Premature Ejaculation

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Introduction

Three of the most common male sexual dysfunctions:

- decreased libido,
- erectile dysfunction (ED), and
- ejaculatory dysfunction (including premature ejaculation [PE] in men ages 18 to 59 years).

One or more conditions can **coexist** in an individual.

Definition

PE is characterized by:

- Ejaculation that *always* or *nearly always* occurs prior to or within approximately **one minute (or two minutes)** of vaginal penetration, either present from the first sexual experience or following a new bothersome change in ejaculatory latency;

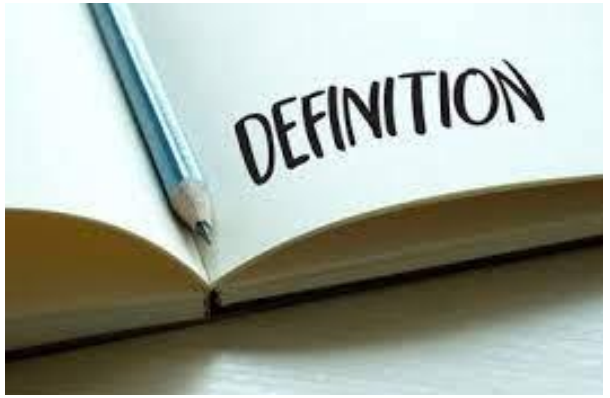
- The **inability to delay** ejaculation on *all* or *nearly all* vaginal penetrations; and

- **Negative personal consequences**, such as distress, bother, frustration, and/or the avoidance of sexual intimacy

Definition

PE can be divided into:

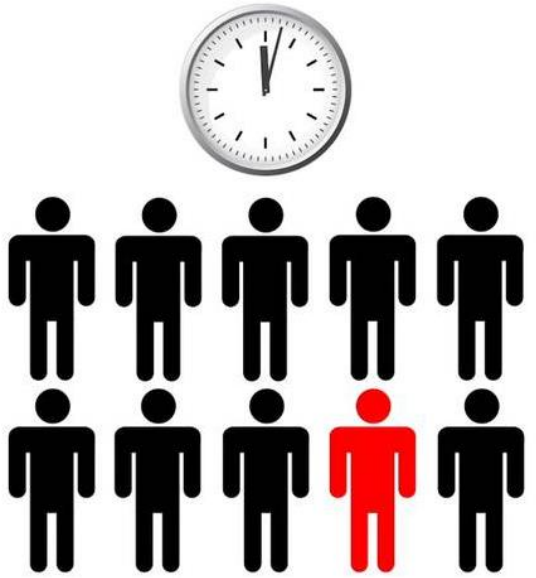
- lifelong
- acquired



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**.

Etiology

Multiple etiologic factors have been identified, including **organic** and **psychogenic** factors.

Any medical disease, drug, or surgical procedure that interferes with either *central* (including spinal or supraspinal) *control of ejaculation* or the *autonomic innervation* to the seminal tract, or sensory innervation to the anatomical structures involved in the ejaculation process, can result in delayed ejaculation, anejaculation, and anorgasmia.

Etiology

Associated factors:

- Low serum testosterone concentrations (**not causal**)
- Lower urinary tract symptoms (LUTS) in older men
- *Surgery* for benign prostatic hyperplasia commonly results in retrograde ejaculation, whereas radical prostatectomy or cystoprostatectomy result in anejaculation.

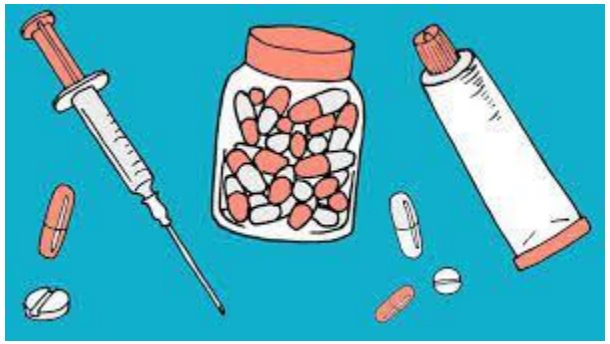
Etiology

- Patients with *longstanding diabetes mellitus* can also develop retrograde ejaculation due to failure of the bladder neck to close during ejaculation.

Ejaculatory latency is **not** affected by circumcision status.

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

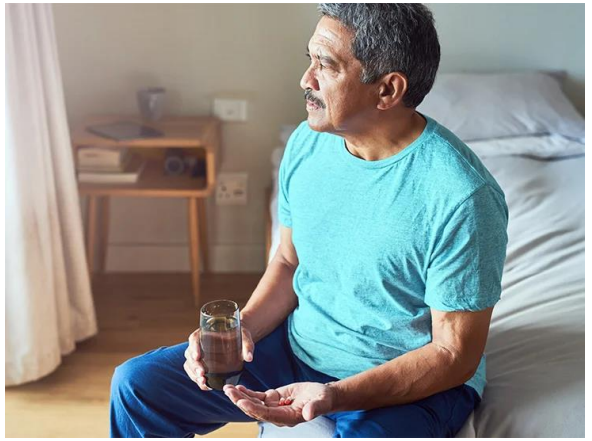
The full therapeutic effect of SSRIs is typically not seen until after **two to three weeks** of therapy, and *symptoms return* if treatment is stopped.

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 non-depressed 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*

Phosphodiesterase Type 5 Inhibitors

For men with both **ED and PE**, it is suggested to start a PDE5 inhibitor first to treat the ED. If the patient still has PE, then add an SSRI.

Phosphodiesterase Type 5 Inhibitors

The main findings of two meta-analyses:

- Both SSRIs and PDE5 inhibitors are more effective than placebo,
- PDE5 inhibitors are either as effective as SSRIs or slightly more effective, and
- combined therapy is more effective than either therapy alone.

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

Phosphodiesterase Type 5 Inhibitors

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%.

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]

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

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

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

Phosphodiesterase Type 5 Inhibitors

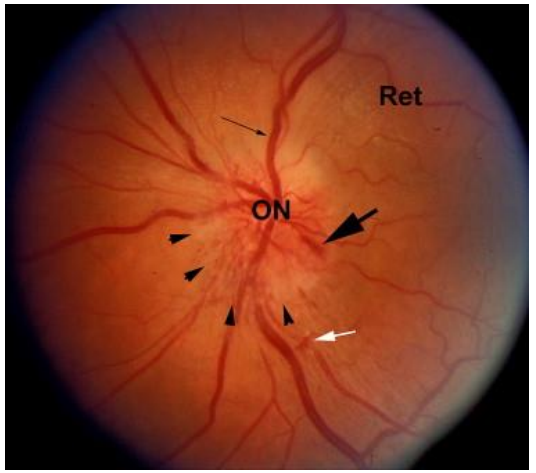
Sildenafil, vardenafil, and avanafil cause increased *sensitivity to light*, blurred vision, or loss of blue–green color discrimination in 2% to 3% of patients. This adverse effect is dose-related with the incidence increasing to 40% to 50% in patients taking sildenafil 200 mg.

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.

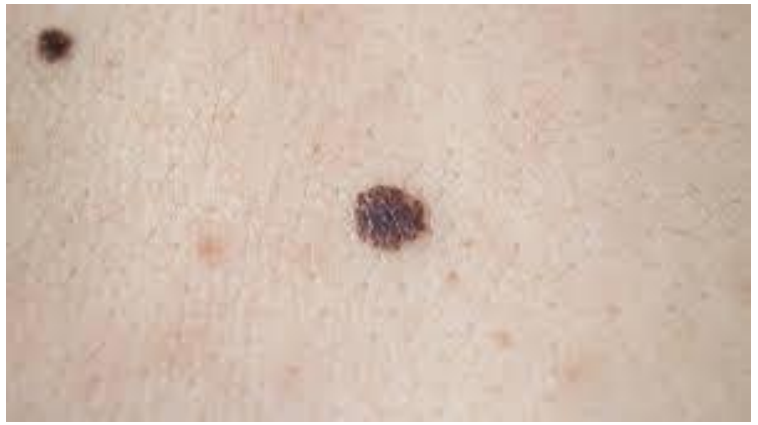
Phosphodiesterase Type 5 Inhibitors

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**.
- 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.

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.