Selective Androgen Receptor Modulators (SARMs): Muscle Growth Without Side Effects?

What SARMs are

Selective androgen receptor modulators (SARMs) are drugs that mimic the effects of testosterone on muscle, but have fewer of its other effects. They stimulate the growth of muscle, but don’t greatly affect the prostate gland, erectile function, or secondary sex characteristics such as facial and body hair, enlargement of the voice box, nor have unwanted side effects like acne.

Naturally, bodybuilders have taken an interest in them. SARMs might provide many of the muscle-growth effects of steroids, but without harmful side effects.

The rationale for SARMs

As people age, they lose muscle mass, and if this goes on long enough, sarcopenia, or muscle-wasting, develops. The only difference between normal muscle loss and sarcopenia is the degree to which muscle has been lost.

Illnesses such as cancer or COPD exacerbate muscle loss, and bedrest such as hospital stays or at home during an illness exacerbate it.

With sarcopenia, elderly and/or ill people become frail, with all that entails for independent living – if someone can’t walk or perform the ordinary tasks of daily living, then they need assistance, which may mean a nursing home.

Muscle loss may also exacerbate illnesses; for example, cancer patients who have lost muscle may not be in a condition to take rounds of chemotherapy.

Doctors would like a way to treat muscle loss without the side effects of testosterone, anabolic steroids, or growth hormone. Pharmaceutical companies have been at work and have developed a number of SARMs, at least one of which
has reached Phase 2 clinical trials in humans.

**How SARMs work**

Testosterone and their synthetic derivatives, known as anabolic steroids, have both androgenic and anabolic effects.

Androgenic effects are those that relate to being male: body and facial hair, enlarged voice box and deep voice, erectile function, male pattern baldness, production of sperm.

Anabolic effects are those related to growth, especially of muscle and, to a lesser extent, bone.

Testosterone and its derivatives have differing ratios of androgenic to anabolic effects. *Synthetic anabolic steroids*, for example, may have 10 times the anabolic effect of testosterone.

Hormones such as testosterone work by attaching to receptors on cell membranes, which then activate cellular signals that start a cascade of biochemical events, leading to the ultimate hormonal effect. Hormonal receptors are found on and in cells of a hormone’s target tissue.

In the case of testosterone, these receptors are found in many tissues, such as muscle, bone, brain, and the prostate gland.

SARMs selectively target certain tissues, mainly muscle. They work on the androgen (testosterone) receptors in muscle, but less so or not at all in other tissues.

In this way, SARMs have a much higher anabolic to androgenic ratio; they build muscle, but have little effect on specifically androgenic effects such as erectile function or the prostate gland.

As such, SARMs have the potential for use in women as well as men. And in men, they shouldn’t produce as much feedback inhibition of the endogenous production of testosterone, so that other male parameters should remain normal.

Clearly, if SARMs were to fulfill their promise, they could be wonder drugs, treating sarcopenia or cancer cachexia (loss of body weight) without side effects.

**Ostarine (enobosarm)**

The SARM that has won the most attention and that has proceeded furthest in human trials is enobosarm, also called Ostarine by the company that developed it.

Of the SARMs, bodybuilders have also paid the most attention to Ostarine.

Researchers did a phase II clinical trial on 120 healthy elderly men (over 60

Average age of both men and women was in the early to mid 60s (depending on treatment group), and the study was double blind, meaning neither the researchers nor the patients knew whether they were getting a placebo nor the dose of Ostarine.

The findings included an increase in muscle mass, and adverse effects were similar to placebo. The greatest increase in muscle was seen at the highest dose of 3 mg a day.

The group taking 3 mg a day saw an increase in lean mass of about 3%, or about 1.2 kg. Increases in lean mass at lower doses were not significant.

Fat mass decreased by about 0.3 kg at the highest dose, and again the changes at lower doses were non-significant.

One subject was forced to discontinue the drug due to an increase in liver enzymes, which returned to normal after cessation of use.

Interestingly, insulin resistance decreased by ~27% at the highest dose, and triglycerides dropped also, which is a beneficial effect. It’s possible greater muscle and less fat mass contributed wholly or partly to this effect.

Also notable is that while total testosterone decreased in men, so did sex hormone binding globulin (SHBG), so that free (active) testosterone did not significantly decrease. This would be expected to preserve endogenous androgenic function. No change in testosterone was seen in women.

All in all, the researchers were pleased with the trial, noting both effectiveness and a relative lack of adverse effects. Worth noting is the conflict of interest statement: all of the researchers are employees of and have stock options in GTx, Inc., the maker of Ostarine.

Questions

Ostarine clearly works at increasing muscle mass and slightly decreasing fat mass, and seems to have a low incidence of side effects.

Will it work for bodybuilders?

The subjects in the study did no resistance training. If they had done so, they probably (in my opinion) could have gained more than 1.2 kg (2.6 lbs) of muscle in the 12 weeks of the trial.

So if someone already lifts weights, would the effect of Ostarine be additive? That’s unknown, but unless the person taking it has low testosterone or some other condition, then perhaps not.
The dose that yielded good results in this study was 3 mg a day, and to my knowledge Ostarine has not been tested at higher doses.

Yet some bodybuilders advocate as much as 75 mg a day.

At such a high dose, this could, maybe, increase the effectiveness of the drug, as well as increase adverse effects, such as liver damage.

Against the idea of increased effectiveness is the concept of saturation: if the drug fills all the androgen receptors, then the receptors are saturated, and adding more of the drug will not increase the effects. However, any potential toxic effects would remain.

The clinical study showed modest muscle gains; admittedly, they are more impressive in the absence of resistance training.

If someone already trains for strength regularly and efficiently, and eats enough protein (1.2 to 1.8 g/kg), then I’m skeptical whether adding a SARM like Ostarine would make a difference to muscle growth (hypertrophy). But it might, especially at higher doses.

Much more remains to be learned about SARMs like Ostarine, whether higher doses work better, whether they could be used in diabetics for insulin resistance, whether the very elderly (say, over 80) can use them safely, and so on.

PS: To see how and why to build muscle without drugs, read my book, *Muscle Up*.

PPS: Check out my Supplements Buying Guide for Men, which includes supplements that will help build muscle.
Former Steroid Users Have Low Testosterone

Have you ever thought about taking anabolic steroids? A new study reports that former steroid users have low testosterone, along with symptoms of hypogonadism, such as increased incidence of depression, fatigue, low libido, and erectile dysfunction.[1. Rasmussen et al., Former Abusers of Anabolic Androgenic Steroids Exhibit Decreased Testosterone Levels and Hypogonadal Symptoms Years after Cessation: A Case-Control Study, http://dx.doi.org/10.1371/journal.pone.0161208]

So you may want to think again.

Androgenic anabolic steroids

Anabolic androgenic steroids (AAS), commonly known merely as anabolic steroids, are synthetic derivatives of testosterone that bodybuilders and other athletes use to increase muscular size and strength. They are, of course, banned in almost all athletics, though to my knowledge they are not tested in the bodybuilding world anywhere, even among so-called “naturals”, who are not supposed to be taking them.

The study looked at 37 current users of anabolic androgenic steroids, 33 former users, and 30 healthy controls. All were between 18 and 50 years old and all regularly lifted weights.

The former users had an average total testosterone of 14.4 nmol/l — that’s 415 ng/dl in American terms — compared to 18.8 nmol/l (542 ng/dl) in healthy controls.

Steroid use also apparently causes your balls to shrink, not to put too fine a point on it. See chart below, which shows testis size according to duration of steroid use, in former users (solid line) and current users (dotted line).
Makes sense, since the chief function of the testes is to make testosterone, and either smaller testes make less testosterone, or since less is being made, the testes then shrink.

**Testosterone replacement therapy and feedback mechanisms**

Testosterone replacement therapy (TRT) can have the same effect while undergoing therapy: testes shrink, fertility is diminished — indeed, exogenous testosterone has been studied as a means of male contraception.

But in contrast to the use of anabolic steroids,

> Rebound of the sperm count to baseline levels occurs within six to 18 months of cessation, and subsequent fertility has been demonstrated.[2. Bassil, Nazem, Saad Alkaade, and John E. Morley. “The benefits and risks of testosterone replacement therapy: a review.” Ther Clin Risk Manag 5.3 (2009): 427-48.]

Again, this makes sense, since testosterone, estrogens, luteinizing hormone (LH), and others all exhibit fine feedback control on the others.
Therefore there appears to be no danger of permanent changes with TRT.

The authors of the paper on steroids write:

> Ongoing AAS abuse causes dramatic increases in plasma androgen levels that ultimately facilitate severe hypothalamic-pituitary-gonadal (HPG)-axis suppression due to negative feedback mechanisms involving testosterone and its metabolites.

As a result of steroid use, the mechanism of feedback control seems to be severely screwed up. Why it doesn’t rebound is a good question, but that seems to be the fact of the matter.

On Twitter it was suggested to me that this steroid-induced suppression of androgens wouldn’t occur if the users had done post-cycle therapy (PCT), which is a course of medication using estrogen antagonists such as Clomid or Tamoxifen.

While this may be necessarily unknown, it’s hard to see how that would affect the long-term decline in testosterone levels. Some of the former steroid users in the study were measured from 2 to 4 years after cessation of steroid use, and there was no association between time since cessation and testosterone levels. However, most of the users were measured from 6 months to one year after cessation, so it’s possible PCT would have made a difference. It’s also possible that some of these users would experience a rebound in testosterone even without PCT; after all, if it takes from 6 to 18 months to see a rebound in users of TRT, perhaps the same holds true in steroid users.

The authors of the study note that everything here is association; the sample could be biased by self-selection, and cause and effect have not been demonstrated. It’s possible, though it seems unlikely to me, that the steroid users had low testosterone to begin with, and that’s what motivated them to start steroid use.

All in all, this is a sobering look at the consequences of steroid use.

**PS:** To see how you can build muscle without steroids, and why you should, read my book *Muscle Up.*

**PPS:** Check out my *Supplements Buying Guide for Men.*

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**Anabolic steroids increase exercise**
tolerance

Anabolic steroids are of course well-known in the sports and bodybuilding worlds as huge performance enhancers; specifically, they add muscle and strength, and cut fat mass. So how do they work? One way is by increasing exercise tolerance. The athlete who uses steroids can return to the gym or the field much more quickly than one who does not use them.

Anabolic steroids increase exercise tolerance.

The influence of an anabolic androgenic steroid (AAS) on thymidine and amino acid uptake in rat hindlimb skeletal muscles during 14 days after a single exhaustive bout of weight lifting was determined. Adult male rats were divided randomly into Control or Steroid groups. Nandrolone decanoate was administered to the Steroid group 1 wk before the exercise bout. [3H]thymidine and [14C]leucine labeling were used to determine the serial changes in cellular mitotic activity, amino acid uptake, and myosin synthesis. Serum creatine kinase (CK) activity, used as a measure of muscle damage, increased 30 and 60 min after exercise in both groups. The total amount of weight lifted was higher, whereas CK levels were lower in Steroid than in Control rats. [3H]thymidine uptake peaked 2 days after exercise in both groups and was 90% higher in Control than in Steroid rats, reflecting a higher level of muscle damage. [14C]leucine uptake was approximately 80% higher at rest and recovered 33% faster postexercise in Steroid than in Control rats. In a separate group of rats, the in situ isometric mechanical properties of the plantaris muscle were determined. The only significant difference was a higher fatigue resistance in the Steroid compared with the Control group. Combined, these results indicate that AAS treatment 1) ameliorates CK efflux and the uptake of [3H]thymidine and enhances the rate of protein synthesis during recovery after a bout of weight lifting, all being consistent with there being less muscle damage, and 2) enhances in vivo work capacity and the in situ fatigue resistance of a primary plantarflexor muscle.

**Effects of Androgenic-Anabolic Steroids in Athletes**

Effects of Androgenic-Anabolic Steroids in Athletes
Androgenic-anabolic steroids (AAS) are synthetic derivatives of the male hormone testosterone. They can exert strong effects on the human body that may be beneficial for athletic performance. A review of the literature revealed that most laboratory studies did not investigate the actual doses of AAS currently abused in the field. Therefore, those studies may not reflect the actual (adverse) effects of steroids. The available scientific literature describes that short-term administration of these drugs by athletes can increase strength and bodyweight. **Strength gains of about 5–20% of the initial strength and increments of 2–5kg bodyweight, that may be attributed to an increase of the lean body mass, have been observed. A reduction of fat mass does not seem to occur.** Although AAS administration may affect erythropoiesis and blood haemoglobin concentrations, no effect on endurance performance was observed. Little data about the effects of AAS on metabolic responses during exercise training and recovery are available and, therefore, do not allow firm conclusions.

The main untoward effects of short- and long-term AAS abuse that male athletes most often self-report are an increase in sexual drive, the occurrence of acne vulgaris, increased body hair and increment of aggressive behaviour. AAS administration will disturb the regular endogenous production of testosterone and gonadotrophins that may persist for months after drug withdrawal. Cardiovascular risk factors may undergo deleterious alterations, including elevation of blood pressure and depression of serum high-density lipoprotein (HDL)-, HDL2- and HDL3-cholesterol levels. In echocardiographic studies in male athletes, AAS did not seem to affect cardiac structure and function, although in animal studies these drugs have been observed to exert hazardous effects on heart structure and function. **In studies of athletes, AAS were not found to damage the liver.** Psyche and behaviour seem to be strongly affected by AAS. Generally, AAS seem to induce increments of aggression and hostility. Mood disturbances (e.g. depression, [hypo-]mania, psychotic features) are likely to be dose and drug dependent. AAS dependence or withdrawal effects (such as depression) seem to occur only in a small number of AAS users. Dissatisfaction with the body and low self-esteem may lead to the so-called ‘reverse anorexia syndrome’ that predisposes to the start of AAS use. Many other adverse effects have been associated with AAS misuse, including disturbance of endocrine and immune function, alterations of sebaceous system and skin, changes of haemostatic system and urogenital tract. One has to keep in mind that the scientific data may underestimate the actual untoward effects because of the relatively low doses administered in those studies, since they do not approximate doses used by illicit steroid users. The mechanism of action of AAS may differ between compounds because of variations in the steroid molecule and affinity to androgen receptors. Several pathways of action have been recognised. The enzyme 5-α-reductase seems to play an important role by converting AAS into dihydrotestosterone (androstanolone) that acts in the cell nucleus of target organs, such as male accessory glands, skin and...
prostate. Other mechanisms comprises mediation by the enzyme aromatase that converts AAS in female sex hormones (estradiol and estrone), antagonistic action to estrogens and a competitive antagonism to the glucocorticoid receptors. Furthermore, AAS stimulate erythropoietin synthesis and red cell production as well as bone formation but counteract bone breakdown. The effects on the cardiovascular system are proposed to be mediated by the occurrence of AAS-induced atherosclerosis (due to unfavourable influence on serum lipids and lipoproteins), thrombosis, vasospasm or direct injury to vessel walls, or may be ascribed to a combination of the different mechanisms. AAS-induced increment of muscle tissue can be attributed to hypertrophy and the formation of new muscle fibres, in which key roles are played by satellite cell number and ultrastructure, androgen receptors and myonuclei.