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# Selective Androgen Receptor Modulators (SARMs) - Current Knowledge and Clinical Applications

**Zachary J. Solomon**[a], **Jorge Rivera Mirabal, M.D.**[b], **Daniel J. Mazur, M.D.**[b], **Taylor P. Kohn**[a], **Larry I. Lipshultz, M.D.**[b,c], and **Alexander W. Pastuszak, M.D. Ph.D.**[b,c]

[a]Baylor College of Medicine, Houston, TX

[b]Scott Department of Urology, Baylor College of Medicine, Houston, TX

[c]Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX

## Abstract

**Introduction:** Selective androgen receptor modulators (SARMs) differentially bind to androgen receptors depending on each SARM's chemical structure. As a result, SARMs result in anabolic cellular activity while avoiding many of the side effects of currently available anabolic steroids. SARMs have been studied in the treatment of breast cancer and cachexia and have also been used as performance enhancing agents. Here, we evaluate and summarize the current literature on SARMs.

**Aims:** To present the background, mechanisms, current and potential clinical applications, as well as risks and benefits of SARMs.

**Methods:** A literature review was performed in MEDLINE using the terms selective androgen receptor modulator, hypogonadism, cachexia, breast cancer, benign prostatic hyperplasia, libido and lean muscle mass. Both basic research and clinical studies were included.

**Results:** While there are currently no FDA-approved indications for SARMs, investigators are exploring the potential uses for these compounds. Basic research has focused on the pharmacokinetics and pharmacodynamics of these agents, demonstrating good availability with a paucity of drug interactions. Early clinical studies have demonstrated potential uses for SARMs in the treatment of cancer-related cachexia, benign prostatic hyperplasia, hypogonadism, and breast cancer, with positive results.

**Conclusion:** SARMs have numerous possible clinical applications, with promise for the safe use in the treatment of cachexia, BPH, hypogonadism, breast cancer, and prostate cancer.

**Correspondence:** Alexander W. Pastuszak, MD, PhD, Assistant Professor, Center for Reproductive Medicine, Scott Department of Urology, Baylor College of Medicine, 6624 Fannin Street, Suite 1700, Houston, Texas, 77030, Telephone: 713-798-6163, Fax: 713-798-6007, pastusza@bcm.edu.

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**Keywords**

Selective Androgen Receptor Modulators; Drug-Related Side Effects and Adverse Reactions; Hypogonadism; Androgens

## INTRODUCTION

The androgen receptor (AR) belongs to the superfamily of steroid hormone nuclear receptors, and the binding of its endogenous ligands (i.e. testosterone and dihydroxytestosterone) modulates its function as a transcription factor.[1] The effects of the interaction between the AR and androgens are complex and vary depending on sex, age, tissue type, and hormonal status. While the AR is widely known for its role in male sexual development and maintenance, it also has important effects on bone density, strength, muscle mass, hematopoiesis, coagulation, metabolism, and cognition.[2][3]

Testosterone and synthetic steroid hormones have found many applications in the clinical setting. One can broadly categorize their effects as anabolic (increased bone density, muscle mass) or androgenic (impaired fertility, virilization, acne). Despite the wide array of medical conditions that could potentially be addressed with the supplementation of steroid hormones, their therapeutic use is often curtailed due to potential side effects, including erythrocytosis, prostate hypertrophy, hepatotoxicity, aromatization to estrogen and testicular atrophy..[4] The use of testosterone therapy in prostate cancer is a topic of controversy and was debated in an article by Jannini et al.[5] The authors conclude that prostate cancer is indeed testosterone dependent. However, androgen receptor saturation in the prostate is thought to occur at subphysiologic serum testosterone levels (60–120 ng/dL). As such, increases in serum testosterone levels above this concentration are note expected to result in further androgen receptor activation and activity.[6] There is no conclusive evidence demonstrating an increased risk of prostate cancer in the setting of testosterone therapy. Of interest, Gravina et al demonstrated a significant reduction in the tumor growth of prostate cancer cells in the setting of supra-physiologic intraprostatic testosterone concentrations.[7]

Selective androgen receptor modulators (SARMs) are small molecule drugs that can exert varying degrees of both agonist and antagonist effects on AR in different tissues. Their actions can be understood by considering the selective estrogen receptor modulators (SERMs) that preceded them. One SERM widely used to treat breast cancer, tamoxifen, acts as an antagonist in the breast, an agonist in the bone and a partial agonist in the uterus. The tissue-specific effects of these agents are precisely what makes them attractive, as they can be tailored to address specific medical conditions while minimizing off-target effects.

Basic laboratory experiments have sought to investigate and optimize the pharmacodynamic and pharmacokinetic properties of SARMs according their desired site of action. SARMs have been chemically engineered to more specifically target AR function in certain tissues while minimizing off-target effects.[8] There is minimal variation between AR structure, but the regulatory milieu of each tissue allows SARMs possess relative tissue-specificity. Animal models have been used to investigate the effect of SARMs on skeletal muscle in both eugonadal and hypogonadal rats.[9] Animal models of muscular dystrophy have been

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used to investigate the use of SARMs in muscle pathology, demonstrating encouraging results.[9,10] SARMs have also been trialed as reversible hormonal contraceptives in rats.[11] While still preliminary studies, researchers have investigated the possible use of SARMs in Alzheimer's disease, prostate cancer, BPH, and osteoporosis.[12–14] SARMs have begun to be studied in the pre-clinical and clinical phases as treatment options for cancer related cachexia, breast cancer, benign prostatic hyperplasia, and hypogonadism.[2,15,16] There are several ongoing Phase 1 or Phase 2 clinical trials investigating the use of SARMs.

In this review, we present the background, mechanisms, and current and future clinical applications of SARMs. We also consider the risks and benefits of SARMs and discuss their potential for misuse.

## METHODS

A literature review was performed in the PubMed/Medline database using the terms selective androgen receptor modulator, hypogonadism, cachexia, breast cancer, benign prostatic hyperplasia, and lean muscle mass. Both basic and clinical studies were included. Currently ongoing clinical trials listed on www.clinicaltrials.gov that are investigating SARMs were reviewed as well.

## HISTORY OF SARMS

An improved understanding of selective estrogen receptor modulators (SERMs) and their mechanisms of action in the 1990s, as well as the growing use of tamoxifen in the treatment of breast cancer, stimulated interest in analogous drugs to modulate the androgen receptor (AR). [17,18] Several labs began working on identifying lead candidates and specific pharmacophores, with early work being centered around a class of aryl-propionamides identified from hydroxyflutamide analogs in 1998.[15] Over the past 20 years the number of bioactive SARMs under investigation has continued to grow, as has our knowledge of their mechanisms of action.

## BIOCHEMICAL AND BASIC SCIENCE BACKGROUND

As demonstrated by the development and clinical use of SERMs like tamoxifen, the key characteristic underlying the therapeutic potential of SARMs is their tissue specificity. While steroid hormone replacement therapy offers many benefits, it can be associated with a high rate of adverse effects, partly due to widespread and nonspecific activation of the AR in many different tissues. The most basic distinction in tissue selectivity lies between anabolic and androgenic effects of steroids and their analogs, with the former being responsible for trophic effects on bone and muscle and the latter having effects on the development and physiology of the genitourinary system..[4]

The AR functions as a nuclear steroid hormone receptor. Its ligand enters the cell, typically by diffusion, and encounters the unoccupied AR in the cytoplasm.[1] Upon binding, the AR dissociates from cytosolic heat shock proteins and migrates to the nucleus where it associates with various co-regulatory proteins. [1] The complex then interacts with specific DNA sequences and acts as a transcriptional regulator of androgen responsive genes.[1,19]

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The intricate and tissue-specific process dictates the transcriptional and thus the cellular response.[19,20] Much work has been focused on determining how different SARMs achieve tissue specificity and partial agonism, though the exact mechanisms remain unclear.[20]

Hikichi *et al.* helped elucidate the mechanisms of tissue specificity in 2015 by investigating an experimental SARM, TSAA-291.[20] Using reporter assays, a method to assess the degree to which a transcription factor activates target genes, the investigators compared dihydrotestosterone (DHT) and TSAA-291.[20] While nearly identical gene responses were observed using reporter assays for skeletal muscle cells, TSAA-19 agonist activity in prostate cells was approximately half that of DHT.[20] Thus, despite binding to ARs in the same tissues, TSAA-291 displayed a different cellular response than DHT in the prostate. This phenomenon was partly explained by the demonstration that TSAA-291 led to a different cofactor recruitment in the prostate and thus different downstream effects.[20] This observation suggests that conformational variations in ligand-AR complexes are at least partially responsible for the unique cellular responses.[1,20] This is further supported by the findings of Unwalla *et al.,* who demonstrated that small variations in SARM conformation can result in substantial effects on activity. [4]

Indeed, the AR is a modular protein with discrete domains responsible for different functions.[21] The AR is maximally active across different tissues when a ligand promotes interactions between the N- and C-terminal AR domains.[21] This is supported by observations that mutations in the AR which disrupt this interaction lead to incomplete virilization in patients.[21] Schmidt *et al.* showed that the ability to reduce N/C interactions is the hallmark of SARMs that display antagonism in androgenic tissues.[21]

Thus, it seems that the ability of SARMs to signal via the AR depends on how their unique conformations interact with the functional domains of the AR, and in turn how those domains interact with the cellular regulatory milieu to target DNA expression. Given that each SARM-AR complex has a different conformation and that tissues have unique patterns of AR expression, co-regulatory proteins levels, and transcriptional regulation, one can imagine the immense diversity and potential for tissue- and action-specific SARMs.[1] Figure 1 shows a simplified SARM-induced signaling pathway.

Given the complex biological actions of steroid hormones and SARMs depending on binding affinity and degree of agonism and antagonism at the AR in different tissue types, high throughput screening methods are being utilized to discover SARMs with favorable biological and pharmacokinetic profiles.[8] For example, Unwalla *et al.* recently published a new SARM compound based on a novel cyanopyrrole structure that selectively promotes muscle growth while having limited androgenic effects in an orchidectomized rat model.[4] Miller *et al.* reported on RAD-140, a potent anabolic SARM with antagonistic effects on the prostate and seminal vesicles, qualities that would make it well suited to treat conditions like BPH while targeting muscle and bone growth.[1] As will be discussed, the optimization of tissue specificity and downstream signaling continues to broaden the potential application of SARMs for contraception, osteoporosis, cachexia, muscular dystrophies, prostate cancer, and Alzheimer's disease.

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# THERAPEUTIC PROMISE OF SARMS

## MALE CONTRACEPTION

SARMs show promise for use as a method of male contraception in animals. Exogenous testosterone interferes with spermatogenesis via negative feedback on the hypothalamic-pituitary-gonadal axis.[11,22] Chen *et al.* demonstrated that administration of a SARM, C-6, markedly suppressed spermatogenesis and reduced peripheral testosterone levels while decreasing testicular and epididymal size.[11] Similar experiments by Jones *et al.* using a SARM, S-23, combined with estradiol benzoate, demonstrated a completely reversible effect on the suppression of spermatogenesis and serum LH and FSH levels.[23] During the experiment, four of six rats demonstrated a complete absence of testicular sperm with no pregnancies observed in mating trials. Once treatment was stopped, mice regained fertility with 100% subsequent pregnancies (6/6) within 100 days after treatment cessation.[23] Notably, S-23 also increased lean muscle mass, bone mineral density, and decreased fat mass in mouse models.[23]

## OSTEOPOROSIS

Many SARMs have trophic effects on bone.[12] Watanabe *et al.* investigated a novel SARM, BA321, which displays binding to both AR and estrogen receptors (ER) without androgenic effects, and can completely restore bone loss in orchidectomized mice. [12] This raises the possibility that a host of different SARMs could prove to be especially effective as adjuncts in treating osteoporosis or other conditions that lead to suboptimal bone density and mineralization.

## PROSTATE CANCER

Prostate cancer may also be ripe for address by SARMs. Pekka *et al.* recently published mouse data showing that a new SARM, FL442, reached high tissues concentrations in the prostate and acted as an AR antagonist in prostate cancer (PCa) cell models with efficacy comparable to that of enzalutamide, an antiandrogen used in the treatment of castration resistant PCa.[24] Notably, FL442 maintained the ability to prevent cell proliferation even in cell lines with AR mutations that conferred resistance to enzalutamide. [24] Likewise, work by Schmidt *et al.* focused on MK-4541, which induces Caspase-3 activity and apoptosis in androgen independent AR positive prostate cancer cell lines while sparing AR- and AR + non-prostate cancer cells.[25] Chisamore *et al.* also demonstrated that administration of MK-4541 resulted in a decrease in plasma testosterone levels, likely through AR-mediated negative feedback signaling through the hypothalamic-pituitary-gonadal axis.[13] These results support the promise of SARMs in treating hormone ablation-resistant disease through the activation of AR-induced expression profiles that are toxic to cancer cells while avoiding the negative effects of traditional antiandrogen therapies.

Another possible application for SARMs in prostate cancer management is tissue targeted imaging.[26] Given that the AR is expressed in all stages of prostate cancer evolution, radioactive iodine-labeled SARMs that achieve high intra-prostatic concentrations could be used for radiological diagnosis, especially for metastatic disease. [21]

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## SEXUAL MEDICINE

Androgens have important effects on sexual functions in both male and females, a fact consistent with the expression of the AR in the genitourinary systems of both sexes.[27–29] While today the treatment of postmenopausal genitourinary symptoms (PGS) in women is typically centered on estrogen-based therapies, historically both androgens and estrogens were used.[28] Indeed, recent double-blind placebo-controlled clinical trials have shown that local vaginal application of dehydroepiandrosterone improves postmenopausal symptoms, including moderate to severe dyspareunia.[28][30] Several studies have evaluated the effects of local vaginal testosterone application, with effects ranging from lower vaginal pH, increased lactobacilli, and improved vaginal maturation index.[28] Several clinical trials using transdermal testosterone for female sexual dysfunction in women with low serum testosterone showed improvements in sexual desire, pleasure and orgasms.[31] For example, treatment with testosterone patches in women with hypoactive sexual desire disorder after bilateral salpingo-oophorectomy increased episodes of satisfying sexual encounters and increased sexual desire.[32]

Given the evidence surrounding the utility of androgens in treating PGS and hypoactive sexual desire in women, SARMs represent a potentially attractive future therapy. Indeed, studies in ovariectomized rats showed that treatment with several halogenated candidate SARMs (S-23, S-24, S-27) led to significant increases in sexual motivation, while the use of other SARMs led to an increase in myometrial thickness to greater than control.[31] This evidence suggests that SARMs could be designed for specific effects on either female libido or reproductive organs.

In men, there is little controversy surrounding the critical role of testosterone in male libido and sexual function. Many trials and studies have established the sexual benefits of exogenous testosterone use for men. For example, in a cohort of hypogonadal men treated chronically with testosterone gel, scores quantifying sexual desire, enjoyment, erection quality, and sexual activity were all markedly and sustainably improved from baseline.[33] Similar to the preclinical data discussed above in regards to SARMs and female sexual function, treatment of male rats with SARMs led to increased sexual behavior.[34] Male rats treated with LGD226, a synthetic SARM, displayed an increased number of mounts, intromissions, and ejaculations compared with a control group. These results were not significantly different to a group treated with fluoxymesterone, a synthetic androgen. These results suggest that SARMs could be as effective as treatment with testosterone and its derivatives in promoting male libido. More research is needed to investigate the effect of SARMs on sexual desire and function in humans of both sexes.

## BENIGN PROSTATIC HYPERPLASIA

Modulation of the AR using SARMs could also have a role in treating benign prostatic hyperplasia (BPH), primarily via immunomodulatory mechanisms.[35] Vignozzi and colleagues demonstrated that activation of the AR by dihydrotestosterone leads to a reduced inflammatory response in cultured human prostatic stromal cells. Another article from the same institution evaluated the role of testosterone on prostate inflammation induced by a high fat diet in a rabbit model.[36] The authors found that testosterone supplementation

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normalized inflammatory changes in the prostate by inhibiting fibrosis and myofibroblast differentiation. SARMs may be attractive in BPH treatment as they modulate the AR. Nejishima *et al.* compared the use of flutamide with S-40542, a novel SARM, in a rat model of BPH.[16] Both agents similiarly decreased prostate weight in a dose-dependent manner, but S-40542 had a weaker effect on the levator ani muscle than flutamide.[16] Additionally, S-40542 showed no effect on testosterone or luteinizing hormone (LH) levels, both of which were increased by flutamide.[16] A different study by Gao *et al.* compared S-1 and S-4, both SARMs, with finasteride and hydroxyflutamide for the treatment of BPH in a rat model.[37] Both finasteride and S-1 selecively decreased prostate weight to a similar extent without changes to the levator ani muscle or to plasma testosterone, follicle stimulating hormone (FSH) or LH levels, all of which were altered by treatment with hydroxyflutamide.[37] S-1 and S-4 decreased 5-alpha-reductase levels weakly, suggesting that they reduced prostate size via a different mechanism than finasteride.[37] These results raise the possibility of future SARMs as adjuncts to or monotherapy for BPH, with minimal side effects.

## ALZHEIMER'S DISEASE

Hypogonadal men demonstrate a decrease in various cognitive processes, including episodic memory, working memory, processing speed, visual spatial processing and executive function.[38] These functions are partially regulated by regions of the brain that are modulated by the AR. [39] Moffat et al. performed a sub-analysis of the Baltimore Longitudinal Study of Aging that included 407 men without dementia who were followed for a mean of 9.7 years. [40] Study subjects underwent medical, physiological, and neuropsychological evaluations as well as laboratory testing for total testosterone and steroid hormone binding globulin. Free testosterone index was calculated based on total testosterone and steroid hormone binding globulin levels. Results showed that higher free testosterone index was associated with better scores on visual and verbal memory, visuospatial functioning, visual-motor scanning and a reduced rate of longitudinal decline in visual memory.

As we continue to elucidate the effects of testosterone on cognition, we can appreciate that SARMs may one day play a role in the treatment of cognitive disorders such as Alzheimer's disease. Androgen depletion is considered a significant risk factor for Alzheimer's disease, and circulating testosterone levels are inversely correlated with levels of Amyloid β(Aβ) in the brains of aged men.[14] Androgens suppress the accumulation of Aβ by upregulating expression of neprilysin, which degrades amyloid. [14] Akita *et al.* recently demonstrated that a novel SARM, NEP28, increases the activity of neprilysin in addition to having systemic anabolic effects with reduced androgenic effects. [14]

## MUSCULAR DYSTROPHY

Another group of diseases which may benefit from interventions with SARMs is the muscular dystrophies. Pilot studies using oxandrolone in boys with Duchenne muscular dystrophy (DMD) demonstrated gains in muscle mass and protein synthesis, but hepatotoxicity and off-target effects on genitalia were major treatment limiting side effects. [9] Cozzoli *et al.* demonstrated the efficacy of GLPG0492, a novel SARM, in a mouse model of DMD.[10] Groups of mice were treated with GLPG0492, methylprednisone, or

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nandrolone. Mice treated with GLPG0492 showed preserved running performance, increases in maximum isometric diaphragm contractile force, and decreased muscle fibrosis.[10] SARMs administered to patients with DMD would theoretically increase muscle mass and protein synthesis levels comparable to that observed with oxandrolone without the off-target side effects.

## CACHEXIA

One of the most promising potential applications of SARMs include conditions where cachexia is a consequence of the disease state or its therapy, including HIV, cancer, immobilization, and chronic glucocorticoid use.[41] In healthy individuals, muscle exists in a state of equilibrium between breakdown and synthesis, and any alteration to the rate of degradation or protein synthesis can favor atrophy or hypertrophy. Efforts attempting to elucidate the cellular mechanisms by which SARMs promote tissue anabolism are ongoing. Shankaran *et al.* used a proteome-wide muscle protein fractional synthesis analysis to demonstrate that SARM treatment in an ovariectomized rat model resulted in an increase in synthesis of contractile proteins such as myosin and actin, and also a small but significant increase in muscle mitochondria biogenesis.[42] Research on GTx-024 (Enobosarm) by Dubois *et al.* in AR knockout satellite cell lines suggests that SARMs also mediate muscle hypertrophy via AR action on vimentin positive resident muscle fibroblasts, likely through upregulation of paracrine growth factor signaling.[43] Jones *et al.* demonstrated that in a rat model of dexamethasone and castration-induced muscle atrophy, both testosterone and S-23, a SARM, reduced muscle atrophy.[41] Rats were divided into four groups and given either vehicle, dexamethasone alone (Dex) to induce muscle atrophy, or dexamethasone plus either testosterone or S-23.[41] Activity of intracellular growth pathways was then analyzed. [41] Both testosterone and S-23 treatment in the Dex model blocked dephosphorylation and thus inactivation of proteins in the PI3/Akt kinase cascade.[41] These signaling pathways are involved in cellular growth and protein synthesis and upregulate the production of downstream targets including mTOR and glycogen synthase kinase. [41] Testosterone and S-23-based treatment of the Dex-model mice also blocked the upregulation and activation of ubiquitin ligases and other proteins that increase cell catabolism, including MAFbx, MuRF1 and FoxO.[41] The overall effect of S-23 and testosterone treatment was to attenuate the catabolic effects of dexamethasone administration. [41] Lastly, a similar experiment was performed in castrated mice to evaluate if S-23 could rescue the mice from castration-induced muscle atrophy. [41] Treatment of the castrated mice led to hypertrophy of the levator ani muscle compared to eugonadal controls, with attenuation of castration-induced reductions in IGF-1 concentrations. [41] Similar results were observed in a mouse model of hind limb immobilization.[44] Taken together, these results support the conclusion that SARMs may reverse and prevent iatrogenic and disease induced catabolism while having minimal effect, or a beneficially antagonistic effect, on androgenic tissues.

## BREAST CANCER

SARMs may be useful in the treatment of breast cancers that express AR.[45] Up to 85% of ER positive breast cancers and 95% of ER negative breast cancers express AR.[46] AR positive tumors are associated with improved overall survival and disease-free survival when compared to AR negative tumors.[45] Androgen receptors in breast cancer likely confer

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survival advantage by modulating ER signaling, which may reduce the risk of metastasis and aggressive disease.[46] There is currently a clinical trial in the recruitment phase seeking to evaluate pembrolizumab and enobosarm co-therapy for the treatment of AR positive metastatic triple negative breast cancer.[47]

## FIELD LEADER? - ENOBOSARM TRIALS

Several clinical trials are assessing the application of SARMs as novel treatment agents for cancer related cachexia, breast cancer, stress urinary incontinence, and prostate cancer.[15,16] A summary of current clinical trials listed on www.clinicaltrails.gov using SARMS can be found in Table 1. As discussed, unique SARMs are being designed to have maximum action at the desired tissue with minimal or antagonistic effects on other tissues, widening the spectrum of potential therapeutic viability in a variety of clinical conditions. Although there are no FDA approved SARMs available for clinical use, Enobosarm has played a central role in several clinical trials. [48]

One hundred and twenty healthy elderly men and postmenopausal women participated in a 12-week double-blind, placebo-controlled phase II clinical trial involving Enobosarm with were 5 dosing groups; placebo, 0.1mg, 0.3mg, 1mg and 3mg of enobosarm.[3] The primary endpoint was total lean body mass (LBM), and secondary endpoints included physical function, insulin resistance, body weight and drug safety.[3] At the highest dosing group (3mg), subjects taking enobosarm saw an average increase in LBM of 1.3 kg, with a 0.6 kg decrease in fat mass.[3] Subjects on enobosarm also had dose-dependent improvements in physical function as measured by stair climbing time, significant reductions in blood glucose and a trend towards lower blood insulin levels.[3] While serum triglycerides trended downwards in subjects taking enobosarm, there were dose dependent reductions in HDL of up to 27% in the 3mg enobosarm group.[3] Men were also found to have significant but expected decreases in sex hormone binding globulin (SHGB), but no changes in free testosterone, DHT, estradiol, FSH or LH levels.[3] Women had similar decreases in SHGB, but with significant reductions in LH and FSH.[3] No changes were observed in total bilirubin, GGT or alkaline phosphatase for any dose of enobosarm, but small increases in hemoglobin and transient increases in ALT were seen in 8 subjects, 7 of which resolved by the end of the 12 weeks.[3]

A second randomized, double-blind, placebo-controlled phase II trial evaluated the use of enobosarm in 159 patients with cancer-related cachexia.[49] Males and postmenopausal females with cancer and over 2% weight loss over 6 months were randomized to take placebo, 1mg or 3mg of enobosarm for 113 days.[49] Both 1mg and 3mg groups saw increases in LBM, with decreased stair climbing times.[49]

Given these results, the Prevention and Treatment of Muscle Wasting in Cancer Patients (POWER) trials, two identical randomized double-blind, placebo-controlled phase 3 trials were designed to assess the ability of enobosarm to prevent and treat cachexia in patients with stage 3 and 4 non-small-cell lung cancer.[2] However, both trials failed to meet the primary endpoints of improvements in LBM and assessments of physical function after showing mixed results.[46,50] Currently enobosarm is being assessed in a different Phase 2 trial to examine its effect on stress urinary incontinence in postmenopausal women (Table 1).

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## SAFER THAN TESTOSERONE?

Testosterone therapy (TTh) is currently the mainstay treatment for hypogonadism and is an option for treating cancer related cachexia.[15,51] Although TTh is effective in treating hypogondal symptoms, it possesses potential side effects that require careful monitoring. [51] TTh can lead to gynecomastia due to estrogen aromatization, erythrocytosis, reduced spermatogenesis, acne, male pattern baldness, and undesirable alterations in serum lipids, among other effects.[51]

Compared with steroidal androgens, SARMs appear to be much better tolerated with few incidences of severe adverse effects. In addition, many of these pre-clinical agents can be administered as oral therapies. This helps to reduce the risk of accidental exposure, as can be seen with topical testosterone, and can significantly improve ease of administration compared to currently available forms of TTh.[2,3,15,43] As described above, Enobosarm treatment led to small increases in hemoglobin in certain subjects, increases in ALT, and decreased serum HDL levels. Other early clinical studies have investigated the safety profiles and pharmacodynamics and kinetics of several candidate SARMs.

GSK2881078, a SARM being investigated by GlaxoSmithKline for muscle growth and strength in subjects with muscle wasting, was tested in a two part, randomized, double-blind, placebo-controlled dose-escalation Phase 1 study to assess safety, pharmacokinetics and pharmacological effects in a small cohort of young men and postmenopausal women.[52] Overall the treatment was well tolerated, with the most common adverse events being constipation, dyspepsia, and nausea (3 of 89).[52] One female subject developed a maculopapular rash with biopsy consistent with a drug reactions, two female subjects developed elevated ALT values 2–2.5 time the upper limit of normal during treatment, and two male subjects experienced muscle soreness and elevated CK levels weeks into the follow up period.[52] GSK2881078 was also associated with reductions in HDL. [52]

PF-06260414, a novel SARM, was also involved in a Phase I trial investigating safety, pharmacokinetics and dynamics.[53] The study was a combination, randomized, double-blind, placebo-controlled, single- and multiple-dose escalation, parallel-group study in 72 healthy adult men of mixed ethnicity.[53] Overall PF-06260414 was well tolerated, with the most common adverse effects (AEs) being headache and increased serum ALT levels, and decreases in serum HDL levels. [53] Most other side effects were considered mild (decreased appetite, URI, and dizziness) except for one moderate AE of fatigue and one severe AE of anxiety that led to drug discontinuation.[53]

LGD-4044, a novel SARM, was tested in a placebo controlled study of 76 healthy men randomized to either placebo treatment, 0.1mg, 0.3mg or 1.0mg of LGD-4033 daily for 21 days.[54] The study assessed the safety, tolerability, pharmacokinetics, and effects of LGD-4033 on lean body mass, muscle strength, stair climbing power and sex hormones. [54] Overall LGD was well tolerated, and the adverse event frequency was similar between placebo and dosing groups. Expected dose dependent suppression of testosterone levels and sex hormone binding globulin levels was seen, with a free testosterone level depression seen only in the 1.0mg group. [54] Lean body mass increased in a dose dependent manner, but there was no significant change in fat mass. [54] HDL levels also fell in a dose dependent

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manner, but both lipid and hormone levels returned to baseline after treatment discontinuation. [54]

Thus, clinical testing has shown SARMs to be well tolerated with mild and infrequent adverse effects. Several of the trials showed no increases in AEs compared to placebo. The most consistent biological alteration shared between most of the tested compounds were decreases in HDL levels and transient increases in ALT. Anabolic androgenic steroids (AAS) like testosterone are known to increase liver transaminase levels, and there have been reports of peliosis hepatis, cholestasic jaundice, and liver malignancies associated with their use.[55] None of the subjects in the above trials had alterations in their bilirubin levels to suggest cholestasis, but several had elevations in ALT, suggesting hepatocellular injury. Liver damage from AAS was initially thought to be due to an idiosyncratic hypersensitivity reaction, but has been shown to be due to intrinsic direct hepatotoxicity of AASs depending on individual susceptibility with genetics playing a role.[56] Thus, it remains to be seen if SARMs may pose a risk of significant hepatotoxicity and further studies are needed to examine the relationship between theses transient ALT elevations and pathologic hepatic changes.

While HDL is negatively associated with the risk of atherosclerotic disease, pharmacologically induced decreases in serum HDL levels have not necessarily been associated with changes in cardiovascular risk.[54] Androgen induced decreases in serum HDL might be secondary to the upregulation of scavenger receptors involved in HDL metabolism. [36] In addition, animal models suggest that the cardioprotective effects of HDL are influenced more by the mechanism of HDL modification rather than changes in HDL levels.[36] Thus, evidence would support that androgen induced changes in serum HDL are not necessarily equivalent to having low HDL at baseline. Considering that SARM administration seems to reduce several cardiac risk factors such as insulin sensitivity and triglycerides, long term studies are needed to determine the effects of chronic SARM treatment on cardiovascular risk. Efforts are also underway to develope SARMs amenable to transdermal delivery in order to maximize local concentrations and minimize systemic side effects, such as lowering HDL-C by binding AR in the liver. [19]

## POTENTIAL FOR ABUSE

The anabolic effects of SARMs and their lack of androgenic side effects have made them of great interest to the bodybuilding community and create the potential for abuse among competitive athletes.[48] Unfortunately, despite the lack of FDA approval, many of the SARMs mentioned in the studies above are available for purchase online, though it is unclear how verifiable their sources are.[57] Forums complete with starter guides for first time users (on subjects like obtaining and interpreting blood work) and links for purchase are easily accessible, and anecdotal experiences and advice are widely shared.[58] In 2008 the World Anti-doping Agency banned SARMs in sports, citing their potential for abuse.[48] A study sponsored by governmental anti-doping organizations in Europe used mass spectrometry to identify S-4 (Andarine) and chemically related impurities in supplements being sold online, suggesting that these online retailers are providing biologically active SARMs in their supplements.[48]

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## CONCLUSION

The AR is a complex signaling apparatus with important effects on tissue development, growth and maintenance. While steroid hormones have valuable clinical applications, their widespread activation of AR receptors gives rise to treatment-limiting side effects. Like the SERMs before them, SARMs and their tissue selectivity demonstrate the potential to revolutionize the treatment of many debilitating diseases. Depending on their chemical structure, SARMs can act as agonists, antagonists, partial agonists, or partial antagonists of the AR within different tissues. Results from recent clinical trials have shown mixed but promising results and basic research continues to raise the idea that SARMs could be powerful and effective treatments in wide variety of conditions, from Alzheimer's disease and osteoporosis to male contraception and BPH.

Continued investigation and development of these agents is called for given their novel mechanisms of action and potential to address and complement conditions with a lack of effective therapies or therapies with unacceptable side effects. Additionally, to date SARMs have consistently been shown to be well tolerated, easily administered via an oral route, and overall lacking in significant drug interactions which can only further increase their future applicability. Like the SERMs before them, the next decades could herald the approval and widespread use of SARMs for an array of indications. However, further studies are currently needed to determine the safety and efficacy of these medications before they are approved for clinical use.

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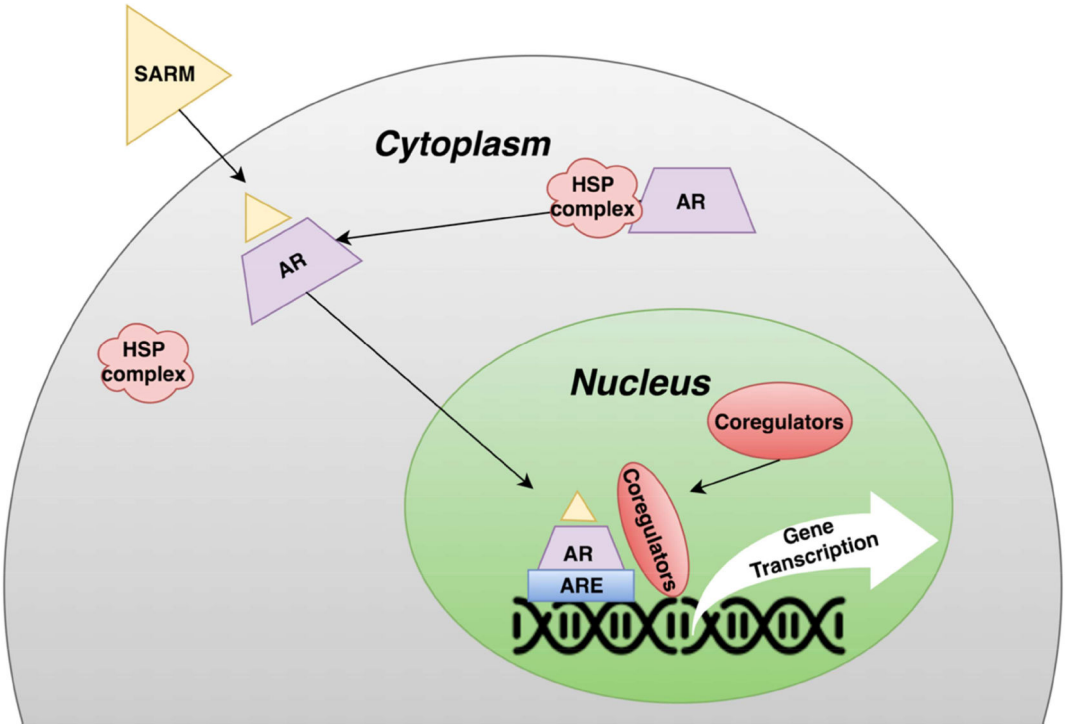


**Figure 1: Mechanism of SARM signaling.**

Like androgens, SARMs enter the cytoplasm, where they displace the androgen receptor from heat shock proteins. Once bound, they translocate to the nucleus and act as transcription factors by binding androgen response elements (AREs). Depending on the tissue type and regulatory environment of the cell, different co-regulatory proteins help determine and modulate the transcriptional response. HSP = Heat shock protein. AR = Androgen Receptor. ARE = Androgen Response Element.

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SARM Review Tables

| Study Title | ClinicalTrials.gov Identifier | Phase | Design | Intervention | Patient Population | Primary outcome | Status |
|---|---|---|---|---|---|---|---|
| Pembrolizumab and Enobosarm in Treating Patients with Androgen Receptor Positive Metastatic Triple Negative Breast Cancer | NCT02971761 | Phase 2 | Intervention model: single group assignment | Enobosarm + Pembrolizumab | Patients with metastatic triple negative breast cancer | Safety and tolerability of treatment, response rate | Recruiting; estimated primary completion June 2018 |
| Study to Assess Enobosarm (GTx-024) in Postmenopausal women with Stress Urinary Incontinence (ASTRID) | NCT03241342 | Phase 2 | Randomized placebo controlled | Enobosarm vs placebo | Postmenopausal women aged 18–80 with stress urinary incontinence | Change in number of stress urinary incontinence episodes | Not yet recruiting |
| A Selective Androgen Receptor Modulator For Symptom Management in Prostate Cancer | NCT02499497 | Phase 2 | Randomized placebo controlled trial | LY2452473 vs placebo | Men who have undergone prostatectomy for prostate cancer | Harbor-UCLA 7-day Sexual Function Questionnaire | Recruiting; estimated primary completion March 2019 |
| Safety, Tolerability, Pharmacokinetic (PK), and Pharmacodynamic Study of GSK 2881078 and Study to Evaluate he Effect of CYP3A4 Inhibition on PK of GSK2881078 | NCT02567773 | Phase 1 | Randomized placebo controlled trial | Part A: GSK2881078 Vs Placebo Part B: GSK2881078 + Itraconazole | Part A: Healthy men aged 50–75, postmenopausal women Part B: Healthy men aged 18–60 | Measures of tolerability and AEs, pharmacokinetic and pharmacoynamic measurements | Completed |
| Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of GSK2881078 in Single and Repeat Doses | NCT 02045940 | Phase 1 | Randomized placebo controlled crossover assignment | GSK2881078 vs placebo | Healthy males aged 18–50 | Safety and tolerability, pharmacokinetics, pharmacodynamics | Completed |
| A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GSK2849466 in Healthy Male Subjects | NCT01696604 | Phase 1 | Randomized placebo controlled crossover assignment | GSK2849466 vs placebo | Healthy males aged 18–50 | Safety and tolerability, pharmacokinetics, pharmacodynamics | Completed |
| Study to Evaluate Safety and Tolerability of Single and Multiple Ascending Doses of PF – 06260414 in Healthy Western and Japanese Male Subjects | NCT02070939 | Phase 1 | Randomized placebo controlled | PF-06260414 vs placebo | Healthy males aged 21–50 | Safety and tolerability, pharmacokinetics, pharmacodynamics | Completed |
| GLPG0492 Pharmacodynamics | NCT01538420 | Phase 1 | Randomized placebo controlled | GLPG0492 vs placebo | Healthy males aged 18–50, post-menopausal women aged 35–65 | Safety and tolerability, pharmacokinetics, pharmacodynamics, effect on protein synthesis in muscle | Completed |