

FUTURE TRENDS IN ERECTILE DYSFUNCTION AND HYPOGONADISM

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Disclosures

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I have no relevant financial relationships or affiliations with commercial interests to disclose.

Erectile Dysfunction – Background

- Definition: Inability to attain and/or maintain sufficient penile rigidity for sexual satisfaction
- Prevalence: Up to 30 million men in the U.S. and 150 million men worldwide
- Negatively affects a man's mental health, his relationship, and his general well-being
 - ▣ Provides opportunity to address multiple men's health issues

2018 AUA Guidelines for Erectile Dysfunction

Erectile Dysfunction: AUA Guideline



Arthur L. Burnett, Ajay Nehra, Rodney H. Breau, Daniel J. Culkin, Martha M. Faraday, Lawrence S. Hakim, Joel Heidelbaugh, Mohit Khera, Kevin T. McVary, Martin M. Miner, Christian J. Nelson, Hossein Sadeghi-Nejad, Allen D. Seftel and Alan W. Shindel

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

Purpose: The purpose of this guideline is to provide a clinical strategy for the diagnosis and treatment of erectile dysfunction.

Materials and Methods: A systematic review of the literature using the Pubmed, Embase, and Cochrane databases (search dates 1/1/1965 to 7/29/17) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of erectile dysfunction. Evidence-based statements were based on body of evidence strength Grade A, B, or C and were designated as *Strong*, *Moderate*, and *Conditional Recommendations* with additional statements presented in the form of *Clinical Principles* or *Expert Opinions*.

Results: The American Urological Association has developed an evidence-based guideline on the management of erectile dysfunction. This document is designed to be used in conjunction with the associated treatment algorithm.

Conclusions: Using the shared decision-making process as a cornerstone for care, all patients should be informed of all treatment modalities that are not contraindicated, regardless of invasiveness or irreversibility, as potential first-line treatments. For each treatment, the clinician should ensure that the man and his partner have a full understanding of the benefits and risk/burdens associated with that choice.

Key Words: physiological sexual dysfunction, men's health, cardiovascular diseases, clinical decision/making, psychological sexual dysfunction

Abbreviations and Acronyms

| | | |
|-------|---|-------------------------------------|
| AEs | = | adverse events |
| AUA | = | American Urological Association |
| ED | = | erectile dysfunction |
| EF | = | erectile function |
| ICI | = | intracavernous injection |
| IU | = | intraurethral |
| PDE5i | = | phosphodiesterase type 5 inhibitors |
| TD | = | testosterone deficiency |
| VED | = | vacuum erection device |

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The complete unabridged version of the guideline is available at <http://urology.com/>.

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History, Examination, and Laboratory Testing

1. Men presenting with symptoms of ED should undergo a thorough medical, sexual, and psychosocial history; a physical examination; and selective laboratory testing. (Clinical Principle)

□ Medical, sexual, psychosocial history:

- Age, comorbid medical and psychological conditions, prior surgeries, medications, family history of vascular disease, substance use
- Risk factors for ED: vascular disease, tobacco use, neurologic disease, endocrinopathies, medication side effects, and psychosocial issues
- History should include partner

□ Key questions:

- Symptom onset / severity / degree of bother
- Problem with obtaining and/or maintaining an erection
- Presence of nocturnal and/or morning erections
- Situational factors (e.g., occurring only in specific contexts)
- Masturbatory erections
- Prior use of erectogenic therapy
- Stable or progressive symptoms (progressive suggests comorbidities)
- Information about changes in libido, orgasm, and penile morphology

History, Examination, and Laboratory Testing

1. Men presenting with symptoms of ED should undergo a thorough medical, sexual, and psychosocial history; a physical examination; and selective laboratory testing. (Clinical Principle)

□ Physical examination:

- VS, including BP and waist circumference
- Assessment for signs of hypogonadism: gynecomastia, under-developed facial/pubic/axillary hair
- Genitourinary examination



□ Laboratory testing:

- Serum BUN/Cr, fasting lipids, Hgb A1c, testosterone, thyroid function, PSA
- Consideration of psychological factors:
 - Depression, anxiety, relationship conflict

General Treatment Principles

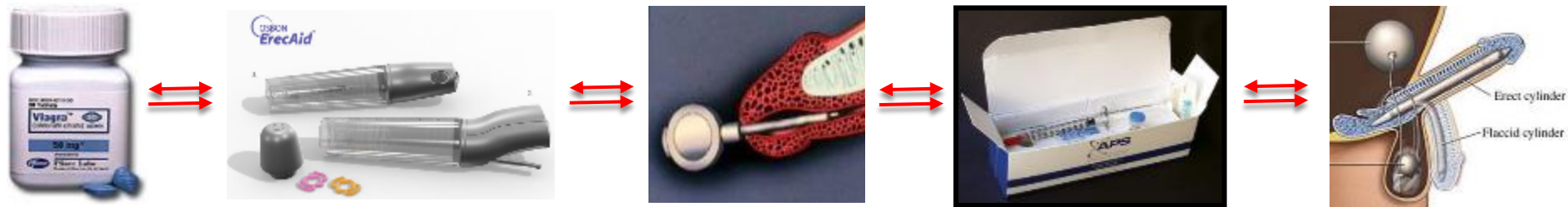
6. For men being treated for ED, referral to a mental health professional should be considered to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship. (Moderate Recommendation; Evidence Level: Grade C)



7. Clinicians should counsel men with ED who have comorbidities known to negatively affect erectile function, that lifestyle modifications, including changes in diet and increased physical activity, improve overall health and may improve erectile function. (Moderate Recommendation; Evidence Level: Grade C)

Shared Decision-Making

Old Paradigm – Step-Wise Approach (1st line, 2nd line, 3rd line)



New Paradigm – Shared Decision-Making

PDE-5 Inhibitors



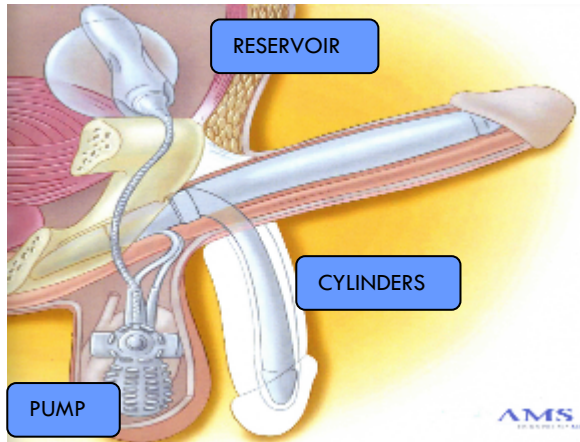
8. Men with ED should be informed regarding the treatment option of an FDA-approved oral PDE5-i, including discussion of benefits and risks/burdens, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)

9. When men are prescribed an oral PDE5-i for the treatment of ED, instructions should be provided to maximize benefit/efficacy. (Strong Recommendation; Evidence Level: Grade C)

10. For men who are prescribed PDE5-i, the dose should be titrated to provide optimal efficacy. (Strong Recommendation; Evidence Level: Grade B)

Penile Prosthesis Implantation

18. Men with ED should be informed regarding the treatment option of penile prosthesis implantation, including discussion of benefits and risks/burdens.



2018 AUA Guidelines – ED Treatment Algorithm

COUNSEL THE MAN AND PARTNER REGARDING:

- The value of psychosocial/relationship support from trained professionals to optimize treatment satisfaction
- The importance of lifestyle change (weight loss, exercise, smoking cessation) to improve erectile function and overall health
- The benefits and risks/burdens of all available ED treatments that are not contraindicated

Using a shared decision-making framework, identify appropriate treatment¹ based on values and priorities of man and partner

PDE5i

Vacuum devices

Intraurethral (IU) alprostadil

Intracavernosal injections (ICI)

Penile prosthesis surgery

ASSESS OUTCOMES, ADVERSE EVENTS (AEs), AND SATISFACTION OF MAN AND PARTNER

IF INADEQUATE EFFICACY AND/OR UNACCEPTABLE AEs AND/OR INSUFFICIENT SATISFACTION, THEN ADDRESS AS APPROPRIATE:

- Dose adjustments (for PDE5i, IU alprostadil, ICI)
- Revisit instructions to maximize efficacy (for all treatments)
- Revisit values and priorities of man and partner with mental health professional to refine values and priorities and/or to address psychosocial or relationship barriers to successful treatment
- Consider alternate treatment

Testosterone

*4. For men with ED, morning serum total testosterone levels should be measured.
(Moderate Recommendation; Evidence Level: Grade C)*



What is Hypo

□ Is it a r

AUGUST 18, 2014

TIME

Manopause?!

Aging, insecurity and the \$2 billion testosterone industry

BY DAVID VON DREHLE



time.com

LowT
Center



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What is Hypogonadism/Low T ?

- Is it a real condition or marketing genius ?
- Depends if we are talking about primary hypogonadism or secondary hypogonadism
 - ▣ Primary hypogonadism is a real condition
 - ▣ Secondary hypogonadism may be a real condition (rare), or may be temporary, reversible, or related to another medical condition or medication
 - ▣ Age-related hypogonadism is likely mixed primary/secondary

Guidelines for T Level for Diagnosis



CONSENSUS

THIS WOULD WORK A LOT BETTER IF YOU'D JUST AGREE WITH THE AUA

Diagnosis of Hypogonadism

2018 AUA Guidelines on Testosterone Deficiency

Evaluation and Management of Testosterone Deficiency: AUA Guideline



John P. Mulhall, Landon W. Trost, Robert E. Brannigan, Emily G. Kurtz, J. Bruce Redmon, Kelly A. Chiles, Deborah J. Lightner, Martin M. Miner, M. Hassan Murad, Christian J. Nelson, Elizabeth A. Platz, Lakshmi V. Ramanathan and Ronald W. Lewis

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

Purpose: There has been a marked increase in testosterone prescriptions in the past decade resulting in a growing need to give practicing clinicians proper guidance on the evaluation and management of the testosterone deficient patient.

Materials and Methods: A systematic review utilized research from the Mayo Clinic Evidence Based Practice Center and additional supplementation by the authors. Evidence-based statements were based on body of evidence strength Grade A, B, or C and were designated as Strong, Moderate, and Conditional Recommendations with additional statements presented in the form of Clinical Principles or Expert Opinions (table 1 in supplementary unabridged guideline, <http://jurology.com/>).

Results: This guideline was developed by a multi-disciplinary panel to inform clinicians on the proper assessment of patients with testosterone deficiency and the safe and effective management of men on testosterone therapy. Additional statements were developed to guide the clinician on the appropriate care of patients who are at risk for or have cardiovascular disease or prostate cancer as well as patients who are interested in preserving fertility.

Conclusions: The care of testosterone deficient patients should focus on accurate assessment of total testosterone levels, symptoms, and signs as well as proper on-treatment monitoring to ensure therapeutic testosterone levels are reached and symptoms are ameliorated. Future longitudinal observational studies and clinical trials of significant duration in this space will improve diagnostic techniques and treatment of men with testosterone deficiency as well as provide more data on the adverse events that may be associated with testosterone therapy.

Key Words: testosterone, hypogonadism, men's health, androgens

Abbreviations and Acronyms

ASCVD = atherosclerotic cardiovascular disease
AUA = American Urological Association
FDA = U.S. Food and Drug Administration
Hct = hematocrit
hCG = human chorionic gonadotropin
LH = luteinizing hormone
MACE = major adverse cardiac event
RCTs = randomized controlled trials
RT = radiation therapy
VTE = venous thromboembolism

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This document is being printed as submitted independent of editorial or peer review by the editors of *The Journal of Urology*.

- ❑ Published 4/3/18
- ❑ Unabridged document is 76 pages
- ❑ COI: Mulhall is consultant/advisor for Pfizer, Lilly, AMS; numerous others

Diagnosis of Hypogonadism

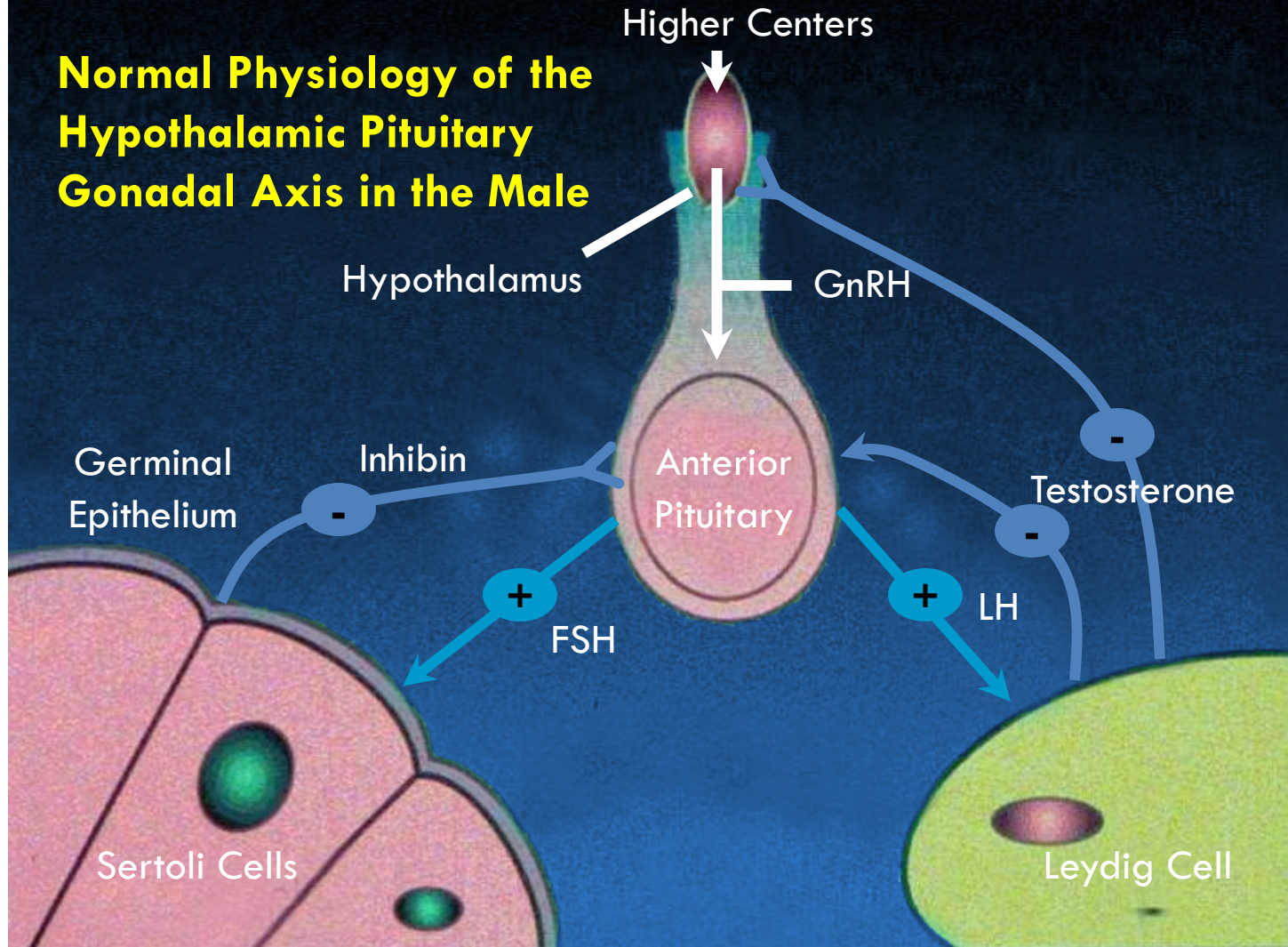
2018 AUA Guidelines on Testosterone Deficiency

Diagnosis of Testosterone Deficiency

1. Clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone. (Moderate Recommendation; Evidence Level: Grade B)
2. The diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. (Strong Recommendation; Evidence Level: Grade A)
3. The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs. (Moderate Recommendation; Evidence Level: Grade B)
4. Clinicians should consider measuring total testosterone in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use even in the absence of symptoms or signs associated with testosterone deficiency. (Moderate Recommendation; Evidence Level: Grade B)



Normal Physiology of the Hypothalamic Pituitary Gonadal Axis in the Male



Who Should Receive TRT?

FDA Drug Safety Communication (3/3/2015)

- TRT is for men with hypogonadism resulting from disorders of the:
 - ▣ Testicles
 - ▣ Pituitary gland
 - ▣ Brain
- “...Testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established.”

Contraindications to TRT

Male breast cancer



Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. (Strong Recommendation; Evidence Level: Grade B)

Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy. (Expert Opinion)

Hematocrit > 55%

Known/suspected hypersensitivity to ingredients used in TRT



The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. (Strong Recommendation; Evidence Level: Grade A)

Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive. (Strong Recommendation; Evidence Level: Grade A)

Untreated sleep apnea



Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). (Moderate Recommendation; Evidence Level: Grade B)

“Alternative Agents”

- For patients...
 - ▣ Still interested in fertility

Clinicians may use aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators, or a combination thereof in men with testosterone deficiency desiring to maintain fertility. (Conditional Recommendation; Evidence Level: Grade C)

in secondary hypogonadism

In patients with low testosterone, clinicians should measure serum luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)

- Normal LH is ~3 mIU/mL and normal range is ~2-4 mIU/mL
- Must use clinical judgement taking into account age, other causes of hypogonadism
- Single level does not take into account pulsatility of LH secretion

“Alternative Agents”

Physiologic Treatment of Secondary Hypogonadism

- SERMs
 - ▣ Clomiphene citrate (Clomid) – (off-label)
- Gonadotropins
 - ▣ Human chorionic gonadotropin (hCG) – (off-label)
- Aromatase Inhibitors
 - ▣ Anastrozole (Arimidex) – (off-label)

Advantages of “Alternative Agents”

□ Advantages

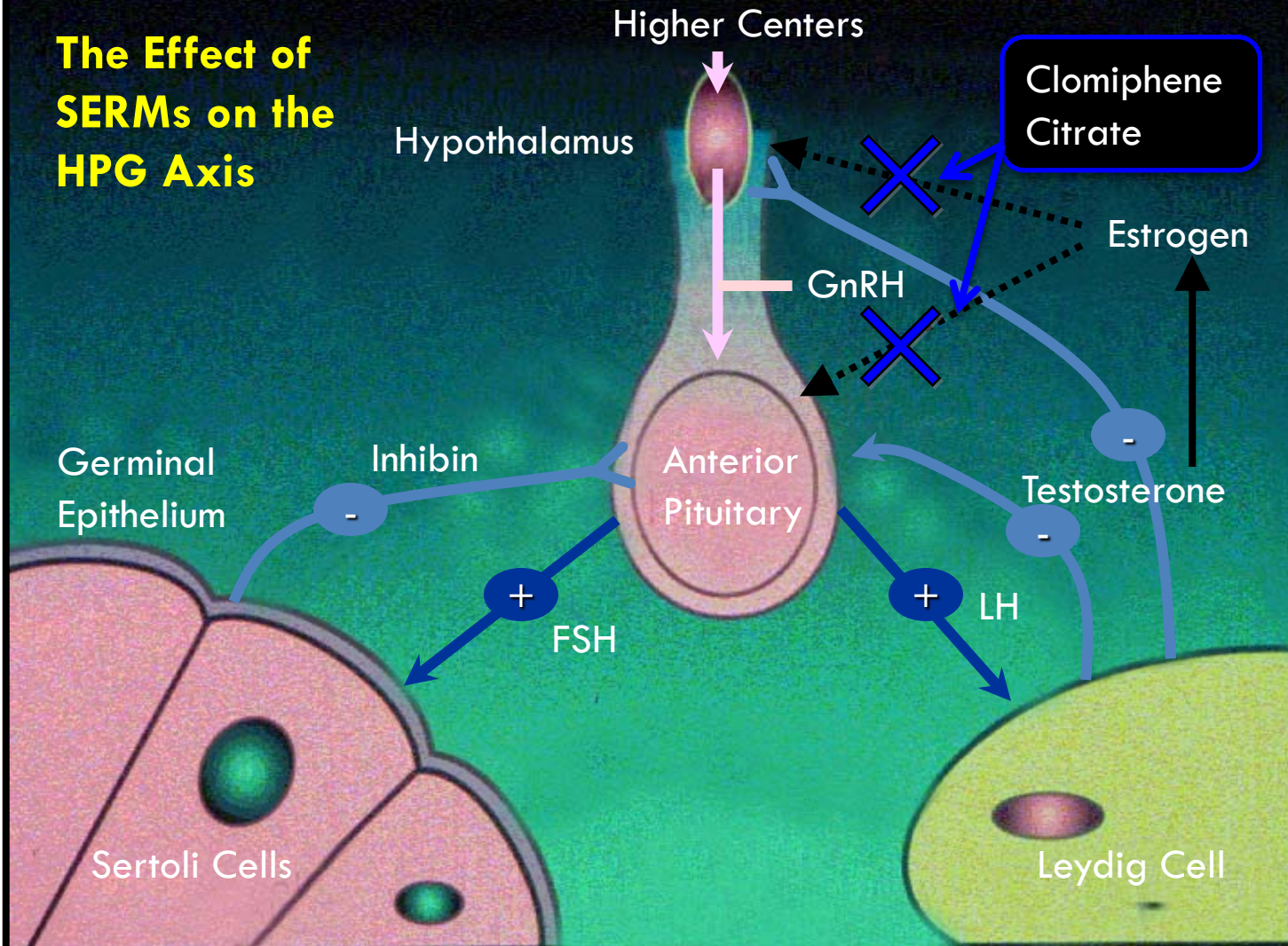
- No risk of transference
- Pills available
- No significant pituitary suppression
- No fertility impairment
- Reliable dosing
- CV risk of testosterone supplementation (?)
- Established safety and efficacy

Clomiphene Citrate (Clomid)

Background

- ▣ Clomiphene citrate (Clomid) = selective estrogen receptor modulator (SERM)
 - Off-label for hypogonadism and male infertility
 - Dosage: 12.5 - 50 mg daily, Typically starting 25 mg daily
- ▣ Mixture of 2 geometric isomers
 - Both modulate estrogen receptor → ↑ FSH and ↑ LH → ↑ T
- ▣ Side effects
 - Gynecomastia, weight gain, hypertension, cataracts, acne, blood clots, blurred vision

The Effect of SERMs on the HPG Axis



Clomiphene in the Literature

- Outcomes of clomiphene treatment in young hypogonadal men
 - ▣ N=86 men
 - ▣ Duration of CC treatment=19 months
 - ▣ All mean T and gonadotropin measurements significantly increased
 - ▣ ADAM scores improved in all domains (except loss of height)
 - ▣ No major side effects
- Clomiphene is safe and effective for long-term management of hypogonadism
 - ▣ N=46 patients
 - ▣ Stable T levels over 3 years
 - ▣ Bone density and ADAM scores improved significantly
 - ▣ No adverse events

Comparison of Clomiphene vs. Testosterone

- Clomiphene vs. Testosterone for Hypogonadism: Comparison of Satisfaction and Efficacy
 - N=93 men
 - T injections (31) or gels (31), or CC (31)
 - Age-matched
 - Similar satisfaction on qADAM
 - No difference in overall hypogonadal symptoms
 - **Conclusion: Clomiphene is safe and efficacious and can be used long-term for treatment of hypogonadism**

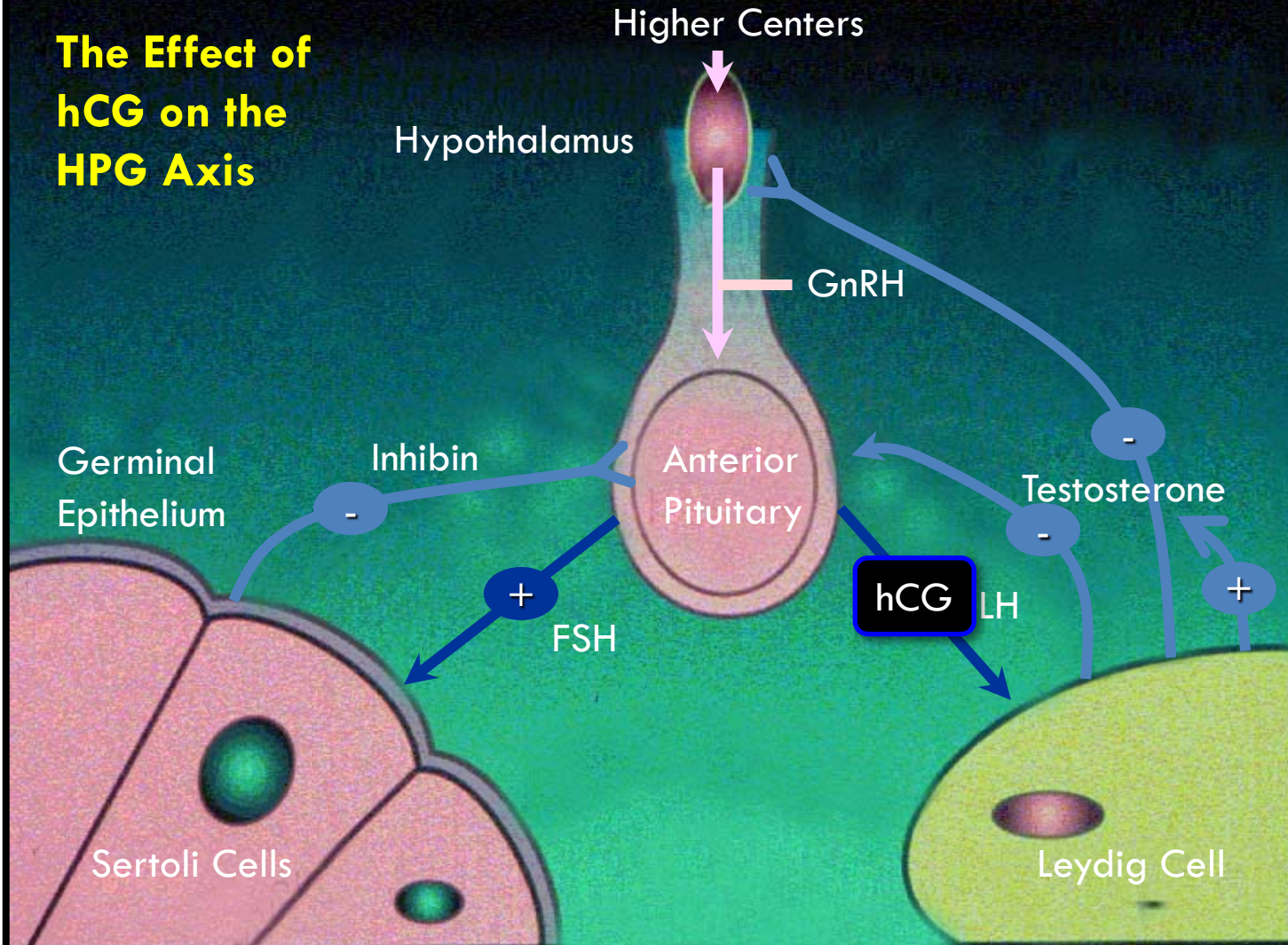
Anastrozole (Arimidex)

- Mechanism
 - ▣ Reversibly binds the aromatase enzyme and blocks aromatization of testosterone to estrogen by adipose tissue
- Role of anastrozole (off-label)
 - ▣ Treatment of secondary hypogonadism with hyperestrogenemia
 - ▣ Use when T:E2 < 10:1
- Dose
 - ▣ Optimal dose is unknown
 - ▣ Varies from 1mg daily to 1mg weekly

Human Chorionic Gonadotropin (hCG)

- Mechanism
 - ▣ LH analog, so used for hypogonadotropic hypogonadism
 - ▣ Stimulates Leydig cell production of T
- Role of hCG (off-label)
 - ▣ Treatment of secondary hypogonadism
 - ▣ Maintain spermatogenesis and intratesticular T with TRT
 - ▣ Recovery of T-induced suppression of spermatogenesis
- Dose
 - ▣ Optimal dose is unknown
 - ▣ Varies from 500 IU weekly to 3000 IU QOD

The Effect of hCG on the HPG Axis



Treatment Algorithm for Secondary Hypogonadism

- Check morning total testosterone, LH, and E2 levels (minimum)
 - ▣ If both LH and T are low, treat as secondary hypogonadism
- Treat underlying issue
- Start clomiphene 25mg daily
 - ▣ Add anastrozole 1mg QD or QOD if T:E2 < 10:1
 - ▣ Consider adding hCG if unresponsive or if recovery of fertility is high priority
- Add exogenous testosterone only as a secondary option

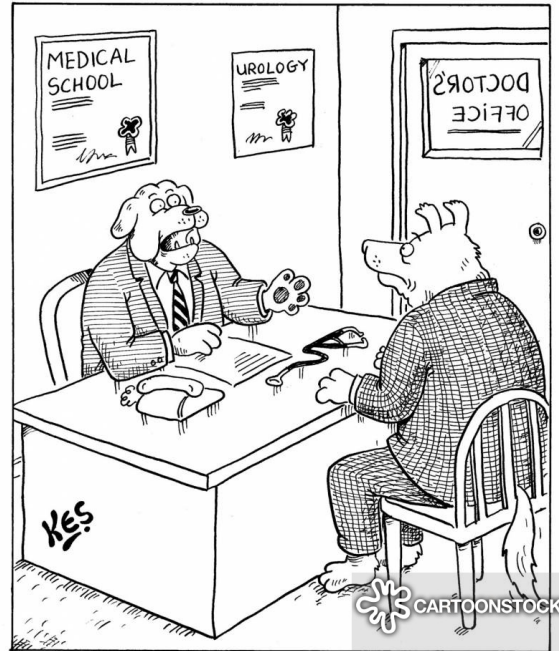
Hypogonadism - Summary

- Diagnose hypogonadism with two morning levels <300 ng/dL coupled with symptoms
- Clinicians should measure LH (Strong recommendation; grade A)
- In men with low LH (secondary hypogonadism), always consider the underlying cause
- Consider TRT primarily for men with primary hypogonadism, and consider “alternative agents” for secondary hypogonadism

Erectile Dysfunction - Summary

- Mental health evaluation, involvement of the partner, and advice on lifestyle are standard components of the management of ED
- The former step-wise approach has been replaced by shared decision-making
 - ▣ All patients should be informed of all treatment modalities that are not contraindicated, regardless of invasiveness or irreversibility, as potential first-line treatments
- Patients should pursue treatments most aligned with their goals and risk tolerance

Thank You!



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"You should either drink less, or expand your territory."