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SELECTIVE ANDROGEN RECEPTOR MODULATORS: A BRIEF NARRATIVE REVIEW

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Abstract:
The popularity of Selective Androgen Receptor Modulators (SARMs) has grown among members of the fitness community. Reports of usage have increased in recent years due to their alleged comparable efficacy to anabolic androgenic steroids (AAS), commercial availability, relative ease of procuring constituents sold as research chemicals, and oral bioavailability. In spite of these perceived benefits, the use of SARMs is encumbered by immense health risks. The composition, pharmacokinetics, route of administration, potential clinical uses, and dangers associated with illicit use will be presented in this brief narrative review.

Keywords: selective androgen receptor modulators, SARM, anabolic androgenic steroids, AAS, ergogenic aids

1. Introduction

In recent years, Selective Androgen Receptor Modulators (SARMs) have been deployed by competitive and recreational athletes alike to enhance athletic performance and improve body composition. Among bodybuilding and fitness communities, SARMs are purported to be safer than their Anabolic Androgenic Steroid (AAS) counterparts since they favorably bind with androgen receptors but are not subject to aromatase or 5α-reductase activity, thus mitigating undesirable androgenic actions in peripheral tissue and organs (Hoffman, 2014). Their use among competitive and recreational athletes has grown prevalent and is magnified by social media, as many users proclaim their efficacy and tout them as a safer alternative to AAS (Hahamyan, Vasireddi, Voos, & Calcei, 2022). Similar to AAS, SARMs encompass a wide range of clinical applications, having been identified as possible treatments for hypogonadism, muscle wasting, breast cancer, and osteoporosis (Machek, Cardaci, Wilburn, & Willoughby, 2020). However, their

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deployment among non-clinical populations, prominently including competitive and recreational athletes, has demonstrated immense health risks as reports of hepatoxicity and myocarditis have emerged (Akhtar, Locke, & Stine, 2021; Padappayil, Arjun, Acosta, Ghali, & Mughal, 2020).

2. Background

SARMs were developed in the late 1990s to preferentially activate androgen receptors in skeletal muscle, sans unwanted androgenic effects, which are common with AAS. Undesirable consequences of AAS use include gynecomastia, infertility, testicular dysfunction, acne, androgenic alopecia (male pattern balding), ischemic heart diseases, thromboembolism, liver and kidney disease, depressive symptoms, lethargy, insomnia, and reduced libido (Hoffman, 2014; Horwitz, Andersen, & Dalhoff, 2018; Machek, Cardaci, Wilburn, & Willoughby, 2020) resulting from broad, non-specific androgen receptor activation. Androgen receptors (AR) comprise the steroid receptor family of ligand-activated transcription factors and are intimately involved in organogenesis, physiology, and pathology of a host of tissues (Narayanan, Coss, & Dalton, 2018) and entail four functional domains: 1) the NH_2-terminal transactivation domain, 2) the DNA-binding domain, 3) the ligand-binding domain, and 4) the hinge region which links the DNA-binding and ligand-binding domains (Machek, Cardaci, Wilburn, & Willoughby, 2020). These domains work in concert to establish and maintain a homeostatic environment for the AR that affords binding to endogenously secreted ligands, consisting of steroid hormones, growth factors, and peptides. AR can be activated by endogenously secreted ligands or via exogenously administered hormones, growth factors, and peptides, which can alter their transcriptional characteristics (Patt, 2020). AR are ubiquitous throughout the body and are located in diverse tissues, including testes, prostate, breast, and uterus. However, endogenous secretion, even within a clinically healthy range, and exogenous administration of steroid hormones at clinically recommended doses, may contribute to unwanted hypertrophy of tissue and organs well-populated by AR. Through their tissue-selective expression of AR-isoforms and enzymatic activity unique to steroid hormones, SARMs are able to evade interaction with AR embedded in liver, cardiac, or gonadal tissue and therefore not stimulate maladaptive hypertrophy or interfere with steroidogenesis (Patt, 2020; Machek, Cardaci, Wilburn, & Willoughby, 2020) since they do not undergo 5α-reductase are not metabolized to dihydrotestosterone, like their AAS counterparts.

Multiple SARM compounds have been identified in the literature, with some demonstrating promise as therapeutic agents in clinical trials. The most commonly deployed SARMs among competitive and recreational athletes are MK-2866, alternatively known or branded as Ostarine, Enobosarm, and GTX-024; RAD-140, also known as Testolone, LGD-4033, also known as VK5211 and marketed as Ligandrol,; and S4, a predecessor to MK-2866, also known as Andarine (Hahamyan, Vasireddi, Voos, & Calcei, 2022). MK-2866 has demonstrated favorable anabolic effects while evoking

minimal effects in the prostate and testes of male rodents (Machek, Cardaci, Wilburn, & Willoughby, 2020). In a clinical trial constituted of elderly men and postmenopausal women, hormetic increases were noted in total lean body mass and concomitant fat losses, as well as improved glucose control, anaerobic power, and lipid profiles (Neil, 2018). No alterations in skin, prostate, liver, kidney, or endocrinological health were noted. However, similar to AAS administration, increases in hemoglobin and hematocrit were observed. Additionally, MK-2866 was shown to increase body weight, lean body mass, and physiological cross-sectional area of muscle among cancer cachexia rodent models (Morimoto, Aikawa, Hara, & Yamaoka, 2017). RAD-140 elicited peripheral tissue-specific androgen action which circumvented prostate AR and was shown to be as effective as testosterone in reducing cell apoptosis (Jayaraman, 2014). Among healthy young men, LGD-4033 was shown to increase lean body mass over a period of 21 days without adversely affecting hemoglobin, prostate-specific antigen, aspartate aminotransferase, alanine aminotransferase, or QT intervals (Basaria, 2013). However, doses as low as 0.3 mg were shown to suppress follicle-stimulating hormone and testosterone, which returned to baseline after discontinuation. In clinical trials, S4, one of the first SARMs to be developed in the 1990s, has been explored as a potential treatment for benign prostatic hyperplasia and as an adjuvant to androgen deprivation therapy during advanced prostate cancer. S4, among other SARMs, could help attenuate muscle wasting and bone loss during cancer treatment and may stimulate appetite (Morimoto, Aikawa, Hara, & Yamaoka, 2017). A recent study revealed that S4 inhibited growth, migration, and proliferation while inducing apoptosis in lung adenocarcinoma A549 cells (Demircan, Yavuz, & Bölük, 2023). In comparison to AAS in clinical applications, SARMs appear to elicit fewer adverse effects, particularly on cardiovascular health; however, the risks of diminished of luteinizing hormone and FSH loom as suppressed endogenous hormone production has been noted in multiple studies (Machek, Cardaci, Wilburn, & Willoughby, 2020).

3. Use Among Competitive and Recreational Athletes

Since they are largely regarded as a safer alternative to AAS, SARMs are popular among bodybuilders and fitness enthusiasts. Social media, including TikTok, YouTube, and Facebook, where many informational videos are posted by influencers masquerading as health and fitness professionals, has contributed to the proliferation of their usage. According to a survey comprising 441 respondents, 343 (78%) reported SARM usage, with 72.3% of respondents comprising the 18–29-year-old age group (Hahamyan, Vasireddi, Voos, & Calcei, 2022). “SARMs” is also a popular search term on multiple search engines, including Google, on which it surpassed “TRT” and “low testosterone” search terms during early 2018 (Efimenko, Chertman, Masterson, Dubin, & Ramasamy, 2021). By mid-2021, videos tagged “SARMs” on the controversial social media platform, TikTok, numbered more than 115 million views (Hahamyan, Vasireddi, Voos, & Calcei, 2022). High profile athletes, including former National Basketball Association star,

Joakim Noah and American football players, Taylor Lewan of the Tennessee Titans and DeAndre Hopkins of the Arizona Cardinals, both of the National Football League, tested positive for SARMs in recent years (Mahoney, 2017; Caron, 2019; Anderson, 2022). Usage among recreational athletes appears to be concerning. A cross-sectional study of male gym goers (N = 2264; 24±6 years) revealed that 2.7% of respondents used SARMs compared to 9% of respondents who reported use of AAS (Hilkens, Cruyff, Woertman, Benjamins, & Evers, 2021).

4. Route of Administration, Dosage, and Stacking

SARMs are orally bioavailable, similar to 17-alpha alkylated anabolic steroids, including methyltestosterone, metandieone, oxandrolone, oxymetholone, stanolozol, and methasterone (Hoffman, 2014). Their oral bioavailability is both convenient and insidious, as it mitigates apprehensions associated with use in comparison to intramuscular and subcutaneous injections. To date, oral ingestion of SARMs remains the sole method of administration. Therapeutic dosages and amounts taken for improvements in performance and body composition vary widely. Dosages ranging from 0.1 to 3.0 mg have proven efficacious and relatively safe in clinical trials. However, daily dosages among athletes, bodybuilders, and fitness enthusiasts may range from 5 mg to 50 mg and are analogous to illicitly used AAS, are often stacked with one or more SARMs being deployed simultaneously. Due to their hypothalamic-pituitary-testicular axis suppressive properties, post-cycle therapy (PCT) is indicated. PCT is routinely implemented following the cessation of AAS cycles, with deployment dependent upon the half-lives of ceased AAS compounds. Selective estrogen receptor modulators (SERMs), such as clomiphene, known by its drug name, Clomid, or tamoxifen citrate, known by its drug name, Nolvadex, are often leveraged to stimulate testosterone production. Additionally, aromatase inhibitors and over-the-counter supplements such as D-aspartic acid, and Tribulus terrestris may be used to normalize hormone production. SARMs and their interactions with other performance enhancing drugs (PEDs), dietary supplements, prescription and over the counter medications, recreational drugs and alcohol, and their effects on existing medical conditions, specifically metabolic or cardiovascular diseases, have not been extensively studied, therefore, possible contraindications for use cannot be readily determined. To safeguard athletes and cultivate an equitable competitive atmosphere, the World Anti-Doping Agency banned SARMs from athletic competition in 2008. In 2017, the Food and Drug Administration (FDA) issued a public advisory warning that SARMs were being found in bodybuilding supplements and may cause adverse health effects. Additionally, the Department of Defense (DOD) has alerted armed service personnel, healthcare providers, and civilian employees that SARMs may adversely affect endocrinological and cardiovascular health (Burmeister, Fincher, & Graham, 2020).

5. Commercial Availability and Purity

Pursuant to FDA and DOD warnings, United States based retailers and websites discontinued their sale of SARMs. Concerningly, SARMs can still be purchased as "research chemicals", which are not indicated for human consumption, from multiple independently operating and "underground" laboratories. SARMs are often sold as serums, contained in vials, with a transfer pipette and are accompanied by explicit hypothetical instructions for use that imply eventual ingestion.

Analysis of 44 dietary supplements marketed as being or containing SARMs revealed that only 52% actually contained one or more SARMs. An additional 39% of the products contained another unapproved drug, 9% of the products did not contain any active ingredient, and substances not denoted on the label were contained in 25% of products (Burmeister, Fincher, & Graham, 2020). It is worth noting that the risk of dangerous supplements being found in dietary supplements is omnipresent. In 2012, a popular pre-workout supplement, Jack3d was found to contain 1-3-dmethylhexaneamine, or DMAA, a powerful stimulant which was previously discontinued in its clinical application as a nasal decongestant for potential safety issues. Others, including batches of a popular male vitality supplement derived from exotic plant extract, Tribulus terrestris, were found to contain traces of androstenedione and AAS nandrolone analogues (Pokrywka, 2014).

6. Safety and Case Reports

Though a recent trial executed by a major pharmaceutical company involving a variant of MK-2866 offered hope in improving muscle strength for patients with chronic obstructive pulmonary disease (Mohan, 2023), SARMs have not advanced past stage II clinical trials due to lingering efficacy and potential safety issues. Nevertheless, usage of SARMs continues among competitive and recreational athletes, especially among males. A report of a 46-year-old male presenting to a facility with a two-month history of abdominal discomfort, skin discoloration, pruritus, and urinary and bowel habit changes, absent significant alcohol consumption or acetaminophen use, revealed that the patient had been using SARMs for six months (Aktar, Locke, & Stine, 2021). The patient's bilirubin levels had risen to 34 mg/dL (nearly 20 times the upper limit) and was consulted for a liver transplant. However, the patient's health improved when they discontinued SARMs and were subsequently removed from consideration for a liver transplant. Hepatoxicity is a concern for prolonged use of SARMs, similar to AAS. A report of a 32-year-old male presenting to a facility with complaints of shortness of breath on exertion, fever, and elevated heart rate revealed acute myocarditis upon further examination (Padappayil, Arjun, Acosta, Ghali, & Mughal, 2020). Elevated creatine kinase and C-reactive protein levels were noted, as was troponin I. The patient had been consuming RAD-140 in conjunction with resistance training to elicit improvements in muscular hypertrophy. Following seven days of discontinuation of SARMs, the patient's

ventricular function and inflammation had improved, and the patient was summarily discharged. RAD-140 was also implicated in a drug-induced liver injury suffered by a previously healthy 22-year-old male who had reported to a facility with jaundice, nausea, fatigue, dark urine, and light stools (Mohamed, 2023). Laboratory tests revealed that the patient had elevated alkaline, phosphatase, alanine transaminase, aspartate transaminase, and bilirubin levels. It was discovered that the patient had been using RAD-140 for 16 weeks continuously. The patient's condition improved upon cessation, and a full recovery was expected. A recent compilation of self-reported adverse side effects associated with the usage of SARMs was presented by Joshi and colleagues (2025). SARM users reported significant changes in biomarkers, including aspartate aminotransferase, alanine aminotransferase, increases in creatine kinase, low-density lipoprotein, and decreases in high-density lipoprotein, total testosterone, and sex hormone binding globulin (Joshi *et al.*, 2025).

7. Conclusion

Although SARMs appear to be a safer alternative to AAS in both clinical and performance enhancement contexts, their long-term effects remain somewhat inscrutable due to the comparative dearth of literature chronicling their safety and efficacy. While they mimic the anabolic activity of AAS, their AR tissue selectivity may not be as precise as once considered due to multiple reports of adverse health effects, including myocarditis and hepatic injury. Fortunately, SARMs are not as readily available commercially as they were just a couple of years ago. The detectability of SARMs via rote gas chromatography mass spectrometry testing (Thevis & Schänzer, 2018) should dissuade both athletes and coaches from their deployment. However, more research needs to be conducted on SARMs to ascertain their viability as a therapeutic agent.

Conflict of Interest Statement

The author declares no conflicts of interest.

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