

Erectile Dysfunction

S.Arasteh, MD

Urologist, Andrologist,

Kidney Transplantation Fellowship

Avicenna Research Institute

Epidemiology

- Erectile dysfunction (ED): the inability to attain and/or maintain penile erection sufficient for sexual performance or satisfaction
- ED affects up to 20% of men worldwide older than 20 years old and worsens with age

- Prevalence:
- 1%–10% for men younger than 40 years
- Approaches 50%–100% for men older than 70 years

- Medical comorbidities, such as metabolic syndrome and cardiovascular disease, are associated with ED
- Lower education and cigarette smoking are additional predictors for developing ED

- The inverse is also true, and ED is now considered a sentinel for future risk of cardiovascular disease

Major ED Risk Factors

- **Multivariate Adjusted Odds Ratio:**
- Diabetes mellitus 2.9
- Hypertension 1.6
- Cardiovascular disease 1.1
- Hypercholesterolemia 1.0
- Benign prostate enlargement 1.6
- Obstructive urinary symptoms 2.2
- Increased body mass index (≥ 30 kg/m²) 1.5
- Physical inactivity 1.5
- Current cigarette smoking 1.6
- Antidepressant use 9.1
- Antihypertensive use 4.0

Pathophysiology

- ED: psychogenic and organic etiologies
- With most having a functional organic disorder
- Organic causes:
 - Vasculogenic (most common)
 - Neurogenic
 - Anatomic
 - Endocrinologic

- Metabolic syndrome and its components→ generalized atherosclerosis→ impaired penile perfusion→ increased vascular resistance + vascular tone→ fibrosis→ a decline in erectile function

Metabolic Syndrome

- A series of biochemical, physiologic, metabolic, and clinical factors that increase the individual's risk of type 2 diabetes mellitus (T2DM), heart disease, and early mortality
- Prevalence: ranges between 10% and 84% of the population
- Risk factors: sedentary lifestyle, excess caloric intake, and higher socioeconomic status

- Erection is a neurovascular event→ ED can be secondary to neuronal dysfunction
- Any disorder of the brain, spinal cord, or peripheral nerves can negatively impact erectile function

- Iatrogenic damage to the cavernosal nerves and vasculature after radical pelvic surgery or after pelvic fracture
- Damage to the peripheral nervous system from diabetes mellitus

- Endocrine disorders such as low serum testosterone, as well as hyperprolactinemia, hyperthyroidism, and hypothyroidism, levels often lead to decreases in erectile function and libido

- ED can be drug induced
- Many antihypertensive medications can lead to reversible ED
- Other drug classes correlated with ED include antipsychotics, antidepressants, recreational drugs, and more

- Diuretics : ED ($\times 2$) \rightarrow Unknown
- β -Blocker (nonselective): ED \rightarrow Prejunctional α_2 -receptor inhibition
- α_1 -Blocker: Decreases ED rate but may cause alteration of ejaculation
- α_2 -Blocker: ED \rightarrow Inhibition of central α_2 -receptor
- ACE inhibitor: Possible reduction in ED
- Angiotensin II receptor blocker: Possibly reduction in ED

Drug-Induced ED and Suggested Alternatives

- Antihypertensive → Thiazide diuretics + General β -blockers
- **ACE inhibitors**
- **Angiotensin II receptor antagonists**
- **Selective β -blockers**
- α -Blockers
- Calcium channel blockers

- Psychotropics → Antipsychotics / Antidepressants / Anxiolytics
- Newer anxiolytics (bupropion, buspirone)

- Antiandrogen
- Androgen receptor antagonists
- Luteinizing hormone–releasing hormone agonists

- Recreational drugs:
- Tobacco → Tobacco cessation
- Alcohol (large volume) → Alcohol in moderate

Clinical Manifestations

- ED manifests with marked difficulty in obtaining erections, maintaining them until completion of sexual activity, and/or a significant decrease in erectile rigidity

- Many men have a poor understanding of ED and its symptoms and may confuse ED with decreased libido or disorders of ejaculation

Diagnosis and Testing

- The diagnosis of ED differs from most urologic diagnoses in that extensive diagnostic procedures are generally not required
- The diagnosis can be made based on the patient's report of consistent inability to attain and/or maintain an erection sufficient for satisfactory sexual intercourse

- Several well-validated questionnaires, such as the Index of Erectile Function (IIEF), are useful adjuncts to the patient's history

- The physical exam should focus on the neurologic, cardiovascular, and genital systems
- Obvious physical signs of hypogonadism: such as small testes or gynecomastia

- Laboratory tests are not mandatory for diagnosis of ED but can help delineate the etiology
- **Recommended laboratory tests include serum chemistries, fasting glucose or hemoglobin A1c, complete blood count (CBC), lipid profile, and morning serum total testosterone**

- Further diagnostic testing such as intracavernosal injection of erectogenic medications with or without penile duplex ultrasonography (PDU) are used at the clinician's discretion to better characterize the arterial or venoocclusive mechanisms of ED

Treatment

- The most recent AUA guidelines advocate that all therapeutic options for ED be offered, with any being a valid initial therapy
- This demonstrates a shift from the traditional escalation from least to most invasive treatments

Counsel the Man and Partner Regarding

- The value of psychosocial/relationship support from trained professional to optimize treatment satisfaction
- The importance of lifestyle change (weight loss, exercise, smoking cessation) to improve erectile function and overall health
- The benefits and risks/burdens of all available ED treatments that are not contraindicated

- Using a shared decision-making framework, identify appropriate treatments based on values and priorities of man and partner:
- PDE5i
- Vacuum devices
- Intraurethral (IU) alprostadil
- Intracavernosal injections (ICI)
- Penile prosthesis surgery

- Assess outcomes, adverse events and satisfaction of man and partner
- If inadequate efficacy and/or in unacceptable AEs and/or insufficient satisfaction, then address as appropriate:
 - - Dose adjustments (for PDE5i, IU alprostadil, ICI)
 - - Revisit instructions to maximize efficacy (for all treatments)

- - Revisit values and priorities of man and partner with mental health professional to refine values and priorities and/or to address psychosocial or relationship barriers to successful treatment
- - Consider alternate treatment

- Lifestyle modification is a primary treatment for ED
- Weight loss, diet, exercise, and decrease in cigarette smoking can lead to meaningful improvements in ED
- Switching or ceasing a causative medication can lead to significant improvement

- The AUA guidelines also propose a referral to a mental health professional to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship

- The most common medications for ED are oral phosphodiesterase type 5 inhibitors (PDE5is)
- These medications augment (but do not induce) the erectile response
- Each PDE5i has similar efficacy but different biochemical properties, and several can be used daily or on demand

- These medications result in **successful sexual intercourse rates of approximately 70%**
- Success may be lower in patients with DM, previous pelvic surgery, or radiation

- Side effects include headache, dyspepsia, flushing, and visual disturbances
- Dose titration is recommended
- The only true contraindication is coadministration with nitrate-containing medications for angina

- Intracavernosal injection (ICI) of alprostadil, papaverine, phentolamine, or a combination is another highly effective pharmacologic therapy
- Because of a higher risk of priapism, it is recommended that the first injection be in clinic and to start with a low dose

- ICI is contraindicated in men with psychological instability, coagulopathy, unstable cardiovascular disease, reduced manual dexterity, and concurrent use of monoamine oxidase inhibitors

- Alprostadil can also be administered as an intraurethral suppository (IUS), albeit with lower success rates (~50%)
- It is thus often used in combination with PDE5i
- IUS should also be tested in the office to avoid the rare case of hypotension

- Vacuum erection devices can be an effective alternate but are often considered cumbersome by patients

- In patients with subnormal testosterone values who are considering ED treatment with PDE5is, they can be counseled that testosterone replacement therapy (TRT) can improve the efficacy of PDE5i but should not be used as monotherapy

- One of the most effective methods of ED treatment is the surgical placement of a penile prosthesis
- Inflatable penile prostheses (IPPs) are more popular than a malleable variant
- IPPs have high patient and partner satisfaction because they can be utilized on demand for as long and as frequently as desired

- On the other hand, implantation is associated with the inherent risks of surgery and leads to irreversible ED if removed
- Device failure is rare
- Loss of penile length is a common complaint but, if present, is minimal
- Patients should be extensively counseled about this risk preoperatively

- Many emerging therapies, such as extracorporeal shock wave therapy, ICI of stem cells, and platelet-rich plasma injections, have shown promising preliminary results
- However, due to lack of quality data, they are **still considered investigational in the 2018 AUA ED guidelines**

Major Depressive Disorder (MDD)

- Depression is the **most important factor** in the description of sexual dysfunction
- **Loss of libido:** affect from **25-75%** of both male and female patients with depression
- **Disorders of arousal** also appear to be relatively common in both men and women with major depression

- Prevalence appears to be correlated with the severity of depression
- Sexual dysfunction is a known side effect of **antidepressant treatment** → affecting up to **58-73%** of those who receive antidepressant treatment

- Distressing to some patients→ may lower the dose of their antidepressant, or discontinue it→ ↑risk for nonresponse or relapse of depression
- Antidepressant-induced sexual dysfunction→ a major obstacle to adherence to effective longterm treatment of depression

What is SAM-e?

- S-adenosyl-L-methionine (SAME), a naturally occurring molecule
- Natural mood elevator
- Available commercially in Europe since the late 1970s as a treatment for depression and other conditions
- Released in the U.S. in a stable, enteric-coated oral formulation as an OTC dietary supplement

- Helps the methylation of protein, DNA, membrane phospholipids and **neurotransmitters**
- Essential for synthesis of **serotonin, dopamine** and **norepinephrine**

- SAdMe: uniformly distributed in the brain where it serves as the major donor of methyl groups required in the synthesis of neuronal messengers and membranes
- The antidepressant efficacy of SAdMe has been studied → a potential therapeutic role of parenteral and oral SAdMe in the treatment of depression

- A small but statistically significant improvement in overall sexual satisfaction among antidepressant non-responders following the administration of adjunctive SAMe

- SAME in SSRI/SNRI nonresponders→ improves both arousal dysfunction and erectile dysfunction
- Independent of change in the degree of depressive symptoms
- Availability of an augmentation strategy that improves sexual dysfunction has the potential to greatly enhance compliance and improve quality of life

- These promising results suggesting the potential utility of adjunctive SAMe in relieving arousal and erectile dysfunction, are merely suggestive and warrant replication

- These benefits were observed only in men: similar to phosphodiesterase inhibitor studies, in which the benefits on sexual functioning were seen in men, specifically with regard to improved arousal and erection rather than libido

- Phosphodiesterase inhibitors → \uparrow NO, leading to a relaxation of smooth muscle of the vessel walls in the penis, which in turn causes vasodilation by increased blood flow to the penis, resulting in erection
- Mechanism of SAME on male arousal and erection is not known
- Its possible mechanism of action: SAME has been associated with high flow mediated vasodilation and may have beneficial effects on vessel walls in an elderly population

- + SAdMe is a regulator of cystathionine beta-synthase, the enzyme that produces hydrogen sulfide in the brain and relaxes smooth muscle in synergy with nitric oxide
- →→ SAdMe may result in vasodilation, increasing the likelihood of penile erection in a fashion analogous to nitric oxide
- Another possible mechanism: SAdMe through its ability to be neuroprotective to dopaminergic neurons may enhance the role dopamine plays in promoting sexual functioning

- A prospectively designed study, employing several different scales measuring sexual dysfunction would be better suited to definitively answer whether adjunctive SAlMe is indeed effective when used in this capacity
- Improvement in other aspects of the sexual response cycle in men, or in women???

- It is not possible to directly generalize the present findings to all patient populations (children, adolescents, patients with active alcohol or drug use disorders, patients with unstable medical disorders, at imminent risk of suicide, or patients who are on non-SSRI antidepressants)

- In conclusion→ adjunctive SAME can have positive benefit on male arousal and erectile dysfunction, independent of improvement in depressive symptoms
- These findings are preliminary, and warrant replication

- Brand name: **ADOMEDS**
- Oral Capsule 400mg
- On empty stomach

Precaution

- Pregnancy and breast feeding
- Bipolar disorder
- Drug Interaction: Levodopa

Side Effects

- Mild gastrointestinal side effects
- Anxiety
- Insomnia

Disorders of Male Orgasm and Ejaculation

Epidemiology

- Ejaculatory dysfunction ranges from premature ejaculation (PE), to delayed ejaculation (DE), to a complete inability to ejaculate
- The 2020 AUA PE guidelines define lifelong PE as poor ejaculatory control, associated bother, and ejaculation within ,2 minutes of initiation of penetrative sex

- Interestingly, although abnormal intravaginal latency times (IVLT) affect only 2.5% of the general male population, a much higher number report having the disorder
- The prevalence (20%–30%) varies widely

- The prevalence of DE is less clear, with studies suggesting that up to 40% of men are impacted and worsening with age
- Retrograde ejaculation (RE) primarily develops after surgical bladder outlet procedures for lower urinary tract symptoms (LUTS)

- Another common cause of DE is the use or abrupt cessation of selective serotonin reuptake inhibitors (SSRIs)
- 5 to 15% of men using SSRIs will have sexual dysfunction, sometimes following the first dose

- Other rare disorders of orgasm and ejaculation include orgasmic headache, painful ejaculation, and post orgasmic illness syndrome
- Although these are rare, painful ejaculation can occur in up to 25% of men with benign prostatic hypertrophy (BPH)/LUTS

Pathophysiology

- EjD:
- Acquired: usually secondary to sexual performance anxiety and/or relationship problems
- Lifelong: secondary to neurobiological and genetic variations

- Almost half of all men with ED also complain of PE, likely secondary to “rushing” sex to avoid premature detumescence
- DE or absent ejaculation has a wide variety of possible etiologies

Clinical Manifestations

- PE is the most common, in which men have a recurrent pattern of ejaculation within 2 minutes of vaginal penetration that is bothersome to the patient and partner
- This can either be lifelong or acquired

- DE (usually after ,25–30 minutes), anejaculation, and anorgasmia constitute the other end of the spectrum
- RE commonly presents after surgical procedures that compromise the bladder neck, such as transurethral resection of the prostate (TURP)

- Aging man: Degeneration of penile afferent nerves
- Psychogenic: Inhibited ejaculation
- Congenital: Müllerian duct cyst / Wolffian duct abnormality / Prune belly syndrome
- Anatomic causes: Transurethral resection of prostate / Bladder neck incision

- Neurogenic causes: Diabetic autonomic neuropathy / Multiple sclerosis / Spinal cord injury / Radical prostatectomy / Proctocolectomy / Bilateral sympathectomy / Abdominal aortic aneurysmectomy / Para-aortic lymphadenectomy /

- Infective: Urethritis / Genitourinary tuberculosis / Schistosomiasis
- Endocrine: Hypogonadism / Hypothyroidism
- Medication: α -Methyldopa / Thiazide diuretics / Tricyclic and SSRI antidepressants / Phenothiazine / Alcohol abuse

Diagnosis and Testing

- Lifelong PE is present since the patient's first sexual experience
- In acquired PE, patients experience IVLT that is markedly reduced from prior sexual encounters
- A significant amount of men who self-report PE fail to satisfy these criteria

- Standardized questionnaires can be used as an adjunct to a full history in diagnosis, especially to evaluate for the commonly concurrent presence of ED
- Physical exam and labs are of limited utility

- All other forms of EjD are similarly diagnosed by history and physical exam. RE may be confirmed by obtaining a postejaculation urine sample for presence of sperm. Other testing should be used as clinically indicated but may be of limited utility

Treatment

- All men with PE should receive basic psychosexual education or coaching, which is often used in conjunction with pharmacologic therapy
- First-line medical treatment includes daily SSRIs, on-demand dapoxetine or clomipramine, and topical penile anesthetics

- On-demand medications are available but allow for less sexual spontaneity
- Tramadol can be recommended if the patient has failed first-line therapy
- Lastly, ED is commonly associated with PE and should be treated first
- Any surgical options for PE are considered experimental

- Dapoxetine: 30–60 mg, On demand, 1–3 hours before intercourse \cap Lifelong PE + Acquired PE
Approved in 50 countries
- Paroxetine, Sertraline, Fluoxetine, Citalopram, Clomipramine: Once daily \cap Lifelong PE + Acquired PE

- Tramadol: 25–50 mg, On demand, 3–4 hours before intercourse \cap Lifelong PE + Acquired PE
¥ Potential risk of opiate addiction
- Level of Evidence: Low [Others: High]
- Topical lignocaine/ prilocaine: Patient titrated, On demand, 20–30 minutes before intercourse \cap Lifelong PE + Acquired PE

- Delayed or absent ejaculation is also treated with psychosexual therapy
- But pharmacotherapy has very limited success
- ED should be treated concurrently
- RE has proven difficult to treat, but case reports have shown success with pseudoephedrine and its analogues, tricyclic antidepressants, and bladder neck reconstruction

