

# Anabolic and Anti-inflammatory Agents to Treat Cachectic Geriatric Patients

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Anabolic hormones are interesting drugs

# Looking for the New Fountain of Youth

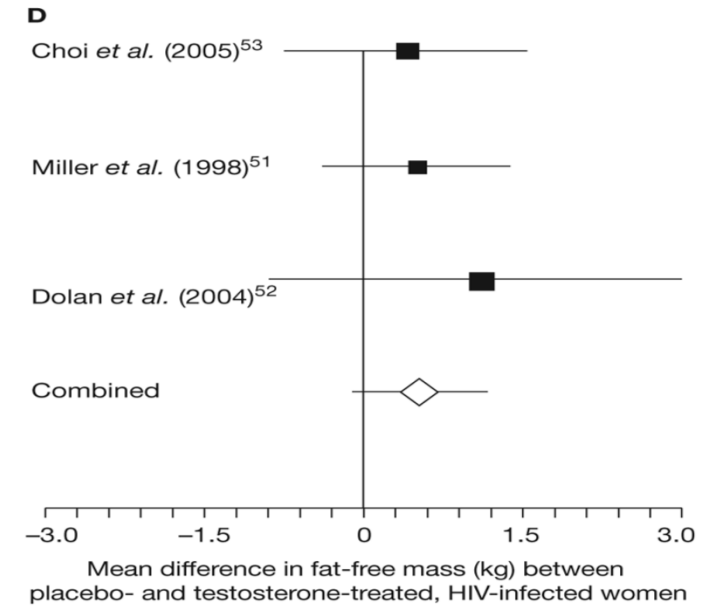
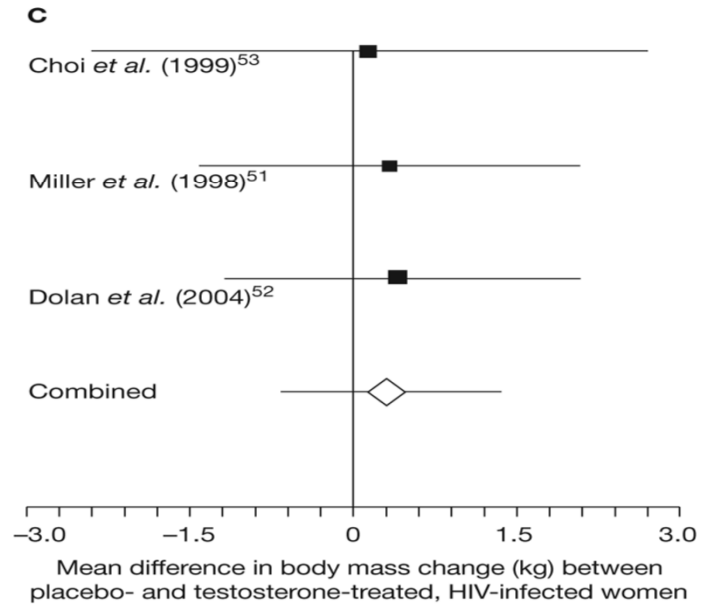
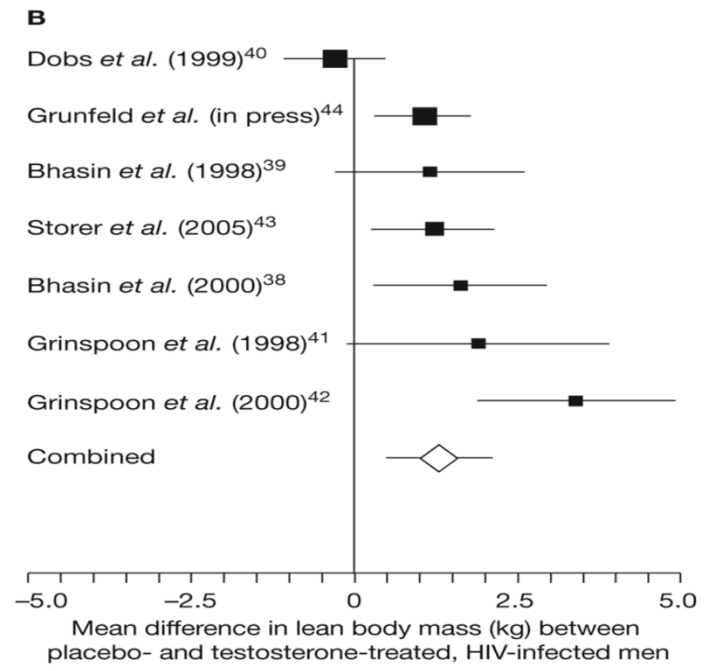
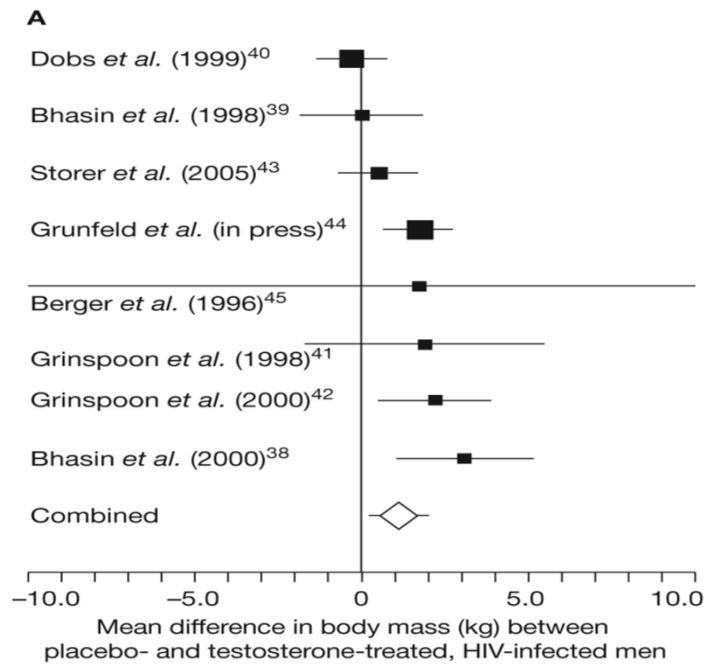
- Testosterone
- Anabolic steroids-  
nandrolone, oxandrolone
- SARM (Ostarine, S4, LGD 2226)
- Megestrol Acetate (MA)
- Growth Hormone (GH)
- Summary/future issues



But then again, anything is possible. This guy could be governor of California one day!

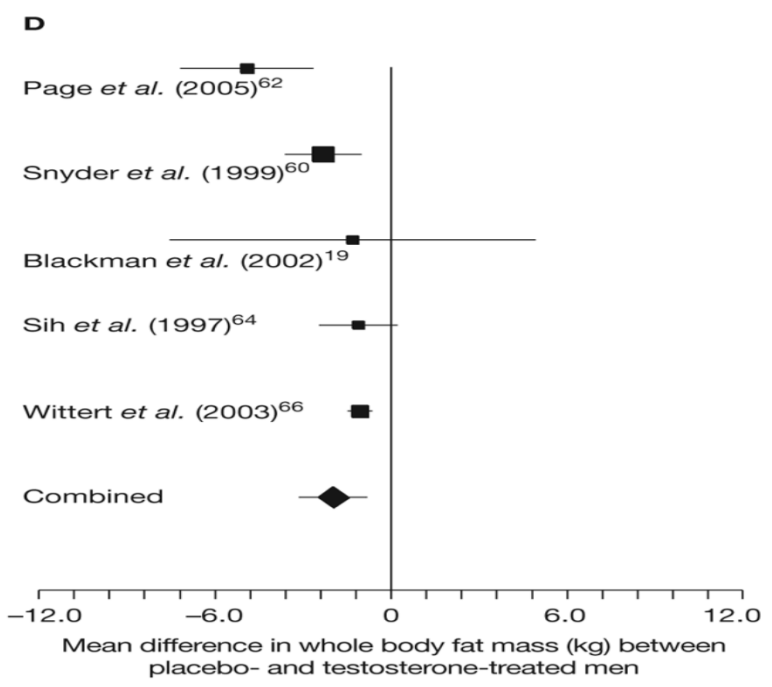
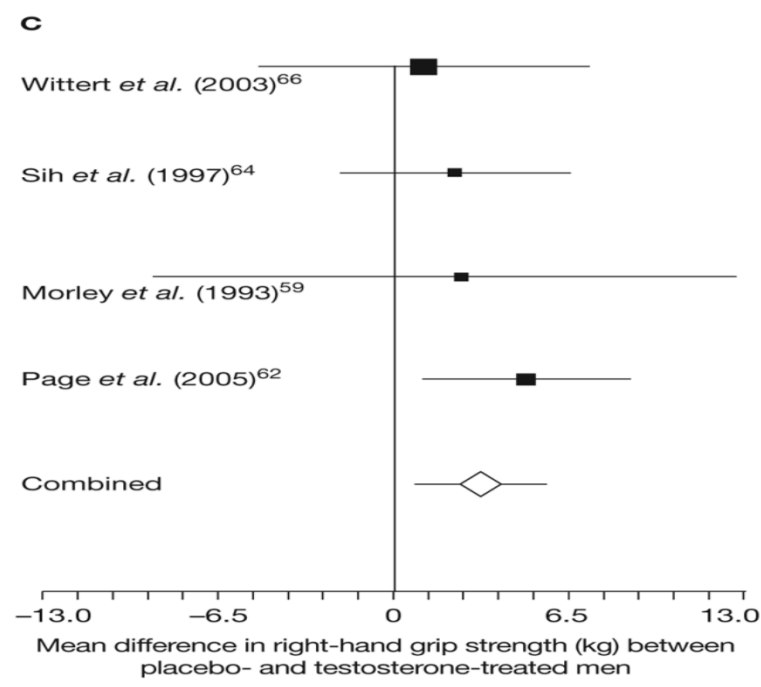
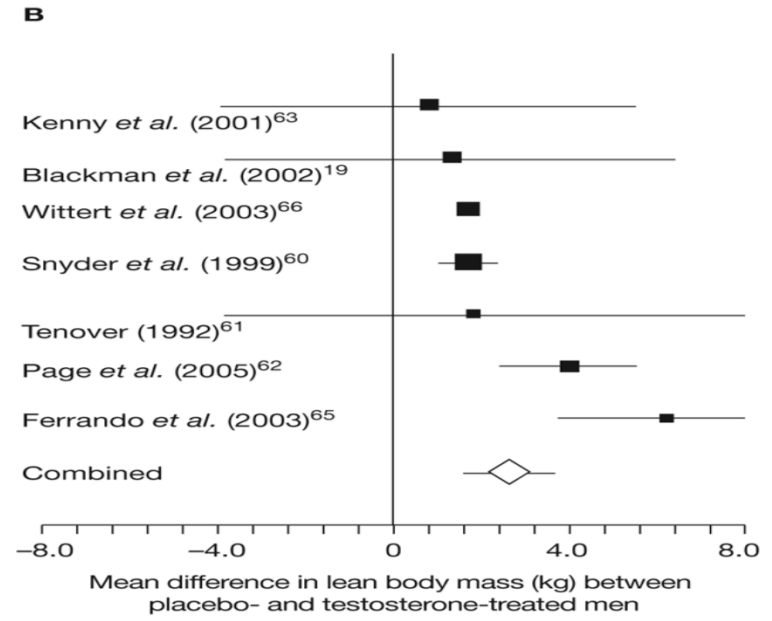
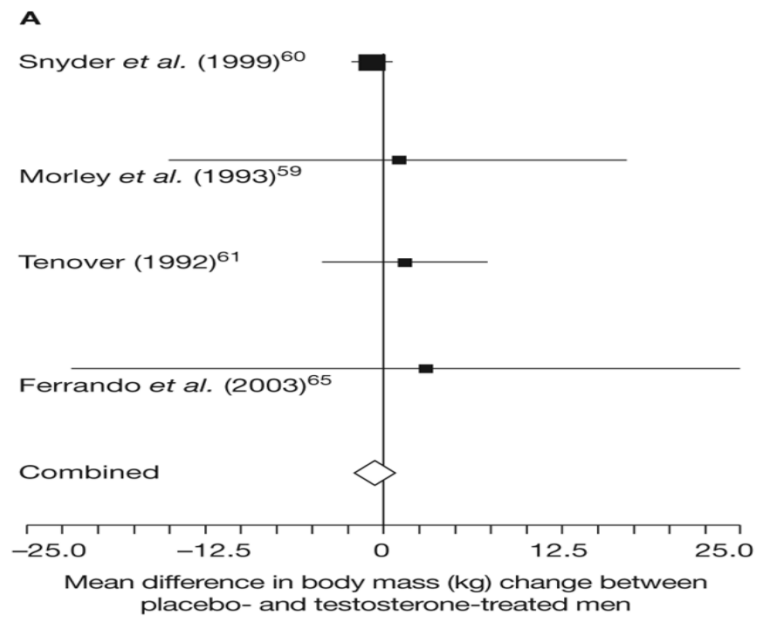
# MECHANISMS OF ANABOLIC EFFECTS OF TESTOSTERONE ON MUSCLE

- Promotes myogenic effect (blocked by AR antagonists; eg, bicalutamide) but inhibits adipogenic effect
- ↑ fractional muscle protein synthesis and improves the reutilization of amino acids by muscle
- ↑ LBM is associated with hypertrophy of both type I and type II fibers



## Testosterone (HIV-infected men )

- >18 years old, 3-6 months on study med
- ↑ FFM (**1.4 kg**), ↑ LBM (**1.3 kg**), and ↑ body weight (**1.1 kg**)
- Significant inconsistency : 57% variation in body-mass and 73% in LBM
- No improvement in quality of life





# Testosterone in Older Men

- No significant weight change
- ↑ LBM (2.7 kg)
- ↑ grip strength (3.3 kg)
- ↓ fat mass (-2.0 kg)
- Reciprocal changes in LBM and fat mass
- Older men are as responsive as young men
- Inconsistent results for FM and LBM from 1 study to another (88% versus 77%)

## Adverse events in randomized, clinical trials of testosterone in older men

- Pooled odds ratios for adverse events in randomized, clinical trials of testosterone in older men.
- All prostate events RR 1.78 (1.07–2.95)\*
- Hematocrit (>50%) RR 3.69 (1.82–7.51)\*
- Atrial fibrillation or arrhythmia 1.22 (0.53–2.81), All cardiovascular events 1.14, Death 0.78

# Summary (T)

- ↑ skeletal muscle mass, strength, and leg power
- Muscle-strength gains are proportional to the increase in muscle mass
- Dose-dependent effects, dose-limiting adverse events
- Older men are as responsive as young men

# Summary (T) cont'd

- Heterogeneity in testosterone levels and the anabolic response
- No improvement in quality of life ( 4 trials in HIV infected men)
- No improvement in contractile properties of skeletal muscle (resistance exercise)
- No effect on exercise capacity, fatigability or endurance measures (max rate of oxygen consumption or lactate threshold)

Grinspoon S, Corcoran C, Askari H, et al. *Ann Intern Med* 1998; 1998; 129:18-26,

Shalender Bhasin\*, Olga M Calof, et al. (Meta-analyses of clinical trials)*Clin Pract Endocrinol Metab.* 2006 March

# Testosterone Side Effects

- Effects on prostate, erythropoiesis, lipid & cardiovascular system( $\uparrow$ LDL, $\downarrow$ HDL & apolipoprotein-1, $\uparrow$ h/h, $\downarrow$ fibrinogen, LVH)
- Masculinization (hair growth, balding)
- Breast tenderness and enlargement
- Behavioral problems
- Fluid retention
- Liver toxicity

# Where Do We Stand (T) ?

- Dose-limiting adverse events
- Can androgen administration improve functional impaired and disabled elderly?
- The Institute of Medicine Expert Panel on the Future of Testosterone Research, did not think there is significant changes in clinical outcomes or disability in older men from all these studies

The Institute of Medicine Expert Panel on the Future of Testosterone Research, (Liverman, CT.; Blazer, DG., editors. Testosterone and Aging: Clinical Research Directions. National Academies Press; Washington, DC: 2004.)

## What Do We Need (T)?

- What **outcomes** should constitute evidence of efficacy?
- **Long-term** large sample studies to resolve persistent concerns about **prostate and cardiovascular** safety (pose significant fiscal and logistic challenges)
- Well controlled, carefully designed studies for women (with adequate doses, adequate formulation & safety evaluation)

# Testosterone

Anabolic effects : osteoanabolism & myoanabolism

Androgenic and estrogenic effects :

- Testosterone converts to → dihydrotestosterone (DHT) (via 5 alpha reductase ( in prostate, skin)) (the most potent endogenous androgens)
- Testosterone → estrogens (gynecomastia) - via aromatase (adipose tissue, bone, CNS)

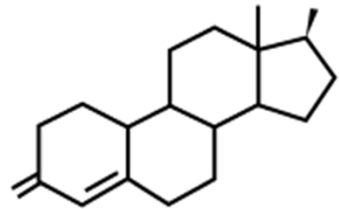
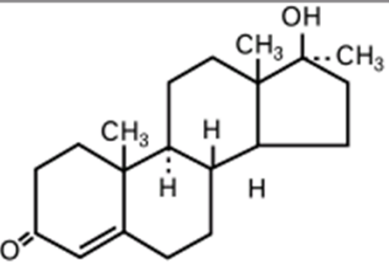


# Selective Androgen Receptor Modulator (SARM)

- A SARM is a small molecule that binds to and selectively modulates androgen receptors depending on tissue type
- Steroidal SARMS (anabolic-androgenic steroids, AAS) - nandrolone, oxandrolone
- Nonsteroidal SARMS

# Steroidal SARMs (Anabolic steroids)

Figure 1 Structure: activity relationship of steroidal SARMs

Structure: activity relationship	Compounds	Chemical structure
Removing 19 methyl increases anabolic activity	19-nortestosterone (nandrolone) series of compounds	 <p>19-nortestosterone</p>
17-alpha alkyl substitutions retard first-pass presystemic metabolism	Many orally active steroidal androgens have 17-alpha alkyl substitutions	 <p>17-alpha methyl testosterone</p>

Increase anabolic(testosterone) effect, also some androgenic effects

# Summary -Steroidal SARMs (Anabolic steroids)

- ↑ weight and LMM

Side effects (lack of tissue specificity):

- Masculinization/ hard looking physique
- Fluid retention (minimum)
- Hepatic toxicity
- Erythrocytosis  
(anabolic-androgenic association)

# What do we need?

Designer Testosterone for men  
and women



Newer drugs may help avoid the Conan the Barbarian look

# Designer Anabolic Steroid for Men

- Stimulatory effect on- muscle mass/strength, bone growth, fat free mass, erythropoiesis
- Enhances libido/sexuality
- Weak or neutral effect on prostate/sex accessory tissues, gonodotropins, hair growth, lipid/cardiovascular risk factors, fluid retention, LFT, gynecomastia

# Designer Anabolic Steroid for Women

- Enhances bone growth, muscle mass
- Neutral effect on virilization
- Neutral effects on fluid retention, lipid profiles, LFT's
- Enhances libido/sexuality
- Well controlled, carefully designed studies in women with adequate doses and formulation for women

# Nonsteroidal SARMs

- Aryl-propionamide (GTX, Inc.), **Ostarine, andarine, S-4**
- Bicyclic hydantoin (BMS)
- Quinolinones (Ligand / TAP), LGD2226, LGD 2941 (osteoporosis)
- Tetrahydroquinoline analogs (Kaken pharmaceuticals)



## Nonsteroidal SARMS cont'd

- Benimidazole, imidazolopyrazole, indole, and pyrazoline derivatives (Johnson and Johnson)
- Azasteroidal derivatives (Merck)
- aniline, diaryl aniline, and bezoxazepinones derivatives (GSK)

**Figure 2 Various structural classes of nonsteroidal SARMs**

Chemotype	Structure	Examples
Aryl propionamide analogs		Ostarine, andarine
Bicyclic hydantoin analogs		BMS 564929
Quinolinones		LGD2226, LGD2941

We can differentiate anabolic (myotrophic) from androgenic effects?(anabolic-androgenic dissociation)?

# Nonsteroidal SARMs

- Mimic and/or enhance testosterone's action in bone, muscle (anabolic effects)
- No testosterone-like action on the prostate and skin (androgenic effects)
- Doesn't cross into the central nervous system to affect lipids and gonadotropin (HPG) secretion (LH,FSH)(mood,behavior,libido)  
(anabolic-androgenic dissociation)

# Ostarine

- Oral, T  $\frac{1}{2}$ : 4-6 hours (rats) and > 24 hours (man)
- In ORX(orchidectomized) rats, partial agonist on the prostate
- Full agonist on levator ani (surrogate marker for muscle)
- Promotes muscle growth and shrink prostate in intact rats
- Prevents acute bone loss in OVX (ovariectomized) rats
- No conversion to DHT (not react w/ 5 alpha reductase; androgenic effect), estrogen (not react w/ aromatase )
- Does not inhibit HPG axis (no reduction in LH,FSH)  
(no reduction of endogenous testosterone synthesis)
- Similar effects to testosterone on libido and anabolic effects

# Ostarine (Elderly)

- 0.1mg, 0.3mg, 1mg, 3mg dose for 3 months
- 60 older men, and 60 post-menopausal women
- ↑ lean mass\* (a dose dependent) in both (1.3 kg compared to baseline ), M (@ 3mg; 1 kg), F (1.7 kg)
- ↓ fat mass at the 3 mg dose (0.6 kg)
- ↑ physical performance (measured by stair climb) (a dose dependent), @ 3 mg in both speed ( $p=0.006$ )\* & power ( $p=0.005$ )\*.
- ↓ LDL & HDL cholesterol (dose dependent) triglycerides

# Ostarine (Elderly)

- No serious adverse events reported
- Minimum LFT changes (one F)
- No change in LH in males, ↓ in post-menopausal women
- ↓ SHBG level @ 1mg & 3 mg dose
- ↓ in blood insulin(17%) and glucose(11%) levels, improvement in insulin resistance(27%) (similar to metformin) (3mg)
- No increase in PSA
- Small changes in erythropoiesis

# Ostarine (Cancer Cachexia Trial)

- 159 patients w/ non-small cell lung cancer, colorectal, non-Hodgkin's lymphoma, CLL, & breast cancer with average of 8.8% wt loss
- Given placebo, 1 mg or 3 mg Ostarine for 16 weeks
- Drop-out rate 33 % (lower than the expected 50 percent rate observed in other cancer supportive care clinical trials)

# Ostarine (Cancer Cachexia Trial)

- Met primary endpoint of  $\uparrow$  lean body mass (compared to baseline):

**Placebo** - 0.1 kg ( p=0.874)

**1mg dose** - 1.5 kg (p=0.001)\*

**3mg dose** - 1.3 kg (p=0.045)\*



# Ostarine (Cancer Cachexia Trial)

- Met secondary endpoint of increased physical performance (stair climb test)

**Placebo** - 0.23 watts (p=0.66)

**1mg dose** - 8.4 watts (p=0.002)\*

**3mg dose** - 10.1 watts (p=0.001)\*

(a dose dependent response)

- No improvement in grip strength & gait speed
- Side effects : fatigue, anemia, nausea, & diarrhea

# SARM's (Summary)

- ↑wt (modest), ↑ LMM, ↓ FM ↓BS (insulin)
- ↑ nitrogen retention, net protein synthesis, & utilization of calories from fat stores or blood glucose for synthetic metabolism rather than storage (as adipose)
- ↓ HDL cholesterol and SHBG
- Mild transient ↑ in LFT's
- Mild leg edema

# SARM's (Summary)

- No 5-  $\alpha$  reduction or aromatization (T/E- libido , behavior, bone & plasma lipids )
- Different in CNS activity of various SARM's
- Can't predict the desired HPG axis profile

## How do SARM's Compare with Other Available Treatment Modalities?

- Preferential anabolic agents(↑wt, ↑ LMM, ↓ visceral adipose tissue )
- Free from the adverse effects like testosterone and growth hormone (anabolic-androgenic dissociation)
- More appeal as anabolic therapy for the frail
- The preclinical data look promising & the efficacy trials are just beginning

# Using SARMs to treat hypogonadal men?

- Not aromatized, nor 5-alpha reduced
- Many functions of T, especially its effects on libido and behavior, bone and plasma lipids require it's aromatization to E
- May need to show efficacy & safety in many more domains of androgen action than has been required of T formulations

# What Do We Need?

- Future research is needed to elucidate the molecular basis of tissue selectivity & to achieve greater potency & tissue selectivity.
- Efficacy (functional & psychosocial outcomes) & safety studies
- Long term CNS effects (mood, behavior & libido)

# Megestrol Acetate

- Synthetic Progestational agent (progesterone receptor)
- Antiinflammatory/ glucocorticoid receptor
- Intrinsic androgen receptor
- Can improve appetite, wt, mostly fat

# Megestrol Acetate

- 26 studies, 3887 patients (30 trials, 4123 pts)
- Oncology : MA ↑'d appetite @ 2 week @ 6-12 weeks; ↑wt gain and ↑HRQOL
- AIDS : MA ↑'d appetite @ 2 weeks @ 6-12 ↑'d wt gain and QOL  
↑'d HRQOL



# Megestrol Acetate - Side effects

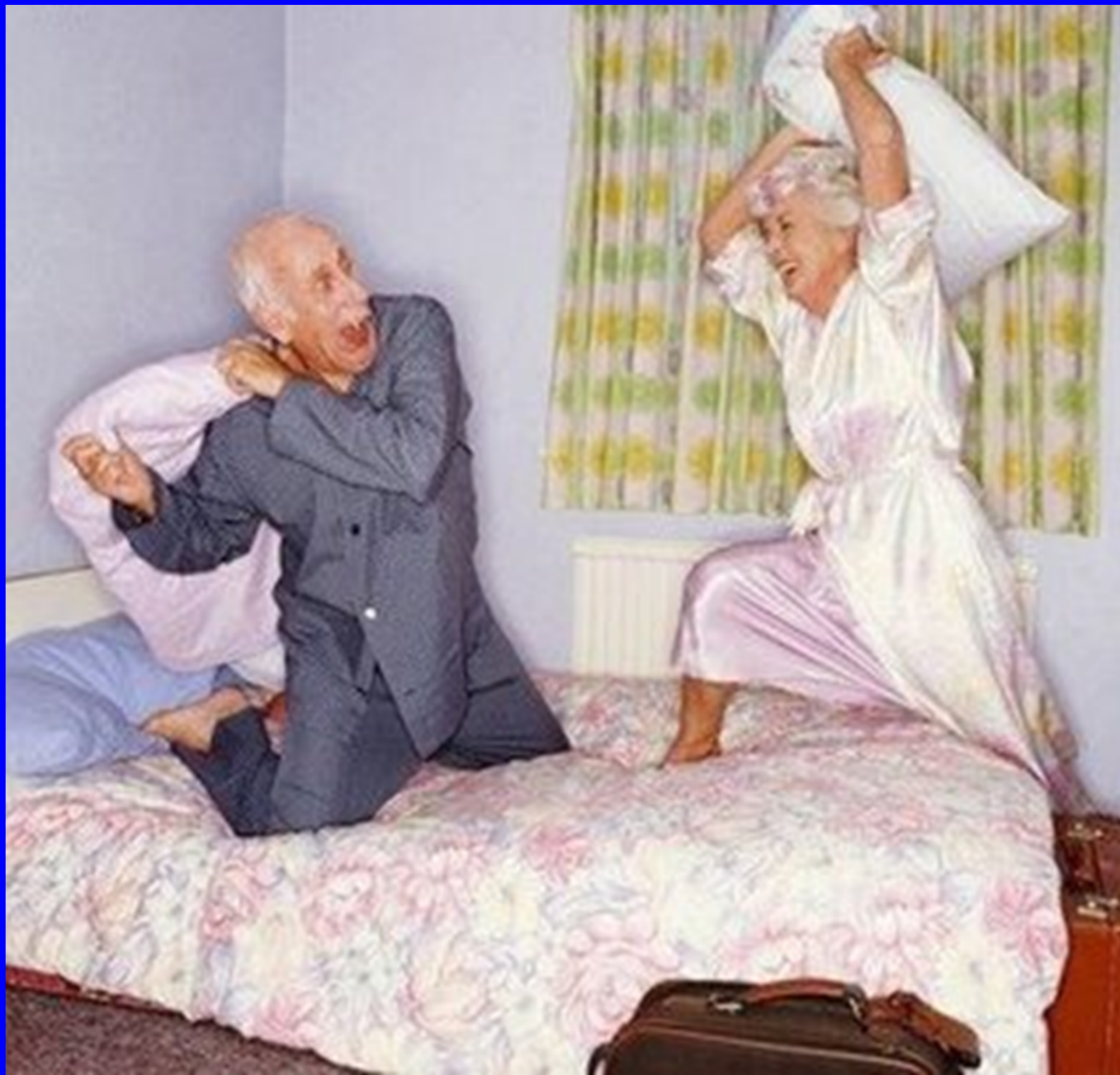
- Edema (lower limbs)\*
- Impotence
- Hyperglycemia
- Thromboembolism
- Adrenal suppression

# MA, MA+T, MA+PRE, MA+T+PRE

- Antianabolic effect on muscle when combined with testosterone
- Resistance exercise attenuated reduction in muscle mass
- When MA combined with testosterone and PRE, PRE had an anabolic effect on muscle mass

## **What do we need?**

**A selective progesterone  
receptor modulator (SPRM)  
that would only stimulate  
appetite ?**



GH might have some unintended side effects

# Growth Hormone (Elderly)

- 18 studies, 220 participants, GH (107 person-years), 69 yrs old, male (67%), BMI 28 kg/m<sup>2</sup>, initial daily GH dose (14 mcg/kg) and duration 27 weeks
- No wt change
- ↑ LBM (+2.1 kg)
- ↓ fat mass (- 2.1 kg)
- ↓ Total cholesterol (-0.29 mmol/L)

# Growth Hormone - Side effects

- **27%** GH study pts required a dose decrease\*
- Peripheral edema\* (50%), more women than men (61% vs 47%)
- **Hyperglycemia\*(22%), and new onset of DM (5%)**
- Carpal tunnel syndrome (19%), malaise, arthralgia (21%)
- Gynecomastia (5%)

# Where Do We Stand (GH)?

- No improvement in appetite or weight
- ↑ LBM & ↓ fat mass in men
- Women treated with GH: no ↑ LBM & no ↓ in FM
- ↑ M & M in critically ill adults study (RR1.9-2.4) (multiple-organ failure, septic shock, uncontrolled infections) Finnish multi center trial
- Glucose dynamics (? dose-related)
- ↑ adverse events

# What do we need (GH)?

- We have not found the right group, dosage, and timing to use GH
- Need to study key functional outcomes (stair climb), psychosocial outcomes (quality of life), and other clinical outcomes (subcutaneous and central adiposity)
- Need longer studies(> 1 yr) for overall death & cancer rate
- Need well controlled, carefully designed studies for women



# Conclusion

- PRE and recombinant GH augment the anabolic response to androgens
- Different hormonal pathways (adiponectin & GH-IGF-1) also improve LMM
- Combinations of SARM's with other agents (antioxidants, anti-cytokine monoclonal antibody, ACTRIIB agonist, RANK, RANKL, MAP kinase inhibitor, MC4-R antagonists and PRE) may work even better than one agent alone

Bhasin S, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996;335..

Blackman MR, et al. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA 2002;288



New hope for the Boomer generation!



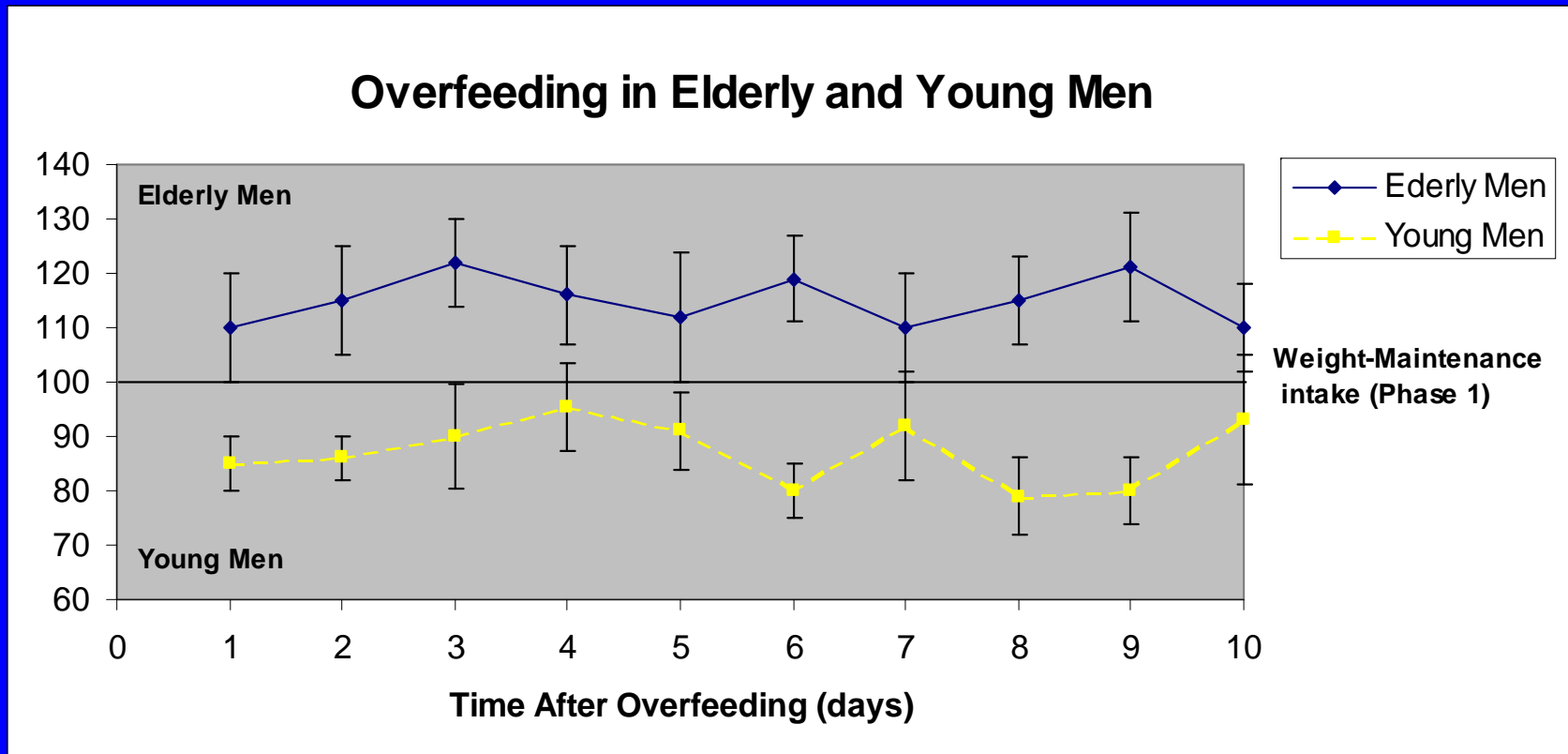
# Mechanisms of SARM's Tissue Selectivity

- Activates different signaling pathways
- Recruits different AR coregulators, corepressors, coactivators ( androgen response element, transcription factor or on endogenous kinase cascade regulation)
- Activates AR inhibitory & antiproliferative kinases (prostate ), activating proliferative or AR-activating kinases and signaling ( bone & muscle)

## SARM Mechanisms cont'd

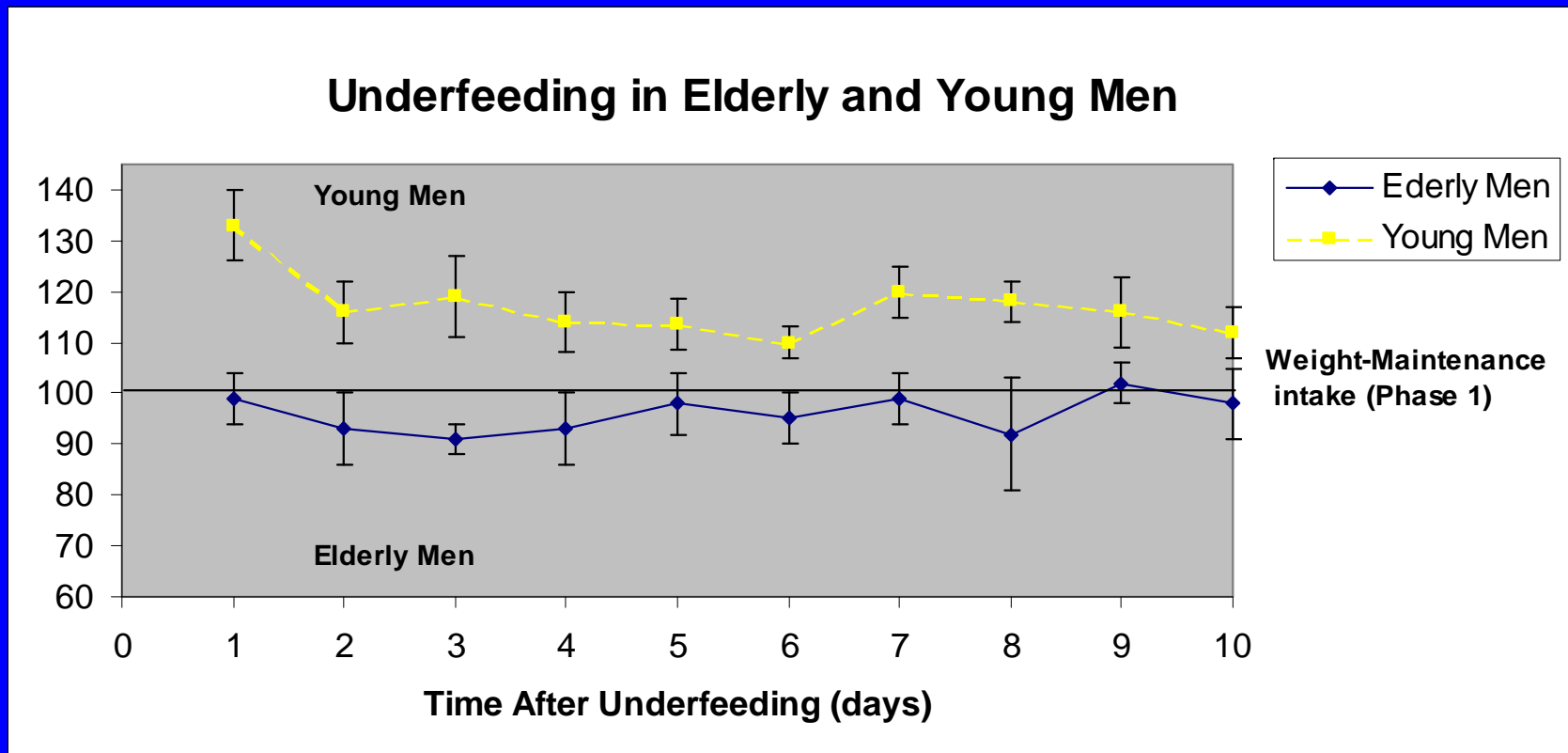
- Difference in phosphorylation of several kinases; ie, PI3K/Akt pathway for DHT, but not for SARM-dependent AR transactivation
- Integrates both the rapid nongenomic (cross-talk w/other signaling pathways via direct protein-protein interaction w/o directly regulating gene expression) & chronic genomic androgenic actions

# Effects of aging on energy requirements and the control of food intake in men



Roberts et al., JAMA 1994

# Effects of aging on energy requirements and the control of food intake in men:



Roberts et al., JAMA 1994

# Effect of starvation and Refeeding

	Control (%)	Starvation	Rehabilitation (weeks)				
		24 weeks	12	16	20	32	58
<b>Weight</b>	<b>100</b>	<b>76</b>	<b>86</b>	<b>99</b>	<b>102</b>	<b>109</b>	<b>102</b>
<b>Fat</b>	<b>100</b>	<b>31</b>	<b>79</b>	<b>117</b>	<b>136</b>	<b>151</b>	<b>110</b>
<b>'Active Tissue'</b>	<b>100</b>	<b>73</b>	<b>80</b>	<b>N.S.</b>	<b>92</b>	<b>95</b>	<b>100</b>

N.S. = Not stated in study

Keys A, Brozek et al. (1950)  
 The biology of human starvation.  
 University of Minnesota press, Minneapolis.



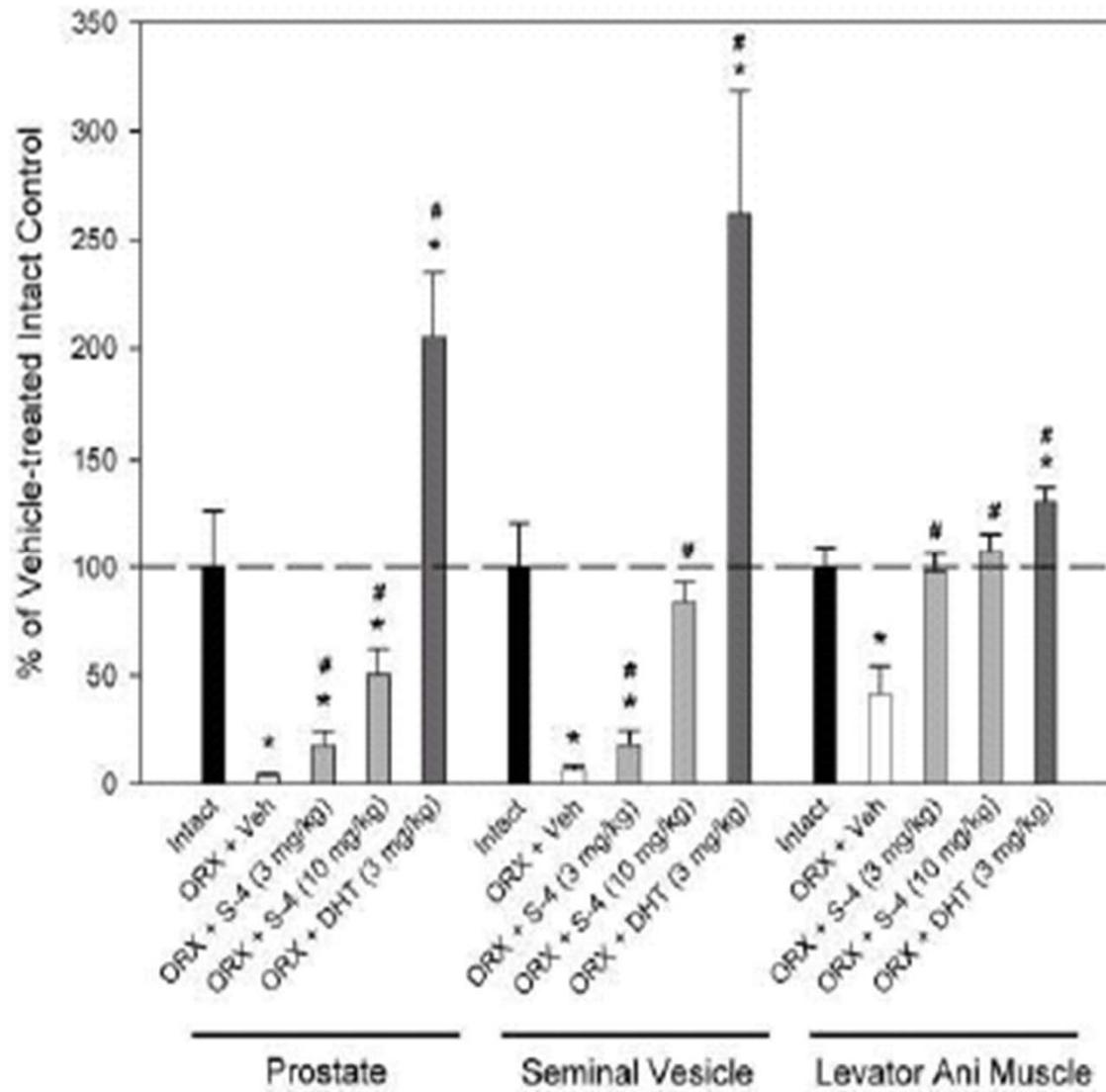
# Relative body composition and physical performance changes:

<b>Variable</b>	<b>% Change from Pre to Final (8 weeks)</b>	<b>% Change from Post to Recovery (5 weeks)</b>	<b>% Change from Pre to Recovery (13 weeks)</b>
<b>Body Composition</b>			
<b>Body Mass</b>	<b>-11.3</b>	<b>20.8</b>	<b>7.1</b>
<b>Fat-free Mass</b>	<b>-6.6</b>	<b>8.8</b>	<b>1.6</b>
<b>Fat Mass</b>	<b>-42.6</b>	<b>190.3</b>	<b>61.7</b>
<b>Physical Performance</b>			
<b>Maximal Lift Capacity</b>	<b>-21.2</b>	<b>27.9</b>	<b>-0.30</b>
<b>Explosive Power</b>	<b>-22.3</b>	<b>29.5</b>	<b>-5.4</b>
<b>Vertical Jump</b>	<b>-17.5</b>	<b>16.5</b>	<b>0.42</b>

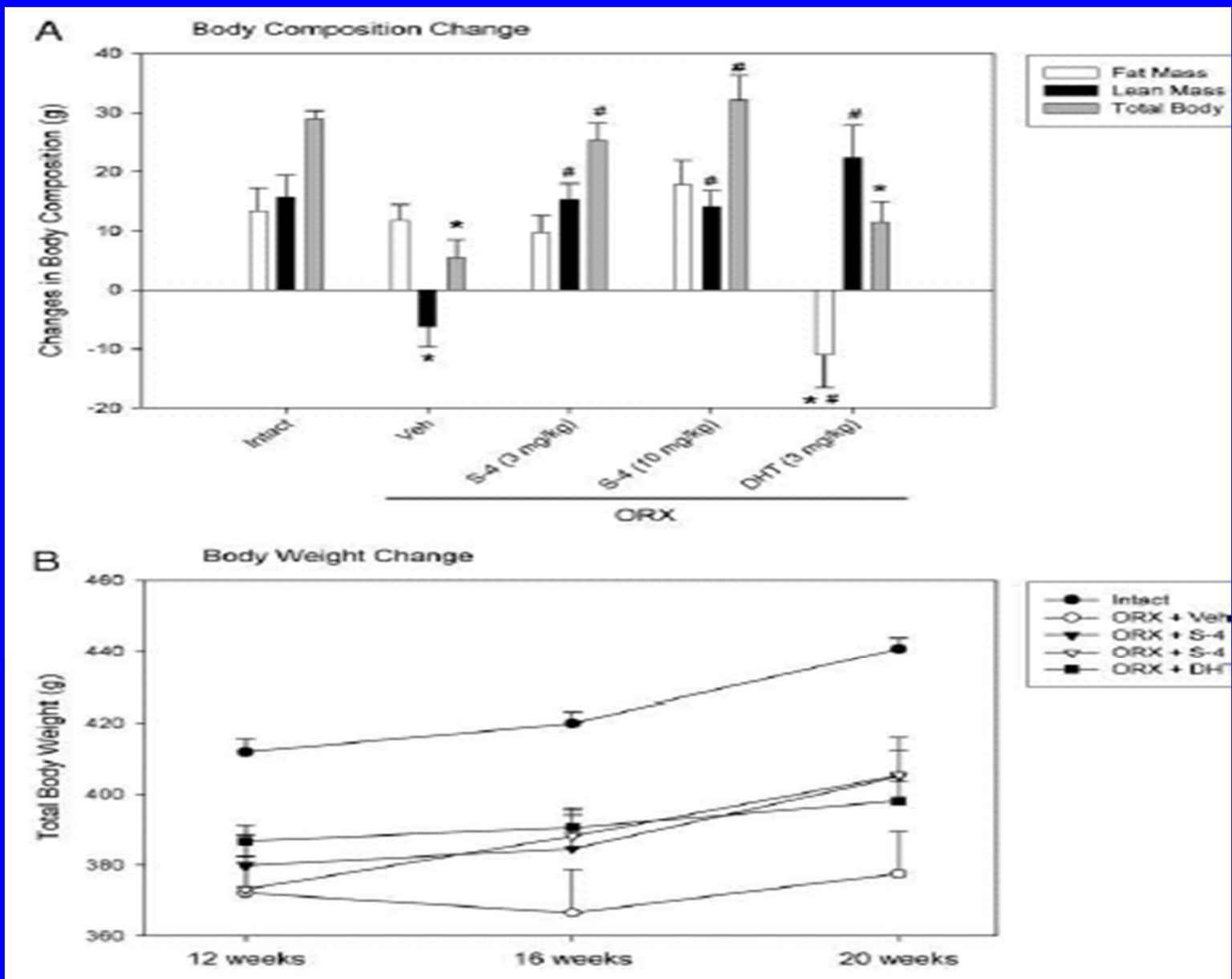
Nindl BC, Friedl KE, et al.  
Int J Sports Med 1997; 18:317-324.

## S-4 (Andarine)

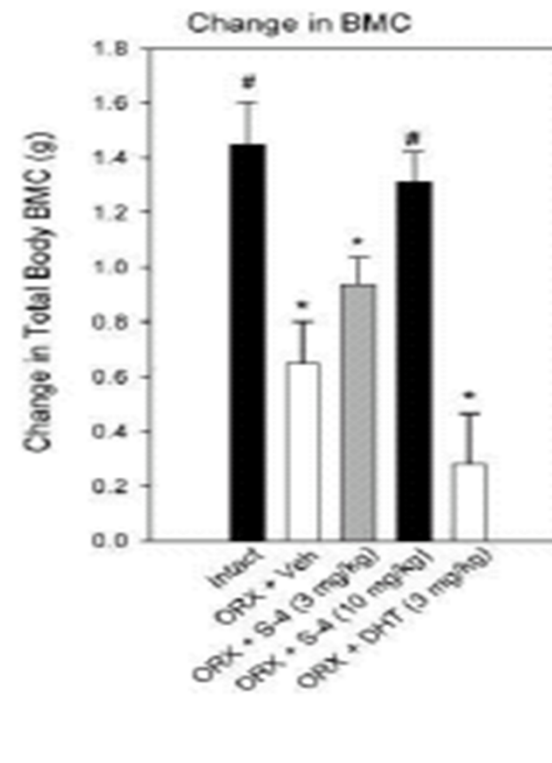
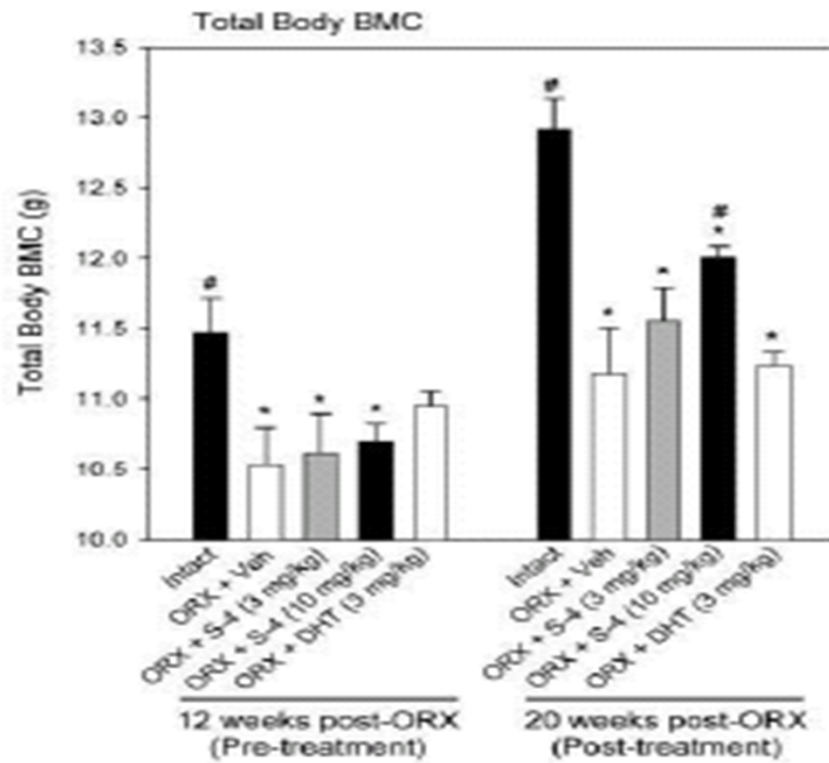
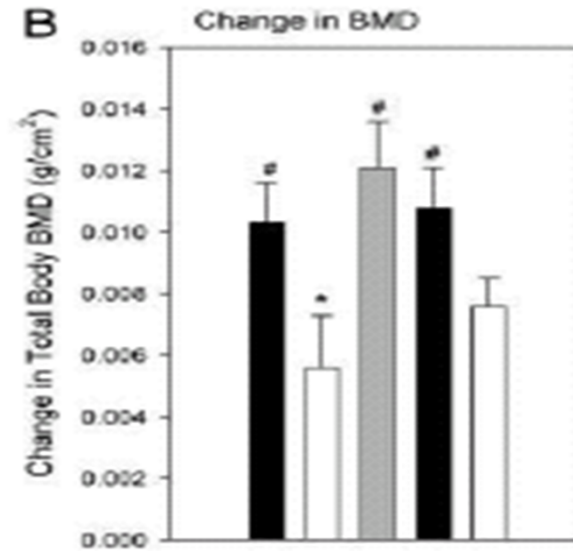
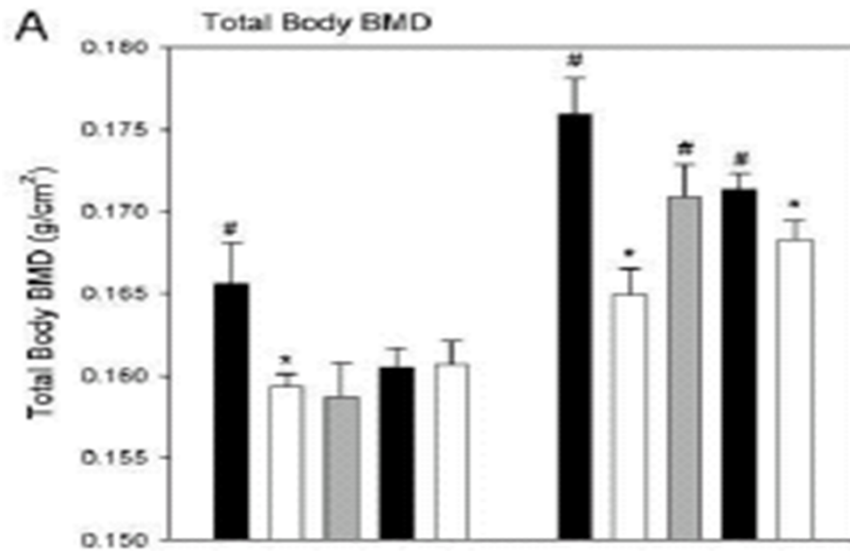
- Weight gain of only a few pounds
  - Improved strength, muscle mass
  - Minimum water retention, liver toxicity, gynecomastia
- (anabolic-androgenic dissociation)



different treatment groups. **(anabolic-androgenic dissociation)**



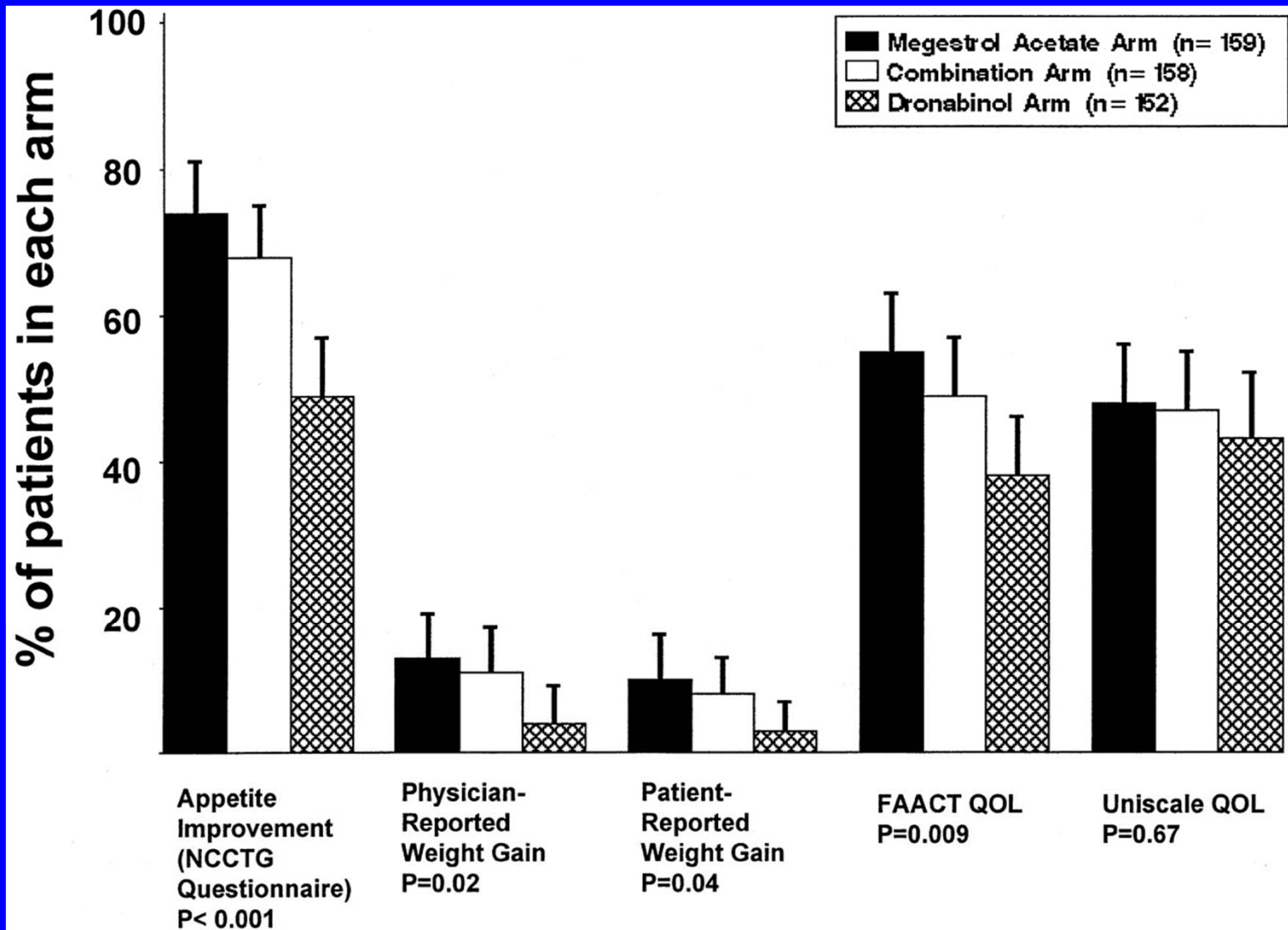
Gao et al. *Endocrinology*. 2005 November ; 146(11): 4887–4897 (increase wt, LBM, decrease FM)



# Testosterone

- Testosterone converts to → **dihydrotestosterone (DHT)** (via 5 alpha reductase ( in prostate, skin) - the most potent endogenous androgen
- Testosterone → estrogens (gynecomastia) (via aromatase in adipose tissue, bone, & CNS)
- Both anabolic(myotrophic) and androgenic

Improved (1) appetite, (2) physician-reported weight, (3) patient-reported weight, and (4) FAACT QOL score (Fisher's exact test,  $P < .001$ ,  $.02$ ,  $.04$ , and  $.009$ , respectively) after *Megestrol acetate* and *Dronabinol* treatment



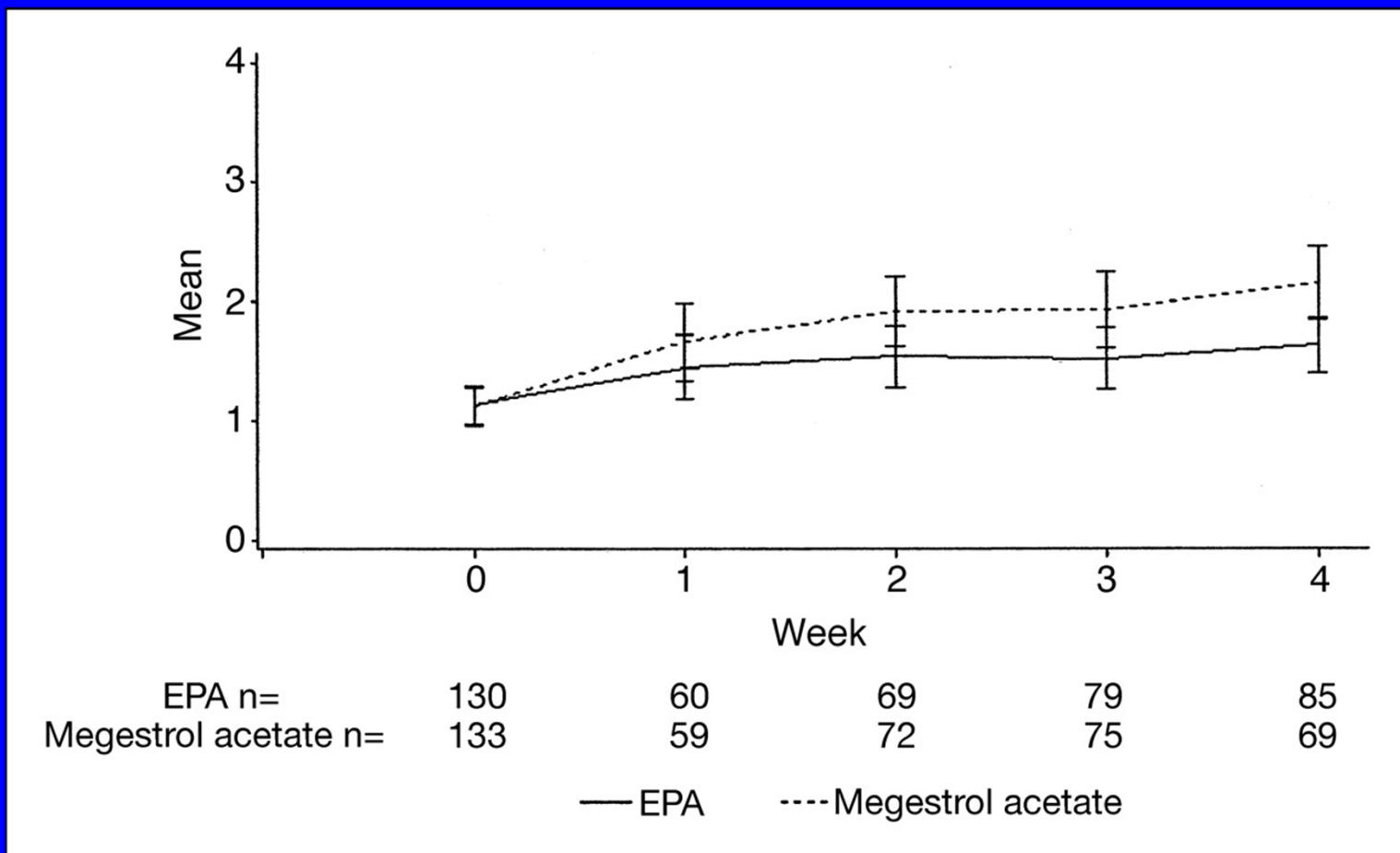
Observed Increases in measurements for 33 study participants with HIV-related weight loss who were randomized to receive 2 months of either *megestrol acetate* therapy or *oxandrolone* therapy, by therapy group.

Variable	Megestrol Acetate group (n = 18)		Oxandrolone Group (n = 15)	
	Change	<i>P</i>	Change	<i>P</i>
<u>Body measurement</u>				
Weight, kg	2.8 ± 4.3	.01	2.5 ± 2.4	.001
<u>Bioelectric impedance analysis estimation</u>				
Fat, kg	1.8 ± 3.0	.16	1.1 ± 2.7	.01
Lean body mass, kg	0.8 ± 2.4	.02	1.2 ± 1.9	.04
Weight gain attributed to lean body mass, %	39		56	

Modified from *Clinical Infectious Diseases*, D. Mikaya Mwamburi, et al., 2004



## Serial assessment of appetite stimulation and the Functional Assessment of Anorexia/Cachexia Therapy: compared *megestrol acetate* with *eicosapentaenoic acid (EPA)* supplement



Jatoi, A. et al. J Clin Oncol; 22:2469-2476 2004