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By Veselin Vasilev

WORD COUNT 6504
TIME SUBMITTED 06-DEC-2024 01:07PM
PAPER ID 113375413

AMALTEA MEDICAL PUBLISHING HOUSE

https://medscience.center/journals/

Words count – 6,501

TYPE OF ARTICLE: Reviews

Reported adverse effects of SARMs in animals and humans: a review

Veselin Vasilev[1], Nikolay Boyadjiev[1,2]

[1]Department of Physiology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria

[2]Research Institute, Medical University of Plovdiv, Plovdiv, Bulgaria

Corresponding author:

Veselin Vasilev

E-mail: v_vasilev1892@abv.**bg**

ABSTRACT

Background and Objectives: Selective androgen receptor modulators are androgen receptor ligands that exhibit pronounced anabolic effects but have tissue selectivity with respect to androgenic ones. Despite the established beneficial effects of non-steroidal SARMs in a number of socially significant diseases, they also exhibit side effects. Our purpose was to present the currently reported adverse effects of SARMs in animals and humans. Clinical trials have been conducted with the non-steroidal group of modulators, but in some of them they were not sufficiently effective, and in others the results have not yet been reported. So far, no non-steroidal SARM has been approved as a drug, but the substances are freely available on the Internet. The frequency of their use is increasing, but this also poses health risks.

Materials and Methods: To be able to write the review we found and screened SARMs articles in Google Scholar, ScienceDirect and PubMed electronic databases.

Results: An increasing number of cases of liver damage due to misuse of SARMs were observed for the period 2020-2024. In both humans and animals, non-steroidal SARMs often cause negative changes in lipid profile indicators, gonadotropic and sex hormones concentrations. Cases of myocarditis, rhabdomyolysis, gynecomastia and tendon rupture have been described in amateurs taking SARMs.

Conclusions: In conclusion, we can say that SARMs are not safe, and it is necessary to take measures to control and limit online trade with them, as well as to achieve greater publicity of information related to their side effects.

Keywords: SARMs, side effects, ostarine, ligandrol

Abbreviations:

AAS – anabolic androgenic steroids

ALT - alanine transaminase

AST - aspartate aminotransferase

FSH - follicle-stimulating hormone

HDL – high-density lipoprotein

LDL – low-density lipoprotein

LH – luteinizing hormone

SARMs – selective androgen receptor modulators

SHBG - sex hormone binding globulin

INTRODUCTION

Selective androgen receptor modulators (SARMs) are divided into two groups: steroidal and non-steroidal. Non-steroidal modulators are the newer and more relevant group, discovered at the end of the last century. They are characterized by the manifestation of tissue selectivity and relatively limited androgenic effects but preserved anabolic ones. This gives a basis to consider non-steroidal SARMs as more sparing compared to anabolic androgenic steroids (AAS). The mechanisms of tissue selectivity of non-steroidal SARMs are still not fully understood [1]. Some of them are related to the resistance of SARMs to enzymes 5-α reductase and aromatase [2]. Another possible explanation for the selectivity is the fact that after non-steroidal SARMs bind to the androgen receptor, it interacts with different coactivators and cosuppressors compared to those with which it interacts after binding of AAS [3]. Clinical trials have been conducted with representatives of the non-steroidal group to evaluate their therapeutic potential in prostate and lung carcinoma, breast carcinoma, urinary stress incontinence, benign prostatic hyperplasia, hypogonadism and chronic obstructive pulmonary disease [4]. However, none of the tested SARM substances have yet been approved for clinical use by regulatory authorities in the United States or Europe [5].

On the other hand, the illegal use of non-steroidal selective androgen receptor modulators is increasing. The substances are most often used by amateur and professional athletes, and in sports there has been an increase in the number of registered positive doping tests [6]. An easy way to obtain non-steroidal SARMs is by purchasing them online [7]. They are also included in various dietary supplements. SARMs are offered unlimitedly on many websites, with the aim of increasing muscle mass and strength, especially in bodybuilding. One of the most common forms in which they are offered is tablets or capsules [7]. In parallel, the number of reported side effects associated with their use is also increasing. The purpose of our article is to present the side effects of non-steroidal SARMs in humans and animals that have been identified so far. They should be known

to sports doctors, professional athletes, and amateurs due to the serious health risks that this group of molecules poses.

MATERIALS AND METHODS

To write this review, we used materials from the following electronic databases: Google Scholar, ScienceDirect and PubMed. The period covered in our study was from the discovery of non-steroidal SARMs in 1998 to the present. During the search, we used the following key phrases: "SARMs", "Selective androgen receptor modulators", "SARMs rats", "SARMs side effects", "Ostarine", "Ligandrol", Testolone", "Andarine". The website https://clinicaltrials.gov was also used by us as a source to find conducted clinical trials with non-steroidal SARMs. We found many studies reporting on the effects of SARMs, but only 56 of them were included in our review. The main criteria for including a study were that it presented information on the occurrence of side effects following the use of non-steroidal SARMs, both in animals and in humans. Articles that presented data only on the discovery process, synthesis and chemical structure of SARMs, on the pharmacokinetics, mechanism of action, doping control related to SARMs or on the described beneficial effects of these molecules were not included, due to non-compliance with our main criteria. All articles used in the review were freely available to us in English. We present the Prisma flow diagram illustrating the process of selection and processing of the results found. (Figure 1)

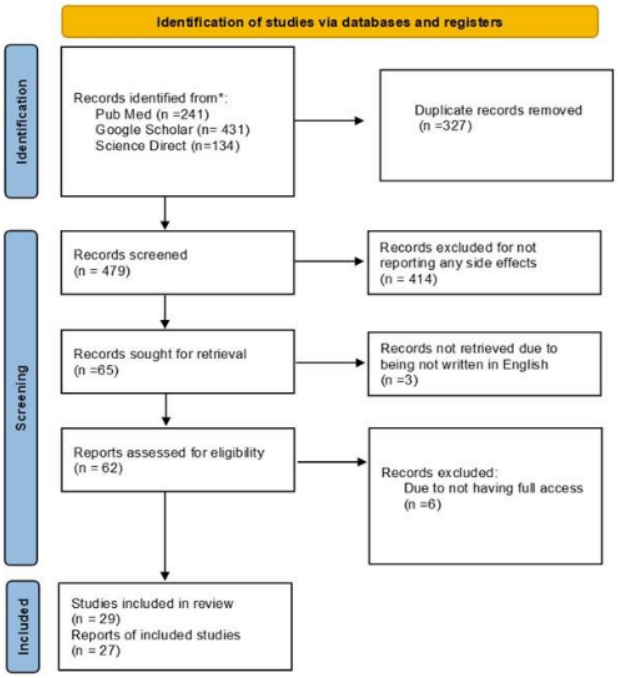

Figure 1. Prisma flow diagram.

RESULTS

Side effects in experimental animals

Side effects on the reproductive system

In healthy rats, JNJ-28330835 reduced plasma concentrations of testosterone and androstenedione compared to the control group [8]. In rats, administration of C-6, at a dose of 10 mg/kg, caused a decrease in the concentrations of gonadotropic hormones and testosterone after two weeks of administration, and after ten weeks, it also suppressed spermatogenesis. A decrease in the size of the testis and epididymis has also been reported [9]. The non-steroidal SARM - JNJ-37654032 (after 6 weeks of administration) also induced a decrease in the size of the testis of rats [10]. MK-4541 caused a decrease in plasma testosterone concentration in healthy male mice at doses of 100 and 200 mg after 5 days of weekly administration for 5 weeks [11]. In intact male rats (over a 14-day period), S-23 at a dose of 0.1 mg lowered LH and FSH by more than 50% [12]. In mice, ostarine (at a dose of 15 mg/kg) lowered the concentration of luteinizing hormone. [13]. It has also been reported that ostarine and ligandrol have a proliferative effect on the uterus in rats, which could also be defined as an adverse effect [14]. In another study, ostarine showed a similar effect on the uterus, but this time in mice [15].

Metabolic side effects

SARM-2f (at doses of 3 and 10 mg/kg, for a period of 14 days) reduced LDL, HDL, triglycerides and total cholesterol concentrations in monkeys [16]. S-42, after 3 weeks of administration, in castrated male rats, reduced plasma triglyceride concentrations. [17]. In an experiment with rats treated with testolone (RAD-140), a decrease in LDL, HDL and triglycerides was reported [18]. The authors also observed an increase in liver transaminases, which were two and a half times above normal, at the highest dose used [18]. Also in rats, in our 8-week experiment with ostarine, (at a dose of 0.4 mg/kg,) we found an increase in serum cholesterol concentration and a decrease in glucose concentration [19]. In another 8-week study, after ostarine administration at doses of 0.4 and 4 mg/kg in ovariectomized rats, serum phosphate and alkaline phosphatase concentrations were increased, and cholesterol was lowered [20].

Other side effects

In our study, in healthy male rats, we found that the combined administration of ligandrol with endurance training had a more negative effect on bone than the isolated effect of the substance [21]. In another of our experiments, again in healthy rats, ostarine caused an increase in heart weight and an increased accumulation of collagen fibers around cardiomyocytes and coronary arteries [22]. Other authors have reported that ostarine increases the accumulation of some of the fibrosis markers such as fibronectin and smooth muscle α-actin in rat, male, cardiac fibroblast cells [23].

Side effects in humans

Side effects reported in clinical trials

In a 12-week clinical trial (phase 2), ostarine was administered to men and women and reduced serum triglyceride and HDL concentrations. In men (receiving doses of 1 or 3 mg per day), a significant decrease in SHBG (sex hormone binding globulin) and total serum testosterone were also reported. In women (only in the 3 mg group), a significant lowering of LH and FSH concentrations was observed. In the groups receiving the 3 mg dose, ostarine induced a decrease in blood glucose, a trend towards a decrease in insulin concentration, as well as significant increases in hemoglobin and hematocrit values [24].

Adverse effects observed after the administration of ostarine, in a clinical trial (NCT00467844) in patients with cancer, were febrile neutropenia, pneumonia, and progression of the malignant disease [25]. In a clinical trial (phase 1) (NCT03088527) in patients with breast cancer, the most common adverse events associated with testolone treatment were: elevated AST and ALT, decreased appetite, and constipation [26]. In another phase 1 trial examining testolone effects, also in patients with breast cancer, adverse events included increased AST, ALT, total bilirubin, dehydration, vomiting, hypophosphatemia, decreased appetite, and weight [27]. In a 56-day clinical trial of the non-steroidal agent GSK-2881078 (administered to both men and women) reversible decreases in HDL, thyroxine, and thyroid-binding globulin concentrations were reported. Only in men there were increases in LDL and liver aminotransferases concentrations [28]. In a clinical trial (NCT03359473) with the same SARM, (administered to women and men at doses of 1 and 2 mg respectively) reversible lowering in HDL and transient increases in liver enzymes were reported [29]. In a third trial with GSK-2881078 (NCT02045940), in healthy men aged 18 to 50 years and postmenopausal women, the substance caused a decrease in HDL, triglycerides, VLDL, apolipoprotein A1. In men, decreases in SHBG, FSH, DHT, and testosterone were also found [30]. Testosterone and SHBG concentrations began to increase several weeks after discontinuation of the active substance intake. The authors also reported constipation, nausea, and dyspepsia associated with GSK-2881078 [30].

When 76 healthy men received ligandrol (LGD-4033) at doses of 0.1, 0.3 and 1 mg for 21 days, a decrease in plasma levels of SHBG, free testosterone, FSH, triglycerides, HDL was observed, but there was no significant change in LDL, LH and total cholesterol [31]. The changes were reversible, the indicators returned to normal values after discontinuation of the intake.

In a clinical trial (phase 2), in 170 women over sixty-five years of age, all with sarcopenia, the intake of MK-0773 caused adverse effects such as an elevation in liver enzymes (ALT and AST) and hematocrit. The increase was transient and reversed after discontinuation of the intake [32]. After administration of PF-06260414, in healthy people of different ethnicities (Japanese and

people from more Western countries), the drug was well tolerated, with milder adverse effects - headache and increased ALT [33]. In another clinical trial (phase 2) (NCT02499497) with the representative of SARMs - OPK-88004 (duration 12 weeks), in patients who have undergone radical prostatectomy for prostate cancer, a dose-dependent decrease in SHBG, total testosterone, HDL and an increase in hematocrit and hemoglobin, but without causing erythrocytosis was reported [34].

Side effects on the liver

In the period 2020-2024 there is an increasing number of clinical reports describing liver injury after the use of different types of SARMs. In all cases known to us [35-57], the patients were men between the age of 19 and 52, who misused the non-steroidal representatives of SARMs, with the aim of rapidly increasing muscle mass and strength. In most cases, only one drug was used, with the highest frequency of use of ostarine and testolone, and in third place was the use of ligandrol. The most common combination of two drugs was ligandrol and testolone, followed by ostarine and ligandrol. There are also two cases with simultaneous use of three non-steroidal representatives of SARMs. The duration of abuse of SARMs, in different clinical cases, varies from 2 to 24 weeks, but most often between 3 and 7 weeks. Information on the daily dose administered is only given in a few cases. It varied from 7.5 to 25 mg daily.

The most common symptoms that led to a visit to the doctor and hospitalization were itching, jaundice with pigmentation of the skin and mucous membranes and darkening of the urine. Other symptoms with high frequency were fatigue, nausea, vomiting, and diarrhea. The less common symptoms were epigastric pain and myalgia. In clinical chemistry tests, in most cases, total bilirubin, AST, ALT, and alkaline phosphatase were all elevated. In four of the cases, an increase in INR (International Normalized Ratio) was also reported, but without change in platelet count. In one case, rhabdomyolysis was also observed [41]. In most clinical cases, during the diagnostic process, imaging studies of the liver (ultrasound, computed tomography, etc.) and liver biopsy were performed. In 7 biopsies, a cholestatic pattern of liver injury was found, in one a hepatocellular pattern, and in 3 biopsies a mixed pattern of liver injury. After exclusion of other possible causes for the clinical presentation (viral hepatitis A, E, B, C, cytomegalovirus and Epstein-Barr virus etc.) in all cases, the diagnosis of drug-induced liver injury (DILI) was accepted. Liver injury is considered clinically significant when: 1) AST is increased by at least 5 times and ALT by at least 2 times the upper limit of normal, in two separate measurements within 24 hours; 2) when total serum bilirubin is above 42.7 μmol/L, in combination with increased liver enzymes; 3) when INR>1.5 and liver enzymes are elevated [58]. In some cases, the presence of SARMs has been detected in patients' urine, blood or scalp hair.

After discontinuation of SARMs intake and provided treatment, gradual recovery of liver function and improvement in clinical and chemical parameters were observed in all patients. No deaths or severe complications have been reported up to now. The time it took for normalizing the liver functional tests has varied from 3 to 12 months, with a median of 5 to 6 months. Only one case has been reported in which a 27-year-old man was considered a potential candidate for liver and kidney transplantation. He used a combination of ostarine, ligandrol and testolone for a period of 3 months. [51]. Ultrasound and organ biopsy revealed cholestatic liver injury and acute tubular renal injury. These findings were accompanied by worsening hyperbilirubinemia [51]. Transplantations were not performed because the patient's condition improved after 2 weeks of plasmapheresis treatment. These data suggest that SARMs-induced hepatotoxicity is reversible after discontinuation of the active substance intake and is likely dose and duration dependent.

Other side effects

In an online survey of 520 people, 343 of whom used non-steroidal SARMs, the most common adverse effects reported were testicular shrinkage, acne and mood swings. Hair loss, irritability and elevated blood pressure were less common [59]. The adverse effects were with the highest frequency when SARMs were used for a period longer than 3 months. The most common adverse effect for ligandrol usage was testicular shrinkage and for ostarine and testolone usage mood swings.

Cardaci et al. reported on a 25-year-old male strength athlete who had a daily intake of ligandrol (10 mg) and MK-677 (a ghrelin agonist and growth hormone secretagogue) (15 mg) for 5 weeks [60]. The substances used increased body weight and fat-free mass but also increased fat mass, total cholesterol, triglycerides, and LDL. Ligandrol and MK-677 also lowered HDL, total and free testosterone, SHBG and FSH. Other adverse effects in this clinical case were increased liver transaminases and a negative effect on bones (lowering of bone mineral content and bone mineral density). Soon after the end of the intake, the values of SHBG, free and total testosterone, AST and ALT started returning to normal [60].

In another clinical case, a 28-year-old man was reported with severely reduced testosterone and SHBG concentrations because of the intake of ostarine, purchased online, for the purpose of self-treatment of a hamstring injury. However, no data on the dose and duration of intake of the substance were provided [61]. In a 27-year-old weightlifter, after two 4-week cycles of taking two different non-steroidal representatives of SARMs (LGD-4033 - 15 mg daily and S-23 at the same dose), a decrease in total testosterone, LH, FSH, HDL and an increase in triglycerides were observed [35]. After stopping the intake, laboratory results started normalizing.

In a 32-year-old man diagnosed with type 1 diabetes, the development of acute myocarditis was reported due to the use of RAD-140 to increase muscle mass and strength. The first symptom was

shortness of breath when climbing stairs, later shortness of breath appeared at rest and became permanent. Tachypnea, tachycardia and increased body temperature also occurred. After the patient was hospitalized, the tests revealed increased values of creatine kinase (MB-fraction), troponin I, C-reactive protein (CRP), D-dimers and natriuretic peptide (type B). The man was diagnosed with a non-ischemic heart injury, which was a consequence of the development of myocarditis. After treatment and significant improvement of the patient, he was discharged on the eighth day. No information was reported on the dose of testolone used [62].

A case of bilateral rupture of the Achilles tendon in a 36-year-old man who completed two 4-week courses using two different representatives of SARMs has also been described. The dose of the substances taken was not reported. After surgical treatment and subsequent immobilization, recovery was without complications [63]. Another reported side effect of SARMs was a reversible bilateral gynecomastia [64]. A 40-year-old man used three substances to increase his muscle mass and strength in the gym. One of the performance-enhancing drugs used was the non-steroidal SARM testolone. Laboratory tests revealed a decrease in the concentrations of total, free testosterone and SHBG. Four months after discontinuation, symptoms completely resolved, and blood tests returned to normal [64].

DISCUSSION

In 2017, the US Food and Drug Administration (FDA) warned against the use of SARMs for bodybuilding due to the risk of heart attack, stroke, or severe hepatotoxicity. Even though no SARMs have yet been approved, abuse of these substances continues [5].

In humans, the most often reported side effects of non-steroidal SARMs are related to impaired liver function and changes in lipid profile parameters. The risk of SARM-induced liver damage appears to depend mainly on the dose and duration of administration. In case of abuse and administration of doses many times higher than those used in clinical trials, the risk increases significantly. A transdermal non-steroidal androgen receptor modulator, LY-305, has been developed [65]. This administration route would significantly lower the exposure of the substance to the liver, which is typical for oral administration. A 4-week study (phase 1) was conducted in healthy men and women, in which LY-305 was administered in the form of a gel. Decrease in HDL was reported, but only in women receiving the substance at the highest dose [65].

In the clinical case of bilateral gynecomastia [64], the patient purchased the used supplements online and was unaware of the presence of SARMs in them due to the use of a different brand name for the product. A study by Van Wagoner et al. also reported the use of names other than the trade name on the label (e.g. S-22, MK-2866, GTx-024, Enobosarm instead of ostarine or LGD-4033 instead of ligandrol or RAD-140 instead of testolone) [7]. In another study, 60 dietary supplements purchased online were examined and it was found that 20 of them contained SARMs, but in some

of them the presence of non-steroidal androgen receptor modulators was not indicated at all on the label [66]. In a third study, Leany et al. found that there may be a discrepancy between the dose of SARMs indicated on the label and the actual dose, or even a complete absence of the active substance [67]. Since SARMs have been included in the WADA (World Anti-doping Agency) list of prohibited substances since 2008, the lack of control over their online sale poses a risk not only to the health of consumers but also to professional athletes in doping control [68]. It is necessary to introduce regulations and establish stricter control by the relevant authorities over the sale of SARMs online.

There is insufficient data on what the adverse effects of SARMs would be in longer-term use. The goal of creating SARMs was to replace anabolic androgenic steroids while maintaining their anabolic effect, but with a better safety profile [2]. Some authors believe that SARMs are safer than anabolic androgenic steroids. For example, Patt et al. compared the influence of AAS and non-steroidal SARMs on steroidogenesis in the adrenal gland. They found that anabolic steroids predispose to the development of hypertension and cardiovascular diseases due to excessive stimulation of mineralocorticoid synthesis. AAS can also cause metabolic disorders by suppressing cortisol production. In contrast, non-steroidal SARMs do not have a significant effect on steroidogenesis in the adrenal gland, which makes them safer [69]. Some of the side effects of AAS include sexual dysfunction and infertility in men, androgenization and menstrual cycle disorders in women, increased risk of stroke and heart attack, causing significant liver diseases, mental and behavioral disorders [70]. In a study of 1189 men who used AAS, increased mortality was found compared to the control group [71]. To our knowledge, similar studies on non-steroidal SARMs are still lacking.

CONCLUSION

With a view to the reported side effects, non-steroidal SARMs can negatively affect the health of their users and information about this should be available to a wider audience. On the other hand, there is data available demonstrating the beneficial effects of SARMs in several socially significant diseases. Some of the clinical trials conducted with non-steroidal SARMs have been terminated due to lack of sufficient efficacy, and in others, there are still no reported results. Non-steroidal modulators are still candidates for the treatment of some diseases, but for now the future of this group of molecules seems unclear. More clinical trials and studies of their long-term effects are needed. SARMs effects on physical working capacity are also not very well known. So, this is another direction for future studies regarding SARMs.

Conflict of interest: We declare that we do not have any financial or personal relationships that might bias the content of this work.

Author's contributions: V.V. and N.B found and screened the articles used; V.V. writing and original draft preparation; N.B. writing—review and editing. Both authors have read and agreed to the final version of the manuscript.

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