

Anabolic-Androgenic Steroids in COPD

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POLL



- Males- are you testosterone deficient
- Would you take testosterone
- Why
- Have you seen physicians use it

Definition of Terms

- Androgenic
- Male characteristics
 - Hair growth
 - Penile enlargement
 - Voice change
- Anabolic
- Protein synthesis
 - Increased muscle mass
 - Increased strength
 - Increased performance

Testosterone actions in Males

- Produced mainly in the testis
 - Small amount produced in the adrenal gland
 - Synthesized from cholesterol
 - Hypothalamus produces Gonadotrophin releasing hormone (GnRH)
 - Acts on the anterior pituitary to increase the production of luteinizing hormone (LH) and follicle stimulating hormone (FSH)
 - LH acts on the Leydig cells in the testis, causing them to produce testosterone
 - FSH & testosterone act on the Sertoli cells in the testis to regulate the production and maturation of spermatozoa.
 - Testosterone in turn acts on the hypothalamus and anterior pituitary to suppress the production of GnRH, FSH and LH, producing a negative-feedback mechanism which keeps everything well-regulated.
 - The small amount produced in the adrenal (in both sexes) is regulated by secretion of adrenal corticotrophin hormone (ACTH), also secreted by the pituitary.

Testosterone actions in Males

- Normal production of testosterone
 - Adult male is 4 to 9 mg·day⁻¹
 - Normal plasma concentration is 700 ng·dl⁻¹ of which 97% is protein bound.
 - Most is excreted in the urine as 17-keto steroids
 - Small amount is converted to estrogens
 - Adult female is approximately .3 mg·day⁻¹
 - Normal plasma concentration is 38-40 ng·dl⁻¹

Types of AAS

- Oil based injectable
 - Fewer side effects
 - More active
 - Long term presence
- Testosterone forms
- Oral forms
 - Water soluble
 - Less active
 - Short term presence
 - Liver & kidney strain

Commonly Abused Steroids

More than 100 different steroids available

Oral

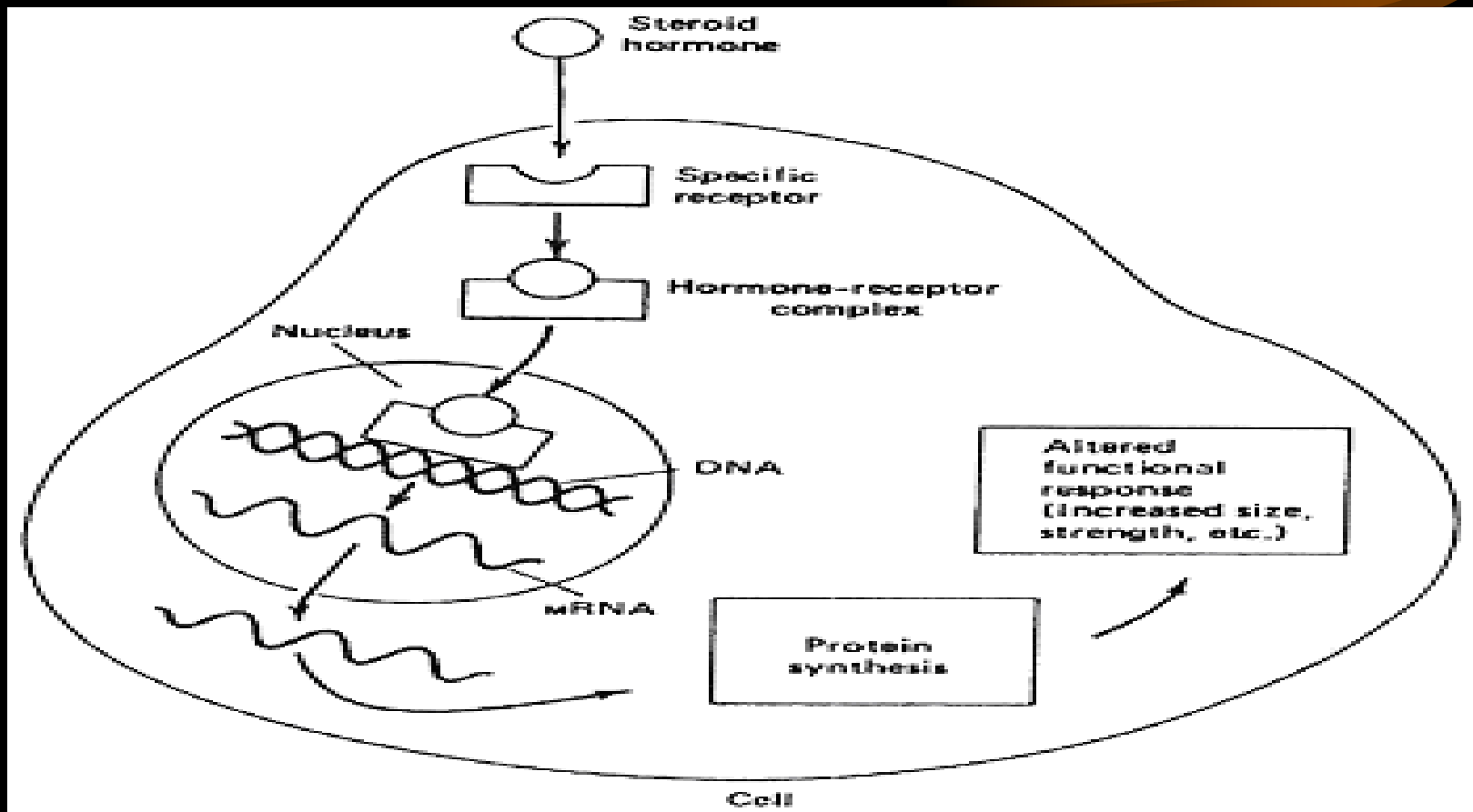
- Oxymethalone (Anadrol)
- Oxandrolone (Oxandrin)
- Methandrostenolone (Dianabol)
- Stanozolol (Winstrol)

Injectable

- Nandrolone decanoate (Deca-Durabolin)
- Nandrolone phenpropionate (Durabolin)
- Testosterone cypionate (Depo-Testosterone)
- Boldenone undecylenate (Equipoise)

Mechanism of Action

How a Steroid Hormone Works



Physiological Effects

- Positive
 - Protein synthesis
 - Lean body mass
 - Decreased body fat %
 - Force production
 - Power
 - Speed
 - Recovery time
- Negative
 - Hypertension
 - Atherogenic effect
 - Hirsutism (excessive hair growth)
 - Liver function
 - Gynecomastia
 - Liver tenderness
 - Testicular atrophy
 - Clitoral enlargement
 - Edema
 - Glucose tolerance

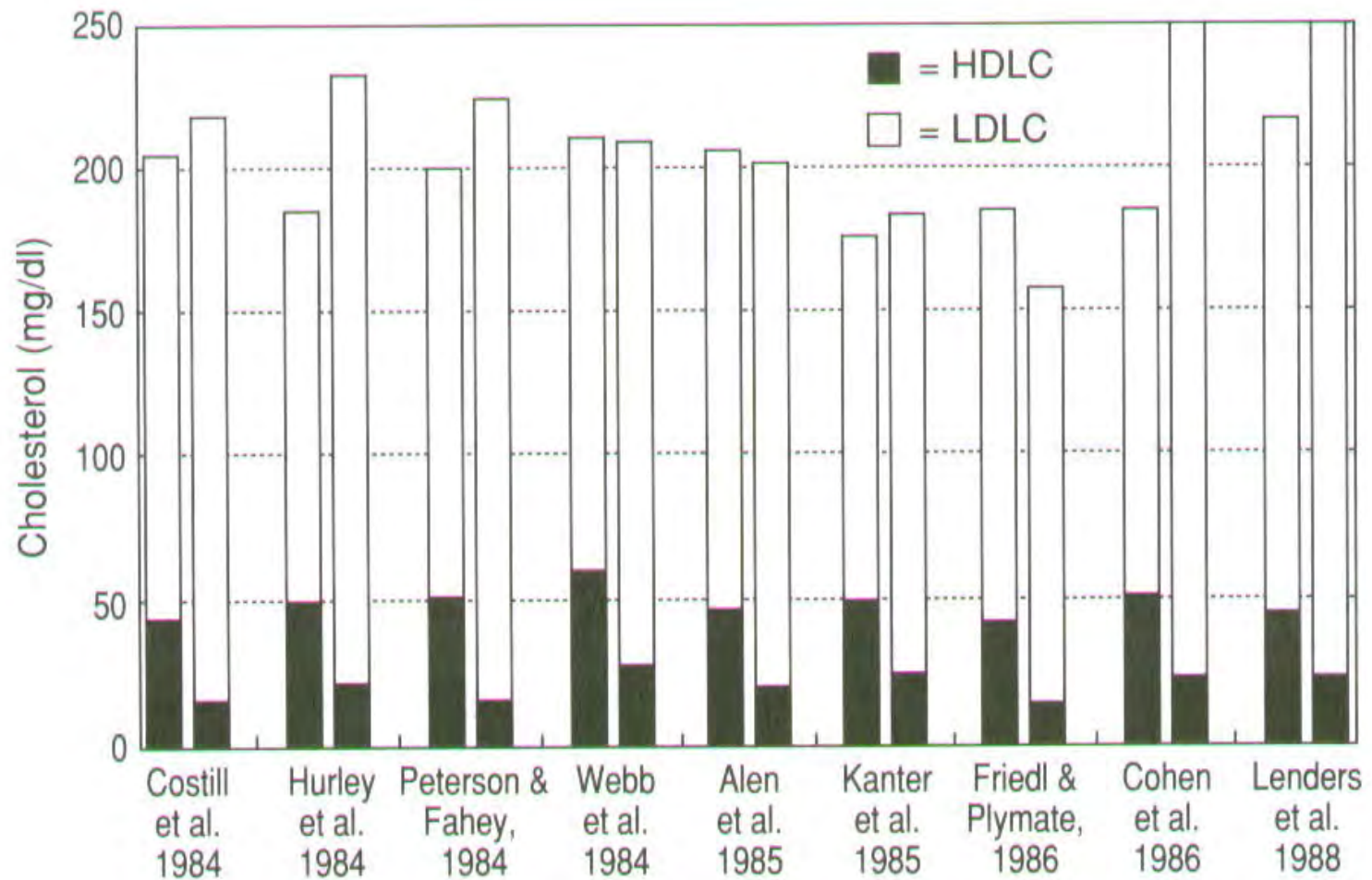


Figure 6.1 Serum lipid measurements without and with androgen self-administration in athletes. The decline in HDLC with androgen administration is consistent across studies, whereas total cholesterol increased significantly in two of the studies. All the studies used 17-alkylated androgens with or without injectable androgens. *Note.* Adapted from Friedl (1990).

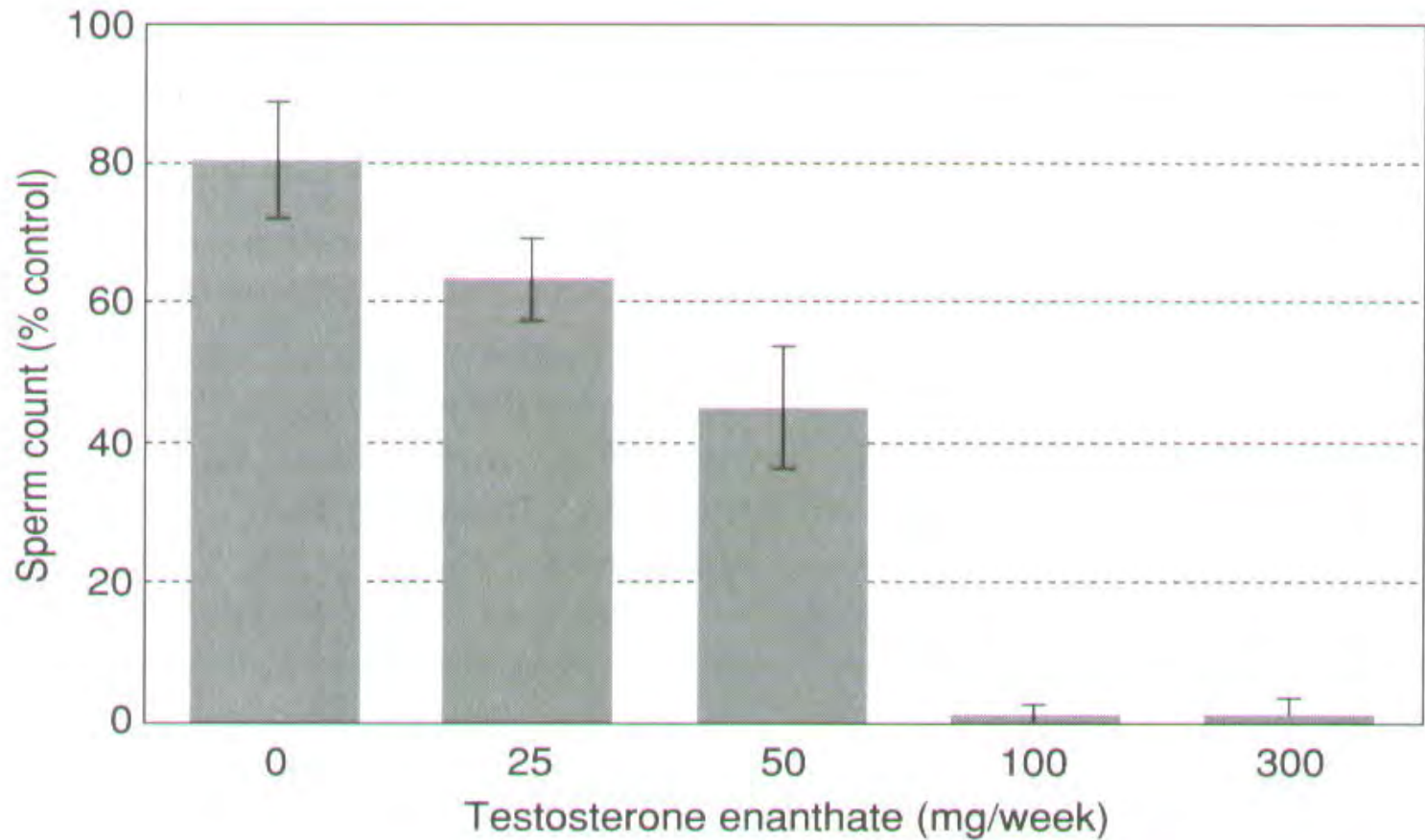


Figure 6.3 Sperm counts, expressed as a proportion of individual baseline values, at different doses of testosterone enanthate administered weekly by intramuscular injection for 6 months. *Note.* Adapted from Matsumoto and Bremner (1988).

Psychological Effects

- Positive

- Euphoria
- Motivational energy
- Aggression
- Libido

- Negative

- Depression
- Anxiety
- Irritability
- Suicidal
- Paranoia
- Hallucinations
- Dependence

Sources of Steroids



- Prescription (minor)
- Smuggled into country
- Diversion for US pharmacies
- Synthesized in clandestine laboratories

Steroidal Supplements

- Often taken because user believes they have anabolic effects
- Common supplements
 - Dehydroepiandrosterone (DHEA)
 - Androstenedione (street name Andro)
- Can be converted to testosterone (or estrogen)
- Effect of large doses unknown

Prevalence of Usage



- Research data as of 1990
- 1 million American users
 - 260,000 adolescents
- Unpublished data
 - 4th and 5th grade students

Scope of Steroid Abuse



- Use is increasing in adolescents (8th grade and higher)
- Steroid abuse is highest in males but use in young women is increasing at a faster rate than in young males

Reasons for Steroid Abuse

- Improve performance in sports
- Increase muscle size/reduce body fat
 - Muscle dysmorphia
 - Behavioral syndrome of distorted body image
 - Men think they look small and weak
 - Women think they look fat and flabby

Reasons for Steroid Abuse

Some people have experienced physical or sexual abuse

- One series of interviews with male weightlifters who abused steroids reported 25% had memories of childhood physical or sexual abuse
- In women weightlifters, twice as many of those who had been raped reported using anabolic steroids or compounds
- Of those women weightlifters who had been raped, almost all increased bodybuilding activities after the attack believing that the increased size and strength would discourage further attacks

Reasons for Steroid Abuse

- Some adolescents abuse steroids as a pattern of high risk behavior. This pattern may also include:
 - Drinking and driving
 - Carrying guns
 - Not wearing a helmet while on a motorcycle
 - Using other illicit drugs

How Steroids Are Used



- Dosage forms
 - Oral
 - Injection
 - Creams/gels
- Doses can be 10-100x greater than therapeutic dosages
- Stacking
- Pyramiding

Steroids & Stacking

- Believe that different steroids interact in an additive or synergistic manner
- Above has no scientific basis
- Two or more anabolic steroids taken together
 - Mix oral and injectable
 - May use veterinary compounds

Steroids & Pyramiding

- Dosed in cycles of 6-12 weeks
- Starts with low doses which are stacked
- Dose is slowly decreased during second portion of the cycle to zero
- An additional cycle of no use may be used in which the person still trains
- Believed that the above process allows the body to adapt to high doses and recuperate – No scientific basis for this belief

Adverse Effects & Steroids

- Most data on long-term effects comes from case studies
 - Incidence of life threatening effects appears to be low
 - Serious side effects may be under-recognized and under-reported
- Animal studies
 - In one study, exposing male mice to steroid doses comparable to those abused in human athletes for one-fifth of their life span resulted in a high percentage of premature deaths

Adverse Effects

Hormonal System

Males

- Infertility
- Gynecomastia
- Atrophy of testicles
- Male pattern baldness

Females

- Enlargement of the clitoris
- Excessive growth of body hair
- Male pattern baldness

Effects may be irreversible with continued use

Adverse Effects



- Musculoskeletal system
 - Short stature
 - Tendon rupture
- Cardiovascular system
 - Myocardial infarction
 - Left ventricular hypertrophy

Adverse Effects



- Liver
 - Cancer
 - Peliosis hepatitis (blood filled cysts)
- Skin
 - Acne
 - Cysts
 - Oily skin and hair

Steroids: Adverse Effects



Infections

- Nonsterile injection techniques
- Contaminated steroid products from clandestine labs
- Increased risk for
 - HIV, hepatitis B and C
 - Infective endocarditis
 - Infections/abscess formation at injection site

Samuel Wilson Fussell

“When faced with the syringe, even my own worst fears didn’t matter, I couldn’t stop. Seventeen-inch arms were not enough, I wanted 20. And when I got to 20, I was sure that I’d want 22. My retreat to the weight room was a retreat into the simple world of numbers. Numerical gradations were the only thing left in my life that made sense. Twenty was better than 17, but worse than 22. Bench pressing 315 was better than bench pressing 275, but worse than 365. I was reduced to a world where such thinking ruled, and it was only by embracing it that I could sleep at night.”

Muscle: Confessions of an Unlikely Bodybuilder, 1991

Real Life Example

- 21 year old male using for four weeks
- 1 cc testosterone cypionate (injectable)
- 1 Anadrol tablet
 - Body weight
 - 180 pounds to 210 pounds
 - 1 RM Bench press
 - 225 pounds to 290 pounds

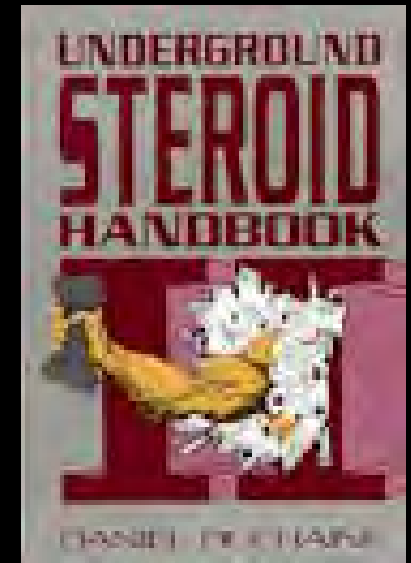
Prescription Doping



- Endometriosis
 - Danocrine
- Muscle tissue damage
 - Ben Johnson
 - Winstrol
- Progesterone administration prior to puberty
 - Eastern Bloc Female Gymnasts

Skeptical Approach

- Reliability of the source!
 - Mesomorphosis
 - Elite Fitness
 - Dan Duchaine
 - Steroid Encyclopedia
 - No Bull (Mick Hart)



Conclusions



- Criminal offense
 - Distribution is a felony
 - 5 years imprisonment and/or \$250,000
 - Possession without a legal prescription
 - Misdemeanor
- Educate people on side-effects
- Long-term studies
- Blood testing
- Ethical alternatives for athletes

COPD and muscle wasting

- Severe COPD 1-year mortality of 26%
- 210 million people are affected worldwide.
- Muscle wasting - 20% of stable COPD outpatients and 50% of hospitalized patients with acute respiratory failure
- COPD is commonly associated with weight loss.

What causes muscle wasting in COPD

- Increased respiratory work lead to elevated resting energy expenditure
- Anorexia and early satiety
- Malnutrition
- Decreased physical activity and deconditioning
- Chronic hypoxia
- Corticosteroid therapy
- Blunted muscle protein synthesis
- Increased muscle protein breakdown
- Interleukin-6
- Tumor necrosis factor- α
- Muscle inflammation
- Decreased Testosterone
- Fifty percent of men with chronic obstructive lung disease have testosterone levels in the hypogonadal range
- Positive correlation between the plasma testosterone level and 6 min walk distances in COPD

Mortality and morbidity effects of reduced lean body mass

- Mortality 30% in 3 years 50% in 5 years.
- Increased healthcare utilization
- Increased risk of re-admission
- Increased risk of trauma
- Quality of life

Why steroids in COPD

- Increased survival with weight gain
- Supraphysiological doses of testosterone increase (lean) body mass in healthy individuals.
- Anabolic steroids in athletes
- Maybe they would help in COPD

Primary Medical Uses of AAS

- Hypogonadism
 - Replacement therapy
- Male infertility
- Breast carcinoma
- Refractory anemias
- Stunted child growth*
- Wasting diseases
 - Tuberculosis
 - Cancer
 - AIDS
- Catabolic conditions
 - Osteoporosis
 - Burn patients
 - Severe infections

Studies looking at anabolic steroids in COPD

Table 1. Trials of anabolic androgenic steroids in chronic obstructive pulmonary disease

Author	No. of patients (M/F)	Study design	Study duration and intervention	Significant results AAS vs. placebo	Not significant results AAS vs. placebo	Comments
Schols <i>et al.</i> [34]	217 (M + F)	RCT, DB	Nandrolone 50 mg (M)/25 mg (F) i.m. every 2 weeks for 8 weeks	↑FFM; CHI; AMC; ↑RMS; ↑12-min WD	FEV ₁	In combination with rehabilitation program and nutritional therapy (420 kcal/day)
Creutzberg <i>et al.</i> [35]	63 (M)	RCT, DB	Nandrolone 50 mg i.m. every 2 weeks for 8 weeks	↑FFM(in patients using glucocorticoids only)	RMS, health status, peak workload, muscle function	In combination with rehabilitation Program
Sharma <i>et al.</i> [36]	16 (M♂F)	RCT, DB	Nandrolone 50 mg (M) or 25 mg (F) i.m. every weeks 2 for 16 weeks	None	Weight, BF, LBM, 6 min WD	Study was discontinued before reaching calculated sample size for 80% power
Casaburi <i>et al.</i> [37]	53 (M)	RCT (4 arms)	Testosterone 100 mg every week i.m. or placebo ± resistance exercise training during 10 weeks	↑Weight ↑LBM; ↓BF leg extensor strength	Blood gas variables, pulmonary function, RMS	In combination with resistance exercise training; patients all had low to low normal testosterone level
Ferreira <i>et al.</i> [38]	23 (M)	RCT, DB	Stanozolol 12 mg p.o. every day during 27 weeks	↑AMC, ↑weight, ↑LBM	BF, RMS, 6 min WD	In combination with respiratoryrehabilitation
Svartberg <i>et al.</i> [39]	29	RCT	Testosterone 250 mg i.m. every weeks 4 for 26 weeks	↑FFM, ↑self-reported erectilefunction, ↑sexual quality of life	Pulmonary function	•
Yeh <i>et al.</i> [40]	128 (M+ F)	OL, NC	Oxandrolone 10 mg p.o. twice daily during 4 months	vs. baseline: ↑weight; ↑BCM	vs. baseline: spirometry	•

AMC, arm muscle circumference; BCM, body cell mass; BF, body fat; CHI, creatine height index; CRQ, chronic respiratory questionnaire; DB, double-blind; F, females; FEV₁, forced expiratory volume in min; FFM, fat free mass; LBM, lean body mass; M, males; NC, noncontrolled; OL, open label; RCT, randomized controlled trial; RMS, respiratory muscle strength; WD, walking distance.

Schols et al

- 217 patients
- Depleted group [body weight less than 90% and/or a FFM less than 67% (men)/63% (women) of ideal body weight]
- Nondepleted group.
- Nutritional therapy with placebo or
- Nandrolone decanoate (women 25mg, men 50 mg; every 2 weeks).
- Depleted patients, nandrolone decanoate did not result in a greater weight gain compared with nutritional therapy alone.
- Body composition indicated a larger increase in muscle mass in the nandrolone decanoate group,
- Weight gain in the nutritional group consisted mainly of fat mass.
- Maximal inspiratory mouth pressure, a measure of respiratory muscle strength, improved significantly more in the nandrolone decanoate-treated patients.

Creutzberg et al.

- 63 male patients with COPD
- Pulmonary rehabilitation program PLUS nandrolone decanoate, 50mg every 2 weeks
- Placebo.
- Greater increase in FFM
- Muscle function, exercise capacity, health status, maximal inspiratory mouth pressure, peak workload, and erythropoietic parameters improved equally in both the treated and placebo groups.
- Subgroup low-dose oral glucocorticoids, nandrolone decanoate resulted in a larger improvement in exercise capacity compared with those receiving placebo.

Sharma et al

- 16 patients with severe COPD
- No structured rehabilitation program
- Nandrolone decanoate-treated patients (men 50 mg, women 25mg; every 2 weeks) did not gain significantly more weight and did not show improvement in physiological function or quality of life as compared with those receiving placebo.

Casaburi et al

- Testosterone enanthate (100mg weekly)
- Placebo
- With or without a standardized program
- Resistance exercise training
- Low normal testosterone levels (<400 ng/dl)
- Greater gains in FFM, muscle size, and muscle strength than placebo
- Testosterone and resistance exercise training combined resulted in greater gains in FFM and strength than either intervention alone.

Ferreira et al

- 23 malnourished (BMI less than 20 kg/m²) male COPD patients
- Stanozolol or placebo was administered for 6 months after one bolus injection of testosterone 250mg at baseline
- Nine of the 10 patients treated with anabolic steroids gained weight, whereas the control group lost weight. LBM, arm muscle circumference, and thigh circumference also increased significantly in the group treated with anabolic steroids.
- No significant change in inspiratory muscle pressure, 6 min walk distance or maximal exercise capacity was shown in either group.

Svartberg et al

- 29 patients with moderate-to-severe COPD
- 250mg testosterone i.m. every 4 weeks versus placebo
- A significant difference in FFM was observed between the two groups after 26 weeks.
- Erectile function and better sexual quality of life in the treatment group
- No significant improvement in pulmonary function compared with placebo.

Yeh et al

- Moderate-to-severe COPD 82
- Involuntary weight loss of more than 10% of ideal body weight
- Oxandrolone 10mg twice a day
- Oxandrolone facilitated weight restoration
- Bioelectric impedance analysis increase in lean tissue
- Karnofsky performance status scores improved
- 6 min walk distance showed a trend for improvement.
- Spirometry findings did not change significantly.
- Adverse events 38% edema, gastrointestinal disorders (mainly nausea), respiratory disorders, skin disorders including alopecia, musculoskeletal complaints, and fatigue.
- 12% of women experienced androgenic side effects.

Summary of studies

- Mild-to-moderate positive effects on muscle mass
- Disappointing effects on muscle function or exercise capacity

Possible explanations for disappointing results

- Relatively low doses aiming to restore normal healthy male testosterone levels.
- 600mg of testosterone per week and nandrolone at 200mg per week few side effects increasing effects on muscle mass and strength, especially when combined with strength training
- It can be expected that the benefits of AAS therapy are less in chronically ill patients, and therefore the administered dose of testosterone in the above-mentioned studies is probably too low to exert a clinically meaningful effect.

Future direction



- Weight loss
- Chronic glucocorticoid therapy
- Severe COPD with functional impairment
- Treatment outcomes should not only be focused on body weight, respiratory muscle function, and body composition, but also functional parameters such as dyspnea scores and quality of life, and health status evaluations should be considered. In addition, clinical parameters such as hospital admissions and frequency of exacerbations should be targets for future trials
- Include exercise and nutrition

Caution



- Advanced ischemic or congestive heart disease
- Hemoglobin levels need to be closely monitored and may limit the maximal tolerated AAS dose
- Lipid profile primarily suppression of HDL cholesterol
- Lowering of the voice, acne, hirsutism, and clitoromegaly
- Recommend against the use of AASs in women with COPD