Male Sexual Disorders

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Erectile Dysfunction

- Definition
  - Persistent or recurrent failure to **achieve** or **maintain** a penile erection to allow for satisfactory sexual intercourse. (impotence)
- Persistent failure
- Must be *distinguished* from disorders of libido or ejaculation, and of infertility.
- More than one disorder may present at the same time. (e.g. *primary hypogonadism*)

Introduction

Type of Dysfunction	Definition
Decreased libido	Decreased sexual drive or desire
Increased libido	Inappropriate and excessive sexual drive or desire
Erectile dysfunction (impotence)	Failure to achieve a penile erection suitable for satisfactory sexual intercourse
Delayed ejaculation	Commonly referred to as "dry sex"; ejaculation is delayed or absent
Retrograde ejaculation	Ejaculate passes retrograde into the bladder, instead of toward the anterior urethra (antegrade) and out of the penis
Infertility	Sperm are insufficient in number, have abnormal morphology, or have inadequate motility, and fail to fertilize the ovum

Epidemiology

- The incidence is *low* in men younger than **40 years** of age.
- The prevalence has been reported to be as high as **80%** in men older than *70 years* old.
- Many patient fail to seek medical treatment. (may be due to the decrease in sexual activity)
- ED is sometimes assumed to be a symptom of the *aging process*.
  - More likely it results from concurrent medical conditions (HTN, DM)
  - Role of medications

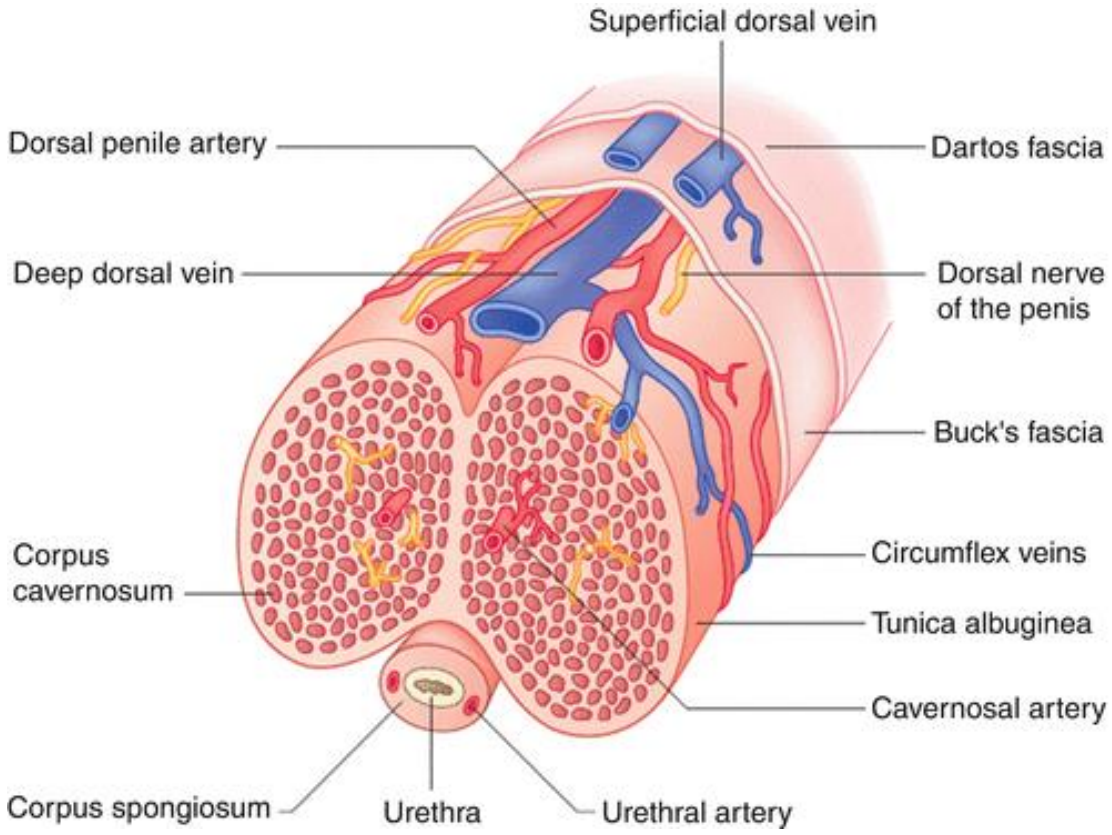
Physiology of a Normal Penile Erection

Vascular system

- Arterial flow into the corpora is enhanced by **acetylcholine-mediated** vasodilation.

Nervous System and Psychogenic Stimuli

- Sacral nerve reflex
- Brain (hypothalamus) role in the conscious patient



Physiology of a Normal Penile Erection

Hormonal System

- Testosterone *circadian rhythm*
- Beginning at age **40 years**, men experience a *gradual decrease* in testicular production of testosterone.
- The European Male Aging Study described three cardinal symptoms of low serum testosterone levels: decreased libido, erectile dysfunction, and loss of spontaneous morning erections.
- Serum concentration of testosterone should always be interpreted in the context of the *patient's symptoms* and physical exam findings.

Physiology of a Normal Penile Erection

- The relationship between serum testosterone and erectile dysfunction
- American Society of Andrology guidelines:
  - Serum testosterone greater than 350 ng/dL (12.2 nmol/L) requires no treatment.
  - Serum testosterone of 230 to 350 ng/dL (8.0-12.2 nmol/L) requires treatment if the patient is **symptomatic**.
  - Serum testosterone below 230 ng/dL (8.0 nmol/L) generally should be treated.

Etiology/Pathophysiology

- **Organic** erectile dysfunction (vascular, neurologic, or hormonal etiologies): approximately *80%* of patients.
- **Psychogenic** erectile dysfunction (less severe symptoms): patients who do not respond to psychogenic stimuli and have no organic cause.

Etiology/Pathophysiology

Social habits

- **Cigarette smoking**: the *vasoconstrictor effect* may compromise blood flow to the corpora and decrease cavernosal filling.
- **Excessive ethanol intake**: may lead to *androgen deficiency*, *peripheral neuropathy*, or chronic liver disease, all of which can contribute to erectile dysfunction.

Drug Class	Proposed Mechanism by Which Drug Causes Erectile Dysfunction	Special Notes
Anticholinergic agents (antihistamines, antiparkinsonian agents, tricyclic antidepressants, phenothiazines)	Anticholinergic activity	• Second-generation nonsedating antihistamines (e.g., loratadine, fexofenadine, or cetirizine) are associated with less erectile dysfunction than first-generation agents • Selective serotonin reuptake inhibitor (SSRI) and multiple receptor reuptake inhibitor antidepressants cause less erectile dysfunction than tricyclic antidepressants. Of the SSRIs, paroxetine, sertraline, fluvoxamine, and fluoxetine cause erectile dysfunction more commonly than venlafaxine, nefazodone, trazodone, bupropion, duloxetine, or mirtazapine • Phenothiazines with less anticholinergic effect (e.g., chlorpromazine) can be substituted in some patients if erectile dysfunction is a problem
Dopamine antagonists (e.g., metoclopramide, phenothiazines)	Inhibit prolactin inhibitory factor, thereby increasing prolactin levels	• Increased prolactin levels inhibit testicular testosterone production; depressed libido results
Estrogens, antiandrogens (e.g., luteinizing hormone-releasing hormone superagonists, digoxin, spironolactone, ketoconazole, cimetidine)	Suppress testosterone-mediated stimulation of libido	• In the face of a decreased libido, a secondary erectile dysfunction develops because of diminished sexual drive
CNS depressants (e.g., barbiturates, narcotics, benzodiazepines, short-term use of large doses of alcohol, anticonvulsants)	Suppress perception of psychogenic stimuli	
Agents that decrease penile blood flow (e.g., diuretics, peripheral β-adrenergic antagonists, or central sympatholytics [methyldopa, clonidine, guanethidine])	Reduce arteriolar flow to corpora	• Any diuretic that produces a significant decrease in intravascular volume can decrease penile arteriolar flow • Safer antihypertensives include angiotensin-converting enzyme inhibitors, postsynaptic α_1-adrenergic antagonists (terazosin, doxazosin), calcium channel blockers, and angiotensin II receptor antagonists[9]
Miscellaneous • Finsteride, dutasteride • Lithium carbonate • Gemfibrozil • Interferon • Clofibrate • Monoamine oxidase inhibitors • Opiates	Unknown mechanism	

From Handler,[12] Lee and Sharifi,[13] and Kennedy.[14]

Diagnosis

With the availability in the late 1990s of **effective medications** for erectile dysfunction *independent of the etiology*, diagnostic evaluation of erectile dysfunction became streamlined.

Diagnosis

Medical history

- Concurrent medical illnesses (eg, hypertension, atherosclerosis, hyperlipidemia, diabetes mellitus, and depression)
- Surgical procedures (eg, perineal or pelvic)
- Discontinuation of social habits

Diagnosis

Physical Examination

- Check for *hypogonadism*.
- Penis should be evaluated for diseases associated with *abnormal penile curvature* (eg, Peyronie's disease).
- Femoral and lower extremity *pulses*
- *Digital rectal examination* in patients 50 years or older
- Assess patient's *cardiac reserve*.

TABLE 66-5 Recommendations of the Third Princeton Consensus Conference for Cardiovascular Risk Stratification of Patients Being Considered for Phosphodiesterase Inhibitor Therapy

Risk Category	Description of Patient's Condition	Management Approach
Low risk	Has asymptomatic cardiovascular disease with <3 risk factors for cardiovascular disease Has well-controlled hypertension Has mild congestive heart failure (NYHA class I or II) Has mild valvular heart disease Had a myocardial infarction >8 weeks ago	Patient can be started on phosphodiesterase inhibitor
Intermediate risk	Has ≥3 risk factors for cardiovascular disease Has mild or moderate, stable angina Had a recent myocardial infarction or stroke within the past 2–8 weeks Has moderate congestive heart failure (NYHA class III) History of stroke, transient ischemic attack, or peripheral artery disease	Patient should undergo complete cardiovascular workup and treadmill stress test to determine tolerance to increased myocardial energy consumption associated with increased sexual activity. Reclassify in low or high risk category
High risk	Has unstable or refractory angina, despite treatment Has uncontrolled hypertension Has severe congestive heart failure (NYHA class IV) Had a recent myocardial infarction or stroke within past 2 weeks Has moderate or severe valvular heart disease Has high-risk cardiac arrhythmias Has obstructive hypertrophic cardiomyopathy	Phosphodiesterase inhibitor is contraindicated; sexual intercourse should be deferred

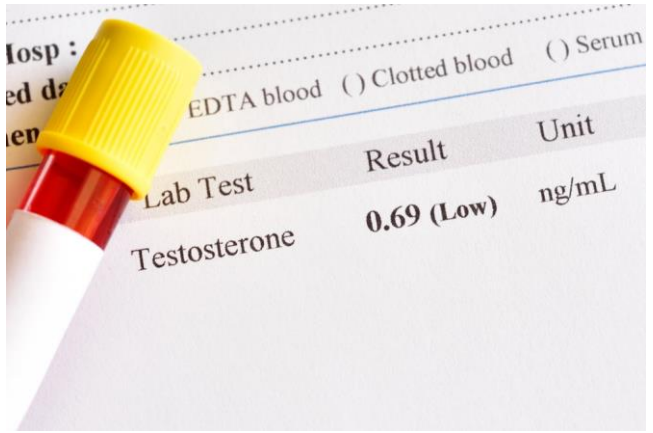
NYHA, New York Heart Association.

From Nehra et al.,[20] Rosen et al.,[21] and Nehra et al.[22]

Diagnosis

Serum testosterone levels should be checked in patients *older than 50 years* and in *younger* patients who complain of decreased libido and erectile dysfunction.

At least **two early morning** serum testosterone levels on different days, approximately *4 weeks apart*, are needed to confirm the presence of hypogonadism.



General Approach to Treatment

- The first step: identify and, if possible, reverse underlying causes.
- Patients should follow a *heart-healthy lifestyle* (no excessive alcohol, no smoking).

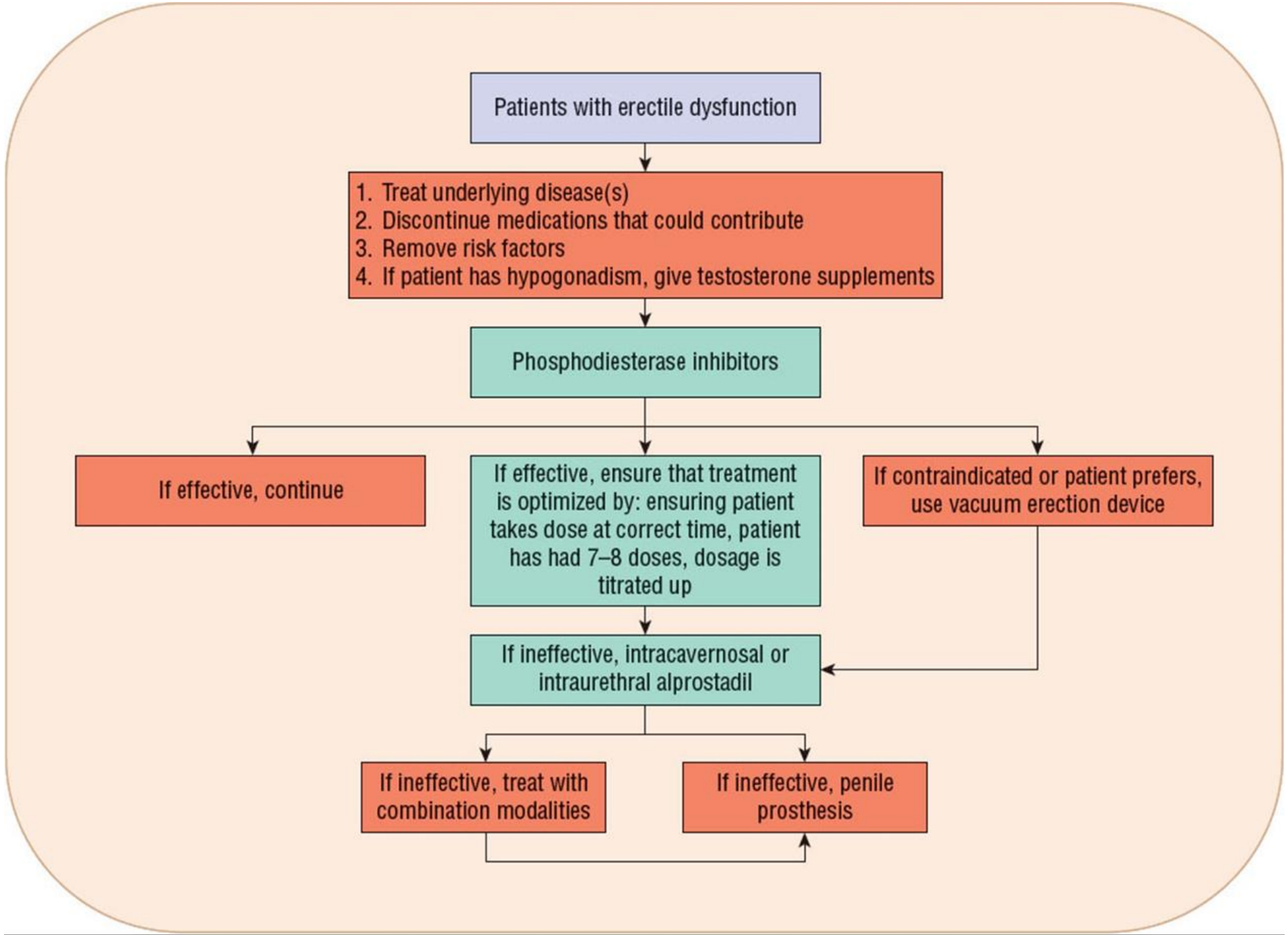
Sufficient in some patients to restore erectile function.

- **Psychotherapy** can be used as *monotherapy* or as an *adjunct* to specific treatments for psychogenic ED.
- Specific treatments
  - Pharmacologic treatment
  - Vacuum erection devices (VEDs)
  - Surgery

General Approach to Treatment

The 2018 American Urological Association guideline on the management of erectile dysfunction, the Fourth International Consultation of Sexual Medicine, the 2010 European Urology Association guideline, and the American College of Physicians clearly identify oral **phosphodiesterase type 5 inhibitors** for **first-line treatment**.

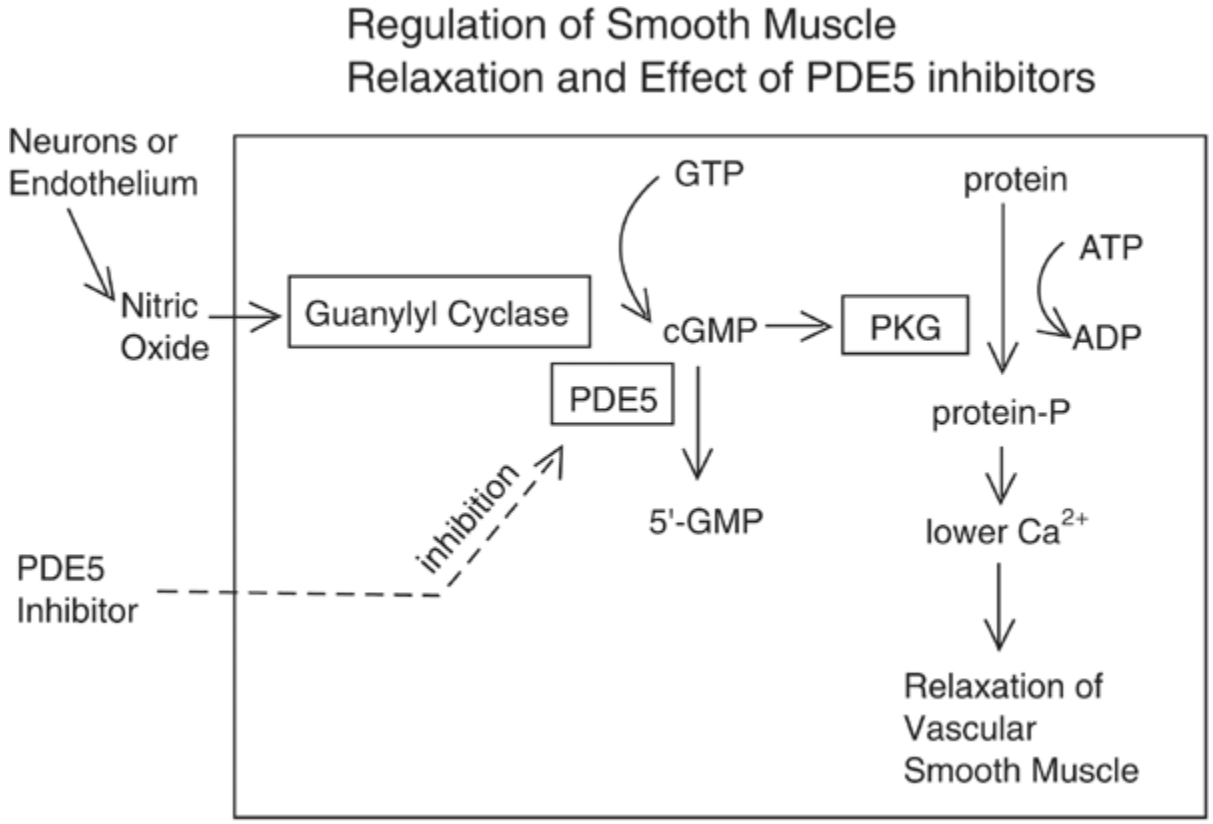
VEDs, intracavernosal injection of erectogenic agents, or intraurethral prostaglandin inserts are second-line treatments.


Patients with erectile dysfunction
1. Treat underlying disease(s)
2. Discontinue medications that could contribute
3. Remove risk factors
4. If patient has hypogonadism, give testosterone supplements
Phosphodiesterase inhibitors
If effective, continue
If effective, ensure that treatment is optimized by: ensuring patient takes dose at correct time, patient has had 7–8 doses, dosage is titrated up
If contraindicated or patient prefers, use vacuum erection device
If ineffective, intracavernosal or intraurethral alprostadil
If ineffective, treat with combination modalities
If ineffective, penile prosthesis

Phosphodiesterase Type 5 Inhibitors

- cGMP is a vasodilatory secondary messenger that decreases intracellular calcium levels, resulting in smooth muscle relaxation, enhanced arterial flow to the corpora cavernosa, and increased blood filling of cavernosal sinuses.

- Catabolism of cGMP in cavernosal tissue is mediated by phosphodiesterase isoenzyme type 5.



Phosphodiesterase Type 5 Inhibitors

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Phosphodiesterase Inhibitor					
Sildenafil	Viagra	50 mg orally 1 hour before intercourse	25–100 mg 1 hour before intercourse. Limit to one dose per day	In patients age 65 years and older, start with 25 mg dose. In patients with creatinine clearance less than 30 mL/minute or severe hepatic impairment, limit starting dose to 25 mg. In patients taking potent P450 CYP3A4 inhibitors, limit starting dose to 25 mg	Titrate dose so that erection lasts no more than 1 hour. Food decreases absorption by 1 hour. Contraindicated with nitrates by any route of administration
Tadalafil	Cialis	5–10 mg orally before intercourse OR 2.5–5 mg orally once daily	10–20 mg before intercourse. Limit to one dose per day; the drug improves erectile function for up to 36 hours 2.5–5 mg once daily. Limit to one dose per day	Dose of tadalafil requires no dosage adjustment in patients 65 years or older. In patients with creatinine clearance of 30–50 mL/min, limit starting dose to 10 mg every 48 hours; if less than 30 mL/min, limit starting dose to 5 mg every 72 hours. In patients with mild-moderate hepatic impairment, limit starting dose to 10 mg every 24 hours. Do not use in patients with severe hepatic impairment. In patients taking potent P450 CYP3A4 inhibitors, limit starting dose to 10 mg every 72 hours	Titrate dose so that erection lasts not more than 1 hour. Food does not affect rate or extent of drug absorption. Contraindicated with nitrates by any route of administration. When taken with large amounts of ethanol, tadalafil may cause orthostatic hypotension

TABLE 66-4 Pharmacodynamics and Pharmacokinetics of Phosphodiesterase Inhibitors

	Sildenafil (Viagra)	Vardenafil (Levitra/Staxyn)	Tadalafil (Cialis)	Avanafil (Stendra)
Inhibits PDE-5	Yes	Yes	Yes	Yes
Inhibits PDE-6	Yes	Minimally	No	Minimally
Inhibits PDE-11	No	No	Yes	Minimally
Time to peak plasma level (hours)	0.5–1	0.7–0.9/1.5	2	0.5–0.8
Oral bioavailability (%)	40	15/21–44	Not determined	15
Fatty meal decreases rate of oral absorption?	Yes	Yes/No[a]	No	No
Mean plasma half-life (hours)	3.7	4.4–4.8/4–6	18	4–5
Active metabolite	Yes	Yes/Yes	No	Yes
Percentage of dose excreted in feces	80	91–95/91–95	61	62
Percentage of dose excreted in urine	13	2–6/2–6	36	21
Onset (minutes)	30	30/60	45	30–45
Duration (hours)	4	4–5/4–6	24–36	4–5

PDE, phosphodiesterase.

[a]When Staxyn is taken with water, the area under the curve decreases by 29%.

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase **isoenzyme 1**

- Found in the *peripheral vasculature*.
- Inhibition has been linked with peripheral vasodilation, which can lower blood pressure, and cause flushing and reflex tachycardia in some patients.

Phosphodiesterase **isoenzyme type 6**

- Is localized to the *rods and cones of the retina*.
- Inhibition has been associated with blurred vision and cyanopsia.
- Sildenafil is the **most potent inhibitor** and **tadalafil** is the *least* potent inhibitor.

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase **isoenzyme type 11**

- Is localized to striated muscle.
- Inhibition has been associated with *myalgia* and *back muscle pain*.
- Tadalafil exerts the greatest inhibitory activity against phosphodiesterase type 11.

Phosphodiesterase Type 5 Inhibitors

Efficacy

- PDE-5 inhibitors allow for **discreet** use.
- All four commercially available PDE-5 inhibitors are considered to be *equally effective*.
- Satisfactory erection
  - Sildenafil: 56-82% of patients
  - Vardenafil: 65-80% of patients
  - Tadalafil: 62-77% of patients
  - Avanafil: 50-55% of patients

Phosphodiesterase Type 5 Inhibitors

- Approximately **30% to 40%** of patients *do not respond*.
- **Follow-up** is always recommended after a phosphodiesterase type 5 inhibitor is initiated.
- Education should include the following points:
  - Foreplay (sexual stimulation)
  - Sildenafil should be taken on empty stomach.
  - At least *five to eight doses* should be used before failure is declared.
  - Dosage titration (up to 100 mg sildenafil or 20 mg tadalafil)
  - Avoid excessive alcohol use
  - Treatment of concomitant medical illnesses.

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 inhibitors should be **avoided** in patients predisposed to developing *priapism*, including men with sickle cell anemia, leukemia, or multiple myeloma.

Long-term use of phosphodiesterase type 5 inhibitors for up to **10 consecutive years** continues to be effective and is **not** associated with *tachyphylaxis*.

Voluntary discontinuation rate:

- Less than 2% per year in clinical trials
- Actual discontinuation rate: 35-47% after 6-24 months

Phosphodiesterase Type 5 Inhibitors

- Some patients with severe *vascular or neurologic disease* will show **minimal or no response** to maximum doses of a PDE-5.
- Suggested strategies:
  - The effectiveness of *switching* among PDE-5 inhibitors is controversial.
  - Switching the patient from an as-needed to a **daily regimen of tadalafil**.
  - *High-dose* phosphodiesterase type 5 inhibitor treatment. (sildenafil 200 mg)
  - PDE-5 inhibitor combined with intracavernosal or intraurethral **alprostadil** in selected patients.

Phosphodiesterase Type 5 Inhibitors

Pharmacokinetics and Drug–Food Interactions

Sildenafil and vardenafil have a *1-hour onset of action* and *short duration* of action. Oral absorption is significantly delayed by 1 hour when either drug is taken within 2 hours of a **fatty meal**.

In contrast, **tadalafil** has a *slower onset of action* of 2 hours, has a prolonged duration of action up to 36 hours, and food does **not** affect its rate of absorption. (greater spontaneity for patients, one dose can last through the *entire weekend*).

Phosphodiesterase Type 5 Inhibitors

Sildenafil and vardenafil have been reported to be effective in some patients **up to 12 hours** after dosing, and *tadalafil* is effective **up to 36 hours** after dosing, which is long after plasma concentrations have declined.

It has been hypothesized that this may be due to the *continued intracellular action* of the phosphodiesterase type 5 inhibitor.

Phosphodiesterase Type 5 Inhibitors

Concomitant ingestion of *ethanol* with phosphodiesterase type 5 inhibitors can result in **orthostatic hypotension** and drowsiness.

Therefore, the manufacturer recommends that patients **avoid** ethanol when taking these medications.

Phosphodiesterase Type 5 Inhibitors

All four phosphodiesterase type 5 inhibitors are *hepatically catabolized* principally by the cytochrome P450 3A4 microsomal isoenzyme.

Tadalafil and the *active metabolite of sildenafil* are excreted in the urine. Both drugs need dose adjustment in significant renal failure.

Phosphodiesterase Type 5 Inhibitors

Adverse Effects

- Most adverse effects are *mild or moderate*, are self-limited, and tolerance to the adverse effects develops with continued use.
- The **most common**: headache (11%), facial flushing (12%), dyspepsia (5%), nasal congestion (3.4%), and dizziness (3%)
- Hypotension (greater BP reduction with sildenafil)

Phosphodiesterase Type 5 Inhibitors

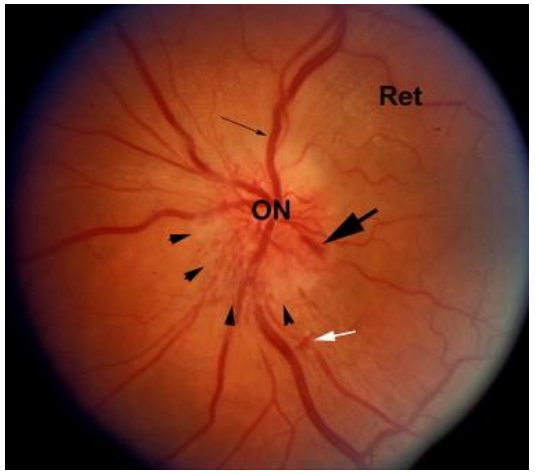
Sildenafil, vardenafil, and avanafil cause increased *sensitivity to light*, blurred vision, or loss of blue–green color discrimination in 2% to 3% of patients. This adverse effect is *dose-related* with the incidence increasing to 40% to 50% in patients taking sildenafil 200 mg.

Phosphodiesterase Type 5 Inhibitors

Visual adverse effects commonly occur at the time of *peak serum concentrations*. Avanafil has moderate and **tadalafil** has *minimal to no inhibitory* activity against phosphodiesterase type 6, and they are associated with a lower incidence of visual adverse effects (less than 1%) when compared to sildenafil and vardenafil.

Phosphodiesterase Type 5 Inhibitors

Nonarteritic anterior ischemic optic neuropathy (**NAION**) is a sudden, unilateral, painless blindness, which may be irreversible. Isolated cases of NAION have been associated with phosphodiesterase type 5 inhibitor use. NAION has developed at variable and *unpredictable* times after starting a phosphodiesterase type 5 inhibitor, ranging from *6 hours* to months or *years* after the first dose.



Phosphodiesterase Type 5 Inhibitors

A patient who experiences sudden vision loss in one eye while taking a phosphodiesterase type 5 inhibitor should be *evaluated* for NAION before continuing treatment.

If NAION is present, the phosphodiesterase type 5 inhibitor should be **discontinued** as there is a 15% to 25% risk of developing NAION in the other eye in the ensuing 5 to 10 years.

Phosphodiesterase Type 5 Inhibitors

Acute unilateral hearing loss

- Causality **not** *established*.
- In the cases reported, the hearing loss occurred *within 1 to 3 days* of starting treatment.
- Variably accompanied by *tinnitus* or *vertigo*, and often resulted in residual hearing loss despite drug discontinuation.
- Immediately stop the medication.

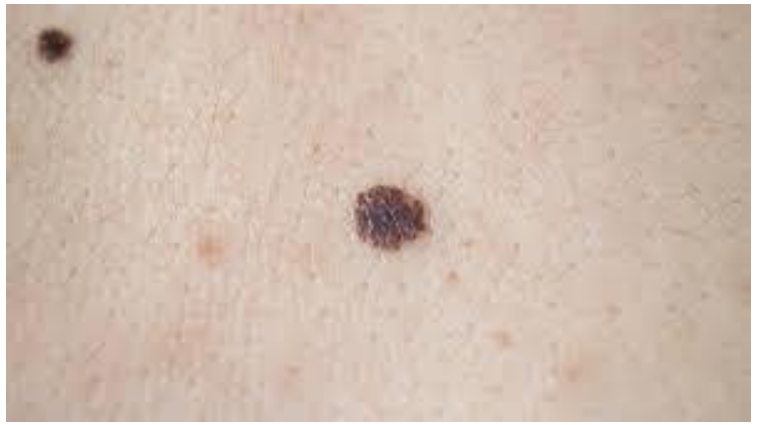
Phosphodiesterase Type 5 Inhibitors

Priapism is a rare adverse effect of phosphodiesterase type 5 inhibitors, *particularly sildenafil and vardenafil*, which have shorter plasma half-lives than tadalafil.

Priapism has been associated with **excessive doses** of the phosphodiesterase type 5 inhibitor or concomitant use with *other erectogenic drugs*.

Phosphodiesterase Type 5 Inhibitors

Recently, sildenafil use has been associated with an increased risk of **melanoma**. However, a *cause–effect relationship* has not been established.



Phosphodiesterase Type 5 Inhibitors

Drug Interactions

- *Sudden and severe hypotension* with **nitrates (8%)**.
- Use of phosphodiesterase type 5 inhibitors is **contraindicated** in patients taking nitrates given by any route at scheduled times or intermittently.

- Nitrates should be withheld for **24 hours** after *sildenafil*, vardenafil, or avanafil administration and for **48 hours** after *tadalafil* administration.

- If a patient who has taken a phosphodiesterase type 5 inhibitor requires medical treatment of angina, **non-nitrate-containing agents** (eg, calcium channel blocker, β-adrenergic antagonist, and morphine) should be used.

Phosphodiesterase Type 5 Inhibitors

- Small decreases in blood pressure with clinically symptomatic orthostatic hypotension in patients taking **α-adrenergics**.
- Interaction with CYP 3A4 inhibitors or inducers.

Alprostadil

Alprostadil, also known as prostaglandin E1, stimulates adenyl cyclase, resulting in increased production of cAMP.

Alprostadil is commercially available as an **intracavernosal injection** (*Caverject*® and *Edex*®) and as an **intraurethral insert** (medicated urethral system for erection [**MUSE®**]).

Alprostadil

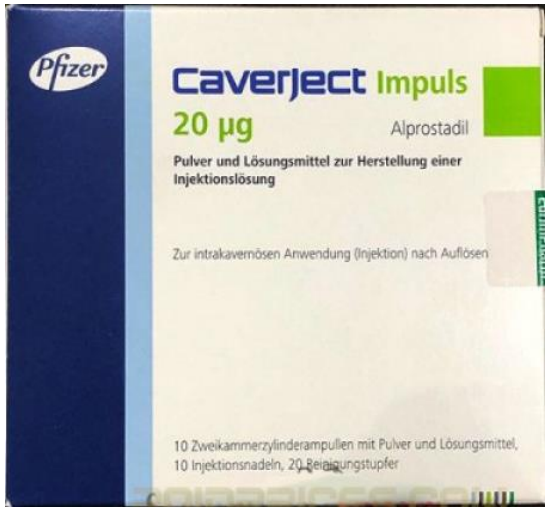
Indications

Both commercially available formulations of alprostadil are **FDA approved** as monotherapy for management of erectile dysfunction. Alprostadil is *more effective* by the **intracavernosal** route than the intraurethral route.

Both formulations of alprostadil are considered **more invasive** than *VEDs* or *phosphodiesterase type 5 inhibitors*. For this reason, intracavernosal alprostadil is generally prescribed after patients do not respond to or cannot use less invasive interventions.

Intracavernosal Alprostadil

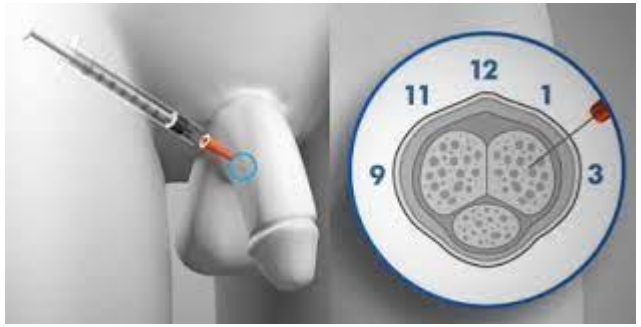
- The overall efficacy is 70-90%.
- The effect is dose-related (mean duration of erection is 12-44 min).
- Tolerance does not appear to occur.



Intracavernosal Alprostadil

Pharmacokinetics

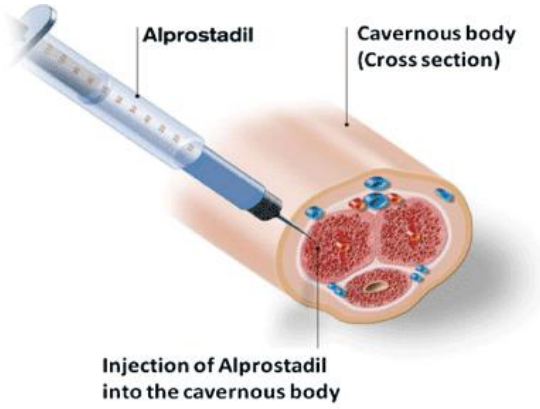
- Intracavernosal injection should be administered into only **one corpus cavernosum**. From this injection site, the drug will reach the other corpus cavernosum.
- *Onset* is within **5-15 min**. The *duration* is not more than **1 hour** (with doses of 2.5-20 mcg)
- **Local** 15-hydroxy dehydrogenase in the corpora cavernosum quickly converts alprostadil to *inactive metabolites*.
- Any alprostadil that escapes into the systemic circulation is deactivated on *first pass* through the lungs.

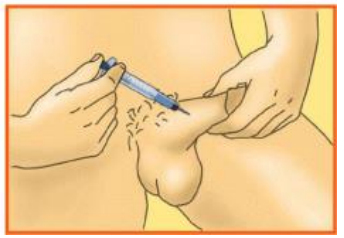


Intracavernosal Alprostadil

Dosing

- The usual dose of intracavernosal alprostadil is 10 to 20 mcg, with a *maximum* recommended dose of **60 mcg**.
- The dose should be administered *5 to 10 minutes* before intercourse.
- Slow dose titration to minimize the likelihood of hypotension.
- After injection the penis should be **massaged** to help distribute the drug.





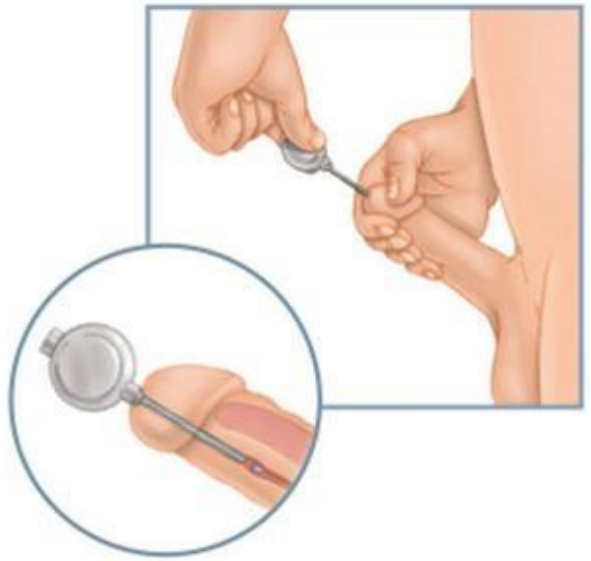
Intracavernosal Alprostadil

Adverse Effects

- Hematoma and bruising (apply pressure for 5 minutes after each injection)
- Infection at injection site
- Cavernosal plaque or fibrosis
- Penile pain
- Priapism
- Rare systemic reactions such as dizziness and hypotension

Intraurethral Alprostadil

- Contains a medication pellet inside a prefilled urethral applicator.
- The usual dosage range of intraurethral alprostadil is 125 to 1,000 mcg, but 500 mcg is typically needed in most patients.
- The dose should be administered **5 to 10 minutes** before sexual intercourse.
- Overall effectiveness is 43-65%.
- The voluntary **dropout rate** is **high**.



Intraurethral Alprostadil

Adverse Effects

- Urethral injury
- Urethral pain
- Vaginal burning, itching, or pain in sexual partners
- Priapism
- Syncope and dizziness

Alprostadil

Prostaglandin E1					
Alprostadil intracavernosal injection	Caverject, Edex	2.5 mcg intracavernosally 5–10 minutes before intercourse	10–20 mcg 5–10 minutes before intercourse. Maximum recommended dose is 60 mcg. Limit to not more than one injection per day and not more than three injections per week	Titrate dose to achieve an erection that lasts 1 hour	Patient will require training on an aseptic intracavernosal injection technique. Avoid intracavernosal injections in patients with sickle cell anemia, multiple myeloma, leukemia, severe coagulopathy, schizophrenia, poor manual dexterity, severe venous incompetence, or severe cardiovascular disease
Alprostadil intraurethral pellet	Muse	125–250 mcg intraurethrally 5–10 minutes before intercourse	250–1,000 mcg just before intercourse. Limit to not more than two doses per day		Patient will require training on proper intraurethral administration techniques Use applicator provided to administer medications to avoid urethral injury

Unapproved Agents

Yohimbine

- A central α_2-adrenergic antagonist
- Has peripheral proerectogenic effects.
- Yohimbine may reduce peripheral α- adrenergic tone, thereby permitting a predominant cholinergic tone.
- The usual oral dose is **6 to 15 mg** *three times per day*.

Unapproved Agents

Based on a meta-analysis of published studies that concluded that yohimbine is **only mildly efficacious** for *psychogenic erectile dysfunction*, the American Urological Association has cautioned against the use of yohimbine. In addition, yohimbine can cause many systemic adverse effects, including anxiety, insomnia, tachycardia, and hypertension.

Unapproved Agents

Papaverine

- A nonspecific phosphodiesterase type 5 inhibitor.
- Not FDA approved for erectile dysfunction.
- **Intracavernosal** papaverine alone is *not commonly* used for management of erectile dysfunction because the large doses required to achieve a therapeutic effect also produce *dose-related adverse effects*, such as priapism, corporal fibrosis, hypotension, and hepatotoxicity.

Unapproved Agents

Phentolamine

- A competitive nonselective α-adrenergic blocking agent.
- Most often as an **intracavernosal injection**.
- *Monotherapy* is **avoided** because large doses are required for an erection, and at these large doses systemic hypotensive adverse effects would be prevalent.
- A ratio of 30-mg papaverine to 0.5 to 1 mg phentolamine is typical, and the usual dose ranges from 0.1 to 1 mL of the mixture.

Vacuum Erection Device

Premature Ejaculation

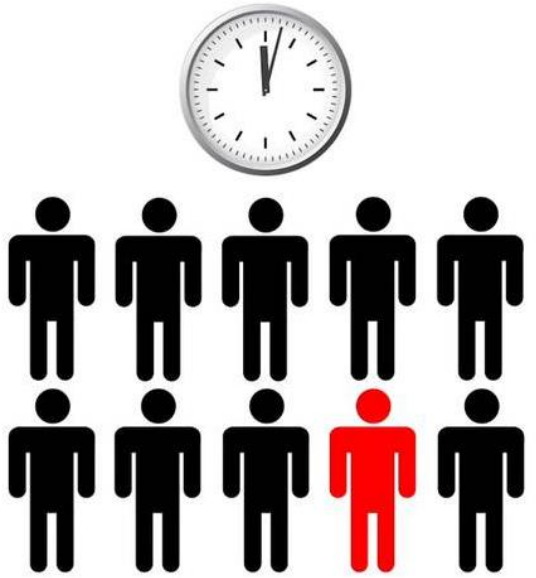
PE is characterized by:

- Ejaculation that *always* or *nearly always* occurs prior to or within approximately **one minute** of vaginal penetration, either present from the first sexual experience or following a new bothersome change in ejaculatory latency;
- The **inability to delay** ejaculation on *all* or *nearly all* vaginal penetrations; and
- **Negative personal consequences**, such as distress, bother, frustration, and/or the avoidance of sexual intimacy

Definition

Using this stringent definition, PE occurs in approximately **4 percent** of the male population, although up to 30 percent of men in community surveys report PE.

Few of these men typically *seek treatment* for their condition.



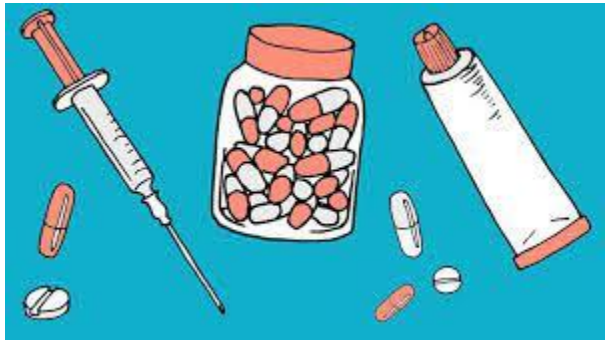
Definition

Approximately *30 percent* of men with PE have **concurrent ED**, which typically results in early ejaculation without full erection.

A wide **range of severity** is seen, with patients ejaculating on or *prior to penetration* in the most severe cases. Patients sometimes present for **infertility concerns**.

Management

Management depends upon the *etiology*, but the mainstays of therapy include selective serotonin reuptake inhibitors (SSRIs), topical anesthetics, and psychotherapy when psychogenic and/or relationship factors are present.



Selective Serotonin Reuptake Inhibitors

SSRIs are considered as the first line agents.

- paroxetine (10 to 40 mg/day),
- sertraline (50 to 200 mg/day),
- fluoxetine (20 to 40 mg/day),
- citalopram (20 to 40 mg/day), and
- escitalopram (10 to 20 mg/day)

SSRIs should be started at the lowest dose and *titrated up* as needed at three- to four-week intervals.

Selective Serotonin Reuptake Inhibitors

A meta-analysis of available trials suggests that **paroxetine** may be the **most effective** (nine-minute ejaculation delay over baseline).

It must be borne in mind that an 8.8-fold increase may still be marginal if baseline ELT is on the order of seconds. The typical range of *absolute change* in ELT from the systematic review suggested an increase of **1-5 minutes**.

Selective Serotonin Reuptake Inhibitors

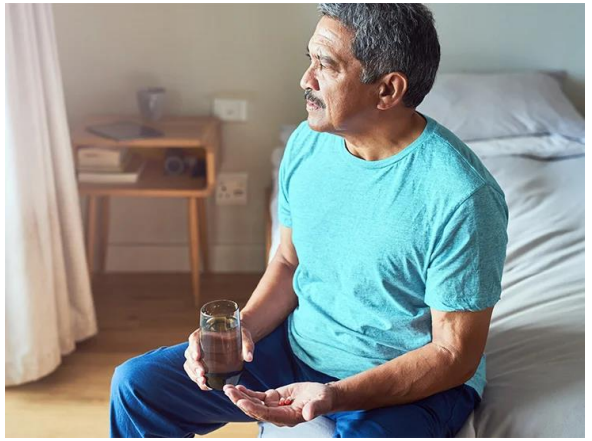
The full therapeutic effect of SSRIs is typically not seen until after **two to three weeks** of therapy, and *symptoms return* if treatment is stopped.

Therapeutic effect usually **sustained** during *long-term use*.

Selective Serotonin Reuptake Inhibitors

On-demand administration of clomipramine, paroxetine, sertraline and fluoxetine 3-6 hours before intercourse is modestly efficacious and well tolerated but is associated with substantially *less ejaculatory delay* than daily treatment in most studies.

On-demand treatment may be combined with either an *initial trial of daily treatment* or concomitant low dose daily treatment.



Selective Serotonin Reuptake Inhibitors

Adverse effects from SSRI treatment of PE have been reported in up 54% of men using these meds although the majority of studies indicate an approximately 1 in 3 chance of AEs.

AEs are usually **minor**, typically start in the first week of treatment and may gradually disappear within 2-3 weeks. They include fatigue, yawning, headache, mild nausea, diarrhea, perspiration, or decreased libido.

Selective Serotonin Reuptake Inhibitors

Adverse effects of SSRIs

- increased risk of upper gastro-intestinal bleeding
- priapism
- weight gain and an increased risk of type-2 diabetes mellitus
- abnormal sperm DNA fragmentation with paroxetine
- declines in semen concentration and normal morphology

Selective Serotonin Reuptake Inhibitors

There are anecdotal reports suggesting that *decreased libido* and *ED* are **less frequently** seen in <u>non-depressed</u> PE men treated by SSRIs compared to depressed men treated with SSRIs.

Treatment with SSRIs should be **avoided** in men with a history of *bipolar depression* due to risk of mania.

Selective Serotonin Reuptake Inhibitors

Patients are often reluctant to begin off-label treatment of PE with SSRIs due to concern about taking an antidepressant, treatment effects below expectations, and cost.

Patients should be advised to *avoid sudden cessation* or rapid dose reduction of daily dosed SSRIs as this may precipitate SSRI withdrawal syndrome.

Clomipramine

If SSRIs are *ineffective* or *not tolerated*, the serotonergic tricyclic **clomipramine** (12.5 to 50 mg/day) is considered to be second-line therapy.

Dapoxetine

Dapoxetine, also appears to be effective. Unlike other SSRIs, which are most effective when taken daily, dapoxetine is taken **on-demand** *one to three hours* before intercourse.

In RCTs, dapoxetine 30 mg or 60 mg taken 1-2 hours before intercourse is more effective than placebo from the first dose, resulting in a 2.5 and 3.0-fold increase in IELT, increased ejaculatory control, decreased distress, and increased satisfaction.

Dapoxetine

The most common are nausea, diarrhea, headache, and dizziness. AEs were **severe** enough to lead to discontinuation in just **4%** of subjects taking the 30 mg dose and 10% of subjects taking the 60 mg dose.

Dapoxetine

Comparison with SSRIs

- **lower** rate of *adverse effects* compared with daily SSRIs
- **no** indication of an increased risk of *suicidal ideation* or suicide attempts
- **little** indication of *withdrawal symptoms* with abrupt cessation
- **no** drug-drug *interactions*

Tramadol

Tramadol, an analgesic that has some activity at opioid receptors but also *inhibits reuptake of serotonin* and norepinephrine, may also be effective. Tramadol is recommended by the AUA PE Guidelines as a **second-line agent** (as on-demand) if SSRIs and clomipramine are ineffective or not tolerated.

However, it should be used with extreme **caution**, given the potential risk of *addiction* and side effects associated with opioids.

Topical anesthetics

Topical anesthetics are also more effective than placebo. Multicenter trials with an aerosolized, **lidocaine-prilocaine** spray have been reported to improve ejaculatory latency, ejaculatory control, and sexual satisfaction when applied *topically to the glans penis* five minutes before intercourse.

Topical anesthetics

Diminishing glans sensitivity may inhibit the spinal reflex arc responsible for ejaculation. Topical anesthetics may be associated with significant penile hypo-anesthesia and *possible transvaginal absorption*, resulting in **vaginal discomfort and/or numbness**. Use of a condom or thorough washing of the penis prior to penetration may help prevent these bothersome effects.

α1-adrenoreceptor Antagonists

Clinicians may consider treating men with premature ejaculation who have failed first-line therapy with α1-adrenoreceptor antagonists.

- These drugs may induce ejaculatory dysfunction such as retrograde ejaculation and/or failure of emission.
- Existing efficacy data remains very limited.

Behavioral and Psychological Therapies

Behavioral and psychological therapies are effective in some men. These interventions are designed to achieve a number of goals: improve self-confidence and communication in the relationship and, ultimately, increase the ejaculation latency.