatotoxicity, cardiotoxicity, and ischemic stroke (Bagatell & Bremner, 1996; Rahnema *et al.*, 2014; Shamloul *et al.*, 2014). The 17-alpha alkylated compounds, which are designed to increase oral bioavailability, may be significantly hepatotoxic (Shah *et al.*, 2008; Nasr & Ahmad, 2009; Singh *et al.*, 2009). In our experience, some patients have reported the use of dietary supplement products branded as 'liver protectors', believing that these products mitigate the hepatotoxicity of the 17-alpha alkylated compounds. These 'liver protectors' typically contain N-acetylcysteine, milk thistle extract, and other herbs, none of which have been demonstrated to have any protective effect against oral androgen induced hepatotoxicity.

Regulatory obstacles

Most designer AAS are analogues of compounds initially developed in the 1960s – early generation synthetic androgens abandoned in the pipeline for better alternatives. Permitting the sale of over-the-counter synthetic androgens was likely not the

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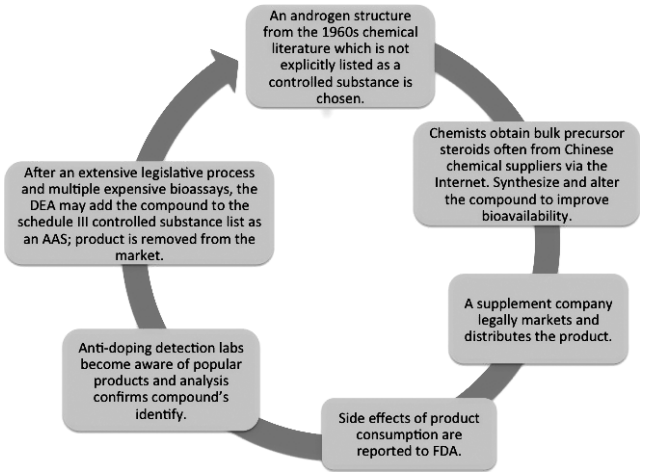
Figure 2 Cyclic process of designer steroid discovery, synthesis, distribution, and regulation.



intent of the Dietary Supplement Health and Education Act of 1994, but because these experimental compounds were discarded early in development, many slipped under the regulatory radar and were not explicitly named in the Anabolic Steroid Control Act of 1990. As such, they remained as uncontrolled substances (DEA rules, 2009). Sources within the sports supplement industry informed us that these products are typically manufactured and sold by smaller scale companies that often disband or change their names when they encounter resistance from regulatory agencies. However, the recent detection of AAS in contaminated vitamin products (Press Announcements, n.d.) suggests the possibility that companies selling non-sports dietary supplements may be affiliated with or may share some manufacturing equipment with these designer steroid companies. Increased media coverage has improved public awareness of AAS in dietary supplements and the FDA has directed warning letters at the manufacturers of some of these products (FDA Warns, n.d.).

Currently, it is economically and technically difficult to classify newer generation designer steroids as DEA Schedule III controlled AAS. The World Anti-Doping Agency prohibits athletes from using any known AAS as well as any unknown related compound (World Anti-Doping Program, 2013). However, to become a DEA Schedule III controlled substance, a designer steroid must undergo multiple bioassays confirming biological activity at the AR regardless of structural similarity to known androgens. The Designer Anabolic Steroid Control act was introduced to the United States Senate in 2012, and proposed preemptive scheduling of all potential anabolic steroids and related compounds, however, this bill was not enacted by the legislature (FDA Law Blog, n.d.). The current regulatory system favors the designer steroid chemist – as fast as the DEA adds substances to the controlled substances list, new compounds emerge in the marketplace to replace the previous generation (Fig. 2). Adding further to this complex regulatory issue, many products may be contaminated with a variety of unlabeled ingredients (Van Thuyne *et al.*, 2006; Lootens *et al.*, 2011). Multiple studies have exposed 'nutraceuticals' containing AAS not included on their product label (Baume *et al.*, 2006; Van Thuyne *et al.*, 2006; Lootens *et al.*, 2011).

CONCLUSION

Over the past decade, potent oral AAS have become more accessible to the public than ever before. The anabolic steroid subculture, something that had been clandestine and typically limited to elite athletes and hardcore bodybuilders for over 30 years (Rahnema *et al.*, 2014), is now readily available over-the-counter. It is paramount for physicians to understand the widespread availability of these potentially harmful substances when evaluating patients for a variety of conditions from hypogonadism and infertility to acute hepatotoxicity. It should be noted that adverse effects reported from designer steroid use do not necessarily occur with clinical use of medical testosterone owing to differences such as route of administration, standardized dosing, and physician supervision. Most physicians are unfamiliar with specific androgens that may be available in dietary supplements, and we have highlighted six of the most popular, currently available, and legally sold compounds. Further research is needed to accurately estimate the prevalence of use of designer steroids, but their persistent availability over-the-counter for more than 10 years suggests the potential for significant exposure (Kanayama *et al.*, 2001). Patients should be advised against the use of dietary supplements known or suspected to contain designer steroids owing to reported adverse effects, theoretical effects of exogenous synthetic androgens, and an inability to accurately determine product contents, doses, and purity. Determining whether specific products contain AAS is difficult without chemical analysis (Geyer *et al.*, 2008), especially as there is no guarantee of label accuracy and the chemical names listed on product labels often do not follow modern conventional nomenclature. Owing to such a high prevalence of intentional and accidental contamination of bodybuilding and sports supplements reaching the consumer the question arises if the legality of labeled ingredients even matters (Cohen, 2012), prompting a broader concern with good manufacturing practice (GMP) and the FDA regulation of dietary supplements in general.

DISCLOSURES

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors contributed to writing and preparation of the manuscript.

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