Erectile dysfunction for primary care providers

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Introduction: *Erectile dysfunction (ED) affects more than half of men between the ages of 40 and 70 years and is associated with a significant decline in quality of life. ED in an otherwise healthy man should be considered a sentinel event for endothelial dysfunction and cardiovascular disease. Such a person should be carefully evaluated for undiagnosed risk factors including hypertension, diabetes, lipid disorders, and obesity.*
Objective: *To understand that erectile dysfunction is prevalent and may be the first sign of undiagnosed cardiovascular risk factors.*
Materials and methods: *Literature review.*
Results: *Current literature suggests that physicians should screen all men for ED, and if present, rule out concomitant cardiovascular risk factors.*
Conclusion: *ED is prevalent and may be the first sign of undiagnosed cardiovascular risk factors. With the advent of safe and effective phosphodiesterase type-5 inhibitors (PDE-5i), most patients reporting dissatisfaction with erectile function can start treatment right away. Preventative care algorithms should include screening men 40 years of age or older for ED.*

Key Words: erectile dysfunction, phosphodiesterase type-5 inhibitors, PDE-5 inhibitors, endothelial dysfunction, cardiovascular disease

Introduction

Erectile dysfunction (ED) affects more than half of men between the ages of 40 and 70 years[1] and is associated with a significant decline in quality of life.[1-3] ED in an otherwise asymptomatic man should be considered a sentinel event for endothelial dysfunction and development of cardiovascular disease. Patients should be carefully evaluated for undiagnosed risk factors, including hypertension, diabetes, lipid disorders, and obesity.[4-7] To emphasize this point, a prospective, population based study was able to use a single question about erectile quality to predict which men would eventually suffer from an acute myocardial infarction, stroke, and sudden death, independent of the risk factors used in the Framingham risk profile.[8] With greater emphasis on preventative medical care, asking men about ED is a low effort, high yield way for physicians to screen for undiagnosed cardiovascular risk factors. Since cardiovascular disease-related events typically develop 5-7 years following the onset of ED,[9] it seems reasonable to start screening men early—possibly in their forties. Screening for and initiating treatment of ED is straightforward and offers an opportunity to improve a man's quality of life, but may also uncover hypogonadism as well as cardiovascular risk factors that warrant treatment.

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Definition

The National Institute of Health (NIH) has defined ED as "*The consistent inability to obtain or maintain an erection satisfactory for sexual function*".[10] An emphasis on "satisfactory" should be made since it absolves the provider from needing to objectively determine what degree of ED exists. In other words, the patient qualifies for treatment if they, or their partner, report dissatisfaction with erectile quality. Quantifying erectile response with such instruments as rigi-scans, snap gauges, or a duplex scan can be left for those involved with research protocols.

Prevalence

ED affects more than half of men between the ages of 40 and 70 years.[1] Generally speaking, a man's age predicts his chance of having some degree of ED. For instance, a 50-year-old and a 70-year-old have a 50% and 70% chance respectively of having some degree of ED. Fortunately, most of these men report only partial loss of erectile function, with only 10% of men having complete loss of erections. The prevalence of ED in the United States is 52%, with a lower but still significant prevalence noted across other industrialized nations.[11-12]

Erectile physiology

A succinct description of erectile physiology has been succinctly described by John Carter and illustrated in Figure 1.

"In the penis, the erectile bodies are the paired dorsal corpora cavernosum and the single ventral corpus spongiosum surrounding the urethra. These contain sinusoids, which are terminal arterioles with an outer layer of smooth muscle, and venules. Normally the sinusoids are in a state of contraction while the venules are maximally dilated. Sexual stimulation triggers the release of nitric oxide (NO) from endothelial cells of arteries and sinusoids of the corpus cavernosum. NO activates guanylyl cyclase to increase cGMP production. Through several interactions, elevated concentrations of intracellular cGMP result in hyperpolarization of the muscle cell membrane and lower intracellular calcium concentration, which produces relaxation of the corpous cavernosum and penile arteriolar smooth muscle. With this relaxation come a fall in arterial resistance and an increase in arterial blood flow into the sinusoids. The dilated sinusoids passively compress the venule against the tunica albuginea, occluding venous outflow. The increase arterial inflow and decreased venous outflow produces an erection. Inhibition of [phosphodiesterase type-5 enzymes] PDE-5 [such as sildenafil, vardenafil, or tadalafil—to be discussed later] results in higher concentrations of cGMP, enhancing the effects of the NO pathway. Without sexual stimulation and the release of NO, however, no change in cGMP will occur and PDE-5 inhibition will have not effect, so spontaneous erections are not induced".[13]

Etiology

ED is considered a natural consequence of aging, where risk is found to parallel age. An exception was found with increasing levels of protective high-density lipoprotein (HDL); the Massachusetts Male Aging Study (MMAS) found that no male with an HDL over 90 experienced ED.[14] Moreover, a follow-up MMAS study found that exercise was the factor most likely to preserve erectile function irrespective of age-related changes.[15]

Age aside; there are several comorbid factors that independently worsen ED. The pathophysiology of ED is often classified as organic, psychogenic, or a combination of the two. Organic causes include neurologic (5%), hormonal (3%), vasculogenic (70%) and pharmaceutical (10%), while psychogenic accounts for 10% of ED.

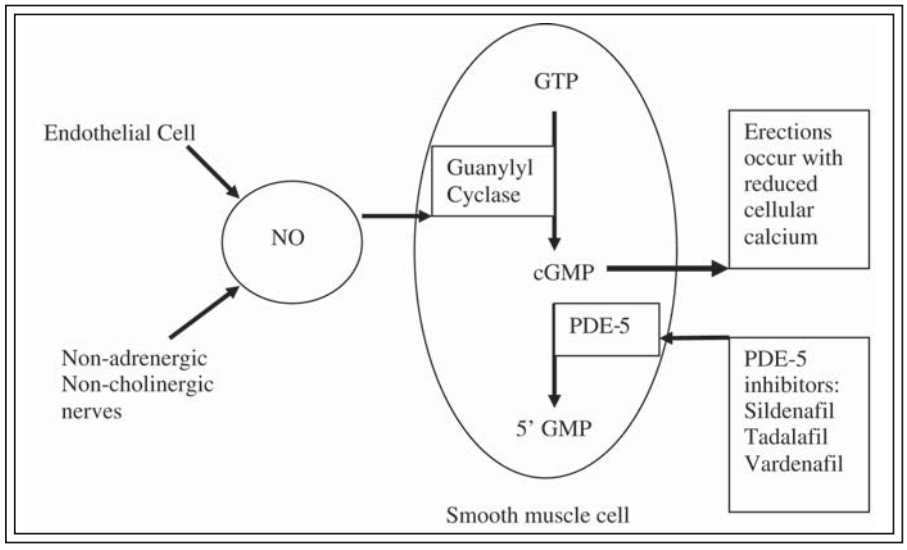


Figure 1. Erectile physiology

Neurologic

ED results from either a neuropathy (central or peripheral) or a traumatic neurological injury. Common etiologies include stroke and spinal cord injury, surgery, trauma, multiple sclerosis, Parkinson's, Alzheimer's disease, diabetes, and alcohol consumption.

Stroke/spinal cord injuries: These are classified into upper or lower cord lesions. Whereas patients with upper lesions may still have reflexogenic erections, only a few of those with lower lesions—involving the lumbar or sacral regions—are able to obtain a psychogenic erection.[16] Reflexogenic erections require

ongoing stimulation and the resultant erection, if not pharmacologically assisted, is often not rigid enough for penetration.

Surgery or trauma: Due to the close proximity of the cavernous nerves to the prostate and membranous urethra, radical pelvic surgery, pelvic trauma, and pelvic radiation will often predispose to ED. Prostate cancer treatment is the most common etiology for surgical disruption of cavernosal nerves and a common cause of ED.[17] Although randomized trials are lacking, such patients may benefit from postoperative penile rehabilitation in an effort to preserve or improve erectile function. Penile rehabilitation techniques vary and can be tailored to meet patient preference.[18]

Multiple sclerosis: ED is rare at the onset of multiple sclerosis (MS), however, after several years sexual dysfunction will eventually affect 70% of MS patients. This etiology is multi-factorial with neurogenic lesions the predominate cause while psychological and medication side effects play an important secondary role.[19] Since no reliable tests are available at present, neurogenic ED requires minimal investigation.[20]

Parkinson disease: Parkinson's is a hypokinetic basal ganglion disorder associated with loss of dopamine-containing cells from the substantia nigra. The central nervous system dopamine pathways interact with the nonadrenergic, noncholingergic (NANC) pathways, which mediate penile erections.[21-22] ED results from a paucity of dopamine interaction with NANC nerves.

Alzheimer disease: Alzheimer's is associated with ED and correlates with the onset of Alzheimer symptoms.[23] Loss of erection was reported in 53% of patients, and was not related to depression, age of onset, nor degree of cognitive impairment.[24]

Diabetes mellitus: Diabetes (both types I and II) is one of the most common causes of ED, leading to a 3-fold increase in prevalence of ED compared with non-diabetic men.[25] Diabetes affects small vessels, cavernous nerves, endothelial cells, and trabecular smooth muscle all of which will contribute to developing ED. Diabetes-associated peripheral neuropathies often compromise both cholinergic and NANC nerve function.[26] Additionally, the pre-diabetic condition, insulin resistance, may also be associated with ED by reducing NO production by down-regulating endothelial nitric oxide synthetase (eNOS) activity.[27]

Alcohol consumption: In the short-term, alcohol consumption has a sedating effect which often causes some degree of erectile dysfunction. In addition, chronic alcohol exposure (over 600 milliliters, or just less than three 8-ounce glasses, per week) predisposes to ED by causing polyneuropathies.[28] Heavy alcohol abuse may lead to liver damage and a resultant build up of estrogens—which can alter the hypothalamic-pituitary axis causing hypogonadism.

Hormonal

Hormonal etiologies for ED include hyperprolactinemia, hypogonadism, and either hypo- or hyper-thyroidism. Hyperprolactinemia leads to hyogonadotropic hypogonadism in men with a resulting decrease in libido and erectile dysfunction. However, since administration of dopamine agonist appears to improve ED state while testosterone supplementation does not, it is not clear whether the mechanism of ED is attributable to hypogonadism in these patients.[29] Elevated prolactin levels with subsequent discovery of pituitary mass by MRI make this a relatively straight forward disease process to screen for.

Hypogonadism (unrelated to hyperprolactinemia) and its related state of low libido is screened for by drawing a morning testosterone level between 8:00 am to 11:00 am. Those with a low testosterone (varies by lab) may be treated with exogenous testosterone with the goal of raising total testosterone into the 300 ng/dl-500 ng/dl range.

Screening for thyroid dysfunction should be considered in those who manifest signs for symptoms of hyper- or hypo-thyroidism.

Vasculogenic

Vasulogenic etiologies are the most frequent organic cause for ED and include both a restriction of arterial inflow, and a venous leak. Arterial insufficiency, with limited cavernosal arterial inflow, is predominate within this category with causes including: 1) trauma or surgical disruption to the cavernosal arteries, 2) atherosclerosis, or 3) other endothelial disorders brought on by hypertension, lipid disorders, diabetes, radiation, or smoking.

Veins traverse the corpora cavernosa and are normally passively compressed during a rigid erection, preventing venous outflow to maintain an erection. Veno-occlusive dysfunction may be the result of trauma to the tunica albugenia (penile fracture or development of a Peyronie's scar) as well as anatomically large veins that are difficult to occlude. Operations involving arterial revascularization or venous ligation are difficult to perform and are not durable. Therefore, unless there is a focal arterial lesion in a young male, vascular reconstruction is not routinely recommended.

TABLE 1. **Contrasting psychogenic and organic ED**

Organic	Psychogenic
Gradual onset	Acute onset
Global	Situational
Constant	Varies
Lacks nocturnal erections	Normal nocturnal erections
Poor erection	Good erection prior to affecting situation
Anxiety is secondary	Anxiety is primary
Fear is secondary	Fear is primary

Psychogenic

Psychogenic causes for ED range from situational anxiety and relational difficulties to more overt psychiatric disorders (and the medications used for their treatment). Depression often results in a loss of libido along with a loss of interest in pleasurable activities such as sexual activity.[30] On the other hand, it is well known that ED often leads to depression and performance anxiety. Having said that, only 10% of men with ED will have a pure psychogenic cause. Table 1 can be used to help in discerning between psychogenic and organic ED.

Medication

Medication-induced ED is estimated to occur in up to 25% of men. Blood pressure medications are frequent culprits with thiazide diuretics often quoted as the most prevalent pharmaceutical affecting erectile function. While not as frequent, non-specific alpha blockers clinically have the most severe effects on erectile function.[31] If a patient complains of ED after starting a particular medication, consider changing to a different class of medication whenever possible. Besides medication substitution, other strategies may include dosage reduction, drug holidays, or watchful waiting. If use of the offending medication is non-negotiable, consider supplementing the patient with a PDE-5i (see treatment section).

Opiates are currently one of the most commonly used (and abused) medications. When used chronically, opiates can result in a syndrome of low testosterone called opioid induced androgen deprivation (OPIAD).[32] Like opiates, steroid use can also suppress endogenous testosterone production. Such patients should be screened for hypogonadism and treated with a testosterone replacement regimen.[33]

Other recreational drugs should not be overlooked. Nicotine users have a 2-fold increased risk for ED. Besides increasing the risk for atherosclerosis and vascular diseases, nicotine causes vasoconstriction of the internal pudendal artery.[34] However, remission of ED symptoms has been realized in those men who have either discontinued smoking or reduced their body mass index (BMI).[35] Cocaine and marijuana can decrease libido, delay ejaculation, and cause ED. Marijuana does this by lowering testosterone, while the effect of cocaine on erectile function is less clear. Amyl nitrate "poppers," like nitroglycerine use, is a contraindication for concurrent PDE-5i use.

Clinical evaluation of ED

As previously stated, ED in an otherwise asymptomatic man should be considered a sentinel event for endothelial dysfunction and cardiovascular disease. Such a person should be evaluated for hypertension, diabetes, lipid disorders, and obesity.[4-7] A thorough history, physical exam, and brief laboratory evaluation is necessary prior to treating a man for ED.

History

A complete medical and sexual history is an important part of the initial evaluation. Validated questionnaires, such as the modified International Index for Erectile Function (IIEF-5) and the Sexual Encounter Profile (SEP) can be used to quantify a patient's degree of sexual dysfunction.[36-37] The history should focus on identifying underlying medical conditions which not only predispose to ED, but are also a risk to the patient's long-term health. Although treating these conditions will not reverse erectile loss, intervening should slow progression of ED. In addition, a focused history should touch on comorbid conditions such as depression, Peyronie's disease, premature ejaculation, and lower urinary tract symptoms (LUTS). A direct correlation between worsening LUTS and greater degrees of ED has been demonstrated in several epidemiological studies.[38-39] Successfully treating either ED or LUTS may positively impact both conditions. Lastly, a review of medication use and past surgeries may offer insight into additional ED risks.

Physical exam

Occasionally, the physical exam can provide direct evidence for the cause of ED. Examples include a Peyronie's plaque, chordee, micropenis, or genetic syndromes such as Kallmann's or Kleinfelter's. Indirect evidence for ED-risk includes evaluation of diminished peripheral pulses, elevated blood pressure, atrophic

testicles, or a lack of secondary sex characteristics such as voice qualities and hair distribution. Lastly, testing for genital and perineal sensation along with the bulbocavernosus reflex is useful in assessing for possible neurogenic ED.

Laboratory

Laboratory testing is recommended to identify conditions that contribute to ED. Typical tests include a fasting glucose, lipid profile, testosterone level, and if the patient is symptomatic, thyroid function tests. Testosterone levels should be evaluated at the outset in patients reporting low libido or, if small testes are noted on physical exam. In addition, a testosterone level could be checked in those men who report an inadequate response to PDE-5i use. If the testosterone level is low, a central process (hypothalamus or pituitary) should be ruled out by obtaining prolactin and leutenizing hormone (LH) levels.

TABLE 3. **PDE-5i adverse events**

	Sildenafil	**Tadalafil**	**Vardenafil**
Headache	Yes	Yes	Yes
Flushing	Yes	Yes	Yes
Dyspepsia	Yes	Yes	Yes
Back pain	No	Yes	No
Blue vision	Yes	Rare	Rare
Nitrate warning	Yes	Yes	Yes
Antiarrhythmic precaution	No	No	Yes

Modified from: Lue TF, Broderick GA. Evaluation and non-surgical management of erectile dysfunction and premature ejaculation. In: Campbell-Walsh Urology. Kavoussi LR, Novick AC, Partin AW, Peters CA, Wein AJ (Eds.). Philadelphia: Saunders Elsevier, 2007, 774. Reprinted with permission.

Treating ED

With the advent of effective oral medication for ED, primary care physicians currently manage the majority of cases of male sexual dysfunction.[31] To streamline ED treatment, a 3-tiered algorithm has been proposed, Table 2. First-line treatment options include the PDE-5i, which currently include sildenafil, tadalafil, and vardenafil. All three PDE-5i are safe and well tolerated, have similar efficacy and metabolic profiles, while having similar contraindications and warnings, Table 3.[31] In general, 74% of men will report improved erections when using PDE-5i.[40]

Risk for cardiac events surrounding sexual activity is a concern often raised by patients. Two separate Princeton Consensus Panels have clarified a patient's propensity for a cardiac event by developing guidelines that stratify patients into "low risk," "intermediate risk," and "high risk" Table 4.[41-42] Low risk patients are cleared for sexual activity. High-risk patients are advised against having sexual activity. Intermediate risk patients require further cardiac evaluation with subsequent reclassification into the low or high-risk categories.

Although safe and well tolerated in most patients, there are situations where PDE-5i should not be prescribed. These situations are listed in Table 5. Historically, concomitant use of alpha blockers with PDE-5i was discouraged for fear of orthostatic hypotension. This warning has been relaxed; the current recommendation is to simply separate administration of these two agents by 4 hours. Combining nitroglycerine or nitrate compounds (including amyl nitrate) with PDE-5i is well known for its risk of significant hypotension. An absolute contraindication exists regarding their combined use.

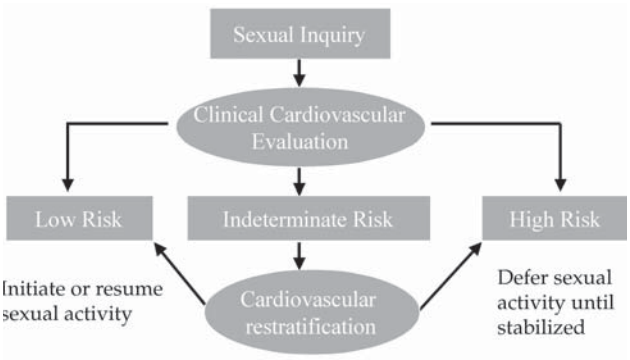
TABLE 2. **Current guidelines for treating ED**

First-line
- Treat reversible causes
- Lifestyle modification (weight loss, tobacco cessation, exercise)
- Oral agents (sildenafil, vardenafil, tadalafil)

Second-line
- Intracavernous injections (Caverject, Edex, Tri-mix)
- MUSE (Medicated Urethral System for Erection)
- Vacuum erection device

Third-line
- Surgical prosthesis
- Some men respond to hormonal therapy, penile revascularization, or sex therapy

TABLE 4. **Sexual activity and cardiac risk: Princeton guidelines**



Low risk
- < 3 major cardiac risk factors
- Uncomplicated past MI (> 6-8 weeks ago)
- Mild valvular disease

High risk
- Unstable angina
- Recent MI (< 2 weeks)
- Uncontrolled hypertension
- Moderate-to-severe valve disease (aortic stenosis)

Intermediate risk
- > 3 major cardiac risk factors
- Recent MI (2-6 week ago)
- LV dysfunction or congestive heart failure (NYHA II)

Modified from: DeBusk R, Drory Y, Goldstein I, Jackson G, Kaul S, Kimmel SE, Kostis JB, Kloner RA, Lakin M, Meston CM, Mittleman M, Muller JE, Padma-Nathan H, Rosen RC, Stein RA, Zusman R. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. Am J Cardiol. 2000;86(2):180. Reprinted with permission.

An additional concern among PDE-5i users is the development of nonarteritic anterior ischemic optic neuropathy (NAION). This is a condition resulting in blindness secondary to an ischemic injury to the optic nerve head. Edema of the axons within the optic disk may cause capillary ischemia resulting in nerve damage. Patients at risk for NAION have similar cardiovascular risk factors that have predisposed them to ED. There is little basis for modifying the current guidelines for PDE-5i use. Having said that, it is recommended that PDE-5i use should be avoided in men who have already experienced NAION in one eye, and medical attention sought if visual field or acuity loss occurs after PDE-5i use.[13]

Most men will experience improved erectile quality using PDE-5i. However, for complex or difficult to treat cases, consultation with a cardiologist, endocrinologist, psychologist, or urologist may be indicated. A urological consultation would be necessary for those patients requesting surgical intervention (a penile prosthesis) or, may be considered for providers who are not comfortable recommending second-line treatment options such as intracorporal injections, vacuum erections assist devices, or venous constriction devices.

Conclusion

Erectile dysfunction is prevalent and may be the first sign of other undiagnosed cardiovascular risk factors. With the advent of safe and effective PDE-5i, most patients can be treated by primary care physicians after ruling out and/or treating organic causes that may be harmful to the patients overall health. Preventative care algorithms should be optimized by screening men 40 years or older for ED.

TABLE 5. **PDE-5 inhibitor warnings**

Myocardial infarction within 90 days
Angina: unstable or during sexual activity
NYHA class II (or greater) heart failure within 6 months
Stroke within 6 months
Hypotension (< 90/50) or uncontrolled hypertension (> 170/100)
Uncontrolled arrhythmias
Tendency to develop priapism (sickle cell, leukemia)
Heredity degenerative retinal disorders (retinitis pigmentosa)

Modified from: Lue TF, Broderick GA: Evaluation and non-surgical management of erectile dysfunction and premature ejaculation. In: Campbell-Walsh Urology. Kavoussi LR, Novick AC, Partin AW, Peters CA, Wein AJ (Eds.). Philadelphia: Saunders Elsevier, 2007, 777. Reprinted with permission.

Take-home messages

When to refer to urology:

Patient desires surgery.
Patient fails non-surgical treatment.
Provider not comfortable with second-line treatment options.
Patient fails second-line treatment options.
Patient with low testosterone who desires to preserve fertility potential.
Patient with penile abnormality (Peyronie's disease).

ED = ED*

Erectile dysfunction = Endothelial Dysfunction
Erectile dysfunction = Emotional dysfunction (depression)
Erectile dysfunction = Endocrine dysfunction (low testosterone)

*Compliments of Claude Laroche, MD, Family Practitioner, Clinique Medicale Cadillac, Montreal, Quebec, Canada

Disclosure

Dr. JC Trussell is a member of the Speaker's Bureau for Pfizer. □

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DISCUSSION

Question (Dr. Miner):
How would you distinguish ED from other sexual dysfunctions (such as anejaculation and premature ejaculation?

Answer (Dr. Trussell):
I distinguish between ED and other sexual dysfunctions by history. For example, I ask patients if their "early detumescence" occurs due to an untimely (early) ejaculation (premature ejaculation) or, if they loose their erection without ejaculation (venous leak). I discern anejaculation from retrograde ejaculation by asking if the patient senses orgasm or not. For those patients without antegrade ejaculation, I order a post-ejaculate urine looking for sperm (retrograde ejaculation).

Question (Dr. Greenberg):
What is the academic rationale for using PRN versus daily continuing dosing of ED treatment medications?

Answer (Dr. Trussell):
The rationale for daily PDE-5i use is that a sustained therapeutic plasma level can be obtained in 5 days. FDA has approved dosage for Tadalafil in 2008. Theoretically, this may allow patients to take a smaller dose (possible fewer adverse events) while minimizing the need to time sexual activity. Fortunately, there has not been evidence for loss of efficacy through 12 months of daily Tadalafil use. Additional studies are needed to determine if daily dosing is more effective, more cost effective, and quite possibly, beneficial for the treatment of other symptoms such as lower urinary tract symptoms (LUTS).

Question (Dr. Laroche):
Please discuss your clinical algorithm when considering intracavernous injections or MUSE.

Answer (Dr. Trussell):
For those patients who are unable to take oral agents (for example, exposure to nitrates) or who report an incomplete response, I recommend moving to second-line therapies. These therapies include MUSE, injection therapy, and the vacuum erection device. I find that injection therapy is more reliable and start with a low dose: 10 mcg for those with organic ED, 5 mcg for those who have a psychogenic component. With MUSE I start with the 1000 mcg dose.