10:30 – 11:15 am

The Prostate: BPH and Beyond

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Mohit Khera, MD, MBA, MPH: Consultant for American Medical Systems; Auxilium; and Coloplast.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

- Apply diagnostic and treatment strategies to men with BPH
- Review the AUA 2014 updated BPH guidelines
- Apply diagnostic and treatment strategies to men with ED
- Discuss the relationship between ED and cardiovascular disease

Case #1

- David is 64 y/o male with a 6 month history of hesitancy, urgency, frequency and nocturia x 3
- AUA symptom score 27
- PMH: DM, HTN
- Sx: cholecystectomy
- Social: no tob, occ ETOH
- PE: DRE 60 grams
- Labs: PSA 3.2
- Next step?

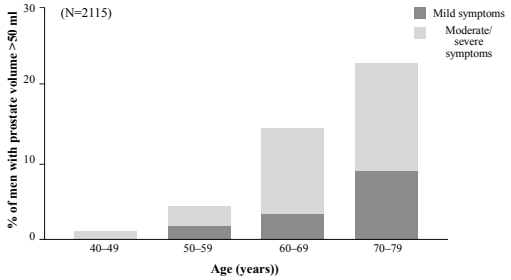
AUA = American Urologic Association

Prevalence of BPH

Age (years)	Prevalence
31-40	8%
51-60	40-50%
80+	80%

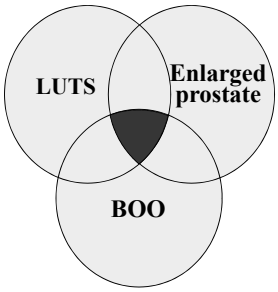
Guess HA et al. Prostate 1990; 17:241.

Natural History of BPH: Relationship Between Symptoms and Prostate Volume



Adapted from Girman CJ et al *J Urol* 1995;153:1510-1515.

Pathophysiology of Clinical BPH: Overlapping but Independent Features



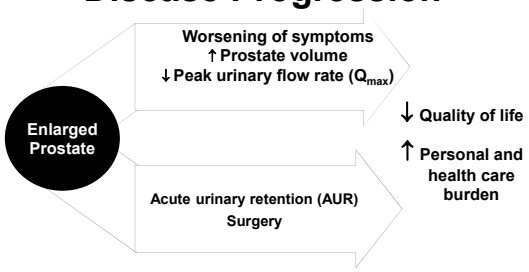
Adapted from Nordling J et al. In *Benign Prostatic Hyperplasia*. Plymouth, United Kingdom: Health Publication, 2001:107-166.

LUTS= lower urinary tract symptoms
BOO= bladder outlet obstruction

Pathophysiology of Clinical BPH: Predictive Risk Factors

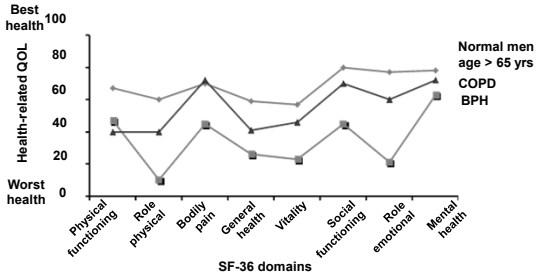
- Increasing age
- Prostatic enlargement
- Lower-urinary-tract symptoms (LUTS)
- Decreased urinary flow rate
- Elevated prostate-specific antigen (PSA)

Importance of Arresting Disease Progression



Rhodes T et al. *J Urol.* 1999;161:1174–1179. Kirby RS et. al. *Benign Prostatic Hyperplasia.* Oxford, UK: Health Press, 1995. Roehrborn CG et al. *Urology.* 1999;53:473–480. McConnell JD et al. *N Engl J Med.* 1998;338:557–563. Hong SJ et al. *BJU Int.* 2005;95:15–19. Fenter TC et al. *Am J Managed Care.* 2006;12:S90–S98.

Health-Related Quality of Life: BPH Compared with Another Chronic Disease (COPD)



COPD = chronic obstructive pulmonary disease; QOL = quality of life
Hong SJ et al. *BJU Int.* 2005;95:15–19.

LUTS – Bladder or Prostate?

LUTS = Lower Urinary Tract Symptoms

- Voiding (Obstructive)
  - Incomplete urination
  - Stopping / starting
  - Weak stream
  - Pushing / straining
- Irritative (Storage)
  - Frequency
  - Urgency
  - Nocturia

1. AUA Guidelines on Management of Benign Prostatic Hyperplasia *J Urol.* 2003 170(2):530-547.
2. Nordling J et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia.* Plymouth, UK: Health Publication Ltd; 2001:107166.

AUA Symptom Index Scoring

SCORE	INTERPRETATION
0-7	Mild
8-19	Moderate
20-35	Severe

Diagnosis of BPH

LUTS: History

- How long?
- Most bothersome symptom? **Degree of bother?**
- Voiding (Obstructive)
  - Incomplete urination
  - Stopping/starting
  - Weak stream
  - Pushing/straining
- Irritative (Storage - OAB)
  - Frequency
  - Urgency
  - Nocturia
- Other: fluid intake, UTI, pain, hematuria, LE swelling
- IPSS/AUA Symptom Score

1. AUA Guidelines on Management of Benign Prostatic Hyperplasia *J Urol.* 2003 170(2):530-547.
2. Nordling J et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia.* Plymouth, UK: Health Publication Ltd; 2001:107166.

LUTS
History - Other Causes of Symptoms

- Local Pathology
  - Infection
  - Bladder stones
  - Bladder tumor
  - Prostatitits
  - BPH
  - Prostate cancer
- Metabolic
  - Diabetes
  - Polydipsia
- Medications
  - Diuretics
  - Antidepressants
  - Antihypertensives
  - Hypnotics & sedatives
  - Analgesics & narcotics
- Other Factors
  - Psychological
  - Nocturnal polyuria
    - CHF
    - Liver disease
  - Neurologic

LUTS: Exam

- Digital rectal exam
  - Estimate prostate size, asymmetry, induration, nodule or bogginess (exclude carcinoma or chronic prostatitis)
  - Check for rectal sphincter tone
- Bladder percussion/palpation for distention
- Focused neurologic examination
  - Rule out neurologic conditions that might contribute to voiding dysfunction

Adapted from Anderson RJ. *Hospital Practice.* 1998;March:11-21.

LUTS: Labs/Studies

- Urinalysis – rule out other urinary tract pathology
- PSA – appropriately aged male to screen for prostate cancer
- Upper tract imaging – only if recurrent UTI, hematuria, renal insufficiency, urolithiasis or prior urinary tract surgery
- Urodynamics/cystoscopy NOT required for initial evaluation or prior to starting therapy in standard patient
- Urolflow

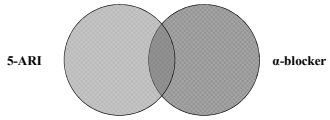
Adapted from Anderson RJ. *Hospital Practice.* 1998;March:11-21.

Male LUTS
When Should Therapy Be Started?

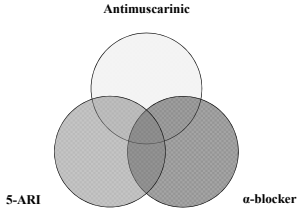
- Absolute indications
  - Urinary retention
  - Renal insufficiency
  - Recurrent UTI
  - Recurrent hematuria
  - Bladder stones
- Otherwise…are you bothered?
  - Poor flow
  - Nocturia
  - Frequency

BPH:
Treatment Options

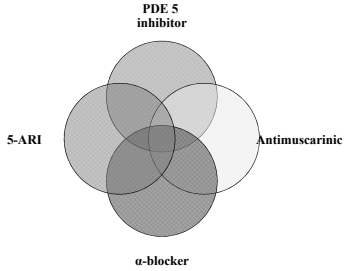
Evolution of Medical Therapy for LUTS/BPH/BOO/BPE



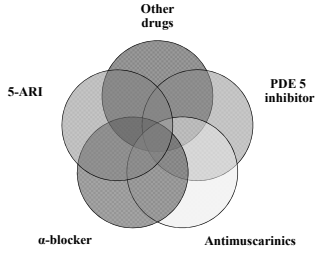
Evolution of Medical Therapy for LUTS/BPH/BOO/BPE



Evolution of Medical Therapy for LUTS/BPH/BOO/BPE



Evolution of Medical Therapy for LUTS/BPH/BOO/BPE



α-Blocker Therapy

- α -adrenergic receptors found at bladder neck and smooth muscle capsule of prostate
- α-1 receptors have many subtypes: A1a,A1b,A1d, A1L
- A1a found in prostate gland and bladder neck

Alpha blockers: how to choose?

Agent	Trade name	Typical titration schedule	Available dosing	Advantages	Disadvantages
Prazosin	Minipress	1 mg QD x1wk 1 mg BID x 1wk then 2 mg BID	1, 2 mg	-Low cost	-BID dosing -↑↑ Side effects
Terazosin	Hytrin	2 mg qhs x 1wk 5 mg qhs x 1wk then 10 mg qhs	2, 5 and 10 mg	-QD dosing	-Need to titrate -↑ side effects
Doxazosin	Cardura	2 mg qhs x 1wk 4 mg qhs x 1wk then 8 mg qhs	2, 4 and 8 mg	-QD dosing	-Need to titrate -↑ side effects
Alfusozin (long acting)	Uroxatral	No titration needed	10 mg	-QD dosing -No titration -↓ retrograde ejaculation	
Tamsulosin	Flomax	No titration needed	0.4 and 0.8 mg	-QD dosing -No titration -Low side effects	- May need to titrate
Silodosin	Rapaflo	No titration needed	8 mg	-QD dosing -No titration -No impact on BP or HR	-Higher RE and cost

Alpha-blockers Adverse Events

- Asthenia
- Postural hypotension
- Dizziness
- Somnolence
- Nasal congestion
- Retrograde ejaculation

Intraop Floppy Iris Syndrome (IRIS)

- Risk with tamsulosin or other alpha-blockers
- Flaccid iris during cataract surgery
- Impacts surgical technique – well known in ophthalmologic community
- Benefit of stopping alpha-blocker pre-op not helpful

5-alpha Reductase Inhibitors Finasteride/Dutasteride

- Blocks conversion of testosterone to DHT
- Reduces volume of enlarged prostate as DHT primary androgen responsible for prostate growth
- Reduces risk of AUR/surgery by 50% (prostates $\geq$ 40 gm)
- Reduces PSA by 50%
- Takes 3-6 months to show maximal effects
- Common side effects: erectile dysfunction, decreased libido, decreased ejaculate volume

Finasteride and Prostate Cancer

- The PCPT enrolled 18,882 men and randomized to placebo vs. finasteride 5 mg daily for 7 years
- Reduction of prostate cancer by 24.6% in the treatment arm, with an increased rate of development of Gleason 7–10 prostate cancers (37% treatment vs 22.2% placebo)
- Subsequent reanalysis found multiple counterarguments against the increased risk for HGPC:
  - Lack of reliability of Gleason scoring following 5ARI treatment
  - Reduction in prostate volume and subsequent increased detection of malignancy
  - Increased sensitivity of PSA as a prostate cancer detection marker in the finasteride group

5.2 Increased Risk of High-Grade Prostate Cancer

Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). *[See Indications and Usage (1.3) and Adverse Reactions (6.1)]* Similar results were observed in a ~~1-year placebo~~-controlled clinical trial with another 5α-reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs ~~0.5%~~ placebo). 5α-reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5α-reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

Geller et al Eur Urol, 1995. **27**(4): p. 267-73.

Tadalafil for Once Daily Dose

- FDA Indications
  - ED
  - BPH
  - ED + BPH
- Side effects
  - Headache (4.1%)
  - Dyspepsia (2.4%)
  - Back pain (2.4%)
  - Nasopharyngitis (2.1%)

Tadalafil full prescribing information 2011

Surgical Options

- Transurethral resection of the prostate (TURP)
- Open prostatectomy
- Minimally invasive options
  - Transurethral microwave therapy (TUMT)
  - Greenlight laser
  - Transurethral needle ablation (TUNA)
  - Urolift™

Complementary Medicines

- Serenoa repens (saw palmetto)
- Cernilton (Rye Grass Pollen)
- Permixon
- Pygeum africanum (african plum)
- Stinging nettle (urtica dioica)
- African star grass (hypoxis rooperi)
- Pumpkin seeds (cucurbita peopo)
- Pruce (picea)
- Pine (pineas)
- Zinc

Saw Palmetto

- Lack of evidence
  - Few trials
  - Study limitations: poor design, small numbers, variable drug preparation
- 2006 NEJM RCT*
  - 225 men, moderate-severe BPH, saw palmetto vs. placebo
  - No advantage with saw palmetto at one year
    - AUA score
    - Peak flow
    - Prostate size
    - Bother score/QOL
- Multiple formulations problematic without FDA regulation

*Bent, et al, NEJM. 2006: 354: 557-566.

When to Refer to a Urologist

- DRE reveals palpable nodules or irregularities
- PSA level of >4 ng/dL or PSA doubles in 1 year
- Inadequate response to medication
- Refractory LUTS
- Refractory cases, medical complications such as
  - Refractory AUR
  - Gross hematuria
  - Bladder stones
  - UTIs
  - Renal insufficiency

1. Moul. Postgrad Med. 1993;94:141-146,151-152.
2. Dull. Fam Pract Recert. 1998;20:43-45,51-52,59-60,68-70.
3. Murphy et al. The American Cancer Society's Informed Decisions. 1997:605-609.
4. Quick Reference for Clinicians Number 8: Benign Prostatic Hyperplasia. Rockville, Md: AHCPR; 1994
5. AUA Guidelines on Management of Benign Prostatic Hyperplasia (2003) AUA Practice Guidelines Committee. *J Urol.* 2003 170(2):530-547.

Updated 2014 AUA BPH Guidelines

- Laboratory tests should include prostate-specific antigen testing and urinalysis to exclude infection or other causes for LUTS
- The routine measurement of serum creatinine levels is not indicated in the initial evaluation of men with LUTS secondary to BPH
- If storage symptoms predominate, an overactive bladder from idiopathic detrusor overactivity is the most likely cause if flow study result shows no indication of bladder outlet obstruction (BOO)
- For coexisting BOO and overactive bladder symptoms, the patient can be treated with combination alpha-blocker and anticholinergic therapy
- For LUTS resulting from BPH with predominant BOO symptoms, alpha-blockers are the first treatment of choice

Conclusions

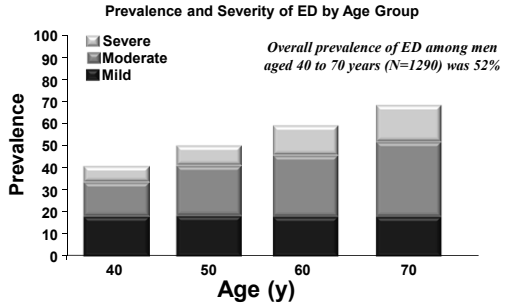
- BPH is a common condition that impacts patients' quality of life
- Complications of untreated BPH include acute urinary retention, urinary tract infections, bladder calculi, bladder damage, renal impairment and hematuria
- Alpha blockers - first line therapy for men with bothersome LUTS
- Combination therapy with anticholinergics can be considered for certain patients
- 5-alpha reductase inhibitors may be appropriate second line therapy
- The role of alternative medicines in BPH is unclear

Erectile Dysfunction: Diagnosis and Treatment

Case #3

- Bill is a 59 y/o male with a 2 year history of worsening ED. He is unable to maintain his erections. He is happily married but ED causing stress in marriage.
- PMH: HTN, gout
- PSx: hernia, TURP
- Social: smokes 2ppd, occ ETOH
- PE: testis- 18cc bilaterally, DRE- 50 grams and benign, B DP pulses 1+
- Labs: PSA 2.5
- Next step?

Massachusetts Male Aging Study (MMAS)



- The overall prevalence of mild, moderate, and severe ED was 17.2%, 25.2%, and 9.6%, respectively

Feldman HA, et al. *J Urol*. 1994;151(1):54-61.

Most Men With ED Do Not Receive Treatment

- In a study of 6,228,509 men with ED[1]
  - 25.4% received treatment (ie, PDE5 inhibitor, injection or urethral prostaglandins or androgen replacement)
  - 74.6% were untreated
- In a population-based study of men 40 years and older with ED, 77% were not receiving pharmacotherapy with a PDE5 inhibitor[2]
- Potential reasons for not seeking treatment[3]
  - Feelings of shame
  - Concern that the physician won't take the sexual problem seriously

1.Cakir O, et al. *J Urol*. 2013;189(4S):e570; 2. Foster SA, et al. *Curr Med Res Opin*. 2013;1-9; 3. Gerster S, et al. *Int J Impot Res*. 2013;25(2):56-62.

Etiologies of ED[1-3]

Vasculogenic	Cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, smoking, major surgery (radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)
Neurogenic	Spinal cord and brain injuries, Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke
Local penile (cavernous) factors	Peyronie's disease, cavernous fibrosis, penile fracture
Hormonal	Hypogonadism, hyperprolactinemia, hyper- and hypothyroidism, hyper- and hypocortisolism
Drug-induced	Antihypertensives, antidepressants, antipsychotics, antiandrogens, recreational drugs
Psychogenic	Performance-related issues, traumatic past experiences, relationship problems, anxiety, depression, stress

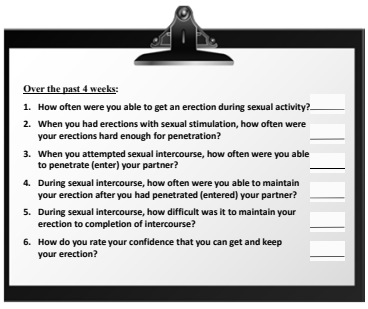
1. Wespes E, et al. European Association of Urology Guidelines on Male Sexual Dysfunction: erectile dysfunction and premature ejaculation. 2013. http://www.uroweb.org/gls/pdf/14_Male%20Sexual%20Dysfunction_LR.pdf. Accessed November 24, 2013; 2. Shamloul R, Ghanem H. *Lancet*. 2013;381(9861):153-165; 3. Grant P, et al. *Clin Med*. 2013;13(2):136-140.

Efficacy Measures: IIEF-EF

International Index of Erectile Function (IIEF) Erectile Function (EF) Domain

Measured on a 30-point scale

No ED	25–30
Mild ED	17–25
Moderate ED	11–16
Severe ED	≤10



Over the past 4 weeks:

1. How often were you able to get an erection during sexual activity?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
6. How do you rate your confidence that you can get and keep your erection?

Rosen RC, et al. *Urology*. 1997;49(6):822-830.

Efficacy Measures: Sexual Encounter Profile

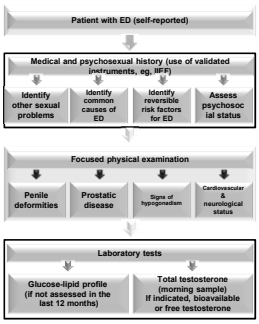
SEP2

"Were you able to insert your penis into your partner's vagina?" Y ☐ N ☐

SEP3

"Did your erection last long enough to have successful intercourse?" Y ☐ N ☐

Diagnostic Evaluation of Men with ED



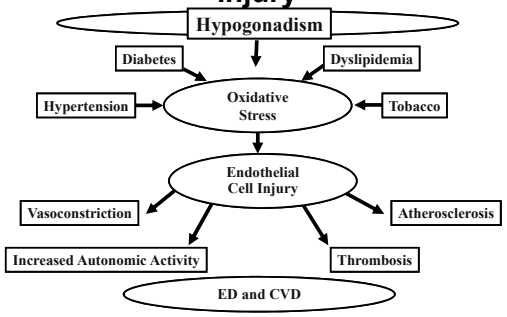
Adapted from Wespes E, et al. European Association of Urology Guidelines on Male Sexual Dysfunction:

Correlation Between ED and CVD

- Thompson et al. 2005[1]
  - 4,247 men without ED followed prospectively
  - 57% with ED at 5 years
  - Men with ED had a significantly higher incidence of developing CVD
- Montorsi et al. 2005 [2 3]
  - Prevalence of ED was 49% in men with symptomatic CAD.
  - Patients noticed ED on average 39 months before the onset of angina.

[1] Thompson et al JAMA 2005; 294:2996
[2] Montorsi et al Eur Urol 2003; 44:360
[3] Montorsi et al AJC 2005; 96(12): 19M

Common Link Between ED and Cardiovascular Disease: Endothelial Injury



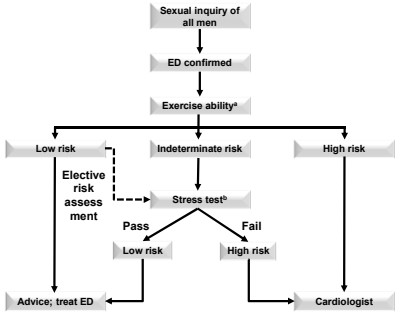
Adapted from Dzau, et al., *Am J Cardiol*., 1997;80:33I-39I; Cooke, Dzau., *Annu Rev of Med.*, 1997;48:489-509; Solomon, et al., *Heart.*, 2003;89:251-254.

Cardiac Risk Stratification

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, <3 risk factors for CAD (excluding sex)	≥3 risk factors for CAD (excluding sex)	High-risk arrhythmias
LVD/CHF (NYHA class I or II)	Mild or moderate, stable angina	Unstable or refractory angina
Post−successful coronary Revascularization	Previous (>6-8) or recent MI (2-6 weeks)	Recent MI (<2 weeks)
Controlled hypertension	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Mild valvular disease	Noncardiac sequelae of atherosclerotic disease (eg, stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
		Uncontrolled hypertension
		Moderate-to-severe valvular disease

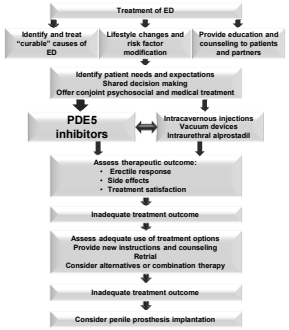
1. Wespes E, et al. European Association of Urology (EAU) guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. 2013. http://www.uroweb.org/gls/pdf/14_Male%20Sexual%20Dysfunction_LR.pdf Accessed November 24, 2013; 2. Nehra A, et al. *Mayo Clin Proc.* 2012;87(8):766-778.

Cardiac Risk Impacts ED Management: Princeton III Consensus Recommendations



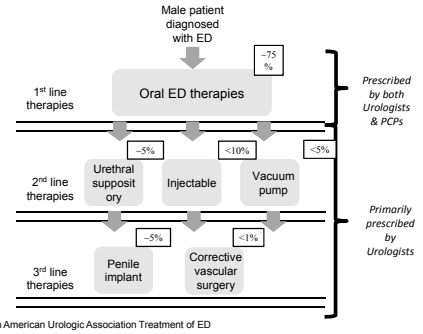
[a]Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing 2 flights of stairs in 10 seconds.
[b]Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.
Nehra A, et al. *Mayo Clin Proc.* 2012;87(8):766-778.

Treatment Algorithm for ED



Adapted from Wespes E, et al. European Association of Urology Guidelines on Male Sexual Dysfunction: \2013.

Current ED Treatment Approaches



Source: Adapted from American Urologic Association Treatment of ED Guidelines,
emedicine.com, L.E.K. Consulting Interviews and analysis.

Androgens Enhance PDE5i Efficacy

- Shabsigh et al.[1]
  - 75 hypogonadal men (T<400 ng/dl) failed sildenafil 100mg
  - Randomize to testosterone gel or placebo
  - All men received sildenafil 100 mg as needed for 12 weeks
  - IIEF significantly improved in TRT vs placebo (4.4 vs 2.1, p=0.029)
- Rosenthal et al.[2]
  - 24 hypogonadal men failed 3 trials of sildenafil 100mg within 3 months
  - Started on 4 weeks of testosterone gel and then restarted on silendafil
  - After 16 weeks, 92% of men who initially failed sildenafil therapy reported improvements in potency
- Khera et al. [3]
  - Multicenter registry of hypogonadal men (n=849) treated with TRT and followed for 12 months
  - Patients already on PDE5i therapy also had a significant increase in BMSFI scores after starting TRT

[1]Shabsigh et al. *J Urol.* 2004 Aug;172(2):658-63.
[2]Rosenthal et al. Urology 2006 Mar; 67(3):571-4
[3] Khera et al JSM 2011 Nov;8(11):3204-13

Medical Therapy of ED

- **Sildenafil April 1998**
- **Vardenafil August 2003**
- **Tadalafil: November 2003**
- **Avanafil: January 2014**

PDE5 Inhibitors: Pharmacokinetics

	Sildenafil[1]	Tadalafil[2]	Vardenafil[3]
T_{max} (min)	60	120	60
Terminal $t_{1/2}$ (hrs)	4	17.5	4-5
Impact of a high fat meal	Mean delay in T_{max} of 60 minutes; mean reduction in C_{max} of 29%	Rate and extent of absorption are not influenced by food	Reduction in C_{max} of 18-50%
Recommended administration times	~60 minutes before sexual activity	~60 minutes before sexual activity	Use as needed prior to sexual activity

1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020895s033lbl.pdf; 2. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021368s012lbl.pdf; 2003; 3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021400s010lbl.pdf

Avanafil

- T_{max} (min): 30-45min
- Terminal $t_{1/2}$ (hrs): 5 hours
- Impact of a high fat meal:
  - Rate of absorption is reduced, Tmax of 1.12 to 1.25 hours and a mean reduction in Cmax of 39% (200 mg)
  - 3.8% decrease in AUC
- Recommended administration times: 15 minutes prior to intercourse

IMPORTANT SAFETY INFORMATION

- Administration of PDE5is with any form of organic nitrates, either regularly and/or intermittently, is contraindicated. PDE5is have been shown to potentiate the hypotensive effects of nitrates
- Patients with the following characteristics (recent serious cardiovascular events, resting hypotension or uncontrolled hypertension, unstable angina, angina with sexual intercourse, New York Heart Association Class 2 or greater congestive heart failure, or hereditary degenerative retinal disorders, including retinitis pigmentosa) were not included in the clinical safety and efficacy trials. PDE5is are therefore not recommended for those patients
- Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors. Patients should be stable on alpha-blocker therapy prior to initiating treatment with a PDE5 inhibitor. In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose

Summary

- ED is a progressive disease with the prevalence increasing with age
- Patients with ED should have a cardiovascular assessment as ED and CVD often present simultaneously
- PDE5is are considered an effective first-line therapy for ED
- Patients not responding to PDE5i can either be referred to a Urologist or second-line therapies can be utilized
  - Vacuum erection device
  - Intra-urethral suppositories
  - Intercavernosal injection therapy