

# Erectile Dysfunction: Clinical Guidelines (1)

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## ABSTRACT

**Purpose:** According to a survey, the Massachusetts Male Aging Study, 52% of men beyond 40 years of age may have some degrees of erectile failure, and it is projected to affect 322 million men worldwide by 2025. We present a framework for the evaluation, treatment, and follow-up of the male patient who presents with erectile dysfunction.

**Materials and Methods:** A comprehensive review of the literature was conducted using the MEDLINE database for all articles from 1975 through 2004 on male sexual dysfunction and the most pertinent articles are discussed.

**Results:** Remarkable progress has been made in the treatment of erectile dysfunction (ED). Erectile dysfunction is a common condition associated with aging, chronic illnesses and various modifiable risk factors. Erectile dysfunction can be due to vasculogenic, neurogenic, hormonal, and/or psychogenic factors as well as alterations in the nitric oxide/cyclic guanosine monophosphate pathway or other regulatory mechanisms. The number of consultations from new patients presenting with erectile dysfunction and resulting costs for health care systems are increasing. Urologist should be the evaluating physician who supervises the surgical, medical, and hormonal treatment and who refers the patient, as necessary, to other members of the multidisciplinary team.

**Conclusion:** Erectile dysfunction has a significant negative impact on quality of life. Male sexual dysfunction, especially erectile dysfunction, necessitates a comprehensive medical and psychologic evaluation involving both partners. All possible risk factors should be outlined and corrected, when feasible.

**KEY WORDS:** impotence, pathology, treatment outcome, penile erection, physiology

## Introduction

Erectile dysfunction (ED) is defined as persistent or recurrent inability, for at least three months duration, to achieve and/or maintain an erection sufficient for satisfactory sexual performance.<sup>(1)</sup>

Erectile Dysfunction is currently the preferred term instead of 'impotence' as the latter term lack specificity and has negative connotations.<sup>(2)</sup> ED does not refer to penile curvatures, spontaneous or drug-induced prolonged erections, and painful erections. ED must also be distinguished from other sexual disorders such as premature ejaculation, anorgasmia, and lack of desire, although ED may occur concurrently with these other sexual disorders.

Sexuality, including erection, is a complex biopsychosocial process. The physician and collaborating specialists should possess broad knowledge about human sexuality. In cases of erectile dysfunction, problems may be lifelong or acquired, and global or situational. Adequate attention to these details during the history will educate the often-uninformed patient regarding the complex nature of sexuality, and prepare him for understanding treatment and outcome realities. Cultural, social, ethnic, religious, and national/regional perspectives will significantly influence patient and partner expectations, needs, and priorities. The rational selection of therapy by patients is only possible following appropriate education, including information about sexuality and all treatments for erectile dysfunction.

Although not always possible on the first visit, every effort should be made to involve the patient's sexual partner early in the therapeutic process.

ED compromises overall quality of life and is associated with depression, anxiety and the loss of self-esteem.<sup>(3)</sup> This paper focuses on various aspects of erectile dysfunction. It reviews the epidemiology, physiology, causes, and treatments that have been shown to be effective, along with potential new therapies for this disease.

### Impact of Erectile Dysfunction

Erectile Dysfunction is a significant and common medical problem affecting many men worldwide. Cause-specific assessment and treatment of male sexual dysfunction will require recognition by the public and the medical community that erectile dysfunction is a part of overall male sexual dysfunction. Erectile dysfunction is a very common medical condition leading to fear, loss of image and self-confidence, and depression. The multifactorial nature of erectile dysfunction, comprising both organic and psychologic aspects, may often require a multidisciplinary approach to its assessment and treatment. This review addresses these issues, not only as isolated health problems, but also in the context of social and individual perceptions and expectations. Erectile dysfunction is often assumed to be a natural concomitant of the aging process, to be tolerated along with other conditions associated with aging. This assumption may not be entirely correct. For the elderly and for others, erectile dysfunction usually occurs as a consequence of specific illnesses or of medical treatment for certain illnesses. Physicians, health educators, and patients and their families are sometimes unaware of this potential complication. Whatever the causal factors may be, the embarrassment among patients and health care providers in discussing sexual issues becomes a barrier to pursuing treatment.

Erectile dysfunction can be effectively treated with a variety of methods. Many patients and health care providers are unaware of these treatments, and the dysfunction thus often remains untreated, compounded by its psychological impact. Concurrent with the increase in the availability of effective treatment methods, new diagnostic procedures have developed that may help in the selection of an effective, cause-specific treatment. This review was designed to address

these issues and to define the state of the art.<sup>(4)</sup>

### Epidemiology

Historically, the prevalence of erectile dysfunction has been difficult to estimate due to the fact that it is not life threatening, patients often do not seek treatment, and literature terminology for the condition has been confusing. In the United States, the Massachusetts Male Aging Study, reported in 1994, provided data on the prevalence of erectile dysfunction in a general population of men who were 40 to 70 years of age.<sup>(5)</sup> The combined prevalence of all degrees of erectile dysfunction was 52% (fig. 1,2). The category with the highest prevalence was moderate erectile dysfunction with a rate of 25%, followed by minimal erectile dysfunction at 17% and complete erectile dysfunction at 10%.<sup>(5)</sup>

As many as 50% of men between ages 40 and 70 are affected by transient ED and inadequate erections.<sup>(6)</sup> The incidence of ED is projected to increase sharply over the next 25 years. It may also be a biobehavioral marker for diabetes mellitus, depression, and/or cardiovascular disorders.<sup>(7)</sup>

Data from studies of the prevalence of erectile dysfunction in the general population based on

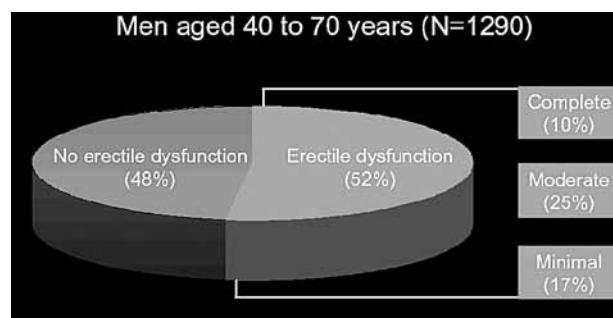


FIG. 1. Prevalence of erectile dysfunction in a general population, the Massachusetts Male Aging Study

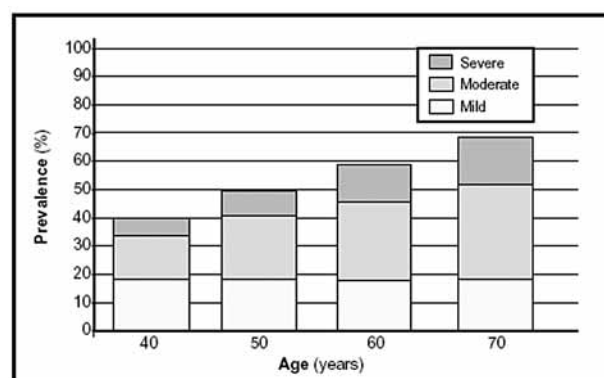


FIG. 2. Prevalence of erectile dysfunction with age in the Massachusetts Male Aging Study

surveys of samples of men indicate that the results are dependent on the definition used for erectile dysfunction. The period of data retrieval and the population surveyed also affect prevalence. It has been suggested that by age 45 many men will have experienced erectile dysfunction, and the results of a recent projection suggest that as many as 322 million men worldwide will have it by 2025.<sup>(8)</sup> Large differences are present in the prevalence of ED between countries. For example, the prevalence of moderate to severe ED at ages 40 to 70 years was 34.8% in the United States, according to the Massachusetts Male Aging Study (MMAS),<sup>(5)</sup> 39% in Japan, 21% in Italy, 15% in Brazil, and 16% in Malaysia.<sup>(9)</sup> The prevalence of ED in Iranian men is 18.8%.<sup>(10)</sup>

Although the populations studied and methods used varied considerably, the results of recent epidemiologic studies indicate that erectile dysfunction is a common problem that is associated with age and has a significant impact on quality of life. Further studies on the worldwide prevalence of erectile dysfunction with respect to racial, ethnic, socioeconomic, and cultural variability are needed. To our knowledge, the reasons for such large differences are unclear, but they may reflect medical and psychological factors, particularly in the setting of possible racial, socioeconomic, cultural, and racial differences.

### Erectile Physiology

A normal erectile mechanism entails an intact nervous system and adequate blood supply to the penis and a competent veno-occlusive mechanism of the penis. Penile erection and detumescence are homodynamic events that are regulated by corporal smooth muscle relaxation and contraction respectively. In the flaccid state, a dominant sympathetic influence prevails, and the arteries and corporal smooth muscle are tonically contracted. There is a constant but minimal blood flow into the lacuna spaces (sponge-like penile tissue).

After sexual stimulation, parasympathetic activity increases resulting in vasodilatory effects. This decreases the peripheral resistance bringing about tremendous increase in blood flow through the cavernous and helicine arteries. Relaxation of corporal smooth muscle increases compliance and the expansion of the lacuna spaces compresses the outflow veins (subtunical veins) resulting in maintenance of erection. Detumescence occurs when sympathetic activity (following orgasm)

increases the tone of the helicine arteries and the corporal smooth muscle. Normal erectile process begins with sexual stimulation in the brain (perception, desire, etc) from where impulses are transmitted via the spinal cord and the pelvic nerve to the penile corpus cavernosum (corporal smooth muscle).

Corporal smooth muscle contraction is modulated by the sympathetic nervous system via the release of norepinephrine and activation of post-synaptic  $\alpha$ 1-adrenergic receptors. On the other hand, relaxation is mediated by acetylcholine released by the parasympathetic nervous system and a second neurotransmitter, nitric oxide (NO), or a nitric oxide releasing substance.<sup>(11)</sup> Nitric oxide increases intracellular levels of cyclic guanosine monophosphate (cGMP) in the corporal cavernosal smooth muscle (CCSM), which acts to relax cavernosal tissue, perhaps by activating protein kinase G and stimulating phosphorylation of proteins that regulate corporal smooth muscle tone. The actions of the parasympathetic nervous system, nitric oxide and cGMP permit rapid blood flow into the penis and the development of an erection.<sup>(12)</sup> The exact mechanisms that are involved in nitric oxide/cyclic guanosine monophosphate induced penile corporal smooth muscle relaxation are unknown. However, it has been proposed that cyclic guanosine monophosphate activates protein kinase G, leading to the phosphorylation of proteins regulating corporal smooth muscle tone.<sup>(10,13)</sup>

### Causes of Erectile Dysfunction

The two main categories of erectile dysfunction are psychologic and organic (fig. 3).<sup>(14,165)</sup> ED can occur as a result of a neurological disorder affecting the central nervous system or anywhere in the erection pathway, an arterial disorder, as in generalized arteriopathy or localized as seen after pelvic surgery or radiotherapy, or a defective veno-occlusive mechanism, either congenital or acquired. Less commonly, ED can result from endocrinological factors (abnormal hormonal milieu) and penile or cavernosal factors (e.g. fibrosis and curvatures). Psychological processes such as depression, anxiety, and relationship problems can impair erectile functioning by reducing erotic focus or otherwise reducing awareness of sensory experience. This may lead to inability in initiating or maintaining erection.

In most patients with ED, both organic and psychogenic components exist. Every man who has

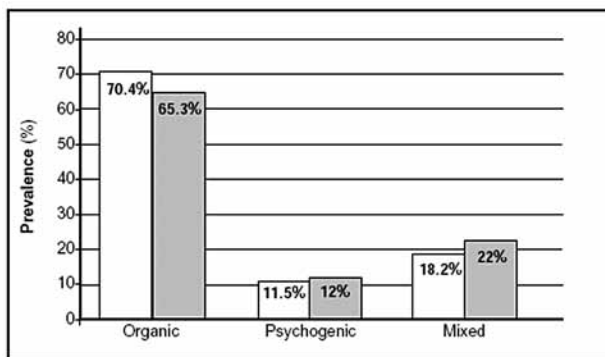


FIG. 3. Underlying etiology of erectile dysfunction (pooled data)

some problem with erectile function develops performance anxiety, and determining whether psychologic factors are the main problem or merely a minor accompaniment may be difficult. Organic erectile dysfunction is due to vasculogenic, neurogenic, hormonal, medical, and pharmacologic or cavernosal smooth muscle abnormalities or lesions; whereas, psychogenic erectile dysfunction is due to central inhibition of the erectile mechanism without a physical injury. The most common cause of the organic component of erectile dysfunction is vascular (arterial or venous) abnormalities,<sup>(16)</sup> often associated with atherosclerosis and diabetes mellitus.<sup>(17-19)</sup> Most of these causes affect the intrapenile vasculogenic mechanisms, either arterial or venous. Another common finding is a decrease in local NO, which is thought to be the main neurotransmitter in initiating the erectile process. Fibrosis may also be present within the corpora cavernosa, which can limit their expandability, prevent the venules from compressing against the tunica albuginea, and thereby allow venous leakage from the penis.

### Vascular Causes

Vascular disease, in particular, is thought to be the most common cause of organic ED.<sup>(20)</sup> There are several pathophysiological mechanisms of vasculogenic ED, including impaired arterial inflow, impaired smooth muscle cavernosal relaxation, chronic ischemia induced increased cavernosal smooth muscle contraction, cavernosal fibrosis, veno-occlusive dysfunction, and chronic or episodic hypoxemia. If the corpora cavernosa cannot expand and fill with blood, decreased erectile firmness occurs. Atherosclerotic disease is the cause of approximately 40% of erectile dysfunction in men older than 50 years.<sup>(21)</sup> Thickening of the arterial walls results in a reduced blood flow throughout the body and can lead to impotence.

Arteriosclerosis is associated with aging and accounts for 50% to 60% of impotency cases in men above 60. Risk factors for arteriosclerosis include hypertension, diabetes mellitus, smoking, and hyperlipidemia. Smoking is the most significant risk factor for impotence related to arteriosclerosis.<sup>(22)</sup>

Although atherosclerotic plaques or damages by trauma or irradiation may decrease blood flow to the penis, vascular causes of ED are more often due to a failure of neural, muscular, or chemical factors. Venous leakage occurs when incomplete filling of the corpora, or Intracavernosal fibrosis, causes failure of the veins to be pressed shut against the tunica albuginea. Therapeutic approaches to treating vasculogenic ED need to address these mechanisms. The following general pathophysiological mechanisms have been identified:

**Veno-occlusive dysfunction.** In the full erectile state increased blood volume and compression of the relaxed trabecular smooth muscle against the relatively rigid tunica albuginea lead to a reduction in venous outflow (referred to as the veno-occlusive mechanism). A venous leak can result from injury, disease, or damage to the veins in the penis.<sup>(22)</sup>

**Hypoxemia.** Hypoxia has profound effects on blood vessel tone (vasoconstriction) and induces production of various factors, such as platelet-derived growth factor, endothelin-1 and vascular endothelial growth factor (VEGF).<sup>(23)</sup> It is now well established that vascular diseases, including hypercholesterolemia,<sup>(24)</sup> atherosclerotic vascular occlusive disease,<sup>(25)</sup> blunt trauma,<sup>(26)</sup> radiation,<sup>(27)</sup> and diabetes mellitus,<sup>(28)</sup> can interfere with the intricate vascular mechanisms underlying normal erection. Hypoxemia, sleep apnea, and respiratory failure are also increasingly recognized as causes of erectile dysfunction.<sup>(29)</sup>

Infrequent erections deprive the penis of oxygen-rich blood. Without daily erections, collagen production increases and eventually may form a tough tissue that interferes with blood flow. The spontaneous erections in men while sleeping or awake may be a natural protection against this process.

### Neurological Causes

Erectile function can be impaired as a result of a cerebrovascular accident (CVA or stroke), demyelinating diseases, or even seizure disorders. Brain and spinal cord injuries or paraplegia can

cause ED when the transfer of nerve impulses from the brain to the penis is blocked. Multiple sclerosis, Parkinson's disease, epilepsy, stroke, Guillain-Barré syndrome, trauma and Alzheimer's disease are other nerve disorders that sometimes also result in ED.<sup>(30,31)</sup>

Tumor and trauma to the spinal cord can also be causative factors of erectile dysfunction. Trauma to the spinal cord or pelvic region can damage the veins and nerves needed for erection. Autonomic and peripheral sensory nerves may be damaged by trauma or transurethral resection of the prostate. In a study on 1267 patients with ED by Hatzichristou et al,<sup>(32)</sup> a neurological cause of impotence was recorded in 145 men (11.4%), of whom 54 (4.2%) had undergone major pelvic surgery, including radical prostatectomy in 27, radical cystectomy in 20 and rectal surgery in 7. A total of 34 patients (2.7%) had multiple sclerosis, 33 (2.6%) had paraplegia due to spinal cord injury, 12 (0.9%) had disc hernias, 5 (0.4%) had Parkinson disease, and 7 (0.6%) had other causes of neuropathy. In 2 of the 12 patients with disc hernias who underwent surgery, erectile function was restored postoperatively.

### **Hormonal Causes**

Hormonal perturbations may contribute to sexual dysfunction, especially erectile dysfunction. Adult males with severe androgen deficiency (hypogonadism) often experience loss of sexual interest, impaired seminal emission, and decreased frequency and magnitude of nocturnal erections. A progressive decline in testosterone occurs after the seventh decade, and testicular or hypothalamic-pituitary dysfunction is the etiology. Hormone imbalances can result from kidney or liver disease.<sup>(22)</sup>

Hypothalamus has an essential role in integration and control of male reproductive and sexual functions.<sup>(33)</sup> The gonadotropin-releasing hormone (Gn-RH) is synthesized and secreted in the median preoptic area (MPOA), and the hypothalamus controls pulsatile gonadotropin secretion and serum testosterone levels necessary to maintain spermatogenesis, libido and, at least in the rat, function of the corpus cavernosal smooth muscle and perineal muscles involved in penile erection.<sup>(34)</sup> Most problems revolve around dysfunction of the hypothalamic-pituitary-gonadal axis and are associated with either excess prolactin or decreased testosterone levels. Other endocrine disorders that may be suggested as the

most likely associated with impairment of libido or erectile function include hypothyroidism, hyperthyroidism, adrenal insufficiency, or excessive levels of adrenal corticosteroids. In such cases, patients may experience a generalized fatigue or weakness from the effects of the illness. The attribution of a causal role of endocrine abnormalities to ED has ranged from 2% to 23%,<sup>(35)</sup> but current understanding of the erectile mechanisms seldom permits assignment of a single causative factor. However, it is commonly agreed that androgens profoundly affect male sexual function overall and erectile physiology specifically.

Hyperprolactinemia, which can be due to medications, hypothyroidism with increased thyrotropin, chest wall injuries, or compression of the pituitary stalk, can result in sexual problems. Rarely, a patient may demonstrate an excess of a variant large prolactin molecule, macroprolactin, which is biologically inert and therefore incapable of causing sexual dysfunction. In a study of 4,803 asymptomatic men by Miyake et al 14 patients (0.29%) had a serum prolactin of greater than 50 ng/ml.<sup>(36)</sup> The incidence of prolactinoma in men was estimated to be 1:1,600 in that study. About 80% of men with a prolactin level greater than 50 ng/ml complain of diminished libido and erectile dysfunction because excess prolactin can suppress secretion of gonadotropin-releasing hormone.<sup>(37)</sup>

As men age, they undergo a number of hormonal changes, including a marked decrease in serum levels of testosterone and free testosterone.<sup>(38)</sup> Aging was negatively correlated with bioavailable testosterone and positively correlated with luteinizing hormone levels. Bioavailable testosterone and its ratio to luteinizing hormone showed a close association with sexual behavior, whereas total testosterone, estradiol and prolactin did not. Although testosterone and free testosterone, like sexual function, decrease with age, the contribution of these hormonal changes to the development of erectile dysfunction is thought to be only minor.<sup>(39)</sup>

Any major medical illness or surgical procedure can suppress the central axis and cause secondary hypogonadism. Primary hypogonadism due to autoimmune destruction of the testicles occurs in some men as they age. A related cause is unilateral mumps orchitis occurring during the early adult years, with later failure of the "good testis." Congenital causes include Klinefelter's syndrome,

Kallmann's syndrome, and myotonic dystrophy. The incidence of hypogonadism in patients with acquired immunodeficiency syndrome (AIDS) is quite high.<sup>(40)</sup> Hypogonadism is defined as a free testosterone level that is below the lower limit of normal for young adult control subjects. Previously, age-related decreases in free testosterone were accepted as "normal", but this concept has been challenged. Similarly, several clinical conditions that were once accepted as normal age-related disorders are now thought to lead to medical problems, for example, hypertension, osteoporosis, and menopause.<sup>(41)</sup>

### **Medical Causes**

Any medical condition that can cause general debility has the potential to decrease sexual desire and performance. Pain, shortness of breath, angina, muscle weakness, or a cerebrovascular accident may be responsible for the dysfunction. The most common medical conditions associated with sexual difficulties are diabetes mellitus and hypertension, possibly because of the microvascular and neurovascular changes that are inherent in these conditions.

Cigarette smoking can cause vascular insufficiency as well as a decrease in intrapenile NO levels. Smoking contributes to the development of impotence, mainly because it compounds the effects of other disorders of the blood vessels, including high blood pressure and atherosclerosis. For example, a study in 2001 concluded that among men with high blood pressure, smoking causes a 26-fold increase in erectile dysfunction.<sup>(42)</sup>

ED in cases of diabetes may be associated with peripheral nerve damage but may involve diminished endothelial production of NO as well.<sup>(43)</sup> Chronic hyperglycemia associated with diabetes mellitus damages the nerves and small blood vessels throughout the body.<sup>(30)</sup> Some antihypertensive medications, heart medications, tranquilizers, antidepressants, and sedatives contribute to or cause ED.

Given the age of the patient population, patients in ED trials also typically have a significant incidence of lower urinary tract symptoms, the presence of which is increasingly being recognized as an independent risk factor for ED.<sup>(44)</sup> The prevalence of benign prostatic hyperplasia (BPH) increases with age, and the presence of BPH increases the risk of erectile dysfunction.<sup>(45)</sup> Namasivayam et al noted that more than half of

a cohort of 140 men with BPH also had some degree of erectile dysfunction.<sup>(46)</sup> However, it is not clear whether the presence of BPH increases erectile dysfunction risk independent of age, or whether the increased risk is due to the fact that the prevalence of both conditions is increased in the elderly. Current evidence appears to support the latter of these two possibilities.<sup>(47)</sup>

In Peyronie's disease, collagen tissue is converted to fibrous tissue for unknown reasons; hence, a palpable fibrous plaque is created in the tunica albuginea. The usual manifestation is a bending of the penis to one side during erection, which can occasionally be painful.<sup>(21)</sup>

Nutritional states associated with ED are malnutrition and zinc deficiency. Blood diseases associated with ED are sickle cell anemia and leukemias.

### **Surgical Causes**

Surgery or irradiation of the prostate, bladder, colon, or rectum may damage the nerves and blood vessels involved in erection. Procedures on the brain and spinal cord, retroperitoneal or pelvic lymph node dissection, aortoiliac or aortofemoral bypass, abdominal perineal resection, radical prostatectomy, transurethral resection of the prostate, cryosurgery of the prostate and cystectomy can also result ED.

### **Pharmacological causes**

Both prescription and over-the-counter medications have been shown to be the cause of erectile problems in as many as 25% of cases.<sup>(48)</sup> Common medications associated with ED are antidepressants, antipsychotics, antidepressants, tranquilizers, antihypertensives, antiulcer drugs such as cimetidine, hormonal medication such as, finasteride (Proscar), or dutasteride (Avodart), drugs that lower cholesterol, and mind-altering agents such as marijuana, heroin, and cocaine (table 1). The incidence of erectile dysfunction in patients receiving various types of antihypertensive drugs was examined in the Treatment of Mild Hypertension Study.<sup>(49)</sup> At 24 months the incidence of an inability to achieve an erection ranged from 2.8% in the doxazosin ( $\alpha$ -blocker) group to 15.7% in the chlorthalidone (diuretic) group compared with 4.9% in the placebo group. The incidence of an inability to maintain an erection ranged from 4.2% in the doxazosin group to 17.1% in the chlorthalidone group versus 6.8% in the placebo group.

**TABLE 1.** *Sexual side effects of common prescription medications*

Type of drug	generic name	Sexual side effects
<i>Antihypertensive medications</i>		
Diuretics	Spirolactone	Decreased libido, breast swelling, impotence
	Thiazides	Impotence
	Furosemide	None
Centrally acting agents	Methyldopa	Decreased libido, impotence
	Clonidine	Impotence
	Reserpine	Decreased libido, impotence, depression
$\alpha$ -Adrenergic blockers		
	Prazosin	“Dry” (retrograde) ejaculation
	Terazosin	“Dry” (retrograde) ejaculation
$\beta$ -Adrenergic blockers		
	Propranolol	Impotence, decreased libido
	Metoprolol	Impotence, decreased libido
Combined $\alpha$ - and $\beta$ -adrenergic blockers		
	Labetalol	Inhibited ejaculation
Nonadrenergic vasodilator		
	Hydralazine	None
Sympathetic nerve blocker		
	Guanethidine	Impotence, “dry” (retrograde) ejaculation
Angiotensin-converting enzyme inhibitors		
	Captopril	None
	Enalapril	None
	Lisinopril	Impotence in a small percentage (1%) of cases
<i>Psychiatric medications</i>		
Antidepressants		
Tricyclics		
	Amitriptyline	Inhibited ejaculation, impotence
	Amoxapine	Decreased libido, impotence
	Desipramine	Inhibited ejaculation
	Doxepin	Inhibited ejaculation, impotence
	Imipramine	Inhibited ejaculation, impotence
	Maprotiline	Inhibited ejaculation
	Nortriptyline	Inhibited ejaculation
	Protriptyline	Inhibited ejaculation, impotence
Atypical agent	Trazodone	Priapism
Monoamine oxidase inhibitors		
	Isocarboxazid	Inhibited ejaculation
	Phenelzine	Inhibited ejaculation, decreased libido
	Tranylcypromine	Inhibited ejaculation
Antipsychotic medications		
Phenothiazine group		
	Thioridazine	Inhibited ejaculation, priapism, decreased libido
	Chlorpromazine	Inhibited ejaculation
	Mesoridazine	Inhibited ejaculation, decreased libido
	Fluphenazine	Inhibited ejaculation, decreased libido
Serotonin reuptake inhibitors		
	Fluoxetine	Anorgasmy (8%)
	Perphenazine	Inhibited ejaculation
	Trifluoperazine	Inhibited ejaculation
Thioxanthene group		
	Chlorprothixene	Inhibited ejaculation
	Thiothixene	Inhibited ejaculation, impotence
Butyrophenone		
	Haloperidol	Inhibited ejaculation
Antimania medication		
	Lithium carbonate	Possible impotence
<i>Antiulcer medications</i>		
	Cimetidine	Decreased libido, impotence, gynecomastia
	Ranitidine	None
	Famotidine	None
<i>Antifungal agent</i>		
	Ketoconazol	Impotence

Although single medications can induce erectile dysfunction, the adverse effects of medications are often additive. This situation is particularly frequent in older men who are taking multiple medications, and partial or complete erectile dysfunction often results. A psychologic component can make partial erectile dysfunction progress to complete erectile dysfunction.<sup>(50)</sup>

Most psychotropic drugs can affect libido or erectile function, either through a direct action or by increasing prolactin or decreasing testosterone levels. Although antidepressants may cause erectile dysfunction in susceptible patients, they may also be beneficial in improving libido in depressed men. Antihypertensive medications may cause erectile dysfunction either by drug-specific effects or by decreasing the systolic blood pressure and thereby decreasing the intracavernosal penile pressure. This effect is especially prevalent in patients with diabetes or hypertension who have underlying microvascular disease. Results of the Massachusetts Male Aging Study also indicated a higher probability of erectile dysfunction in association with certain treated medical conditions.<sup>(5)</sup>

Long-term use of alcohol and illicit drugs may affect the vascular and nervous systems and are associated with ED.<sup>(50)</sup>

Ketoconazole, aminoglutethimide, and similar drugs actually decrease the production of testosterone. Most of the earlier antihypertensive agents—such as reserpine, guanethidine, and hydralazine—caused sexual dysfunction. Some evidence suggests that exposure to estrogen-like chemicals, such as those found in DDT and other pesticides, may contribute to erectile dysfunction.

Some adrenergic blocking agents may cause sexual problems, but dysfunction with angiotensin-converting enzyme inhibitors or calcium channel blockers is less common. Some drugs (spironolactone, cimetidine, flutamide, or cyproterone acetate) may block the peripheral androgen receptors. Cimetidine may assume a greater importance because it can now be purchased without a prescription. Drugs such as methyl-dopa, spironolactone, digoxin, and metoclopramide may raise prolactin levels. Thiazide diuretics, finasteride, anticholinergic agents, and pain medications can cause erectile dysfunction.<sup>(51)</sup>

### ***Psychological causes***

Psychological impotence tends to develop rapidly

and be related to a recent situation or event. The patient may be able to have an erection in some circumstances but not in others. Being able to experience or maintain an erection upon waking up in the morning suggests that the problem is psychological rather than physical. It should be strongly noted that in virtually every case of impotence there are emotional issues that can seriously affect the man's self-esteem and relationship. Depression, guilt, stress, and anxiety all contribute to a loss of libido and to ED.<sup>(30, 31)</sup>

### ***Emotional causes***

Anxiety. It has both emotional and physical consequences that can affect erectile function. Generally, what we view as the psychogenic causes of ED have performance anxiety as their final common pathway. This anxiety may be present in just about any man who has once or twice been unable to sustain an erection. He starts thinking about performance whenever he gets into any kind of difficulty during sex, whether it's because he has an arterial diminishment in the flow to his cavernous artery or because he may feel guilty about something.

Impotence may be caused by *depression*. Depression is strongly associated with erectile dysfunction. In depressed men, sexual problems (diminished libido, erectile dysfunction, and premature ejaculation) are common, but the antidepressant medications routinely prescribed to counter the manifestations of depression are themselves associated with a range of adverse effects on sexual function.<sup>(5)</sup> Other psychological causes of ED are bereavement, tiredness, stress hang-ups for instance and guilt about sex.

### ***Problems in relationships***

Problems in a relationship may affect potency. Partners of men with erectile dysfunction may feel rejected and resentful, particularly if the affected man does not confide his own anxieties or depression. Both partners commonly experience guilt for what they each perceive as a personal failure. Tension and anger frequently arise between people who are unable to discuss sexual or emotional issues with each other. It can be very difficult for the man to perform sexually when both partners harbor negative feelings.

### ***Socioeconomic Issues***

Losing a job or having lower income or education increases the risk for impotence.



## Evaluation and Assessment of Erectile Dysfunction

Patients usually do not volunteer their problem with ED. Screening should be employed if the doctor suspects that his patient has ED. Screening is advised for males around 40 years of age, especially if they have risk factors such as: a. Diabetes, b. Hypertension, c. Hyperlipidemia, d. Heavy smoking, e. Cardiac disease, and f. Depression.

### Standard Questionnaires

An acceptable screening tool using a 5-question questionnaire is as follows: <sup>(52, 53)</sup>

1. *How often were you able to get an erection during sexual activity?*

Almost never or never: 1, A few times (much less than half the time): 2, Sometimes (about half the time): 3, Most times (much more than half the time): 4, Almost always or always: 5,

2. *When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?*

Almost never or never: 1, A few times: (much less than half the time): 2, Sometimes (about half the time): 3, Most times (much more than half the time): 4, Almost always or always: 5,

3. *When you attempted intercourse, how often were you able to penetrate (enter) your partner?*

Almost never or never: 1, A few times (much less than half the time): 2, Sometimes (about half the time): 3, Most times (much more than half the time): 4, Almost always or always: 5,

4. *During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?*

Almost never or never: 1, A few times (much less than half the time): 2, Sometimes (about half the time): 3, Most times (much more than half the time): 4, Almost always or always: 5,

5. *During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?*

Extremely difficult: 1, Very difficult: 2, Difficult: 3, Slightly difficult: 4, Not difficult: 5,

All questions are preceded by the phrase 'Over the past 4 weeks.'

**Instructions for Scoring:** Add the scores for each item 1-5 (total possible score =25).

ED Severity Classification: Total score 5-10 (severe); 11-15 (moderate); 16-20 (mild); 21-25 (normal).

**Note:** Individuals who have been sexually active

and have attempted sexual intercourse in the past three months should only complete the above questions. For sexually inactive individuals, the questionnaire may be answered for the last period of time (three months or longer), during which the individual was sexually active.

Should the patient be found to have ED from the above questionnaire (i.e. total score 20 or less), a subjective bothersome questionnaire may be useful:<sup>(54)</sup>

*If you were to spend the rest of your life with your erectile condition, the way it is now, how would you feel about that?*

Very dissatisfied: 1, Rather dissatisfied: 2, Mixed, about equally satisfied: 3, Rather satisfied: 4, Very satisfied: 5.

For patients suspected to be suffering from depression, a two-question screening tool may be useful:<sup>(55)</sup>

- *During the past month, have you often been bothered by feeling down, depressed or hopeless?*

- *During the past month, have you often been bothered by little interest or pleasure doing things?*

Although normal aging can result in a decline in sexual performance, persistent erectile dysfunction should be investigated. The appropriate evaluation of all men with erectile dysfunction should include a comprehensive sexual, medical and psychosocial history, physical examination and focused laboratory studies.

### Evaluation of the couple

Ideally, the couple should undergo assessment together at the first visit or soon thereafter. A discussion about the partner is important. Is the patient married, single, divorced, or widowed? Because newer relationships may have adjustment problems, the duration of the relationship is important, as is the age disparity between the partners. The health of the partner is very important; 15% of men report a decreased sexual frequency or ability because of health problems that their partners are experiencing, and the men are infrequently aware of this connection.<sup>(56)</sup> In addition, potential psychosocial factors should be addressed to elucidate patient view of the erectile problem, which remains a relevant part in every evaluation.<sup>(57)</sup> The interviewer should determine whether any relationship problems exist between the partners or whether external stresses may be a predominant factor. Using a goal-oriented evaluation can increase the value of self-reporting by cross-checking the reliability of patient reports

with specific questions. Clinically we could demonstrate that deterioration in erectile function is relevant and that patients report reliably.

### ***Comprehensive Sexual, Medical and Psychosocial History***

A sexual history is needed to accurately define the patient's specific complaint and to distinguish between true erectile dysfunction, changes in sexual desire, and orgasmic or ejaculatory disturbances. The patient should be asked specifically about perceptions of his erectile dysfunction, including the nature of onset, frequency, quality, and duration of erections; the presence of nocturnal or early morning erections; and his ability to achieve sexual satisfaction. Psychosocial factors related to erectile dysfunction should be probed, including specific situational circumstances, performance anxiety, the nature of sexual relationships, details of current sexual techniques, expectations, motivation for treatment, and the presence of specific discord in the patient's relationship with his sexual partner. The sexual partner's own expectations and perceptions should also be sought since they may have an important bearing on diagnosis and treatment recommendations. Other essential components of history taking should cover the following:

- *Altered sexual desire*
- *Ejaculation*
- *Orgasm*
- *Sexual related genital pain*
- *Lifestyle factors*
- *Smoking*
- *Chronic medical illness:* hypertension, diabetes mellitus, atherosclerosis, and cardio-vascular risk factors including hyperlipidemia, renal and hepatic dysfunction
- *Pelvic / perineal / penile trauma:* bicycling injury, motor vehicle accident, etc.
- *Medications / recreational drug use:* antihypertensives, antidepressants, alcohol, cocaine
- *Past surgery:* radical prostatectomy, laminectomy, vascular bypass surgery
- *Neurological illnesses:* spinal cord injury, multiple sclerosis, lumbosacral disc injury
- *Endocrinological illnesses:* hypogonadism, hyperprolactinemia, thyroid disease
- *Sexually transmitted diseases:* gonorrhea
- *Psychiatric illnesses:* depression, anxiety<sup>(4)</sup>

Psychosocial history should cover symptoms of depression, altered self esteem, past and present partner relationships, past and present sexual

practices, history of sexual trauma/abuse, job and social position satisfaction, economic position and educational attainment.

#### **Sample of Psychosocial Assessment Questions:**

- *"Do you suffer from depression or other mood problems?"*
- *"How are your relationships with family members and other important people in your life?"*
- *"Do you have any difficulties in your work situation?" (if applicable)*
- *"How is your current relationship with your partner? How was it in the past?"*
- *"Were you ever the victim of sexual abuse (forced to have sex)? If yes, what effect did this have on you then or now?"*

#### **Sample of Sexual History Questions:**

- *"Many men of your age start to experience sexual difficulties, if you have such a problem, I would be happy to discuss this further":*
- *"Could you describe your sexual problem?"*
- *"When did your erection problems begin?" "Please describe the circumstances."*
- *"How was your sexual functioning prior to this time?"*
- *"How are your erections that you achieve with masturbation or those that occur with sleep or upon awakening early in the morning?" (The discussion of masturbation is a sensitive issue that is often influenced by cultural and religious perspectives).*
- *"How strong is your desire for sex, now and in the past?"*
- *"Do you have difficulties in ejaculating, either too fast or slow, either now or in the past?"*
- *"Is your partner able to become aroused and reach climax when you have sex together?"*
- *"What has been your partner's reaction to your current sexual difficulties?"*
- *"What has been the effect of your sexual difficulties on your partner relationship?"*
- *"What has been the effect of your sexual difficulties on your overall lifestyle?"<sup>(4)</sup>*

If nocturnal or morning erections are present and strong, it will direct the evaluation toward psychologic causes, or it may simply mean that a certain medication might have decreased its concentration (and its adverse effect) during the night.<sup>(58)</sup>

### ***Physical Examination***

Medical examination of erectile dysfunction should first include a detailed medical and sexual history, as well as a complete physical exami-

nation with attention paid to the cardiovascular, neurological and genitourinary systems. Physical examination is directed toward possible signs of hypogonadism, hyperthyroidism, examination of the external genitalia to exclude penile and testicular pathology such as testicular atrophy, inflammation and cancer, and digital rectal examination of the prostate. Blood pressure measurements with the patient supine and standing, and palpation of peripheral arteries of the lower extremities are part of the standard physical examination. In addition, a baseline neurological examination is done, consisting of motor activity, perineal and external genitalia sensation (light touch and pinprick) and reflexes (Cremasteric, bulbocavernosus and plantar). The bulbocavernosus reflex is tested with the physician's finger in the rectum directed laterally to where the muscle is inserted. A moderate squeeze on the glans penis will cause the bulbocavernosus muscle to contract if the reflex arc is intact. A screening neurologic examination is necessary.

### Diagnostic Tests

Four diagnostic testing are used for evaluation of ED:

- 1- Blood tests
- 2- Vascular assessment
- 3- Sensory studies
- 4- Nocturnal penile tumescence and rigidity testing (Rigiscan test)

#### Blood Tests

There is no consensus on the role of laboratory screening in men presenting with erectile dysfunction. Chemistry testing should evaluate for anemia, increased plasma glucose levels, or impaired renal function. Thyroid testing should be done if clinically indicated. Other hormone screening should include serum testosterone and prolactin levels. The "normal" range for testosterone is controversial. The Massachusetts Male Aging Study confirmed that free testosterone decreases 1.2% per year and bioavailable testosterone decreases 1.0% per year, while the sex hormone-binding globulin increases 1.2% per year, between the ages of 40 and 70 years. For this reason, free or bioavailable testosterone assays are preferred over measurement of the total testosterone level. Because of the diurnal variation of testosterone secretion, obtaining several morning samples or pooling of multiple samples is advisable. A minimum of two subnormal values should

be obtained before treatment. If the testosterone level is low, or even borderline, a serum LH level should be obtained to distinguish primary from secondary hypogonadism. Compensated primary hypogonadism is present when the testosterone level is normal but the LH level is increased. Further testicular failure can be anticipated. Whether to establish a follow-up schedule for the patient or to initiate treatment is an individual clinical decision.<sup>(59-61)</sup> Routine screening of TSH, total serum cholesterol and hemoglobin A1c is warranted in men presenting with erectile dysfunction.<sup>(62)</sup>

#### Vascular Assessment

Several diagnostic modalities have been used to evaluate vascular impotence to permit appropriate treatment and surgical intervention.

*Penile color duplex ultrasonography:* Vascular flow to the corpora cavernosa may be quantified with the use of a penile Doppler examination. Lue et al pioneered sonographic evaluation of erectile dysfunction.<sup>(63)</sup> With the patient supine the duplex probe is placed on the ventral side at the base of the penis, and a baseline image of the penis is obtained in the longitudinal and transverse planes, including measurements of the blood flow in the cavernous arteries. A dose of 20-microgram prostaglandin E1 is injected intracavernously using a 27½-gauge needle. The internal diameter of the cavernous arteries and flow parameters are measured 5, 10, 15 and 20 minutes thereafter, and 15 to 20 minutes after stimulation response are graded clinically by the aforementioned criteria. Reference values for normal peak flow and end diastolic flow velocities were more than 30<sup>(64)</sup> and less than 5 cm per second,<sup>(65)</sup> respectively. Three measurements of all parameters are made, with mean values use for calculations. Shabsigh et al concluded that penile duplex ultrasonography with papaverine injection appeared to be a useful objective method to evaluate vasculogenic impotence, which correlated well with nocturnal penile tumescence monitoring.<sup>(66)</sup> The resistance index are calculated as (peak flow velocity- diastolic flow velocity)/peak flow velocity in the phases of evolving erection at 10 minutes and maximal erectile response at 20 minutes after injection.<sup>(67)</sup> Clinically suspicion of venous leakage arises when the patient has an excellent arterial response to an injected vasodilator and greater than 30 cm. per second peak systolic velocity yet a high diastolic flow after self-

stimulation. High diastolic flow indicates low intracavernous pressure and suggests venous leakage at this stage, which is accompanied by inadequate or transient rigidity after self-stimulation. Quam et al found that venous leakage on cavernosometry was predicted when end diastolic flow was greater than 5 cm. per second.<sup>(68)</sup>

If an erection capable of penetration is obtained, a physiologically significant vascular deficiency is excluded. It has also been suggested that endogenous epinephrine, generated by a patient's embarrassment, fear, or anxiety, can affect the validity of the test results.

**Dynamic infusion pharmaco-cavernosometry:** Dynamic infusion pharmaco-cavernosometry has been established as a comprehensive approach in the diagnosis of cavernovenous leakage.<sup>(69)</sup> Dynamic infusion pharmaco-cavernosometry is performed with the patient supine on an angiography table. A 19-gauge needle is inserted dorso-laterally in the right corpus cavernosum about halfway down the shaft and 20-micrograms prostaglandin E1 is injected. Ten minutes after intracavernous injection, body temperature physiological saline solution is injected through the needle with a high flow mechanical pump.<sup>(69)</sup> The solution is injected with increasing flow rates starting at 40 ml. per minute and increases incrementally by 40 ml. per minute every minute until full rigid erection is achieved. Rigid erection, evaluate subjectively by digital palpation, is found to be sufficient for easy vaginal penetration. The flow rates needed to induce and maintain erection are then recorded. A flow rate of less than 15 ml per minute to maintain erection was considered normal. Montague et al concluded that infusion cavernosometry in the evaluation of impotence may be uncertain and limited, and should be considered together with nocturnal penile tumescence testing for an accurate diagnostic assessment.<sup>(70)</sup> Patients are considered to have venous leakage at maintenance flow rate of greater than 15 ml. per minute. It was reported that a minimum maintenance rate of 25 ml per minute is required for operative candidates who complained of venogenic impotence.<sup>(71)</sup>

**Pharmaco-cavernosography.** Cavernosography is performed with injection of a low osmolality contrast medium diluted 1:4 with 2,500 microns/l. heparinized saline solution to avoid any risk of thrombosis of the cavernous bodies. Serial film is then taken with a 100-mm camera, and the corpora cavernosa and penile venous network are stud-

ied in oblique and anteroposterior projection. At the end of the procedure disconnecting the needle to clear the contrast material emptied the corpora. Any venous leak can be demonstrated at obtained films.<sup>(72)</sup>

**Penile Brachial Index.** The penile brachial index (PBI) is a measurement that compares blood pressure in the penis with the blood pressure taken in the arm. Problems with the arterial flow to the penis can be detected using this method.

Interestingly, investigators have suggested that a low PBI, which should indicate decreased penile blood flow, correlates better with coronary artery disease than it does with erectile dysfunction. Routine measurement is not recommended. The one instance in which the PBI may be of value is in the pelvic steal syndrome. A minor blockage of a small artery may not cause symptoms in the relatively inactive state of foreplay; thus, an erection may be normal. After penetration and pelvic thrusting, however, shunting of the blood to the pelvic musculature may cause detumescence prematurely. This condition is diagnosed by obtaining a PBI before and after exercise on a treadmill or with multiple deep knee bends; a PBI decrease of 0.15 or more is presumptive evidence of the pelvic steal syndrome.<sup>(73)</sup>

### **Sensory Studies**

The sensitivity of the skin of the penis to detect vibrations (biothesiometry) can be used as a simple office nerve function-screening test. This involves the use of a small vibrating test probe placed on the right and left side of the penile shaft as well as on the head of the penis. The strength of the vibrations is increased until patient can feel the probe vibrating clearly. Although this test does not directly measure the erectile nerves, it serves as a reasonable screening for possible sensory loss and is simple to perform. More formal nerve conduction studies are only performed in selected cases

### **Monitoring Night-time Erections**

Tests that monitor nighttime erections may be used to determine if the causes of erectile dysfunction are more likely to be psychological. Neither of the following methods is helpful in determining a physical cause for erectile dysfunction.

**Snap-Gauge Test.** The snap-gauge test monitors the man's ability to achieve an erection during sleep. It is a very simple test. When the man goes

to bed, he places bands around the shaft of his penis. If one or more breaks during the course of the night, it provides evidence of an erection. In this case, a psychological basis for the erectile dysfunction is likely.

*Nocturnal Penile Tumescence Monitoring.* A non-invasive tool in the diagnosis of penile erectile capacity is the recording of nocturnal penile tumescence with the RigiScan device. It provides simultaneous continuous measurement of tumescence and rigidity. The measurement of nocturnal penile tumescence and rigidity is useful, especially to distinguish between psychologic and organic erectile dysfunction.

A portable monitor for home use, called the RigiScan monitor, measures both penile rigidity and tumescence. It can be set up easily in the office of any interested physician. The test can help distinguish between organic and psychologic erectile dysfunction, either in the initial assessment of the patient or after organic medical factors have been corrected but the difficulty persists. Severe psychoses may be associated with abnormal nocturnal penile activity, as may sleep apnea or nocturnal myoclonus. This type of testing is expensive, and some results are questionable because of the unfamiliar surroundings and the startle response. It is still regarded by some, however, to be the "gold standard" for distinguishing psychogenic from organic erectile dysfunction.<sup>(74,75)</sup> Interpretation of nocturnal penile tumescence was based on multiple parameters, including duration of registration greater than 5 hours per night, frequency of tumescence 1 to 2 times per night, duration of erection 10 minutes or longer, increase in penile tip and base 2.5 cm or greater and penile rigidity 60 percent or greater at tip and base. According to these criteria nocturnal penile tumescence monitoring was evaluated as normal or abnormal.<sup>(76)</sup> Others have demonstrated the role of nocturnal penile tumescence monitoring in the evaluation of vasculogenic impotence. Nocturnal penile tumescence testing was compared to penile duplex ultrasonography to measure the integrity of the cavernous arteries as well as to pharmaco-cavernosometry to measure directly venous function.<sup>(70)</sup> Normal nocturnal penile tumescence testing correlates well with duplex ultrasound and cavernosometry, and reflects probable normal function of penile arterial and venous systems. However, when nocturnal penile tumescence is abnormal, we cannot predict the results of vascular system function-

ing. In this case the nocturnal penile tumescence test should be regarded as only 1 important element in the comprehensive assessment of sexual dysfunction.<sup>(76)</sup>

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