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Erectile Dysfunction

Authors

Thushanth Sooriyamoorthy[1]; Stephen W. Leslie[2].

Affiliations

[1] University of Birmingham
[2] Creighton University School of Medicine

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Continuing Education Activity

Erectile dysfunction is a widespread condition in males over 40 years of age all over the world. It has a variety of causes and is often treatable. Left untreated, it can be the source of severe emotional stress to both patient and partner. This activity reviews the evaluation and treatment of erectile dysfunction and highlights the role of the interprofessional team in managing patients with this condition.

Objectives:

- Outline the etiology of erectile dysfunction.
- Describe the patient history associated with erectile dysfunction.
- Outline the management considerations for patients with erectile dysfunction.

Access free multiple choice questions on this topic.

Introduction

Erectile dysfunction (ED), formerly termed impotence, is defined as the failure to achieve or maintain a rigid penile erection suitable for satisfactory sexual intercourse.[1] While no specific time period is part of this definition, some have suggested that the condition needs to persist for six months. It is a common condition in men aged over 40 years, with the prevalence increasing steeply with age and other co-morbidities.[2]

Erectile dysfunction can be a symptom of a wide range of underlying pathologies and is an important but underutilized cardiovascular risk factor.[3][4][5][6][7] Any disease process which affects penile arteries, nerves, hormone levels, smooth muscle tissue, corporal endothelium, or tunica albuginea can cause erectile dysfunction. It is generally acknowledged that erectile dysfunction is closely related to cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension, among other disorders. Endothelial dysfunction appears to be the other common pathway in these patients.[8]

While the vast majority of patients with ED will have organic disease, some may have a primary psychological issue; particularly younger men. Even when the underlying cause is organic, there are almost always psychological consequences to ED regarding marital and relationship issues, cultural norms and expectations, loss of self-esteem, shame, anxiety, and depression, among others. Erectile dysfunction can cause considerable emotional damage to the patient and their partner as well as have a significant impact on their quality of life. On the bright side, erectile dysfunction is almost always treatable.

Etiology

It is important to note that the cause of erectile dysfunction is often multifactorial. It is useful to distinguish early, whether the condition has an obvious underlying psychological cause or an organic etiology. Depression, performance anxiety, and other sexual disorders can be strong contributing factors even when organic causes also exist. Aging is an important factor contributing to erectile dysfunction. As patients age, cardiovascular diseases, hypertension, and other co-morbidities play an increasingly significant role in this condition. Diabetes mellitus and metabolic syndrome can

affect several organ systems resulting in the accelerated deterioration of erectile function and can disrupt the mechanisms underpinning erections on a molecular level.[8][9] Other causes of erectile dysfunction include neurological diseases (such as multiple sclerosis), hormonal causes (e.g. hypogonadism, thyroid), traumatic (e.g. pelvic fractures, spinal cord injuries), hyperlipidemia, stroke, sleep apnea, COPD, glaucoma, multiple sclerosis, sequela of priapism, depression, prostatic hyperplasia with lower urinary symptoms (BPH with LUTS), iatrogenic (e.g. post transurethral resection of the prostate) and a variety of medications (antidepressants, antihypertensives, antipsychotics, opioids, and recreational drugs).[10][11][12][13][14][15][16][17][18]

Cardiovascular Disease and Erectile Dysfunction

Cardiovascular disease is a very significant risk factor for erectile dysfunction. Almost 50% of men with known coronary artery disease proven by cardiac catheterization have significant erectile dysfunction.[19] Part of the reason for this is that the coronary arteries and the penile cavernosal arteries are similar in size and tend to develop atherosclerotic problems similarly. Since the cavernosal arteries are smaller, they will tend to develop blockage from atherosclerotic plaques earlier resulting in vasculogenic ED years before the clinical appearance of coronary artery disease. Both cardiovascular disease and ED involve endothelial cell dysfunction in their pathophysiology.[20]

These patients will often demonstrate subclinical atherosclerosis long before any overt ED by as much as ten years. The cavernosal arteries being of smaller diameter means that vasculogenic ED often precedes coronary artery disease, myocardial infarctions and strokes by up to five years.[3][21] Younger men who present with unexplained ED appear to have a very significant increase, up to fifty-fold, of their cardiovascular risk in later life compared to an age-matched control group.[4][22] Patients should be informed that ED is a significant indicator of underlying heart disease and they should be referred for further cardiovascular risk screening and treatment.[3][4][5][6][7][22]

The Prostate Cancer Prevention Trial Database showed that having ED increased their cardiovascular risk roughly equivalent to the risk of smoking or having a family history of myocardial infarctions.[23] A meta-analysis of 14 studies totaling over 90,000 men with erectile dysfunction, found that men with ED enjoyed 44% more cardiovascular events, 62% more myocardial infarctions, 39% more strokes and a 25% increased risk of death compared to patients presenting without ED. Erectile dysfunction correlates with an increased risk of CV events.[24]

This means that erectile dysfunction has useful independent predictive value for future cardiovascular events and is why all patients with ED should be screened for cardiovascular risk.[21] If their cardiovascular risk is intermediate, non-invasive testing for subclinical atherosclerosis and/or an exercise stress test is suggested, but if they are high risk, a formal cardiology referral is recommended.[4][25][26][27]

Besides cardiovascular disease, there are strong correlations between ED, hypertension, hyperlipidemia, diabetes, hypogonadism, obesity, smoking, alcoholism, benign prostatic hyperplasia (BPH) with lower urinary symptoms (LUTS), depression, and premature ejaculation.

- About 40% of men with ED will have hypertension while 35% of all hypertensive men will also have ED.[28][29][30]
- Hyperlipidemia is found in about 42% of men with ED.
- Undiagnosed diabetes is up to three times as likely in men with erectile dysfunction (28%) compared to non-diabetic men with normal erections (10%).[28][31][32]
- Among men over 50 years of age, diabetics are roughly twice as likely to have ED (46%) compared to non-diabetics (24%).[33]
- The longer a patient has diabetes and the more severe, the greater the risk of ED.[33]
- One-third of diabetic men will have hypogonadism which may partly explain the high correlation between diabetes and ED.[34]
- Up to 35% of all men with ED will also have hypogonadism and about 6% will have abnormal thyroid function.[35][36] While testosterone deficiency can negatively impact erectile function, vascular disease and diabetes are far more likely causes of ED.[37]

- Obesity is associated with a 50% increase in ED compared to men of normal weight.[38] One-third of the obese men with ED who enrolled in a weight loss program resolved their ED problem in 2 years.[39]
- In smokers who quit, erectile quality improved 25% after one year.[40]
- Heavy alcohol users also report an increased risk of ED compared to the general population.[31] The precise cause is uncertain but is thought to be due to direct alcoholic toxicity to the corporal endothelium, loss of corporal smooth muscle tissue, and early neuropathy.[41]
- There is a strong correlation between BPH with LUTS and ED. The majority of men with symptomatic BPH, up to 72%, will also have ED.[42][43][44]
- Patients with depression are almost 40% more likely to have ED than normal men without depression. Conversely, the incidence of depression in men with ED is almost three times greater.[45]
- Obesity and morbid obesity are significant risk factors for ED. Treatment of obesity with bariatric surgery has been shown to significantly improve sexual performance.[46][47][48]
- At least 30% of patients with ED will also have premature ejaculation and possibly as many as 60%.[28] [49] Successful treatment of the ED will often alleviate the premature ejaculation, due to reduced performance anxiety. If not, premature ejaculation can be alleviated much more easily once the erectile dysfunction has been successfully treated.

One-quarter of all cases of ED are thought to be due to prescription medications. Of the twelve most commonly prescribed medications in the US, eight list erectile dysfunction as a possible side effect.[35][50] These drugs would include most antidepressants (especially SSRIs), cimetidine, ketoconazole, spironolactone, sympathetic blockers (methyldopa, clonidine, and guanethidine), thiazide diuretics, and other antihypertensives. (Angiotensin Converting Enzyme (ACE) inhibitors and calcium channel blockers are the least likely to cause ED.) Beta-blockers are only a minor contributor to ED, while alpha-blockers actually improve erectile function.[51][52]

Of the prostate cancer patients who undergo radical prostatectomy surgery, 85% can expect erectile dysfunction post-operatively compared to an ED rate of only 25% for men who received definitive radiation therapy.[53][54] (This data refers to patients who did not have ED prior to their prostate cancer treatment.) Interestingly, the use of robotic surgery for radical prostatectomies has not changed the post-operative incidence of ED.

The role of bicycle riding in ED is somewhat controversial. Traditional racing bicycle seats place considerable pressure directly on the perineal nerves as well as the pudendal and cavernosal arteries which suggests it could be a potential problem to serious cyclists.[55][56] A 2020 meta-analysis of 3,330 cyclists compared to 1,524 non-cycling controls indicated a significantly increased risk of ED in the cyclists.[57]

Epidemiology

It is difficult to obtain accurate values for the true prevalence of erectile dysfunction, as many patients fail to seek any medical attention and many physicians are reluctant to ask patients about their sexual health. The best available data indicates that 52% of men in the US between 40 and 70 years of age suffer from erectile dysfunction.[1][31][58] It is estimated that at least 30 to 50 million men in the US and at least 150 million men globally have ED.[59][60] These values are likely a gross underestimate of the actual number of men with ED due to reporting bias, cultural factors, a general failure by many physicians to inquire about their male patient's sexual health and embarrassment issues.[58]

It is known that the prevalence of erectile dysfunction is closely related to age and the presence of other co-morbidities such as diabetes, hypogonadism, and cardiovascular disease.[58] The best available data from the Massachusetts Male Aging Study indicates an overall prevalence of 52% with the incidence clearly increasing with age.[31] At age 40, about 40% of men are affected while 70% will report having ED by age 70.[31] These findings were confirmed by the National Health and Social Life Survey and other similar studies.[61][62]

Pathophysiology

The critical process in penile erection activity is the relaxation of the intracavernosal smooth muscle. This permits increased blood flow into the corpora cavernosa which fills with blood and compresses the emissary veins, reducing

venous outflow. The process is under the control of the paraventricular and medial preoptic nuclei of the hypothalamus. The signals travel through the parasympathetic nervous system to the parasympathetic nerves of the S2-S4 sacral plexus and then to the penis via the cavernosal nerves. Nitric oxide released by the cavernous nerve terminals initiates the erectile process while nitric oxide from endothelial cells acts to maintain it.

Nitric oxide stimulates the production of cyclic guanosine monophosphate (cyclic GMP) when it enters the smooth muscle. Protein kinase G is activated by cyclic GMP which opens potassium channels while closing calcium channels. Low intracellular calcium causes the intracavernosal smooth muscle tissue to relax resulting in increased arterial flow with simultaneous veno-occlusive activity. The result of all this is a rigid erection with minimal blood flow into or out of the corpora once the erection is established. The corporal smooth muscle contracts again when the cyclic GMP is degraded by penile phosphodiesterase and the process reverses. Pathology arising from any of the above processes can result in erectile dysfunction.[63][64]

History and Physical

A thorough medical history, detailed sexual history, and physical examination are required before embarking upon any treatment or further investigations. It is also important to obtain a complete medication list including supplements, particularly if targeting prostate problems as they often contain anti-androgens.

We have found it useful to give the patient a scoring system so they can better communicate the degree of their erectile rigidity with 100% being the best and hardest they ever had, 0% being absolutely flaccid and 50% being just barely hard enough for penetration. This simple scoring system has made it much easier for patients to clearly indicate how rigid their erections are and track their progress after treatment. Alternately, a questionnaire, such as the International Index of Erectile Function Questionnaire (IIEF), can be given to the patient to fill out in private. The questionnaire has been validated and found useful for monitoring the severity of erectile dysfunction and treatment efficacy.[65]

Typical sexual history questions include:

- How hard or rigid an erection can you now get (with 50% being just barely enough for penetration)?
- What is the best or hardest erection you can get right now?
- How long can that erection last?
- Does the penis feel numb or in any way unusual?
- Does the penis lose rigidity during foreplay?
- Does the penis lose rigidity only when attempting vaginal penetration?
- Does the penis stay erect and rigid until immediately after penetration? (This could be from anxiety or a venous leak.)
- Do you still get morning erections?
    - If so, are the morning erections any better or longer-lasting than the erections you get when having intercourse?
    - If not, when was the last time you had a good, morning erection?
- Any overnight erections? If so, how hard are they?
- Does the hardness of the erection vary much from one day to the next?
- Has there been any time or recent circumstance when the erection worked any better such as with masturbation or an alternate partner?
- How is erectile rigidity with masturbation compared to when attempting intercourse?
- When was the last time your erections worked normally and you had sexual intercourse?

- When did the erection trouble begin?
- Did it start suddenly or gradually? (sudden, unexplained onset of ED is almost always psychogenic)
- Was there any significant change in your life that happened at about the same time as the erection trouble started? New relationships or medications?
- Is the main problem insufficient rigidity or maintenance?
- Is the problem stable or getting worse?
- Is there any history of a particularly traumatic sexual event in your past?
- What do you use for contraception?
- Have you already tried any treatments? If so, what?
- Are ejaculation and orgasm normal even if the erections are not?
- How hard does the erection get at ejaculation?
- Do you feel your general interest in sexual activity is roughly normal?
- How often would the patient want to have sexual intercourse if his erectile dysfunction were successfully treated?
- Does your partner agree with that frequency?
- Does your partner know you are here seeking treatment? If so, are they encouraging?
- Would your partner be willing to become involved in treatment?
- How often do you and your partner currently attempt intercourse?
- Which of you usually initiates sexual activity and how?
- What will happen to your relationship if the erection trouble isn't successfully treated?
- Are the erections straight or curved?
- Is there a problem with libido, interest, ejaculation, or orgasm? If so, when did these other symptoms start?
- Would you be satisfied if we could get the erections up to 65% or 75% and they would last for 10 or 15 minutes? If not, what would you consider a successful treatment?

Other helpful things to elicit in the patient history include vascular risk factors (e.g. hypertension and diabetes); lifestyle factors (such as smoking, activity level, alcohol intake, and the use of any recreational drugs), and general medication history.[66] With the patient's permission, the partner should also be present for history as they can give a different perspective on the relationship and their views are very useful in measuring the response to therapy. Having the sexual partner involved in the treatment process greatly improves the outcome. The partner may also provide a different perspective on the nature of sexual dysfunction as well as relationship issues not otherwise forthcoming directly from the patient.

A full general and cardiovascular examination should be undertaken, as erectile dysfunction could be the first symptom of underlying vascular disease. Peripheral pulses should be checked and blood pressure measured. The genitalia should be carefully inspected, looking at the testicular size (hypogonadism), signs of infection (such as redness and discharge in acute balanoposthitis), the presence of penile fibrosis or plaques (as in Peyronie disease), and phimosis (the inability to retract the foreskin). Hair distribution, breast size (gynecomastia), and a detailed neurological examination are helpful. The cremasteric reflex should be evaluated. (This is done by gently scratching or stroking the upper, inner thigh while observing the scrotum. A normal reflex would be retraction or elevation of the ipsilateral testicle. This reflex will be normal if the thoracolumbar erection center is intact.)

Erectile dysfunction can be the first symptom of otherwise silent cardiovascular disease, so a full cardiovascular workup should be completed in all patients without an obvious cause of their ED.[22][67]

Evaluation

It is often difficult and awkward for many primary care physicians to verbally inquire about their patient's sexual health. This is understandable based on cultural norms and potential embarrassment. We have found the following phraseology to be very acceptable when vocalized in a way that indicates, by intonation, the questioner is expecting that everything will be OK. *"How is your sex life? Everything working OK for you?"* Men without a sexual problem are likely to respond with a quick "everything's fine" as a response. If the patient hesitates with his response or indicates that things are "not like they used to be", this should indicate that there is a potential sexual disorder that warrants further inquiries and investigation.

Psychogenic ED and Mental Health

It's very helpful to distinguish between obvious psychological and organic causes of ED as well as to verify that the patient actually has erectile dysfunction and not another type of sexual disorder such as premature ejaculation. Careful questioning should be able to determine if the patient has actual, organic erectile rigidity failure or some other sexual problem. Items in the history that point towards a psychological etiology include: sudden onset of the erectile dysfunction (especially if related to a new partner or a major life-changing event), situational ED, normal erections with masturbation or a different partner, the presence of good morning erections and high daily variability in erectile rigidity. Obvious cases of psychogenic ED should be referred to an appropriate mental health professional. Even without obvious psychological issues, involving mental health experts can help deal with associated problems such as reducing performance anxiety, promotion of treatment adherence, improving relationship issues, identifying interpersonal conflicts, and setting realistic expectations for the couple.[68]

It is often difficult and awkward for a physician to recommend a mental health evaluation for a patient, especially at their first visit. We have found a few ways to explain and justify a mental health consultation that make it easier for the patient to accept the referral:

- A mental health assessment is part of our routine evaluation; we recommend for everyone with ED.
- It's just for a one-time evaluation; an opinion. If no problems are found, that's it.
- It's just like a blood test; if everything is normal, we go on and if not, we deal with it.
- We take vital signs (blood pressure and temperature) at every office visit for the same reason; because problems in these areas are not always obvious, yet if not diagnosed and treated they can cause the patient serious harm.
- Most patients with ED will not have an underlying psychological cause, but just having ED will damage relationships, increase stress, diminish self-esteem, and create anxiety; all of which interferes with a successful outcome.
- Identifying any emotional, anxiety, or relationship issues early means they can be dealt with properly and, if nothing is found, we just go on.

Blood Testing

There are no specific tests absolutely required for the initial evaluation of ED, but many physicians will order routine blood testing to include a complete blood count and electrolytes as well as baseline renal and liver function tests, HgbA1c to screen for diabetes mellitus, and a lipid profile. Checking a morning testosterone level is recommended by the 2018 AUA Guidelines on Erectile Dysfunction, but some experts feel it is not absolutely necessary unless there are other symptoms suggestive of hypogonadism, such as loss of sexual desire or testicular atrophy on physical examination. However, if not measured initially, a morning testosterone level should certainly be checked to rule out hypogonadism if patients fail oral PDE-5 ED therapy.

Other blood tests that may reasonably be requested include LH and prolactin (if hypogonadism is found) and sickle cell in the African/Caribbean patient. Thyroid function (TSH) may also be optionally measured.

Patients with abnormal laboratory testing are referred back to their primary care for further evaluation and treatment.

In our specialty clinic, we routinely order a complete blood count (CBC), a comprehensive metabolic panel (CMP which includes liver and renal function), a lipid profile, TSH level, HgbA1c, and a morning testosterone assay on all

new patients presenting for evaluation of their ED unless these tests have been recently performed and the results known.

Shared Decision Making

The currently recommended approach to the patient with erectile dysfunction, according to the 2018 AUA Guidelines Statement on ED, is by Shared Decision Making, where the physician informs and educates the patient and his partner, using the best available evidence, about the various, appropriate treatment options available to them and whether any further diagnostic testing is reasonable or advisable. A frank discussion about the pros and cons of testing and treatment ultimately leads to an informed patient's choice that corresponds to the couple's values and preferences.[69] This is similar to the old "goal-oriented" approach of famed urologist Dr. Tom Lue, who urged physicians to focus on realistically discussing therapeutic options with patients to facilitate their personal treatment selection rather than pursuing extensive testing which ultimately doesn't significantly affect outcomes.

The basis for this approach is that, with the possible exception of psychotherapy for purely psychogenic ED, there is no effective cure for erectile dysfunction, so identification of the underlying cause is only useful for detecting other potential health issues and comorbidities. Given this fact, the focus changes from expensive diagnostic testing, that will not significantly affect the outcome, to facilitating patient treatment selection after a frank and detailed discussion of his reasonable therapeutic options. With this in mind, no other investigations are generally required for patients with ED, although specialized testing may be helpful in selected individuals.

Further Testing (Optional)

All of the following tests for patients with ED should be considered optional for selected patients only.

Penile Biothesiometry is a simple office screening test for penile neuropathy using skin vibrational threshold sensitivity. The blunt tip of a vibrating probe is sequentially placed on the right and left shaft as well as the glans. The intensity of the vibrations is varied and the patient is asked to indicate when he just begins to feel the tip vibrating. The minimal intensity of the probe vibrations that the patient can detect would be his threshold vibrational sensitivity which can be compared to normal standards. Five separate readings are done at each site and the results averaged; then compared to normal values based on age.[70] While not directly testing erectile nerves, it serves as a reasonable, safe, and inexpensive office test of the penis for neuropathy. More specialized nerve testing can be done on patients who test positive.[70][71][72] It's been suggested that patients with an abnormal biothesiometry test might by somewhat hypersensitive to intracavernosal injection therapy due to denervation hypersensitivity, but this has not been confirmed.

Nocturnal Tumescence Testing (NPT) is helpful in differentiating psychogenic from organic erectile dysfunction. Testing involves measuring the frequency, tumescence (circumference changes), duration, and maximal rigidty of nocturnal erections. Nocturnal erections require complete functioning of the neurovascular axis and normally occur during REM sleep. A normal functioning male has between 3 and 6 erections a night, with a mean duration greater than 30 minutes, maximal rigidity greater than 70% at both base and tip as well as an increase in circumference of over 3 cm at the base and 2 cm at the tip.[73] This is repeated, usually for three nights. Men with purely psychogenic ED will typically demonstrate normal NPT tracings while those with organic problems will show abnormal nocturnal erectile activity. Hypogonadism will often cause a decrease in rigidity while maintaining some tumescence on NPT studies.[74][75] NPT monitoring was once thought to be necessary to reliably distinguish psychogenic from organic erectile dysfunction, but today it is rarely used or necessary.

Penile Duplex Doppler Ultrasound measures arterial vascular flow and checks for cavernous veno-occlusive dysfunction (venous leak).[76] It may also be useful after penile trauma, post-priapism, Peyronie disease, and ED patients who fail to respond to oral agents.[76] The study is typically done by giving the patient an intracavernosal injection of a vasoactive drug, usually 20 micrograms of prostaglandin E1. (This also serves as a clinical trial of penile injection therapy.) Following the injection, the peak systolic velocities (PSV) are measured. A normal value is >35 cm/sec. while a value of <25 cm/sec. suggests arterial insufficiency. The value of <25 cm/sec was found to have 100% sensitivity and 95% specificity for patients with abnormal pudendal arteriography.[77] Hypertensive patients who have vasculogenic ED as demonstrated by a significantly reduced cavernosal arterial flow on duplex ultrasound should be referred for a full cardiac evaluation due to their increased cardiovascular risk.

Cavernous veno-occlusive dysfunction (often called venous leak by patients) can also be demonstrated using ultrasound. This finding represents the failure of penile corporal rigidity despite adequate arterial inflow. It is demonstrated by rapid detumescence despite consistently normal peak systolic and end-diastolic velocities (EDV >5 cm/sec).[78] Measuring the vascular resistive index (RI) can aid in the diagnosis of veno-occlusive dysfunction. This is calculated by using the formula: RI = (PSV-EDV)/PSV. An RI <0.75 is consistent with veno-occlusive dysfunction.[79] The main benefits of this investigation are that it is non-invasive and it can accurately exclude both penile arterial and venous dysfunctions. However, the results are very user-dependent and abnormal anatomy can give erroneous readings. Further, the information provided would not change treatment for the vast majority of patients. Hypertensive patients who have vasculogenic ED and demonstrate significantly reduced cavernosal arterial flow on duplex ultrasound should be referred for a full cardiac evaluation.

Dynamic Infusion Cavernosometry and Cavernosography are used for patients in whom a site-specific venous leak is suspected. This is usually for patients who have suffered pelvic/perineal trauma or those who have primary erectile dysfunction (have never been able to achieve an erection). These tests usually precede corrective vascular surgery. Two needles are placed in the penis to simultaneously infuse saline and measure intracavernous pressure. The inability to raise intracavernous pressure to match the mean systolic blood pressure with the saline infusion or the sudden fall in intracavernous pressure after stopping the saline infusion both demonstrate veno-occlusive dysfunction. Cavernosography shows the site of the veno-occlusive dysfunction.[80]

Pudendal arteriography clearly illustrates the arterial vasculature of the penis.[81] It is typically reserved for young patients with erectile dysfunction secondary to trauma where revascularization surgery is being considered. The anatomy of the internal iliac, internal pudendal, and penile arteries are carefully studied. The inferior epigastric arteries are also examined for their potential use in penile revascularization.

Endothelial Cell Dysfunction can be tested by various means such as the penile nitric oxide release test, peripheral arterial tonometry, and flow-mediated dilation. There are also various serum markers such as C reactive protein, endothelin 1, vascular cell adhesion molecule-1 as well as the presence of endothelial progenitor cells and microparticles.[82] None of these tests for endothelial cell function has much current clinical utility and they are of research interest only at the present time.

Treatment / Management

Initial treatment involves improving general health status through lifestyle modifications. This not only improves erectile function but reduces cardiovascular risk. Recommended lifestyle modifications would include increased physical activity, switching to a Mediterranean diet and/or nutritional counseling, stopping smoking, drugs, and alcohol, gaining good control of diabetes, lipids, and cholesterol. The patient's drug history should be carefully reviewed to remove or alter the doses of any offending medications.

Men who have a psychological cause should be offered psychosexual counseling. With the patient’s consent, this should be offered to the partner as well.

L-Arginine is an amino acid supplement that is the essential substrate for the production of Nitric Oxide Synthase, the enzyme that produces nitric oxide in the body. Supplemental L-arginine has been shown to increase nitric oxide synthase levels which should theoretically improve erection function. In fact, several studies have actually shown some efficacy in treating mild to moderate ED with L-arginine supplementation (1,500 mg to 5,000 mg).[83]

Oral phosphodiesterase-5 inhibitors (PDE-5 inhibitors), such as sildenafil and tadalafil, are usually the first-line treatment of erectile dysfunction. They are effective in a wide range of etiologies including cardiovascular disease, diabetes, and hypogonadism.[84] They act by decreasing the degradation of cyclic GMP via phosphodiesterase inhibition, which increases the relaxation of cavernosal smooth muscle and cavernosal arterial blood flow. It is important to note that PDE-5 inhibitors do not initiate the erectile response. Sexual stimulation is required to release nitric oxide from the vascular endothelium and penile nerve endings to commence the erectile process. PDE-5 inhibitors are highly effective and have an overall success rate of up to 76%.[85]

Side effects will occur in about 40% of patients but are usually mild. The most common side effects are headache, indigestion, nasal stuffiness, and mild visual changes such as temporary light sensitivity or bluish coloration to vision. There have been rare reports of permanent blindness from non-arteritic anterior ischemic optic neuropathy with PDE-

5 inhibitors.[86][87] There are also rare reports of usually unilateral deafness, typically starting within 24 hours of ingestion, related to these drugs.[88][89][90] Fortunately, these reactions are quite rare, but patients should be appropriately informed.

Different PDE-5 inhibitors have varying half-lives, which can influence the patient's final selection. It is important to note that these drugs should be used with some caution with antihypertensives and alpha-blockers. They should not be used at all with nitrates due to potentially dangerous, profound hypotension. Patients who fail PDE-5 inhibitor therapy should try at least one other PDE-5 medication as up to 50% of initial treatment failures will respond to a different PDE-5 drug. Testosterone levels should be checked in patients who fail PDE-5 therapy, if not measured earlier. Those who are hypogonadal might benefit by adding testosterone supplementation to their PDE-5 inhibitor therapy.[91]

It is important to instruct patients on how to correctly take their medication. For example, sildenafil is poorly absorbed and might be totally ineffective if taken with food. It also frequently requires several therapeutic tries before it begins working successfully.

Studies of adding daily L-arginine supplements to sildenafil or tadalafil therapy demonstrate a significant improvement in IEFF scores and erectile function compared to sildenafil or tadalfil monotherapy.[83][92][93]

Testosterone supplementation appears to be more effective as a treatment for low libido than for ED.[94][95] For most men with both ED and hypogonadism, oral PDE-5 inhibitors alone are recommended as the initial therapy. Testosterone supplementation is reasonable in men with proven hypogonadism and ED who have already failed PDE-5 inhibitor therapy or who also have low libido. Hypogonadal patients with borderline erectile rigidity are most likely to benefit from testosterone supplementation. The ED patients who received the greatest benefit from testosterone supplementation were those with the most severe level of hypogonadism.[96] Overall, only 35% of all the hypogonadal men with ED will show significant improvement in their erectile function from testosterone supplementation.[97]

External Vacuum Devices are a good, non-surgical option for many ED patients. The outer cylinder of the device is placed over the penis and pressed to the body to create an airtight seal. The patient then uses a small, hand-operated (or battery-powered) vacuum pump to create negative pressure around the penis, which engorges the corpora with blood. This artificial erection is then maintained by placing an elastic band around the base of the penis. The vacuum can then be released leaving the artificial erection which can be maintained for up to 30 minutes. Practice with the device seems to improve outcomes and some degree of manual dexterity is required. The efficacy rates of these devices have been high, generally about 70% to 80%, but the patient satisfaction rates are lower.[98][99]

External vacuum device therapy is safe, effective, and is also the most inexpensive long term therapy for ED. It can also be used frequently if desired. However, the use of the device initially requires practice for optimal performance and is impossible to hide completely. It remains a good, safe, and effective noninvasive option for patients who deem it practically acceptable.

Intraurethral Prostaglandin E1 (alprostadil) pellets (also called Medicated Urethral System for Erection or MUSE) are available for use as urethral suppositories. The pellets are small, about the same size as a grain of rice. The patient first voids and then places the tip of the insertion device inside the urethral meatus and pushes the plunger. This deposits the prostaglandin E1 pellet into the pre-moistened distal urethra where it will dissolve with a gentle hand massage. The medication is absorbed through the urethra and makes its way to the corpora cavernosa where it causes muscle relaxation resulting in an erection. Overall efficacy is reportedly good, generally at about 50% to 65%.[100][101] One large, double-blinded, placebo-controlled study of over 1500 men with chronic ED found that 2/3 responded to intraurethral prostaglandin E1 pellet therapy sufficiently to have intercourse.[101]

Intraurethral prostaglandin E1 pellets are commercially available in 4 different strengths, but the 2 largest dosages are used most often (500 and 1,000 mcg.) Side effects include urethral burning and somewhat variable efficacy even from the same dosage, possibly depending on the precise site of pellet application. It is used relatively infrequently due to its high cost, the variability of efficacy and the frequent need for patients to purchase at least six doses at a time as that is how they are supplied to the pharmacy.

Intracavernosal Injections with prostaglandin E1 (alprostadil) are frequently the next choice of therapy if oral PDE-5 inhibitors are unsuccessful.[98] Intracavernosal injections of papaverine, (an alpha-blocker and vasodilator) as a

therapy for ED was first described in 1988 and has delivered good results.[102] Since then, several agents have been found that can cause smooth muscle relaxation, vasodilation, and erections when injected, alone or in combination, into the corpora cavernosa. These include papaverine, prostaglandin E1 (alprostadil), phentolamine, and atropine.[103][104][105]

The single-agent used most frequently today is prostaglandin E1 as it has fewer systemic side effects and good efficacy while offering reduced priapism risk and less fibrosis compared to other agents. It's the body's most effective, natural smooth muscle relaxant. It works via its effects on increasing cavernosal cyclic AMP levels.

A single injection is done on the side of the penile shaft near the base, to avoid the urethra (ventrally) and the dorsal neurovascular bundle. A single injection is sufficient as the corpora cavernosa share vascularity.[106][107] We usually recommend the patient switching sides to minimize scarring. Insulin type, 1 cc syringes are typically used with short, 27 to 30 gauge needles.

Intracavernosal injection therapy has been shown to be highly effective in up to 94% of patients.[108] However, prostaglandin E1 is relatively expensive and somewhat painful when injected into the corpora. Combination therapy has become popular using a more or less standard combination of papaverine 30 mg, phentolamine 1 mg, and prostaglandin E1 20 mcg./cc (known as "TriMix") or adding 0.2 mg of atropine to make "QuadMix". These combinations need to be prepared by a compounding pharmacy. In general, they are about twice as effective as prostaglandin E1 alone, tend to cost less, and usually avoid the discomfort associated with intracavernosal prostaglandin E1 injections when used alone. Dosages and concentrations can be adjusted to double strength levels if needed.

The initial trial dosage is usually 0.2 to 0.25 cc's. This is slowly increased to give the patient a rigid erection for a reasonable time period, which should be no more than 90 minutes and optimally only about 45. Patients need to be carefully counseled not to exceed the recommended dosage for them as it is extremely tempting to inject more medication "just to be sure" or because the initial effect appeared sub-optimal. Physicians should be prepared to offer a priapism antidote (usually a diluted phenylephrine solution) either in their office or in the Emergency Department.

If the corpora cavernosa are healthy with good vascularity, intracavernosal injections are almost always going to be successful. Failure of intracavernosal injection therapy is a good diagnostic indicator of vasculogenic ED.

Side effects from intracavernosal injections include pain, priapism, bleeding or bruising at the injection site, and scarring of the tunica.

It is absolutely critical that patients be warned not to increase the injected dosage without the approval of their physician, not to mix it with other ED agents such as PDE-5 inhibitors, and to go to the nearest Emergency Department for reversal therapy if their erection lasts longer than 4 hours to prevent permanent damage to the corpora.

Combined therapy with both intracavernosal injections (or intraurethral prostaglandin pellets) plus the addition of a PDE-5 inhibitor can be very effective if neither treatment alone is successful.[104][109][110][111] The two treatments use different chemical mediators (cyclic AMP for injections, cyclic GMP for PDE-5 inhibitors) which synergistically enhances their combined activity. While effective, the risk of priapism is also increased and experience with this type of combined therapy is limited. Nevertheless, it is worth a clinical trial before considering penile prosthesis surgery or giving up entirely in patients who are not surgical candidates.[112]

Penile prostheses are a surgically invasive treatment; this is typically offered when all other, less intrusive measures fail or are otherwise unacceptable. These devices are surgically inserted into the corpora cavernosa in order to restore erectile function artificially. There are two main types available: malleable and inflatable. The malleable prosthesis can be physically manipulated into a straight or bent position, in accordance with the patient’s wishes. The inflatable type becomes erect by activating a small pump in the scrotum which fills the inflatable penile balloon cylinders from a hidden fluid reservoir surgically implanted in the lower abdomen. Older men, with limited manual dexterity or mental issues, find the malleable prostheses more manageable while most men, especially from younger generations, typically prefer the inflatable devices due to their more natural operation and function. Patients with diminished pelvic or penile sensation are probably better served by inflatable devices to avoid possible ulcers and erosions due to excessive pressure from the malleable rods on the skin which they would not be able to feel.

Complications from these devices include erosion, leakage, infection, and possible mechanical failure. Early inflatable penile prostheses had many problems including infections, penile deformities, aneurysm formation, leakage, pump failures, and other mechanical issues. Current devices have fixed these problems and are quite reliable mechanically. The current mechanical failure rate for inflatable prostheses are <5% over 5 years.[113][114] Other improvements include antibiotic or hydrophilic coatings which further reduce the risk of infection.[115][116][117][118][119] The overall infection rate for penile prostheses is now only about 3% but might be as high as 10% in patients with prior implants, diabetes, or spinal cord injuries.[120][121]

Although many men will not wish to have surgery, penile prosthesis implantation procedures are found to have very high patient satisfaction scores (about 90%).[122][123] Long term results are not quite as good with only 41% of patients indicating they are still using their penile prosthesis after 20 years.[122][124]

Penile revascularization surgery can be considered in a small, minute subgroup of patients, estimated at about 5% of all ED patients.[125] This is ideally considered for the young patient (less than 30 years of age) with erectile dysfunction following pelvic/perineal trauma, who has sustained an isolated vascular injury. Arterial insufficiency must be demonstrated on penile Doppler ultrasound and then identified on a formal arteriogram. The revascularization operation is performed by anastomosing the inferior epigastric artery to the dorsal artery of the penis or directly to the corpus cavenosum. Long term results are only marginal.

Arterial balloon angioplasty has been done successfully for focal arterial stenosis of the pudendal or penile arteries, but improvement does not usually last due to recoil arterial narrowing and restenosis unless drug-eluting stents are also used. This is not yet the standard of care and is only useful in men with focal, identifiable, arterial stenosis in vessels large enough to accept a stent.[126][127][128]

Venous ligation surgery can be done for veno-occlusive dysfunction. This involves embolizing or ligating the penile veins (e.g. the deep dorsal vein). Currently, this surgery is not recommended as long term results do not show lasting efficacy.[126][129]

Low-intensity shockwave therapy has shown efficacy, particularly in patients with severe ED not responding to PDE-5 inhibitors.[130][131][132][133] Its presumed mechanism of action is through improved cavernosal hemodynamics, induction of endothelial cell proliferation and activation of endogenous stem cells as well as from penile revascularization. Shockwave therapy increases angiogenic factors that promote neovascularization, restores smooth muscle activity, and attracts stem cells. It also increases vascular endothelial growth factor, neuronal nitric oxide synthase, and other, similar natural bioactive agents.[134] In other words, its exact mechanism of action is not well understood, but it does seem that the effect is dose dependent with 3,000 pulses per session give better results than 1,500 or 2,000.[131] While early results appear promising in optimal candidates, some studies have shown no effect.[135] Meta-analysis of all the currently available studies have demonstrated that low-intensity shockwave therapy generally provides a clinically significant short-term improvement in erection rigidity and functoin, but the lack of long term data makes it difficult to recommend at this time.[136] Overall, low intensity shockwave therapy appears to be a reasonable, safe and moderately effective initial therapy for relatively healthy men with mild to moderate erectile dysfunction, with an overall success rate at 30 months of about 40%. Negative risk factors that limited successful outcomes include advanced age, hypertension, smoking, obesity, hyperlipidemia, high pre-therapy SHIM (Sexual Health Inventory for Men) scores, and lengthy duration of ED. Low-intensity shockwve therapy has been found to be relatively useless in men with severe ED.[137] The therapy is still considered investigational in the US and is not FDA approved at this time.

Penile Rehabilitation Therapy After Prostate Cancer Treatment

There are a number of studies looking at penile rehabilitation therapy after radical prostatectomy surgery that suggest a benefit, but there is no consensus on the exact treatment selection, duration, or timing. The majority of the published studies suggest a combination of PDE-5 inhibitors together with external vacuum device therapy offers the best results although intraurethral pellet therapy and intracavernosal injections have also been used successfully. Tadalafil offers a theoretical benefit over sildenafil based on its longer half-life and pharmacokinetics, but there is insufficient data to make any formal recommendation. Early use of penile rehabilitation treatment is recommended lasting up to 1 year after surgery, but the exact timing has not been adequately studied.[138][139][140][141]

It also seems reasonable that penile rehabilitation techniques should also help prostate cancer patients who select definitive radiation therapy, but again there is insufficient data to support any recommendation. Nevertheless, with sildenafil and tadalafil now being generic and available at low cost, there seems to be little harm in recommending their early use after either definitive prostate cancer treatment.

Differential Diagnosis

The main differential diagnosis for erectile dysfunction would be hypogonadism, loss of libido, depression with low mood, and other psychological conditions. It may be the first manifestation of diabetes or cardiovascular disease as well as depression. It is also important to differentiate between true erectile dysfunction and other sexual disorders such as premature ejaculation. This is usually easily accomplished just by obtaining a good sexual history.

Prognosis

Prognosis is dependent on the cause, with psychosexual causes generally having a good response to counseling. It appears that most causes of erectile dysfunction respond favorably to oral PDE-5 inhibitors.[142] If not, there are multiple other options for treatment including external vacuum devices, intraurethral prostaglandin pellets, intracavernosal injections, and combined therapy. It is unusual for patients to fail all of these non-surgical options, but even then we still have penile prosthesis implantation surgery that remains highly successful. Almost every patient with ED can be successfully treated with currently available therapies.

Complications

Complications of erectile dysfunction are predominantly emotional, both to the patient and his partner. It can cause a strain on relationships and negatively impact the quality of life of these patients. Of course, the cardiovascular pathologies and diabetic complications that may accompany this condition come with their own health issues.

Priapism from PDE-5 inhibitor medications is relatively uncommon at only about 3% of all priapism cases despite the widespread use of these drugs. Penile injection therapy is involved in about 8.8% of priapism cases and trazodone in about 6%, while second-generation antipsychotic drugs are responsible for 33.8%.[143]

Treatment for drug-induced priapism is intermittent intracavernosal injections of diluted phenylephrine solution, 200 mcg at a time, about 5 to 10 minutes apart until detumescence or a maximum dose of 1 mg of phenylephrine has been delivered. If this fails, a surgical shunting procedure will be necessary. Treatment should begin quickly as permanent corporal fibrosis can occur with delayed therapy.[144][145]

Deterrence and Patient Education

One of the most important messages to the public would be that this condition is treatable and men should seek help if they suffer from erectile dysfunction. To prevent the condition, positive, healthy, basic lifestyle choices should be addressed such as smoking, diet, and exercise.[146] It is also paramount to aggressively treat existing medical conditions, such as diabetes, obesity, and hypertension, properly.

Pearls and Other Issues

Extensive and expensive diagnostic testing for ED is not warranted as there are no curable organic causes. Basic blood tests for testosterone level, lipids, HgbA1c, thyroid, renal, and kidney function are reasonable but more extensive testing is unnecessary for the vast majority of patients. Instead, the focus of treatment is generally to assist the patient in selecting the optimal therapy for him and then giving it a clinical trial. Penile prosthesis surgery is reserved for those patients who have failed all other treatment options and are still highly motivated to have erectile function restored.

When oral PDE-5 agents don't work, make sure they are being taken properly and check a testosterone level.

Don't forget about external vacuum devices. While a bit mechanical and obvious, they are reliable and work reasonably well in the majority of patients. In one study, where 1500 ED patients were carefully taught, counseled, and followed, the success rate in achieving an adequate erection was an astonishing 94.5%.[99]

Yohimbine has been used for decades as an oral therapy for ED, primarily before the advent of PDE-5 inhibitors. It is a tree bark extract that supposedly has both a central and peripheral effect on erectile function. It blocks presynaptic alpha-adrenergic receptors which decrease adrenergic tone while increasing cholinergic effects. It is safe and inexpensive with no significant side effects. The problem with yohimbine is that, in properly done studies, it does not appear to be significantly more effective than a placebo and it needs to be taken three times daily. Therefore, its use is not recommended in the 2018 AUA Guidelines on Erectile Dysfunction. Nevertheless, there is renewed interest in using yohimbine in combination with PDE-5 inhibitors, but there is insufficient data at this time to recommend it.[147][148][149]

Trazodone is a sedative and antidepressant that is often still used as a sleep aid.[150] It was noted that there was a high risk of priapism in patients taking trazodone, so some practitioners began using it off-label to treat ED.[151][152][153] While it has clearly shown some good activity in treating ED, particularly in men with psychogenic erectile dysfunction, its effectiveness when used in combination with PDE-5 inhibitors and optimal dosage have not yet been established, although a dose of 150 - 200 mg has been suggested.[154]

In the difficult ED patient who has failed all other treatments short of penile prosthesis surgery, consider a trial of combined therapy with a full dose intracavernosal injection, such as 1 cc. of "TriMix" or "QuadMix", together with a PDE-5 inhibitor. While data is limited and the risk of priapism is somewhat increased, there is a reasonable chance this will work and obviate the need for surgery.

Venous leak surgery is not recommended due to poor outcomes.

A number of other ED treatments are currently considered investigational only. Such experimental treatments include low-intensity extracorporeal shockwave therapy, intracavernosal stem cell installation, endovascular revascularization with angioplasty of the pudendal or penile arteries, and platelet-rich plasma therapy.[126][134] Of these, stem cell therapy appears to be the most promising and is being actively investigated, but for now, it is still considered experimental.[155]

Warn patients about the dangers of taking dietary supplements that claim to improve sexual performance, confidence, or stamina. Many of these products, from one third to half, have been found to contain PDE-5 inhibitors which can be dangerous for patients taking nitrates for cardiovascular disease.

Short Evaluation and Treatment Summary

Inquire about sexual health in all adult male patients. Use a non-threatening, non-judgmental intonation and use phraseology such as *"How is your sex life? Everything working OK for you?"*

Be aware that if the patient gives a qualified or hesitant answer, it probably indicates he has a sexual problem.

The next step is a careful medical and sexual history together with a comprehensive physical examination.

Clues to possible psychological causes include sudden onset of ED, high erectile variability, good morning erections, and good erections with masturbation or alternate partners.

Refer to psychogenic sexual disorders to appropriate mental health providers.

No specific testing for ED is required, but a blood panel consisting of a morning testosterone level, CBC, CMP, liver and renal function, lipid panel, HgbA1c, and TSH would not be unreasonable.

No other tests are required or recommended for the vast majority of ED patients.

Employ "shared decision making" by carefully discussing the pros and cons of all the various treatment options, that are not contraindicated, with the patient and his partner if possible.

First-line therapy is usually with oral PDE-5 inhibitors. Make sure the patient takes them correctly.

Try at least two different oral agents before moving on to other therapy. Check a serum, morning testosterone level in all men who fail oral PDE-5 therapy.

Intracavernosal injections are usually the next treatment but don't forget intraurethral suppositories and external vacuum devices.

If even 1 full cc. of double strength "TriMix" or "QuadMix" injections aren't working, and all other non-surgical therapies, such as external vacuum devices, have been tried unsuccessfully, consider a trial of combined therapy by asking the patient to take an oral PGE-5 inhibitor about an hour before the "Trimix" injection. This can be tried before going on to penile prosthesis surgery. Combined therapy of this type carries a high risk of inducing priapism so it should be used cautiously. We typically will try it only on patients who have failed all other treatment options and are considering a penile prosthesis or just giving up. Failure of this combined therapy to work indicates severe damage to the corpora cavernosa which may only be relieved by a penile prosthesis implant.

Enhancing Healthcare Team Outcomes

Erectile dysfunction is mainly managed in the community setting with the help of primary care physicians, specialist nurses, pharmacists, and psychologists. However, patients who are unresponsive to initial management should be referred to secondary services, classically urologists, for further investigations and management.[156] Prompt diagnosis and treatment can reduce the emotional stress felt by patients and their partners.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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