

# Testosterone, Estrogen, and Progestogen, Oh My!

Emily Van Klompenburg, PharmD, BCACP  
Assistant Professor of Pharmacy Practice  
South Dakota State University  
College of Pharmacy and Allied Health Professions  
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## Financial Disclosure

- I have had no financial relationship over the past 24 months with any commercial sponsor with a vested interest in this presentation.

## Pharmacist Learning Objectives

- List the diagnostic criteria for testosterone therapy.
- Determine appropriate monitoring parameters for testosterone therapy.
- Identify the effects of estrogen deficiency as related to menopause.
- Discuss treatment strategies for vasomotor and genitourinary symptoms of menopause.

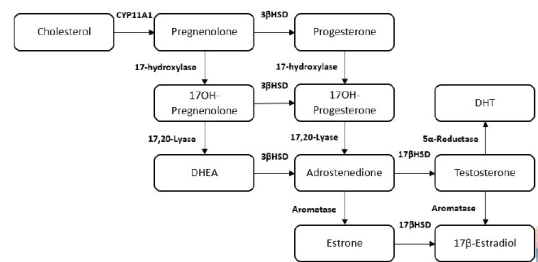
## Technician Learning Objectives

- List the available testosterone therapy formulations.
- Recognize the hormones that are related to menopause.
- Discuss the difference between topical vaginal and systemic estrogens for treatment of menopause symptoms.

## Acronyms

- Gonadotropin-Releasing Hormone (GnRH)
- Follicle-Stimulating Hormone (FSH)
- Luteinizing Hormone (LH)
- Sex Hormone Binding Globulin (SHBG)
- Free Testosterone (FT)
- Total Testosterone (TT)
- Testosterone (T)

## Sex Hormones



# Hypogonadism

## Hypogonadism

- Low serum testosterone levels in males
- Clinical presentation depends on the age of onset of testosterone deficiency
  - Fetal development – Underdeveloped male genitals
  - Puberty – Inhibit development of muscle mass, voice deepening, growth of body/facial hair, growth of penis and testicles
  - Adulthood – Decreased sex drive, decreased energy, depression
- "Low T"
  - Up to 25% of men treated with testosterone do not have their testosterone tested prior to starting testosterone
  - Those treated with testosterone, almost half do not have testosterone levels checked
  - One-third men treated with testosterone do not meet the criteria of hypogonadism

J Clin Endocrinol Metab. 2018.  
J Clin Endocrinol Metab. 2018.

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## Pathophysiology

- Primary Hypogonadism
  - Surgical removal of the testes for the treatment of prostate or testicular cancer
  - Testicular trauma or disease
  - Chemotherapy
- Secondary Hypogonadism
  - Hypothalamic (LH-releasing hormone) or pituitary disorders (LH)
  - Hyperprolactinemia (pituitary tumors or chronic renal failure)

J Clin Endocrinol Metab. 2018.  
J Clin Endocrinol Metab. 2018.  
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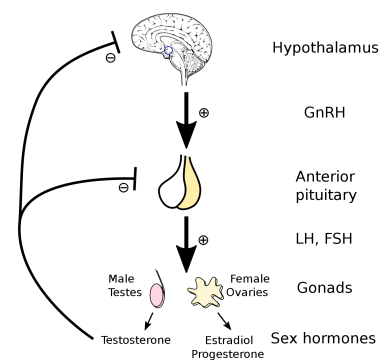


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## Clinical Presentation

- Reduced energy
- Reduced endurance
- Diminished work and/or physical performance
- Fatigue
- Visual field changes (bitemporal hemianopsia)
- Anosmia
- Depression
- Reduced motivation
- Poor concentration
- Impaired memory
- Irritability
- Infertility
- Reduced sex drive
- Changes in erectile functional

J Clin Endocrinol Metab. 2018.

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## Diagnosis

- Clinical diagnosis of testosterone deficiency
  - Low total testosterone serum concentration
  - AND
  - Signs and/or symptoms of low testosterone
- Avoid treating based only off total testosterone serum concentration

J Clin Endocrinol Metab. 2018.

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## Serum Testosterone Concentrations

- Total Testosterone concentrations should be measured on two separate mornings while fasting
  - Diurnal variation with peak values in the morning and day-to-day variation
  - Testosterone is suppressed by food
  - Up to 30% of men with an initial low T have a normal T level on repeat measurement
- If initial TT concentrations are at or near the lower limit of the normal range
  - Determine Free Testosterone concentrations
- Do not test for testosterone deficiency when:
  - Recovering from acute illness
  - Taking short-term use medications that suppress testosterone concentrations
    - Opioids, glucocorticosteroids

J Urol. 2018.  
J Clin Endocrinol Metab. 2018.



## Serum Testosterone Concentrations

- Serum TT concentration represents the sum of unbound and protein-bound T in circulation
- Most of the circulating testosterone is bound to SHBG and albumin
  - Only 2% to 4% of circulating T is unbound or free
- Serum TT concentration
  - 300–900 ng/dL – typical normal range
  - 300 ng/dL – lower limit of normal
  - <150 ng/dL – greatly below lower limit of normal

J Urol. 2018.  
J Clin Endocrinol Metab. 2018.



## Treatment of Hypogonadism with Testosterone Therapy

- Prior to initiating treatment
  - Obtain hemoglobin, hematocrit, and PSA
- Counsel patient on
  - May improve erectile function, low sex drive, anemia, bone mineral density, lean body mass, and depressive symptoms
  - Inconclusive whether testosterone therapy improves cognitive function, diabetes, energy, fatigue, lipid profiles, and quality of life measures

J Urol. 2018.  
J Clin Endocrinol Metab. 2018.



## Treatment of Hypogonadism with Testosterone Therapy

- Goals of Therapy
  - Normalize total testosterone levels
    - Target range of 450–600 ng/dL
  - Improve symptoms or signs of low testosterone
- Oral testosterone is rapid metabolized by the liver
  - Difficult to maintain normal serum levels
  - Most products are topical preparations or injections

J Urol. 2018.  
J Clin Endocrinol Metab. 2018.



## Contraindications to Testosterone Therapy

- Prostate cancer
- Breast cancer
- Severe lower urinary tract symptoms
- Erythrocytosis (Hct >50%)
- Severe untreated sleep apnea
- Uncontrolled heart failure
- Recent cardiovascular event

J Urol. 2018.  
J Clin Endocrinol Metab. 2018.



## Topical Testosterone Formulations

- Gels, creams, liquids, patches
- Daily administration
  - Provides relatively stable serum testosterone concentrations
- Typically applied to upper arms, shoulders, or torso
  - Some products may be applied to the thigh area

J Urol. 2018.  
J Clin Endocrinol Metab. 2018.



## Injectable Testosterone Formulations

- Intramuscular injection
- IM injection every 1 to 3 weeks
  - Increased variance of serum testosterone between injections
- Shorter dosing intervals
  - 50-100mg weekly
  - 100 to 200mg every 2 weeks are used.

J Urol. 2018;  
J Clin Endocrinol Metab. 2018.



## Monitoring Testosterone Therapy

- Topical Testosterone Formulations
  - Repeat serum total testosterone 2 to 4 weeks after initiation
- Intramuscular Testosterone Formulations (testosterone cypionate or enanthate)
  - Repeat serum total testosterone at midpoint between injections
- Long-acting intramuscular testosterone (testosterone undecanoate)
  - Repeat serum total testosterone halfway between the first two 10-week injections
- After therapeutic levels (450-600 ng/dL) have been achieved
  - Repeat serum total testosterone every 6-12 months
  - Consider PSA, Hct/Hgb

J Urol. 2018;  
J Clin Endocrinol Metab. 2018.



## Discontinuing Testosterone Therapy

- After 3 to 6 months of testosterone therapy.
- If serum testosterone levels are within normal physiologic ranges AND sign/symptom improvement
  - Continue testosterone therapy with monitoring every 6-12 months
- If serum testosterone levels are within normal physiologic ranges BUT patient does not experience sign and symptom improvement
  - Discontinue testosterone therapy

J Urol. 2018;  
J Clin Endocrinol Metab. 2018.



## Testosterone Therapy Safety

- Low testosterone increases risk of major adverse cardiovascular events
  - Inconclusive if testosterone therapy decreases cardiovascular risk
- Risk of polycythemia
- Potential risk in prostate cancer develop
- Exogenous testosterone may affect spermatogenesis
- Testosterone topical preparations (gels, creams, liquids) have potential for transference to others
  - Follow directions for use and avoid skin-to-skin contact with unwashed/uncovered area where drug has been applied

J Urol. 2018;  
J Clin Endocrinol Metab. 2018.



## Menopausal Hormone Therapy



## Menopause

- Permanent cessation of menses following the loss of ovarian follicular activity
  - Causes acute decline in circulating estrogen levels
- Defined as one year without menses
  - Ovaries progressive failure to produce estrogen
  - Late 30s – estrogen production starts to decline
  - Mid 50s – estrogen production ceases
- Median onset at age 51 year (40-58 years)



Menopause 2020

## Menopause

- Occurs naturally in stages
  - Perimenopause (usually in 5<sup>th</sup> decade)
  - Menopause
  - Postmenopause (1 year after menses cessation and beyond)
- Induced menopause
  - Bilateral oophorectomy or iatrogenic ablation of ovarian function
  - Women who have undergone a hysterectomy are more likely to have an earlier menopause



Menopause 2020

## Pathophysiology

- Approximately 2 million follicles in ovaries at birth (female infant)
  - Majority of follicles undergo atresia
- Controlled by hypothalamic-pituitary-ovarian axis during reproductive years
  - Hypothalamus secretes GnRH →
  - Stimulates pituitary to release FSH & LH →
  - Regulates ovarian function and follicle maturation occurs →
  - GnRH, FSH, and LH influenced by negative feedback from estradiol and progesterone
    - Estradiol is produced by *dominant follicle*
    - Progesterone is produced by *corpus luteum*



Menopause 2020  
Oxford's Pharmacotherapy 2021

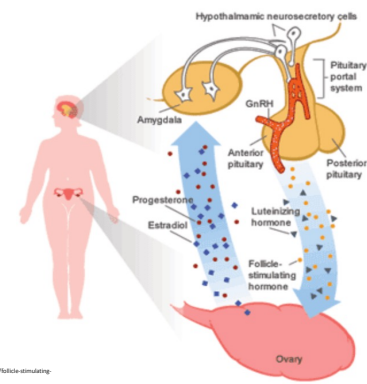


Image from: <https://www.openpr.com/news/2942094/follicle-stimulating-hormone-market-rapidly-growing-in-medical>



Menopause 2020

## Pathophysiology

- Changes during menopause
  - Number of follicles decrease with aging with few remaining at menopause
    - Follicle is no longer primary site of estradiol and progesterone synthesis
    - Postmenopausal ovary primarily secretes androstenedione
- As estradiol and progesterone levels decline, negative feedback to HPO axis causes more FSH to be released
  - FSH stimulates more follicles per cycle leading to estradiol overproduction
  - Elevated FSH levels indicate both peri-menopause and menopause
    - FSH level of 10-12 IU/L on day 2 or 3 of menstrual cycle indicates diminished ovarian reserve
    - FSH level >40 IU/L when ovarian has completely ceased



Menopause 2020  
Oxford's Pharmacotherapy 2021

## Clinical Presentation

- Vasomotor Symptoms (VMS)**
  - Sleep disturbances
  - Mood changes
  - New-onset depression
- Genitourinary Syndrome of Menopause (GSM)**
  - Vulvovaginal atrophy (VVA)
  - Urinary tract symptoms (including pelvic floor disorders)
- Sexual dysfunction



Menopause 2020

## Treatment

- Menopause is a natural life event, not a disease.
- Goals of therapy
  - Relieve symptoms
  - Improve quality of life
  - Minimize adverse effects
- Determine if patient is experiencing bothersome VMS, GSM, or both

Menopause 2022  
Diffré's Pharmacotherapy 2023

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Algorithm for Pharmacologic Management of Menopausal Symptoms

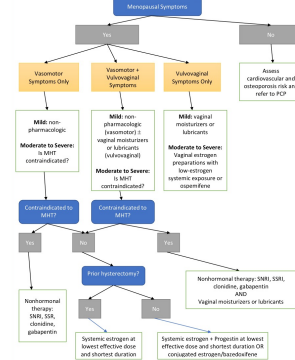


Image adapted from: Diffré's Pharmacotherapy 2023.

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## Estrogen Clinical Pearls

- Hormone therapy relieves VMS and is considered first line therapy for moderate to severe menopausal VMS
- Chronic unopposed systemic estrogen use increases the risk for endometrial hyperplasia and endometrial cancer
  - Adding progestogen prevents endometrial overgrowth and decreases risk of endometrial cancer
  - Women with intact uterus who take estrogen should also take progestogen
  - Women who have had a hysterectomy can take estrogen unopposed (without progestogen)
- Vaginal estrogens deliver low systemic doses and the endometrial hyperplasia risk is not increased
- Use the lowest effective dose for the shortest amount of time that addresses treatment goals

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## Available Estrogen Preparations

- Conjugated equine estrogens (CEE)
  - Includes estrogen sulfate
  - In postmenopausal women, estrone sulfate is a naturally occurring estrogen
  - Precursor for the formation of estrone and estradiol
- Synthetic conjugated estrogens (CE)
  - Blend of synthetic estrogen substances including estrone sulfate, equilin sulfate, estradiol sulfate
- Micronized 17 $\beta$ -estradiol
  - Identical to the structure of estradiol that is produced by the ovaries
  - Estradiol is reversibly converted to estrone
- Ethinyl estradiol
  - Synthetic estrogen primarily used in combination with a progestin in hormone contraceptives

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## Progestogens Administered with Estrogen

- Progestogens (synthetic progestins and progesterone) coadministered with estrogen in women with a uterus
  - Medroxyprogesterone acetate, norethindrone acetate, and micronized progesterone
- Synthetic Progestin
  - Medroxyprogesterone acetate, levonorgestrel, and norethindrone acetate
- Naturally Occurring Progestin
  - Micronized progesterone
  - Structurally identical to the progesterone produced by the corpus luteum

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## Contraindications to MHT

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen- or progesterone-dependent neoplasia
- History of venous thromboembolism
- Active or recent arterial thromboembolic disease (CVA, MI)
- Liver dysfunction or disease

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## Vasomotor Symptoms (VMS)

- Nonpharmacologic (*Mild symptoms*)
  - Wearing layered clothing that can be removed or added as necessary
  - Lowering room temperature
  - Decreasing intake of hot spicy foods, caffeine, and hot beverages
  - Exercise
  - General good health practices

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## Vasomotor Symptoms (VMS)

### Pharmacologic (Moderate to Severe symptoms)

- Hormonal (estrogen +/- progestogen)
  - Intact uterus: systemic MHT
    - Estrogen plus progestogen
    - Estrogen agonist/antagonist (bazedoxifene)
  - Hysterectomy
    - Estrogen therapy unopposed by progestogen
- Nonhormonal agents
  - SSRI, SNRIs, gabapentin

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## Genitourinary Syndrome of Menopause

- Nonpharmacologic (*Mild symptoms*)
  - Nonhormonal lubricants and moisturizers

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## Genitourinary Syndrome of Menopause

### Pharmacologic (Moderate to Severe symptoms)

- Vaginal estrogen therapy (cream, tablet, ring)
  - Unopposed low dose vaginal estrogen therapy is appropriate
    - No increased risk of endometrial hyperplasia or endometrial cancer
  - Therapeutic response
    - Initial therapy: 2 weeks of daily estrogen administration
    - Maintenance therapy: decrease administration to 2-3 times weekly
- Selective estrogen receptor modulator (SERM)
  - Ospemifene 60mg daily
    - Full estrogen agonist effect in vaginal epithelium to improve dyspareunia

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## Discontinuing Estrogen Therapy

- No clinically proven optimal method to stop hormone therapy
  - VMS will recur in ~50% of women after discontinuation
- Expert opinion is to gradually decrease hormone therapy doses over time versus abrupt discontinuation
- VMS generally improves with time, but GSM generally worsens due to estrogen deficiency
  - GSM treatment options should be provided when systemic hormone therapy is stopped
- Most women will be able to stop hormone therapy within a few years of starting
  - Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years

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## Estrogen Therapy Safety

- MHT is relatively safe when initiated in healthy women <60 years or within 10 years of menopause onset
- MHT prevents bone loss and reduces fracture risk in healthy postmenopausal women
  - Discontinuing MHT results in rapid bone loss
- MHT appears to be cardioprotective
  - May have increased incidence stroke, transient ischemic attack, and systemic embolism
- MHT does not appear to increase risk of breast cancer

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## Questions?

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## Pharmacist Learning Assessment Question #1

A 57-year-old male is presents to his PCP with complaints of low sex drive, changes in his erectile function, decreased energy. His PCP has the patient complete two fasting serum testosterone labs on two separate mornings, with the labs resulting as 187 ng/dL and 232 ng/dL. He is diagnosed with clinical hypogonadism and is started on testosterone therapy. The patient is given a prescription for testosterone cypionate, inject 100mg IM every two weeks.

Which of the following describes the diagnostic criteria for hypogonadism for this patient?

- A. Low sex drive, changes in erectile function, and decreased energy
- B. Fasting serum testosterone level of 187 ng/dL
- C. Fasting serum testosterone level of 232 ng/dL
- D. A & B
- E. All the above



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## Pharmacist Learning Assessment Question #2

A 57-year-old male is presents to his PCP with complaints of low sex drive, changes in his erectile function, decreased energy. His PCP has the patient complete two fasting serum testosterone labs on two separate mornings, with the labs resulting as 187 ng/dL and 232 ng/dL. He is diagnosed with clinical hypogonadism and is started on testosterone therapy. The patient is given a prescription for testosterone cypionate, inject 100mg IM every two weeks.

After 3 months of testosterone therapy, his PCP would like to recheck his testosterone level. When should the testosterone level be checked in regard to his injection?

- A. The day after injecting testosterone cypionate (e.g., Day 1).
- B. At the halfway point between injections (e.g., Day 7).
- C. The day before injecting testosterone cypionate (e.g., Day 14).
- D. The lab can be checked without regard to the injection.



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## Pharmacist Learning Assessment Question #3

A 49-year-old perimenopausal female reports genital dryness, discomfort and pain during sexual intercourse, and dysuria. Which of the following best describes the symptoms this patient is experiencing.

- A. Genitourinary Syndrome of Menopause
- B. Vasomotor Symptoms
- C. Testosterone Deficiency
- D. Vulvovaginal Atrophy



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## Pharmacist Learning Assessment

### Question #3

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## Pharmacist Learning Assessment

### Question #4

A 54-year-old postmenopausal woman complains of hot flushes, mood changes, discomfort during intercourse, and vaginal dryness. All symptoms are considered moderate to severe. She has a history of asthma, type 2 diabetes, and has had a hysterectomy. Which of the following is the most appropriate treatments for her menopausal symptoms?

- A. Vaginal lubricants and systemic estrogen
- B. Vaginal lubricants and SSRI
- C. Vaginal estrogen and systemic estrogen and progestogen
- D. Vaginal estrogen and SSRI



## Pharmacist Learning Assessment

### Question #4

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## Technician Learning Assessment

### Question #1

Testosterone is available in which of the following formulations?

- A. Oral tablet
- B. Topical gel
- C. Intramuscular injection
- D. B & C
- E. All the above



## Technician Learning Assessment

### Question #1

Testosterone is available in which of the following formulations?

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## Technician Learning Assessment

### Question #2

Menopause is caused by a deficiency of which hormone?

- A. Estrogen
- B. Progesterone
- C. Follicle-Stimulating Hormone (FSH)
- D. luteinizing hormone (LH)



## Technician Learning Assessment Question #2

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## Technician Learning Assessment Question #3

A 56-year-old postmenopausal female has been prescribed a vaginal estrogen tablet for Genitourinary Syndrome of Menopause (genital dryness, discomfort and pain during sexual intercourse, dysuria, etc.) Which of the following is the most appropriate route of administration for this prescription?

- A. Intramuscular
- B. Rectal
- C. Oral
- D. Intravaginal



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## Thank you!

Emily.vanklombenburgh@sdstate.edu