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Recreational Use of Selective Androgen Receptor Modulators

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ABSTRACT: Selective androgen receptor modulators (SARMs) are anabolic compounds that bind to androgen receptors. They have been studied as potential treatments for cancer, osteoporosis, sexual dysfunction, multiple sclerosis, Alzheimer's disease, and muscle wasting. Recently, SARMs have been placed in various supplements marketed to fitness enthusiasts. SARMs have been found to reduce endogenous testosterone, affect cholesterol levels, and alter liver function. Recreational users of SARMs may take them in combination with each other on a cyclical basis. They may also practice postcycle therapy, which involves the use of SERMs in between cycles to help restore hormone balance. Pharmacists should be aware of the adverse side effects of SARMs use in order to advise individuals of the potential risks.

In their role as a critical link between healthcare providers and patients, pharmacists must recognize that individuals may not always be entirely forthcoming about the agents they use. Selective androgen receptor

modulators (SARMs), which are becoming increasingly popular as performance-enhancing supplements due to their lean muscle mass-building, fat-cutting, endurance, and recovery properties, may be one example. People who take or consider taking products containing SARMs recreationally include fitness enthusiasts, bodybuilders, and those with physically demanding jobs. In 2008, SARMs were banned from sports by the World Anti-Doping Agency.[1] In 2017, the FDA issued a public advisory stating that SARMs were being included in bodybuilding products and that these compounds posed an increased risk for heart attack, stroke, and liver damage.[2] In response to the FDA's public warning on SARMs, the Council for Responsible Nutrition, the trade organization for the dietary-supplement industry, introduced voluntary guidelines that encouraged that SARMs not be included in dietary supplements.[3] The Department of Defense's (DOD) "Operation Supplement Safety" has also warned armed services personnel, healthcare providers, and DOD civilians that SARMs may artificially lower endogenous testosterone and have detrimental effects on liver function and cholesterol levels.[4]

A recent study determined the chemical identity and the amounts of ingredients in dietary supplements and products marketed and sold through the Internet as SARMs and compared the analyzed contents to their product labels.[5] Among the 44 products marketed and sold as SARMs that were tested, only 52% actually contained one or more SARMs. An additional 39% of the products contained another unapproved drug. No active compound was detected in 9% of the products, and substances not listed on the label were contained in 25%. The amount of active compound in the product matched that listed on the label in only 41% of the products, and the amount of the compounds listed on the label differed substantially from that found by analysis in 59%. These findings highlight an alarming lack of regulatory oversight and pose significant safety concerns regarding these products.

The most popular SARMs currently on the market include Ostarine (MK-2866), Ligandrol (LGD-4033), Testolone (RAD-140), and Andarine (GTx-007, S-4).[6] Despite the growing use and purported safety of SARMs in the fitness and bodybuilding communities, very few clinical studies aimed at understanding their pharmacokinetic profiles and identifying potential adverse effects and drug interactions have been performed.[7] Consequently, their long-term effects on the body remain largely unknown. Clinical experience with SARMs is largely from illicit use rather than clinical studies.[7] Additionally, in the fitness community, SARMs are taken at doses and

durations that are higher than those tested clinically. The interactions of SARMs with other substances (e.g., alcohol and other drugs) with chronic use, particularly at high doses, remains unknown.

Currently, it is legal to sell and buy SARMs that are marketed simply as research chemicals, which commonly occurs online. However, it is illegal to sell and buy those that are packaged in capsules for human consumption and/or labeled as dietary supplements.[8] Furthermore, they cannot be marketed to the public as dietary supplements, and claims regarding their benefits cannot be made.[8] Here we review the current clinical literature to assess the health benefits versus risks of using SARMs as performance enhancers.

Nonsteroidal SARMs: Alternative to Androgenic-Anabolic Steroids

Discovered in the late 1990s, SARMs are performance-enhancing agents that stimulate anabolism (i.e., increase muscle mass and strength) and facilitate recovery from exercise.[9] SARMs are not anabolic steroids; rather, they are synthetic ligands that bind to androgen receptors (ARs).[9] Depending on their chemical structure, they function as full agonists, partial agonists, or antagonists.[9] Each SARM-AR complex possesses a different conformation, and various tissues (e.g., skeletal muscle, bone, prostate, brain, skin, liver) display a unique pattern of AR expression.[9] It is, thus, in a tissue-selective manner that SARMs mediate coregulators and transcription factors or signaling cascade proteins to promote anabolic activity.[10] Nonsteroidal SARMs serve as an attractive alternative to anabolic-androgenic steroids because they have fewer limitations.[7] In contrast to steroidal androgen preparations, SARMs display high oral bioavailability.[11] Nonsteroidal SARMs also exhibit diminished androgenic activity because they are not metabolized to dihydrotestosterone (DHT) by 5 alpha-reductase, an enzyme that is highly expressed in androgenic tissues.[11] They are also not metabolized to estrogen by aromatase.[11] For these features combined, nonsteroidal SARMs have been deemed to be advantageous over their steroidal counterparts.[11] Indeed, SARMs have shown substantial therapeutic promise for male contraception and in the treatment of osteoporosis, prostate cancer, sexual dysfunction, benign prostatic hyperplasia, Alzheimer's disease, muscular dystrophy, breast cancer, and muscle wasting associated with cachexia and sarcopenia.[9] Fueled, at least in part, by the perception that SARMs are safer than anabolic steroids, recreational users are now leveraging the various anabolic profiles of different SARMs to selectively achieve results in terms of "bulking" and "cutting."[12,13] *Bulking* refers to a muscle-gaining phase that

combines a weight-gain diet with intense weight training, whereas *cutting* refers to a fat-losing phase that combines adherence to a strict weight-loss diet with aerobic exercise and less-intense weight training. Anecdotal evidence claims that different SARMs yield different results in terms of bulking versus cutting, which is why bodybuilders and other fitness enthusiasts commonly use them in combination (or *stacked*) with each other.[12,13]

Ostarine/Enobosarm/GTx-024/MK-2866/S-22

Ostarine is an orally bioavailable, nonsteroidal SARM that was developed by Gtx, Inc. in the late 1990s primarily for the treatment of muscle wasting and osteoporosis. Ostarine is the best clinically characterized SARM. The few published clinical trials have examined its potential for treating skeletal muscle deficits seen with stress urinary incontinence, breast cancer, non–small-cell lung cancer, and cancer-related cachexia. In clinical trials conducted thus far,[14-16] a significant increase in total lean body mass was consistently observed, including in cancer patients.[14,15] In some studies, there was also an accompanying decrease in total fat mass with no difference in total body weight.[14] Common low-grade side effects included headache, nausea, fatigue, and back pain.[14] Other observed effects were transient elevation in the alanine transaminase (ALT), reductions in high density lipoprotein (HDL), blood glucose, insulin, and insulin resistance.[14] These altered parameters all returned to normal upon cessation of treatment. Information provided on personal blogs and commercial websites advises fitness and bodybuilding enthusiasts to supplement with ostarine at dose ranges from 10 mg to 30 mg for at least 12 weeks.[17] These doses are 10 times those studied clinically. Anecdotal evidence suggests that taking ostarine at these high doses over this extended time period can adversely lead to lowered testosterone levels.[17] The side effects of decreased testosterone include reduced sex drive, erectile dysfunction, infertility, muscle weakness, loss of bone density, weight gain accompanied by increased body fat, insomnia, and depression.[18] Potential drug-drug interactions between ostarine (and its major metabolite) and itraconazole, probenecid, celecoxib, and rosuvastatin have been examined with little evidence of clinically relevant drug interactions.[19] According to one website promoting SARMs, it is recommended that SARMs be “stacked” for enhanced and differential benefits.[13] Whether taking higher doses of multiple SARMs chronically poses a risk for adverse drug-drug interactions remains unknown.

Ligandrol/LGD-4033/VK5211

Ligandrol is another orally bioavailable SARM. Developed by Ligand Pharmaceuticals, there has been only one clinical trial involving the drug.[20] In the placebo-controlled study, 76 healthy men were randomized to placebo or 0.1 mg, 0.3 mg, or 1.0 mg LGD-4033 daily for 3 weeks. The drug was well tolerated, with no serious adverse drug-related events. Hemoglobin, prostate-specific antigen, aspartate aminotransferase (AST), ALT, and QT intervals were not altered at any dose. At the 1.0 mg dose, follicle-stimulating hormone and free testosterone were significantly suppressed; there was no change in luteinizing hormone. Hormone levels returned to normal when the treatment was discontinued. Lean body mass increased dose-dependently, but there were no statistically significant changes in fat or appendicular skeletal muscle mass. Strength and stair-climbing speed and power trended toward a dose-dependent improvement but were not statistically significant. Total and low density lipoprotein (LDL) cholesterol did not change significantly from baseline at any dose. Although HDL increased at the 0.3 and 1.0 mg doses, it returned to normal upon discontinuation. Triglyceride levels decreased from baseline at all doses. Headache and dry mouth were the most common side effects. In a recent case report, a healthy 24-year-old man displayed signs of hepatocellular liver injury.[21] These symptoms developed a week after drug cessation. The man had a history of binge drinking, was not on regular medications, and had no previous history of liver disease. Of concern, this hepatotoxicity lies within the spectrum of liver injury associated with androgenic anabolic steroids.

Many online blogs tout Ligandrol as being extremely effective for enhancing performance, bulking (vs. cutting), muscle hardening, increasing vascularity, gaining size, and enhancing recovery.[22] Fitness enthusiasts are advised to take between 5 mg and 10 mg daily for 6 to 10 weeks, along with the disclosure that there is a risk of testosterone suppression at doses greater than 10 mg.[22] Similar to ostarine, Ligandrol is often stacked with other SARMs for a heightened benefit.[13] Anecdotal side effects described in the fitness and bodybuilding arenas include nausea, fatigue, headaches, and low libido, which may all be attributable to reduced testosterone.[22]

Testolone/RAD-140

Testolone is a SARM used primarily for the treatment of muscle wasting and breast cancer. Developed by Radius Health, Inc., Testolone is reportedly still in first-stage clinical trials, with results expected later this year. Thus, little is currently known about its safety. One recent case report, however, describes significant liver injury in a 49-year-old man who had taken the drug (dose not

reported).[21] Elevations in bilirubin, AST, ALT, and creatinine indicated mixed hepatocellular-cholestatic liver injury. Liver histology also revealed inflammation. However, all liver tests had completely normalized at 12 months following his initial presentation. For gaining lean muscle mass and strength in the gym, SARMs users anecdotally recommended that Testolone be taken at 5 mg to 30 mg daily for 8 to 16 weeks.[23] There is additional anecdotal evidence of side effects including sleeplessness and lethargy.[24]

Andarine/GTx-007/S-4

To date, there are no human clinical studies with Andarine. In the fitness community and on various online forums, it is touted as a muscle-boosting supplement that elicits weight loss and promotes muscle building and repair.[25] However, it is regarded as being comparatively weaker than other popular SARMs, so it is commonly stacked with other SARMs.[25] Using Andarine by itself at 25 mg per day purportedly improves mood and general wellness, whereas increasing the dose to 50 mg per day only modestly boosts strength, lean mass, and fat burning.[25] For bulking, it is recommended that Andarine (50 mg) be stacked with Testolone (10 mg) daily for 8 to 12 weeks.[25] For strength, it is suggested that Andarine (50 mg) be stacked with Ligandrol (10 mg) daily for 2 to 3 weeks.[25] For cutting, it is advised that it (25 mg) be stacked with Cardarine (20 mg, a non-SARM, paroxisome proliferator-activated receptor-delta agonist) daily for 12 weeks.[25] For body recomposition (i.e., simultaneously losing fat and gaining muscle), it is recommended that Andarine (50 mg) be stacked with both Ostarine (25 mg) and Cardarine (20 mg) daily for 9 to 12 weeks.[25] The primary side effects reported with Andarine are altered vision (i.e., yellow-tinged) and suppression of testosterone.[25]

SARMs and Postcycle Therapy

In the fitness and bodybuilding communities, it is generally recognized that a weeks-long SARM regimen likely lowers testosterone levels.[26,27] In order to maintain gains in muscle mass and strength, facilitate the body's recovery from any potential hormonal imbalance, and expedite the elevation of testosterone levels to normal, it is recommended on numerous nonmedical, online forums that periods of postcycle therapy (PCT) be incorporated in between each cycle of SARMs use.[26,27] Many different PCT formulations that claim to naturally increase testosterone, reduce estrogen, stabilize cortisol, and enhance liver health are available commercially. These formulations may include, but are not limited to, ingredients such as the aromatase inhibitor arimistane (an antiestrogen supplement) and D-aspartic acid (DAA).[26] Other

common PCT supplements are Clomid (clomiphene citrate) and Nolvadex (tamoxifen).[27] These are prescription drugs in the United States but may be acquired online through foreign sources. Clomid is a selective estrogen receptor modulator (SERM) that increases testosterone production, thereby preventing gynecomastia.[27] Clomid is advised when the SARM cycle is heavy, as it acts as a strong PCT.[27] However, it also carries the most reported side effects—mood swings, headaches, and altered vision at high dosages.[27] Nolvadex is a less potent SERM that works similarly.[27] Although formulations including natural extracts and non-SERM ingredients are theoretically safer than Clomid and Nolvadex, their effectiveness has not been scientifically proven.[27]

Recreational SARMs users recommend that the PCT dosage be front-loaded when testosterone levels are lowest, thereby lowering the dose required when testosterone levels are closer to or returned to normal.[28] Users also advise that PCT therapy be started immediately the day after a SARM cycle is done, typically lasting 4 weeks.[26] To complicate matters, the length and even necessity of a PCT cycle are influenced by the strength and dose of the SARM used.[28] Until there are concrete clinical data, the potential adverse effects of cycling SARMs with PCT supplements will remain unknown.

Conclusion

SARMs are investigational drugs that have been studied for more than 20 years, yet none have received FDA approval, even for conditions in which the benefits might outweigh any significant risks. Much of the evidence regarding the performance-enhancing benefits and overall safety of SARMs is anecdotal rather than founded on scientific investigation. The few clinical investigations of SARMs have identified heart attack, stroke, and liver damage as potentially serious health risks. Individuals who are most likely to use SARMs recreationally include bodybuilders, fitness enthusiasts, and those with physically demanding jobs such as police officers and firefighters. In addition to what is available for purchase online, popular OTC products labeled as SARMs include SARM-X and Osta-Plex, which can currently be found at some nutritional supplement stores.

Pharmacists have an obligation to educate the public on the potential health risks associated with SARMs use. Pharmacists should recognize that individuals may not disclose all supplements used and should inquire about their use when it is pertinent. Even when a complete list of supplements is provided, users may be unaware of all the compounds that are actually contained within them.[5,29] Pharmacists should caution individuals about

supplement use, particularly when the source may be questionable, and help them understand that supplements are not regulated as prescription drugs are. When a person discloses a health issue, it is important for the pharmacist to have the proper knowledge to identify all possible causes. The pharmacist should especially consider the use of SARMs if an individual's profile matches a group that typically uses performance-enhancing supplements and/or is experiencing adverse effects that are associated with SARMs use or PCT.

The content contained in this article is for informational purposes only. The content is not intended to be a substitute for professional advice. Reliance on any information provided in this article is solely at your own risk.

Resources

For more information about SARMs or supplements in general, pharmacists can consult or refer the following online resources:
Operation Supplement Safety: www.opss.org
National Institutes of Health: https://nccih.nih.gov/health/supplements/wiseuse.htm
Counsel for Responsible Nutrition: www.crnusa.org
Independent Product Testing: www.consumerlab.com/

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