Sexual Disorders in Men

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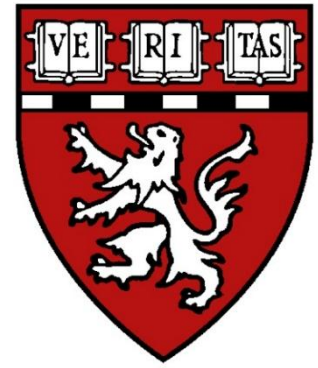
13th Annual Endocrine Summit, Mumbai, India

BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S HOSPITAL



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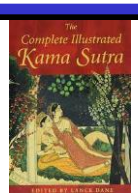
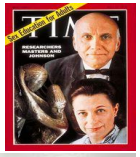
- Equity interest/stock: FPT, Xyone
- Not speaking to represent:
  - ABIM Endocrinology Board

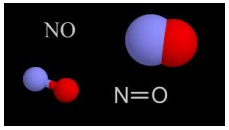
Lecture Outline

- Epidemiology of sexual dysfunction in men
- Biochemical and physiological basis of penile erections
- Disorders of sexual function
- Diagnosis and medical treatment of ED
- Guidelines for use of PDE5 inhibitors

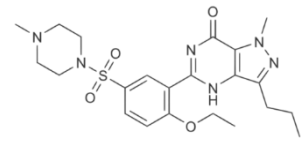
Historical Evolution of Sexual Medicine







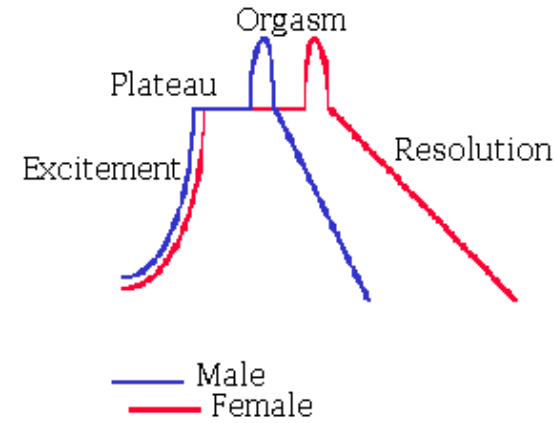
- Kama Sutra: Ancient Indian text on the art of love
- Michael Kinsey: Wide variation in sexual practices
- Masters and Johnson: Sexual response cycle
- John McKinlay: High prevalence of sexual dysfunction
- The Discovery of NO as a mediator and availability of Viagra as an oral drug for ED



Viagra

The Sexual Response Cycle

- The Excitation Phase
- The Plateau Phase
- The Orgasmic Phase
- The Relaxation Phase
-



Masters E, Johnson V. Human Sexual Response. Little Brown and Co., Boston, MA 1966

Changing Views of Sexual Disorders

Old View	New View
Sexual response cycle is circular and sequential.	Sexual response cycle is more complex and not always circular.
Sexual disorders are related to mental health problems. Psychotherapy a key part of treatment.	Sexual disorders are mostly the result of medical disorders, and often affect mental health. Treated medically.
Prevalence largely unknown; viewed as low.	Prevalence high. •ED and premature ejaculation are the most common disorders in men.

DSM-5 Classification of Sexual Disorders

Four Categories

- Male hypoactive sexual desire disorder
- Erectile dysfunction
- Premature ejaculation
- Delayed ejaculation

Main Differences from DSM-IV

- DSM-5 lists male HSDD as a separate entry.
- Male orgasmic disorder has been renamed *delayed ejaculation.*
- Male dyspareunia, male sexual pain, sexual aversion disorder have been removed.
- DSM-5 includes a duration of approx. 6 months.
- Sexual disorder must have caused significant distress.

Sungur MZ, Gunduz A. A comparison of DSM-IV-TR and DSM-5 definitions for sexual dysfunctions: critiques and challenges. J Sex Med 2014;**11:**364-373.

Hypoactive Sexual Desire Disorders

- Persistent or recurrent deficiency (or absence) of sexual fantasies and desire for sexual activity for 6 or more months
- Not better explained by another disorder, direct physiologic effects of a substance (drug, medication), or general medical condition
- Causes distress: low desire is not always pathologic

Structured interview is the key to the diagnosis!

Sungur MZ, Gunduz A. A comparison of DSM-IV-TR and DSM-5 definitions for sexual dysfunctions: critiques and challenges. J Sex Med 2014;**11:**364-373.

HSDD: Pathophysiologic Factors and Significance

Causes

- Androgen Deficiency
- Systemic illness and medications: SSRIs, GnRH agonists, anti-androgens, anti-convulsants
- Depression and other mental health problems
- Secondary to other causes of sexual dysfunction: fear of failure
- Relationship and differentiation problems

Why is it important to diagnose HSDD

- Evaluation may lead to detection of (treatable) androgen deficiency
- HSDD may have adverse health consequences
  - Can lead to emotional gridlock and cessation of physical affection
  - Can lead to ED
  - Low sexual desire may impede or reduce effectiveness of treatments for other sexual disorders.

Alexander et al, 1998; Wang et al, 2000; Bagatell et al, 1996; Pridal and LoPiccolo 2000

Role of Testosterone in Spontaneous vs Induced Sexual Response

- Compared to eugonadal men, hypogonadal men had:
  - Lower self-reported sexual activity, feelings and thoughts
  - Lesser number of spontaneous erections
  - Similar erectile response to visual erotic stimulus
- Testosterone replacement of hypogonadal men:
  - Increased sexual feelings and thoughts, and sexual activity
  - Increased number of spontaneous erections
  - But did not change erectile response to visual erotic stimulus

Spontaneous, but not stimulus-induced, erections are testosterone dependent.

Testosterone stimulates sexual thoughts and feelings.

Kwan et al, J Clin Endocrinol Metab 1983;57:557-62

Testosterone and Penile Erections

- Testosterone is a potent vasodilator and increases penile blood flow by blocking L-type calcium channels.
- T deficiency leads to cavernosal smooth muscle atrophy, lack of effective venous occlusion, and reduced rigidity.
- Testosterone induces penile NOS expression in castrated rats.
- Correcting testosterone deficiency improves sexual desire and erectile function.

Lugg et al, 1996; Penson et al, 1996; Jones et al, 2007

Erectile Dysfunction: Definition

- Recurrent/consistent inability to attain and/or maintain penile erection sufficient for sexual activity for 6 or more months
- Bother/ distress: acknowledgement of the subjective complaint of erectile inability by the patient (or patient and partner)

Diagnosis of ED is made entirely by patient's self-report. The single most important step is to ask the patient about his sexual function in an open-ended and nonjudgmental manner

Lewis RW et al. J Sex Med 2004; 1:35-39

Derogatis LR, Burnett AL. J Sex Med 2008; 5: 289-300

Epidemiology of Erectile Dysfunction

- ED is the most prevalent sexual disorder in men
- In India; one estimate ~10% of men; 170 million men worldwide.
- Mass Male Aging Study: 52% of men, 40-70 years of age, have some degree of ED
- Rates higher in middle-aged and older men with T2DM and CAD

John McKinlay

MMAS (Feldman et al, J Urol 1994)
NHLHS (Laumann et al, JAMA 1999)

Risk Factors: ED is a Manifestation of Systemic Atherosclerosis

Risk factor	ED Prevalence (%)	
	Complete	Moderate or complete
Heart disease (smoker)	57	78
Depression (severe)	41	90
Diabetes	28	56
Hypertension	20	40
Heart disease (nonsmoker)	21	62
HDL-C <30 mg/dL	17	48
General population	**9.6**	**35**

Feldman HA et al. *J Urol*. 1994;151:54-61.

ED as a Marker of CVD

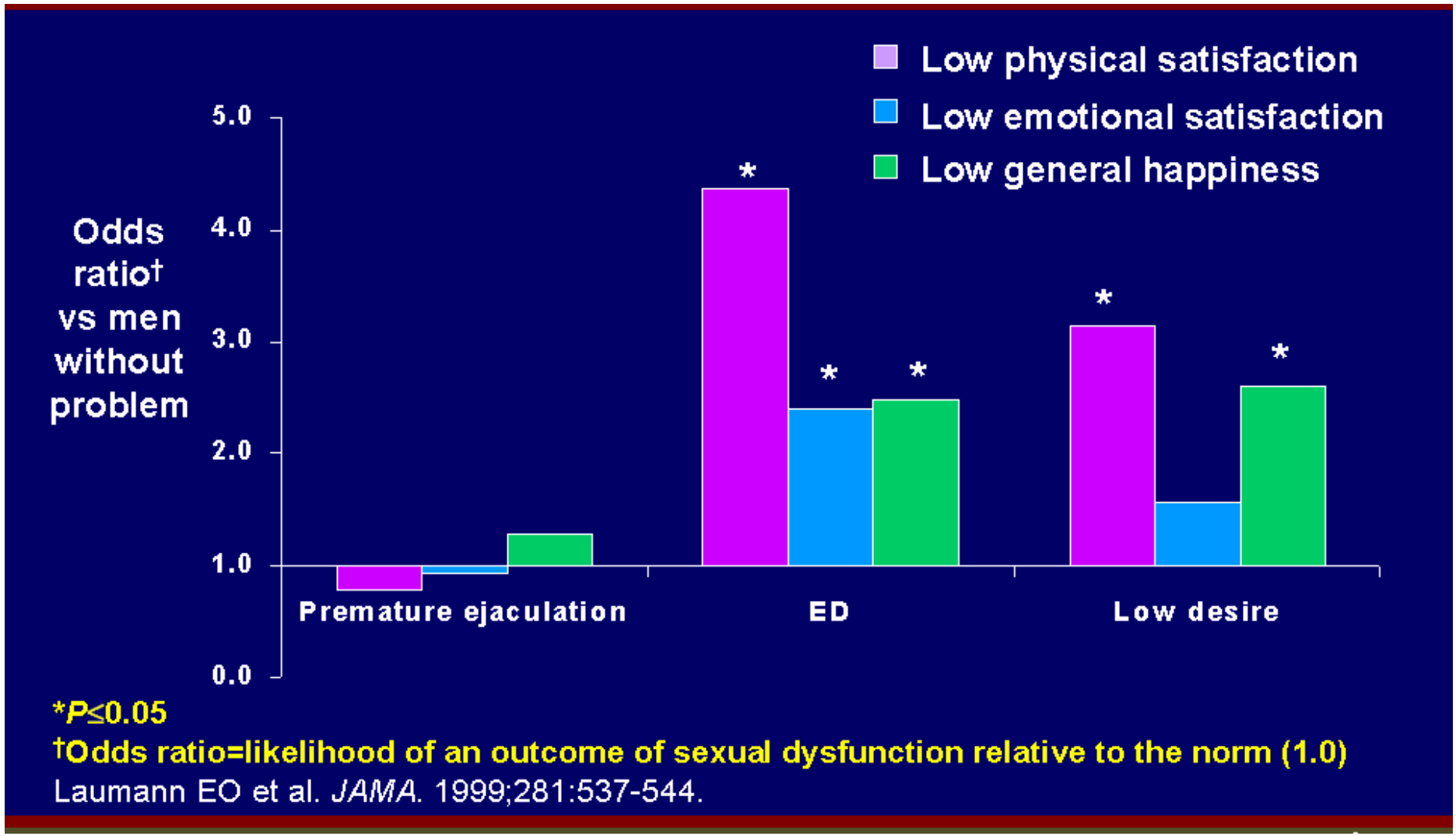
- ED is an independent predictor of subsequent CAD, especially in younger men.
- ED precedes the symptoms of CAD by several years years and cardiovascular events such as myocardial infarction or stroke by 3-5 years
- ED associated with increased risk of death due to CVD.

•Men presenting with ED should be evaluated for CVD.
•ED management should include treatment of underlying CVD and CV risk factors.

Lower Urinary Tract Symptoms and ED

- LUTS is a stronger predictor of ED than other risk factors (Cologne Male Study; Multinational Study of Aging Male).
- Mechanisms that regulate bladder detrusor and cavernosal smooth muscle share similarities (NO, slow K channels, calcium channels, Rho kinase)
- Therapies for LUTS (5AR inhibitors, surgery) may affect erectile function.
- Some PDE5 inhibitors are approved for LUTS.

ED Adversely Affects Quality of Life



*$P \leq 0.05$

†Odds ratio=likelihood of an outcome of sexual dysfunction relative to the norm (1.0)

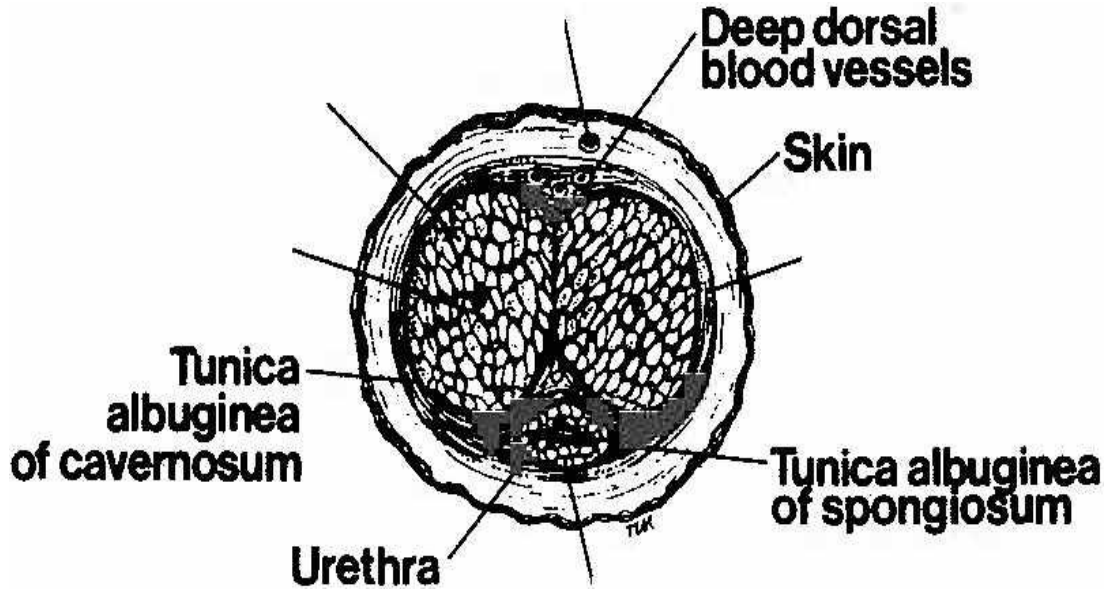
Laumann EO et al. *JAMA*. 1999;281:537-544.

The Five Minute ED Evaluation

- History
  - Evaluate psych factors (depression, anxiety) and relationship issues
  - Ascertain risk factors
    - » Diabetes, Hypertension, CVD, CKD
    - » Prostate disease: Prostate surgery, LUTS
    - » Medications: Anti-depressants, hptn drugs, vasodilators, nitrates
    - » Risk factors that might affect choice of therapy (nitrate use, CAD)
- Physical Examination
  - Postural BP, peripheral pulses, evidence of T deficiency, perineal sensation, penile plaque/ curvature
- Lab Tests
  - FBG, A1c, creatinine
  - Lipids
  - Testosterone

Bhasin S, Bassoon R. Sexual Dysfunction. In: Williams' Textbook of Endocrinology, 2019 (16th ed)

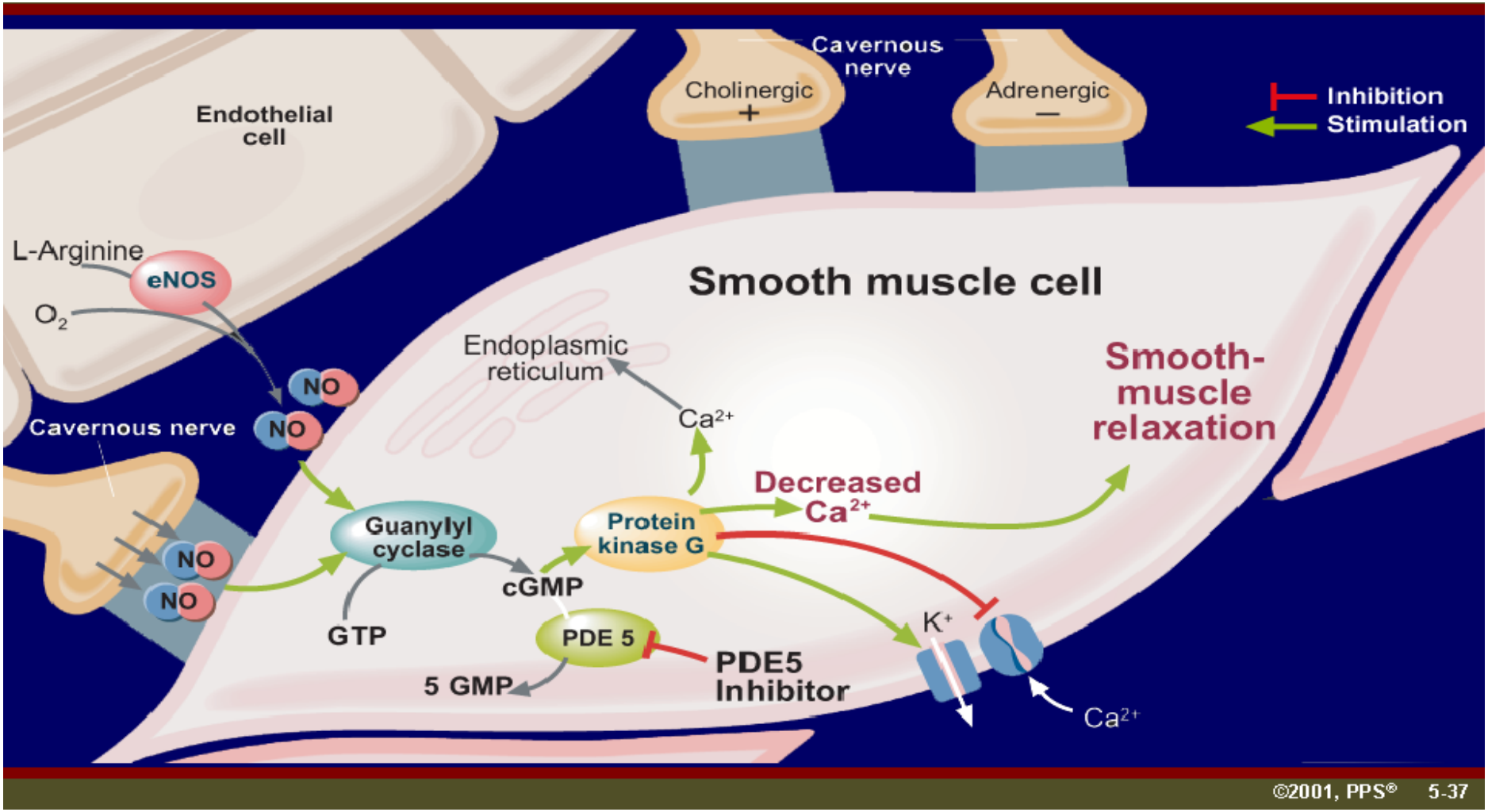
Mechanism of Penile Erection



- Cavernosal smooth muscle relaxation
- Increased blood flow into the penis
- Occlusion of venous outflow

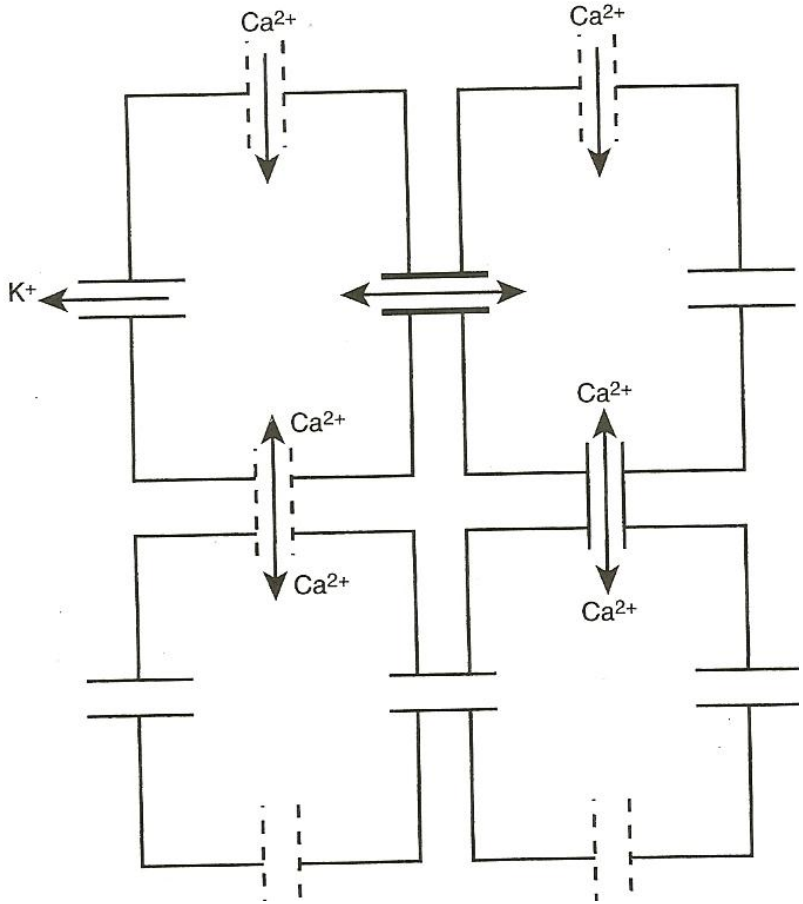
Bhasin S, Basson R. Sexual Dysfunction, Williams' Endocrinology 2020

Nitric Oxide / cGMP Key Mediators of Penile Erection

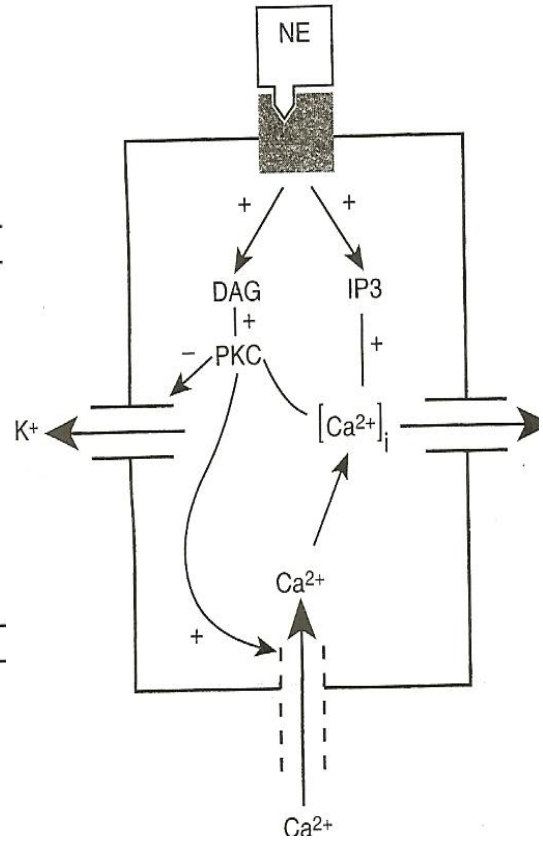


Lue T, NEJM 2000;342:1802

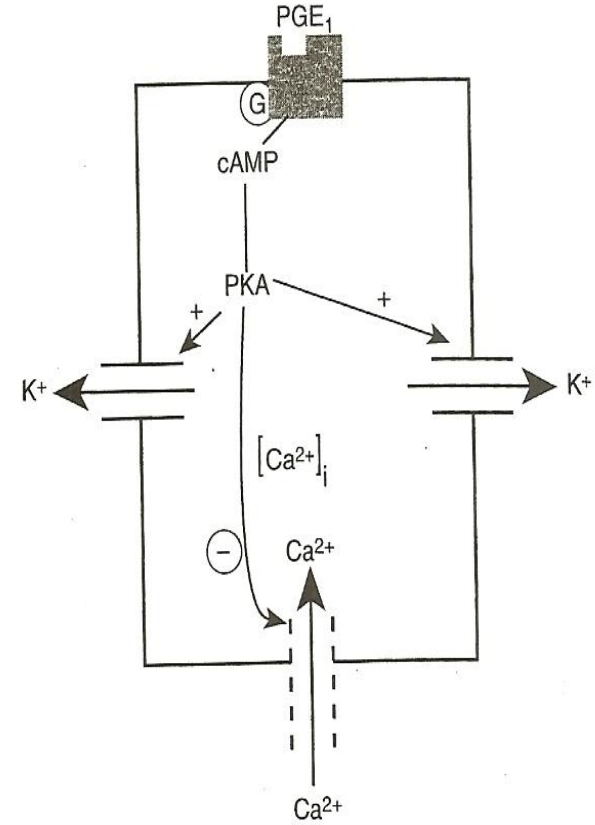
Neurotransmitters Regulate Smooth Muscle Contractility by Regulating Intracellular Ca2+



Cavernosal Smooth Muscle Cells Form A Functional Syncytium

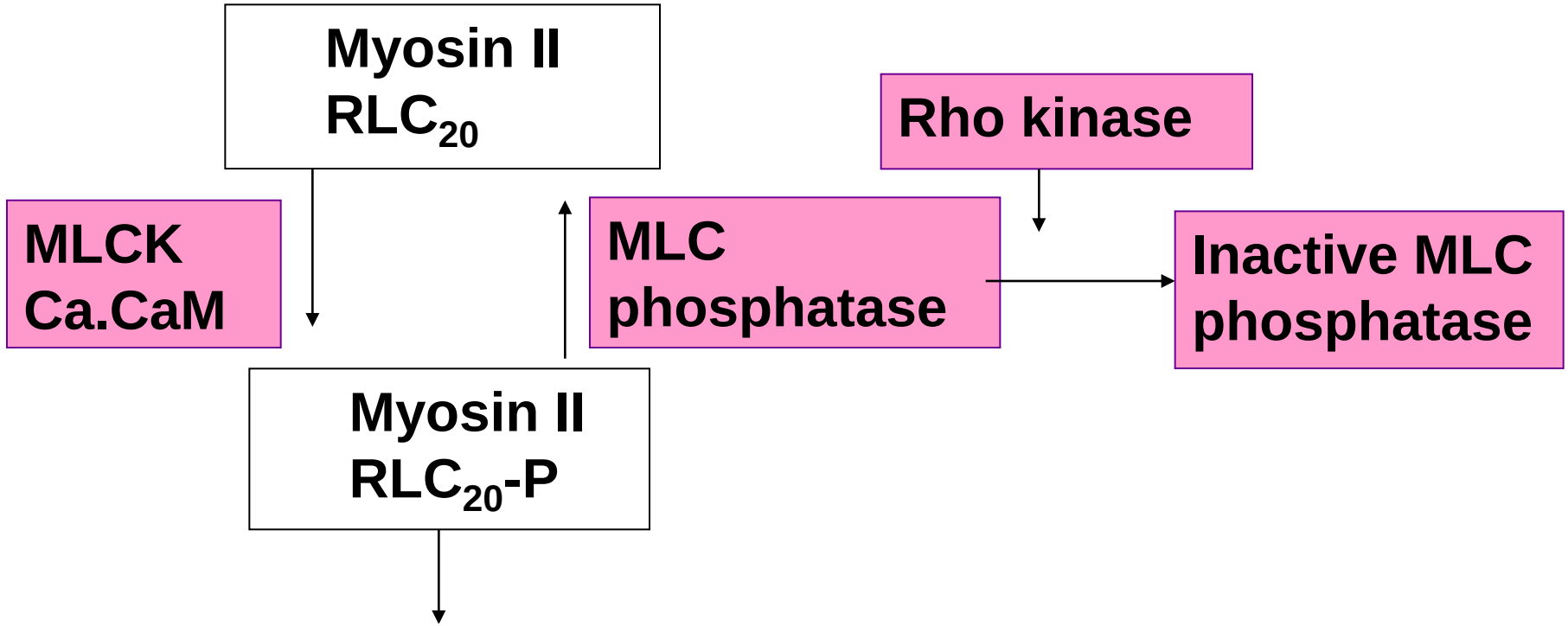


Norepinephrine

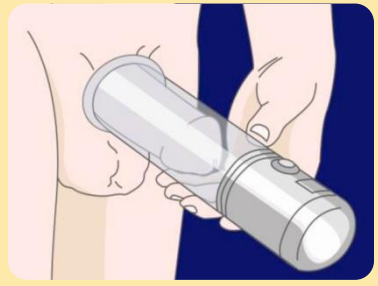
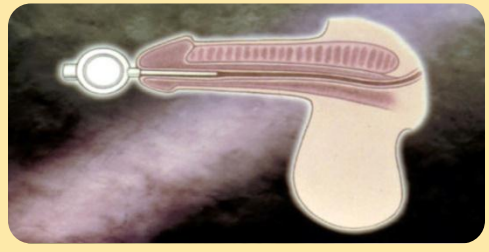
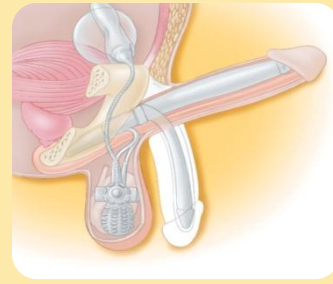
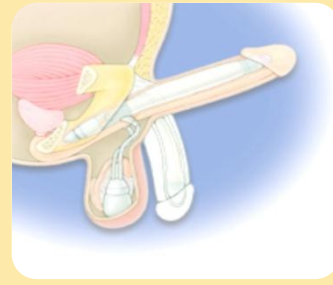
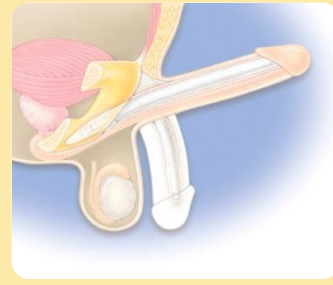


PGE1

Rho Kinase Regulates Sensitivity to Intracellular Calcium



A Step Approach to the Management of ED

First-Line Therapy	Second-Line Therapy	Third-Line Therapy
• Oral medications: PDE-5 inhibitors  • Couples/Sexual Counseling  • Optimize treatment of T2DM/ CVD; rule out T deficiency	• Vacuum Erection Device  • Intraurethral alprostadil  • Intracavernosal injection 	• Surgical prosthesis   

First-Line Therapy: Selective PDE5 Inhibitors

	Sildenafil	Vardenafil	Tadalafil	Avanafil
Commercial Name	Viagra	Levitra	Cialis	Stendra
Onset (min)	30 - 60	30 - 60	60 - 120	**15 – 30**
Duration of action (hours)	Up to 12 hours	Up to 10 hours	**Up to 36 h**	Up to 6h
Selectivity for PDE6 (Retina)	Least selective		Most selective for retina	
Selectivity for PDE11 (Muscle)	Less selective	Most selective	Least selective for muscle	
Effect of food/alcohol	Cmax decreased	Minimal	Not affected	Not affected

Burnett AL et al. Erectile dysfunction: AUA guideline. J Urol 200:633-41, 2018

Adverse Events Associated with PDE5 Inhibitors

Adverse event	Sildenafil	Vardenafil	Tadalafil
Headache	13%	16%	15%
Flushing	10%	12%	4%
Dyspepsia	5%	4%	12%
Nasal congestion	1%	10%	4%
Dizziness	1%	2%	2%
Abnormal vision*	2%	<2%	-
Back pain*	-	-	7%
Myalgia*	-	-	6%
Hearing problems	Infrequent	Infrequent	Infrequent

Wespes et al, Brock et al, and Morales et al.

*, These adverse effects are related to nonselective inhibition of phosphodiesterase isoforms in other tissues.

Key Points About PDE5 Inhibitors

- PDE5Is will not be effective unless sexual activity is initiated.
- Dose titration is necessary to optimize benefit to side effect ratio.
- Most men needing PDE5Is are likely to have underlying CAD.
  - Most men who can climb two flights of stairs without chest pain can engage in sex with a stable partner.

ACC/AHA Recommendations for the Use of PDE5Is by Men with Cardiac Disease

- PDE5Is contraindicated in men taking nitrate drugs regularly.
- If patient uses short acting nitrates only infrequently, PDE5I use should be guided by risk consideration. Contraindicated within 24 h of nitrate use.
- The patients should be warned that concurrent nitrate and PDE5I use could result in marked hypotension.
- In men with pre-existing CAD, the risks of inducing cardiac ischemia during sexual activity should be assessed before prescribing PDE5Is.
- Men taking anti-hypertensive medication should be warned about the possibility of sildenafil-induced hypotension.

Cheitlin et al. Circulation 1999;99:168-177.

Management of Erectile Dysfunction

66 years old man with T2DM, hypertension, and CAD complains of difficulty in achieving and maintaining erections. He takes metformin, lisinopril, hydrochlorthiazide, aspirin, atorvastatin, and sublingual nitroglycerine when he has chest pain. BMI 34 kg/m2, HR 72/min, BP 128/80. He is well virilized, testes 25 mL b/l. Penis 8 cm unstretched, no palpable plaque. Total T 450 ng/dL, free T 125 pg/mL, LH 5 U/L, FSH 5 U/L. The best option for treating his ED is:

A. Tadalafil
B. Intracavernosal injections of alprostadil
C. Intraurethral PGE1 suppository
D. Abstinence as sexual activity may not be safe for him

Management of Erectile Dysfunction

55 years old man with T2DM and hypertension was prescribed sildenafil 50 mg, as needed, for ED. He calls your office, frustrated that he took the pill but did not experience an erection; in addition, he had a headache the next morning. The best next step is to:

A. Increase the dose to 100 mg
B. Change to tadalafil
C. Switch to IC injections of alprostadil
D. Advise him on proper use of sildenafil

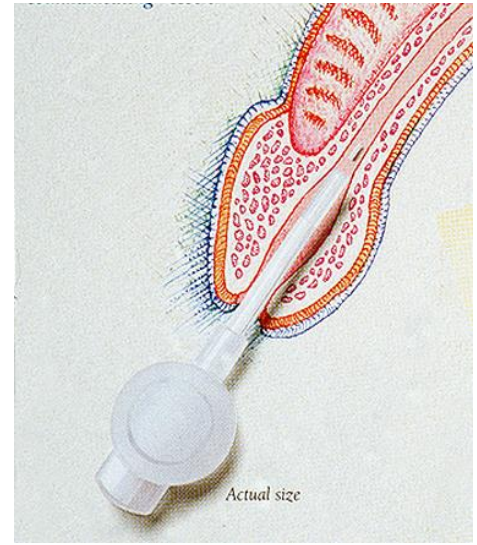
Management of PDE5I Nonresponders

- Is the patient taking the medication properly?
  - 1-2 hour before the planned sex
- Is the dose adequate?
- Is there adequate sexual / erotic stimulation stimulation?
- Is there a relationship problem?
- Is the patient experiencing adverse effects?
  - If not, escalate the dose to maximal tolerated.
- Does the patient have testosterone deficiency?

In true non-responders, consider daily tadalafil, or second line therapies (IC injection), or combination therapies (vacuum pump plus PDE5Is).

Intraurethral Alprostadil

- Mechanism of Action: Activates cAMP and PKA and inhibits intracellular Ca^{2+}
- Efficacy
  - Responder rate: ~33-40%
- Side Effects
  - Pain, bleeding, hypotension
- Contraindications
  - Priapism history

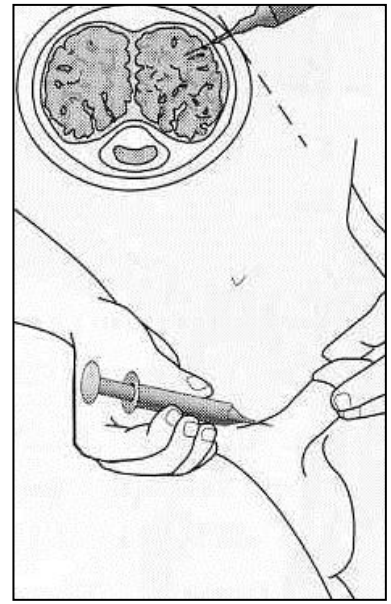


Kim ED, McVary KT. J Urol 1995;153:1828-1830.

Intracavernosus Pharmacotherapy

- Mechanism of Action: corporal smooth muscle relaxant effects
- Available drugs: PGE1, alprostadil, phentolamine, papaverine, and combinations
- Efficacy: Highly efficacious
- Side Effects: Pain, hematoma, penile fibrosis, priapism
- Contraindications: priapism; coagulopathy

Injection technique



Linet OI, Ogrinc FG. N Engl J Med 1996;**334:** 873-877.

Treatment of Priapism

- Oral alpha adrenergic agonists: brethine or psudoephedrine
- IC injection of phenylephrine
- Withdraw blood from corpora cavernosum
- Surgical detumescence

Important to provide a 24-hour hotline for patients to enable easy access to your office and a urologist to manage priapism.

New Therapies for ED

- Novel PDE5 inhibitors (udenafil, SLx-2101, mirodenafil)
- Selective melanocortin receptor-4 (MC-4) agonists (Melanotan II, PT-141, THIQ)
- Rho kinase inhibitors: Fasudil (HA-1077; Asahi Kasei Pharma); Y-27632 (Mitsubishi-Pharma)
- Guanylate cyclase activators
- Other targets:
  - CGRP
  - VIP
  - Hexarelin analogs
- Gene therapy
  - SloK channels

Ayurvedic Medicines for ED

Common herbs

- Ashwagandha
- Vajikarana
- Cinnamomum cassia
- Gensing extracts
- Rho kinase inhibitors*: Butea frondose, syzygium aromaticum, Butea superba, Mucuna pruriens*
- Other herbal combinations

Many herbs contain natural PDE5Is, cGC activators, and Rho kinase inhibitors, offering good rationale for their use.
However, variability in formulations, limited published info about their clinical pharmacology, and paucity of efficacy trials data have barriers to their use in clinical practice.

Key Points

- ED, a common disorder, greatly affects men's self-esteem.
- ED is a sentinel of heart disease and diabetes and offers an opportunity to diagnose and treat cardiometabolic disorders.
- PDE5Is are safe and effective in treating ED of all causes. Their common AEs are related to their non-selectivity.
- Failure to respond to PDE5Is is typically related to improper use or suboptimal dose.
- Most men with ED can be treated medically.

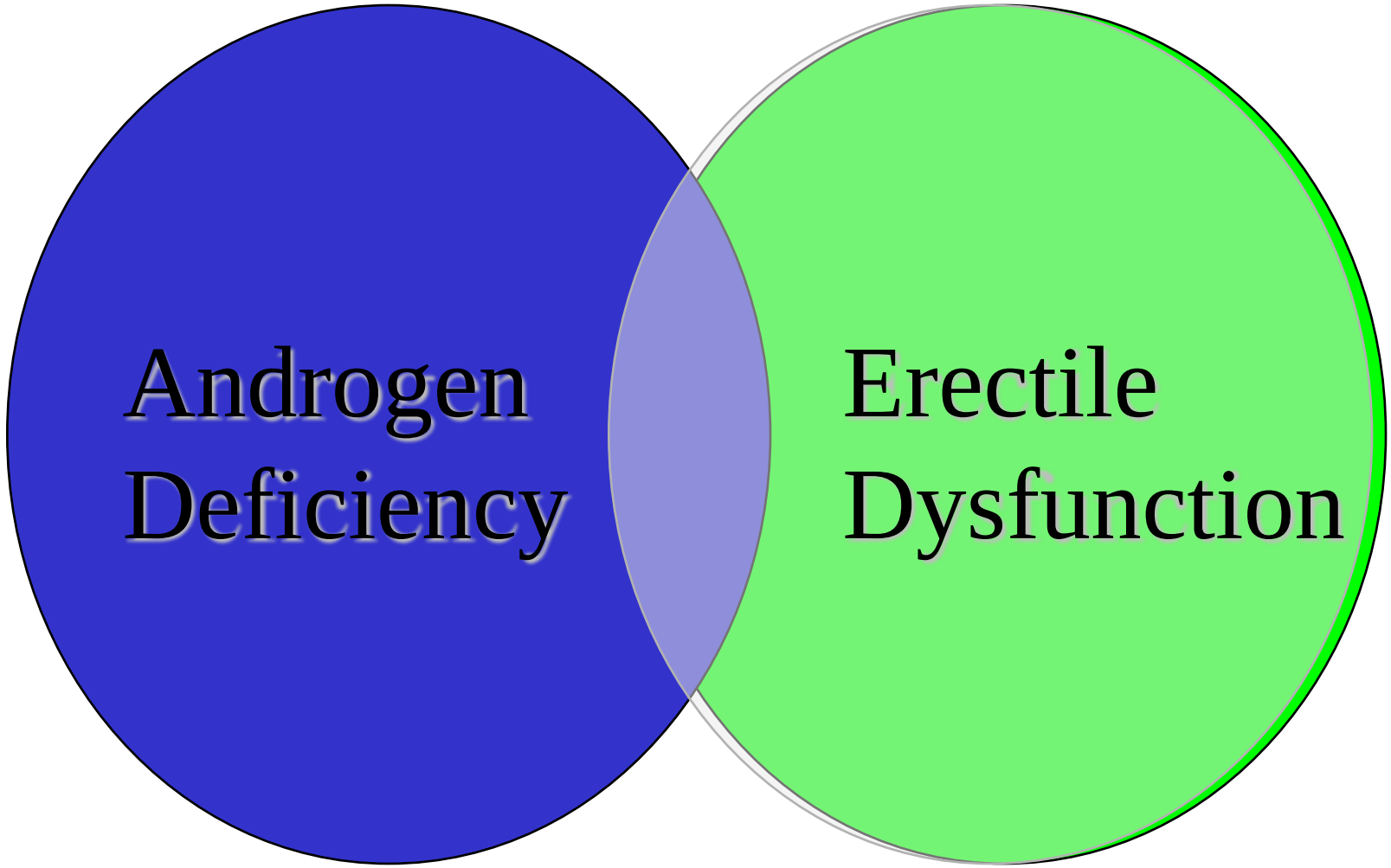
- Thank you!

Management of Erectile Dysfunction

69 years old man with T2DM, hypertension, and CAD complains of difficulty in achieving erections. He had a MI 3 months ago and underwent coronary artery angioplasty. He is ambulatory and can climb stairs to his bedroom without chest pain. He takes metformin, lisinopril, hydrochlorthiazide, aspirin, and atorvastatin. BMI 38 kg/m2, HR 76/min, BP 138/88. He is well virilized, testes 25 mL b/l. Penis 8 cm unstretched, no palpable plaque. Total T 390 ng/dL, free T 105 pg/mL, LH 5 U/L, FSH 5 U/L. The best option for treating his ED is:

A. Sildenafil citrate
B. Intracavernosal injections of alprostadil
C. Intraurethral PGE1 suppository
D. Abstinence as sexual activity may not be safe for him

Androgen Deficiency and Erectile Dysfunction are Independently Distributed Conditions



New PDE5 Inhibitors

- **Objectives: improved biochemical specificity/catalytic site affinity profiles/oral bioavailability, to improve clinical efficacy and safety/tolerability**
- **Intervention (for subjects with erectile dysfunction)**

  - Udenafil (Dong-A PharmTech Co), available in South Korea

  - Lodenafil (Brazil), completed Phase III trials

  - Mirodenafil (SK Chemical), available in South Korea

  -SLX-2101 (Surface Logix), undergoing Phase II trials

Guanylate Cyclase Activators

- **Mechanism of Action: heightened guanylate cyclase activation independent of nitric oxide stimulation**
- **Compounds in preclinical evaluation**

Brioni JD et al. Int J Impot Res 2002; 14: 8-14
Kalsi JS et al. J Urol 2003; 169: 761-6

Rho-Kinase Inhibitors

- Mechanism of Action: inhibition of the main effector pathway for penile smooth muscle contraction, induced by norepinephrine, angiotension II, endothelin-1
- Compounds under clinical investigation
  - Fasudil (HA-1077; Asahi Kasei Pharma)
  - Y-27632 (Mitsubishi-Pharma)
- Compounds in preclinical evaluation
  - SAR-407899 (Sanofi-Aventis)

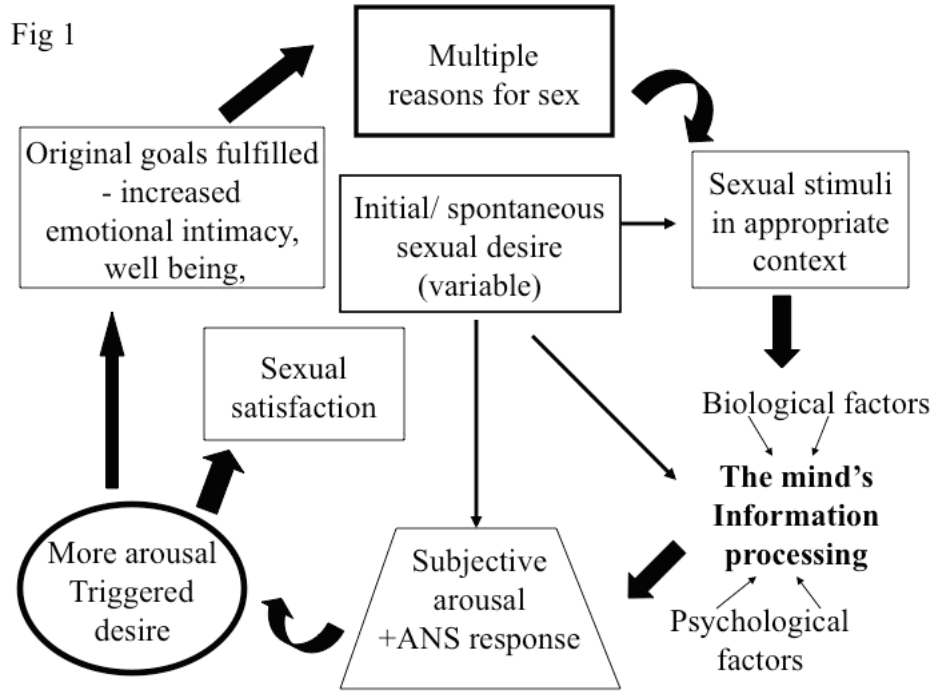
Chitaley K et al. Nat Med 2001; 7: 119-22
Lohn M et al. Hypertension 2009; 54: 676-83

Making a Diagnosis of ED

The single most important step is to ask the patient about his sexual function in an open-ended and nonjudgmental manner:

- How is your sex life?
- Many men have difficulty getting erections. Are you experiencing any difficulty in your sex life?
- How is your relationship with your sexual partner?

Revised View of Sexual Response Cycle



Bhasin S, Bassoon R. Sexual Dysfunction. In: Williams' Textbook of Endocrinology, 2019 (16th ed)

Hypoactive Sexual Desire Disorder *Must* Involve Distress

A diagnosis of Hypoactive Sexual Desire Disorder is appropriate *only* if the person reports “distress”.

- Low sexual desire is not necessarily pathologic.
- “High desire” and “low desire” are systemic positions in a sexual relationship (*Schnarch 2000*).
- Low sexual desire may be an adaptation to relationship and differentiation issues (*Schnarch 2000*).

Management of Erectile Dysfunction

62 years old man with T2DM, hypertension, and CAD complains of difficulty in achieving and maintaining erections. He is in a new relationship and this makes him anxious. He takes metformin, lisinopril, hydrochlorthiazide, aspirin, and atorvastatin. BMI 38 kg/m2, HR 76/min, BP 138/88. He is well virilized, testes 25 mL b/l. Penis: no palpable plaque. Total T 390 ng/dL, free T 105 pg/mL, LH 5 U/L, FSH 5 U/L.

The best option for treating his ED is:

A. Testosterone replacement therapy
B. Sildenafil citrate
C. Psychotherapy
D. Intracavernosal injections of alprostadil

Intracavernosus Pharmacotherapies

Trade Name	Drug	Dosages	Efficacy (intercourse)
Caverject	Alprostadil (Prostin VR)	5-40 ug/ml	~70%
Edex	Alprostadil (Prostin VR)	5-40 ug/ml	~70%
Bi-mix	Alprostadil + Phentolamine	20 ug/ml + 0.5 mg/ml	~90%
Bimix Androskat (EU)	Papaverine + Phentolamine	30 mg/ml + 0.5 mg/ml	~90%
Tri-mix	Alprostadil + Papaverine + Phentolamine	10 ug/ml + 30/mg/ml + 1.0 mg/ml	~90%

Bhasin S, Bassoon R. Sexual Dysfunction. In: Williams' Textbook of Endocrinology, 2019 (16th ed)