Men's Health: Practical and Guidelines-Based Solutions to Frequent Chief Complaints

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Assistant Professor of Urology
University of Oklahoma HSC

OU Physicians UROLOGY

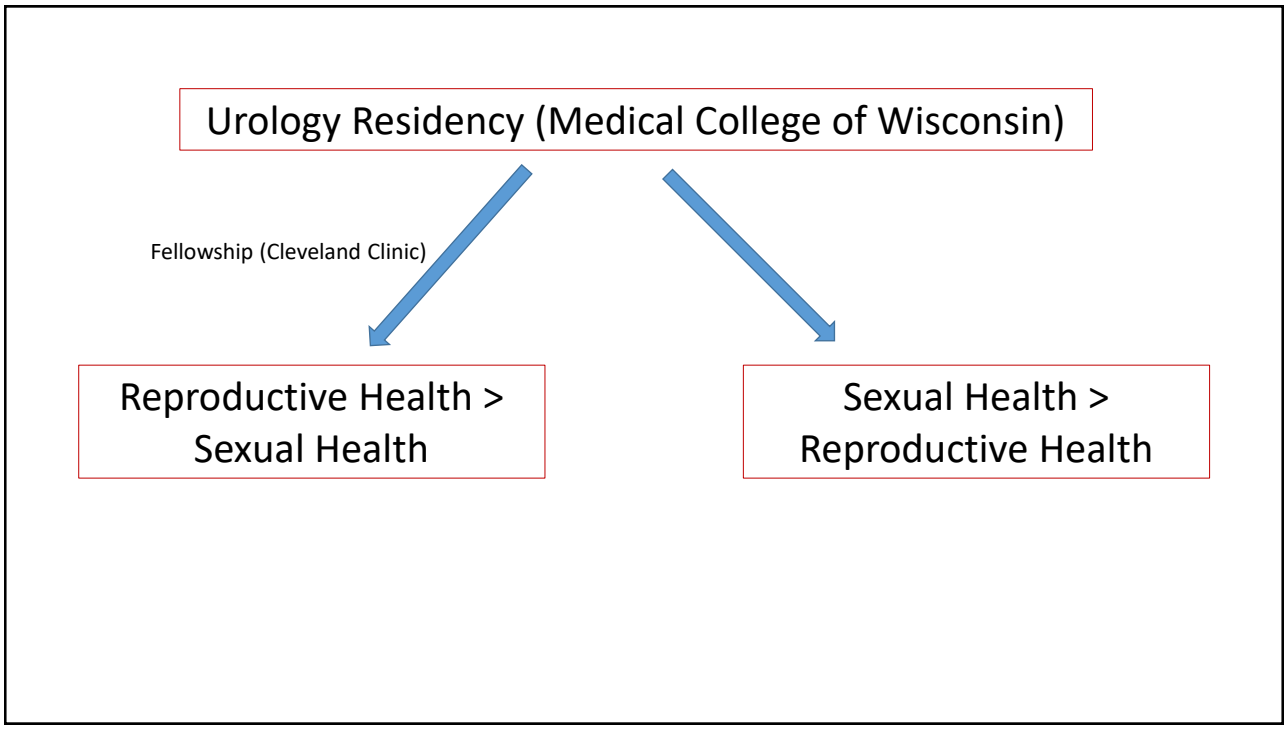
OU Health

No disclosures

Objectives

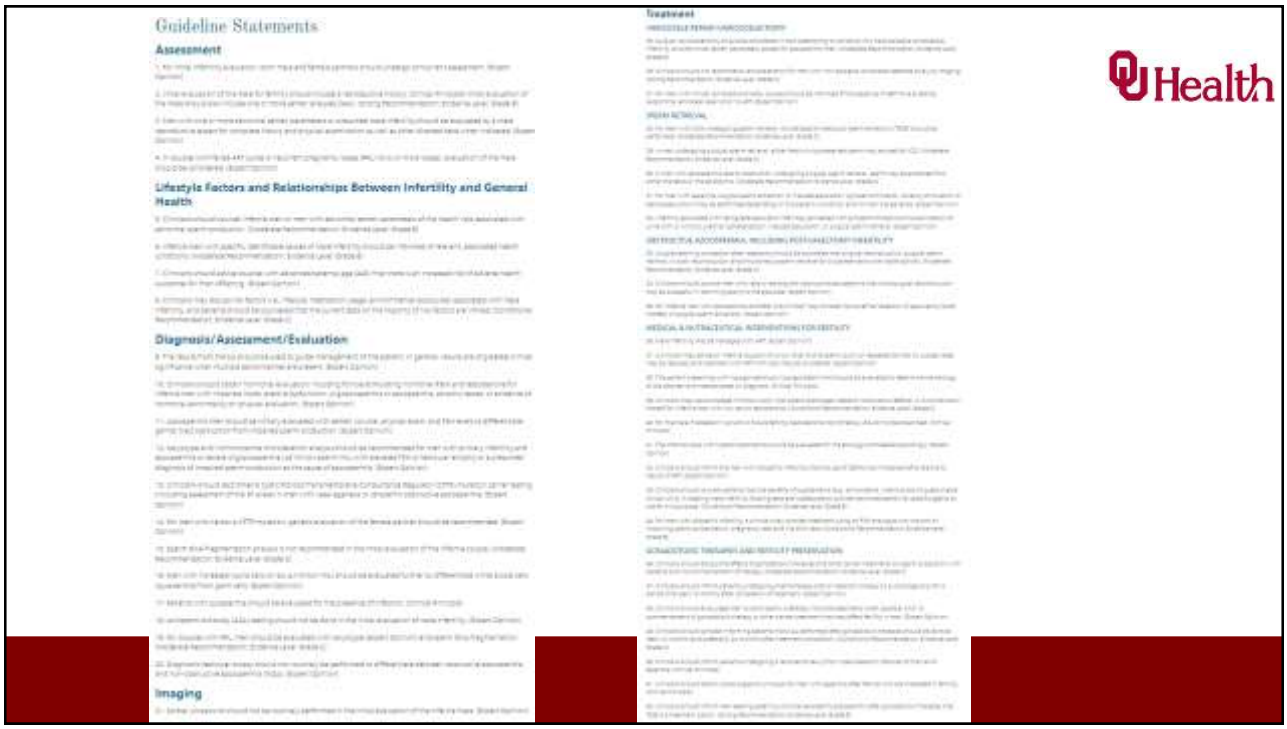
- Describe a modern Urologic Men's Health practice
- Apply AUA guidelines to common scenarios in outpatient care
  - The infertile male with hypogonadal symptoms
    - Evaluation
    - Options for medical management
    - Considerations for erectile dysfunction
  - The aging male with erectile dysfunction
    - Connections between cardiovascular risk
    - Role of testosterone and replacement
    - Treatment algorithm and considerations

What does a men's health specialist do ?


Urology Residency (Medical College of Wisconsin)
Fellowship (Cleveland Clinic)
Reproductive Health > Sexual Health
Sexual Health > Reproductive Health

Men's Health is Life Long

[Sexual and Reproductive Health - American Urological Association (auanet.org)]



Guideline Statements

Assessment

Lifestyle Factors and Relationships Between Infertility and General Health

Diagnosis/Assessment/Evaluation

Imaging

Treatment

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Case #1

- 29 year old male with 12 months of infertility
  - No prior children (primary)
- Hypogonadal Symptoms
  - Decreased libido, fatigue
- Recent onset of ED

Next Steps?

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Assessment

1. For initial infertility evaluation, both male and female partners should undergo concurrent assessment. (Expert Opinion)

2. Initial evaluation of the male for fertility should include a reproductive history. (Clinical Principle) Initial evaluation of the male should also include one or more semen analyses (SAs). (Strong Recommendation; Evidence Level: Grade B)

3. Men with one or more abnormal semen parameters or presumed male infertility should be evaluated by a male reproductive expert for complete history and physical examination as well as other directed tests when indicated. (Expert Opinion)

Diagnosis/Assessment/Evaluation

9. The results from the SA should be used to guide management of the patient. In general, results are of greatest clinical significance when multiple abnormalities are present. (Expert Opinion)

10. Clinicians should obtain hormonal evaluation including follicle-stimulating hormone (FSH) and testosterone for infertile men with impaired libido, erectile dysfunction, oligozoospermia or azoospermia, atrophic testes, or evidence of hormonal abnormality on physical evaluation. (Expert Opinion)

T = 188 ng/dL

SA:
Vol 2cc
Conc 13M/mL
Motility 45%
Morphology 5%

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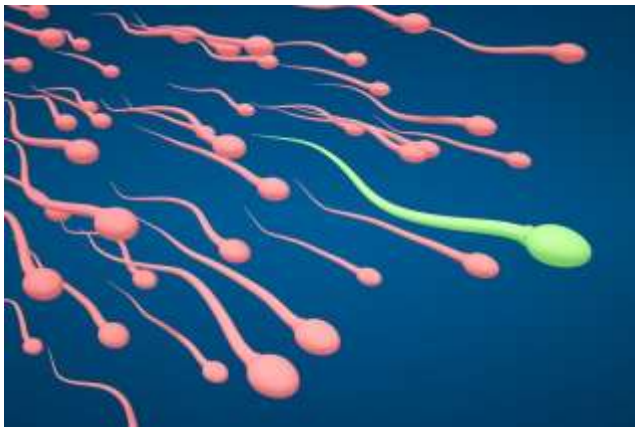
GUIDELINE STATEMENT 16

16. 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)

GUIDELINE STATEMENT 23

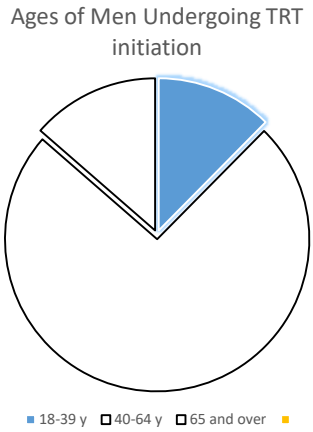
23. Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive. (Strong Recommendation; Evidence Level: Grade A)

Considerations in the Hypogonadal Male Desiring Fertility



Age and Hypogonadism

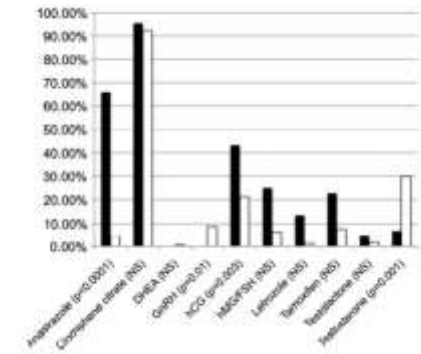
- From 2000 to 2011:
  - 12.4% of new TRT users in US were under 39 years old
- Kolettis et al
  - 7% of male patients seeking care for infertility were on TRT at the time of consultation
  - 4th most common etiology of infertility



Layton et al 2014

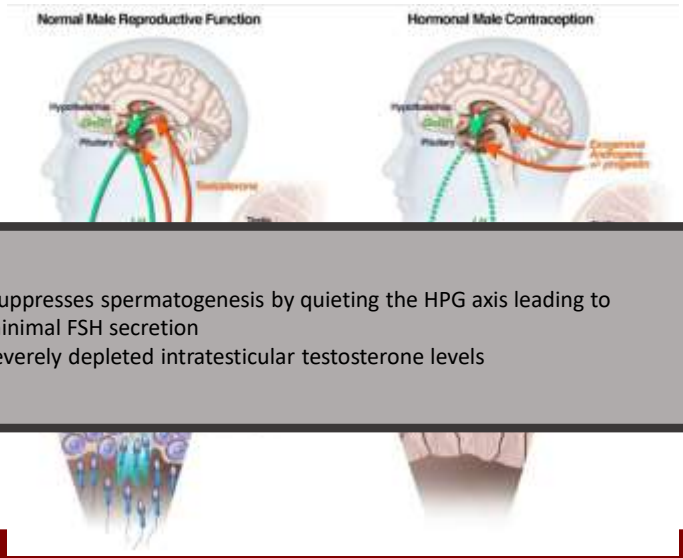
Empirical Medical Therapy for Idiopathic Male Infertility: A Survey of the American Urological Association

Edmund Y. Ko, Kashif Siddiqi, Robert E. Brannigan and Edmund S. Sabanegh, Jr.*



- 30% of general urologists would treat infertility with TRT
  - 7% of fellowship trained

TRT: Impact on HPG axis and ITT

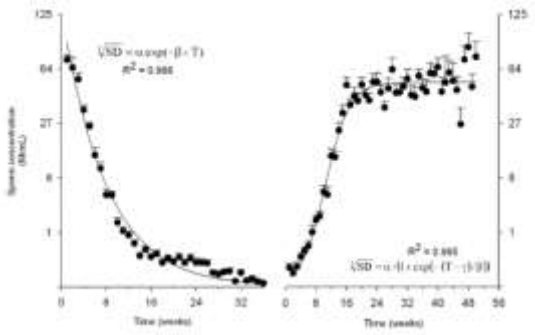


TRT suppresses spermatogenesis by quieting the HPG axis leading to
1. minimal FSH secretion
2. severely depleted intratesticular testosterone levels

Rates of suppression and recovery of human sperm output in testosterone-based hormonal contraceptive regimens*

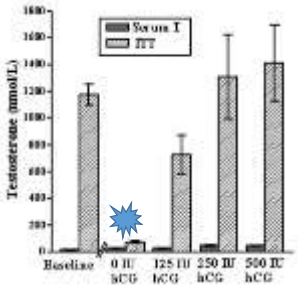
Lam P. Ly, Peter Y. Liu, David J. Handelsman

- 14000 samples from 2 WHO proof of concept studies
- Men received 200mg TE weekly and were studied with monthly SA → suppressed for total of 12 months
- Study population** → eugonadal men with normospermia
- Suppression
  - T1/2 – 5.5 weeks
  - <5M/mL – 9 weeks
  - <1M/mL – 13 weeks
  - 65% azoo at 6 months, mean time to azoo 4 months
- Recovery
  - Average plateau – 53M/mL (85% of baseline)
  - T1/2 – 12.6 weeks



TRT Suppresses Intratesticular Testosterone (ITT)

- RTC with 29 men on IM testosterone + placebo or HCG
- Placebo (no HCG) → ITT suppressed 95% after 3 weeks of T
- ITT >>>>> Serum T
  - Serum T value is ~1% of ITT



Low-Dose Human Chorionic Gonadotropin Maintains Intratesticular Testosterone in Normal Men with Testosterone-Induced Gonadotropin Suppression

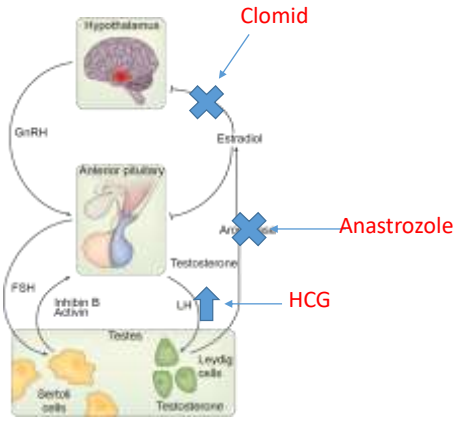
Treatment options

27. 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)

1. LH agonist
→Human chorionic gonadotropin
Sub Q 500-5000IU QoD

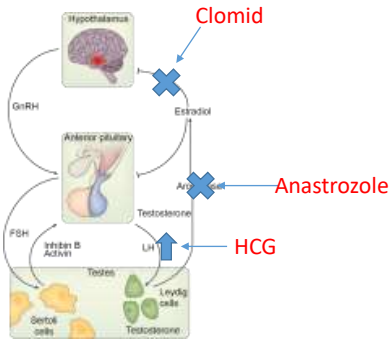
2. Selective Estrogen Receptor Modulator
→Clomid Non-FDA approved
PO 50mg QoD / 25mg daily

3. Aromatase Inhibition
→Anastrazole Non-FDA approved
PO 1mg QoD / daily



HCG as monotherapy?

- Indications
  - Central Hypogonadism (Congenital or acquired)
    - Clomid / Anastrazole are not indicated



Concomitant Intramuscular Human Chorionic Gonadotropin Preserves Spermatogenesis in Men Undergoing Testosterone Replacement Therapy

Tung-Chin Hsieh, Alexander W. Pastuszak, Kathleen Hwang and Larry I. Lipshultz*,†

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Can spermatogenesis be preserved with T 200mg weekly with 500 IU of HCG QoD?

- 26 patients with 6.2 month follow up:
  - Pre TRT level: 207 ng/dL
  - Post TRT level: 1055 ng/dL
- No impact on semen parameters was observed

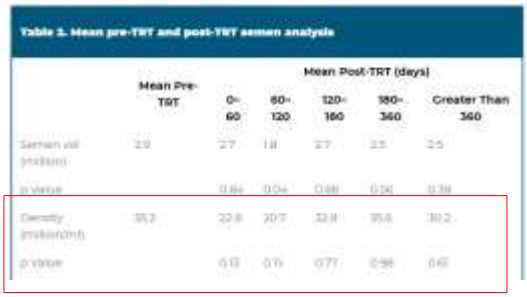


Table 1. Mean pre-TRT and post-TRT semen analysis

	Mean Pre-TRT	Mean Post-TRT (days)				
		0–60	60–120	120–180	180–360	Greater Than 360
Semen vol (mililiters)	2.9	2.7	1.8	2.7	2.5	2.5
p value		0.84	0.04	0.88	0.24	0.38
Density (million/ml)	35.2	22.8	20.7	32.8	35.6	30.2
p value		0.13	0.15	0.77	0.98	0.42

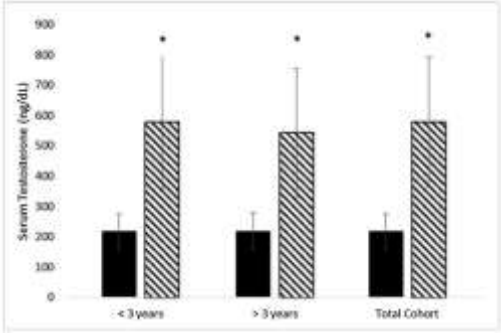
HCG is $120 for 10000 IU
Cost can be prohibitive

Hsieh et al. J Urol 2013

Long-Term Safety and Efficacy of Clomiphene Citrate for the Treatment of Hypogonadism

Sarah C. Krzastek, Devang Sharma, Natasha Abdullah, Mark Sultan, C. Luke Machen, Jessica L. Wenzel, Alex Ellis, Xizhao Chen, Mehraban Kavoussi, Raymond A. Costabile, Ryan P. Smith, and Parviz K. Kavoussi

- 400 men with a mean baseline T of 218 ng/dL
- Mean testosterone change was 427.53 ± 173.14 ng/dl
- 78% reported an improvement in hypogonadal symptom
- 120 men were treated for >3 years
  - treatment duration - 52 months
  - 77% reported subjective improvement
  - 8% reported side effects



Krzastek et al. J Urol 2019.

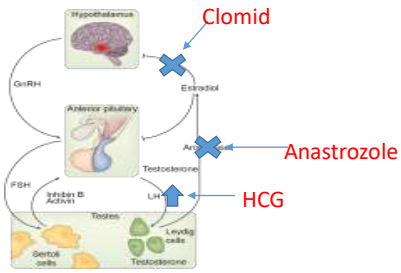
Outcomes of anastrozole in oligozoospermic hypoandrogenic subfertile men

Ohad Shoshany, M.D.,[a] Nikita Abhyankar, M.D.,[a] Naem Mufarreh, M.S.,[b] Garvey Daniel, M.D.,[a] and Craig Niederberger, M.D.[a]

[a]Department of Urology, University of Illinois at Chicago, Chicago; and [b]Loyola University, Chicago, Illinois

86 men with hypogonadism + <u>T/E ratio <10</u>

- 4 patients did not demonstrate expected ↑T and ↓E
- 3 pt did not maintain ↑T at 4 months
- 9% SE



Hormonal analysis in 86 men with hypoandrogenism treated with anastrozole.

Parameter	Baseline	At 3 wk	At 4 mo	*P* value*
Total T (ng/dL)	258.4 ± 10.8	509.2 ± 20.4	449.9 ± 19.5	<.0001
Bioavailable T (ng/dL)	128.8 ± 4.7	297.5 ± 12.7	N/A	<.0001
E_2 (pg/mL)	40.8 ± 1.9	24.6 ± 2.1	23.2 ± 2.2	<.0001
T/E_2 ratio	6.98 ± 0.33	34.5 ± 6.5	24.2 ± 3	<.0001

Counseling Summarized

- We recommend against testosterone monotherapy for correction of hypogonadism
- We have 3 options to restore appropriate T levels and improve symptoms while also potentially improving your sperm counts
  - HCG (+TRT)
  - Clomid (normal estrogen)
  - Anastrazole (T/E < 10:1)

- Role for the PCP:

1) Initiate work up for infertility / symptoms
2) Understand the effect of exogenous testosterone on spermatogenesis
3) Refer for infertility OR consider treatment in the absence of desired fertility

WHAT ABOUT MY ED!?

Treatment of Hypogonadism

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GUIDELINE STATEMENT 14

14. Patients should be informed that testosterone therapy may result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms. (Moderate Recommendation; Evidence Level: Grade B)

After 3 months of treatment with clomid his Testosterone improves to 450ng/dL

+ nocturnal erections
+ masturbatory erections
-- maintaining erections during penetrative intercourse

Every sexual problem has a psychological element

GUIDELINE STATEMENT 6

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)

- Psychogenic ED "where psychology meets biology"
  - Sympathetic nervous system activation → Vasoconstriction / opposes genital blood flow
  - Brain takes the breaks off of sympathetic nervous system → psychogenic erection
- Psychotherapy and psychosexual counseling
  - Not always necessary, but very rarely negative
  - Patient +/- partner
  - Goals
    - Reduce Anxiety
    - Integrate ED treatment
  - In lieu of medical treatment or as an adjunct
  - May allow for transition off of medical therapy

Case 2

- 71 yo obese male (BMI 32) presents with 3 years of progressive ED. He has not seen a physician in 6 years. He denies any medical problems.

SHIM – Sexual Health Inventory for Men

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GUIDELINE STATEMENT 2

2. For the man with ED, validated questionnaires are recommended to assess the severity of ED, to measure treatment effectiveness, and to guide future management. (Expert Opinion)

OVER THE PAST 6 MONTHS

1. How do you rate your confidence that you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No Sexual Activity	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than half the time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than half the time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than half the time)	Almost Always or Always
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5 **TOTAL:** _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED **8-11 Moderate ED** **12-16 Mild to Moderate ED** **17-21 Mild ED**

- Taken at baseline and after intervention
- Stratifies risk of CVD
- Impacts treatment decisions
  - "Clinical" improvement
    - Mild ED → Δ2
    - Moderate ED → Δ5
    - Severe ED → Δ7

Work Up

- SHIM 12 (Mild – moderate)
- AM testosterone 420 and 480 ng/dL

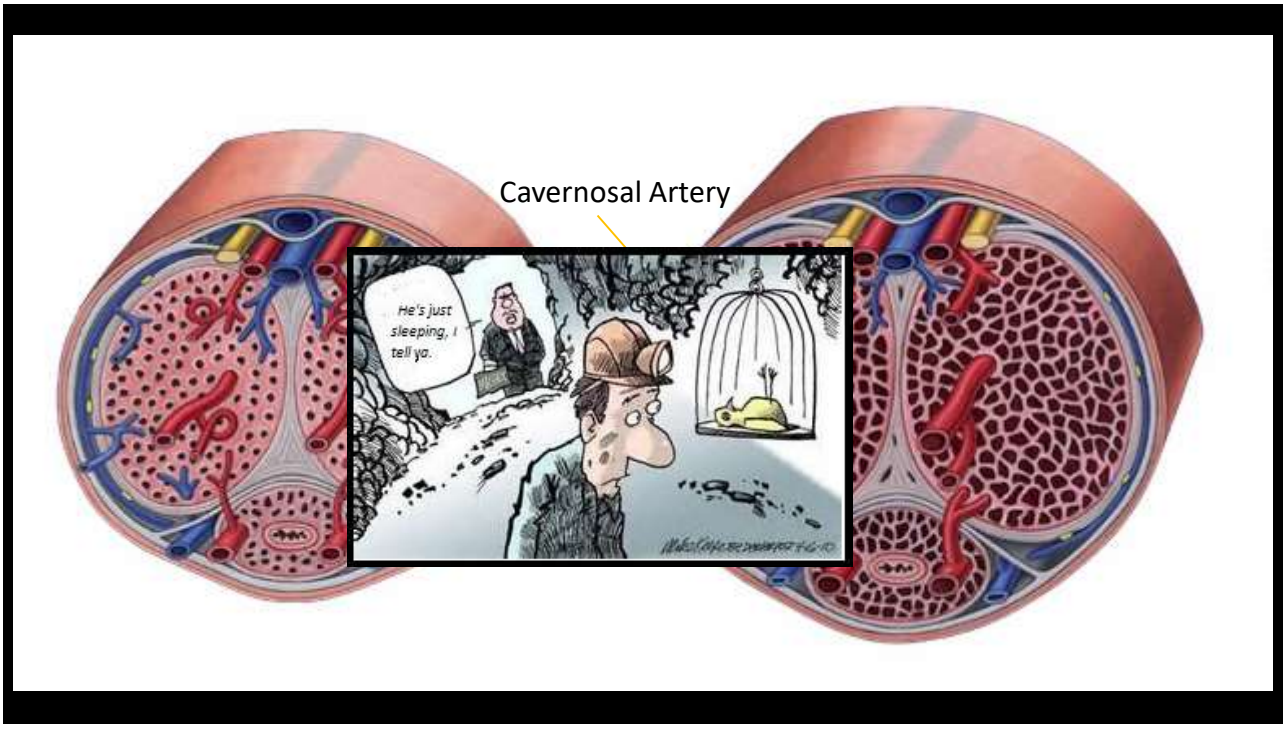
Next Steps

1) General health screening / work up for CVD
2) Discussion of options for ED treatment

ED provider a pivotal opportunity to discuss and address cardiovascular risk!!!

GUIDELINE STATEMENT 3

3. Men should be counseled that ED is a risk marker for underlying cardiovascular disease (CVD) and other health conditions that may warrant evaluation and treatment. (Clinical Principle)


Cavernosal Artery
He's just sleeping, I tell ya.

Bad for Your Heart = Bad for Your Penis

- Erectile Dysfunction ← CVD
  - shared clinical risk factors
  - overlapping pathophysiology
- Predictors of future cardiac event: ED = smoking = family history of MI
  - Time window between ED onset and a CAD event of 2 to 5 years
- 15% of men with ED will have a heart attack or stroke in 7 years
- ED is far more predictive of CV events in younger men

Its time for an intervention!

TABLE 1

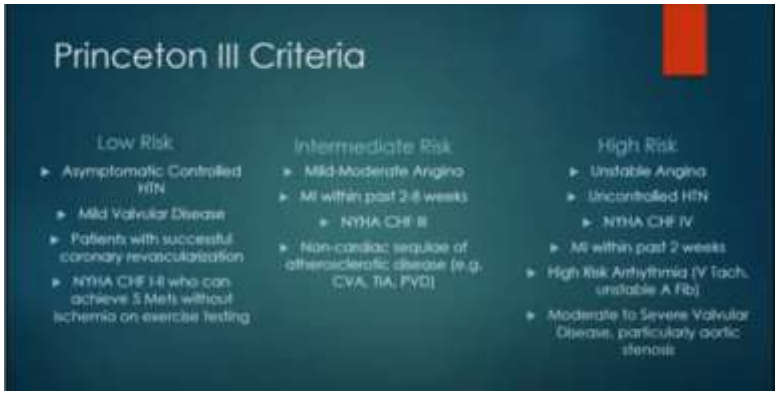
Relative Risks for Men With Erectile Dysfunction

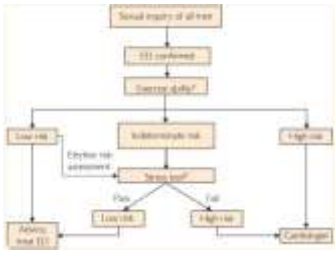
	Relative risk	95% Confidence interval	*P* value
Overall	1.48	1.25-1.74	<.001
Coronary heart disease	1.46	1.31-1.63	<.001
Stroke	1.35	1.19-1.54	<.001
[illegible]	1.19	1.05-1.34	.005

The Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease

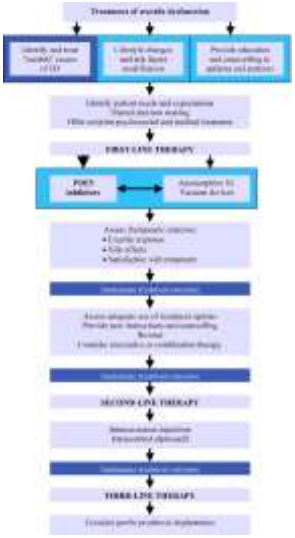
"Ask a Doctor if your Heart is Healthy Enough for Sex"

- Exertion of sexual activity ranges from 3-6 Mets (walking 3mph – dancing)
- Sexual activity is an independent risk factor of cardiac events





Evolution of Treatment algorthim



Lifestyle Changes: Simple but not Easy

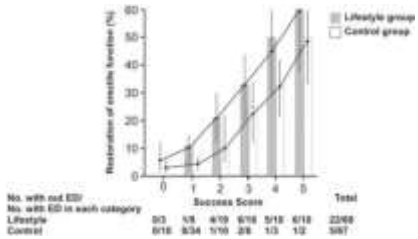
- Four pillars of lifestyle changes
  - Diet
  - Exercise
  - Sleep
  - Stress reduction

***All shown to independently improve ED + associated comorbidities

Esposito et al 2009

Diabetic men randomized to lifestyle change vs general advice

Goals
- Wt loss > 5 %
- Saturated fat <10% of energy
- Unsaturated fat >10% of energy
- Fiber 15g
- Moderate exercise >30 min/day at least 5 days per week



↑benchmarks → ↑resolution of ED

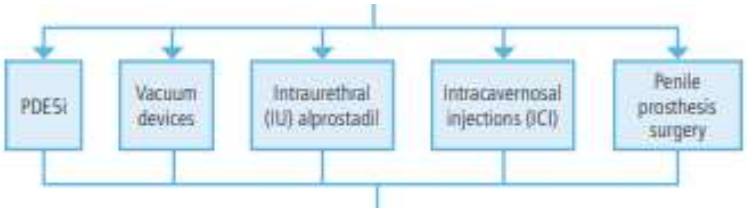
ED decreased from 66% to 44% of the study population

GUIDELINE STATEMENT 7

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)

"All that sounds great but I am ready for ED treatment now"

Treatment options



Phosphodiesterase Type 5 Inhibitor

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Table 1: Phosphodiesterase Type 5 Inhibitors

Drug Name	Trade Name	Tmax (hours)	Serum Half Life (hours)	Dosage (mg)
Sildenafil	Viagra®, Revatio®	1	3 - 5	25-100
Vardenafil	Levitra®, Staxyn®	1	3 - 5	5-20
Tadalafil	Cialis®	2	18	5-20
Avanafil	Stendra™	0.5 - 1.5	~6	50-100

GUIDELINE STATEMENT 8

8. Men with ED should be informed regarding the treatment option of an FDA-approved oral phosphodiesterase type 5 inhibitor (PDE5i), including discussion of benefits and risks/burdens, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)

Contraindications: Nitroglycerin (Nitrostat), Isosorbide (Mononitrate)

GUIDELINE STATEMENT 9

9. When men are prescribed an oral PDE5i for the treatment of ED, instructions should be provided to maximize benefit/efficacy. (Strong Recommendation; Evidence Level: Grade C)

WITH SEXUAL ACTIVITY!

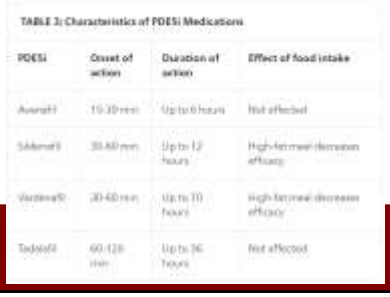


TABLE 3: Characteristics of PDE5i Medications

PDE5i	Onset of action	Duration of action	Effect of food intake
Avanafil	15-30 min	Up to 6 hours	Not affected
Sildenafil	30-60 min	Up to 12 hours	High-fat meal decreases efficacy
Vardenafil	20-60 min	Up to 10 hours	High-fat meal decreases efficacy
Tadalafil	60-120 min	Up to 36 hours	Not affected

PDE5i – Other Considerations

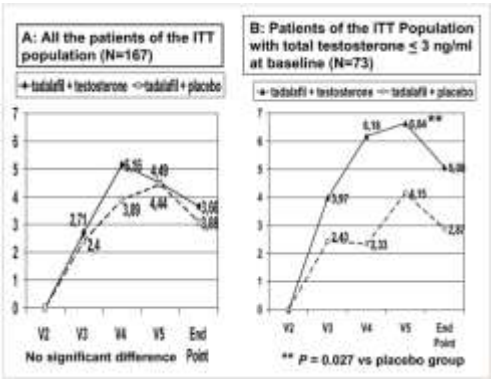
- Concomitant alpha blockers
  - Don't take w/ in 4 hours of tamsulosin → hypotension, dizziness
  - Start low dose
- BPH
  - Cialis low dose daily – can subtract meds
- Renal impairment
  - Cialis – don't use daily dose
- SE - Headache, flushing, nasal congestion, vision changes, dyspepsia, priapism

PDE5i – Other Considerations

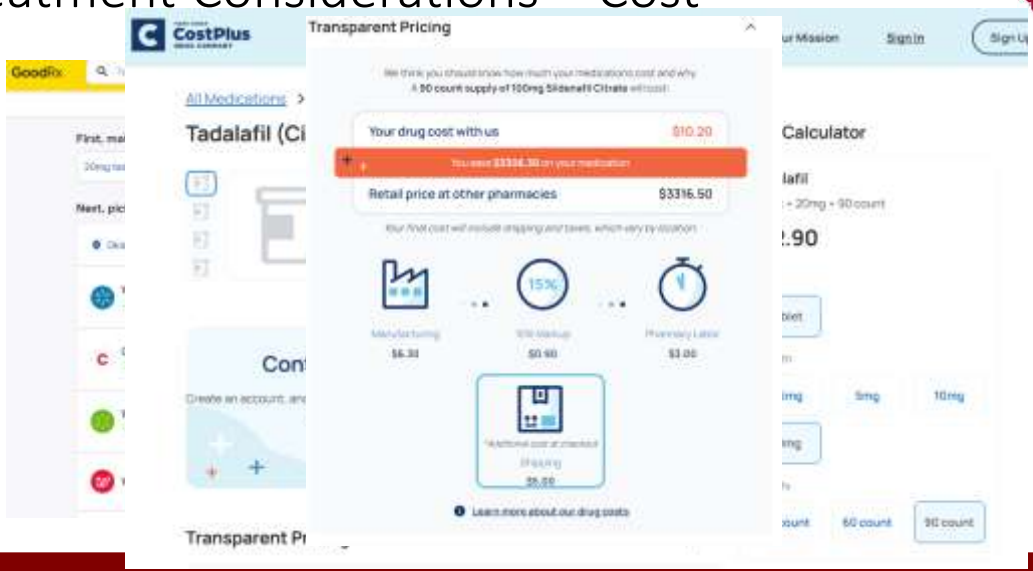
GUIDELINE STATEMENT 12

12. Men with ED and testosterone deficiency (TD) who are considering ED treatment with a PDE5i should be informed that PDE5i may be more effective if combined with testosterone therapy. (Moderate Recommendation; Evidence Level Grade C)

- Corona 2017: Meta-analysis of 14 RTC of T therapy
  - T therapy increased SHIM a men of 2.3 vs placebo
  - Testosterone therapy is not an effective mono-therapy for ED
  - Exceptions
    - Young pt
    - Very low T levels
    - Mild ED
- Buvat 2011: 173 men with ED who failed PDE5i
  - Eugonadal men vs Hypogonadal men were treated with testosterone
  - Only hypogonadal men benefited from TRT



Treatment Considerations – Cost



Costplusdrugs.com

PDE5i Counseling Summarized

- These medications are low-risk if taken properly
- Testosterone supplementation will not be beneficial as your levels are normal
- When accounting for cost – Viagra and Cialis are your best two options
  - Viagra
    - faster onset, shorter duration
    - must think about timing with food
  - Cialis
    - longer onset, weekend pill
    - food doesn't matter
    - Secondary benefits if LUTS are present

What other options are there?

Other AUA Guideline Treatment Options

GUIDELINE STATEMENT 14

14. Men with ED should be informed regarding the treatment option of intraurethral (IU) alprostadil, including discussion of benefits and risks/burdens. (Conditional Recommendation; Evidence Level: Grade C)

GUIDELINE STATEMENT 13

13. Men with ED should be informed regarding the treatment option of a vacuum erection device (VED), including discussion of benefits and risks/burdens. (Moderate Recommendation; Evidence Level: Grade C)

GUIDELINE STATEMENT 16

16. Men with ED should be informed regarding the treatment option of intracavernosal injections (ICI), including discussion of benefits and risks/burdens. (Moderate Recommendation; Evidence Level: Grade C)

GUIDELINE STATEMENT 18

18. Men with ED should be informed regarding the treatment option of penile prosthesis implantation, including discussion of benefits and risks/burdens. (Strong Recommendation; Evidence Level: Grade C)

"I'll start with the pills"

"My doctor says I need my prostate checked"

Index Patient 4: Age 70+

GUIDELINE STATEMENT 5

The Panel does not recommend routine PSA screening in men age 70+ years **or** any man with less than a 10 to 15 year life expectancy. (*Recommendation, Evidence Strength Grade C*)

PSA Screening
Average Risk Male: From 55 to 69 every 2 years

Visit Summary

- Your ED may be a sign of silent cardiovascular disease
- Lifestyle changes will benefit your ED and other possible medical conditions
- Several treatment options exist for erectile dysfunction, with specific benefits and drawbacks to each

Role of the PCP

1. Eval/treat/refer as appropriate for CVD and associated risk factors
2. Proper counseling for PDE5i – can treat hypogonadism if comfortable
3. Refer PDE5i failure or for detailed discussion of alternative treatments

Conclusions

- Men's Health entails a number of overlapping conditions that evolve as men age
- AUA guideline exist to aid urologists and primary care physicians
- Options exist beyond testosterone for the male desiring fertility
- Erectile dysfunction is an important diagnosis as a window of opportunity to improve the overall health of male patients
- Shared decision making guides erectile dysfunction treatment

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Thank you!

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