Erectile Dysfunction and Testosterone Therapy

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Objectives

- To define and recognize erectile dysfunction
- How to approach and test
- Overview to initiate treatment
- To understand the role of the Urology ED Clinic
- Other aspects of hypogonadism: the role of bioavailable testosterone

Definition of Erectile Dysfunction (ED)

- ED is the persistent inability to attain and/or maintain an erection sufficient to permit satisfactory sexual intercourse
- More accurate estimates of the prevalence of ED have become possible due to the development of the International Index of Erectile Function (IIEF) in 1998
- It is recognized that desire, orgasmic capacity and ejaculatory capacity may be intact in the presence of ED or may be deficient to some extent and contribute to the sense of inadequate sexual function

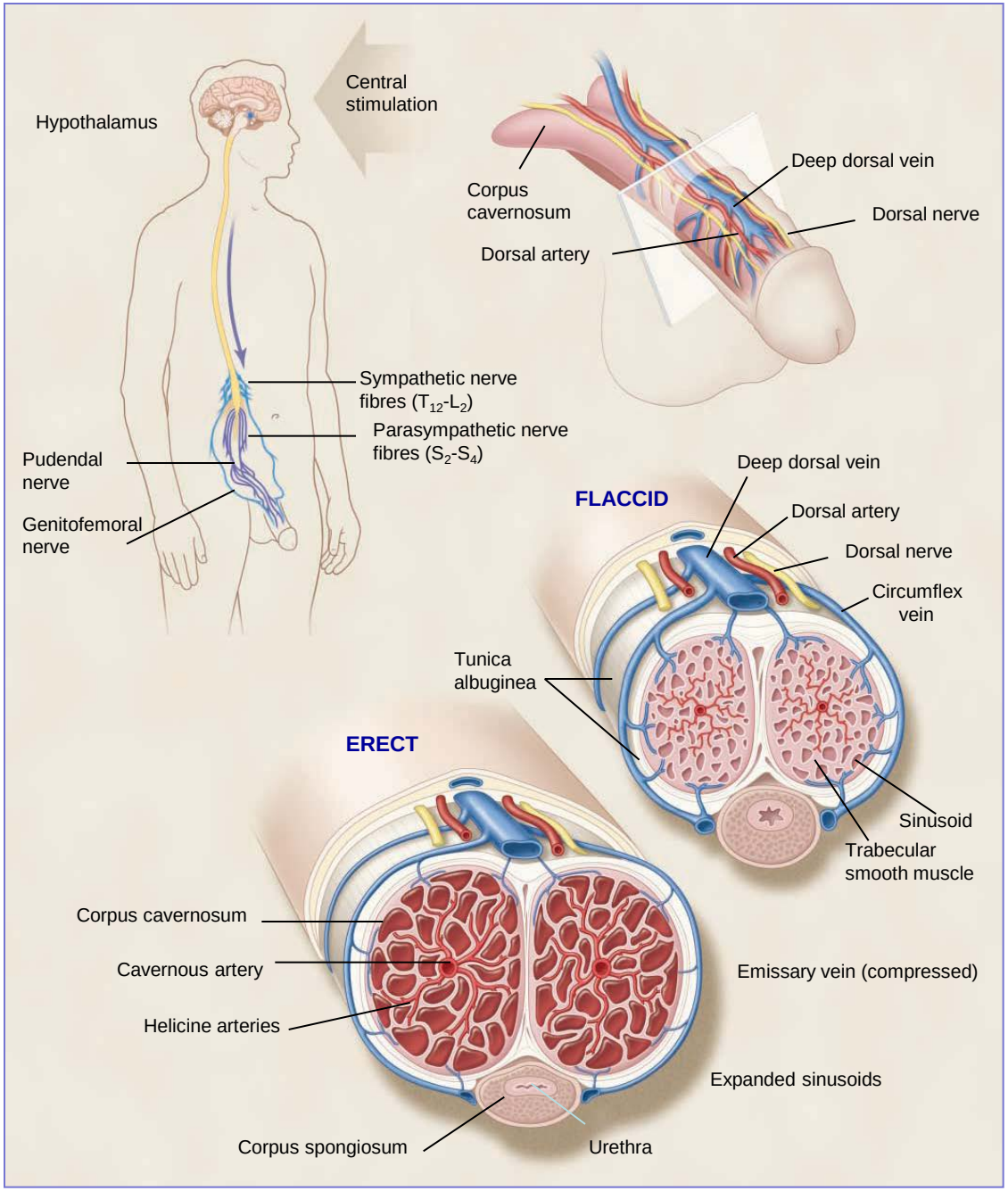
- NIH Consensus Conference. JAMA 1993;270:83-90.
- Canadian Urological Association Guidelines Committee. CJU 2002;9:1583-7.
- Hackett G et al. British Society for sexual medicine guidelines. J Sex Med 2008;5:1841-65.

What are the risk factors contributing to ED

Anatomy and mechanism of penile erection

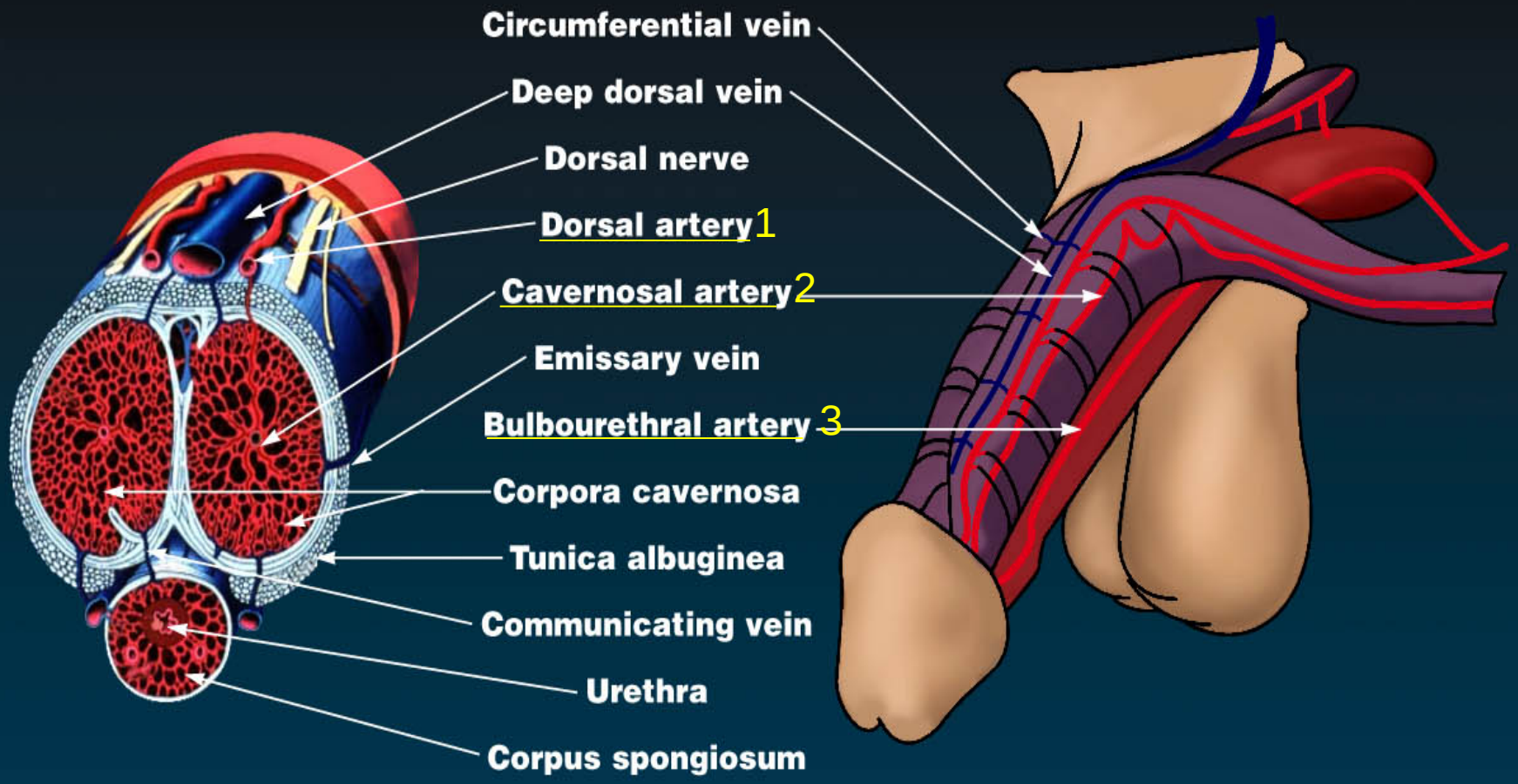
The erection pathway can be triggered by direct genital stimulation and by auditory and visual stimulation, which act in concert to increase penile blood flow.

The penis has a highly specialized anatomical structure that allows a massive increase in blood flow to be trapped within the inelastic layers surrounding the penis (the tunica albuginea), which causes rigidity and expansion of the cavernous smooth muscle.

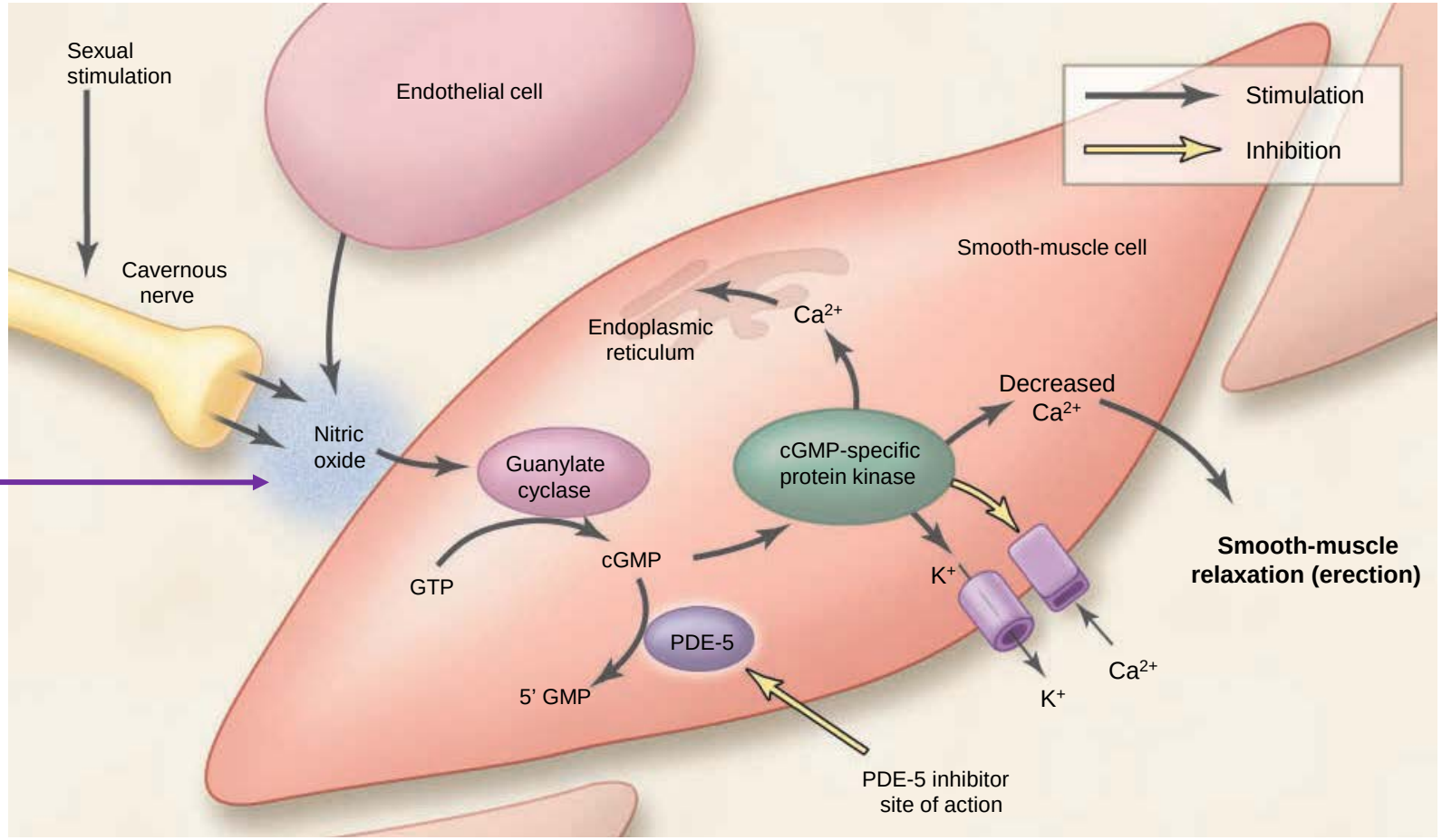


Fazio L & Brock G. CMAJ 2004;1701429-37

Penile Anatomy and Circulation



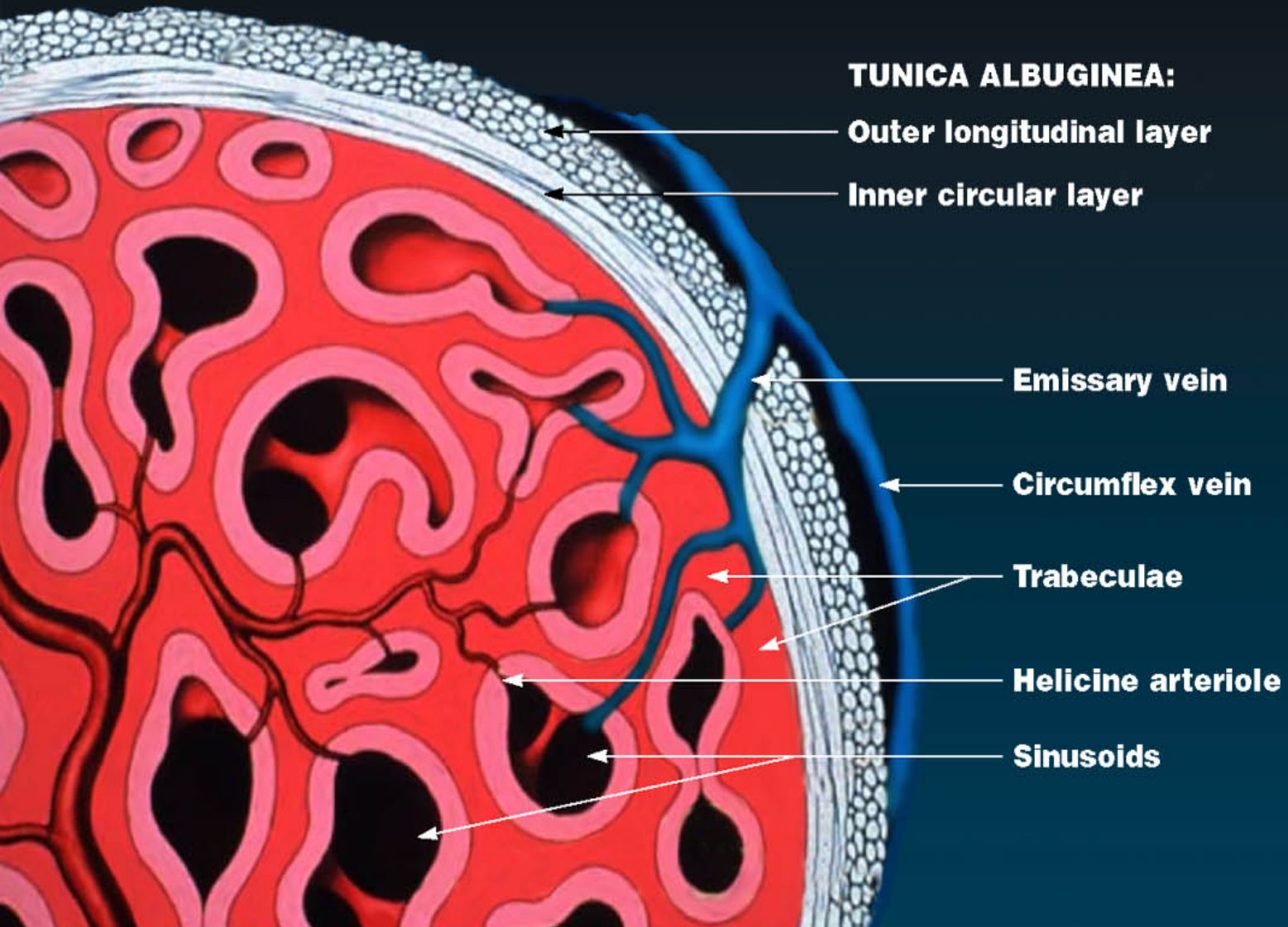
Cellular perspective of the erection pathway



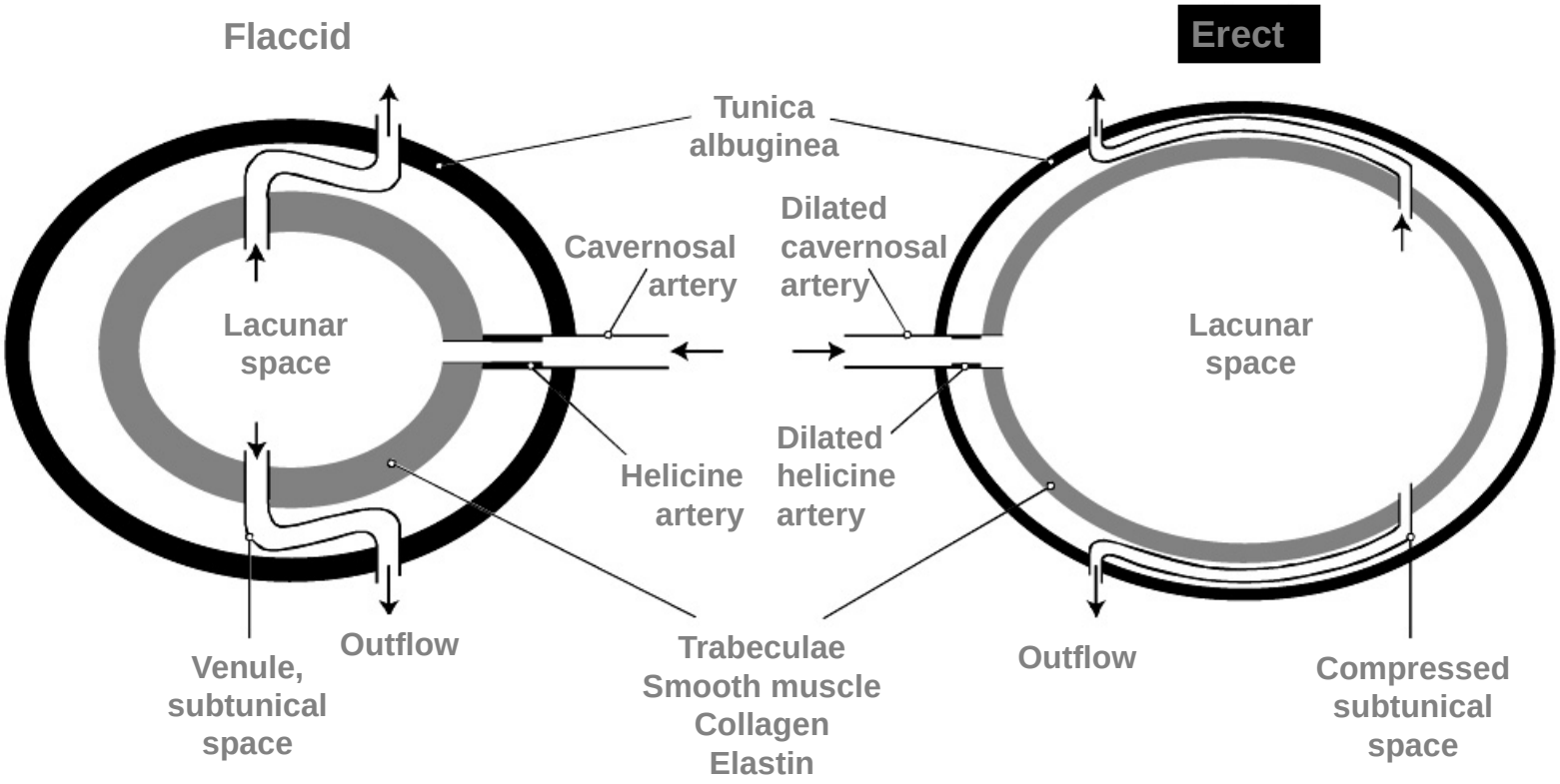
The signal (nitric oxide) is released from nerve endings or from endothelial cells and activates a cascade reaction, which ultimately leads to an increased cellular concentration of cGMP (cyclic guanosine monophosphate). This second messenger molecule induces a series of events that lead to smooth-muscle relaxation through a reduction in the intracellular calcium ion concentration. The enzyme PDE-5 (phosphodiesterase type 5) reverses this effect by metabolizing the cGMP to GMP rapidly.
The clinically important inhibitors of this enzyme (**sildenafil/Viagra, vardenafil /Lavitra and tadalafil/Cialis**) all act to promote smooth-muscle relaxation by their ability to allow cGMP to accumulate when nitric oxide is released, as is the case when sexual stimulation is present.

Fazio L & Brock G. CMAJ 2004;1701429-37

Physiology of Penile Erection



Physiology of Penile Erection



Adapted from Kramer et al, 1989.

Erectile Dysfunction:

- Erectile dysfunction is estimated to affect as many as 100 million men worldwide.
- Prevalence of erectile dysfunction increases with age, but erectile dysfunction is not a necessary consequence of aging.
- Social impact of erectile dysfunction can be significant.
- Erectile dysfunction is underdiagnosed due to a reluctance of patients and healthcare providers to discuss sexual function.
- Erectile dysfunction is an important public health problem.

Data for Responses - the ED Question by Age:

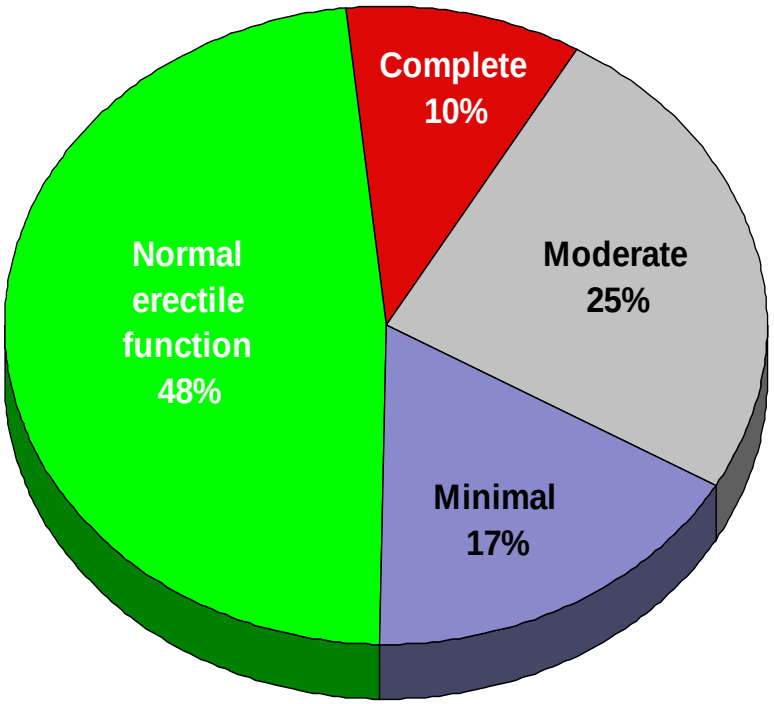
†The exact question asked was as follows: "How would you describe your ability to get and keep an erection adequate for satisfactory intercourse?"

Age, y	Response†			
	Always or Almost Always Able	Usually Able	Sometimes Able	Never Able
All	65.0	16.5	12.3	6.2
20-29	81.0	12.5	4.7	1.8
30-39	88.4	7.8	3.4	0.4
40-49	71.7	20.0	7.0	1.2
50-59	56.5	19.6	19.9	4.0
60-69	28.7	27.5	27.0	16.7
70-74	18.8	21.0	38.7	21.5
≥75	5.7	16.8	30.1	47.5

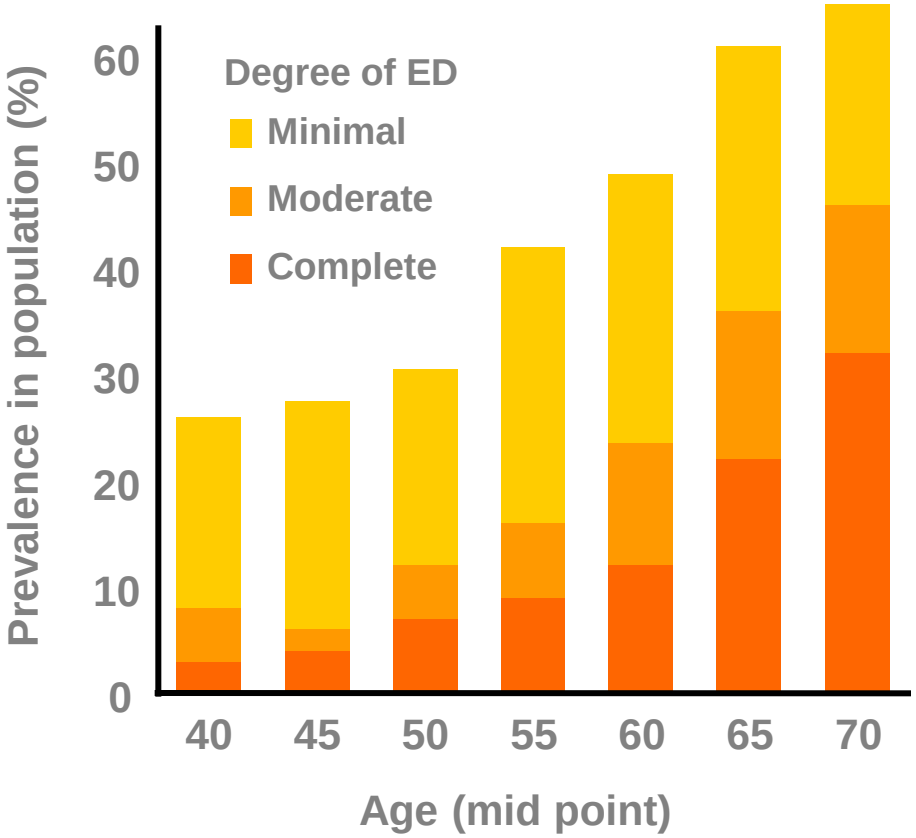
Saigal CS. Arch Int Med 2006;166: 2097-112
Corona G et al. Int J Impot Res 2004;16:395-402

High Prevalence of ED

Prevalence



Age and prevalence

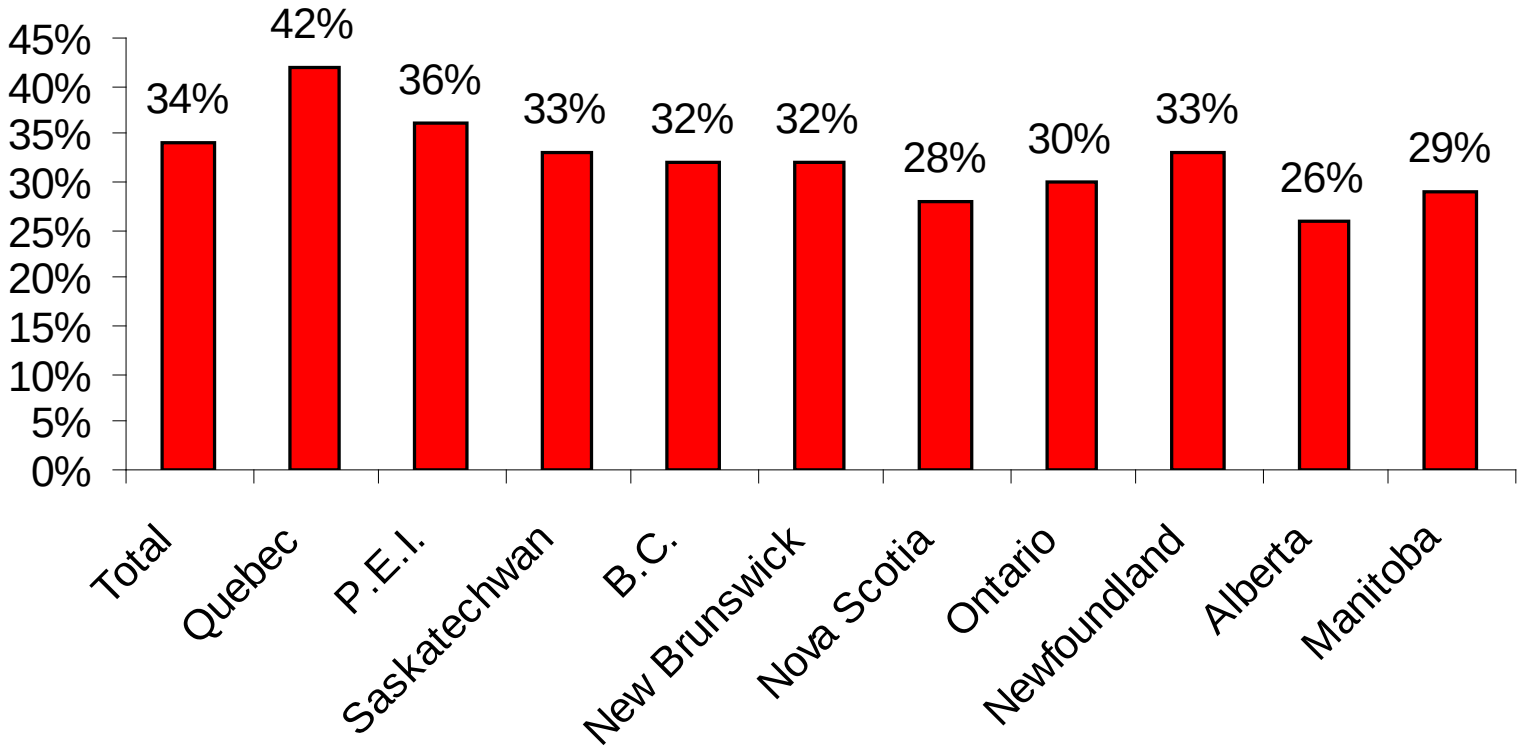


1. Feldman HA, et al. J Urol 1994;151:54-61.

2. McKinlay JB. Int J Impot Res 2000;12(suppl 4):S6-11.

Incidence of Erectile Dysfunction

- One-third (34%) of men over 40 suffer from ED.
- Levels are similar across the country, although are slightly higher in Quebec and P.E.I and slightly lower in Manitoba, Alberta and Nova Scotia.



Base: total men with SHIM scores of 21 and below (n=4,539)

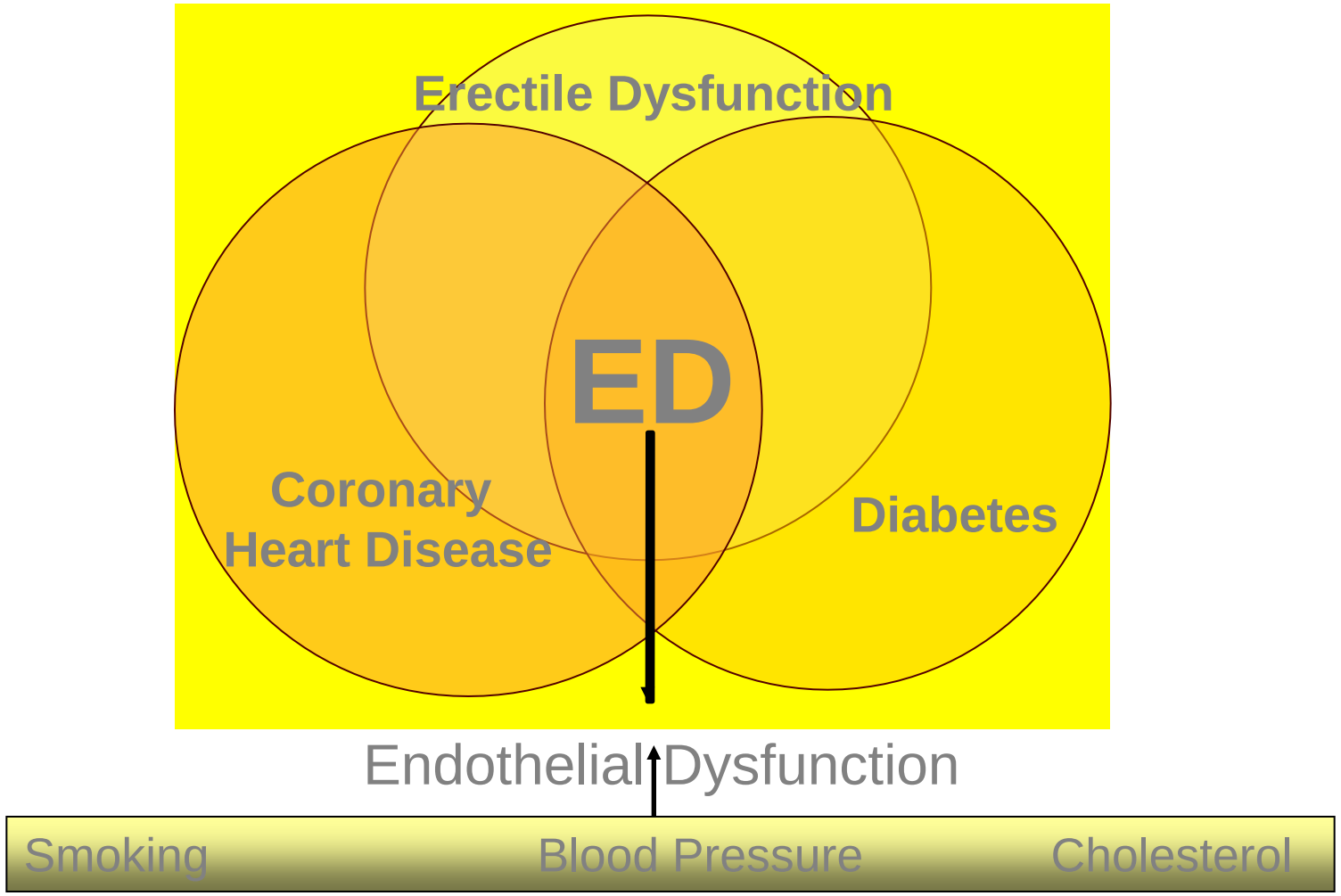
Associations Between ED and Various Comorbid States

Comorbid Diagnosis	ED Absent*	ED Present*	Prevalence of ED Among Men With a Comorbid Diagnosis, %
Diabetes mellitus	3 675 146	3 572 607	49.3
Obesity	16 206 023	4 990 098	23.5
Heart disease	3 055 592	3 344 306	52.3
Hypertension	13 124 111	7 184 282	35.4
Smoking	20 088 443	3 543 914	15.0

*Data are given as number percentage [95% confidence interval] of subjects for each age group. Percentages may not total 100 because of rounding.

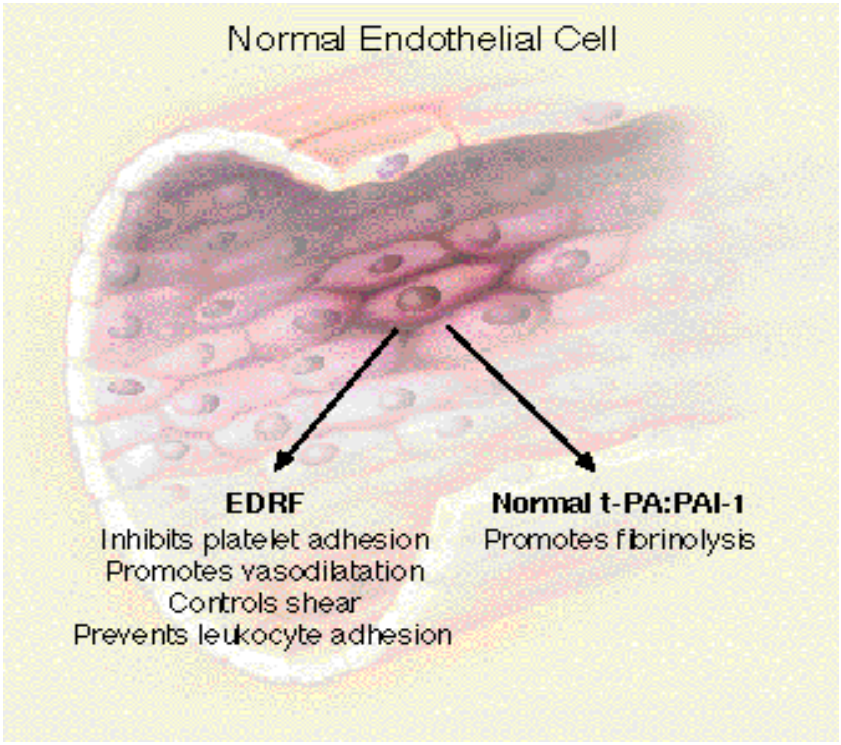
Saigal CS. Arch Int Med 2006;166: 2097-12

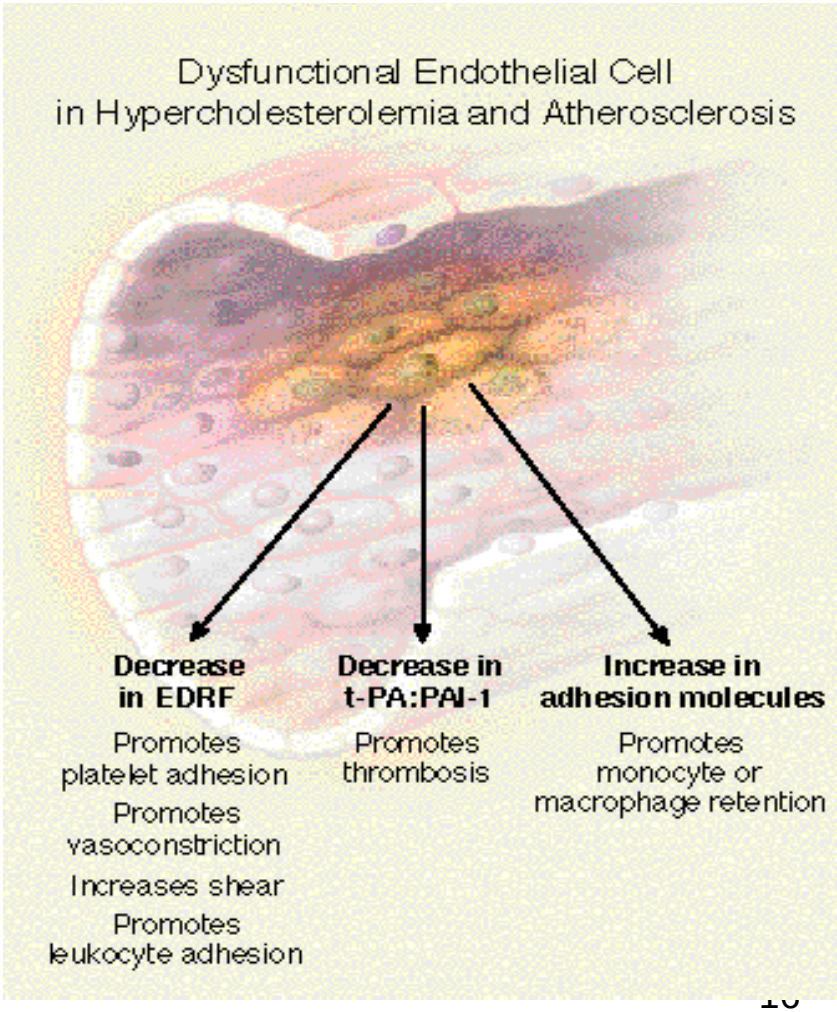
Risk Factors Associated with ED



Adapted from Jackson G. Int J Clin Pract. 2004;58:358-62.

Endothelial Function is Altered in Ischemic Heart Disease





EDRF: Endothelium derived relaxing factor
tPA: Tissue plasminogen activator
PAI-1: Plasminogen activator inhibitor-1

Clinical Clues to causes of sexual dysfunction

Finding	Cause
Rapid onset	Psychogenic
	Genitourinary trauma – eg. radical prostatectomy
Non-sustained erection	Anxiety
	Vascular steal
Depression or use of certain drugs	Depression
	Drug-induced
Complete loss of nocturnal erections	Vascular disease
	Neurologic disease

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Causes of Erectile Dysfunction

Classification	Causes
Aging	an indirect risk factor as it is associated with direct risk factors
Vasculogenic	Cardiovascular and ischemic heart disease, atherosclerosis, hypertension, peripheral vascular disease, venous incompetence, cavernosal disorders, major surgery (retroperitoneum), radiotheraphy (retroperitoneum)
Psychological/Psychogenic disorders	• Depression, Anxiety • Generalized type (lack of arousability, disorders of sexual intimacy), Situational type (eg, partner-related, performance-related issues, from distress
Neurogenic-central causes	Multiple sclerosis, multiple atrophy, Parkinson disease, tumors, stroke, disk disease, spinal cord disorders, Pudendal nerve injury
Neurogenic-peripheral causes	Diabetes mellitus, alcoholism, uremia, polyneuropathy, surgery (pelvic or retroperitoneal, radical prostatectomy)
Anatomic-structural	Pyronie disease, penile fibrosis (after pelvic readiotherapy or pelvic surgery), penile trauma (penile fracture), congenital curvature of the penis, micropenis, hypospadius, epispadius
Hormonal	Primary hypogonadism (eg, late onset gonadism), secondary hypogonadism/hypogonadotropic hypogonadism (eg, hyperprolactinemia), hyper- and hypothyroidism, Cushing disease, Addison disease
Drug- and/or substance-induced	• Antihypertensives (thiazides and β-blockers are most common), antidepressants, antipsychotics, antiandrogens, antihistamines • Marijuana use, alcohol abuse, narcotics, cigarette smoking*
Other disease	Diabetes mellitus, hyperlipidemia, renal failure, chronic obstructive lung disease

• Smoking has an adverse effect on erectile function as it accentuates the effects of other risk factors, eg vascular disease and hypertension.

• Wespes E et al. Eur Assoc Urol 2009
• Alberson M et al. Med Clin N Am 2011;95:201-12
• Fazio L & Brock G. CMAJ 2004;170:1429-37

Frequency of decreased erectile function rigidity and ejaculatory dysfunction by medication class

Medication class	Decreased erectile rigidity	Ejaculatory dysfunction
β-adrenergic antagonists	Common	Less common
Sympatholytics	Expected	Common
α_1 agonists	Uncommon	Uncommon
α_2 agonists	Common	Less common
α_1 antagonists	Uncommon	Less common*
Angiotensin-converting enzyme inhibitors	Uncommon	Uncommon
Diuretics	Less common	Uncommon
Antidepressants	Common†	Uncommon‡
Antipsychotics	Common	Common
anticholinergics	Less common	Uncommon

•Patients able to ejaculate, but retrograde ejaculation is seen in 5%-30%
† Uncommon with serotonin reuptake inhibitors
‡ Delayed or inhibited ejaculation with serotonin reuptake inhibitors.

Andreoli et al. Andreoli & Carpenter's Cecil Essentials of Medicine, 8th Ed, 2010. Saunders, Elsevier Inc.

How to approach and test

Basic diagnostic work-up in patients with erectile dysfunction

European Association of Urology Guidelines-Sexual Medicine

Recommendations
Clinical use of a validated questionnaire related to ED may help assess all sexual function domains and the effect of a specific treatment modality
Physical examination is needed in the initial assessment of ED to identify underlying medical conditions associated with ED
Routine laboratory tests, including glucose-lipid profile and total testosterone, are required to identify and treat any reversible risk factors and modifiable lifestyle factors
Specific diagnostic tests are indicated by only a few conditions

Hatzimouratidis K et al. European Association of Urology Guidelines-Sexual Medicine. European Urology 2010;57:804-14.

Basic diagnostic work-up in patients with erectile dysfunction

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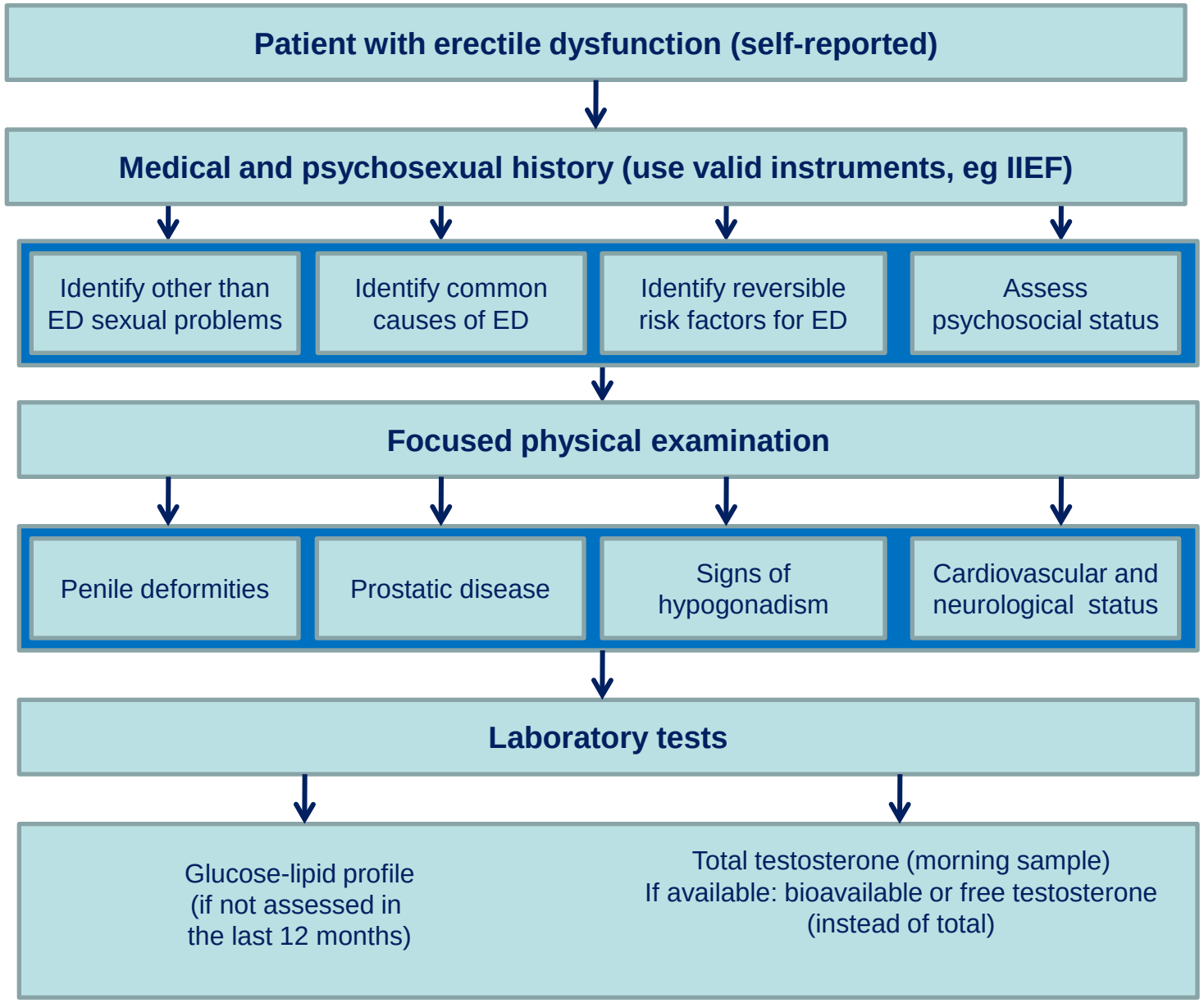

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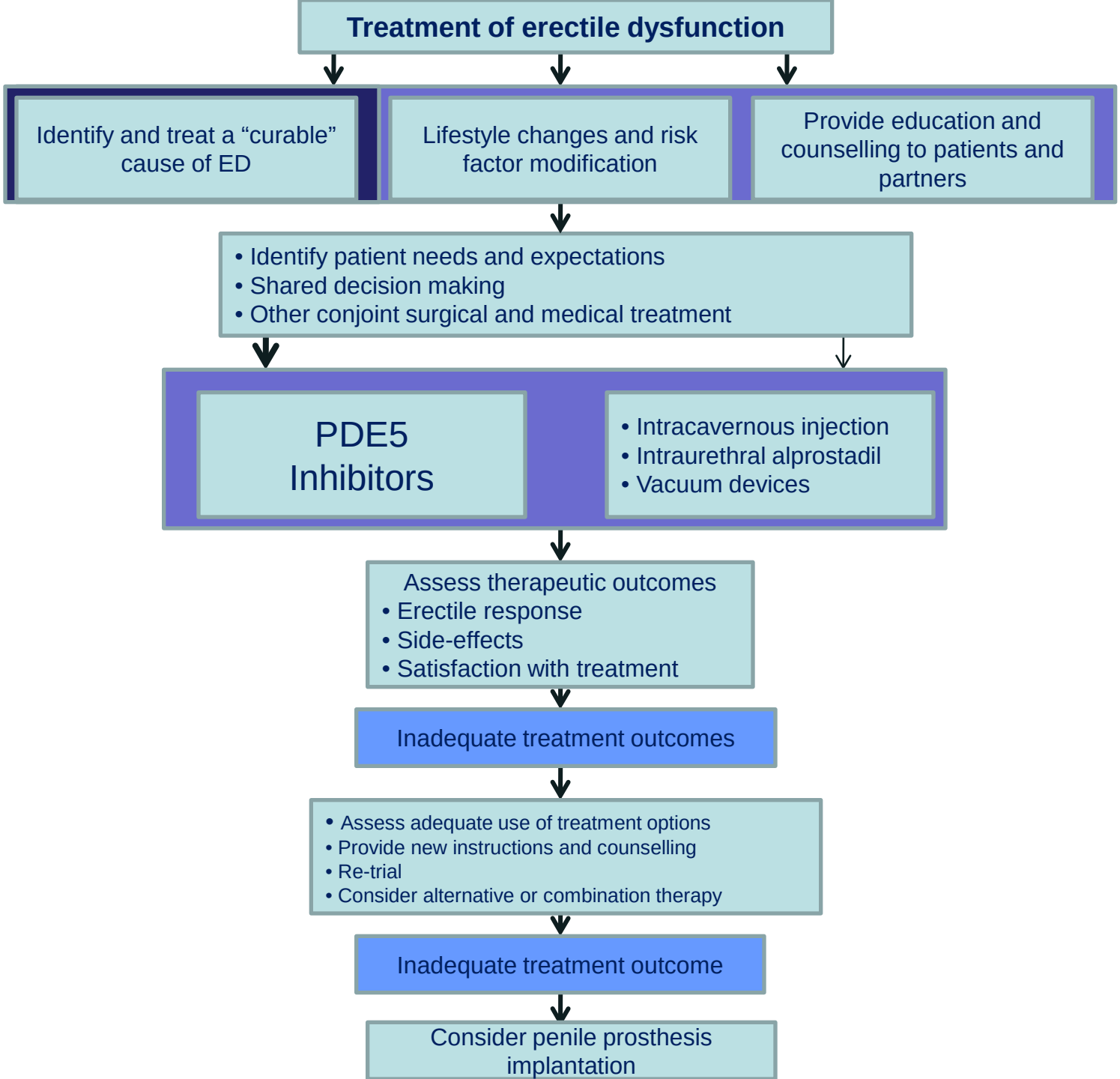
Specific examinations and tests

Indications for specific diagnostic tests	Specific diagnostic tests
Patients with primary erectile disorder (not caused by organic disease or psychogenic disorder)	Nocturnal penile tumescence and rigidity using Rigiscan Vascular studies • Intracavernous vasoactive drug injection • Duplex ultrasound of the cavernous arteries • Dynamic infusion cavernosometry and cavernosography • Internal pudendal arteriography
Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery	
Patients with penile deformities (eg, Peyronie's disease, congenital curvature) that might require surgical correction	
Patients with complex psychiatric or psychosexual disorders	Neurologic studies (eg, bulbocavernosus reflex latency, nerve-conduction studies)
Patients with complex endocrine disorders	Endocrinologic studies
Specific tests may also be indicated at the request of the patient or his partner	Specialised psychodiagnostic evaluation
For medicolegal reasons (eg, penile prosthesis implant, sexual abuse)	

Hatzimouratidis K et al. European Association of Urology Guidelines-Sexual Medicine. European Urology 2010;57:804-14.

Overview to initiate treatment



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Recommendations for the treatment of erectile dysfunction (ED)

Recommendations
Lifestyle changes and risk factor modification must precede or accompany ED treatment
Pro-erectile treatments must be given at the earliest opportunity after radical prostatectomy.
If a curable cause of ED is found, treat the cause first
PDE5-Is are first-line therapy.
Daily administration of PDE5-Is may improve results and restore erectile function
Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5-Is
Testosterone replacement restores efficacy in hypogonadic nonresponders to PDE5-Is
A vacuum constriction device can be used in patients with stable relationship
Intracavernous injection is second-line therapy.
Penile implant is third-line therapy.

Hatzimouratidis K et al. European Association of Urology Guidelines-Sexual Medicine. European Urology 2010;57:804-14.

The role of the Urology ED Clinic

SEXUAL HEALTH INVENTORY FOR MEN – (SHIM) IIEF-5

BASED ON THE

INTERNATIONAL INDEX OF ERECTILE FUNCTION

OVER THE PAST 6 MONTHS:

1. How do you rate your **confidence** that you could get and keep and erection?		Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	No sexual activity 0	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) you partner?	Did not attempt intercourse 0	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Did not attempt intercourse 0	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
When you attempted sexual intercourse, how often was it satisfactory for you?	Did not attempt intercourse 0	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5

SCORE_____

Add the numbers corresponding to questions 1-5. If your score is 21 or less, you may be showing signs of erectile dysfunction and may want to speak with your doctor.

Capital Health

Male Sexual Health Questionnaire

Date:___/___/___

Epidemiology

Age: ___ Sexual partner: Yes___ No__ Multiple__ Occasional __

Marital status: Married __ Single __ Divorced__ Widow__ Common-law__

Erections

Duration of ED: _____yrs ____mo Onset of ED: Sudden___ Gradual___ Intermittent_____

Erection Quality:

__Gr. 0 (No erection)
__Gr. 1 (Increase in size, not rigid)
__Gr. 2 (Not rigid enough to penetrate)
__Gr. 3 (Penetrate, not completely rigid)
__Gr. 4 (Completely rigid)

Morning :

__Gr. 0 (No erection)
__Gr. 1 (Increase in size, not rigid)
__Gr. 2 (Not rigid enough to penetrate)
__Gr. 3 (Penetrate, not completely rigid)
__Gr. 4 (Completely rigid)

Erection with self-stimulation: Yes___ No___ Morning: Always__ Often__ Rare__ Never__

Duration of erection: _____minutes

Pain with erection: Yes____ No____ Curve with erection: Yes____ No____

Comments:_____

Treatment to Date

Counseling_____: Successful: Yes___ No___

PDE-5____: Viagra___ Cialis___ Levitra____ MUSE____ Successful: Yes___ No___

Intercavernosal injection____: Type_____ Dose:____ Successful: Yes___ No___

Vacuum erection device____: Successful: Yes___ No___

Penile implant____: Successful: Yes___ No___

Comments:_____

Intercourse

Ejeculation: Normal____ Premature____ Delayed____ Retrograde____ None____

Orgasm: Normal____ Absent____ Painful____ Unknown____

Libido: Normal____ Low____ Increased____

Number of successful intercourses in the last 3 months: _____

Comments:_____

Social

Smoking: Ppd____ # yrs____ Ex-smoker____ Pipe____ Partner____

Alcohol: None____ Social____ Moderate____ Heavy____ Recovering Alcoholic____

Non-prescription drugs: No____ Yes____ (If yes, list in comment section below)

Stressors: Financial____ Employment____ Social____ Other_____

Comments:_____

Partner History

Relationship: Stable____ Unstable____ No current____

Discussed erectile difficulties with partner: Yes___ No___ Partner have sexual concerns: Yes___ No___

Partner's attitude: Supportive/Concerned____ Indifferent____ Angry/Resentful____

Comments:_____

Medical History

HTN____ Spinal Cord Injury____ Depression____ Stroke____

IHD____ Multiple Sclerosis____ Prostate cancer____ Diabetes: IDDM or NIDDM

PVD____ Parkinson's Disease____ Hypothyroid____

Comments:_____

Surgical History

CABG____ Pelvic radiation____ Thyroidectomy____ Hernia____

Vascular____ Back/Disc surgery____ A-P repair____ RRP____

Comments:_____

Medications

1_____ 3_____ 5_____ 7_____ 9_____

2_____ 4_____ 6_____ 8_____ 10_____

Comments:_____

Physical Examination

Vitals: BP: ____mmHg HR____ RR____ Weight____ Height____

General: Gynecomastia: Yes___ No___ Facial hair: Yes___ No___ Pubic hair: Yes___ No___

Femoral Pulses: Norm bilat/unilat___/___ Dec Bilat/unilat___/___ None bilat/unilat___/___

Penis: Normal___ Abnormal___ Peyronie's plaque___ Scars___

Testis: Normal___ Abnormal: Number___ Location___ Size___ Consistency___ (see comments)

Scrotal content: Normal___ Abnormal___ (see comments section)

Prostate: Normal___ Abnormal___ (see comments section) Size____ g

Abdominal: Normal___ Abnormal___ (see comments section)

Neurological: Normal___ Abnormal___ (see comments section)

Comments:_____

Investigations to Date

Lab: TT____ BAT____ LH____ FSH____ Prolactin____ PSA____ Other____

Comments:_____

Plan/Follow-up

_____

_____

_____

General Considerations before initiating pharmacological treatment for ED

- **Before initiating treatment, patients should be informed that sexual stimulation is essential for the efficacy of the drugs**
- **Although some may experience limited efficacy after the first trial, patients should be informed that results generally improve with repeated dosing**
- **A minimum of six attempts should be made before treatment is considered a failure**
  - **Daily tadalafil 2.5-5 mg**
- **Between 30-50% of non-responders may be converted to responders through**
  - **Re-education on proper dosing techniques**
  - **Dose escalation**

Alberson M et al. Med Clin N Am 2011;95:201-12
Berookhim BM et al. Med Clin N Am 2011;95:213-21

Oral treatments for male sexual dysfunction

Medication	Mechanism	Pros and Cons	Dosing	Cost
Sildenafil (Viagra)	Inhibits phosphodiesterase-5 enzyme, allowing cyclic GMP to accumulate within the penis	100 mg effective in 75% of men	Take one hour before sex and effective up to four hours	**$65.96 for 4 x 100 mg tabs**
		Side effects: headaches dyspepsia, vasodilatation, diarrhea and blue tinge of vision	Stimulation needed for erection	
		Contraindicated if using nitrates	Dose: 25-100 mg	
Vardenafil (Levitra)	Same as Sildenafil	Similar efficacy/side effects to Sildenafil, but no visual effects	Similar onset and duration of action as Sildenafil	**$70.82 for 4 x 20 mg tabs**
			Dose: 2.5-20 mg	
Tadalafil (Cialis)	Same as Sildenafil	Similar efficacy/side effects to Sildenafil, but no visual effects	Similar onset of action as Sildenafil	**$72.45 for 4 x 20 mg tabs**
			Duration of action is up to 36 hours	**$136.31 for 28 x 2.5 mg tabs**
		Low-back pain	Dose: 2.5-20 mg (daily 5 mg x 14 d)	

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The role of the Urology ED Clinic
Second-line therapy
Who should be referred

- **Patients in whom PDE5 pathway is disturbed/diminished NO availability will benefit far less from PDE5Is:**
    - **Degeneration of erectile tissue after radical prostatectomy**
    - **Severe diabetes**
    - **Atherosclerosis**
    - **Metabolic syndrome**
    - **Aging**
    - **Hypogonadism**

Alberson M et al. Med Clin N Am 2011;95:201-12

Suppositories, injections and devices for male sexual dysfunction

Treatment	Effect	Pros and Cons	Usage pattern	Cost
Suppository				
MUSE	alprostadil (prostaglandin E_1) in gel form delivered by applicator into meatus of penis	Can be used twice daily. Not recommended with pregnant partners.	Inserted 5-10 minutes before sex. Effects last one hour.	
Penile injection				
TriMix	Combines papaverine 18-25 mg, phentolamine 1-2 mg, and alprostadil 10-25 μg/mL	Effective in 92% of 116 patients in original study Prolonged erection, bleeding, fibrosis (?)	1-2 times/week	≈$60
Device				
Vacuum pump	Removes air from chamber over penis, creating a vacuum and drawing blood into penile cavernosae. Elastic tourniquet at base holds blood in penis.	One time expense. Safe if erection not maintained more that one hour (30 minutes). May not be acceptable to partner. Penis is hinged at base. May interfere with ejaculation.	Inflated just before sexual activity. Erection lasts until elastic ring removed	$70-700

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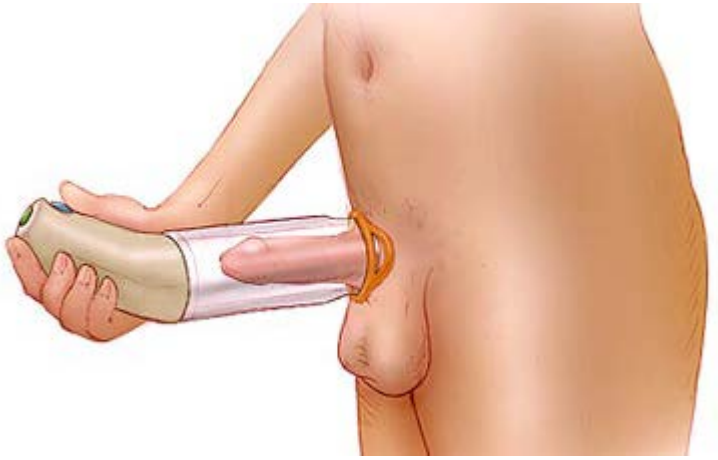
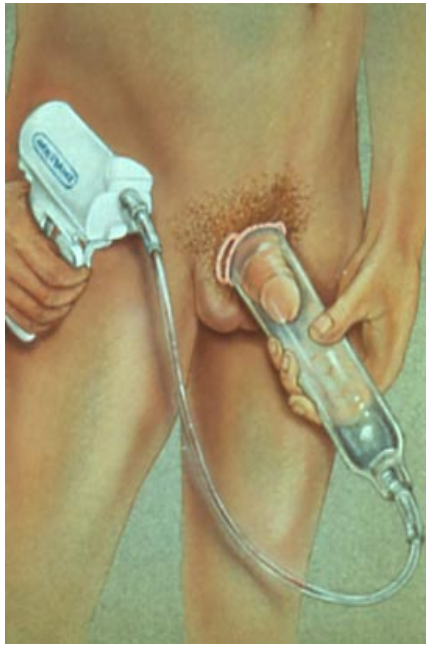
Education: Vacuum pump for erectile dysfunction

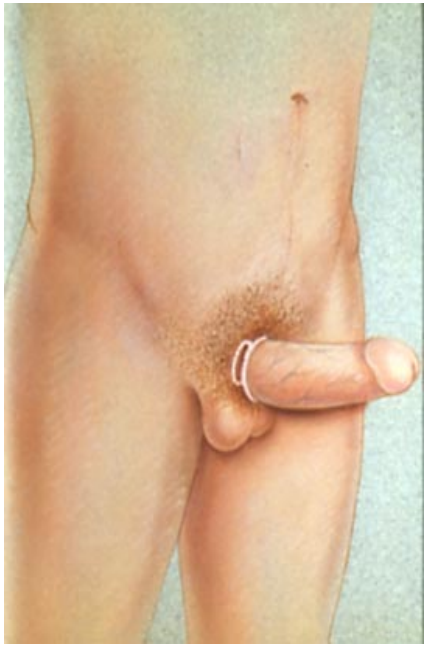
- Using a pump may be a good option if erectile dysfunction medications don't work and penile implant surgery isn't a good choice and may also help regain sexual function following prostate surgery.:
  - Less risk of side effects or complications
  - Cost: initial only
  - Non-invasive
  - Can be used with other treatments
  - Benefits following surgery

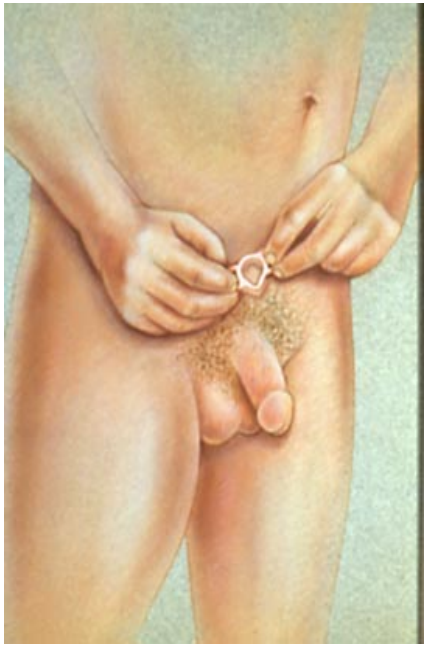


Treatments for Erectile Dysfunction

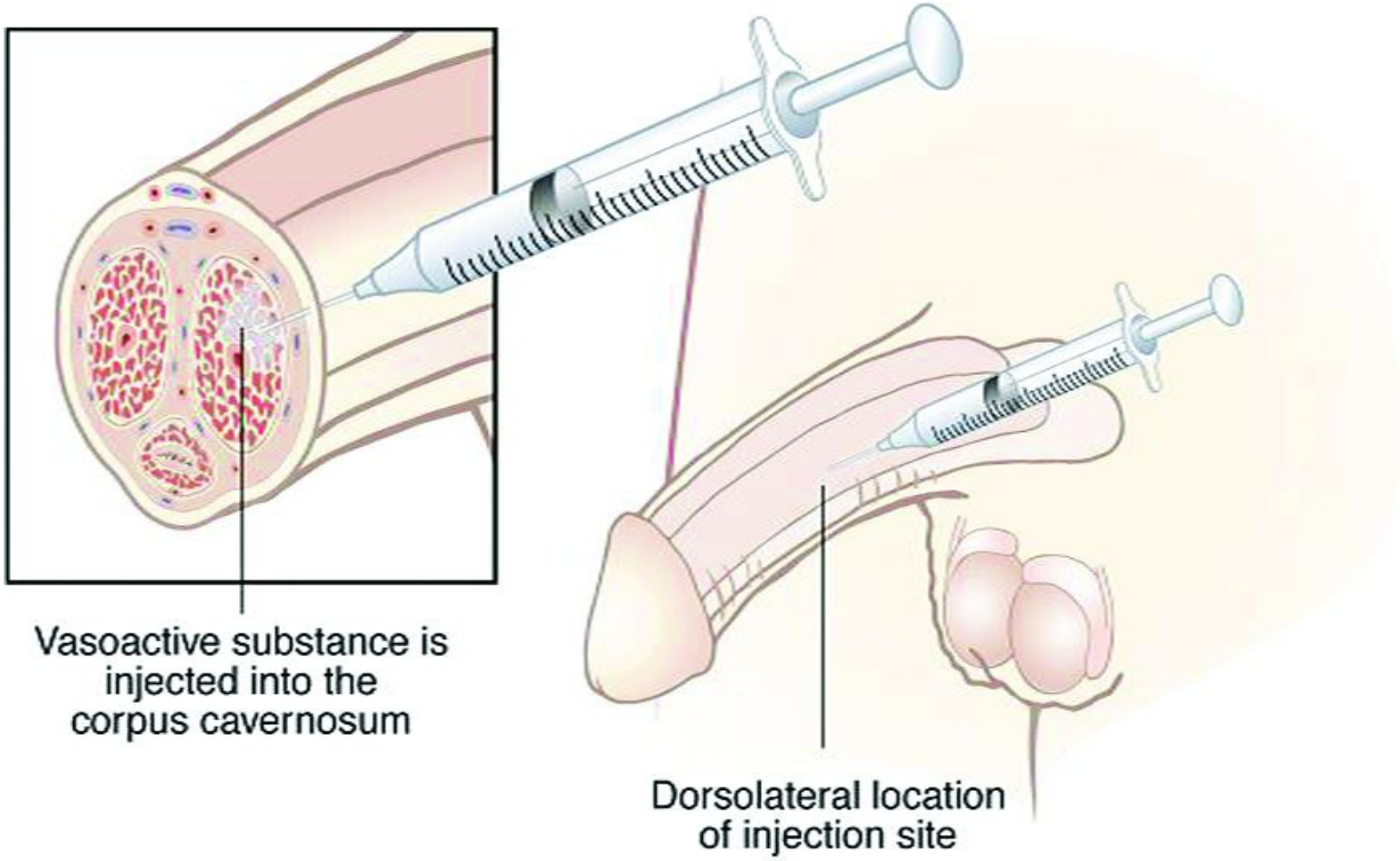
Vacuum and Constriction Device



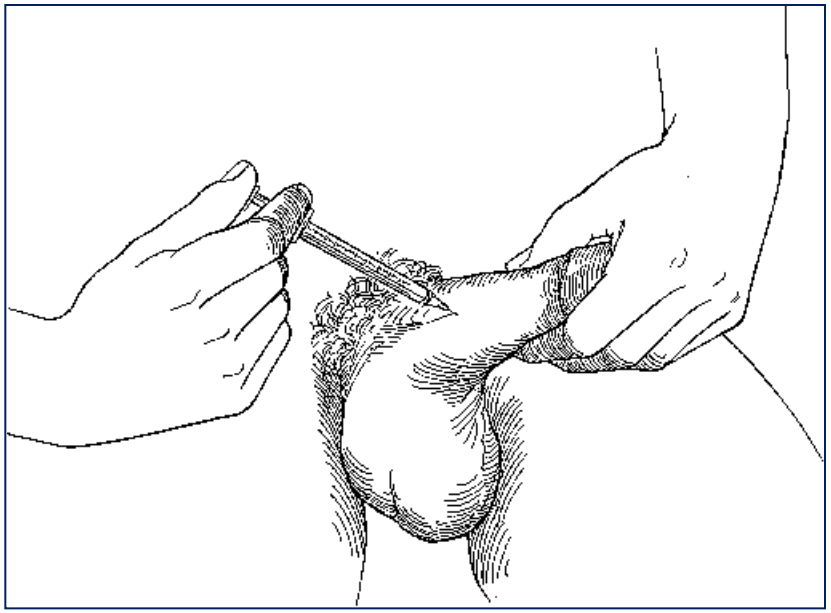


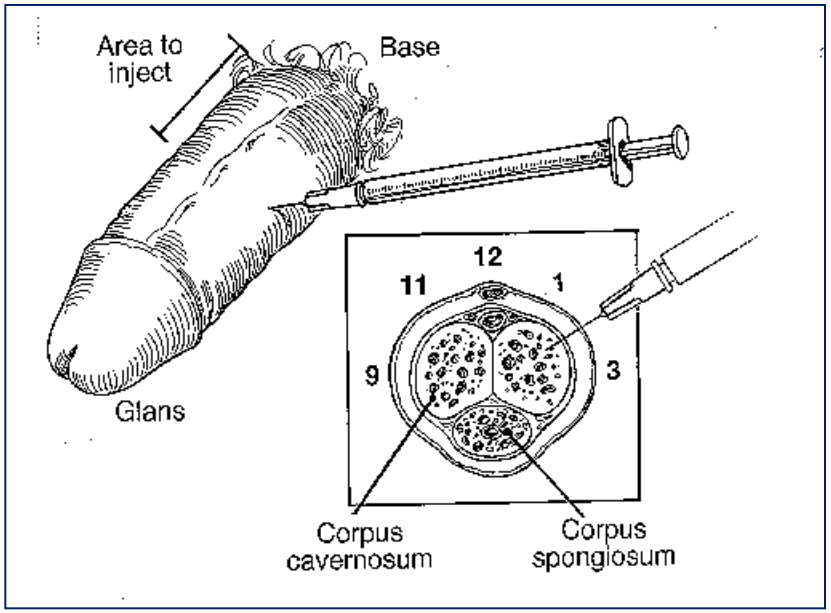


Intracavernosal injection



Education: Intracavernosal injections





- To be fully effective, the medication must be injected directly into one of the penile erectile bodies, the corpus cavernosum.
- The medication will diffuse to the other side of the penis so that symmetrical erection is achieved.

Intraurethral (IU) Therapy:

Alprostadil (MUSE®)

- Efficacy
  - **Moderately effective; clinical experience suggests 1 in 3 patients respond at home**
  - **Improved with constriction band (Actis®)**
- Adverse Effects
  - **Local: Penile pain**
  - **Systemic: Dizziness/hypotension, syncope**

Invasive Treatment Options

- Penile prosthesis implantation
- Venous/arterial surgery

Third-line therapy
Surgery

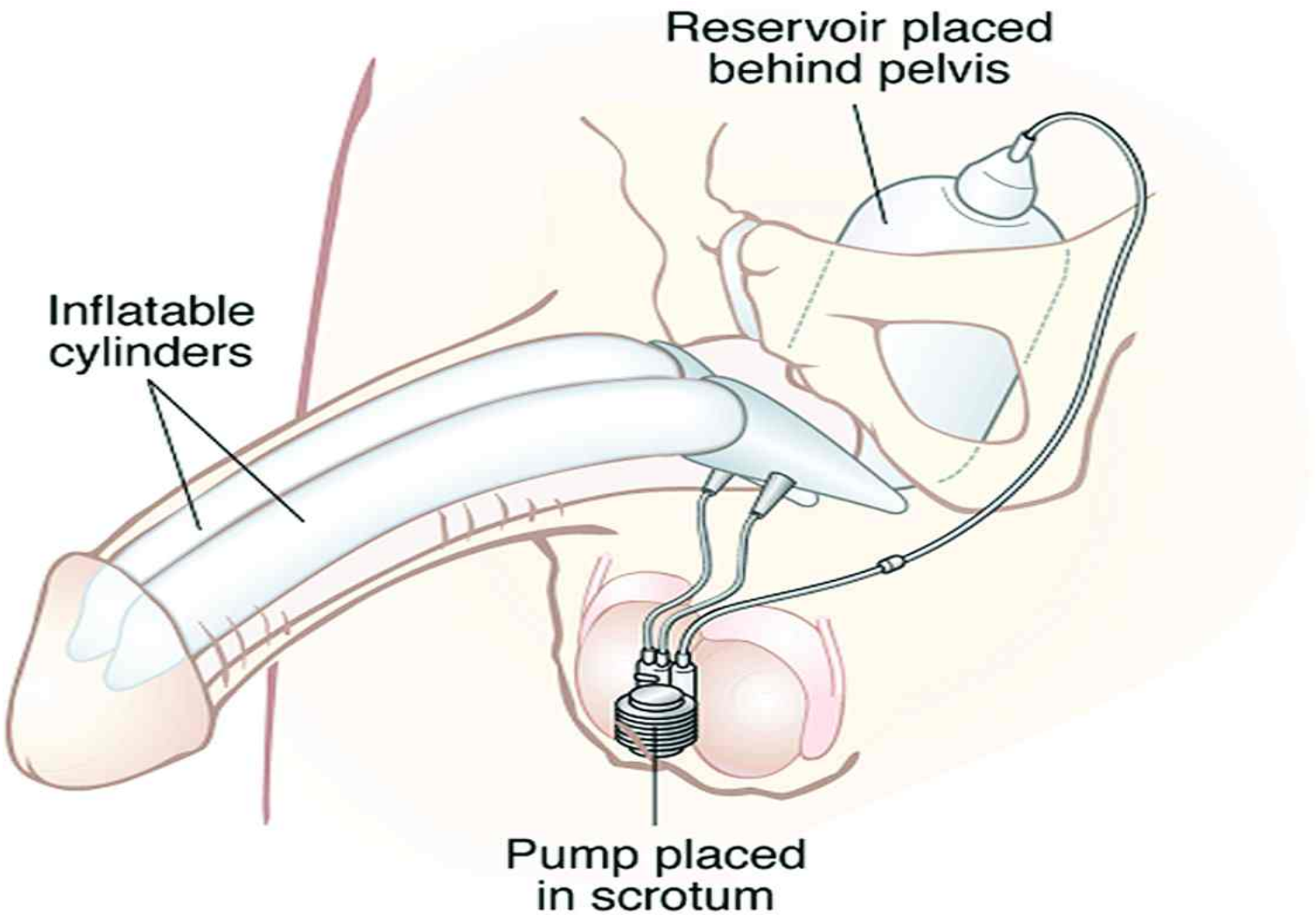
- Implantation of penile prosthesis in whom pharamacologic therapy is ineffective:
  - Inflatable
  - Malleable

- Patients should be made aware that surgery is irreversible

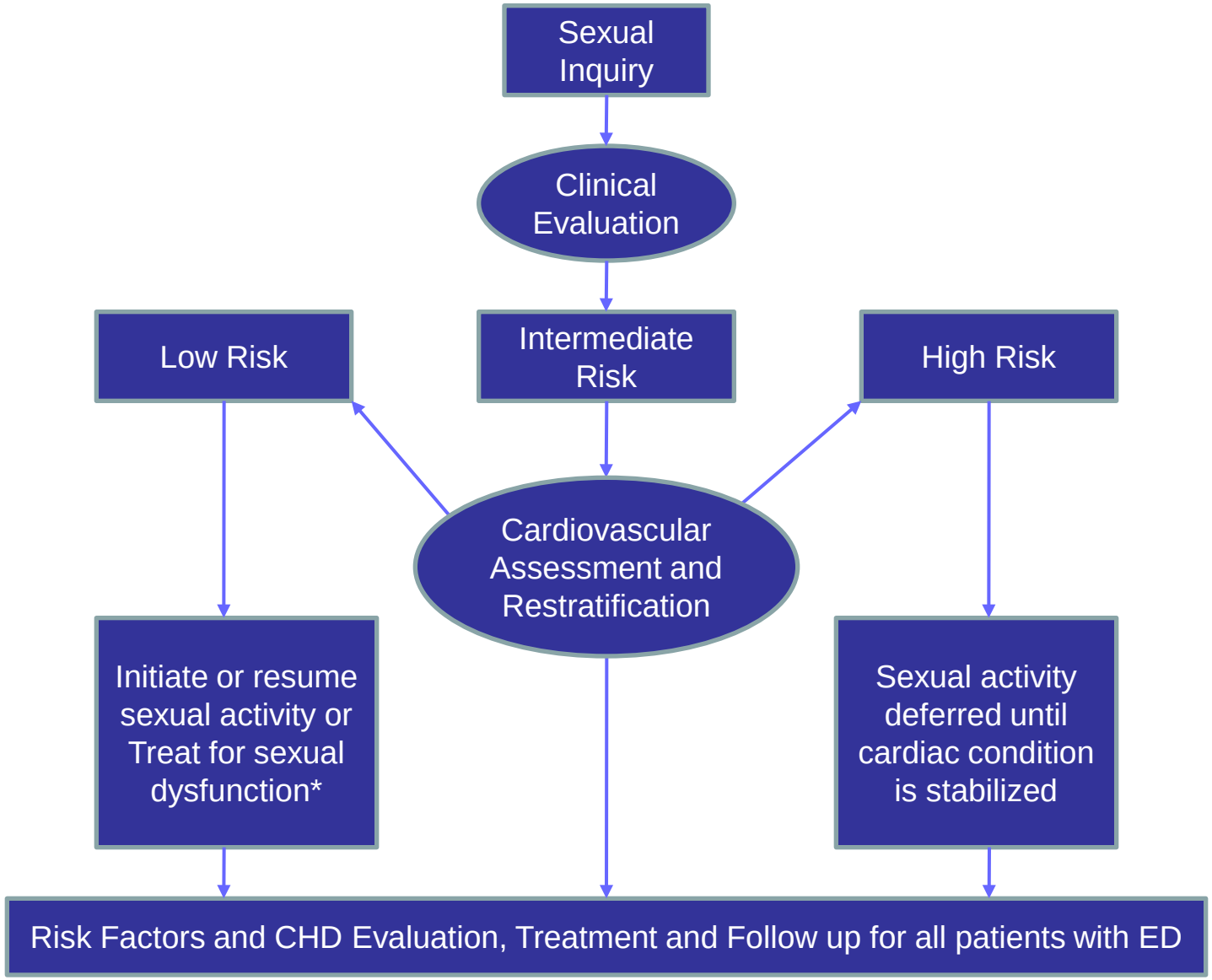
- Reported satisfaction rates are 70%-90%

- Adverse events:
  - Mechanical failure: 50% after a 10-year interval
  - Infection: 1-3%
  - Erosion: rare

PENILE PROSTHESIS



Sexual activity/dysfunction and cardiac risk: the Princeton II algorithm



- Kostis JB. Am J Cardiol 2005;96:313-321
- Alberson M et al. Med Clin N Am 2011;95:201-12
- Hackett et al. J Sex Med 2008; 5:1841-65

Other aspects of hypogonadism

the role of testosterone and bioavailable testosterone

Testosterone Deficiency Syndrome (TDS)

- Characterized by:
  - Deficiency in serum testosterone (T) levels
  - ± changes in receptor sensitivity to androgens
- Also known as:
  - Hypogonadism
  - Late-onset hypogonadism (LOH)
- Formerly termed: Andropause

Clinical Manifestations[1,2]

- *Decreased libido*
- *Decreased vitality*
- *Fatigue*
- *Mood changes*
- *Insomnia*
- *Anemia*
- *Delayed ejaculation*
- *Flushes*
- *Erectile dysfunction*
- *Decreased muscle mass*
- *Increased visceral body fat*
- *Testicular atrophy*
- *Weakness*
- *Osteopenia/osteoporosis*
- *Loss of facial, axillary and pubic hair*

Manifestations may present alone or in combination

1. Liu PY, et al. *J Clin Endocrinol Metab*. 2004; 89:4789-4796.
2. Zitzmann M, et al. *J Clin Endocrinol Metab*. 2006;91:4335-4343.

Prevalence

- Crude prevalence rate in Canada:
  - 25% of men aged 40 to 82 years are biochemically testosterone deficient[1]
- Prevalence rates expected to rise with life expectancy (LE)
  - Over the next 40 years LE in North America will increase by 4.8 years[2]
- Yet <10% of affected men receive T therapy[3]

1. Morley JE, et al. *Metabolism*. 2000;49:1239-1242.
2. United Nations DoEaS, Affairs Population D. World Population Prospects: The 2006 Revision, Highlights;Working Paper No. ESA/P/WP.202; 2007.
3. Carruthers M. *Aging Male*. 2009;12:21-28.

Barriers to Proper Diagnosis & Management

- Lack of physician awareness on associated diseases
  - Metabolic Syndrome (MetS)[1]
  - Diabetes[1]
  - Cardiovascular disease[2-4]
- Lack of physician awareness on the ability of testosterone replacement therapy (TRT) to reduce disease symptoms
- Controversy regarding prostate health[5]
- Lack of Canadian guidelines for distribution

1. Heufelder AE,et al. *J Androl*. 2009;30:726-733.
2. Malkin CJ, et al. *Heart*. 2004;90:871-876.
3. Pugh PJ, et al. *Eur Heart J*. 2003;24:909-915.
4. Malkin CJ,et al. *Eur Heart J.* 2006;27:57-64.
5. Wang C, et al. *Eur J Endocrinol.* 2008;159:507-514.

Clinical Disorders or Conditions Associated with a High Prevalence of Low T[1]

- Type II diabetes mellitus
- Metabolic syndrome
- HIV-associated weight loss
- Treatment with opioids, glucocorticoids or ketoconazole
- Osteoporosis or low trauma fracture at a young age
- End-stage renal disease and maintenance hemodialysis
- Chronic obstructive pulmonary disease
- Infertility
- Sellar region mass, disease, radiation or trauma
- Use of street drugs
- Liver disease

***** Patients with these clinical disorders/conditions are considered "high risk" and should be screened for testosterone deficiency**

1. Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91:1995-2010.
2. Morales A, et al. *CUAJ*. 2010;4:268-274.

Diabetic Men Are at High Risk

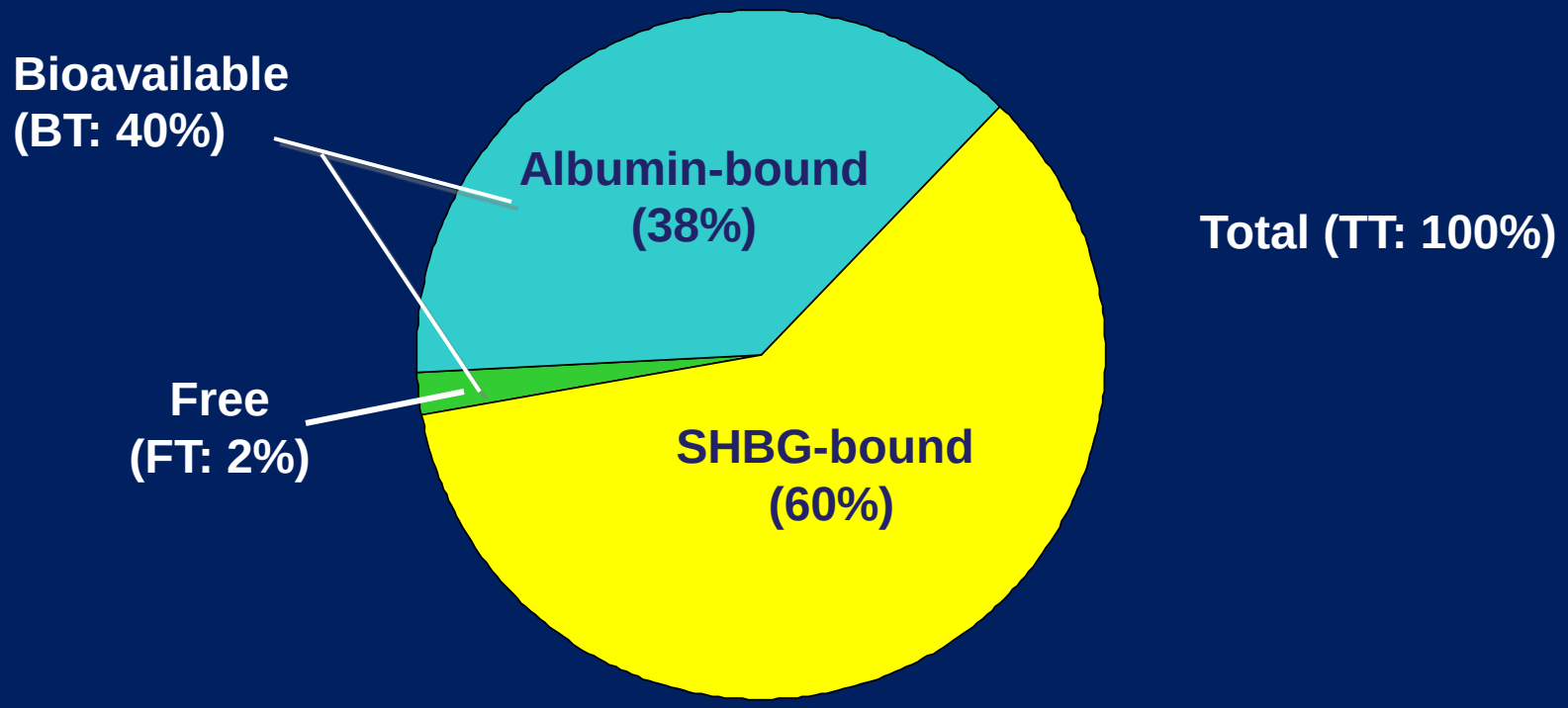
- 33% of men with diabetes have hypogonadism
- 34%-45% of men with diabetes have ED[2]
- Men with higher levels of T (15.6-21.0 nmol/L) have a 42% lower risk of Type II diabetes

***** Men with Type II diabetes should be screened for testosterone deficiency[4]**

1. Dhindsa S, et al. *J Clin Endocrinol Metab*. 2004;89:5462-5468.
2. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2008;32:S1-S201.
3. Ding EL, et al. *JAMA*. 2006;295:1288-1299.
4. Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91:1995-2010.

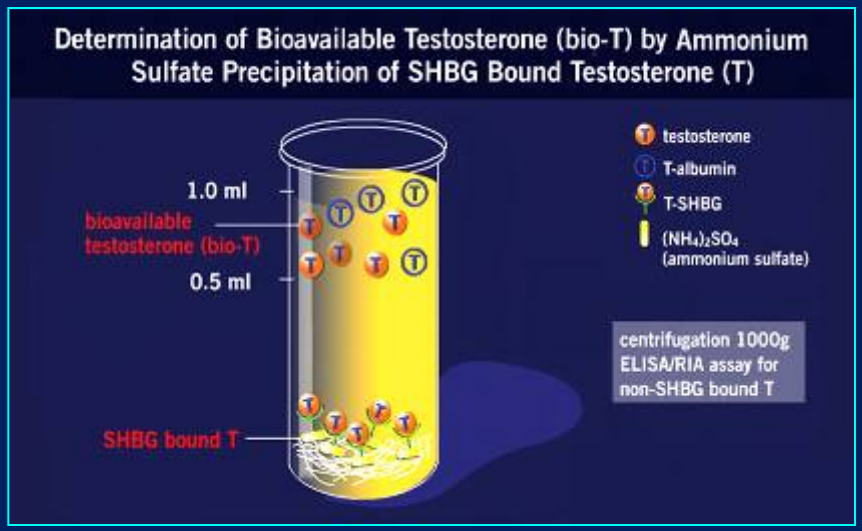
Measurement Tests for T

Forms of T


Bioavailable
(BT: 40%)
Albumin-bound
(38%)
Free
(FT: 2%)
SHBG-bound
(60%)
Total (TT: 100%)

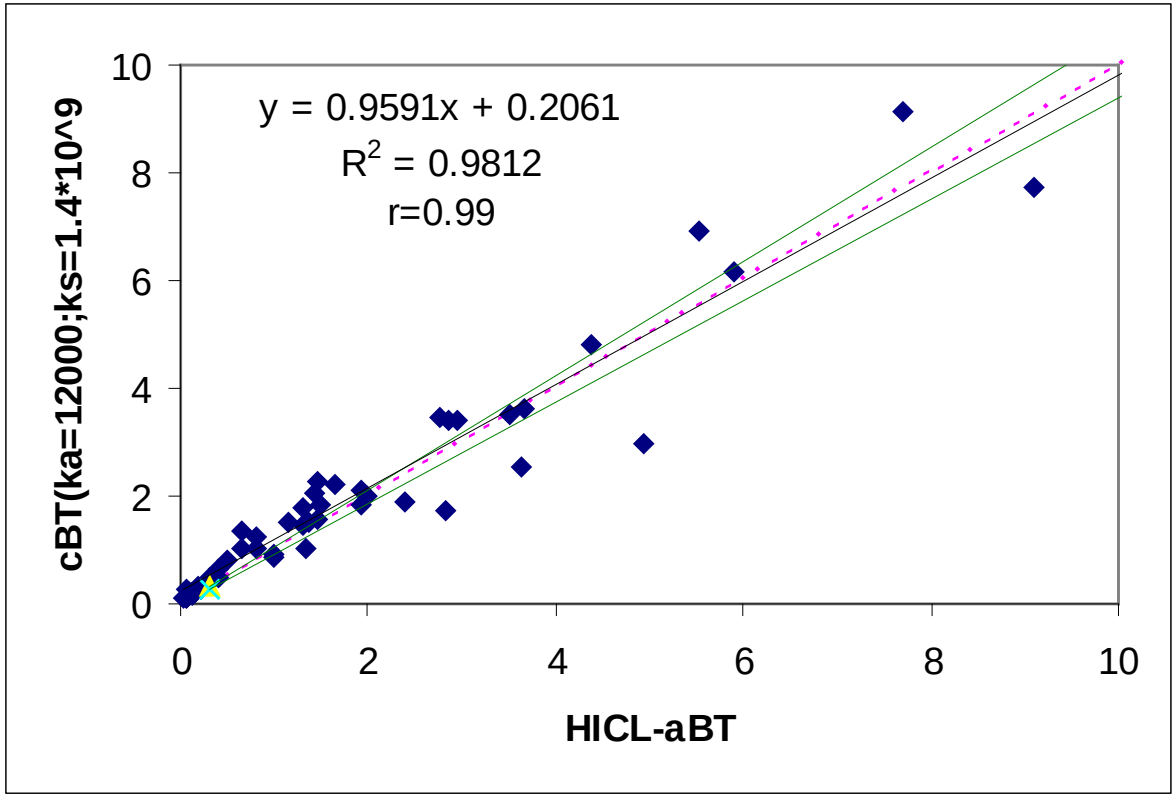
Measurement Tests for T

- Measured BT is the gold standard
  - Ammonium sulphate precipitation correlates well with symptoms of TDS[1]
- If measured BT is unavailable or unaffordable, acceptable alternatives are[2,3]:
  - TT *or*
  - Calculated free T (cFT) *or*
  - Calculated bioavailable T (cBT)
  - Free calculator for cFT and cBT4: http://www.issam.ch/freetesto.htm

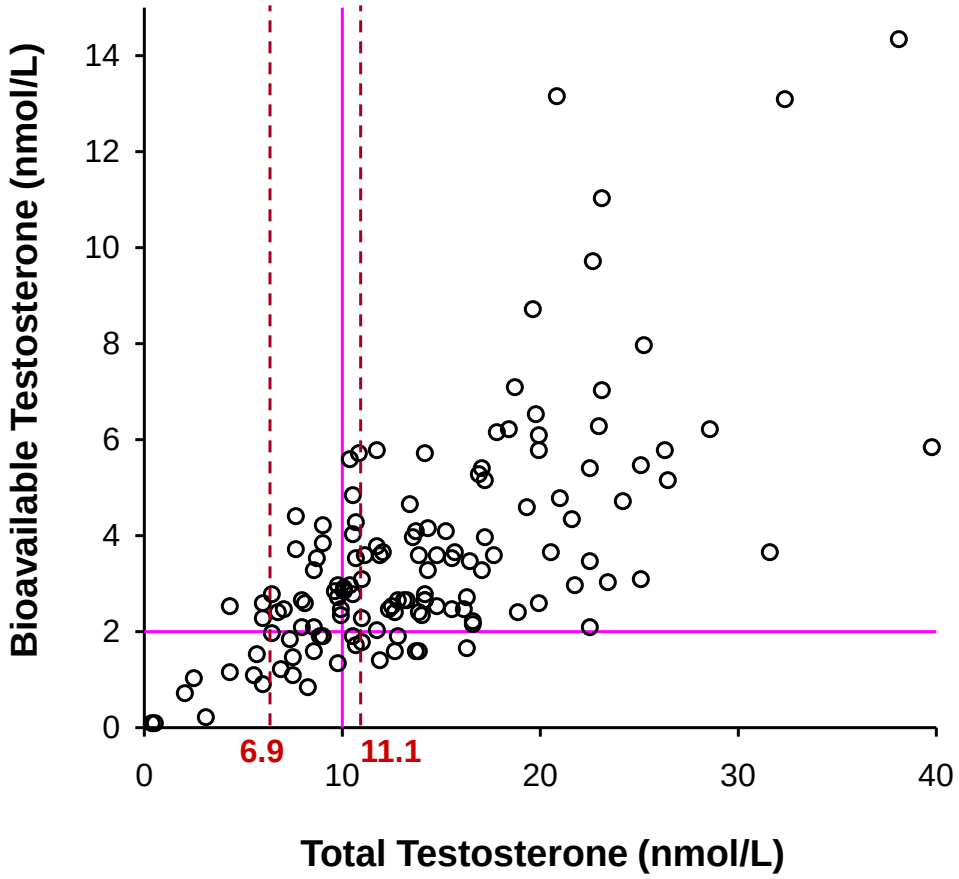


1. Rosner W, et al. *J Clin Endocrinol Metab.* 2007;92:405-413.
2. Vermeulen A, et al. *J Clin Endocrinol Metab*. 1999;84:3666-3672.
3. Morales A, et al. *CUAJ*. 2010;4:268-274.
4. International Society for The Study of the Aging Male. Free & Bioavailable Testosterone calculator. http://www.issam.ch/freetesto.htm. Accessed March 29, 2010.

Calculated Bioavailable Testosterone at Capital Health to Hospitals In Common Laboratory-Toronto



Low levels of bioavailable testosterone can be present within normal total testosterone levels



Rosner W et al: Endocrine Society Position Statement.
J Clin Endo Metab 2007;92:405-13

Low/Borderline T Requires Confirmation

- Repeat T
- Plus, measures of:
  - SHBG
  - Luteinizing hormone (LH)
  - Follicle-stimulating hormone (FSH)
  - Prolactin
- Other tests/serum markers that may be included:
  - Complete blood count (CBC)
  - Ferritin
  - Thyroid-stimulating hormone (TSH)
  - Prostate-specific antigen (PSA)
  - Digital rectal exam (DRE)

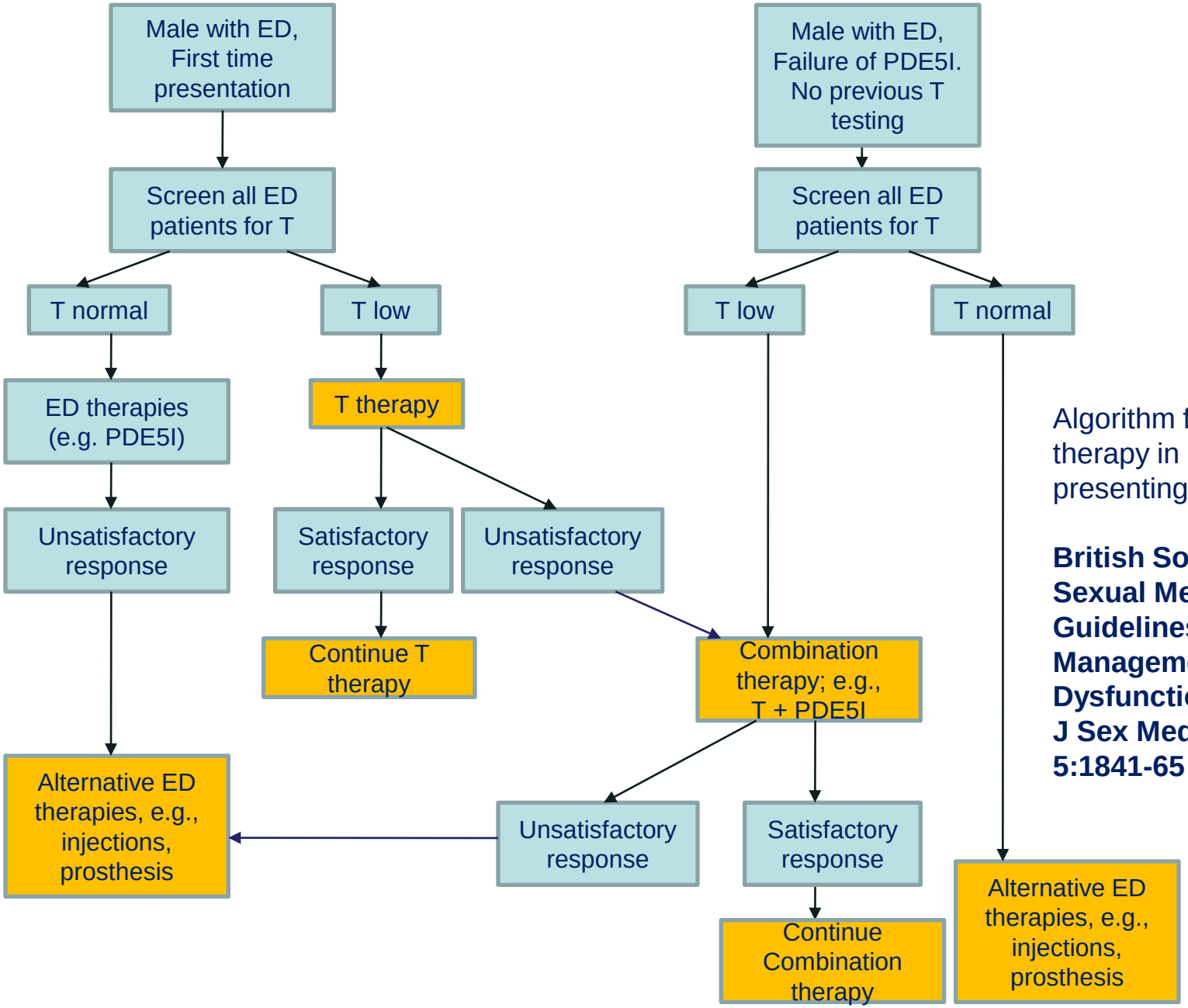
Hypogonadism and Testosterone Replacement Therapy

British Society for Sexual Medicine Guidelines on the Management of Sexual Dysfunction

Hackett et al. J Sex Med 2008; 5:1841-65

- Androgen deficiency increases with age but its management remains controversial
- As well as sexual dysfunction, it is also associated with Osteoporosis, Dyslipidemia, NIDDM, Metabolic syndrome, Depression

- Diagnosis of androgen deficiency:
  - Non-specific clinical features
  - Blood testing for testosterone:
    - Should be drawn in the morning: 08:00-11:00
    - Repeated after 2-3 weeks as a single assay may be misleading (pulsatile release)
    - Men with total serum testosterone < 11 nmol/L might benefit from a trial of testosterone replacement therapy for ED and should be managed according to the BSSM Guidelines.
    - There is no evidence that giving testosterone to men with ED and normal androgen levels restores or improves their erectile function
    - Hypogonadal men restored to the eugonadal state with testosterone replacement may experience:
      - A general improvement in sexual function
      - Improved erection
      - Restored or enhanced responsiveness to PDE5 inhibitors



Algorithm for androgen therapy in a man presenting with ED

British Society for Sexual Medicine Guidelines on the Management of Sexual Dysfunction
J Sex Med 2008; 5:1841-65

Testosterone Therapies

Intramuscular (IM) Injectables

Generic Name	Dosage
Testosterone cypionate[1] (Depo-Testosterone)	200 mg every 2 weeks (Max. dose 400 mg per month)
Testosterone enanthate[2] (Delatestryl)	100-400 mg every 1-4 weeks

1. Prescribing Information: Depo-Testosterone (testosterone cypionate injection USP, Sterile Solution) 100 mg/mL. Kirkland, Québec: Pfizer Canada Inc.; 2007.
2. Prescribing Information: Delatestryl (testosterone enanthate, Solution for Injection) 200 mg/mL. Mississauga, Ontario: Theramed Corporation; 2007.

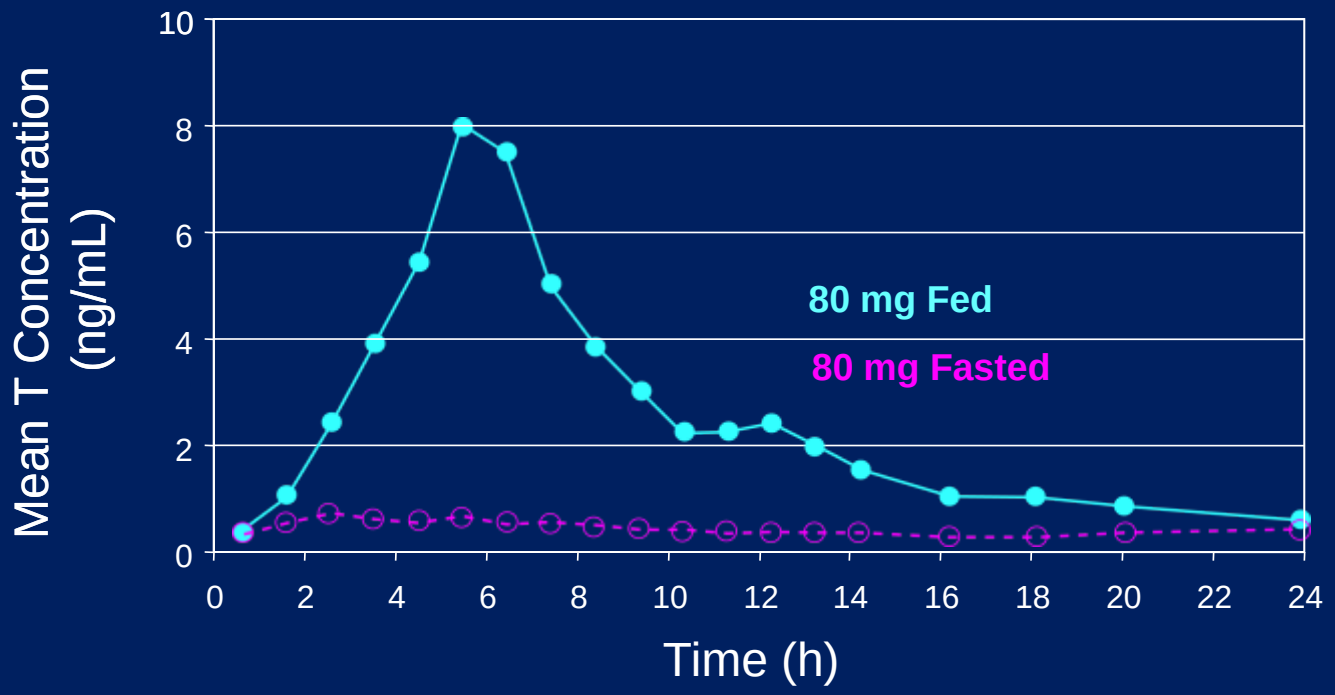
Oral Medication

Generic Name	Dosage
Testosterone undecanoate[1,2] (Andriol)	120-160 mg daily divided in 2 doses[a]

This dose should be taken for 2-3 weeks. Subsequent dosages may be reduced to 40-120 mg daily.

1. Product Monograph: Andriol (testosterone undecanoate capsules) 40 mg. Kirkland, Québec: Schering-Plough Canada Inc.; 2008.
2. Product Monograph: pms-Testosterone (testosterone undecanoate capsules) 40 mg. Montréal, Québec: Pharmascience Inc.; 2009.

The Effect of Food on Absorption of Testosterone Undecanoate[1]



- T undecanoate should be taken with a normal meal or breakfast to achieve proper T levels

1. Product Monograph: Andriol (testosterone undecanoate capsules) 40 mg. Kirkland, Québec: Schering-Plough Canada Inc.; 2008.

Transdermal T Gels

Testosterone 1% Gel (Testosterone USP[1])

Testosterone 1% Gel (Testosterone, Ph.Eur[2])

- Dosage: 5-10 g daily, to deliver 50-100 mg of testosterone

1. Product Monograph: AndroGel (testosterone gel) 1%. Markham, Ontario: Abbott Laboratories, Limited.; 2010.
2. Product Monograph: Testim (testosterone gel) 1%. Malvern, Pennsylvania: Auxilium Pharmaceuticals Inc.; 2009.

Side Effects of T Formulations

Reported Side Effects for Testosterone Products[1,2]	
AS Reaction: Irritation, Redness, Rash	Increased PSA
Acne	High Blood Pressure
Enlarged Prostate	Increased RBC Count
Change in Mood / Depression	Prolonged or Painful Erection
Sleep Disturbances	Aggression / Aggressive Behaviour
Breast Enlargement	Breast Pain
Hair Loss / Baldness	Weight Gain
Headache	Dizziness

1. Prescribing Information: Depo-Testosterone (testosterone cypionate injection USP, Sterile Solution) 100 mg/mL. Kirkland, Québec: Pfizer Canada Inc.; 2007.
2. Prescribing Information: Delatestryl (testosterone enanthate, Solution for Injection) 200 mg/mL. Mississauga, Ontario: Theramed Corporation; 2007.
3. Product Monograph: Andriol (testosterone undecanoate capsules) 40 mg. Kirkland, Québec: Schering-Plough Canada Inc.; 2008.
4. Product Monograph: pms-Testosterone (testosterone undecanoate capsules) 40 mg. Montréal, Québec: Pharmascience Inc.; 2009.

Potential Benefits of TRT

- **Enhanced:**
  - Overall health/survival
  - Strength
  - Sexual desire
  - Energy
  - Emotional well-being
  - Cognition
  - Bone mineral density
  - Glycemic control
  - Cardiovascular health
  - Erectile function
  - May improve some symptoms of MetS
- **Reduced:**
  - Body fat

MetS = Metabolic Syndrome

Contraindications to TRT

- TRT is absolutely contraindicated in patients with:
  - Breast cancer
  - Prostate cancer
  - *** PSA/DRE prior to initiating TRT: refer if abnormal
- TRT may worsen:
  - Erythrocytosis
  - Untreated obstructive sleep apnea
  - Severe congestive heart failure
  - *** Do not initiate TRT until these medical issues have been addressed
- TRT is not suggested during biological fatherhood as it may cause infertility in young men
- TRT can reduce overall body fat content

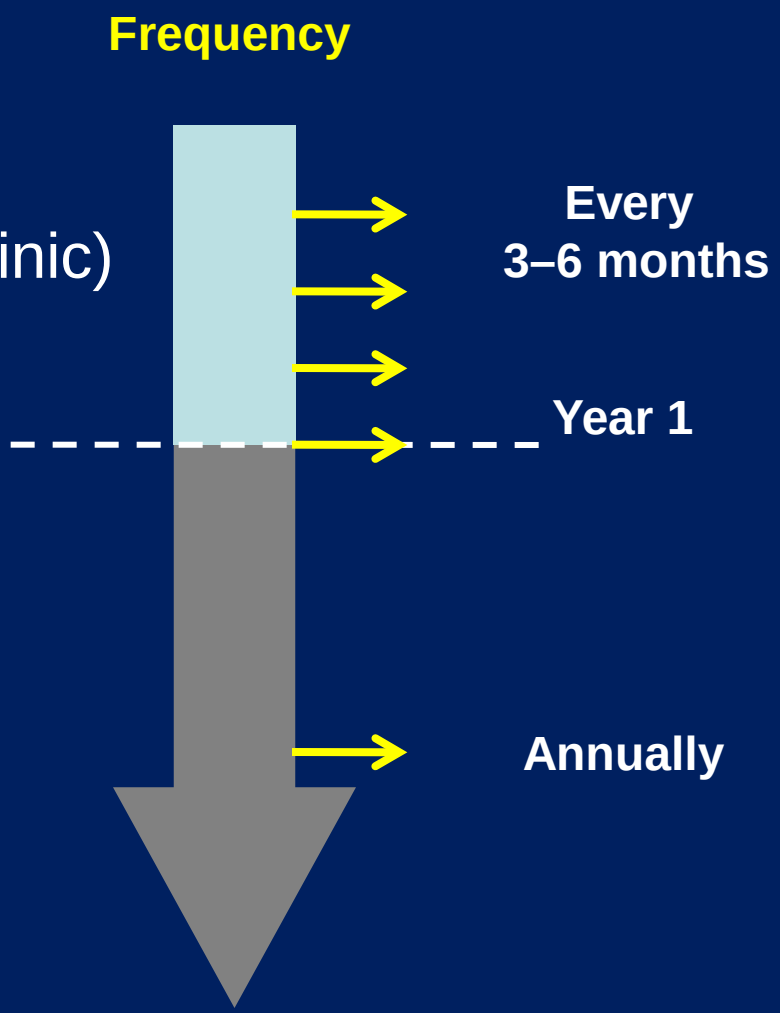
1. Bhasin S, et al. *J Androl*. 2001;22:718-731.
2. Calof OM, et al. *J Gerontol A Biol Sci Med Sci*. 2005;60:1451-1457.
3. Rhoden EL, et al. *N Engl J Med*. 2004;350:482-492.
4. Wang C, et al. *J Clin Endocrinol Metab*. 2000;85:2839-2853.

Alternative Treatments to TRT

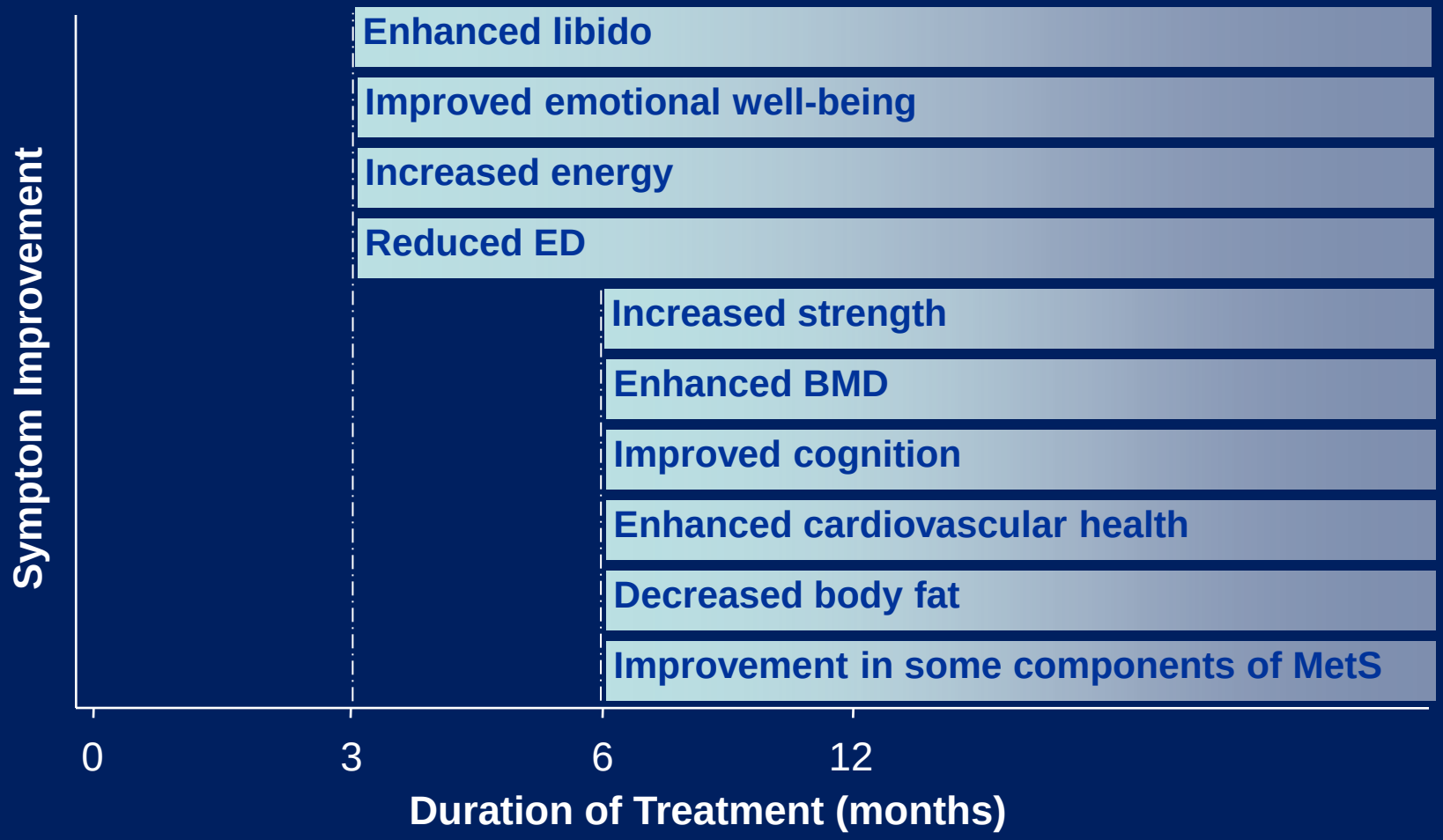
Approach	Anticipated Outcome(s)
Diet and exercise	Healthy weight reduction[1] Improved muscle strength[2] Enhanced emotional well-being
Bisphosphonates	Increased BMD[3]
Antidepressants	Enhanced emotional well-being
Continuous Positive Airway Pressure (CPAP)	Treatment of sleep apnea[4]
Phosphodiesterase-5 inhibitors	Improved erectile function[5]
Discontinuation of opioids	Improvement in multiple symptoms of hypogonadism[6]

Monitoring

- At each appointment monitor:
  - Symptom response (clinic)
  - Changes in blood parameters
    - T
    - Hemoglobin
    - Hematocrit
  - PSA/DRE
    - Refer if abnormal



Timeline of Symptom Improvement



MetS = Metabolic Syndrome

1. Morales A, et al. *CUAJ*. 2010;4:268-274.

Other endocrine disorders in hypogonadism and ED

Hyperprolactinemia

- Hyperprolactinemia is associated with ED, loss of sexual interest and anorgasmia
- Frequently accompanied by androgen deficiency
  - because high prolactin suppresses LH production leading to hypogonadism
- High prolactin should be excluded in all men with reduced sexual interest, however moderate elevation of prolactin is unlikely to cause ED
- Causes of hyperprolactinemia
  - Medical and physical stress
  - Drugs: major tranquilizers
  - Prolactin secreting pituitary tumor
  - Chronic renal failure
  - big-big prolactin: a complex of prolactin and immunoglobulin

Hyper- and hypothyroidism

Acknowldgement

Thanks to Drs. John Grantmyre and Jerzy Gajewski for the slides and educational material he provided

Thank you