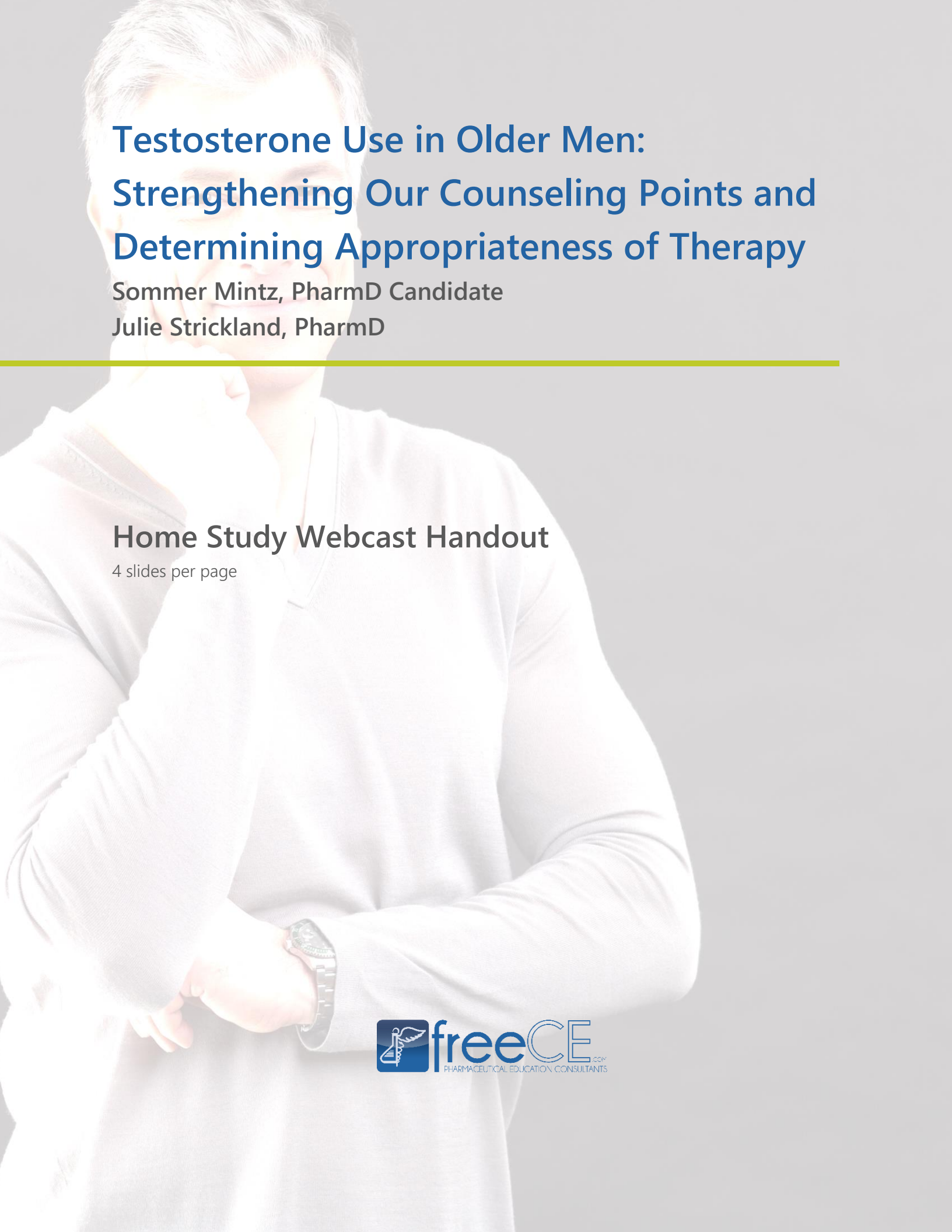




Testosterone Use in Older Men: Strengthening Our Counseling Points and Determining Appropriateness of Therapy

Sommer Mintz, PharmD Candidate
Julie Strickland, PharmD

Home Study Webcast Handout

4 slides per page

Testosterone Use in Older Men: Strengthening Our Counseling Points and Determining Appropriateness of Therapy

ACTIVITY DESCRIPTION

This activity will discuss when testosterone replacement therapy is clinically indicated as well as how help personalize therapy based on a variety of formulations. Side effects and monitoring will also be discussed to equip healthcare practitioners with the tools necessary to improve patient care for patients considering or receiving testosterone replacement therapy.

TARGET AUDIENCE

The target audience for this activity is **pharmacists** and **nurses** in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES

After completing this activity, the **pharmacist** will be able to:

- Determine when testosterone therapy is deemed appropriate vs inappropriate
- Describe the advantages and limitations associated with various testosterone formulations
- Identify monitoring parameters and potential side effects associated with testosterone replacement therapy

After completing this activity, the **pharmacy technician** will be able to:

- Recognize when testosterone therapy is deemed appropriate vs inappropriate
- Describe the advantages and limitations associated with various testosterone formulations
- Recognize when to alert the pharmacist regarding patient complaints of side effects potentially associated with testosterone replacement therapy

ACCREDITATION

Pharmacy



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Nursing

PharmCon, Inc. is approved by the California Board of Registered Nursing (Provider Number CEP 13649) and the Florida Board of Nursing (Provider Number 50-3515). Activities approved by the CA BRN and the FL BN are accepted by most State Boards of Nursing.

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<http://www.nursecredentialing.org/RenewalRequirements.aspx>

Universal Activity No.: 0798-0000-17-053-H01-P

Credits: 1.0 contact hour (0.1 CEU)

Release Date: 02/16/2017

freeCE Expiration Date: 2/16/2020

ACPE Expiration Date: 2/16/2020

ACTIVITY TYPE

Knowledge-Based Home Study Webcast

FINANCIAL SUPPORT BY

Pharmaceutical Education Consultants, Inc.



Sommer Mintz, PharmD Candidate

Medical University of South Carolina

ABOUT THE AUTHOR

Sommer is a 2017 PharmD candidate expected to graduate from the Medical University of South Carolina in May. She has worked in retail pharmacy as a technician and a pharmacy intern for going on six years with experience in independent pharmacy compounding as well as chain pharmacies. She is passionate about ensuring patients are counseled appropriately, and she wishes to initiate outreach programs centered around hosting classes to educate patients on the management of common disease states through pharmacological and nonpharmacological methods.

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Julie Strickland, PharmD

Pharmcon

ABOUT THE AUTHOR

Julie Strickland is a PharmD graduate of the University of South Carolina College of Pharmacy. She has experience in both chain and independent pharmacy practice, including ownership, with specific interests in patient safety and promoting positive patient outcomes. She now serves in Conway, SC as the Director of Continuing Education here at PharmCon.

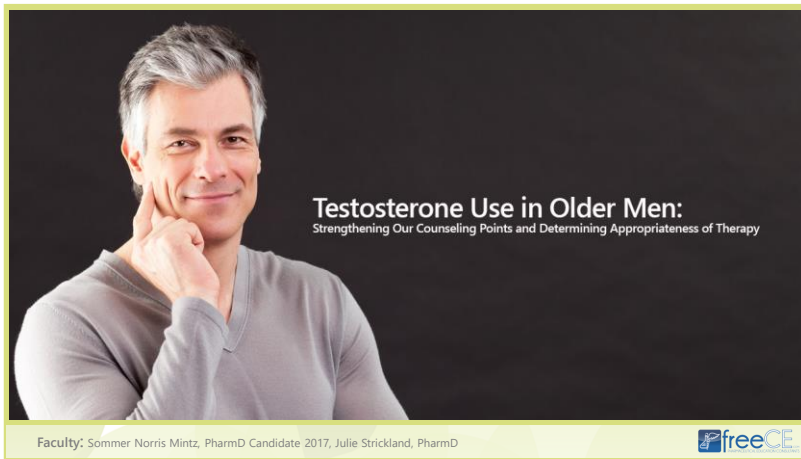
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Objectives

- Determine when testosterone therapy is deemed appropriate versus inappropriate
- Describe the advantages and limitations associated with various testosterone formulations
- Identify monitoring parameters and side effects associated with testosterone replacement therapy



Introduction

- Endogenous testosterone declines with age
- Symptoms:
 - Sexual function
 - Mobility
 - Energy

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Background

- Testosterone replacement
 - Decrease in fat
 - Increased muscle mass

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



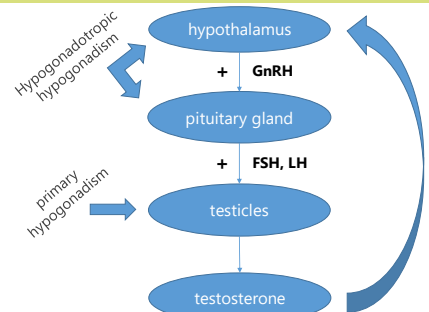
Background

- Male hypogonadism – main use for years
- Cosmetic use
 - Desire to look and feel better
- Long-term safety & benefit not studied
- FDA approved indications:
 - Primary hypogonadism
 - Hypogonadotropic hypogonadism

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624
Aveed [package insert]. Endo Pharmaceuticals Inc., Malvern, PA; October 2016



Feedback Loop



Walker WH, Cheng J. *The Journal of the Society for Reproduction and Fertility* 10:1530[rep.1.00358]



Diagnosis

- Criteria:
 - Signs/symptoms
 - Serum testosterone <300 ng/dL
- Signs and Symptoms:
 - Fatigue
 - Loss of strength and muscle mass
 - Sexual dysfunction
 - Depression

Bhasin S, Cunningham GR, Hayes FJ, et al. *J Clin Endocrinol Metab* 2010;95:2536-59



High Risk Disease States

- Type II Diabetes
- Infertility
- Weight loss associated with HIV
- Certain medications
 - Opioids
 - Glucocorticoids

Bhasin S, Cunningham GR, Hayes FJ, et al. *J Clin Endocrinol Metab* 2010;95:2536-59



Type II Diabetes Mellitus

- Twice as likely
- Inverse relationship:
 - Testosterone and body mass index
 - Testosterone and waist-to-hip ratio
 - Testosterone and sex-hormone binding globulin
- Positive correlation:
 - Testosterone and insulin sensitivity

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab 2010;95:2536-59



Infertility

- Low testosterone can CAUSE
- HOWEVER:
 - Exogenous administration stops feedback loop
 - Endogenous production declines or stops
 - Worsen infertility

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab 2010;95:2536-59



HIV

- 20-25% men with HIV have low testosterone
 - Associated with progression
- Short term therapy appropriate (3-6 months)
- Goals:
 - Maintain healthy weight
 - Increase lean body mass and strength

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab 2010;95:2536-59



Medications

- Opioids
 - Suppress hypothalamic-pituitary-gonadal axis
 - Symptoms of androgen deficiency
- Glucocorticoids
 - Suppress hypothalamic-pituitary-gonadal axis
 - Short term therapy appropriate
 - Goals:
 - Maintain lean body mass
 - Maintain bone mineral density

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab 2010;95:2536-59



The Endocrine Society's Clinical Guidelines

- Treatment Goals:
 - Improve sexual function
 - Secondary sex characteristics
 - Improve bone mineral density
 - Better sense of overall well-being

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab. 2010;95:2536-59.



Treatment Population

- 65+ years old
- Clinical signs/symptoms
- Serum testosterone level: <275-300 ng/dL
- Primary hypogonadism OR hypogonadotropic hypogonadism

Snyder PJ, Bhasin S, Cunningham GR, et al. N Engl J Med. 2016;334(7):611-624.



Treatment Precautions

- AVOID:
 - Prostate or breast cancer
 - Prostate nodule
 - PSA > 4 ng/mL
 - PSA > 3 ng/mL + high risk of developing prostate cancer
 - African American
 - First degree relative
 - Hct > 50%
 - Risk of thrombosis and stroke
 - Obstructive sleep apnea not being treated
 - Urinary tract symptoms

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab. 2010;95:2536-59.



Treatment Adverse Events

- Bump in hematocrit and erythrocytosis
 - Risk of thrombosis and stroke
- Skin oiliness and acne
 - Stimulates sebaceous glands to produce more oil
- Subclinical prostate cancer detection

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab. 2010;95:2536-59.



Products Available

Type of Administration	Brand	Generic
Oral	Androxy	Fluoxymesterone (US only)
	Android	Methyltestosterone (US only)
	Methitest	
	Testred	Testosterone undecanoate (Canada only)
	Andriol	

Advantages

- Dose flexibility
- Self-administration

Limitations

- Lipid changes
- Variability in response
- Hepatotoxicity

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab. 2010;95:2536-59.
Snyder PJ, Bhasin S, Cunningham GR, et al. N Engl J Med. 2016;374:111-124.
Hewlett A, Rahn AJ, Chan T, et al. Can J Endocrinol. 2010;54:500-10.
Cunningham GR, Torma SM. J Clin Endocrinol Metab. 2011;95:58-62.



Products Available

Type of Administration	Brand	Generic
Parenteral	Depo-Testosterone	Testosterone cypionate
	Delatestryl	Testosterone enanthate
	Aveed	Testosterone undecanoate (US only)

Advantages

- Administration frequency
- Low cost

Limitations

- Injection site pain
- Testosterone fluctuations
- Rare cough
- Excessive erythrocytosis



Products Available

Type of Administration	Brand	Generic
Transdermal Patch	Androderm	testosterone

Advantages

- Convenient
- Mimics normal level changes

Limitations

- Greatest risk of skin irritation
- Low potency steroid cream

Bhasin S, Cunningham GR, Hayes FJ, et al. J Clin Endocrinol Metab. 2010;95:2536-59.
Snyder PJ, Bhasin S, Cunningham GR, et al. N Engl J Med. 2016;374:111-124.
Cunningham GR, Torma SM. J Clin Endocrinol Metab. 2011;95:58-62.
Miller J, Britto M, Fitzpatrick S, et al. Endocr Pract. 2011;17:574-83.



Products Available

Type of Administration	Brand	Generic
Transdermal Gels & Solutions	AndroGel 1%	testosterone
	AndroGel 1.62% (US only)	
	Fortesta 2% (US only)	
	Testim 1%	
	Axiron 2%	

Advantages

- Less skin irritation
- Small fluctuations in levels

Limitations

- Person-to-person transfer
 - Wash hands
 - Cover site with clothing



Products Available

Type of Administration	Brand	Generic
Pellet	Testopel (US only)	testosterone

Advantages

- Long-acting (last 3-6 months)
- Convenient

Limitations

- Difficult to adjust dose
- Pain and inflammation
- Can slough out
- Potential for infection



Products Available

Type of Administration	Brand	Generic
Buccal	Striant (US only)	testosterone

Advantages

- No large fluctuations
- Can eat and drink after product placement

Limitations

- Mouth or gum irritation
- Taste change



Products Available

Type of Administration	Brand	Generic
Nasal Gel	Natesto	testosterone

Advantages

- Person-to-person transfer risk minimal

Limitations

- Dosed three times daily
- Avoid in patients with allergies
- May cause:
 - Nasopharyngitis
 - Nasal discomfort
 - Scabbing
 - Sinusitis
 - Rhinorrhea



Effects of Testosterone Treatment in Older Men

P.J. Snyder et al.

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Methods

- Inclusion:
 - 65 y/o or older
 - Serum testosterone average <275 ng/dL
- Exclusion:
 - History of prostate cancer
 - MI or stroke in past 3 months
 - Unstable angina
 - Severe depression

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Methods

- AndroGel 1% vs. placebo gel
 - Initial: 5 g daily
- Goal: normal range for men 19-40
- Primary Outcomes:
 - Sexual activity
 - 6-minute walk test
 - Fatigue

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Assessment

- Tested upon conclusion:
 - Total and free testosterone
 - SHBG
 - Estradiol
 - Dihydrotestosterone
- PSA and DRE monitored throughout study
- Prostate nodule/increase in PSA by 1 ng/mL or more → prostate biopsy

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Statistical Analysis

- Significance:
 - 6-minute walk test
 - 50% men in testosterone group increased walk distance by 50 meters or more
 - FACIT-Fatigue score
 - Functional Assessment of Chronic Illness – Fatigue
 - Increase by 4 or more points from baseline
 - PDQ-4 score
 - Psychosocial Daily Questionnaire
 - Change from baseline

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Results

- 91% treatment group: average serum level >275 ng/dL months 3-12
- Comorbidities:
 - Obesity 62.9%
 - HTN 71.6%
 - MI 14.7%
- Significance not seen with each subgroup
- Significance seen when all patients included:
 - 6-minute walk distance
 - PDQ-4 score
 - FACIT-Fatigue score

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Adverse Events

- Prostate cancer during – 1 in treatment group
- Prostate cancer after – 2 in treatment group, 1 in placebo group
- Hgb increase by 17.5 g/dL or more: 7 in treatment group
- CV events (MI, death from CV events, stroke): 7 each group

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Strengths and Limitations

Strengths

- Double blind, placebo controlled
- Adequate sample size
- Low drop-out rate

Limitations

- 65+ years old
- Low testosterone average
- Generalizability

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Testosterone Therapy and Cardiovascular Events Among Men

Lin Xu, Guy Freeman, Benjamin J Cowling, and C Mary Schooling

Xu L, Freeman G, Cowling B, Schooling C. *BMC Medicine* 2013; 11:108



Methods

- Systematic review & meta-analysis
- 27 placebo-controlled, randomized trials
- Inclusion:
 - Studies including CV events in both groups
 - Any RCT of testosterone vs placebo
- Exclusion:
 - Trials lasting <12 weeks
 - RCT of androgen other than testosterone

Xu L, Freeman G, Cowling B, Schooling C. *BMC Medicine* 2013; 11:108



Methods

- Primary outcomes:
 - Composite cardiovascular events
 - Cardiac disorders
 - Vascular disorders (DVT not included)
 - Cardiovascular events or complaints

Xu L, Freeman G, Cowling B, Schooling C. *BMC Medicine* 2013; 11:108



Statistical Analysis

- Pooled odds ratio 1.54
 - Potential CV harm associated with testosterone
- Study structures included were conducted similarly
- Some studies favoring placebo may not have been included

Xu L, Freeman G, Cowling B, Schooling C. *BMC Medicine* 2013; 11:108



Results

- Varied by source of funding
- Statistical significance:
 - Studies not funded by pharmaceutical companies

Xu L, Freeman G, Cowling B, Schooling C. *BMC Medicine* 2013; 11:108



Strengths and Limitations

Strengths

- Randomized
- Placebo-controlled
- Meta-analysis

Limitations

- Can't include ongoing trials
- Severity of events varied
- Trial termination
- Bias

Xu L, Freeman G, Cowling B, Schofield C. BMC Medicine 2013; 11:108



Application

- 65 years old or older
- Signs and symptoms
- Hypogonadism (serum testosterone <275-300 ng/dL)

Snyder PJ, Bhasin S, Cunningham GR, et al. N Engl J Med. 2016;334(7):611-624



Monitoring

- Signs and symptoms
 - After 3-6 months
 - Annually
- Serum testosterone
 - After 3-6 months
 - According to product
- Hematocrit:
 - Baseline
 - After 3-6 months of therapy
 - Annually
- Bone mineral density
 - After 1-2 years of therapy

Bhasin S, Cunningham GR, Hayes FI, et al. J Clin Endocrinol Metab 2010;95:2536-59



Monitoring

- DRE
 - Baseline PSA >0.6 ng/mL
 - After 3-6 months of therapy
 - According to guidelines for prostate cancer
- Consult urology:
 - PSA increases >1.4 ng/mL
 - PSA velocity >0.4 ng/mL/year
 - Prostate abnormality
 - AUA/IPSS score >19
- Formulation –specific adverse events

Bhasin S, Cunningham GR, Hayes FI, et al. J Clin Endocrinol Metab 2010;95:2536-59



Labeling Changes

- Anabolic androgenic steroids
 - Class III
- Abuse and dependence
 - Adults and adolescents
 - Athletes and body builders
- Prescribers: measure levels if abuse suspected
- Safety risks:
 - Stroke
 - Heart attack
 - Hostility and aggression
 - Heart failure
 - Withdrawal symptoms

Food and Drug Administration Web site: <http://www.fda.gov/Drugs/DrugSafety/ucm526206.htm>,
Food and Drug Administration Web site: <http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm>



Conclusion

- Statistically significant results
 - Sexual function
 - 6-minute walk distance
 - Vitality
- Long term benefits unknown
- Monitoring parameters and contraindications

Snyder PJ, Bhasin S, Cunningham GR, et al. *N Engl J Med*. 2016;334(7):611-624



Pharmacist Role

- Counseling
- Determining appropriateness of therapy
- Monitoring for dependence



Exam Questions:

1. Which product should be avoided in a patient with eczema?
 - a. Striant
 - b. Androderm
 - c. Depo-Testosterone
 - d. Natesto
2. When should serum testosterone levels be drawn for a patient receiving testosterone cypionate every two weeks?
 - a. One week after injection
 - b. Five weeks after the third injection
 - c. Five hours after administration
 - d. Immediately prior to the next dose
3. In which patient population is therapy deemed inappropriate?
 - a. Baseline hematocrit of 45%
 - b. Weight loss associated with HIV
 - c. Baseline PSA greater than 4 ng/mL
 - d. Patient being treated for obstructive sleep apnea
4. What is an appropriate goal level for serum testosterone?
 - a. 4 ng/mL
 - b. 100 ng/dL
 - c. 250 ng/dL
 - d. 350 ng/dL
5. Which therapy would be least appropriate for a patient with a busy lifestyle who may forget medication administration easily?
 - a. Natesto
 - b. Delatestryl
 - c. Androderm
 - d. Methitest

6. All the following are potential side effects of exogenous testosterone replacement therapy EXCEPT:
 - a. Acne
 - b. Infertility
 - c. Potential for stroke or thrombosis
 - d. Increased risk for bone fractures
7. Which product has a REMS program regarding anaphylaxis and potential for serious pulmonary oil microembolism associated with it?
 - a. Aveed
 - b. Depo-Testosterone
 - c. Delatestryl
 - d. Methitest
8. While skin irritation is a potential side effect of Androderm, which of the following is recommended to combat mild topical irritation?
 - a. Benadryl
 - b. Cold compress
 - c. Hydrocortisone 1% cream
 - d. Triamcinolone 0.1% ointment
9. What would be an appropriate dose of testosterone cypionate?
 - a. 100 mg every other week
 - b. 150 mg weekly
 - c. 200 mg weekly
 - d. 150 mg every other week
10. Where is an appropriate site of application for Axiron 2%?
 - a. the abdomen
 - b. the genitals
 - c. under the arms
 - d. the thighs