Treatment of Erectile Dysfunction

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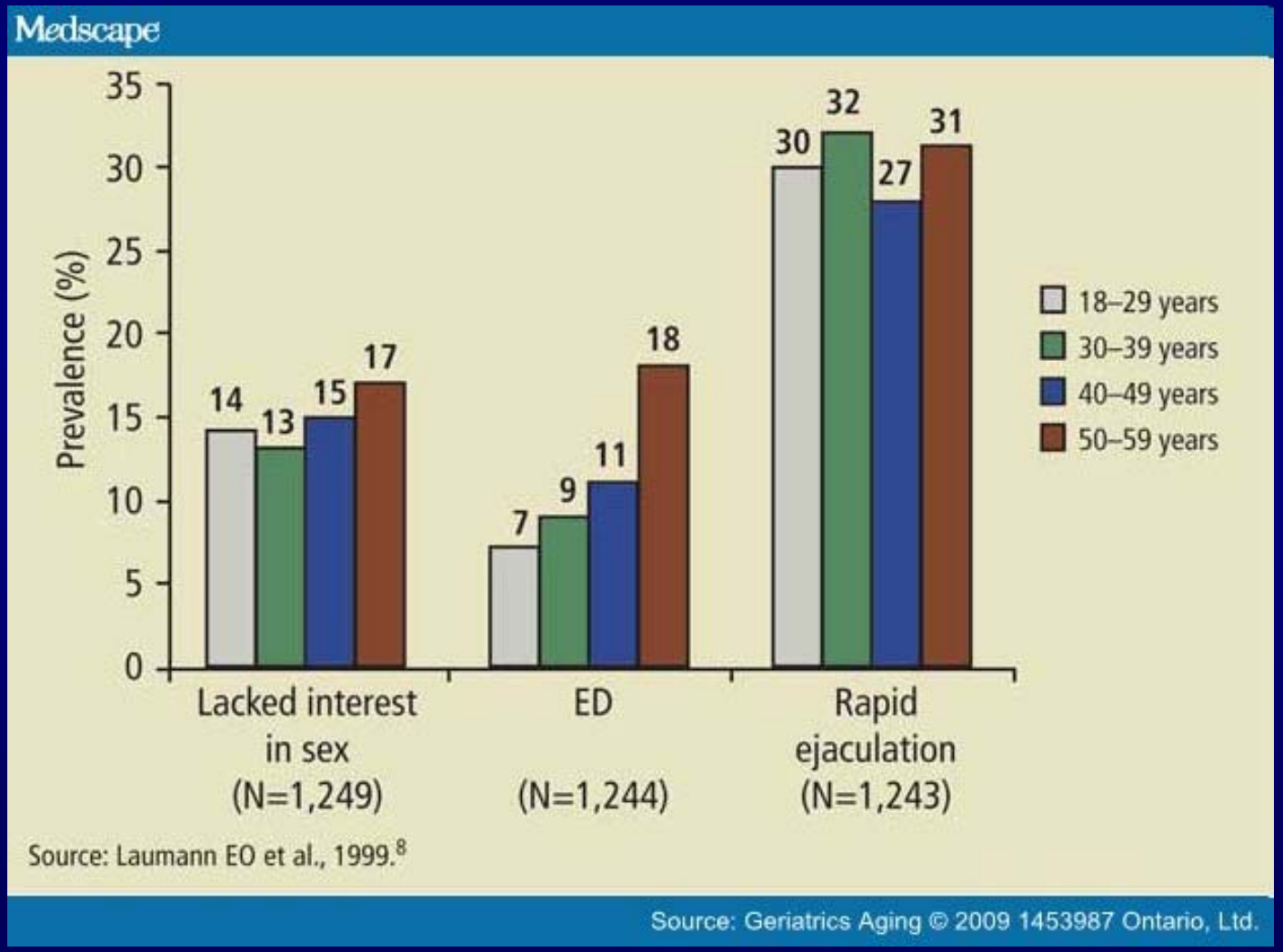
Objectives

1. Recognize patients at risk for erectile dysfunction
2. Identify medications that may cause erectile dysfunction
3. Understand pharmacokinetic and pharmacodynamic differences between the PDE-5 inhibitors and how those impact therapy
4. Identify drug interactions and adverse effects of PDE-5 inhibitors
5. Describe the rationale and clinical evidence supporting daily dosing of PDE-5 inhibitors
6. Demonstrate how to monitor a patient being treated for ED

Types of Male Sexual Dysfunction

- Decreased libido
- Increased libido
- Erectile dysfunction
- Delayed ejaculation
- Retrograde ejaculation
- Infertility

Prevalence of Male Sexual Dysfunction



Pathophysiology of ED

ED can result from a single abnormality or combination of abnormalities of the four systems necessary for erection:

1. Vascular
2. Neurologic
3. Hormonal

Organic ED (80% of patients)

4. Psychogenic – 20% of patients

Other Patient Populations at Risk for ED

- Patients post radical prostatectomy
- Patients post cancer treatment
- Spinal cord injuries
- Low testosterone

- Patients taking certain medications

Table 1. Risk Factors for Erectile Dysfunction.*

Risk Factor	Mechanism or Cause	Treatment
Metabolic syndrome	Endothelial dysfunction and down-regulation of nitric oxide synthase	Diet, exercise, and associated weight loss
Lower urinary tract symptoms of benign prostatic hyperplasia	Possible decrease in nitric oxide in the penis, bladder, and prostate	Use of a PDE5 inhibitor
Cardiovascular disease	Possible endothelial dysfunction in penile vasculature	Use of a PDE5 inhibitor with caution; contraindication with nitrate use
Tobacco smoking	Possible endothelial dysfunction, associated atherosclerosis, and sympathetic overactivity	Smoking cessation
Central neurologic conditions†	Disruption of descending neural control of proerectile processes	Medical treatment
Spinal cord injury	Dependent on the extent and location of the spinal lesion; nonsustained reflex erections commonly maintained	Use of a PDE5 inhibitor (depending on the level of injury)
Depression or social or marital stress	Unknown	Counseling, lifestyle change (e.g., weight loss, exercise), medical treatment
Endocrinologic conditions‡	Disruption of testosterone-mediated up-regulation of nitric oxide synthase; low testosterone levels from hyperprolactinemia-influenced changes in the hypothalamic–pituitary axis	Correction of underlying endocrine disorder; possible use of a PDE5 inhibitor
Diabetes mellitus	Vasculopathy from endothelial dysfunction and autonomic neuropathy	Appropriate glycemic therapy

* PDE5 denotes phosphodiesterase type 5.
† Neurologic conditions include Parkinson's disease, hemorrhagic or ischemic stroke, tumors, Alzheimer's disease, the Shy–Drager syndrome, and encephalitis.
‡ Endocrinologic conditions include hypogonadism, hypothyroidism, hyperthyroidism, and hyperprolactinemia.

Medications that may cause ED

Drug Class	Example
Diuretics	Thiazides, spironolactone
Antihypertensive drugs	Beta-blockers, Ca^{2+} channel blockers
Cardiac or cholesterol drugs	Digoxin, gemfibrozil, clofibrate
Antidepressants	SSRIs, TCAs, Lithium, MAO-I
H2 antagonists	Ranitidine, cimetidine
Hormones	Progesterone, estrogens, corticosteroids
Chemotherapeutic agents	Methotrexate, cyclophosphamide
Recreational drugs	Alcohol, cocaine, marijuana, nicotine, opioids
Anticholinergic agents	Disopyramide, anticonvulsants
Anti-androgens	GRH antagonists, flutamide
Antipsychotics	Olanzapine, risperidone

Evaluation of Patients with ED

HISTORY

- Sexual – other sexual dysfunction
- Medical – Comorbidities (CV disease, diabetes)
- Psychologic – depression, stressors, social relationships
- Medication history

PHYSICAL EXAM

- Neurologic, genitourinary, peripheral pulses, prostate

Evaluation of Patients with ED

LABORATORY TESTS

- Serum prostate specific antigen (PSA) for men > 50 years old
- Testosterone levels in certain patients
- Fasting blood glucose

OTHER

- Ultrasound or arteriography to assess vascular function and arterial insufficiency

Therapy of Erectile Dysfunction

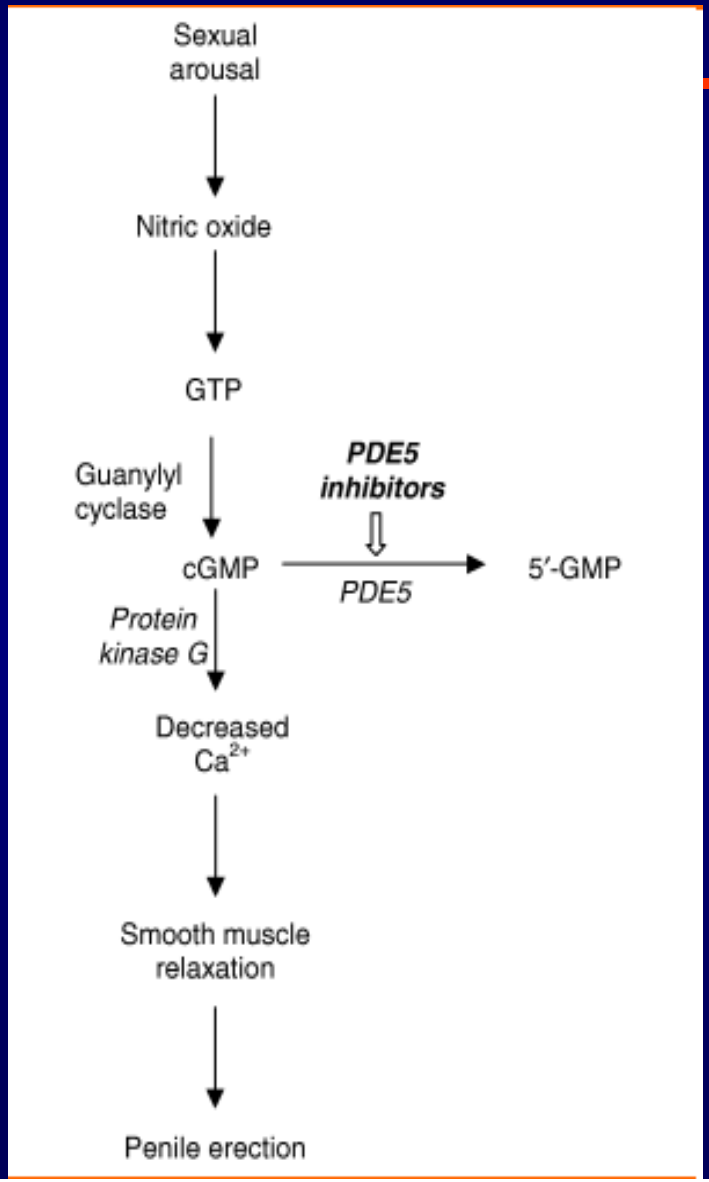
- Possible Therapies:
  - Oral therapies
  - Surgical treatment
  - Injections
  - Mechanical Devices
  - Lifestyle modifications

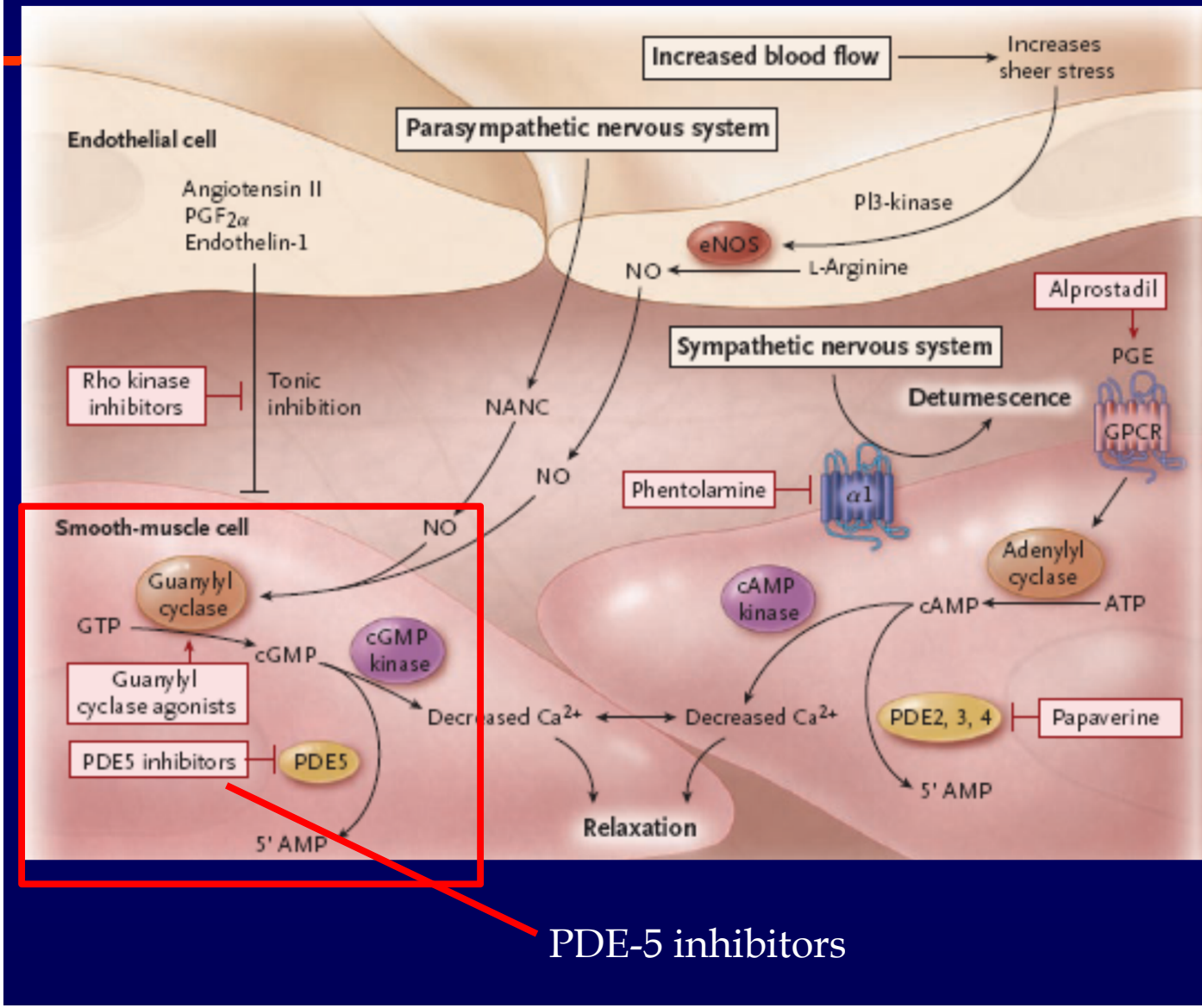
Therapy of Erectile Dysfunction

- Oral therapies are:
  - Non-invasive
  - Easily administered
  - Effective
  - Well-tolerated

- Phosphodiesterase-type-5 (PDE-5) inhibitors are first line therapy

Pharmacology of PDE-5 Inhibitors





PDE-5 inhibitors

Pharmacokinetics of PDE-5 Inhibitors

Parameter	Sildenafil (single 100mg dose)	Vardenafil (single 20mg dose)	Tadalafil (single 20mg dose)	Avanafil (single 200 mg dose)
Bioavailability (%)	41	15	Undetermined	Undetermined
Change in C_{max} with food	29% decrease	20% decrease	No change	No change
T_{max} (hrs)	0.83	1	2	0.5-0.75
Half-life (hrs)	3.7	3.3-3.9	17.5	5
Hepatic metabolism route	CYP3A4	CYP3A4	CYP3A4	CYP3A4
Duration of Action	4-5 hours	4-5 hours	Up to 36 hours	Up to 6 hours

Pharmacodynamics of PDE-5 Inhibitors

		Fold-Selectivity			
PDE isozyme	Locations of Isozymes	Sildenafil	Vardenafil	Tadalafil	Avanafil
1A	Heart, liver and muscles	290	480	20,000	>10,000
1B		1100	510	21000	>10,000
1C		110	190	11000	>10,000
5	Corpus Cavernosum, vascular, visceral muscles	1	1	1	1
6	Retina	7	3	780	120
11A	Heart, liver, pituitary, prostate	1500	1100	14	>10,000

e.g. sildenafil is 7-fold more selective for PDE-5 compared to PDE-6

How Differences in Pharmacodynamics Are Relevant

- Differences in selectivity for PDE-5 determine adverse effects
- Most adverse effects result from inhibition of PDE-1, PDE6, and PDE-11

Isozyme and Adverse Effect	Notes
PDE-1: vasodilation, tachycardia and flushing	Tadalafil may be less likely to cause
PDE-6: visual disturbances	Tadalafil less likely to cause, maybe avanafil also
PDE-11: back pain, myalgia?	Tadalafil more likely to cause

How Differences in Pharmacokinetics are Relevant

- Longer half-life of tadalafil allows patient to take medication hours-days before sexual activity
- However, tadalafil may take longer to be effective than vardenafil and sildenafil
- Sildenafil and vardenafil should be taken on an empty stomach
- Since all are metabolized by CYP3A4, pay attention to possible drug interactions

PDE-5 Inhibitors

- All 3 PDE-5 inhibitors are equally effective
  - ~70% of patients successfully achieve erection
- Effectiveness is dose-related
- 30-40% of patients will not respond to PDE-5 inhib.
- Do not use with other ED therapies
- At least half of non-responders benefit from education
  - For best response engage in sexual stimulation
  - Patients who do not respond to first dose should continue for at least 4 times before failure is declared

Sildenafil (Viagra)

- Dose: 25-100 mg 60 minutes before desired effect
- Duration of Effect: ~ 4 hours
- Use a dose of 25 mg in patients with severe renal dysfunction or hepatic impairment (daily dosing)
- Patients should take on an empty stomach
  - Separate from food by 2 hours

Vardenafil (Levitra)

- Dose: 2.5-20 mg once daily (10mg ODT)
- Usual dose = 10mg one hour prior to sexual activity
- Duration of Effect: ~4-5 hours
- Reduce dose with concomitant CYP3A4 inhibitors or in patients with moderate-severe liver dysfunction
- Patients should take on an empty stomach
  - Separate from food by 2 hours
  - ODT does not need to be spaced from food

Tadalafil (Cialis)

- Dose: 2.5 – 20 mg once daily
- Usual dose = 10 mg prior to sexual activity
- Duration of Effect: up to 36 hours
- Reduce dose with concomitant CYP3A4 inhibitors or in patients with moderate-severe liver dysfunction
- Can take without regard to food

- Only PDE-5 inhibitor that improves BPH symptoms
  - Urology 2013;82:667-673

Avanafil (Stendra)

- Dose: 50-200 mg
- Usual dose: 100 mg – works in as little as 15 minutes*
- Duration of Effect: up to 6 hours
- Do not use with strong CYP3A4 inhibitors
- Reduce dose to 50 mg when using with moderate CYP3A4 inhibitors.
  - Erythromycin, diltiazem, fluconazole, verapamil
- Take without regard to food (reductions in Cmax are called “not significant”)
- May be taken with alcohol (< 3 drinks)

Patient Preference

- Patient preference should be taken into account when selecting therapy
- Tadalafil and Sildenafil comparisons:
  - In 3 studies, majority of patients (70-90%) prefer tadalafil vs. sildenafil

Daily Administration

- Rationale:
  - PRN use of PDE-5 inhibitors is not as effective in some patients
    - Diabetic patients
    - Patients with neurological damage
    - Patients with severe vascular disease
    - Patients with prostate cancer undergoing radical prostatectomy
  - Anxiety from having to plan sexual activity may reduce efficacy
  - Perceived lack of spontaneity may lead to drug D/C
  - Daily dosing may modify the disease (vascular)

Daily Administration

- Tadalafil is only drug approved for daily use (2.5-5 mg daily)
  - Favorable pharmacokinetic profile allows constant steady state concentrations ~ tadalafil 20 mg twice per week.
  - Daily use more effective than PRN use and patient satisfaction is also higher
  - Daily use may be associated with fewer adverse effects if lower dose can be used

J Sex Med 2005;2:415-425

Daily Administration – Adverse Effects

- Adverse effects are not more frequent with daily dosing compared to PRN dosing.
- Most common adverse effects:
  - dyspepsia,
  - back-pain,
  - flu-like symptoms
- One study reported headache less common with daily dosing than with PRN dosing

Side Effects of PDE-5 Inhibitors

Sildenafil	**Vardenafil**	**Tadalafil**	Avanafil
Headache	Flushing	Headache	Headache
Flushing	Headache	Dyspepsia	Flushing
Dizziness	Dyspepsia	Dizziness	Nasal congestion
Dyspepsia	Nausea	Flushing	Back pain
Nasal congestion	Dizziness	Nasal congestion	Dizziness
Altered vision	Rhinitis	Back pain, myalgia	

Drug Interactions

- CYP3A4 inhibitors:
  - Cimetidine
  - Erythromycin, clarithromycin
  - Ketoconazole, itraconazole
  - Ritonavir, saquinavir
- Nitrates
  - Do not use within 24 hrs of sildenafil or vardenafil and 48 hrs of tadalafil
- Alpha-blockers

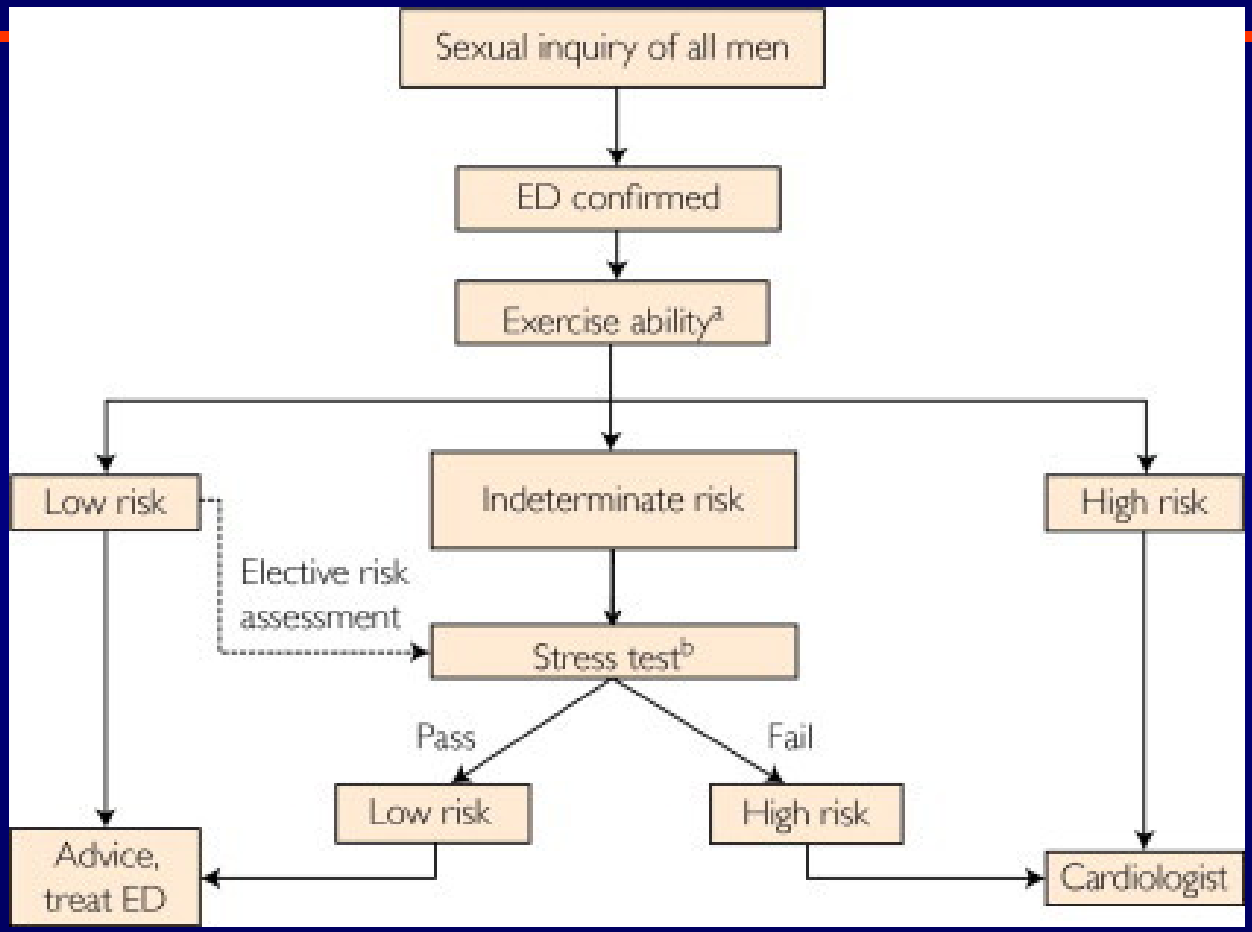
Contraindications

Do NOT use PDE-5 inhibitors with:

- Nitrates (nitroglycerin, isosorbide dinitrate, etc.)
- Nicorandil
- Alpha-blockers (doxazosin, terazosin)

- In patients with:
  - High or intermediate risk of coronary artery disease
  - Retinitis pigmentosa
  - Nonarteritic anterior ischemic optic neuropathy

Guidelines for Treatment of ED in men with cardiovascular disease



Mayo Clin Proc 2012;87:766-778.

2ndary Treatment Options

- If PDE-5 inhibitors are unsuccessful:
  - Intracavernosal injection – alprostadil
  - Intraurethral tablets – alprostadil
  - Vacuum devices
  - Surgical Prostheses
  - Testosterone therapy – for testosterone deficiency

Intracavernosal Injection

- Alprostadil, papaverine, phentolamine -

- May be used alone or in combination
- Inhibit sympathetic inhibition to encourage relaxation of smooth muscle
- Patients need to be trained in sterile methods and injection technique (27 or 30 gauge needle)
- Side effects – penile pain (50%), priapism (6%), hy
- Papaverine hepatoxicity if drug goes systemic
- Dose is 1.25-20 mcg 5-10minutes before desired effect

Intraurethral Alprostadil

- Developed as less invasive alternative to injections
- Patient education for administration technique
- Systemic effects – uncommon
- Priapism and fibrosis less common than with injection.
- DiPiro Figure 66-6 for technique of administration
- Dose – 125-1000 mcg taken 5-10 min before desired effect

Supplement Therapy for ED

- FDA warning:
  - Do not take supplements that claim to increase sexual stamina, confidence, and performance and/or claim to contain prescription-strength doses of sildenafil or tadalafil
  - 1/3 to ½ of "natural" products for sexual enhancement contain synthetic chemicals, (PDE-5 inhibitors or analogs of PDE-5 inhibitors)
  - Patients who take nitrates for cardiovascular disease may have drastic BP reductions with these supplements.

Testosterone Replacement
- DiPiro Table 92-6 -

- Goal: Correct the symptoms of hypogonadism
  - Malaise, ↓ libido, loss of muscle strength, depression
- Restore serum testosterone concentrations to 300-1100 ng/dL
- Measure serum testosterone in morning with luteinizing hormone (LH) concentrations
  - Distinguish primary from 2ndary hypogonadism
  - Primary: elevated LH, Secondary: reduced LH
- Variety of products: oral, transdermal, IM, buccal, SQ implants

Generic name	Trade name	Route	Dose	Cost[a]	Testosterone metabolites[b]	Circadian rhythm[c]	Side effects
Testosterone undecanoate[d]	Andriol	Oral	120–200 mg/d	N/A[d]	Elevated DHT	No	Poor absorption, gastrointestinal effects
Buccal system	Striant	Transbuccal	30 mg twice/d	$190.30	Normal	No	Gum irritation
Testosterone enanthate and cypionate	Depo-testosterone, Delatestryl, Testoviron Depot	Intramuscular	200–400 mg every 2–3 wk	$8.30	Elevated DHT Elevated estradiol	No	Mood swings, breast tenderness, polycythemia, infertility
Testosterone implants	Testopel	Subcutaneous	600–1200 mg every 4–6 mo	N/A	Elevated DHT Elevated estradiol	No	Extrusion, gynecomastia, polycythemia, fluid retention
Scrotal patches	Testoderm	Transdermal	10–15 mg/d	$131.54	Elevated DHT	Yes	Dermatitis, misplacement
Nonscrotal patches	Androderm, Testoderm TTS	Transdermal	4–6 mg/d	$131.54	Normal	Yes	Dermatitis
Gel	Androgel, Testogel, Androtop, Testim	Transdermal	5 g 1% gel/d	$186.00	Normal	Yes	Partner absorption

[a] Per month of treatment of the least expensive preparation in that class (generics included when possible).
[b] Effect of the testosterone preparation on testosterone metabolites estradiol and dihydrotestosterone (DHT).
[c] Efficacy of the testosterone preparation at reproducing the circadian pattern of testosterone secretion in eugonadal men.
[d] Not currently available in the United States.

Patient Monitoring

- Outcomes:
  - Improvement in quantity and quality of erections
  - Avoidance of adverse drug reactions and drug interactions

- Assessment after 1-3 weeks for efficacy/toxicity
- Each patient will be different, so patient satisfaction is key
- If not effective with adequate trial:
  - Ensure maximum doses used
  - Switch to another PDE-5 inhibitor for trial
  - Surgical treatment reserved for patients who fail drug treatment

Female Sexual Dysfunction

- Flibanserin (Addyi®)
  - FDA indication: treatment of premenopausal women with acquired, generalized hyposexual desire disorder (HSDD)
  - Centrally acting 5-HT receptor agonist/antagonist that ↓ 5-HT, and ↑ dopamine and NE
  - Dose: 100 mg taken once daily at bedtime
  - Not for postmenopausal females
  - Not indicated to enhance sexual performance

Flibanserin

- SE: dizziness, somnolence, N/V, fatigue, dry mouth
- SYNCOPE! (worsened by alcohol)
  - Do not drink alcohol until next day
  - Management – patients lie supine seek care if symptoms don't resolve
  - CNS depression – can happen alone and can be exacerbated with other CNS depressants

Flibanserin

ENZYME	EXAMPLE	Management	Concentration Effect	Consequence
CYP3A4 Inhibitors	Azole Antifungals, HIV meds, clarithromycin, diltiazem, verapamil, etc.	AVOID	↑ flibanserin concentrations	↑ risk hypotension
Weak CYP3A4 Inhibitors	Oral contraceptives, cimetidine, fluoxetine, etc.	Careful using multiple weak inhibitors	↑ flibanserin concentrations	↑ risk hypotension
CYP2C19 Inhibitors	PPIs, SSRIs, Benzos	Caution	↑ flibanserin concentrations	↑ risk hypotension
Digoxin PGP substrates	Digoxin, sirolimus	↑ monitoring digoxin conc	↑ digoxin conc	↑ digoxin toxicity
CYP3A4 inducers	Anticonvulsants, rifampin, St. John's Worst	AVOID	↓ flibanserin concentrations	↓ flibanserin effectiveness