Issues in the Assessment and Treatment of Erectile Dysfunction: Individualizing and Optimizing Therapy for the "Silent Majority"

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Introduction

"There exist fundamental rights for the individual, including the right to sexual health and a capacity to enjoy and control sexual and reproductive behavior in accordance with a social personal ethic -- freedom from fear, shame, guilt, false beliefs and other factors inhibiting sexual response and impairing sexual relationships -- freedom from organic disorders, disease and deficiencies that interfere with sexual and reproductive function."

--World Health Organization Guidelines[1]

"Erectile dysfunction is a major healthcare issue and acts as a marker for other common major diseases. It therefore deserves attention, consideration, proper investigation, and appropriate treatment."

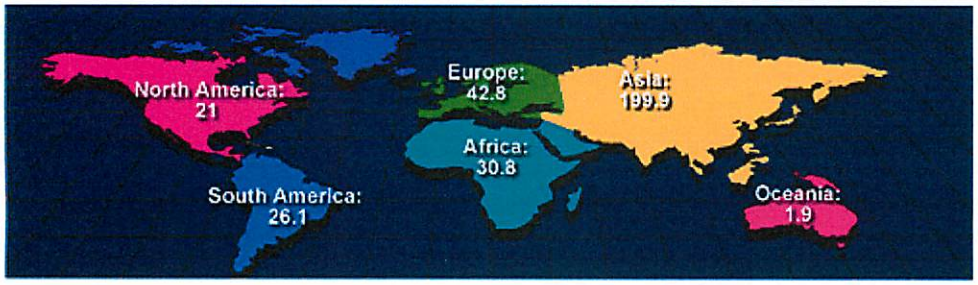
--United Kingdom Management Guidelines for Erectile Dysfunction[2]

Although estimates vary depending upon the epidemiologic methods used, studies focusing on the United States indicate that up to 30 million American men -- including up to 52% of those aged 40 to 70 years -- have erectile dysfunction (ED).[3,4] Indeed, ED accounts for more than 500,000 ambulatory visits to healthcare professionals each year.[5]

The current global prevalence of ED is more than 150 million. Given the advancing median age in Western industrial countries, together with population growth in developing nations, this figure is projected to increase to more than 320 million by the year 2025.[6] Current and projected prevalence data are depicted in Figures 1 and 2.

Estimated global prevalence of erectile dysfunction in millions (1995). Data from Aytaç IA, et al. *BJU Int.* 1999;84:50-56. © 2002, Rete Biomedical Communications Corp.

Projected Global Prevalence of Erectile Dysfunction in Millions (2025)



Data from Aytaç IA, McKinlay JB, Krane RJ. *BJU Int.* 1999;84:50-56. © 2002, Rete Biomedical Communications Corp.

Projected global prevalence of erectile dysfunction in millions (2025). Data from Aytaç IA, et al. *BJU Int.* 1999;84:50-56. © 2002, Rete Biomedical Communications Corp.

As with other chronic disorders, the prevalence of ED increases with advancing age. The Massachusetts Male Aging Study estimated an ED prevalence of approximately 40% in men aged 40 years and 67% in those aged 70 years.[4] According to this study, about 1 in 7 men aged 70 years has severe ED, or the complete inability to attain and/or maintain an erection, compared with 1 in 20 men at age 40.

The percentage of patients with ED varies with the population analyzed. In one study, 7.7% of men screened for prostate cancer had experienced no erections in the past 12 months.[7] Although the prevalence of ED varies from study to study, self-reported data likely underestimate the true dimensions of the problem.

The increase in the rate of ED with advancing age, coupled with underreporting and undertreatment of ED, is a common cross-cultural phenomenon.[8-12] These trends have been observed in regions of Europe, Asia, Africa, and Australia.

The Need for Effective Treatment

Adults of all ages view sexual activity as a key issue in quality of life (QOL). In the United States, 91% of married adult men and 84% of married adult women ranked a satisfying sex life as important.[13] It is therefore not surprising that ED is significantly associated with reduced QOL and emotional stress that can damage relationships between partners.

ED can compromise self-image and self-esteem, and many men associate the core values of manhood with sexual function.[14,15] Low levels of life satisfaction, as well as reduced levels of physical and emotional satisfaction and overall well-being, are associated with ED, particularly when it is psychogenic.[16,17] Conversely, restoration of erectile function with intracavernosal injection therapy (ICIT) has been associated with improved mental health (P = .007), social health (P = .004), and self-esteem (P = .01).[18]

According to a US National Institutes of Health Consensus Development Panel on Impotence, "In men of all ages, erectile failure may diminish willingness to initiate sexual relationships because of fear of inadequate sexual performance or rejection. Because men, especially older men, are particularly sensitive to the social support of intimate relationships, withdrawal from these relationships because of such fears may have a negative effect on their overall health."[3]

Despite the availability of safe and effective therapeutic options, ED remains underreported, underdiagnosed, and undertreated. Approximately 70% of ED goes undiagnosed,[19] and, according to a general medical practice survey, less than 12% of men with ED received treatment for it.[20]

Some men with ED may feel stigmatized by their condition, which, in turn, may discourage them from seeking and continuing with treatment, and thereby compromise quality of care.[21,22] Patients must be informed of the highly prevalent nature of ED, the availability of various treatments, and the appropriate use of these treatments to optimize their safety and efficacy.

That the advent of oral therapy with selective phosphodiesterase type 5 (PDE5) inhibitors expanded the market for ED treatments is unequivocal: some 2.9 million prescriptions for sildenafil were written within its first 8 months of market availability.[23] A concerted advertising and public-education campaign ushered in a veritable revolution in ED care, increasing candor about ED and the willingness of many men to undergo treatment. Many patients with ED find that oral therapy is the most desirable approach, and both the benefits and noninvasiveness of such treatment render it a first-line approach when indicated.[1]

Optimizing Efficacy Through Counseling and Education

As with the treatment of other lifestyle-related chronic diseases, there is no "magic bullet" for ED; risk modification, together with treatments that are tailored to the patient's and partner's needs, is the recommended therapeutic approach. Thus, clinical advances such as PDE5 inhibition do not obviate, but rather augment, the need for education and counseling for men with erectile insufficiency.[24]

Evidence for the contention that men receiving ED treatment are in need of education abounds. Even with the advent of PDE5 inhibitor therapy, treatment discontinuation rates remain a problem.[25-28] In one survey, 59% of patients with severe ED at baseline reported that PDE5 inhibitor therapy did not meet their expectations.[25] In another study, 39% of men considered sildenafil inadequate after 2 months of treatment.[27] In a short-term follow-up, 38% of men did not renew their prescriptions for PDE5 inhibitors; 83% cited lack of efficacy and 8% cited drug-associated adverse events.[26] These trends persisted at subsequent follow-up visits.

Furthermore, a recent study showed that 47% of men taking sildenafil discontinued treatment when interviewed 18 to 21 months after initiation.[28] Of this group, 46% cited dissatisfaction with drug performance, 27% cited cost issues, and nearly 8% cited adverse events. It is likely that thorough education and counseling to accompany treatment would improve outcomes and discontinuation rates in cases such as these.

Misperceptions Concerning Sexual Function

Patients and their partners often harbor different or inaccurate notions concerning "normal" sexuality. Fear, shame, guilt, and various societal and cultural beliefs or notions can temper the outcome of, or represent obstacles to, patients' seeking effective ED therapy. For example, in a Danish survey, nearly 40% of 439 men aged 51 years reported sexual dysfunction, but only 7% believed that their problems were abnormal, and only 5% intended to pursue treatment.[12]

In fact, healthy men remain sexually active with advancing age: 89% at ages 50 to 59 years, 84% at ages 60 to 69 years, and 71% at ages 70 to 79 years were sexually active, according to a recent European survey.[29] Many are sexually active once weekly. However, with advancing age, the proportions of male patients reporting sexual unhappiness are equal to, if not higher than, in their younger counterparts.

Physiologic changes that affect sexuality do occur as men and women age.[30] Men experience fewer spontaneous erections, need more sexual stimulation, and have less firm erections and/or a reduced need for ejaculation to experience pleasure. Women experience slower vaginal lubrication and increased vaginal sensitivity and dryness, among other changes. However, men and women may regard these changes differently. One study suggested that men overestimate the importance of erectile function as a determinant of the overall quality of a relationship, whereas women are less likely to define their female identity based on sexual function.[14]

Patient-Physician Communication

In a US poll, 76% of healthy adults revealed concerns that their physicians would have no treatment for sexual problems.[13] In addition, 71% thought that physicians would dismiss sexuality concerns, and 68% stated that they would feel uncomfortable discussing sexual problems with their physicians, in many cases to spare *the physician* of embarrassment. These findings underscore the need for physicians to proactively begin frank discussions of sexual function with their patients.

Unfortunately, many physicians have received inadequate education and training concerning the assessment of ED, which includes taking a detailed medical, sexual, and psychosocial history. They may also be unfamiliar with the proper administration of available

therapies, drug-associated adverse events, and ways to individualize therapy. In a recent study of 85 family physicians who had been in practice for approximately 15 years, only 15% reported that they routinely inquired about ED in men older than 40 years, and 51% reported that they inquired about ED in patients with documented risk factors.[31] Although these physicians prescribed PDE5 inhibitor therapy, they were not as comfortable recommending other treatment modalities, such as ICIT. Finally, in today's clinical practices, time constraints and financial disincentives may discourage healthcare providers from initiating conversations with their patients about sexual concerns.

However, ED need not be difficult or time consuming to assess and treat.[2] Because ED may be a marker for other conditions, such as hypertension, diabetes mellitus, peripheral vascular disease, coronary artery disease (CAD), and major depressive disorder, physicians should maintain an increased index of clinical suspicion and inquire about ED in men over the age of 40 years.[32]

Patients should be informed about the advantages and disadvantages of various treatment options and be provided with advice on treatment outcomes and information on their relative ease of use. Men with ED should also know what to do in case of treatment-related complications or side effects.

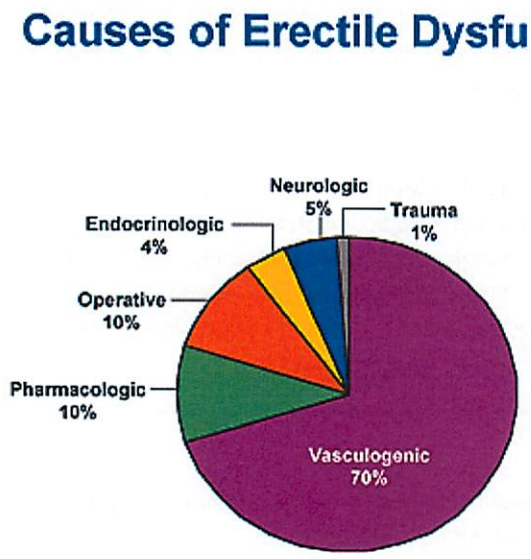
Finally, and perhaps most importantly, physicians must remember that treatment approaches should be tailored to the medical and lifestyle needs of the individual. Such needs include effectiveness, tolerability, ease of administration, noninvasiveness, painlessness, and compatibility with partner preferences.[33,34] Ideally, care should be individualized by involving the patient's partner in treatment and thus promoting appropriate expectations for sexuality and treatment outcome.[3]

Etiology of ED

Normal erectile function requires coordination of vascular, neurologic, hormonal, and psychological factors. Any interference with 1 or more of these factors may result in ED. The etiology of ED is thus frequently multifactorial.

Etiologic concepts have undergone striking revisions in the past 2 decades as knowledge of the normal physiology of penile erection and the pathophysiology of ED has progressed. First and foremost, although the prevalence of ED increases with advancing age, ED is no longer regarded as an inevitable consequence of aging. Second, although it was formerly believed that most cases of ED were primarily psychogenic, it is now recognized that organic causes of ED play a much more significant etiologic role.

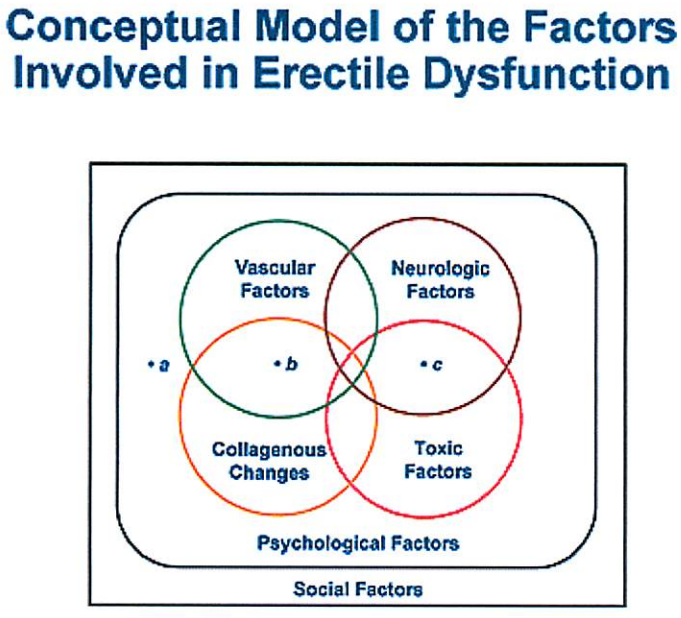
Most authorities concur that purely psychological mechanisms are operative in 1 of every 3 to 5 patients and that strictly organic or mixed causes are responsible for the remaining cases.[35-37] Vascular causes represent the majority (approximately 70%) of these etiologic factors, followed by pharmacologic and operative (10% each), neurologic (5%), endocrinologic (4%), and traumatic (1%) (Figure 3).[37]



Lue TF, ed. Impotence and infertility. *In*: Vaughan ED Jr, Perlmutter AP, eds. *Atlas of Clinical Urology*. Vol 1. Philadelphia, Pa: Current Medicine, Inc; 1999. Reproduced with permission.

Causes of erectile dysfunction. Reproduced with permission from Lue TF, ed. Impotence and infertility. *In*: Vaughan ED Jr, Perlmutter AP, eds. *Atlas of Clinical Urology*. Vol 1. Philadelphia, Pa: Current Medicine, Inc; 1999.

Psychogenic issues may include situational or performance anxiety, relationship difficulties, and depression or other mental illnesses. In men with depression, ED may be associated with decreased libido. Organic causes include cardiovascular disease, diabetes mellitus, and spinal cord injury. In virtually all cases, including those in which organic factors are involved, social and psychological factors also come into play (Figure 4).[38]



Doerfler E. *J Am Acad Nurse Pract*. 1999;11:117-123. Reproduced with permission.

Conceptual model of the factors involved in erectile dysfunction. Point *a* depicts a man in his 30s whose erectile dysfunction is due to difficulties in a relationship. Point *b* depicts a man in his 40s with Peyronie's disease. Point *c* depicts a man whose erectile dysfunction was caused by exposure to lead in his workplace. In all cases, social and psychological factors are at work. Note that all 6 of the major etiologies and aggravating factors may be present in the center of the diagram. Reproduced with permission from Doerfler E. *J Am Acad Nurse Pract*. 1999;11:117-123.NO, nitric oxide. Adapted with permission from Lue TF. Erectile dysfunction. *N Engl J Med*. 2000;342:1802-1813. Copyright © 2000 Massachusetts Medical Society. All rights reserved.Adapted with permission from the BMJ Publishing Group. Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. *BMJ*. 2000;321:499-503.

Risk Factors and Comorbidities

The likelihood of developing ED is increased by a number of factors: psychological, neurologic, hormonal, vascular, and pharmacologic. The likelihood of ED may also be increased as a result of systemic diseases (eg, CAD, hypertension, diabetes) and/or aging (Table 1). Factors predictive of ED may be further divided into "modifiable" and "unmodifiable" categories.

Table 1. Classification and Common Causes of Erectile Dysfunction

Category of Erectile Dysfunction	Common Disorders	Pathophysiology
Psychogenic	Performance anxiety Relationship problems Stress	Loss of libido, overinhibition, impaired NO release

	Depression	
Neurogenic	Stroke Alzheimer's disease Spinal cord injury Radical pelvic surgery Pelvic injury Diabetic neuropathy	Failure to initiate nerve impulse, interrupted neural transmission
Hormonal	Hypogonadism Hyperprolactinemia	Loss of libido, inadequate NO release
Vasculogenic (arterial or cavernosal)	Atherosclerosis Hypertension Diabetes mellitus Trauma Peyronie's disease	Inadequate arterial flow, impaired veno-occlusion
Drug-induced	Antihypertensives Antidepressants Antiandrogens Alcohol abuse Cigarette smoking	Central suppression, decreased libido, alcoholic neuropathy, vascular insufficiency
Other systemic diseases and aging	Diabetes mellitus Chronic renal failure Coronary heart disease	Multifactorial, resulting in neural and vascular dysfunction

NO, nitric oxide. Adapted with permission from Lue TF. Erectile dysfunction. *N Engl J Med.* 2000;342:1802-1813.

Most amenable to correction are reversible factors, which are often exogenous in origin, such as smoking, alcohol or drug abuse; obesity; and physical inactivity. Therapy with certain classes of prescription drugs may also result in ED; in some cases, it may be possible to switch to an agent with a lower risk of sexual dysfunction (Table 2).[2] Anxiety and other psychological or emotional stressors should be confronted and, if possible, resolved.

Table 2. Drugs Associated With Erectile Dysfunction

Type of Drug	Examples	Alternative Drugs With Lower

		Risk of Erectile Dysfunction
Antihypertensives	Beta-adrenergic blockers (propranolol, atenolol); thiazide diuretics (cyclopenthiazide, chlorothiazide); hydralazine	Alpha-adrenergic blockers; angiotensin-converting enzyme inhibitors; calcium channel blockers
Diuretics	Thiazide diuretics; potassium-sparing diuretics (spironolactone); carbonic anhydrase inhibitor (acetazolamide)	Loop diuretics (furosemide, bumetanide)
Antidepressants	Selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline); tricyclic antidepressants (amitriptyline, imipramine); monoamine oxidase inhibitors (phenelzine)	Newer agents, such as bupropion, may have lower risk, but data are needed to confirm
Antipsychotic agents	Phenothiazines (chlorpromazine, thioridazine); carbamazepine; risperidone	Newer agents may have lower risk, but data are needed to confirm
Hormonal agents	Cyproterone acetate; luteinizing hormone-releasing hormone analogues; estrogens	Depends on diagnosis and available options
Lipid regulators	Gemfibrozil; clofibrate	Statins (pravastatin, simvastatin)
Anticonvulsants	Phenytoin; carbamazepine	Need neurologist's opinion
Antiparkinson agents	Levodopa	Need neurologist's opinion
Gastrointestinal reflux disease and ulcer-healing drugs	H_2 antagonists (cimetidine, famotidine, ranitidine)	Proton-pump inhibitors (omeprazole, esomeprazole)
Miscellaneous	Allopurinol; indomethacin; disulfiram, phenothiazine antihistamines; phenothiazine antiemetics (prochlorperazine)	Cyclizine may replace prochlorperazine

Adapted with permission from the BMJ Publishing Group. Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. *BMJ*. 2000;321:499-503.

Endogenous risk factors for ED include diabetes, hypertension, CAD, and depression. Indeed, ED may serve as an important risk marker for these and other disorders.[39-41] For example, in 2476 Spanish men, there was a significant positive correlation of ED with diabetes, hypertension, hypercholesterolemia, peripheral vascular disease, lung disease, cardiac problems, rheumatism, and allergy that was unrelated to medications or use of tobacco and alcohol.[8] Attempts should be made to modify these risk factors, in part because such conditions may be life-threatening in their own right.

An increased incidence of depression has also been noted in men with ED. This appears to be distinct from the reactive type of depression that might occur secondary to ED, and has led to the recognition of a possible syndrome linking depression and ED.[42,43] Identifying depression and referring patients to an appropriate mental healthcare provider can help to optimize ED treatment compliance and outcome.

Lifestyle Changes to Improve Risk Factors

Obesity and/or sedentary behavior are potential risk factors that lend themselves to correction. Indeed, overweight men may be more likely to suffer from ED compared with their slimmer counterparts. In a review of 1981 men between the ages of 51 and 88 years who had served as controls in an unrelated study, 34% reported moderate to severe ED.[44] Of interest, men with a waistline of 42 inches or more were nearly twice as likely to have symptoms of ED compared with men whose girth measured 32 inches or less, even after adjusting for other factors such as age, hypertension, and smoking. In another study, significantly less ED was reported in nonobese men than in their overweight counterparts.[45]

Limited observations have been made on the effect of weight loss on ED. In one study, ED was significantly associated with obesity ($P = .006$), with baseline obesity predicting higher ED risk regardless of subsequent weight loss.[46] Even when initiated at middle age, increased physical-activity regimens significantly reduced the risk of developing ED over a 9-year period in a Boston cohort study.[46]

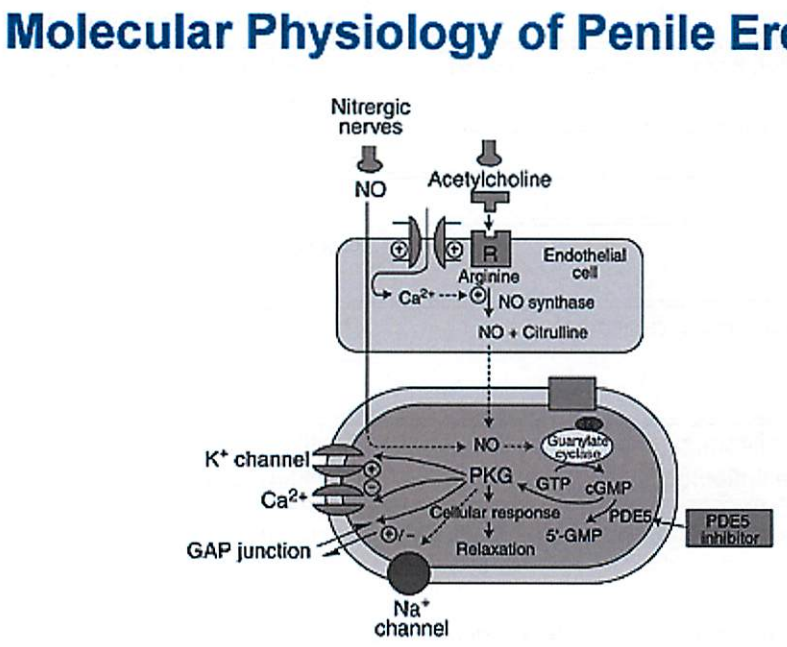
Case studies and retrospective analyses have shown that smoking increases the risk of moderate or complete ED 2-fold.[47] The association of ED with risk factors such as CAD and hypertension may also be amplified by cigarette smoking. The prevalence of

ED in former smokers is no different from that in individuals who have never smoked, implying that smoking cessation may decrease the risk of ED.

Excessive alcohol intake has been reported in association with ED.[48] The mechanism is unknown, but may be related to alcohol-induced liver disease and to a subsequent change in estrogen-androgen ratios. However, some data do not suggest a significant association between ED and alcohol intake.[46]

Anatomy and Physiology of Normal Erection and Pathophysiology of ED

Penile erection is a complex physiologic process that occurs through a coordinated cascade of neurologic, vascular, and humoral events. Figure 5 depicts the physiologic events that occur in normal penile erection.[37]



Lue TF, ed. Impotence and infertility. *In*: Vaughan ED Jr, Perlmutter AP, eds. *Atlas of Clinical Urology*. Vol 1. Philadelphia, Pa: Current Medicine, Inc; 1999. Reproduced with permission.

Molecular physiology of penile erection. cGMP, cyclic guanosine monophosphate; G, G protein; GAP, guanosine triphosphatase activating protein; GTP, guanosine triphosphate; NO, nitric oxide; PDE5, phosphodiesterase type 5; R, receptor. Adapted with permission from Lue TF, ed. Impotence and infertility. *In*: Vaughan ED Jr, Perlmutter AP, eds. *Atlas of Clinical Urology*. Vol 1. Philadelphia, Pa: Current Medicine, Inc; 1999.

From an anatomic standpoint, the penis is highly vascular, invested with a rich supply of smooth muscle erectile tissue, and harbors numerous sinusoids, all of which render it well suited to accommodate the enhanced perfusion of the penis underlying physiologic erection.

Within the penis, erection begins with vasodilatation of the cavernous artery and helicine arterioles in association with relaxation of the trabecular erectile tissue. These actions cause engorgement of blood in the sinusoidal spaces of the corpora cavernosa and spongiosum, and penile erection results. The expansion of penile blood volume leads to compression of subtunical venules by the resistant fibrous outer covering, the tunica albuginea, with occlusion of venous outflow and physiologic erection.

Voluntary or reflexogenic contraction of the ischiocavernous and bulbocavernous musculature contributes to the increase in intracavernosal pressure, which may reach or exceed mean arterial pressure.[49,50]

Penile erection is initiated by sexual stimuli, including auditory, visual, and olfactory stimuli, and erotic cognitions. Spinal cord sexual arousal occurs as a result of tactile stimulation of the penis. The neurotransmitter mediating these sexual signals is nitric oxide (NO), initially termed endothelium-derived relaxing factor.[51] NO is produced by the endothelium in the absence of cholinergic or adrenergic influences.[52,53]

NO stimulates smooth muscle guanylate cyclase, upregulating synthesis of cyclic guanine monophosphate (cGMP), which plays a pivotal role in penile arteriolar vasodilatation and relaxation of penile corporeal smooth muscle. Oxygen levels are important in NO-mediated responses, which vary widely from penile flaccidity to erection. Decreasing oxygen tension levels progressively inhibit NO responses, and elevation of oxygen to normal levels restores NO-dependent activities.[54]

Both cholinergic and adrenergic influences are significant in penile erection and detumescence. Parasympathetic fibers and acetylcholine, the release of which may be stimulated by tactile sensory stimuli to the penis, enhance penile blood flow and smooth muscle relaxation.[55] Sympathetic (adrenergic) fibers and norepinephrine neurotransmission help to maintain the penis in its flaccid state.[56]

Detumescence is mediated by adrenergic nerve terminals whose neurotransmitter, norepinephrine, activates alpha-adrenergic receptors (found chiefly in the thoracolumbar region of the spinal cord). Activation of these receptors produces vasoconstriction of the penile vasculature and decompression of penile venules, which result in detumescence. Incomplete corporeal smooth muscle relaxation resulting from impairment of the NO-induced relaxing mechanism or from augmented alpha-adrenergic activity has been proposed as a mechanism of ED.[57]

Prostaglandin E_1 (PGE_1) is produced during erection by the penile musculature and activates adenylate cyclase, which alters ion-channel permeability and results in calcium release by the smooth muscle cells. (Although the PGE_1 pathway is not thought to play a major intrinsic proerectile role, it is considered to be important as a therapeutic approach.)

These smooth muscle cells then relax, allowing increased blood flow.[58] Dynamic vascular studies have demonstrated that venous outflow obstruction and the resultant entrapment of arterial blood in the penis are essential in the initiation and maintenance of a rigid erection.[59]

Failure of these vascular phenomena, as seen with venous leakage, can result in ED.[60] Venous leakage may be of traumatic origin, resulting in abnormal venous communication between the corpora cavernosa and the glans penis. Leakage may also result from the failure of emissary veins to close, as in Peyronie's disease.[59] An unusual cause of ED is a traumatic or congenital arteriovenous fistula between the pudendal artery and a pelvic vein. An elevated penile content of corporeal connective tissue, possibly related to a decrease in oxygen, has been proposed as a mechanism for defective veno-occlusion.[61]

Phosphodiesterases are essential in regulating intracellular cGMP activity through enzymatic hydrolysis (to 5'-GMP), thus terminating its second-messenger function.[2] Multiple PDEs exist throughout the body; their isoforms vary depending on the specific function that they perform. In cGMP penile activity, the PDE5 isoform terminates the vasodilator and smooth muscle-relaxing effects of cGMP. Inhibition of this process by PDE5 inhibitors forms the basis for recent developments in the oral therapy of ED.

Treatment Implications

Recent advances in elucidating the physiology of penile erection and possible mechanisms of ED have spawned the development of new pharmacologic agents. These agents exploit or potentiate normal physiologic mechanisms producing penile erection or modify the pathophysiologic factors leading to ED.

The physiologic response produced by sexual arousal is potentiated -- not engendered --by PDE5 inhibitors. These agents selectively and competitively inhibit hydrolysis of cGMP, the second messenger responsible for NO-induced penile smooth muscle relaxation and increased penile blood flow. Indeed, although approximately 30% to 40% of sildenafil users reported improvements in relationships with partners and/or QOL,[62] PDE5 inhibitors are without benefit in the absence of sexual arousal. This is a critical concept for the patient and his sexual partner to understand.

Because adrenergic stimulation, primarily of alpha-2 receptors, is responsible for penile detumescence and maintenance of flaccidity, agents such as phentolamine, which block alpha-adrenergic stimulation, have been used in the treatment of ED. These agents have been most effective when applied topically to the urethra and may also be useful with ICIT or as oral therapy (in Mexico and other non-US markets), although the latter is of questionable efficacy.

Several vasoactive agents, including synthetic PGE_1, have been administered by ICIT either alone or in combination with other agents. They enhance penile blood flow and erection by promoting smooth muscle relaxation and penile arteriolar dilatation. The latter processes occur either by direct action on the smooth muscle of the corpora and penile arterioles or by increased intracellular levels of cGMP through stimulation of NO release.[63,64]

Assessment and Diagnosis of ED

The past 2 decades have witnessed an emerging acceptance of, and candor about, ED as a significant medical problem. In addition, the availability of safe and effective agents for the treatment of ED has increased dramatically in recent years. Despite these advances, however, no uniform consensus recommendations are available to guide the diagnosis and management of patients with ED, although guidelines from the United States,[3] United Kingdom,[2] and World Health Organization (WHO)[1] have been issued.

A "process of care" model for the evaluation and treatment of ED was developed by a group of medical specialists, including representatives from primary care, internal medicine, endocrinology, psychiatry, psychology, and urology.[65] The key components of this model are summarized in Table 3.

Table 3. Key Components of "Process of Care" Model

• Rational approach to diagnosis and treatment
• Emphasis on clinical history-taking and focused physical examination
• Specialized testing and referrals in predefined situations
• Stepwise management approach with ranking of treatment options
• Incorporation of patient's and partner's needs and preferences in the decision-making process (goal-directed approach)

Adapted with permission from Padma-Nathan H. Diagnostic and treatment strategies for erectile dysfunction: the 'Process of Care' model. *Int J Impot Res.* 2000;12(suppl 4):S119-S121.

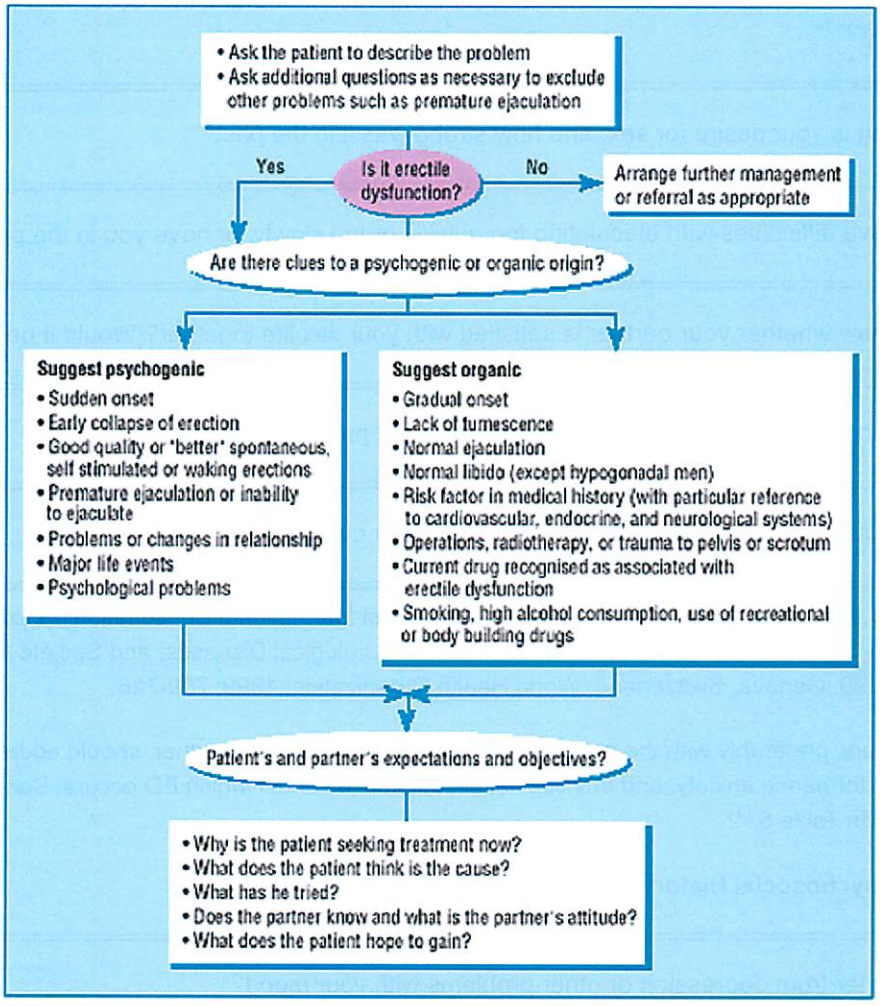
A multidisciplinary approach should be used whenever necessary to diagnose ED, to determine a therapeutic regimen, and to optimize outcomes. For example, a patient with ED who has diabetes might benefit from coordinated care by a urologist and an endocrinologist. Marriage counselors, sex therapists, psychiatrists, nurses, and other allied-care professionals may also be important to therapeutic success.

History

The first step in the diagnosis of ED is to take a thorough medical, sexual, and psychosocial history. The general medical history may disclose 1 or more distinct causes of ED, including the presence of comorbid conditions, use of provocative medications, and history of substance abuse.[2] The medical history often helps the provider distinguish between psychogenic and organic components of ED.

Figure 6 depicts a simple algorithm for history taking and lists characteristics and risk factors that suggest either psychogenic or organic elements of ED.[2]

History Taking in the Assessment of ED



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History taking in the assessment of erectile dysfunction. Reproduced with permission from the BMJ Publishing Group. Ralph D, McNicholas T. *BMJ*. 2000; 321:499-503.

Taking a sexual history helps to distinguish ED from other abnormalities in sexual function, such as ejaculatory and orgasmic disturbances and loss of sexual desire.[3] The sexual history should include questions about the frequency and duration of sexual activities, the quality and degree of penile erections, and the presence or absence of nocturnal erections.[2] Any sexual problems that the female partner experiences, such as dyspareunia or vaginal dryness, should be ascertained and addressed as well.

Suggested questions to ask are presented in Table 4.[1]

Table 4. Sample Sexual History Questions

• "Many men your age start to experience sexual difficulties. If you ever have such a problem, I'd be happy to discuss this further."
• "Could you describe your sexual problem?"
• "When did your erection problems begin? Please describe the circumstances."

• "Tell me about your sexual life and your satisfaction in the past."
• "How are your erections that you achieve with masturbation, or those that occur with sleep and upon waking early in the morning?"
• "How strong is your desire for sex, and how strong was it in the past?"
• "Do you have difficulties with ejaculating too quickly or too slowly, or have you in the past?"
• "Do you know whether your partner is satisfied with your sex life together? Would it be helpful for me to talk with her?"
• "What has been your partner's reaction to your sexual problems?"
• "What effects have your sexual difficulties had on your overall lifestyle?"

Jardin A, Wagner G, Khoury S, et al. Recommendations of the 1st International Consultation on Erectile Dysfunction. Cosponsored by the World Health Organization, International Consultation on Urological Diseases, and Société Internationale d'Urologie. Paris, France: July 1-3, 1999. Geneva, Switzerland: World Health Organization; 1999: 709-726.

A psychosocial history, preferably with the participation of the patient's sexual partner, should address stress, depression or other mood disorders, performance anxiety, and any special circumstances under which ED occurs. Sample psychosocial history questions are listed in Table 5.[1]

Table 5. Sample Psychosocial History Questions

• "Do you suffer from depression or other problems with your mood?"
• "Have you seen a psychiatrist, therapist, or other mental health professional in recent years? If you have, would you describe the circumstances and outcome?"
• "How are your relationships with family members, friends, and other important people in your life?"
• "How is your relationship with your partner right now? How was it in the past?"
• "Were you ever the victim of sexual abuse? If yes, what effect did this have on you then, and what effect does it have on you now?"
• "Do you have any difficulties in your work situation?"
• "Is your economic situation contributing significant stress in your life?"

Jardin A, Wagner G, Khoury S, et al. Recommendations of the 1st international consultation on erectile dysfunction. Cosponsored by the World Health Organization, International Consultation on Urological Diseases, and Société Internationale d'Urologie. Paris, France: July 1-3, 1999. Geneva, Switzerland: World Health Organization; 1999: 709-726.

Focused Physical Examination

The physical examination of a patient with ED does not differ substantially from that performed routinely by a primary care physician and need not take a long time. Emphasis should be placed on the genitourinary, vascular, and neurologic systems. Vital signs, including blood pressure and heart rate, should be recorded.

Body habitus and hair distribution should be noted for suggestion of hypogonadism or congenital conditions. The genitalia should be carefully examined for testicular size and consistency, as well as penile plaques and deformities (as seen in Peyronie's disease). A rectal examination may be performed to evaluate the size and consistency of the prostate and to assess the bulbocavernous reflex.

As mentioned above, ED may serve as a marker for other conditions including diabetes, hyperlipidemia,[66] hypertension,[67] CAD, and/or depression.[42] To rule out these conditions, selected laboratory tests may be necessary. The WHO recommends administering a fasting blood glucose or glycosylated hemoglobin (HbA_{1c}), lipid profile (if not done in the past 12 months), and hypothalamic-pituitary-adrenal axis assessment (serum testosterone).[1]

The above recommendations apply to the "standard" ED patient (ie, a man over the age of 50 years who is in good physical and mental health and has experienced ED gradually over at least 1 year).[68] However, more advanced diagnostic tests should be performed when the patient shows evidence of a significant endocrine, psychogenic, or vascular condition. The following investigative procedures may be considered in such a "nonstandard" patient.[68]

For an individual with suspected hypogonadism, tests may include total serum testosterone, free testosterone or bioavailable testosterone, serum luteinizing hormone, serum prolactin, and thyroid function. ED may indicate hyperprolactinemia in a small minority of patients; very depressed testosterone levels are routinely observed in the vast majority of these men. In cases where psychogenic ED plays a major role, absent or insufficient erections during sexual activity but normal erections on awakening or in response to visual sexual stimulation may be experienced. Nocturnal penile tumescence and rigidity with or without polysomnography may be tested to rule out organic causes of ED.[68]

Patients who have suspected vasculogenic ED should undergo intracavernous injection (ICI) testing using vasoactive drugs.[68] If the ICI test is abnormal, duplex ultrasonography of the corpora cavernosa should be conducted; this test may indicate vascular pathology. Arteriography should be performed if penile arterial revascularization is being considered. Cavernosometry can be used to rule out corporo-venous occlusive dysfunction; dynamic infusion cavernosometry and cavernosography provide the most sensitive means of identifying the site of the abnormality and quantifying its severity.[68]

Treatment Options for ED

Tailoring Therapy to Individual Patient Needs

Before starting any therapy for ED, the physician should begin the process of devising a treatment plan with both the patient and his sexual partner. Both individuals should be in agreement as to their expectations, motivation for therapy, and lifestyle preferences. Treatment should be tailored to these concepts and considered in the context of traditions, ethnicity, and socioeconomic conditions. If necessary, the couple may be referred for counseling at this stage.

The chosen treatment should meet the needs and preferences of the patient and his partner on a number of levels. Ease of administration is a key issue. For example, a man with poor manual dexterity or arthritis might have difficulty self-administering transurethral (TU) therapy or ICIT. The need to plan sexual activity in advance with certain ED treatments should also be considered.

Some of these issues may be addressed with proper education. The physician should provide both the patient and his partner with unbiased information about the methods of administration, degree of invasiveness, reversibility, duration of therapy, and cost of treatment. The couple should be advised about potential side effects. For example, flushing, which may occur with PDE5 inhibitors, may be unnerving. Patients should also receive education about more serious side effects that might require medical care, such as priapism, which can result from ICIT or TU therapy (see below).

Measures that may be taken to maximize efficacy should be discussed. For example, a man who takes PDE5 inhibitor therapy needs adequate sexual stimulation in order to have an erection. Certain oral agents need to be taken on an empty stomach or within a given window relative to intercourse for maximum effectiveness. As with the "timing" of oral agent dosing for maximal efficacy,

setting aside time to self-administer ICIT before sex involves a certain amount of planning, and the patient should understand that ICIT may reach a peak effectiveness within 5 to 15 minutes after injection.

First-line Therapy for ED: Oral Agents

Oral agents for ED include PDE5 inhibitors, such as sildenafil citrate; centrally acting agents, such as apomorphine; and alpha-blockers, such as phentolamine (in certain markets).

PDE5 Inhibitors

The only currently available PDE5 inhibitor is sildenafil. Two other agents in this class of drugs, tadalafil and vardenafil, are under investigation (described below). Clinical evidence has shown that PDE5 inhibitors are safe and effective. They may be used in a broad spectrum of patients with mild to severe ED of psychogenic, organic, or mixed origin associated with a wide range of conditions, including diabetes, cardiovascular disease (if not treated with nitrates), pelvic surgery, spinal cord injury, and Parkinson's disease. The PDE5 inhibitors are highly acceptable to many patients and their partners and are also well tolerated.[69] Advantages associated with these agents include relative painlessness (in patients without adverse effects such as headache), reversibility, convenience, and the production of a relatively "natural" erection and sexual encounter.

Several educational points regarding sildenafil therapy should be made clear to patients and their partners in order to optimize this agent's efficacy. First, PDE5 inhibitors facilitate -- but do not engender -- an erection, meaning that adequate sexual stimulation is necessary, especially with advancing age. The impact of psychological stimulation diminishes with age; therefore, increased sensory input, such as manual stimulation of the genitalia, may be needed to achieve an erection, particularly in older men and in those who have endured a long period of abstinence.

Second, because sildenafil reaches maximum plasma levels between 30 and 120 minutes after dosing (median, 60 minutes),[70] patients are best advised to plan to have sexual intercourse approximately 1 hour after taking sildenafil in order to maximize its proerectile effects. Further, food consumption, particularly of high-fat meals, reduces the rate of absorption, thereby delaying time to maximum concentration by about 60 minutes; the mean maximal concentration is also reduced (by 29%) after high-fat meals.[70]

The physician should also explain possible side effects of PDE5 inhibitors to patients and their partners. These include vasodilator effects, such as headache, flushing, and dyspepsia. Sildenafil has a roughly 9- to 10-fold selectivity for PDE5 over PDE6, which is found in the retina. Perhaps because of this, a small minority (3%) of patients experienced visual disturbances, including blue-green aura, in registration studies.[70] A balance between efficacy and tolerability can be achieved in some cases by fine-tuning the dosage over a range of 25 to 100 mg. Finally, sildenafil treatment can potentiate the hypotensive effects of organic nitrates and NO donors; therefore, treatment with this PDE5 inhibitor is absolutely contraindicated in men taking either long- or short-acting nitrates.[70,71]

Centrally Acting Agents

Sublingual (SL) apomorphine, a centrally acting dopamine agonist, is available in some non-US markets. This oral therapy is convenient, rapidly acting (10 to 25 minutes to erection onset), and moderately effective in treating ED. In a recent randomized, double-blind, placebo-controlled crossover trial[72] involving 194 men with ED (mean age, 57 years), the proportion of sexual-intercourse attempts resulting in erections of sufficient rigidity for intercourse according to patient ratings was approximately 47% with apomorphine SL 3 mg compared with 32% with placebo ($P < .001$). The main side effect with apomorphine, which has emetic properties, is nausea, which was reported by 7.0% and 1.1% of patients taking 3 mg apomorphine SL and placebo, respectively.[72]

Alpha-Blockers

The plant extract yohimbine is an alpha-2-adrenoceptor antagonist. It exerts peripheral cholinergic effects that are potentially desirable for the management of ED.[73] Its efficacy is limited, however, and it may be more useful in patients with psychogenic than with organic ED. The American Urological Association consensus position states that yohimbine is not effective in treating organic ED. This agent may induce nervousness, and is contraindicated in patients who are under psychiatric care and/or are taking antidepressants. Further studies of this drug taken on an "as-needed" basis are necessary.

Another alpha-blocker, oral phentolamine, is currently available in Mexico and certain South American countries. The US Food and Drug Administration has suspended US trials of this agent. Phentolamine 40 to 80 mg has been shown to improve erections in 37%

to 45% of men, respectively, vs 16% of those receiving placebo.[74] Patients who take phentolamine may need to plan sexual activity in advance because the time to maximum concentration is 30 to 60 minutes, and the half-life is 5 to 7 hours.[75]

Second-line Therapy for ED: ICIT and TU Vasoactive Treatment

Approximately 30% of patients do not respond to PDE5 inhibitor therapy, and another 15% have contraindications.[76] For these men, ICIT or TU therapy with vasoactive agents may be indicated.

ICIT

The principal drugs administered in ICIT are phentolamine, papaverine, and PGE_1. Phentolamine is an alpha-1- and alpha-2-adrenergic receptor inhibitor that is also prescribed for oral therapy in some non-US markets. Both PGE_1 and papaverine are very effective alone or in combination; the combination of phentolamine and papaverine is effective in approximately 69% of men.[77]

Papaverine alone produces adequate erections in fewer patients; however, it may be of use in patients suffering from spinal cord injury or neurologic disease, who tend to be younger than the average ED patient and need smaller doses of the agent for efficacy.[77]

Monotherapy with PGE_1 may be more effective -- and smaller doses may be needed -- in patients with neurogenic or psychogenic ED or spinal cord injury. Patients with diabetes or venous leak may be less sensitive (responsive) to PGE_1 alone compared with other ED patients. PGE_1 alone appears to be more effective than papaverine alone and about as effective as papaverine plus phentolamine.

Chronic treatment with PGE_1 injections can restore the ED patient's ability to experience spontaneous erection by enhancing penile hemodynamics. In a recent open-label study conducted in Canada,[78] 67 of 70 men (96%, mean age 58 years) with vasculogenic ED experienced penile rigidity that was suitable for sexual intercourse during a titration phase, at a median dose of 15 mcg. During a subsequent 12-month self-treatment phase carried out in the patients' homes, 46 of 54 men (85%) with available data reported return of spontaneous erections. Further, Duplex ultrasonography in 38 men demonstrated significant postinjection increases (vs baseline) in peak systolic velocity in the cavernosal arteries, as well as in cavernosal artery diameters.

Triple combination papaverine-phentolamine-PGE_1 therapy is associated with a success rate of 92% and is superior to papaverine alone, PGE_1 alone, and papaverine plus phentolamine.[77,79] Of interest, smaller volumes of injections are needed with this triple combination therapy than with the individual treatments.[77] The combination may also result in a lower overall incidence of priapism compared with the other ICIT treatments.[77] As the principle of combination therapy with ICIT becomes increasingly accepted, it is likely that other combinations will be tested and used. For example, a 4-drug regimen that includes papaverine, phentolamine, PGE_1, and atropine has been shown to be effective.[80]

Other agents used in ICIT include vasoactive intestinal polypeptide plus phentolamine. This combination, which is highly effective but results in vasoactive side effects (flushing) in 70% to 80% of patients, is currently available in some non-US markets.[76]

ICIT is widely applicable and has few absolute contraindications. Relative contraindications include poor manual dexterity, obesity, and concurrent anticoagulant therapy. Some patients are loath to self-inject. In this case, education of the patient and his partner can be useful. Sometimes a cooperative partner can inject the man if he cannot self-inject. Individuals need time and a relaxed atmosphere to become comfortable with ICIT. Educational videos, well-versed assistants or nurses, booklets, and telephone hotlines are helpful resources for patients who have difficulty with this technique.

Trial injection at the physician's office should be performed as a diagnostic measure and to instruct the patient and his partner, if she is willing. Fine-tuning the dosage may be time-consuming. Ideally, several office visits should take place to ensure that the patient is comfortable and competent with ICIT. During these visits, the healthcare provider should discuss issues such as side effects, injection-site rotation, postinjection pressure to prevent hematoma, and frequency and duration of treatment.[77]

The significant potential adverse effect of ICIT is prolonged penile erection, generally a painful erection unrelated to sexual activity that lasts for 4 to 6 hours and may be associated with penile fibrosis. This effect, termed priapism, needs to be considered a medical emergency, with treatment instituted within 6 to 12 hours. Although a variety of approaches exist, most medical centers initially attempt detumescence with an intracorporeal alpha-agonist. The current treatment of choice is an ampule of phenylephrine diluted

in 19 mL of normal saline. This produces a final concentration of 500 mcg/mL. A tuberculin 1-mL syringe is used to deliver the drug, which is diluted in 0.1- to 0.2-mL increments each over 1 to 2 minutes until the erection subsides.

Penile fibrosis is the unfortunate usual consequence of untreated priapism and may preclude the possibility of future erectile function in severe cases. Small-nodule formation at the injection site or distant from the site of injection is fairly common among men who regularly use ICIT.

Although ICIT requires a substantial amount of patient education and office time, it has advantages once an individual and his partner have adapted to and persist with therapy. High patient and partner satisfaction rates (81% to 90%) over time have been reported.[81,82] A number of patients and partners appreciate the reliable proerectile effects associated with ICIT, which may promote an especially rigid, rapidly occurring, long-lived erection. ICIT may be useful in combination with oral agents for patients with severe ED.[76] It may also be effective in patients with veno-occlusive dysfunction; 69% of men using the 4-drug combination including atropine remained satisfied with treatment and continued to use ICIT after 16 months.[80] In one study, younger men, those with short ED history, and those with ED due to radical prostatectomy were particularly satisfied with ICIT and preferred it to vacuum devices.[83] In another study, patients with psychogenic ED had higher satisfaction rates with ICIT than did patients with organic ED.[84]

On the other hand, suboptimal acceptance of and adherence to ICIT have been demonstrated. Approximately 15% to 22% of men decline more than a single trial injection of ICIT,[84,85] many because of "needle phobia" and/or a recent history of pelvic surgery. Discontinuation rates are approximately 40% at 3 months and 70% to 80% by 3 years.[84,85] Multivariate analyses showed that men who discontinued ICIT were more likely to have concomitant premature ejaculation, low responses during psychophysiologic screening, lack of spontaneous erections before ICIT, and an organic component in the etiology.[86] However, a number of patients discontinue ICIT for a positive reason -- namely, recovery of spontaneous erections.

Penile pain is common with ICIT and may present a particular problem in those who have diabetic neuropathy or nerve injury. Unpleasant vasoactive effects, such as flushing, may also occur. Physicians should educate the patient about priapism and the need to seek immediate medical attention to prevent fibrotic or other serious complications if this event occurs. Changes such as nodules and plaques are seen in up to 11.7% of patients using ICIT.[87] Patients who have poor liver function or a history of alcoholism are not good candidates for ICIT that involves papaverine because of this agent's potential for hepatotoxicity.[77]

TU Vasoactive Treatment

For postsurgical or needle-phobic patients who cannot use or choose not to use oral agents, TU vasoactive treatment may be more suitable than ICIT. In 2 multicenter, placebo-controlled studies,[88,89] TU with alprostadil (a synthetic form of PGE_1) proved effective in 43% of men with organic ED; the adjunctive use of an adjustable constriction device together with TU alprostadil in patients with organic ED led to successful sexual intercourse in 69%.[50] Advantages of TU therapy are similar to those of ICIT and include local application, minimal systemic effects, and few drug interactions. In addition, TU therapy has a lower risk of priapism compared with ICIT.

Although TU vasoactive therapy is associated with minimal systemic adverse effects, local side effects and efficacy that is considered by many to be inferior to the overall efficacy profile of ICIT may constrain the clinical utility of this approach.[50] Penile pain and urethral burning occur in approximately 32% and 12% of users, respectively,[50] and the female sexual partner may experience vaginal burning as well. TU therapy is slower to induce erection than ICIT.

The first TU application (usually a 500-mcg dose) should take place in the physician's office in case of potential complications, such as urethral bleeding, vasovagal reflex, hypotension, or priapism.[50] As with ICIT, TU therapy may require extensive patient education and office visits to optimize therapeutic outcomes.

Third-line Therapy for ED: Vacuum Devices

The least invasive ED treatment options, apart from psychosexual counseling, are vacuum erection (constriction) devices. Vacuum devices consist of an external cylinder fitted over the penis, which pumps out air and allows the penis to fill with blood; a constriction ring around the base of the penis maintains the erection.

The devices are particularly useful in patients who need help initiating and maintaining an erection, such as patients who have undergone radical prostatectomy or have veno-occlusive dysfunction.[90] Vacuum devices are also appropriate following penile vascular surgery or prosthesis removal, in which case the implant can help to prevent shortening of the penis; and grafting for

Peyronie's disease, in which case the implant can help to stretch the graft.[90] Relative contraindications include severe penile deformity; sickle-cell disease; bleeding disorder or anticoagulation therapy; and recurrent priapism.

Studies have shown varying results with regard to the acceptability and efficacy of vacuum devices. Based on recent data, approximately 1 in 3 men who achieve a satisfactory erection with either a vacuum device or sildenafil will prefer to continue with the vacuum device.[91] As with any other kind of ED therapy, patient education is important. Improper technique or misuse of these devices can lead to penile trauma, including petechiae and/or a dusky discoloration of the glans.

Furthermore, use of vacuum devices may not be consistent with a "natural" sexual experience for the patient and his partner. The device is somewhat cumbersome, and the patient may experience discomfort, penile numbness, and/or trapped ejaculate. The vacuum-device user may also experience pain secondary to local hypoxemia, and the partner may find the penis cold because the constriction ring of the device limits blood inflow. Vacuum devices are contraindicated in patients who have coagulopathies or are taking anticoagulant therapy.

Fourth-line (Invasive) Therapy for ED: Prosthesis Implantation and Other Surgery

Penile implants are viable invasive treatment options for many patients with severe ED, many of whom have organic ED. Semirigid implants are either mechanical or malleable.[37]

Prostheses represent a sound option in patients with fibrotic corporeal bodies as a result of Peyronie's disease, priapism, or trauma, as well as in men with either a suboptimal result with, or an aversion to using, oral agents, ICIT, or vacuum devices. Of interest, surgical implantation of a penile prosthesis may be a more acceptable approach in a man who has received a favorable report from an acquaintance who has successfully undergone the procedure.[37] However, such procedures may exceed certain patients' financial resources.

Both inflatable and rod implants have distinct advantages and disadvantages in practical use (Table 6).[37] Semirigid and malleable implants, which do not need to be inflated for each sexual encounter, may be particularly sound options for men with poor manual dexterity. Such devices also tend to be less susceptible to malfunction than are inflatable prostheses, and their implantation is less technically demanding for the surgeon.[37] On the other hand, some patients may find them inconvenient for use during physical activity. Malleable rods offer adequate rigidity for sexual intercourse, are easy to implant, and have a low mechanical failure rate.

Table 6. Advantages and Disadvantages of Inflatable and Semirigid Penile Implants

Type of Implant	Advantages	Disadvantages
Inflatable implants	More natural feel and appearance	More complex surgery
	Better rigidity and flaccidity	Higher repair rate
	Easier sizing	More difficult for patient to operate
Semirigid rods	Easier to insert	Inconvenient during physical activity
	Less prone to malfunction	Endoscopy is difficult
	Simple to operate	Spring-back may make positioning a problem

Adapted with permission from Lue TF, ed. Impotence and infertility. *In*: Vaughan ED Jr, Perlmutter AP, eds. *Atlas of Clinical Urology*. Vol 1. Philadelphia, Pa: Current Medicine, Inc; 1999.

Unitary hydraulic (inflatable) prostheses were introduced in 1985 and initially had excellent acceptance.[92] Long-term follow-up showed that multicomponent inflatables were also superior in terms of patient satisfaction and mechanical reliability.[92] Inflatable prostheses are best-suited to men who may require repeated TU procedures (eg, patients with bladder cancer) and those who have prostatism or urethral stricture.

For patients with Peyronie's disease, penile deviation, and ED, combining prosthesis implantation with plastic surgical correction of penile curvature may be optimal.[93] In one study, 88% of patients were satisfied with this treatment and reported satisfactory sexual intercourse for a mean follow-up period of almost 7 years.[94] If significant penile curvature exists after cylinder implantation, several options may be used to achieve straightening, including corporeal plication, glanuloplasty, formal plaque incision or excision with or without grafting, and penile modeling.

In the general ED population, approximately 80% of patients and their partners are satisfied with their prostheses.[95] Of note, men with diabetes and their partners were also satisfied with this treatment in one study (81% and 83%, respectively).[96]

To optimize both treatment outcomes and patient satisfaction with prostheses, a number of patient-selection criteria and educational issues need to be considered.[37] From the surgical perspective, patients who may be considered suitable candidates for penile implants are men with fibrotic corporeal bodies as a result of priapism, trauma, Peyronie's disease, or prior removal of an implant. From the patient-lifestyle perspective, prostheses should be considered for men who are loath to apply a vacuum device or take other medications, have had an unfavorable outcome using such devices or ICIT, and/or are acquainted with someone who has had a satisfactory outcome after penile implantation.[37]

The patient who is contemplating penile implantation must have realistic expectations concerning the surgical outcome.[37] The urologist must explain that an implant will provide the patient with a firm penis -- either permanently hard with a rod implant or alternately flaccid and hard with an inflatable device. On the other hand, no prosthesis can be expected to restore the original length or girth of the natural erection. Further, the implant exerts no influence per se on other phases of the sexual response, including libido, penile sensitivity, and ejaculation.[90]

Historically, approximately 5% to 15% of implants failed within the first 5 years, and some needed to be replaced within 10 to 15 years.[90] Prostheses are mechanical devices and, as such, may be subject to mechanical problems, including fluid leak, perforation or pain, and/or contamination/infection.[90] These risks must be fully explained to the prospective implant candidate.

Other surgical options for ED include penile-vein ligation and arterial revascularization.[97-99] These procedures may be useful in a small subset of highly selected patients with arteriogenic ED who are young and have discrete arterial lesions secondary to traumatic pelvic or perineal injury. By contrast, most older patients with arteriogenic ED are not candidates for arterial revascularization. Complications include hematoma, infection, occlusion of anastomoses, and penile shortening.

Investigational Treatments for ED

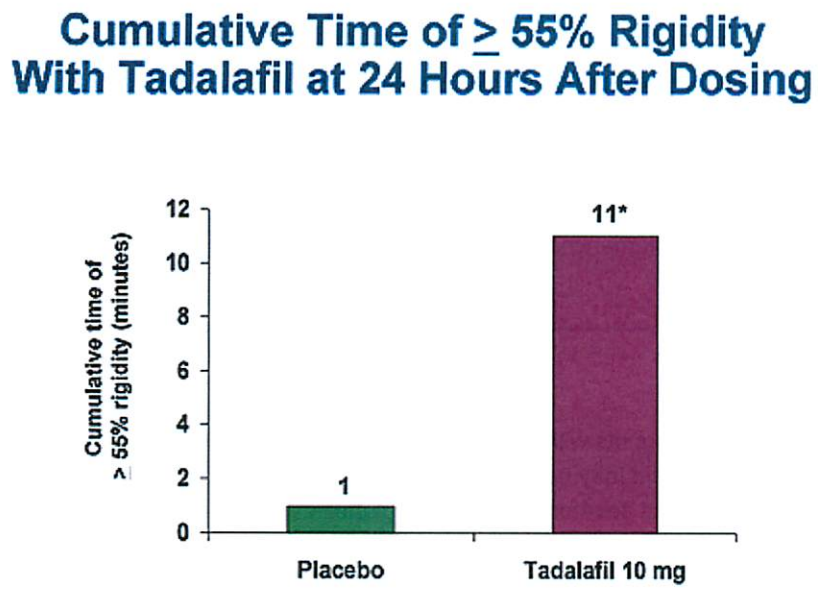
PDE5 Inhibitors Under Development

Tadalafil is a potent, selective, reversible PDE5 inhibitor that is under regulatory review in the United States and other countries as an oral therapy for ED. Like sildenafil, tadalafil is taken on an as-needed basis. The broad window of therapeutic responsiveness, together with a pharmacokinetic profile that is not influenced by either food or alcohol intake, may render tadalafil a highly convenient treatment option. Patients and their partners may not need to do as much planning with tadalafil because sexual intercourse need not be timed or synchronized with peak plasma concentrations, and neither food nor alcohol intake restricts the use of this PDE5 inhibitor.

In a randomized, double-blind, placebo-controlled trial[100] involving 179 men (mean age, 56 years) with mild-to-severe ED of varying etiologies, approximately 70% of intercourse attempts proved successful among men randomized to tadalafil taken as needed at a maximum daily dose of 10 mg or 25 mg, compared with approximately 27% in placebo controls (*P* â‰¤ .005). Such treatment also significantly enhanced the Erectile Function, Orgasmic Function, Intercourse Satisfaction, and Overall Satisfaction domains of the International Index of Erectile Function.[101] Moreover, treatment with tadalafil 20 mg administered on an as-needed basis normalized erectile function in the majority of patients, a significant increase over placebo.[102]

The terminal half-life of tadalafil is 17.5 hours, and the maximum plasma concentration is reached within 2 hours.[102] In clinical trials conducted under various conditions, this pharmacologic profile translated into a broad window of therapeutic responsiveness, ranging from as early as 16 minutes to 24 hours.

A pilot, double-blind, crossover RigiScan[TM] study[103] demonstrated that men with ED who received a single tadalafil dose (10 mg) exhibited a significantly longer cumulative time of penile rigidity â‰¥55% (*P* = .001 vs placebo) during visual sexual stimulation 24 hours after dosing (Figure 7).



*P = .001. Based on data from Rosen RC, et al. Program and abstracts of the 96th Annual Meeting of the American Urological Association; June 2-7, 2001; Anaheim, California.

Cumulative time of >/= 55% rigidity with tadalafil at 24 hours after dosing. *P = .001 vs placebo. Following 30-minute visual sexual stimulation session. Based on data from Rosen RC, et al. Program and abstracts of the 96th Annual Meeting of the American Urological Association; June 2-7, 2001; Anaheim, California.

Among men treated with tadalafil 20 mg, approximately 80% of intercourse attempts were successful from more than 4 hours to 24 hours after dosing (Figure 8).[102] Further data concerning the effects of tadalafil on multiple sexual-intercourse attempts over 24 to 36 hours after dosing will be presented at the 97th Annual Meeting of the American Urological Association in Orlando, Florida.[104]

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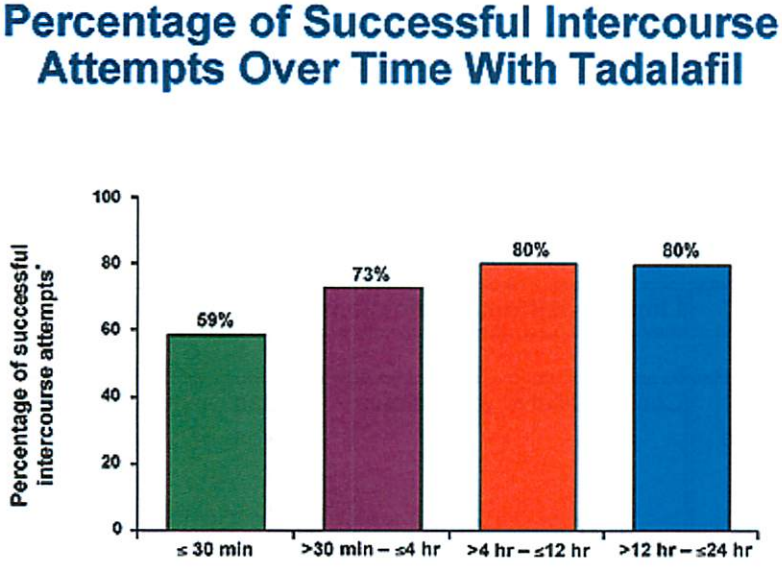

*As measured by SEP Question 3. Data on file. Lilly ICOS LLC, Indianapolis, Indiana, and Bothell, Washington. 2002.

Percentage of successful intercourse attempts over time with tadalafil. Percentage of successful intercourse attempts was computed as the proportion of "yes" responses to the Sexual Encounter Profile Question 3 ("Did your erection last long enough for you to complete intercourse with ejaculation? [yes/no]"). Data on file. Lilly ICOS LLC, Indianapolis, Indiana, and Bothell, Washington. 2002.

Vardenafil, which has also demonstrated significant proerectile effects compared with placebo in men with broad-spectrum ED,[105,106] has also been administered as needed at daily doses of 10 to 20 mg, but is a shorter-lived agent. Like sildenafil, vardenafil is rapidly absorbed, with a time to maximum plasma concentration of about 40 minutes and a half-life of about 4.4 to 4.8 hours.[107] These properties need to be explained to patients in order to optimize therapeutic responses.

Both tadalafil and vardenafil have been well tolerated in clinical trials,[100,105] with adverse-event profiles similar to that of sildenafil. Flushing, dyspepsia, and headache, typically mild to moderate and transient, have been among the most common adverse events with each agent. Based on clinical findings to date, the visual disturbances encountered with sildenafil do not seem to be a problem with either tadalafil or vardenafil.

Other Investigational Agents

Other therapies that are investigational at this time include oral agents with alpha-blocking capacity and, in certain patient populations, testosterone supplementation. Androgen replacement may be useful in a minority of patients, including men with documented hypogonadism based on laboratory findings, such as sex-hormone binding globulin and bioavailable testosterone.[108]

A meta-analysis showed that testosterone supplementation resulted in erection in 65% of patients, compared with 17% of patients who received placebo ($P < .0001$).[109] Patients with primary testicular failure seem to be more responsive to this treatment than are those with secondary failure. Transdermal testosterone administration appears to be superior to oral or intramuscular administration. However, a small study of 40 men suggested favorable results with oral dehydroepiandrosterone sulfate. Healthcare providers should remember that severe ED may be a marker for hyperprolactinemia and/or low testosterone, each of which warrants adequate laboratory assessment.

Topical vasoactive and androgenic agents are also under development, but study data are inconclusive and further investigation is warranted.[110,111]

Conclusions

ED affects growing proportions of men across the world, yet this health problem remains vastly underdiagnosed, underreported, and undertreated. Healthcare providers should be aware of risk factors for ED and should initiate conversations with their patients about this problem. Clinicians should also understand that ED may be a marker for other serious disorders, such as CAD, diabetes, and depression.

Not every treatment for ED is appropriate for every patient, but, given the variety of available therapeutic options, an effective and safe clinical management strategy can be formulated and tailored to the individual medical and lifestyle needs and preferences of the patient, along with those of his partner (Table 7). Education of the patient and his partner is essential for reducing treatment discontinuation and optimizing treatment outcomes.

Table 7. Optimizing Treatment: Patient Education and Selection

Treatment	Educational Points	Limitations/Contraindications	Potential Candidates
First-line/Oral Agents			
PDE5 inhibitors (sildenafil)	Sexual stimulation required for erection; vasoactive effects include headache, flushing	Contraindicated with nitrates	Broad range of patients; mild-to-severe ED; psychogenic, organic, or mixed origin; concomitant diabetes; pelvic surgery; Parkinson's disease; spinal cord injury
Centrally acting agents (apomorphine)*	Rapid-acting	Nausea; not available in US market	Patients in non-US countries seeking rapidly acting oral treatment
Yohimbine	Limited efficacy; short half-life (schedule sexual activity quickly after dosing)	Contraindicated in patients under psychiatric care or taking antidepressants; may cause	Psychogenic ED

		nervousness; not effective in treating organic ED	
Phentolamine*	Need to plan sexual activity in advance	Contraindicated with sildenafil; commonly causes nasal congestion	Patients in non-US countries seeking oral treatment other than PDE5 inhibitors
Second-line			
ICIT	Requires patient education and time to learn proper technique/fine-tune dosing; trial injection in office; involves both partners; immediate medical attention if priapism occurs; injection-site rotation; adherence to treatment; vasoactive side effects with some agents	Relative contraindications include poor manual dexterity, obesity, anticoagulant therapy, aversion to needles; priapism/fibrotic changes are possible; penile pain; papaverine contraindicated with poor liver function	Psychogenic, organic, or mixed origin; veno-occlusive disorder; patients taking oral agents who need additional therapy ("salvage therapy"); combination ICIT therapy generally effective in broader range of patients than monotherapy or therapy with 2 agents
TU	First dosed in office, then fine-tuned; like ICIT, may require intensive patient education and multiple office visits	May cause pain, priapism, urethral irritation/bleeding, hypotension; vaginal burning in female partner; higher side-effect profile than ICIT; inappropriate for patients with poor manual dexterity or diabetic neuropathy	Patients who cannot use oral agents and are needle-phobic or postsurgery
Third-line			
Vacuum erection device	Requires some education to learn technique	Contraindicated in patients with coagulopathies; improper use can cause penile trauma; may be inconsistent with "natural" sexual experience; partner may find penis cold	Broad range of patients; psychogenic, organic, or mixed origin
Fourth-line/Surgical			
Semi-rigid/ malleable implant	Explain surgical procedure and possible complications from surgery; mechanical reliability, possible need to replace	Invasive; possible complications from surgery; costly; painful	Organic ED; diabetes; patients requiring permanent/long-term therapy; poor manual dexterity; high surgical risk
Inflatable implant	Explain surgical procedure and possible complications from surgery; mechanical reliability, possible need to replace	Invasive; possible complications from surgery; costly; painful	Organic ED; diabetes; patients requiring permanent/long-term therapy; Peyronie's disease; bladder cancer; prostatism; urethral stricture
Arterial revascularization	Explain surgical procedure and possible complications from surgery	Invasive, possible complications from surgery; costly; painful; not appropriate for most older patients with arteriogenic ED	Young men with arteriogenic ED, discrete arterial lesions secondary to pelvic or perineal trauma
Other			
Androgen	Explain possible side effects with hormonal therapy	Useful only in specific cases with hormonal origin	Documented hypogonadism based on lab findings; primary testicular failure

*Available only in non-US markets. ICIT, intracavernosal injection therapy; TU, transurethral. Based on data from Lue TF. Erectile dysfunction. *N Engl J Med.* 2000;342:1802-1813 and Lue TF. *Contemporary Diagnosis and Management of Male Erectile*

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