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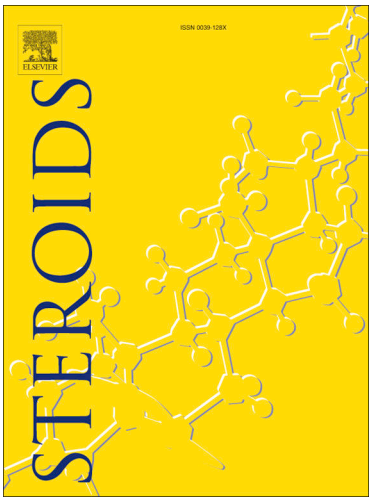

Considerations, Possible Contraindications, and Potential Mechanisms for Deleterious Effect in Recreational and Athletic Use of Selective Androgen Receptor Modulators (SARMs) in Lieu of Anabolic Androgenic Steroids: A Narrative Review

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ABSTRACT

Anabolic androgenic steroids (AAS) are testosterone and testosterone-derivative compounds sporadically employed by athletes and increasingly used recreationally to acquire a competitive edge or improve body composition. Nevertheless, users are subject to undesired side effects majorly associated with tissue-specific androgen receptor (AR) binding-mediated actions. More recently, selective AR modulators (SARMs) have gained popularity towards delivering androgen-associated anabolic actions with hopes of minimal androgenic effects. While several SARMs are in preclinical and clinical phases intended for demographics subject to hypogonadism, muscle wasting, and osteoporosis, several athletic organizations and drug testing affiliates have realized the increasingly widespread use of SARMs amongst competitors and have subsequently banned their use. Furthermore, recreational users are haphazardly acquiring these compounds from the internet and consuming doses several times greater than empirically reported. Unfortunately, online sources are rife with potential contamination, despite a prevailing public opinion suggesting SARMs are innocuous AAS alternatives. Considering each agent has a broad range of supporting evidence in both human and non-human models, it is important to comprehensively evaluate the current literature on commercially available SARMs to gain better understanding of their efficacy and if they can truly be considered a safer AAS alternative. Therefore, the purpose of this review is to discuss the current evidence regarding AAS and SARM mechanisms of action, demonstrate the efficacy of several prominent SARMs in a variety of scientific trials, and theorize on the wide-ranging contraindications and potential deleterious effects, as well as potential future directions regarding acute and chronic SARM use across a broad range of demographics.

Keywords:
Selective androgen receptor modulator, anabolic androgenic steroids, drug testing, skeletal muscle; selective estrogen receptor modulator; hypogonadism

INTRODUCTION

The abuse of anabolic substances for performance persists as a prominent issue in athletic demographics [1]. Individuals have historically utilized anabolic androgenic steroids (AAS) in an attempt to enhance their exercise training performance outcomes and subsequent recovery [2, 3]. Since the initial speculation of Soviet Doping in the 1952 Olympic games and the subsequent synthesis of methandrostenalone, several AAS ([which are typically classic androgens such as testosterone, dihydrotestosterone (DHT), and 19-nortestosterone [structurally identical to testosterone with the 19th carbon removed]) derivatives have been developed [4]. With varying effects, elimination half-lives, and contraindications, all androgens have history of abuse when used with the intent of improving strength and body composition [4, 5]. The clear competitive advantage these anabolic compounds infer led to the creation of stringent regulations enforced by entities such as the International Olympic Committee (IOC) and the World Anti-Doping Agency (WADA), ultimately becoming amended into the Controlled Substances Act in 1990 as schedule III substances [4]. Interestingly, most who use AAS are not competitors, but recreational users who desire an improved aesthetic/muscular appearance [5, 6]. The internet is the most common source for procuring AAS and ancillary drugs, whereby suppliers will typically bundle packages that include combinations of testosterone, synthetic androgens, and colloquially denoted post-cycle therapy (PCT) compounds [5]. Unfortunately, illegal and unregulated abuse of AAS can lead to several unwanted side effects in males. Testicular atrophy, fluid retention, breast pain, gynecomastia, oily skin, and alopecia are typical androgenic-related side effects, but some also experience mood disturbances including depressive symptoms, lethargy, insomnia, and decreased libido [5, 6]. Furthermore, prolonged use can result in hepatotoxicity, as well as damage to the cardiovascular, renal, immunologic, and hematological systems [7-15]. While males have been reported to abuse AAS two-to-three times greater than females, use it not precluded from either sex [6]. Females may experience masculinization with clitoral hypertrophy, hair growth (hirsutism), decreased breast size, menstrual irregularities, widening of the upper torso, and voice deepening, as well as symptoms related to hypomania and depression [4, 16, 17]. The majority of side effects (i.e. reduced sperm production, impotence, testicular atrophy, etc.) in males resolve after cessation; however, many of the adverse changes in women may be irreversible. Chronic use may further result in cardiovascular disease incidence via alterations in hematological parameters related to erythropoiesis, endothelial function, and/or serum lipid profiles, as well as an associated risk in males with prostate cancer [6, 18-20]. Supraphysiological doses of androgens are, therefore, clearly dose-limiting, whereby their positive impacts on physical function are curtailed by substantial adverse risk [21].

The plethora of AAS-mediated side effects have been the impetus to discover androgens that have beneficial anabolic activity with reduced or substantially limited androgenic activity [4, 21]. Pharmaceutical companies have made great strides in the development of metabolic agents that demonstrate anabolic activity in skeletal muscle and bone, whilst lacking cross-reactivity with other steroid receptors, and are not substrates for eit[22]her 5α-reductase nor aromatase (thereby lacking conversion to DHT and estradiol, respectively) [23, 24]. One of the prominent leading compound categories are selective androgen receptor modulators (SARMs) [21]. These agents were developed as more favorable alternatives to AAS, with comparable androgen receptor (AR) affinity and minimal androgenic impacts [25, 26]. Many SARMs exist as non-steroidal compounds (quinolones, tetrahydroquinolones, tricyclics, bridged tricyclics, aryl propionamides, aniline, diaryl aniline, bicylclic hydantoins, benzimidazole, imidazolopyrazole, indole, and pyrazoline derivatives), which in-part mediate their unique effects [4, 21]. SARMs are being clinically investigated for their roles outside of performance, positioned for treatment of hypogonadism, osteoporosis, cancer cachexia, and aging-related decrements in strength and/or muscle function (i.e. sarcopenia or pre-sarcopenia) [21, 27-29]. Furthermore, recent clinical trials have further demonstrated potential SARM-mediated tumor growth suppression, whereby select compounds in clinical and pre-clinical trials positively modulate breast cancer cells via tissue-specific AR [22, 30-32]. In brief, a multiplicity of SARM compounds have been developed for their potential role in ameliorating the aforementioned pathologies, and several investigations have demonstrated mechanistic efficacy in their ability to selectively act in anabolic fashion (improved skeletal muscle size and function, as well as attenuate bone decrements) via AR modulation, all whilst having minimal androgenic effects (action in prostate, seminal vesicles, testes, and accessory tissues) [21, 25, 33-35]. These compounds potentially act via tissue-specific distribution, interactions with enzymatic conversion of testosterone, differential AR structure modulation, and/or selective coregulator protein recruitment [25, 34, 36]. Unfortunately, the attractive aspects of SARMs have also garnered attention as a novel recreational performance enhancing compounds [27]. In 2008, WADA banned SARMs in absolute due to their inherent abuse risk and the then-present detection of various SARM metabolites in athlete urine samples in 2010 [26, 33, 37]. Consequently, SARM misuse has steadily increased over the last decade, whereby nearly 40 cases were reported via WADA doping control sample analysis in 2016 [38]. Similar to AAS and other ancillary performance enhancing substances, SARM providers are commonly found on the internet and small laboratories both within and outside the US are able to synthesize these compounds for global distribution [26, 27].

Notwithstanding the several investigations and comprehensive reviews existing to illustrate both the efficacy of SARMs as promising clinical agents, as well as the contraindications for AAS use in recreational and competitive athletes, there is a dearth of evidence reporting on chronic use of the former

[24]. There is also a stark paucity of any literature evaluating the potentially very serious implications of SARM abuse in otherwise healthy recreational and competitive demographics. Therefore, the purpose of this narrative review is to *1)* discuss the current evidence regarding AAS and (postulated) SARM mechanisms of action, *2)* demonstrate the efficacy of several prominent SARM compounds in a variety of scientific trials, as well as *3)* theorize on the wide-ranging contraindications and potential deleterious effects, as well as potential future directions regarding acute and chronic SARM use for a full breadth of subject demographics.

LITERATURE SEARCH METHOD

The primary databases used during our literature search included PubMed and Google Scholar from 2000 until May 2020. We formatted our search strategy terms describing the efficacy and mechanisms of action in AAS, SARMs, and ancillary compounds (i.e. growth hormone, stimulants, etc.), as well as for compounds that encapsulate typical post-cycle therapy protocols. Specifically, general terms for mechanisms included “androgen”, “androgen receptor”, “estradiol”, “estrogen receptor”, “luteinizing hormone”, “follicle stimulating hormone”, “gonadotropins”, “hypothalamic-pituitary-gonadal axis”, and “hypothalamic-pituitary-ovarian axis”. Furthermore, we included the general terms “anabolic androgenic steroids”, “testosterone”, “dihydrotestosterone”, “selective androgen receptor modulators”, “growth hormone”, “selective estrogen receptor modulators”, “aromatase inhibitors”, “human chorionic gonadotropin”, as well as compound specific terms for other commonly used compounds, including “enobosarm”, “ostarine”, “YK11”, “ligandrol”, “LGD-4033”, “cardarine”, “GW-50156”, “stenabolic”, “SR9009”, “tamoxifen”, “clomiphene”, and “bazedoxifene”.

THE ANDROGEN RECEPTOR

Androgen Receptor Structure, Androgens, and Ligand Binding Mechanisms

The AR is a 110-kDa receptor belonging to a superfamily of nuclear transcription factors found in nearly all tissues [4, 36]. Specifically, skeletal muscle AR content also depends on factors such as fiber type and contractile activity [4]. The four functional domains of the AR are the NH_2-terminal transactivation domain (A/B domain), the DNA-binding domain (DBD), the ligand-binding domain (LBD), and the hinge region that links the DBD and LBD [36, 39]. Furthermore, the NH_2-terminal transactivation domain (activation function 1 [AF-1]) functions in a ligand-independent manner to create a constitutively active receptor facilitating transactivation, and the ligand-dependent carboxy-terminal

transactivation domain (activation function 2 [AF-2]) located in the LBD is essential for activation of ligand binding [36, 39, 40]. The LBD forms a ligand-binding pocket and mediates the interaction between AR and heat shock proteins (HSP). HSP90, HSP70, HSP40, and HSP70 and 90 organizing protein (HOP) maintain the AR function in a stable, inactive, and soluble state within the cytoplasm in preparation for ligand-binding [41]. Additionally, the hinge region contains a ligand-dependent bipartite nuclear localization signal (NLS) that has previously been shown to interact with importin protein, ultimately mediating nuclear trafficking. As previously mentioned, classical endogenous androgens that serve as AR ligands include testosterone, DHT, and 19-nortestosterone. The signal for androgen production begins with gonadotropin releasing hormone (GnRH) via hypothalamic secretion, resulting in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary [42]. Subsequently, LH stimulates the Leydig cells of the testes in men to produce testosterone and facilitates intratesticular insulin-like growth factor (IGF-1) levels, promoting LH receptor upregulation, steroidogenesis, and maturation. Female activity of the hypothalamic-pituitary-ovarian (HPO) axis functions similarly, but with phasic characteristics associated with menstrual cycle phases [43].

Less than 40% of testosterone travels bound to albumin, while the remaining is bound to sex-hormone binding globulin (SHBG) and a small percentage (0.5-2.5%) circulating unbound (i.e. free). Interestingly, SHBG-bound testosterone may also dissociate in organs such as skeletal muscle, liver, and brain to become biologically active [4]. Testosterone and its synthetic derivatives are steroidal, lipophilic hormones and thus typically enter the cell and bind to their indwelling receptor [4]. Testosterone may also convert to DHT via enzymatic action of 5α-reductase in prostate and skin, or converted by aromatase (ubiquitous NADPH cytochrome P450 19A1) to estradiol in adipose tissue, bone, and in the central nervous system [44-47]. DHT is the predominant androgen in prostate, whereas testosterone enacts primarily in skeletal muscle and bone. Despite similar AR-androgen bound structures between testosterone and DHT, the latter is a much more potent androgen with substantial affinity in the prostate [25]. When bound, AR normally dimerizes and becomes transactivated as an active DNA-binding complex, translocating into the nucleus to bind to inverted repeat DNA androgen response elements (ARE) on AR-regulated genes [7, 48]. Additionally, ligand binding facilitates AR release from the HSP complex and phosphor-activates HSP27 for HSP90 replacement to further encourage nuclear translocation [49]. These events ultimately lead to increased AR-responsive gene transcription and subsequent protein translation [4]. Full AR activation requires the physical interaction between the AF-1 and AF-2 domains, denoted the N/C interaction; this interaction has been demonstrated as essential for AR-dependent gene regulation and activation, cofactor recruitment, and chromatin binding [40]. With special regards to exercise performance, the interaction between the AR-activated DNA-binding complex and ARE is pivotal for controlling rates of muscle protein synthesis of contractile and non-contractile

proteins [50]. It is worth noting that while commonly forming homodimers, AR has also been known to form unliganded heterodimers with receptors including the estrogen receptor (ER), glucocorticoid receptor, and the testicular orphan receptor 4 to reduce receptor transactivation in response to ligand concentrations [36, 51-53]. Steroid receptors can also interact with other DNA-binding proteins to result in altered steroid receptor transcriptional activity [36, 54-57]. Consequently, androgen-AR binding additionally promotes enhanced receptor stability, increasing its half-life from one to six hours [4].

Testosterone's structure is described as a 19-carbon steroid with an oxo group at position 3, a hydroxyl group at position 17, and a double bond at position 4; it is composed of 3 cyclohexane rings and 1 cyclopentane ring with methyl groups at positions 10 and 13 [4]. Testosterone disassociates three times faster than DHT or synthetic androgen from the AR, and therefore has a reduced ability to stabilize the androgen-receptor complex unless administered exogenously in larger doses [4]. Afterwards, the AR is subsequently dissociated from its ligand and recycled from the nucleus to the cytoplasm [4]. Ultimate receptor (cytoplasmic or nucleoplasmic) degradation via the proteasomal system is facilitated by HSP70 as a chaperone necessary for E3 ubiquitin ligase recruitment, which is thought as resulting from a reduction in same-receptor transactivational activity after up to four rounds of transcription [41, 58]. With specific regard to testosterone's 5-7-hour half-life *in vivo*, efforts have been made to synthesize testosterone with the intent of altering chemical structure to enhance its bioavailability, convenience of use, and to manipulate desired effects [4, 59]. For example, common substitutes include 17α-alkyl substitutions, making it less susceptible to first pass metabolism and greatly extending its half-life. While this change also makes the compound orally ingestible, it has substantial hepatotoxic impacts (hepatocellular hyperplasia and hepatic damage as per increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase, etc.) and greatly reduces serum high density lipoprotein (HDL) cholesterol levels [60]. Conversely, esterifying testosterone at the 17ß-hydroxyl group increases hydrophobicity and can extend drug action when injected intramuscularly via an oil suspension (i.e. testosterone propionate, enanthate, and cypionate) [4, 21]. Further compounds may also derive themselves from either DHT or 19-nortestosterone, eliciting potential for reduced aromatization (thus maximizing androgenic and minimizing estrogenic activity) and potentially augmenting structural stability to thereby bolster AR-binding affinity [4]. Hoffman et al. [4] details several other common testosterone derivatives, their unique structural changes, and their commensurately differential effects.

Several AR structural characteristics relate to its functionality to interact with coregulatory proteins. Upon ligand binding, conformational changes in AR occur that potentially alter receptor surface topology and interactions with proteins such as coregulators [21]. These proteins are defined by their general ability to interact with nuclear receptors to either enhance or suppress transactivation. Compared

to relatively few corepressors, approximately 300 coactivators have been identified that interact with AR [4]. Incidentally, there are two categories of coregulators: type I and type II. The former functions primarily at the target gene promoter to facilitate DNA occupancy, chromatin remodeling, and the recruitment of general transcription factors (GTFs). Examples include cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) and the transcription factor restricted TATA-binding protein (TBP)- associated factors. Specifically, TBP has been shown to bend DNA to essentially close upstream TATA element sequence distances in relation to GTFs or DNA-binding complexes [36]. Conversely, type II coregulators enable nuclear competency to direct target gene expression via modulating bound AR and ligand folding, along with affecting receptor stability or facilitating the N/C interaction to promote AR transcriptional activity [36]. Following AR-DNA binding, these coactivators facilitate transcription in a tissue-dependent manner, with different cell types expressing differential coregulatory proteins [34]. While the AF-1 region is only implicated in transactivational activity in AR lacking LBD, it may function to recruit coactivators and/or GTFs [36]. Furthermore, the AF-1 region may also make coactivator association possible as an interaction surface. The AF-2 region reacts to ligand binding, causing both it and helix 12 to fold back across the ligand binding pocket. The broad nuances in AR-ligand binding and the consequences of protein-protein interactions between the active complex and the DNA response elements have ultimately led to conception of compounds that manipulate these events.

Impact of Selective Androgen Receptor Modulator Mechanisms

Historically, nonsteroidal AR antagonists (i.e. anti-androgens), include bicultamide, flutamide, and nilutamide. These compounds bind to the AR whilst preventing androgenic action as an important characteristic in prostate cancer treatment [25]. The obvious caveat is that these compounds are unable to generate the beneficial anabolic effects of androgen-AR binding. The auspicious discovery of aryl propionamides, structurally similar to bicultamide and hydroxyflutamide, presented an opportunity to develop a series of substances that could accomplish both anti-androgenic and pro-anabolic effects. Therefore, SARMs were developed as AAS substitutes with aspirations of high AR affinity, favorable bioavailability, oral transmission, and –most importantly– tissue specificity [25, 26]. Unlike androgen-derived compounds, SARMs exist in several classes that have unprecedented potential for biochemical modifications as preferential alternatives. These classes include steroidal SARMs via chemical modification of testosterone, as well as non-steroidal quinolones, tetrahydroquinolones, tricyclics, bridged tricyclics, aryl propionamides, aniline, diaryl aniline, bicylclic hydantoins, benzimidazole, imidazolopyrazole, indole, and pyrazoline derivatives [4, 21]. Although most SARMs are being investigated *in vitro* and within rodent model preclinical research, a select few first-generation

compounds are in phase I trials as promising treatments for hypogonadism, frailty, cancer cachexia, and aging-mediated detriments in skeletal muscle and/or bone [21, 29]. Unfortunately, while many promising SARMs exist, there is no consensus on their mechanisms of action or clear distinctions between their individual, unique effects.

Juxtaposed to traditional AAS use, SARMS are postulated to elicit anabolic effects without undesirable androgenic outcomes via several potential avenues. These potential mechanisms have been that these ligands are uniquely distributed in different tissues, have tissue-specific interactions with 5α-reductase activity and/or aromatase, or elicit non-genomic molecular actions [25]. Gao & Dalton [25] contend that abrogating the effect of 5α-reductase is a likely mechanism for SARMs' minimal androgenic effects, referencing research that demonstrates inhibition via finasteride relegates the role of "primary androgen" in prostate tissue to testosterone [61]. Others hypothesize the way SARMs bind to the AR is what primarily enhances or represses their effect relative to conventional AAS (see Figure 1). While DHT maximally activates the full gamut of androgen-responsive genes, SARMs may act between the spectrum of full agonist to maximal antagonist. It is possible SARMs modify AR structure differently than traditional androgens, specifically at the N/C interaction site or via tissue-specific coactivator/corepressor recruitment to the AR transcription complex [34]. Altered SARM ligand-AR binding may result in tissue-specific gene regulation mediated by reduced N/C interaction, whereby previous *in vitro* investigations have demonstrated SARM-mediated, androgen-independent AR activation without NH_2 and carboxy terminal interplay [21, 62]. Specifically, previous *in vitro* investigations have determined that SARMs, enobosarm and YK11, activate the AR whilst simultaneously blocking the N/C interaction that is necessary for full agonist function [63, 64]. Considering that the AR has two separate NH_2 terminals that interact with different coregulators, differential recruitment of coactivators and corepressors may mediate SARM effects as well [36]. Furthermore, selective coregulator recruitment may also impact the AR DBD and its ability to recognize specific DNA sequences [36].

[Figure 1 about here]

EXISTING EVIDENCE ON SARM COMPOUNDS

A multiplicity of SARMs have been used for clinical and pre-clinical purposes (see Table 1). Nevertheless, this review will primarily focus on generalizing the findings of the more empirically supported compounds that have gained significant traction amongst recreationally active demographics (i.e. those using SARMs or substances labeled as such for aesthetic and/or performance enhancement) [26, 27, 40]. In parallel to AAS, several compounds that do not act on the AR are also typically marketed

and sold under the SARM "moniker". These compounds include (but are not limited to) the growth hormone (GH) secretagogue, MK-677, the peroxisome proliferator-activated receptor ß/δ (PPARß/δ) agonist, GW501516, and the nuclear receptor reversed-viral erythroblasts (REV-ERB) agonist, SR9009. Therein also lies the potential for "stacking" regimens, whereby users will commonly compile the use of several compounds; this practice is common in AAS users as well, where larger AAS doses (~500-1500mg combined) are concurrently administered with GH, IGF-1, insulin, and stimulants (i.e. high-dose caffeine, amphetamine and ß-adrenergic agonists [ephedrine/ephedra and clenbuterol]) to maximize muscle gain and fat loss [4, 5, 42]. Nevertheless, the use of these relatively new, non-SARM ancillary compounds are beyond the scope of the current review. As previously stated, the SARMs described in detail below are not created equal and thus have varying potential to act along the anabolic *and* androgenic spectrum.

GTx-024/ Enobosarm/ MK-2866/ Ostarine

GTx-024, commonly denoted in the literature as enobosarm, is currently one of the leading SARMs for future clinical application [21]. Similar to other SARMs, it is orally bioavailable and nonsteroidal, demonstrating increased muscle mass and bone density, as well as minimal androgenic side effects in the prostate and testes in male rodents [23]. It also demonstrates a favorably extended 24-hour half-life, relative to its predecessor S-4 (4-hours; discussed in detail below) [24, 66]. Dubois et al. [67] utilized a satellite cell AR knockout rodent model to illustrate enobosarm enacts anabolic effects both via AR and AR-independent action, similar to androgens. Following orchiectomy, the effect of DHT and enobosarm were compared against a sham operation for two weeks. Surprisingly, enobosarm reversed decrements in levator ani size, as well as *adenosyl methionine decarboxylase 1* (*Amd1)* and *myostatin* expression levels (both genes are strongly regulated in skeletal muscle) [67]. In an subsequent phase II 86-day trial in healthy elderly men and postmenopausal women administered (0.1, 0.3, 1.0, and 3.0mg/day enobosarm), Dalton et al. [23] demonstrated dose-dependent increases in total lean body mass and commensurate decreases in total fat mass with the highest dose (3mg/day) compared with placebo. Additionally, the 3mg/day group saw decreased blood glucose and a statistically significant improvement in functional stair climb power versus the placebo group. Both the 1.0mg/day and 3.0mg/day groups saw improved insulin resistance and decreased serum triglycerides (TAG), along with reductions in total cholesterol [23]. The same group reported similar findings in a prior phase I trial, where enobosarm facilitated an increase in lean mass without adverse effect in skin or prostate amongst 48 healthy young-to-middle aged men and 23 elderly men [23]. Of particular interest, enobosarm does not significantly alter low density lipoprotein (LDL) cholesterol, free testosterone, DHT, estradiol, FSH, or LH, but SHBG was

reduced in the 3mg/day group, along with both HDL and total testosterone in the 1.0mg/day and 3.0mg/day groups. Also in this study, the postmenopausal women only experienced decreases in LH and FSH in the 3mg/day group, as well as reductions in SHBG with the 1mg/day and 3mg/day group. Finally, it is worth noting small but significant increases in hemoglobin and hematocrit, coupled with a transient elevation in ALT in eight subjects [23].

A recently more novel potential enobosarm use exists in the realm of urinary incontinence, which denotes involuntary bladder urine leakage amongst women commonly with decreased pelvic muscle strength [68]. This phenomenon has been associated with various surgeries, aging, childbirth, menopause, and pregnancy, but has become increasingly well detailed in a multiplicity of female athletic demographics [68-72]. Female athletes specifically have a 177% higher risk of urinary incontinence relative to sedentary women [72]. Incidentally, the pelvic floor muscles contain high levels of AR, and thus are a relevant target for SARM therapy [64, 73]. Ponnusamy et al. [64] employed enobosarm and a structurally similar compound, GTx-027, in ovariectomized (OVX) and sham operated female rodents using doses of 0 (vehicle control), 0.5, 2.5, or 5g daily for 28 days. While they did not observe any discernable bodyweight differences between treatments and control, there were seemingly dose-dependent increases in coccygeus and more modest gains in pubococcygeus (pelvic floor) muscles. Furthermore, treatment with 0.5g of either SARM demonstrated attenuations in myostatin (negative modulator of skeletal muscle mass) and MAFbx/atrogin-1 (implicated in protein catabolism) that statistically resembled the sham condition [64]. An additional phase II clinical trial employing (1 or 3mg/day) enobosarm for 12 weeks in postmenopausal women aimed to assess potentially differential urinary incontinence frequency; however, this investigation has since failed to meet their primary goal of reducing episodes/day by 50% relative to placebo [74]. Despite ostensibly mixed findings, this area of the literature is continuing to develop and thus further research is reasonably warranted before definitive claims can be made.

LGD-4033/ Ligandrol

LGD-4033 is a nonsteroidal SARM with a pyrrolidinyl-benzonitrile core structure that binds to the AR with high affinity and selectivity, demonstrating anabolic activity in muscle and bone without noteworthy action in the prostate [75, 76]. Furthermore, this particular SARM has an appreciable half-life of 24-36 hours. Basaria et al. [75] used doses of 0.1, 0.3, and 1.0g administered to healthy men aged 21-50 years for 21 days. Despite a three-fold increase in serum LGD-4033 concentrations, subjects saw no significant increases in strength (one rep maximum leg press and 12-step stair climb test) relative to placebo; however, there were dose-dependent increase in lean body mass (LBM). Total and LDL

cholesterol did not change, whereas TAG decreased. Subjects in all dosing protocols saw dose-dependent suppression of SHBG following 21 days of administration. The highest dosed group (1.0mg/day group) saw suppressed free testosterone and FSH, as opposed to unchanged LH. Nevertheless, all reduced blood markers returned to baseline 35 days following LGD-4033 cessation [75].

RAD140/ Testalone

RAD140 was developed as a promising candidate among several analogues in efforts for preclinical testing. Designers found this compound had excellent AR affinity, demonstrating maintenance of the levator ani muscle in castrated rodents at a dose as low as 0.03mg/kg, reaching effects similar to sham operated controls at 0.3mg/kg [77]. Furthermore, RAD140 had consistent tissue selectivity, failing to stimulate prostate or seminal vesicles at any given dose. In a subsequent examination, investigators evaluated the effects of RAD140 in intact male rats, administering multiple doses (0.1, 0.3. 1.0, 3.0, 10.0. and 30.0mg/kg) alongside a vehicle control and 0.5mg/kg testosterone propionate for 11 days. The SARM increased levator ani muscle above intact control with the lowest dose of 0.1mg/kg, notably without stimulating prostate until the highest dose of 30.0mg/kg. Furthermore, the same group investigated the effects of RAD140 on lean and fat mass in intact primates (cynomolgous monkeys) given three doses (0.01, 0.1, and 1.0mg/kg) for 29 days [77]. Although fat mass was not discernably altered, the authors note a qualitative (but not significant) effect on increasing LBM as per dual energy x-ray absorptiometry (DEXA). Serum testosterone was suppressed in all three groups to nearly half of the original baseline values, with consistent, seemingly dose-dependent decreases in TAG, LDL (except 0.01mg/kg group, which saw an 8% increase), and HDL. Liver enzymes were minimally affected at any dose, demonstrating favorable liver tolerance.

Separately, Jayaraman et al. [78] examined the effects of RAD140 for potential neuroprotective effects. Androgens plays a unique role in neuropathy, whereby they facilitate the reduction of deleterious ß-amyloid (ßA) plaques, promote synapse formation and neurogenesis, upregulating brain derived neurotropic factor, as well as sustaining neuron survival. Androgens upregulate the expression of ßA-degrading neprilysin [33]. Episodic memory, working memory, processing speed, visual spatial processing, and executive function are also modulated by AR binding. Incidentally, RAD140 (and related RAD192) displayed neuroprotective effects similar to both testosterone and DHT in cultured rat hippocampal structures against exposures to ßA and apoptosis activator II [78]. It is worth noting that the minimum effective concentration for RAD140 was greater than that of androgens (30nM vs 10nM) and that no treatment protected against hydrogen peroxide exposure. Jayaraman et al. [78] further investigated the effects *in vivo* rodents administered 1mg/kg RAD140 for two weeks, displaying increased levator ani

muscle size akin to sham-castrated and testosterone-administered-castrated rodents. Furthermore, the SARM was equally as protective as testosterone in protecting rodents from neurotoxic kainite-mediated neuron loss [78, 79]. Overall, it appears that RAD140 represents a promising candidate to not only protect against clinically- and age-related neuropathy, but perhaps as an attractive SARM for athletes suffering from traumatic brain injuries and/or chronic traumatic encephalopathy [80].

S-4/ Andarine

S-4 is a model aryl propionamide SARM with no cross-reactivity between other steroid receptors [81]. Yin et al. [82] demonstrated in rodent models that S-4 managed AR-mediated transcription to 93% that of 1.0nM DHT, as well as causing dose-dependent stimulations of the levator ani muscle with as little as 0.3mg/kg after 14 days. As opposed to several other compounds tested for potential clinical efficacy in this investigation, S-4 was the most successful at sustaining muscle size in castrated animals relative to intact control. S-4 did display androgenic stimulation in prostate and seminal vesicles; however, at a fraction of the intact rodents [82]. In line with the selective effects of SARMs, S-4 not only augments skeletal muscle size and strength, but also demonstrates favorable effects on bone turnover relative to DHT [82, 83]. Nevertheless, there may be a ceiling to effective dosing, whereby the anabolic effects are maximized at lower doses (up to 3mg/kg) with dose-dependent androgenic actions at higher quantities [83]. A later investigation led by Kearbey et al. [81] utilized 120 OVX and sham operated female rodents given a wide range of S-4 doses (0.1, 0.3, 0.5, 0.75, 1.0, 3.0mg/kg), examining body composition via DEXA. They discovered an S-4-mediated dose-dependent decrease in fat mass, whereby 3.0mg/day was able to match the fat mass of intact controls. S-4 also managed the partial or full prevention of OVX-induced BMD loss in doses higher than 0.1mg/day. Specifically, the 3mg/day completely prevented bone loss (versus 0.5 and 1.0 partial protection), and both the 1.0 and 3.0mg doses enhanced cortical thickness and trabecular BMD greater than intact control [81]. Conversely, DHT treated rodents saw significant decreases. Both S-4 and DHT dose-dependently increased bone marrow cell differentiation toward the osteoblast lineage and decreased the number of multinucleated osteoclasts via receptor activator of nuclear factor kappa-B ligand and granulocyte-macrophage colony-stimulating factor stimulation. Overall, S-4 does not appear to alter serum values for GH, hepatic aminotransferases, or serum lipids. Conversely, S-4 dose-dependently impacts serum gonadotropins. [82, 83]. Administration of S-4 in doses as little as 0.5mg/kg suppress LH with weaker effects on FSH, resulting in significant reductions at 3.0 and 10mg/kg [82, 83]. Appearing to be one of the potentially more HPG-suppressive SARMs, S-4 does seem to have meaningful effects on bone metabolism either uninvestigated or not present in many other internet-available compounds.

S-23

The development of S-23 was the result of the attempted optimization of another novel SARM, C-6. Developers of these compounds discovered that structurally altering the *para*-nitro group on the A-ring to a cyano group greatly modifies the *in vivo* pharmacokinetic properties and efficacy of the compound [84]. Jones et al. [84] dosed 42 male rodents with S-23 (rates of 0.01, 0.05, 0.1, 0.5, 1.0, and 3.0mg/day) and estradiol benzoate at 5µg/day (necessary to maintain sexual behavior) for 14 days to examine its effects on body composition via DEXA, serum gonadotropins, and indices related to a potential hormonal role towards male contraception. The investigation discovered a 2-fold higher binding affinity in relation to the predecessor compound and decreased fat mass relative to sole estradiol benzoate (EB) administered controls, but did not result in reductions in total body weight or BMD. Conversely, when co-administered with EB, S-23 dose-dependently decreased fat mass and increased fat free mass. Levator ani muscle was maintained in castrated rodents at doses between 0.1-0.3mg/kg comparable to intact controls [84]. This ability to augment skeletal muscle mass may be related to the findings of Jones et al. [85], whereby S-23 treatment prevented dexamethasone-mediated blocking of the molecular phosphatidylinositol-3 kinase (PI3K)/Akt cascade and abrogated upregulations in ubiquitin ligases. Furthermore, all SARM doses resulted in significant suppression of LH below the detectible limit, whereas FSH was suppressed at only the 0.5 and 0.75mg/kg doses. Regardless, sexual behavior was maintained in all S-23 doses and all spermatogenesis decrement-mediated reductions in fertility rate were 83% and 100% reversible after 70 and 100 days, respectively [84].

YK11

YK11 is a steroidal SARM that exhibits a 19-nor-steroidal nucleus; however, its unique structural features distinguish it from classical AAS [26]. Using an *in vitro* model, Kanno et al. [40] demonstrated YK11 induces myogenic differentiation of mouse myoblast C2C12 cells similar to DHT. Myosin heavy chain (MHC) protein levels were also similar to DHT after seven days. Incidentally, mRNA expression of Myf5 and myogenin was significantly greater in YK11 relative to DHT treatment following four days incubation; although, higher absolute concentrations of SARM were necessary to elicit the effect compared to DHT [40]. Furthermore, follistatin (modulates transforming growth factor-ß [TGF-ß] family members like myostatin) mRNA (Fst) was significantly elevated by YK11 administration but unaffected by DHT. The investigators further used a combination of the AR antagonist, flutamide, and a follistatin inhibitor to illustrate that the effects of YK11 are mediated through AR binding and that YK11-AR

binding-mediated increases in follistatin are essential to observed upregulations in *Myf5*. These findings contend YK11 as a potential greater inducer of myogenic differentiation than DHT and that mRNA expression variations may be sourced in differential coregulator recruitment [40].

A further *in vitro* investigation demonstrated YK11 also significantly impacts bone metabolism. Yatsu et al. [86] saw comparable osteoblast cell proliferation (mediated by AR), increased alkaline phosphatase activity as a key indicator of early stage osteoblast differentiation, as well as calcium deposition between YK11- and DHT-treated mouse MC3T3-E1 osteoblast cells. Furthermore, osteoprotegerin and osteocalcin mRNA were similarly elevated following 14-days of incubation with either aforementioned treatment. The previously highlighted research would contend YK11 has similar effects to DHT in cell culture, but there are striking differences. Aside from causing partial AR-agonism, YK11 only elicited 10-20% of the activity facilitated via DHT [63]. YK11 incubation augmented FK506-binding protein 51 and fibroblast growth factor 18 mRNA similar to DHT, whereas hydroxysteroid 11-beta dehydrogenase 2 mRNA expression was comparatively reduced and specific androgen-regulated gene induction was completely unobserved [63]. Furthermore, many of these observed effects require higher relative doses of YK11 relative to DHT. It is therefore imperative that the impacts of this SARM's differential modulation of the AR be further investigated beyond anabolic endpoints and in future animal models.

SARM-2f, S-101479, & GSK2881078

Neither SARM-2f, S-101479, nor GSK2881078 are among the list of popularized SARMs for recreational use; however, the limited research on these compounds are useful in gaining a more comprehensive perspective towards global SARM effects. In two separate investigations, Furuya et al. [34, 87] used a combination of *in vitro* human osteoblastic cells and *in vivo* animal models to exhibit similar anabolic bone activity between DHT and S-101479 with reduced side effects in OVX rat uterus and clitoral tissues. Although maximal activity of the SARM was only ~30% of DHT, S-101479 dose-dependently increased bone alkaline phosphatase (ALP) compared with vehicle control [34]. The SARM also dose-dependently (3 and 10mg/kg) enhanced bone strength and BMD similar to DHT (20mg/kg), both relative to sham control [87]. Interestingly, the comparative magnitude of coactivator recruitment between S-101479 and DHT was also examined. While DHT recruited all coactivator proteins, S-101479 only recruited three (out of eleven) in lower area under the curve values [34]. S-101479 specifically recruited gelsolin, androgen receptor-associated protein 54 (ARA54), and prospero homeobox 1 (PROX1), that play roles involved in cell migration/adhesion, androgen receptor interaction, and

development of organ systems, respectively. These data shed particular light on coregulator recruitment dictating the selective anabolic: androgenic ratio amongst varying SARMs.

As a more recent SARM candidate, SARM-2f has demonstrated increased muscle weight, stimulated motor activity, greater food intake, and increased sexual behavior in rodents [65, 88-90]. Morimoto et al. [90] administered three doses of SARM-2f (1.0, 3.0, and 10.0mg/kg) to male and female cynomolgus monkeys for 28 days, analyzing body composition (via DEXA) and several serum parameters. The highest dose (10.0mg/kg) displayed body weight gains lasting up to seven days post-cessation, with significant increases in LBM. Surprisingly, the monkey group administered testosterone enanthate at 2mg/kg did not significantly increase LBM. Blood total cholesterol, LDL, and TAG were reduced at all SARM-2f doses. HDL was only reduced in the two highest doses, and there was no overall change in the HDL:LDL ratio. The authors also make note of an important distinction, suggesting the latency to body weight gain may be increased between species, considering rodents saw significant body weight increases by week two, whereas primates actualized gains in four weeks [65, 90]. Similar to S-101479, Morimoto et al. [65] showed SARM-2f elicited significant differences in coregulator recruitment relative to DHT. Amongst the range evaluated, stark differences were seen amongst the protein inhibitor of activated STAT (PIAS) family molecules (i.e. PIAS1, PIAS3, and PIASγ). These proteins play imperative roles via interacting with transcription factors or other coregulators to modulate downstream gene activity, including those involved in cell proliferation and differentiation, as well as apoptosis and immune function [91]. Because S-101479 and SARM-2f appear to be promising clinical therapies, this may likely garner future attention from recreational users for their positive impacts on skeletal muscle and bone. The impressive bone-associated findings inherent to the former and the minimized impact on blood lipids of the latter may incur the (non-empirically supported) impetus to combine these and other SARM compounds.

Special attention should be paid to GSK2881078, a novel SARM that has reached phase I clinical trials in human populations. Two separate investigations by the same group detailed the pharmacokinetics of this compound in both male and female demographics [15, 20]. Following unpublished data on rodents, this group discovered 0.3mg/kg per day GSK2881078 binds AR with over 100-fold selectivity over several other receptor types and restored levator ani muscle size to that of sham-operated animals without significant increases in prostate weight [29, 92]. Along with a massive range in elimination half-lives of between 131-200 hours and up to 23-fold accumulation ratios after 28 days of administration (combined male and female data), healthy men and postmenopausal women saw significantly greater lean mass accrual via DEXA [93]. Incidentally, there were sex-specific differences in drug metabolism, with more consistently longer times to the final detectable concentration and an apparent increased sensitivity to lean mass accrual in females [92, 93]. Both investigations also provided serum biomarkers to

investigate the impacts of GSK2881078 on varying health parameters; however, discrepancies exist between findings. Clark et al. [92] and Neil et al. [93] consistently found reductions in serum testosterone and concurrent attenuations in SHBG. In both studies, subjects also experienced reductions in HDL cholesterol and apolipoprotein A1. The former investigator [50] saw no significant changes in LDL cholesterol, whereas the latter saw increases of ~30% compared with placebo in the highest dose administered to men (1.5 and 4mg), as well as the two highest in women (0.75 and 1.0mg) [93]. While neither investigation saw significant changes in LH, estradiol, or progesterone, Clark et al. [92] saw decrements in subject FSH relative to the equivocal findings of Neil et al. [93]. Curiously, the former used lower doses and shorter study timeframes. Of further interest, Neil et al. [93] also discovered an attenuation in free testosterone regardless of concomitant reductions in SHBG. The differences between these trials potentially lie in their study designs, whereby Neil et al [93] employed an exclusively older subject population (both sexes aged over 50, relative to Clark et al. [92], who recruited women of similar age but men ranging 18-50). Neil et al. [93] also used a drastically longer administration timeframe (up to 56 days versus ~14 days) and much larger doses (up to 4.0mg [males] and 1.5mg [females], relative to 0.75 [males] and 0.35mg [females]). Overall, some of the more concerning findings between these investigations are the incidence of adverse effects. Although cumulatively, both studies would suggest that GSK2881078 is well tolerated with no detectable impacts on adrenal biomarkers, thyroid hormone-mediated effects, or deleterious cardiovascular changes when administrated between 14 and 56 days. Conversely, Clark et al. [92] denoted a small portion of subjects experiencing respiratory tract infections as well as marked (but reversible after 3-weeks cessation) elevations in creatine phosphokinase and ALT. These adverse effects were deemed to be GSK2881078-unrelated; however, Neil et al. [93] discovered the aforementioned ALT increases were significantly correlated to microRNA-122 (a specific intracellular hepatocellular biomarker) at GSK2881078 doses of 1.5mg (r=.845) in males and 0.75mg (r=.462) in females. ALT tended to increase similarly across all doses and both sexes; however, males given 4mg had significantly greater incidence [93]. Therefore, while GSK2881078 seems to be a promising ideal clinically-based SARM candidate, there are important contraindications to consider regarding higher dosages in extended timeframes. It is apparent that further research is required to comprehensively evaluate the discrepancies existing between trials and confirm the risk for hepatotoxicity.

[Table 1 about here]

SARM CONTRAINDICATIONS & POTENTIAL MECHANISMS FOR DELETERIOUS EFFECT

The development of SARMs as a clinical therapeutic countermeasure against skeletal muscle catabolism and improved body composition has garnered the attention of both recreational users and

competitive athletes [26, 33]. In this light, pharmacological efforts have been made in the attempt to test the purity of substances obtained precariously from internet sources, as well as to determine potential metabolites for future doping assessments [26, 27, 37, 76, 95, 96]. Furthermore, the preponderance of literature available on these compounds is strikingly limited, and now since the FDA has recently prohibited their ability to be commercially manufactured and sold, available research data will likely become even more sparse. Aside from the primary candidates undergoing phase I and II clinical trials, several of the SARMs described in this review have been investigated solely in either *in vitro* or rodent research. Despite labels denoting products as "for research use only" or "not for human consumption" as a ploy to deter FDA scrutiny, individuals continue to purchase SARMs to potentially reap the benefits of AAS without unwanted androgenic effects [27]. Unfortunately, SARMs are also subject to contamination phenomena, similar to AAS [5, 27, 42]. A previous investigation purchased 44 SARM products from various online providers and tested their purity against the claimed dosage using mass spectrometry [27]. Their findings illustrated only slightly over half of the tested products were true SARM compounds. Incidentally, 80% of SARM-containing products contained LGD-4033 and enobosarm despite a total of six (inappropriately labeled) tested compounds [27]. Only 41% contained the advertised compound with the claimed dosage. Shockingly, 25% of the tested products contained different amounts (more or less) than listed, 7% had additional unlisted compounds, and 9% had either tamoxifen (SERM originally developed for breast tissue antagonistic activity) or no active compound at all. Considering SARMs lack FDA approval, consumers risk purchasing inert substances or those with minimal and/or undesired effects.

Several SARMs are advertised and subsequently sold at higher doses than evaluated in the literature. Specifically, compounds such as enobosarm and LGD-4033 are being marketed in doses several fold above what has been demonstrated effective in clinical trials, whereby some are being sold in seemingly arbitrary doses given a complete lack of human investigations [26, 27]. Although previous authors claim SARMs are unable to induce dyslipidemia, the existing literature contests this notion [24]. Similar to AAS, SARMs appear to have various compound-specific impacts on serum lipid and other hematological parameters. Previous reviews have stated the primary biological alterations mediated by SARMs are reductions in HDL and transient hepatic aminotransferase increases [21, 33]. While several SARMs collectively attenuate serum TAG levels (enobosarm, LGD-4033, RAD140, SARM-2f, and GSK2881078), the impacts on total cholesterol, LDL, and HDL are less clear. LGD-4033 appears to equivocally affect total cholesterol and LDL, while enobosarm displays similarly unaffected LDL but reduced cholesterol levels [23, 75]. Alternatively, S-4 administration results in no discernable effects on any serum lipid marker, whereas RAD140 and SARM-2f demonstrate reductions in total cholesterol, LDL, and HDL [77, 82, 90]. The effects of GSK2881078 are less clear with consistent decreases in HDL

cholesterol and apolipoprotein A1, but increases in LDL were only displayed in higher doses amidst a homogenously older subject population [92, 93]. These alterations in serum lipid parameters can be contrasted with AAS, which have been known to markedly increase LDL and decrease HDL (especially in 17α-alkylated androgens) [4, 97]. AAS-induced decrements in lipoprotein metabolism and associated serum lipid abnormalities have been strongly connected to coronary heart disease risk [98]. The mechanism for androgen-mediated changes in in blood lipids is not fully understood, but are potentially related to steroid hormone-mediated lipolytic lipoprotein degradation and subsequent removal via apolipoprotein A1 and B synthesis, as well as induction of hepatic triglyceride lipase activity [97, 99]. Furthermore, upregulations in scavenger receptors may specifically be involved in HDL metabolism and reductions [99]. Therefore, efforts are continually enacted to develop SARMs that can be administered transdermally to minimize impacts on HDL via hepatic AR binding reductions [33]. SARMs generally appear to have minimal risk towards hepatic injury, evidenced by either no change in hepatic aminotransferases or small transient increases that do not homogenously occur across all subjects [23, 33, 90]**.** As far as the authors are aware, the effects of SARM administration of hematological values are not well studied, although Clark et al. [92] failed to find any significant changes in heart rate, tachycardia, or impacts on B-type natriuretic peptide following multiple doses of GSK2881078. Conversely, Dalton et al. [23] observed small, but significant increases in both hemoglobin and hematocrit in humans given higher dosed (3mg/day) enobosarm. While this alteration has not been sufficiently replicated, it is imperative to explore the potential parallels with AAS. Similar to the effects on lipoprotein metabolism, AAS-mediated polycythemia and general hematological changes are not well understood [100]. AAS potentially acts on bone marrow to stimulate erythropoietin, increases in mean corpuscular hemoglobin, erythrocyte sedimentation rate, and general endothelial dysfunction [100]. Long-term AAS use is also associated with increased clotting via platelet count and aggregation [6]. Commonly, AAS abuses correct for polycythemia via phlebotomy, otherwise risking issues associated with left ventricular hypertrophy and potentially associated (often conflated with resistance training adaptation) cardiovascular disease [4, 5]. Overall, considering that SARM administration appears to parallel many of the serum abnormalities characteristic of AAS abuse, concern for cardiovascular health may be warranted and many approaches enacted by AAS users may be relevant and justified for recreational SARM use as well.

Delineating the ability of SARMs to suppress the male hypothalamic-pituitary-gonadal (HPG) axis is also difficult to interpret, with compound- and dose-dependent effects on gonadotropins, free and total testosterone, and SHBG. Data on female SARM administration is unfortunately sparse and very few studies address hormones along the HPO axis. Therefore, it could be considered inappropriate to make conclusions or speculations concerning SARM-mediated impacts beyond those in males. Considering marketed SARMs are sold at either the highest clinically demonstrated dose or amounts several times

higher, the clinically evaluated less-suppressive doses are irrelevant for the present discussion. A commonality between several SARM investigations are reductions in SHBG, which is potentially reflected by unchanged free/unbound testosterone concentrations [23, 75, 92, 93]. Furthermore, discrepancies exist between the effects of SARMs on testosterone and gonadotropin levels (see Figure 2). Enobosarm administered to males results in unchanged serum concentrations of free testosterone, LH, and FSH, whereas the same doses in females reduced both LH and FSH [23]. The higher doses did, however, result in reduced SHBG and total testosterone [23]. Conversely, LGD-4033 suppressed total and free testosterone, whilst only suppressing FSH and not LH. While testosterone indices were not evaluated, investigations illustrated both S-4 and S-23 administration significantly suppress LH, beginning to impact FSH at higher doses [81, 82]. Lastly, GSK2881078 has had confounding data regarding its impact on the HPG axis; doses across the limited available evidence reliably reduce testosterone and SHBG but are inconsistent in their ability to affect gonadotropins and free testosterone [92, 93]. The compound-specific and seemingly selective suppression magnitude of these SARMs on the HPG axis remains persistently unknown. Furthermore, several of the remaining SARM compounds are yet to be examined for their potential suppressive impacts or have been disregarded due to immensely reduced gonadotropin levels. A pertinent example is the hydantoin SARM, BMS-564929. While demonstrating excellent anabolic effects in a selective manner, the compound has limited clinical use due to robust suppressions in LH [25, 34].

[Figure 2 about here]

Increasing age in adult men and women often results in declined natural testosterone production and increased SHBG levels that begin around age 35-40, that may eventually lead to reduced testosterone bioavailability and biochemical hypogonadism (<300ng/dl serum total testosterone in men or <20-25ng/dl in women under or over 50 years of age, respectively) [18, 42, 44, 101]. Hypogonadal symptoms amongst men are commonly characterized by lethargy, erectile dysfunction, reduced libido, and reductions in concentration [102]. Androgen deficiency in females is not well elucidated, but can be described by subtle symptoms affecting libido and general mood to potentially induce depressive symptoms, as well as muscle weakness [101]. Additionally, AAS abusers may experience anabolic steroid-induced hypogonadism. This serious condition typically occurs due to alternations between cycles of supraphysiologically-dosed androgens [5]. Excess exogenous androgen results in negative feedback on the HPG axis, resulting in reduced intratesticular testosterone (ITT), blunted gonadotropin levels, and decreased or complete loss of spermatogenesis [42]. AAS-using women are scarcely characterized in the literature, ultimately meaning little is known about how this demographic subset is affected with regards to hypothalamic-pituitary feedback [103]. Notwithstanding a pattern for more modest relative doses

(absolute and chronic administration) and an average fewer number of compounds used (i.e. less stacking), females still experience significant endocrine-related abnormalities [103-105]. Previous data of nandrolone and oxymetholone administration in varying dosages and patterns amongst ovulating women resulted in significantly shortened menstrual cycles. Specifically, both AAS agents depressed plasma LH and progesterone relative to controls, whereas nandrolone alone also depressed plasma FSH [104, 105]. It appears administration relative to menstrual phase is also relevant, whereby women in the early follicular phase had prolonged cycles and ovulation suppression, but early luteal administration shortened cycle length [104]. It is postulated these effects are due to AAS-mediated anti-gonadotropic actions [105]. Considering the impacts of AAS on FSH in females, it's possible that continued use may impair the HPO axis or reduce available aromatase substrate, ultimately attenuating systemic androgen [43, 101].

Physiologic Concerns of SARM Administration

The major separating characteristic between AAS and SARM administration may be the risk related to chronic reductions in circulating gonadotropins and testosterone levels. Several of the SARMs previously mentioned display dose-dependent actions on testosterone (free, total, or both) and upstream gonadotropins, which is made more concerning due to the availability of these compounds in doses above clinical efficacy [23, 27, 75, 81, 82]. Chronic SARM administration may well selectively activate AR signaling, but potentially at the cost of reduced global testosterone levels that play imperative systemic roles as both androgens and via their aromatization to estradiol [21, 23, 92, 93]. Furthermore, while the adrenal medulla expresses LH receptors and is responsible for a minority of testosterone synthesis, previous research has demonstrated SARMs do not impact adrenal steroidogenesis to any meaningful degree [4, 106, 107]. This indicates the physiological "slack" of SARM-mediated testosterone reductions cannot be rescued by adrenal synthesis [107]. Due to the dearth of literature surrounding female administration of supraphysiological AAS, as well as the incongruities surrounding the significance of testosterone's biologic function in male physiology, this section will focus primarily on the impacts of circulating androgens and estrogens known in males specifically [18]. Lastly, the information presented herein may offer a hitherto unexplored avenue by which SARM administration may deter the systemic physiologic functions of both androgens and estradiol in otherwise normal conditions.

Circulating androgen levels play important systemic roles in males. They are involved in normal spermatogenesis, testicular function, hair growth, nitrogen retention, bone density maintenance, as well as muscle mass accretion and distribution [18]. Additionally, testosterone and DHT impart specific biological functions; testosterone promotes myotube differentiation and hypertrophy and DHT is critical in facial and body hair growth, as well as prostate enlargement [77, 108]. It is widely accepted that

androgens enhance myonuclear accretion, improve both type I and type II skeletal muscle fiber cross-sectional area and may even improve exercise tolerance through increased protein synthesis and/or decreased protein breakdown [109-111]. Testosterone's augmentative association with skeletal muscle size and function is in part due to the positive correlations between satellite cell number and changes in both total and free testosterone, as well as testosterone's impact on upregulating follistatin [21]. Within skeletal muscle, direct stimulation of satellite cells causes proliferation and subsequent differentiation into muscle specific nuclei (myonuclei). Incorporation of myonuclei is essential in modulating cellular transcriptional power, and thus are critical for growth and repair processes [112, 113]. Previous rodent models have demonstrated that AAS-administration not only promotes myonuclear accretion, but also long-term retention [114]. Therefore, these data infer a beneficial effect of AAS beyond the timeframe of cessation. Molecular investigations have also discovered testosterone, in part, mediates skeletal muscle hypertrophy not only via intracellular-AR binding, but in conjunction with mTOR [115]. Demonstrated via inhibitors for the extracellular regulated kinase 1/2 (ERK1/2), PI3K, Akt, and AR, Basualto-Alarcon et al. [115] utilized cultured myotubes to illustrate a potential G protein-coupled receptor (GPCR)/membrane bound AR mediates muscle protein synthesis, but that canonical AR binding is required to achieve global, coordinated hypertrophy. Furthermore, testosterone promotes the differentiation of mesenchymal multipotent cells via AR binding, ultimately facilitating the interaction between AR and ß-catenin to form an active AR-ß-catenin complex. This complex results in the activation of T-cell factor-4 (TCF-4) to modulate several wingless-type MMTV integration site (Wnt)-regulated genes, promoting myogenesis and inhibiting adipogenic differentiation [4]. Wnt ligands function to modulate the proliferation and differentiation of satellite cells via ß-catenin-mediated gene regulation [108]. Androgens play further roles in bone homeostasis via proliferation of osteoblast precursors, stimulating osteoblast differentiation and the direct promotion of osteoclast apoptosis [116]. Furthermore, androgens may indirectly facilitate bone homeostasis via upregulating TGF-ß and IGF-1 to stimulate bone formation, downregulating interleukin-6 and its osteoclastogenic effect, as well as inhibiting the resorptive effects of parathyroid hormone [116]. As previously described in the detailed description of RAD140 administration, testosterone plays an established role in neural homeostasis mediated by AR interaction [78]. Apart from preventing accumulation of neurotoxic ß-amyloid plaques and generally stimulating neurogenesis, it functions to maintain several aspects of cognition [33]. Androgens clearly mediate a multiplicity of physiologic functions amongst several tissues beyond skeletal muscle and bone, implying an equally wide range of negatively impacted systems in their selective absence.

Currently, the only studies which have assessed estradiol following SARM administration are two available pharmacokinetic investigations on GSK281078, which ultimately found significant impairments

in serum testosterone without impacted estradiol [92, 93]. Regardless, little data exist examining SARM administration-mediated effects on estradiol concentrations in any other compound. However, it remains a possibility that chronic use of SARMs may cause concomitant dose-or-compound-specific reductions in circulating testosterone resulting in impaired aromatization to estradiol. While hypothetical, this phenomenon may be an increasingly prevalent risk given the availability of procurable SARMs that currently display attenuated gonadotropin and/or testosterone, but in dosages much higher than empirically supported. Although blood testosterone concentrations are at least two-fold greater than estradiol levels, the latter plays essential roles in growth and non-reproductive tissues [44]. In fact, several of testosterone's physiological functions require its eventual aromatization to estradiol, including impacts on libido, behavior, bone, and plasma lipids [21]. Estradiol acts via binding to ER, which is expressed as either α (ERα) or ß (ERß) isoforms [44]. The ERα is the predominant isoform in males, and the general effects of estradiol and subsequent ER-mediated effects can be demonstrated in deficient demographics. Specifically, older men and more so those lacking aromatase (and therefore sufficient estradiol) display decrements in bone homeostasis (increased bone turnover, osteoporosis/osteopenia, bone pain, and frequent fractures) [44, 45]. Estradiol appears more important for bone growth and maintenance relative to androgens, and is essential for normal mineralization and turnover. Furthermore, aromatase administration fails to compensate for insufficient estradiol, further highlighting the importance of the latter [44]. Estradiol also plays an essential role in energy homeostasis whereby deficient men are hyperinsulinemic and show impaired glucose homeostasis [44]. Estradiol impacts beta cell insulin content, insulin gene expression and release, alongside imparting a protective role against beta cell apoptosis in males [44]. ERα rodent knockout models have apparent lipid metabolism impairments as well, with increased relative adipocyte hyperplasia and hypertrophy, commensurate with suppressed ambulation and enhanced appetite [44, 81]. Administration studies in men demonstrate improvements in skeletal muscle lipid metabolism, potentially due to upregulations in mitochondrial gene expression and concomitant lipid oxidation [18]. Estradiol plays a unique role in skeletal muscle metabolism and general oxidative stress. Simultaneous age-induced reductions in both androgens *and* estradiol mediate losses in strength, muscle size, and muscle function [18]. Collins et al. [117] utilized OVX rodents and peri-to-post menopausal women to demonstrate the importance of estradiol in satellite cell maintenance. Their group substantiated that estradiol functions primarily through satellite cell ERα, and that skeletal muscle recovery in response to damaging exercise is limited by estradiol-ERα signaling [117]. Deficiency of this steroid hormone ultimately results in lower satellite cell engraftment. Oxidative stress is also largely mediated by estradiol concentrations, whereby estradiol-ER binding activates mitogen activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells. This facilitates synthesis of enzymes such as manganese superoxide dismutase and glutathione peroxidase, resulting in

enhanced antioxidant capacity [18]. It is also worth noting that while testosterone plays an imperative role in brain function and health, certain physiologic functions may be mediated by conversion to estradiol and subsequent ER binding [78]. Partially substantiated by brain aromatase concentrations, estradiol regulates several behavioral aspects, including sexual tendencies, aggression, vocalization, learning and cognition [44]. Estradiol also complements testosterone in attenuating depression, promoting interneuron communication, and improving spatial memory. Therefore, it is overwhelmingly important to consider not only the role of testosterone, but also the systemic impacts of appropriate estradiol in normal physiology.

Overall, there is credence to suspect reductions in systemic circulating testosterone and associated decrements in estradiol as unconsidered consequences of chronic SARM use. While aromatase-resistant AAS exist, commonly implemented cyclic stacks with testosterone derivatives perpetuate a consistent source of both systemic androgen and aromatase substrate [4, 42]. It is postulated herein that extended exposure to SARMs that induce testosterone suppression might have widespread deleterious effects on physiological function. Chronic suppression of testosterone via high-dose SARM compounds may selectively activate anabolic signaling in lieu of important androgenic effects. Unless users are willing to precariously experiment with combinations of SARMs that differentially impact target tissues, they may risk preferentially enhancing one target over another (i.e. arbitrarily selecting RAD140 to modulate cognitive function over S-4 impacts in bone homeostasis). Unfortunately, combining these compounds represents an even more treacherous endeavor because the preponderance of SARMs are mostly novel and relatively uncharacterized compared with androgen-derivatives. The impacts of systemically reduced androgens may be compounded by a concomitant reduction in aromatase substrate. Therein, potentially substantial reductions in estradiol commensurate via attenuated testosterone conversion may further impair bone homeostasis, negatively impact energy homeostasis and promote excess adiposity, attenuate global capacity to quench free radicals, hinder skeletal muscle function via disruption of the satellite cell compartment, as well as detrimentally affect cognitive function indices. Reductions in systemic estradiol and ERα binding are specifically implicated in glucose intolerance and insulin resistance, exacerbated by increased hunger, subsequent food consumption, in conjunction with lower IGF-1 levels [44, 118]. Estradiol is known to stimulate GH via ERα binding, indicating chronically depressed GH-mediated IGF-1 levels may incur attenuated muscle protein synthesis and contribute to diminished glucose handling [119, 120]. Hence, although SARMs embody a potentially favorable compound in clinical doses and settings, evidence is not yet able to substantiate their use in recreational consumers due to the risk of impaired plasma parameters and/or negatively impacted HPG axis activity.

FUTURE DIRECTIONS AND CONCLUDING STATEMENTS

This review illustrates the enigmatic nature of SARMs. While the previous sections have provided information on AR function, androgen action, and the available literature on compounds commonly marketed as SARMs, there is much to still be elucidated. Future research is foremost tasked with extending investigations on the aforementioned compounds, demonstrating further efficacy in clinically-approved human trials amongst healthy populations, including longitudinal research, whilst also providing novel human investigations amongst the compounds that remain in preliminary stages [24]. It appears enobosarm, GSK2881078, and RAD140 are the most empirically viable SARMs amidst clinical therapies, while the remaining are either under-researched (either lacking human trials or sufficient evidence) or have otherwise ceased production [30, 74, 75, 84, 86, 121-123]. Clearly, few have reached clinical trial stages and those existing have both mixed outcome variables and often inconsistent findings. It is not then unreasonable to surmise that potential SARM candidates are being pharmacologically produced at a speed surpassing the rate at which they can be sufficiently vetted. Furthermore, the ultimate consequences of SARMs in black market-supplied doses may only become known as current and future abusers report potential side effects. Given the popularity of recreational use, doping research is pushed to elucidate short-and long-term metabolites to detect the multiplicity of SARMs available. As previously stated, several of the aforementioned compounds have varied primary outcomes (pharmacokinetic, strength, body composition, etc.), disabling more conclusive statements to be made on individual SARM efficacy and/or their individual effects. The necessity to substantiate SARM mechanisms of action also persists; it is not well understood how each compound uniquely functions, nor is the general operation of SARMs well described. Considering SARMs are not subject to aromatization, they are often perceived as having no effect on the HPG axis [24]. The formerly described investigations, however, clearly demonstrate a wide range of impacts on gonadotropins. Oddly, LGD-4033 administration results in dose-dependent reductions in FSH without concomitant attenuations in LH [75]. This is in direct contrast to enobosarm that experienced no changes in gonadotropins, as well as S-4 and S-23 which either solely inhibited LH or dually (using higher doses) suppressed both gonadotropins [23, 81, 83]. Perhaps LGD-4033 contains some dual receptor cross-reactivity with S-4 and S-23; whereby LGD-4033 antagonizes LH receptors at the Leydig cells to inhibit testosterone whilst maintaining GnRH and simultaneously facilitating normal inhibin-mediated negative feedback at the Sertoli cells (see Figure 2) [42]. Conversely, it can only be speculated based on limited evidence in S-4 and S-23 that these compounds act more robustly on the opposite arm of the HPG axis, inhibiting LH at every dose whilst only affecting FSH at higher dosages. Although we are unaware of any literature investigating the role of either S-4 or S-23 on testosterone suppression, it stands to reason that substantial reductions in LH would lead to decreased androgen concentrations. Since androgens are known to impart negative feedback on FSH via inhibin,

perhaps potentially robust decreases in testosterone following non-steroidal-S-4 and -S-23-mediated LH reductions continue FSH secretion [124]. Conversely, higher doses may act concentration-dependently in a manner similar to the putative LGD-4033 mechanism to antagonize LH receptors and/or to suppress upstream GnRH akin to traditional AAS. Therein remains the possibility that several SARMs modulate activin and/or inhibin to impart negative feedback on gonadotropins. As structurally-related members of the TGF-ß superfamily, it is known that gonadotropins are regulated by the opposite effects of activin and inhibin [125]. Considering inhibin can interact with the activin receptor, perhaps SARMs with differential effects on either gonadotropin may also impact their concentrations. This may represent a promising avenue for LGD-4033 mechanisms specifically, which demonstrated a preferential suppression in FSH with equivocal LH changes at any dose [75]. Nevertheless, these speculations require extensive examination to confirm the potential varying impacts amongst the multiplicity of SARM compounds. It is worth noting that relatively high enobosarm dosages provided via internet distributors (≥20mg per serving) relative to the highest clinically evaluated trials (3mg/day) had no detrimental effects on upstream gonadotropins [23, 27]. This may indicate that enobosarm, with the most modestly suppressive effects and efficacy in human trials, is the most accurate representation of a compound that may elicit the benefits of AAS with the fewest HPG axis impacts.

More efforts are also required to determine specific coregulator recruitment following SARM-AR binding and how exercise modulates the effects of individual compounds. A trial in S-101479 demonstrated that several cofactors, including ß-catenin, were not recruited via SARM ligand binding [34]. Moreover, Spillane et al. [50] discovered that full-body resistance training resulted in both higher upregulations of AR and ß-catenin proteins at 3-and 24-hours post exercise. Mechanical tension can mediate ß-catenin signaling and may therefore compensate for potentially reduced recruitment via SARM administration [126]. It is also unknown if SARMs can interact with the more recently discovered membrane-bound GPCR/AR that facilitate mTOR activation (and upstream PI3K/Akt) [115]. Possibly, activation of this putative receptor may increase cytosolic ß-catenin for AR-coactivation via glycogen synthase kinase 3ß (GSK3ß) phosphorylation downstream of PI3K/Akt. GSK3ß is part of the destruction complex for ß-catenin that tags it for degradation, and thus phosphorylation facilitates complex dissociation and subsequent increased cytosolic ß-catenin [126]. ß-catenin's role in cell-cell adhesion via actin cytoskeleton-adherens junction linking (formed by cadherin and α-catenin) and its release from the complex further frees supervillin protein. Supervillin not only functions to transduce signals from cellular adhesion sites, but can function similar to ß-catenin as a coactivator to modulate gene transcription [36]. Potential attenuations in SARM-induced ß-catenin coregulatory protein recruitment might also be compensated for by exercise-mediated stimulation of kinase cascades via phosphorylation of AR. Focal adhesion kinase (FAK) is commonly phosphorylated in response to mechanotransduction, displaying

significant crosstalk with MAPK to increase AR transcriptional activity [36]. Nevertheless, specific cellular pathways modulated via SARM administration are almost entirely unknown and require elucidation.

Sex-specific SARM effects on humans also remain considerably nebulous. SARMs may represent a more tempting option for female recreational use given potential previous tendencies towards less-androgenic AAS (i.e. oxandrolone) [103]. Regardless, as the latter still imposes risk for permanent masculinization and hepatotoxicity, SARMs are largely uncharacterized for female-specific impacts. Despite the previously mentioned female-directed clinical treatments regarding breast cancer and urinary incontinence, potential HPO axis impacts require further investigation [22, 30-32, 64]. Enobosarm displayed sex-specific differential effects on gonadotropins, with females experiencing decrements in LH and FSH [23]. However, the lowered hormones did not impact estradiol or any other physical/biochemical index. As previously stated, Clark et al. [92] and Neil et al. [93] represent a limited number of trials aimed at determining sex-specific pharmacokinetic differences via GSK2881078 administration. Both employed sex-specific dosing with typically larger male doses, but these investigations collectively found consistently longer female-oriented measurable concentrations following their last dose, as well as a female-favored sensitivity resulting in greater relative lean mass gained. Overall, select trials have investigated the effects of SARMs in female animals, but few beyond those already highlighted have aimed to determine sex-specific differences [64, 81, 90].

No research exists evaluating the impacts of combining SARM compounds, which is especially relevant given the common occurrence of AAS compounds either concerted with one another or with ancillary substances [42]. The combination of compounds that selectively target specific tissues may provide an avenue to avoid the deleterious influence of potentially suppressed systemic peripheral testosterone. Furthermore, given the possibility of chronic SARM-mediated decrements in circulating estradiol, it might be pragmatic to concurrently administer a selective estrogen receptor modulator (SERM). While previous data in tamoxifen has displayed negative impacts on pancreatic beta cells, including concomitant insulin resistance, increased hypertriglyceridemia, and subsequent weight gain, a more novel SERM such as bazedoxifene (BZA) might represent a promising candidate [127-131]. BZA demonstrates ER agonist activity in bone, as well as antagonistic activity in breast and uterus. Furthermore, it facilitates increases in estradiol and bioavailable testosterone, whilst promoting favorable effects on lipid and glucose metabolism [128, 129, 132]. BZA has also displayed further efficacy by restoring the skeletal muscle satellite cell pool in estradiol-deficient mice [117]. Furthermore, the combination of SARMs and SERMs demonstrated credence in an investigation previously referenced by Furuya et al. [87]. Co-administration of S-101479 and raloxifene (1mg/kg each) significantly increased

BMD relative to single treatment of either compound alone. Therefore, perhaps co-administration of these or similar SERMs may facilitate estradiol-mediated systemic benefits during a SARM cycle.

SARMs were developed as safer alternatives to AAS, maximizing anabolic and minimizing androgenic effects. While their intention was originally clinical in nature, recreational and competitive users have become privy to these compounds and their potential for improving body composition and athletic performance. Several trials have managed to demonstrate efficacy in select SARMs, however, there is insufficient research demonstrating potential health risks. Relatively few SARMs have displayed efficacy in human models, and internet providers are quick to advertise doses several times greater than the empirically-based investigations. Furthermore, several of these compounds elicit unfavorable alterations in testosterone, gonadotropins, serum lipids, and other hematological parameters. Insufficient time has elapsed to evaluate the efficacy of anecdotal dosing regimens and whether post-cycle therapies are warranted and might mirror those used in AAS. Additionally, reported SARM-induced fat free mass increases are a mere fraction of that reported in modest doses of testosterone derivatives in similar timeframes (~1.5kg versus ~7kg in SARMs and testosterone, respectively) [21]. The available literature best depicts these compounds as promising clinical agents in hypogonadal, cachectic, as well as aging scenarios, but leaves the use in recreational and/or athletic endeavors both unclear and potentially hazardous due to possible contraindications which have been discussed herein.

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Table Captions

Table 1. List of compounds typically sold commercially as "Selective Androgen Receptor Modulators" and their general effects in various subject populations [23, 24, 26, 27, 34, 37, 40, 64, 67, 75-78, 81, 82, 84, 90, 92-94]

Figure Captions (ALL FIGURES IN COLOR)

Figure 1. A depiction of the differences potentially defining AR-binding between androgens (testosterone & DHT) compared with non-steroidal SARMs. In brief, SARMs ideally denote beneficial anabolic actions in androgen responsive tissues such as skeletal muscle and bone, without unwanted androgenic side effects. They do not undergo conversion to DHT or estradiol, which partially mediates a lack of SARM-induced androgenic impact. The SARM mechanism of action is far from elucidated, but potentially may be sourced in 5α-reductase or aromatase modulation, as well as a potential inability for N/C interaction between the ligand-independent NH_2-terminal transactivation domain (AF-1) located in the DBD and the ligand-dependent carboxy-terminal transactivation domain (AF-2) located in the LBD. Through this incomplete interaction that is typically deemed necessary for full AR agonist activation, SARMs may also impact AR DBD topology and affect the ability of the transcriptional binding complex to recognize specific DNA sequences. Incomplete N/C interaction ostensibly alters coregulator recruitment, indicating that SARMs selectively inducting different coactivators and corepressors, as well as recruiting them in differential magnitudes relative to androgens [21, 25, 34, 36, 40, 50, 64, 65].

ARE = androgen response elements; AF-1 = activation function 1; AF-2 = activation function 2; AR = androgen receptor; DBD = DNA-binding domain; ECF = extracellular fluid; ER = estrogen receptor HSP = heat shock proteins ICF = intracellular fluid; LBD = ligand-binding domain; SARM = selective estrogen receptor modulator

Figure 2. The potential impacts of varying SARMs on the male hypothalamic-pituitary-gonadal axis. Amongst those most comprehensively researched and commercially available compounds with regards to these effects (gonadotropins and testosterone outcomes) are enobosarm, LGD-4033, and S-4. Each display widely varying effects on the axis along the entire feedback system, along with wholly under-researched downstream impacts on systemic physiology. Mechanisms of each SARM and the drug class in general are unclear, but may be sourced in dose-dependent effects and/or the potential for specific receptor-mediated antagonism. We also posit the putatively deleterious impacts of attenuated androgen and subsequent estradiol following high-dose and/or chronic SARM use.

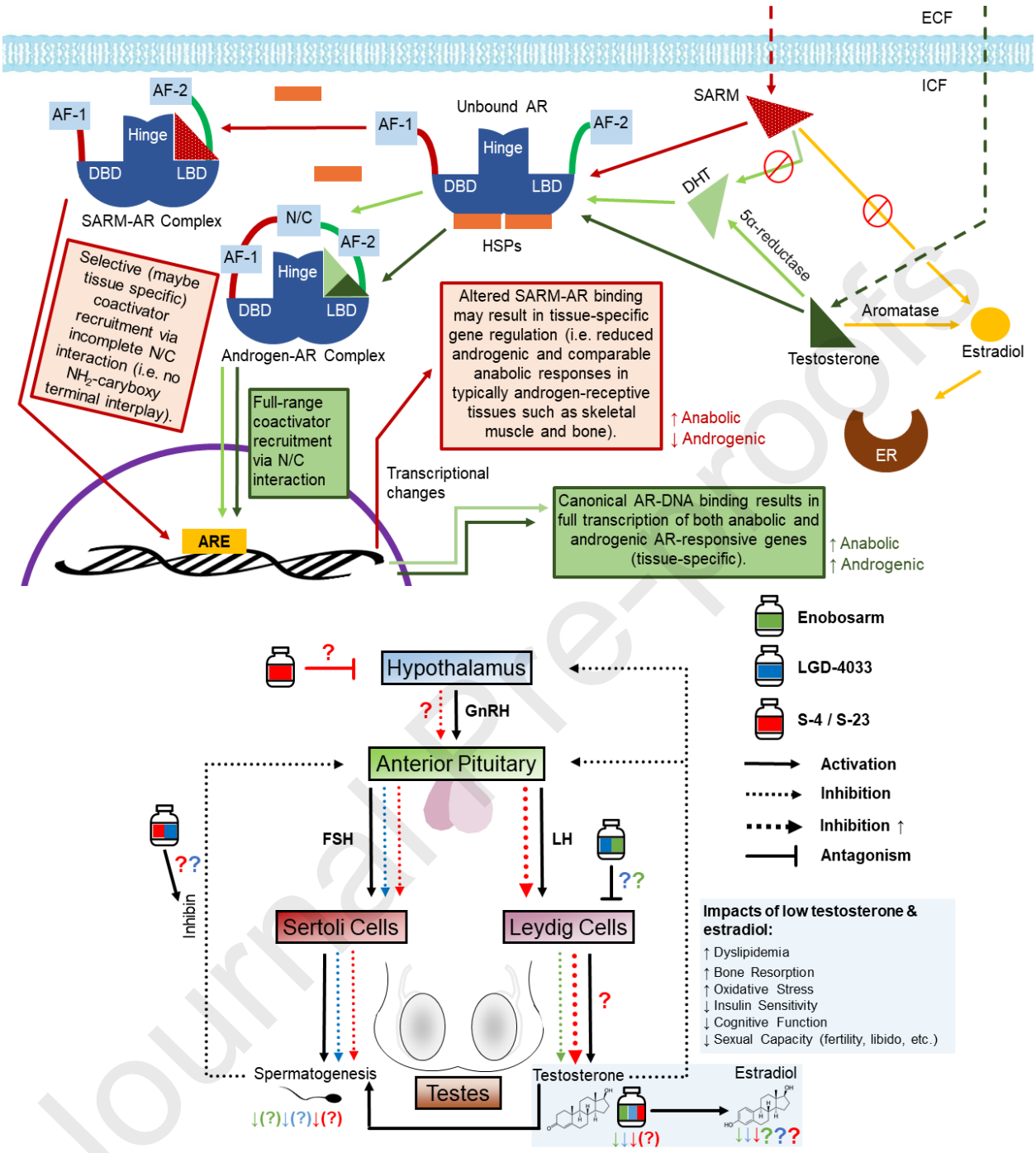
FSH = follicle-stimulating hormone; GnRH = gonadotropin releasing hormone, LH = luteinizing hormone

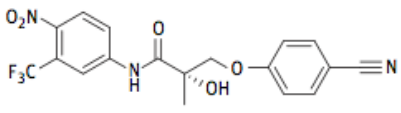
Highlights

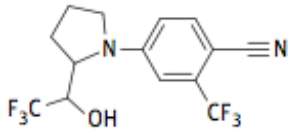
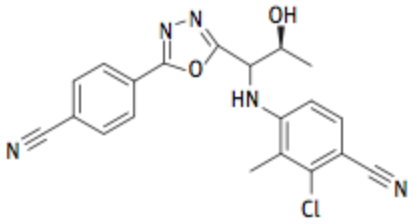
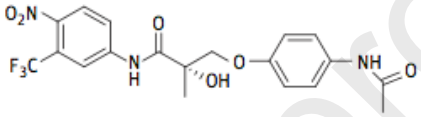
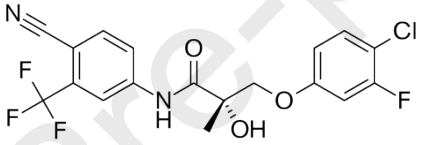
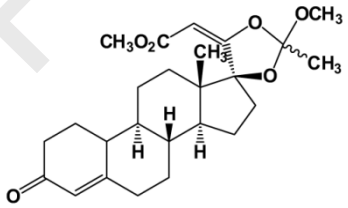
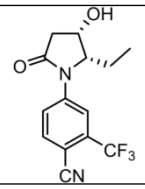
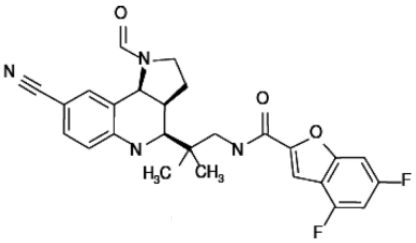
- SARM's were developed to provide clinical androgen benefits without side effects
- SARMs are becoming more common in recreational abuse
- SARMs were recently FDA banned and lack supporting evidence
- SARMs may impact hypothalamic-pituitary regulation with systemic ramifications

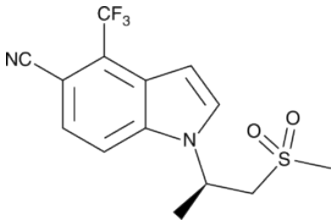
Author Contributions:

SBM & DSW were responsible for the conceptualization and original draft writing of the manuscript. DSW, TDC, and DTW equally contributed to review and editing.



Compound Name(s)	IUPAC Designation	Skeletal Structure	Current Levels of Research Achieved	Empirical *in vivo* Doses
GTx-024, MK-2866, S-22, Ostarine	(2S)-3-(4-cyanophenoxy)-N-(4-cyano-3-trifluorophenyl)-2-hydroxy-2-methylpropanamide		Human Rodent Cell Culture	0.1-5.0mg 3mg/kg (rodent) 14-86 days

LGD-4033, VK5211, Anabolicum Ligandrol	4-((R)-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl))-2-trifluoromethylbenzonitrile		Human Rodent Cell Culture	0.1-1.0mg 21 days
RAD140, Testalone	2-chloro-4-((1R,2S)-1-(5-(4-cyanophenyl)-1,3,4-oxadiazol-y-yl)-2-hydroxypropylamino-3-methylbenzonitrile		Rodent Cell Culture	0.03-10mg/kg 2 weeks
S-4, Andarine, GTx007, acetam-doxolutamide	S-3-(4-acetylamino-phenoxy)-2-hydroxy-2-methyl-N-(40nitro-3-trifluoromethyl-phenyl)-propionamide		Rodent Cell Culture	0.1-10mg/kg 2-8 weeks
S-23	(S)-N-(4-Cyano-3-Trifluoromethyl-Phenyl)-3-(3-Fluoro, 4-Chlorophenoxy)-2-Hydroxy-2-Methyl-Propanamide		Rodent Cell Culture	0.01-3.0mg/day 14 days
YK11	(17α,20E)-17,20,-[(1-methoxyethylidene)bis-(oxy)]-3-oxo-19-norpregna-4,20-diene-21-carboxylic acid methyl ester		Cell Culture	n/a
SARM-2f	4'-[(2S,3S)-2-Ethyl-3-hydroxy-5-oxopyrrolidin-1-yl]-2'-(trifluoromethyl) benzonitrile		Rodent/Monkey Cell Culture	0.02-10mg/kg 14 days - 4 weeks
S-101479	N-(2-(3aS,4S,9bS)-8-cyano-1-formyl-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2,-c]quinolin-4-yl)-2-methylpropyl-4,6-diflurobenzofuran-2-carboxyamide		Rodent/Rabbit Cell Culture	0.1-10mg/kg 8-16 weeks

GSK2881078	(R)-1-(1-(mehtylsulfonyl) propan-2-yl-4-(trifluoromethyl)-1*H*-indole-5-carbonitrile		Human Rodent Cell Culture	0.2-4.0mg 1-56 days

Note: The above list is not an exhaustive list of all selective androgen receptor modulators (SARMs), but rather those specifically underlined in this narrative review