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Erectile Dysfunction
The Scope of the Problem

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INTRODUCTION

Throughout history, men have been dealing with the problems termed sexual dysfunction, impotence, and erectile dysfunction (ED). ED is a difficult and challenging condition affecting millions of men in the United States and throughout the world. In the 1990s and in the 21st century, ED has been defined as the consistent inability to obtain and maintain a penile erection sufficient to permit satisfactory sexual intercourse *(1)*. In the latter half of the 20th century, the issue of ED changed from a subject little discussed and poorly understood to an active area of medical, psychological, and pharmacological research and development. Indeed, the pejorative term "impotence" has been replaced with ED and erectile difficulties. During these

years, the physiology and molecular biology of erection and ED has been carefully studied, and translational research has led to not only an elucidation of the physiology of erection but also to significant progress in the diagnosis and treatment of men with ED. Basic scientific investigation has clarified the anatomy, physiology, and pharmacology of the corpus cavernosum as well as the neurophysiology and vascular physiology of erectile function. Similarly, the mechanism of erection and its dependence upon the neurogenic, arterial, and venous systems to produce erectile rigidity continues to be studied. Further, the importance of androgen support of erectile function, both in the corpus cavernosum level and in the central nervous system, is being examined both clinically and in the basic science laboratories. Investigations into smooth muscle physiology, endothelial cell function, and central nervous system control with the identification of neurotransmitters, such as nitric oxide (NO) and vasoactive intestinal polypeptide, in the corpus cavernosum have led to the design, development, and use of specific pharmacological agents to recreate the normal physiology of the corpus cavernosum and restore erectile function in men previously termed "impotent."

PREVALENCE OF ED

In the United States as well as the rest of the world, ED is highly prevalent. The Massachusetts Male Aging Study (MMAS) particularly has documented the high prevalence, which reaches 52% in men over age 40 yr. MMAS was the first large population-based study of ED in the United States *(2)*. The initial data were collected during 1987–1989 and established a cohort of 1709 men, of whom 1156 were re-interviewed during 1995–1997 *(2)*. The baseline study included questions related to erectile function, such as frequency and quality of erections. The follow-up questionnaire included items related to erectile function plus a single question subjective global self-assessment that classified ED as ranging from none to complete.

The MMAS found that the combined prevalence of mild, moderate, and severe ED was 52% among this cohort of men aged 40 to 70 yr.

This prevalence increases with age and exceeds 70% in men over age 65 yr. The MMAS recorded depression, unhappiness with life, and pessimistic attitudes as significant risk factor predictors for ED *(2)*. With increasing age, there was an increase in ED but, surprisingly, also a significant decrease in libido or desire for sexual activity. Nonmarried men appear to be at higher risk. A subsequent follow-up study of these same men 8 yr later showed that the incidence and prevalence of ED

Table 1
Worldwide Prevalence of Erectile Dysfunction

Population	Age (yr)	%
Cologne, Germany	30–80	19.2
Spain	25–70	18.9
Perth, Australia	40–69	33.9
Krimpen, Netherlands	50–78	11.0
London, UK	16–78	19.0

Data from ref. *6*.

increases with age and that not smoking and regular exercise are factors that predict maintenance of erections as men age. With extrapolation of these data, it is estimated that more than 30 million men in the United States suffer from some degree of ED. The results of a large scale epidemiological study of sexual dysfunction in men throughout the United States demonstrated a high prevalence of ED in men of all ages, with as many as 31% of men complaining of some degree of ED.

Laumann et al. studied 1410 men and 1749 women ages 18–59 yr through analysis of the data from the National Health and Social Life Survey *(3)*. Overall, ED occurred in 5% of men, low sexual desire in 5% of men, and 21% of men, most often in the younger age group, suffered from premature ejaculation. The study demonstrated that sexual dysfunction is a significant public health concern and is widespread in Western society, influenced by health-related and psychological factors. Stress-inducing events influence and increase sexual dysfunction *(3)*. There is a strong association between sexual dysfunction and impaired quality of life on quality-of-life questionnaires. The Men's All Race Sexual Health Study investigated the differences among racial groups and the prevalence of ED *(4)*. Early data from this study confirm that white, black, and Hispanic Americans are equally at risk for ED and that risk factors for the three groups are similar.

Worldwide, epidemiological studies have confirmed the high prevalence rates in men of all ages (Table 1). Aytac et al. *(5)* calculated that the worldwide prevalence of ED will probably increase from 152 million men in 1995 to 322 million in 2025. Much of this increase of 170 million will occur in the developing world, that is, Asia, Africa, and South America, and is associated with the aging world population. Other related changes may be contributing to the increase of ED because it is associated with other diseases that are reaching epidemic proportions, such as obesity and diabetes.

Aytac et al. concluded that this likely increase in the prevalence of moderate to severe ED combined with newly available drug treatments will pose a major challenge for healthcare policy makers to develop and implement policies to alleviate ED. This will be a major problem, particularly in countries in which national health systems are already under stress from existing government funding priorities. Despite this high prevalence, fewer than 10% of men have received therapy for ED.

Despite these revolutions in the understanding and treatment of ED, there are many men who have not sought help for ED and many physicians who are uneasy and resistant to investigation and treatment of ED. Part of the problem includes the issues of men's health. It is estimated that in the United States, men have more than 150 million fewer doctor visits then women, even excluding prenatal visits. This partially accounts for not only the reluctance for ED treatment but also the lower life expectancy for men compared with women. Marwick surveyed patient's expectations and experiences in discussion of sexual issues with their physicians and found that 71% of patients stated that they believed that physicians would not recognize ED as a medical problem, whereas 68% of patients feared that discussing sexuality with their physicians would embarrass their physicians *(7)*.

Since the introduction of sildenafil in 1998, there has been a revolution in the treatment of ED throughout the world. The scientific and marketing efforts of physicians and the pharmaceutical industry have increased the presentation rates of ED by 250, 55, 103, 279, and 90% in the United States, Germany, UK, Mexico, and Spain, respectively, compared with the pre-sildenafil launch period *(7)*. Similarly, prescriptions for the treatment of ED before the introduction of sildenafil were slightly greater than 4 million with the majority of men with ED being treated with intracavernous alprostadil. Shortly after the introduction of sildenafil in the United States, the prescriptions for ED increased 438% to more than 19 million between April 1998 and December 1999 *(7)*. This increase was led by physicians and media who educated the public on the importance of ED and the ability to treat ED effectively. Numerous studies have demonstrated the improvement in quality of life for patients with ED treatment. In 1999, Parkerson et al. studied 1073 men in the United States and Europe with ED who were treated with intracavernous alprostadil *(8)*. These patients were followed for 19 month, and there was a demonstrated improvement in mental status in all groups despite a decrease in physical status associated with increasing age. Interestingly, social status also increased in Europe whereas it did not in the United States. In 1999, Litwin et al. reviewed the quality of

life of 438 men undergoing treatment for carcinoma of the prostate with X-ray therapy or radical prostatectomy *(9)*. These patients included not only nerve-sparing but also non-nerve-sparing radical prostatectomy patients. An evaluation was conducted using the UCLA prostate cancer index. Sexual function during follow-up increased in the first year for all groups whereas function decreased slightly for radiation therapy patients in the second year. However, sexual function improved in all patients, but response was related to age, prediagnosis ED, and non-nerve-sparing radical prostatectomy. It has been estimated that 1 in 10 men worldwide have ED and that it is the most common chronic medical disorder in men over the age of 40 yr.

Patients and their partners must be educated in lifestyle issues that preserve erectile function and, indeed, optimize the response to agents for the treatment of ED. Smoking is one of the most important lifestyle issues that can impact on erectile function. In its follow-up publication, the MMAS reported an increase in ED with smoking in addition to other risk factors such as diabetes, heart disease, and hypertension *(2)*. Indeed, the incidence of ED increased among smokers with some stability in onset if men stopped smoking. The Health Professions Follow-Up Study reported by Bacon et al. examined 32,287 men and demonstrated a relative risk of ED of 2.2 (95% CI, 1.9–2.5) in men who smoked. Indeed, the effects of smoking in the laboratory, and in clinical research, have been widely published *(9)*. Smoking appears to enhance prostacyclin production, increase platelet vessel wall interaction, and reduce endothelium-mediated forearm vessel dilation in chronic human smokers *(10,11)*. Smoking has also been demonstrated to decrease endothelial nitric oxide synthase (NOS) activity and impair the release of NO. Finally, there has been a demonstrated increase in superoxide ion-mediated endothelium-derived relaxing factor degradation in smokers *(10)*.

Therefore, it is important to educate patients that ED can be treated in greater than 80% of men and that lifestyle changes may improve erections or at least stabilize ED. Expectations of excellent outcomes and success with low morbidity and risks are the norm *(12)*. Patients should also be educated and instructed that lifestyle counseling may assist their longevity and healthiness and may also improve not only erectile function but response to ED treatment. These counseling points should include smoking cessation, moderate alcohol intake, reduction in fat and cholesterol, exercise, improvement and compliance with cardiovascular and diabetic medications, stress reduction, depression treatment, and an optimism of ED treatment outcomes and resolution with appropriate management.

ETIOLOGY OF ED

ED has both organic and psychogenic etiologies. When Masters and Johnson published their sentinel work on sexual dysfunction, they felt that organic causes accounted for approximately 10% of the incidence of ED in American men, and psychogenic causes accounted for 90% *(12)*. Now we know that about 60% of patients have organic ED, which we define as vasculogenic, neurologic, hormonal, or smooth muscle abnormalities, including stress and depression. Less than 40% of men truly have psychogenic ED. In fact, we may be labeling some causes as psychogenic simply because we cannot yet identify a specific organic cause. We do know that patients with psychogenic causes, specifically stress disorders and depression, have an overactivity of α-agonists in their corpora cavernosal smooth muscle tissue, resulting in a chemical imbalance inhibiting corpus cavernosum smooth muscle relaxation.

RISK FACTORS FOR ED

When completing a history of a patient with ED, one should inquire about the patient's libido. Physicians used to think that if a patient had decreased desire that this automatically resulted from low levels of androgen hormones, such as testosterone. Indeed, this is not the case because libido level is a far better marker for depression and stress than it is for hypogonadism. Less than 50% of patients who truly are hypogonadal, with testosterone levels less than 100 ng/dL, have low libido, whereas greater than 80% who are depressed have low libido *(14)*. Therefore, although the physician should ask about libido, the patient's response cannot eliminate the need for a testosterone determination. It is also important to determine what medications patients are taking. Medications most often associated with ED are antihypertensives, although antidepressants, particularly the selective serotonin reuptake inhibitor (SSRI) medications, are also culprits. Smoking is also one of the most common risk factors for ED *(12)*.

The Treatment of Mild Hypertension Study examined a group of people with mild-to-moderate hypertension that had not been treated previously and compared various families of antihypertensives with placebo *(15)*. Patients were followed for 2 yr, and among the questions examined was that of erectile function. The incidence of ED was lowest with α-blockers represented by doxazosin, which was the only antihypertensive class to have less ED than placebo.

Studies in our laboratory confirmed this finding. When we reviewed the effect of antihypertensive agents on relaxation of the corpus cavernosum smooth muscle in vitro, we found that classes of agents most

likely to preserve or be hospitable to erectile function included the α-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers, in that order. This is important because modification of antihypertensives and careful selection of agents may preserve erectile function in some patients with significant hypertension.

Diabetes is another major cause for ED. Although it is clear that ED increases as patients age, diabetes is associated with ED at a younger age. A patient who has been diabetic, especially those who have been insulin dependent, for more than 10 yr has greater than a 50% chance of having significant ED. Further, ED is more common with diabetic complications, and, indeed, sildenafil is less effective in men with poorly controlled diabetes or those with multiple diabetes-related complications.

Depression also affects erectile function significantly. The MMAS examined classes of depression, with 1 being minimally depressed and 5 maximally depressed. In class 5 depressions, 60% of men age 61–70 yr had ED. In contrast, ED incidence is less than 10% if a patient is not depressed and is in the 40–50-yr age group *(2)*.Thus, depression is an additive risk factor to age for ED.

Atherosclerosis is perhaps one of the most common causes of ED in the aging male. It has been clearly demonstrated that high levels of cholesterol are destructive to the endothelial cells of the corpus cavernosum that produce the NO *(15)*. Reducing cholesterol levels in laboratory animals demonstrates significant improvement in corpus cavernosum smooth muscle relaxation *(16)*. Similarly, statin drugs have been demonstrated to be helpful in-patients with early ED from hypercholesterolemia.

Testosterone levels are also important in libido as well as corpus cavernosum smooth muscle activity. Testosterone levels change substantially with age *(14)*. Beginning at about age 50 yr, testosterone begins to decline with a subsequent increase in sex hormone-binding globulin that results in a marked diminution of free and bioavailable testosterone. Because NOS activity decreases substantially with a decrease in testosterone level, androgen levels are critical for erectile function. Indeed, animal studies suggest that NOS decreased almost 50% in castrated rats. Such a decrease was prevented or reversed by testosterone replacement. Similarly, there are changes in smooth muscle relaxation in the hypogonadal laboratory animal. Clearly, NO production requires adequate levels of testosterone.

Neurogenic causes of ED are also significant and common. Most often, peripheral neuropathy from diabetes is a cause of ED. Other neurogenic causes of ED include radical prostatectomy where the nerves that supply the penis with signals for corpus cavernosum smooth

muscle dilation are damaged during the pelvic surgical procedure *(17)*. Other pelvic surgical procedures, such as radical colectomy and cystectomy, may also produce this nerve damage, as does pelvic radiation therapy. Neurologic conditions such as multiple sclerosis, stroke, and spinal cord injury have high prevalence of ED.

Other causes of ED, which are significant but less frequently encountered, include venogenic or venous leak *(18)*. Venous leak, or venous incompetence, occurs when the emissary veins draining the corpora cavernosa do not restrict the venous outflow artery from the corpora and allow excessive venous drainage overcoming the arterial inflow. This may be seen as a cause of primary ED or because of conditions, such as aging, priapism, perineal trauma, or Peyronie's disease.

Chronic illnesses are also associated with ED, but many of these patients have concerns regarding their chronic illnesses that override erectile function. Diseases such as multiple sclerosis, Alzheimer's disease, and renal and hepatic failure produce a significant incidence of ED. Indeed, the endocrine abnormalities of renal failure that include hyperprolactinemia and hypogonadism respond best to renal transplantation but can be treated medically in some patients *(19)*.

RESULTS OF ED

What are the results and impact of ED on patients and their partners? Litwin et al. looked at the quality of life measures for patients with ED and their partners *(9)*. Not only were erections deficient, but there was also significant psychological impact on the patient, including decreases in self-confidence, self-esteem, and emotional well-being and an increase in depression. Problems with marital interaction stress within the couple were significantly increased as was the bother score for sexual dysfunction. A subsequent measurement of decreased libido in both patient and partner were identified. Fifty-seven percent of patients reported having difficulty with erections and subsequently developing a loss of interest or loss of sexual desire. Also interesting was the socioeconomic impact of ED on these men. Men in the higher socioeconomic ranges had fewer problems and less bother scores than men in the lower socioeconomic levels. In measuring the impact of ED on the sexual partner, the changes are similar, with a decrease in libido, sexual drive, and marital harmony and an increase in depression and inability to discuss sexual issues. This may result in a loss of communication between the partners and can be disastrous to any marital relationship.

Partners are also affected by the chronic diseases that result in ED. Many wives fear they will harm their spouses. This is especially true

after cerebrovascular accident or myocardial infarction, where the female partner feels that the stress of sexual activity may, in fact, be detrimental to her husband's health.

The pattern of ED begins with decreased penile rigidity and frequency of erectile function and coitus. Patients rarely see their physicians for the first 2 yr after sexual dysfunction begins *(20)*. Although the average frequency of normal patients in the adult range is between one and two encounters every 4–8 wk, patients with ED may have sexual activity less than once yearly. As this frequency decreases, the emotional distance between the partners begins to increase. Their emotional dissatisfaction with their relationship decreases and both of their libidos begin to decline. The frequency of other intimate acts consequently diminishes with a decrease in hugging, kissing, touching, and even talking. Thus, the impact on the couple and their relationship is substantial *(20)*.

ED is a chronic common problem that has a major impact on patients and their partners. It is something that physicians and health care workers must identify because there are excellent ways of effectively treating these patients and resolving their ED before marital discord and couple disharmony ensue. The most important method for caring for these patients is identifying the problem, and identifying the problem can only begin by asking the patient and/or his partner, "Do you have erectile problems; are there problems with your sexual function?" By beginning a dialog with your patients, something can be done to help both patients and partners.

Despite the stress on organic ED, pure psychogenic ED occurs, and, in those patients with organic ED, an emotional aspect of sexual function is virtually always present. The problems of sexuality overlap into relationship issues; self-esteem; moral and cultural values; and patient fears about their bodies, aging, and psychological health. Clearly, the appropriate management and understanding of psychological issues are essential for appropriate evaluation and treatment of patients, gaining their trust, and providing state-of-the-art therapy for patients with sexual concerns and dysfunction.

As a first step, a physician–patient dialogue must be initiated to fully evaluate the clinical abnormalities associated with ED. This begins with a face-to-face interview, a sympathetic history-taking with privacy and physician concern to maintain patient trust, comfort, and openness. A knowledgeable professional medical staff must be available to answer questions that patients initially may be embarrassed to ask physicians. Facilitating this interaction using a standardized questionnaire may open discussions, provide comfort for the patient in initiating conver-

sation, and allow physicians to evaluate the severity of ED. Available standardized questionnaires include the Brief Male Sexual Function Inventory for Urology, the more frequently used International Index of Erectile Function (IIEF), and its short form, the five-question Sexual Health Inventory for Men (SHIM; refs. *21* and *22*). After initiating treatment, such outcomes questionnaires as the Erectile Dysfunction Inventory of Treatment Satisfaction may be useful *(23)*. The Brief Male Sexual Function Inventory for Urology is composed of 11 questions developed to measure sexual drive, erectile function, problem assessment, and overall sexual satisfaction *(22)*. It is a brief, clinically validated and standardized self-administered questionnaire that works well in the office setting. The IIEF, a cross-culturally and psychometrically validated questionnaire, is widely used in clinical trials for medications and other interventions for ED. This 15-item questionnaire is evaluated for multiple domains, including erectile function, ejaculatory function, and desire. Erectile function is graded by severity, based on a scale from 6 to 30. The shorter five-question SHIM is, perhaps, the easiest for patients to take and for physicians to evaluate as a screening instrument (Fig. 1). The Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire, not designed for initial evaluation, is useful for identifying the patient and partner satisfaction from treatment modalities initiated for ED.

In addition to a comfortable, safe environment for the patient to discuss the issue with a physician, an interview with the partner may be helpful in evaluating ED. The partner may provide insight into sexual difficulties, relationship problems, and underlying health concerns that the patient may be uneasy about discussing. This may also identify the partner's approach to and value of intimacy and sexual function in the relationship *(24)*.

The physician–patient interaction, relationship, and interview have been discussed widely, and Marwick has documented that patients are clearly uneasy in bringing up the subject of ED or sexual problems with their physicians *(7)*. Marwick demonstrated that greater than 70% of patients felt that it would be embarrassing to discuss sexual problems and that physicians themselves would be embarrassed and find the problems of ED trivial or insignificant. Therefore, the emphasis is for the physician to initiate questioning and begin the discussion of erectile function in patients seen both for routine visits and treatment of diagnoses associated with risk factors for ED. The use of the SHIM in the office before the visit may facilitate this interaction and initiate a conversation regarding ED.

1. How do you rate your <u>confidence</u> that you could get and keep an erection?

Very low	Low	Moderate	High	Very high
1	2	3	4	5

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

No sexual activity	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
0	1	2	3	4	5

3. During sexual intercourse, <u>how often</u> were you able to maintain your erection after you had penetrated (entered) your partner?

Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
0	1	2	3	4	5

4. During sexual intercourse, <u>how difficult</u> was it to maintain your erection to completion of intercourse?

Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
0	1	2	3	4	5

5. When you attempted sexual intercourse, <u>how often</u> was it satisfactory for you?

Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Somtimes (about half the time)	Most times (much more than half the time)	Almost always or always
0	1	2	3	4	5

SCORE: Add the numbers corresponding to questions 1–5. If your score is 21 or less, you may want to give this form to your health-care professional to determine if you have ED. If so, you may want to discuss safe and effective treatment options with your doctor

Fig. 1. Sexual health inventory for men over the past 6 mo. (Adapted from ref. 21, 22, and Kloner et al. J Urol 2003;170:S46–S50.)

CLINICAL EVALUATION

The adequate evaluation for ED continues to evolve. Before the introduction of sildenafil, there was an emphasis on a goal-directed approach to male sexual dysfunction that included careful identification of the etiology of the ED *(25)*. The goal of this approach was to identify a specific etiology such that more invasive, costly, uncomfortable treatment modalities could be applied based on the patient's treatment goals. In the era of managed care, cost consciousness, and with minimally invasive safe and effective oral medications, extensive evaluation of patients is no longer the first line for patients presenting with ED. However, it is critically important to review the patient's history carefully to identify underlying risk factors, medications, and lifestyle factors that may contribute to ED with hopes that modifying these risk factors will facilitate further treatment with oral agents.

A full sexual history is critical with special attention to risk factors and medications *(20)*. This should be followed by a thorough physical examination, laboratory studies, and appropriate clinical diagnostic studies. ED may be caused by various etiologies or combinations of factors. A history should include a careful sexual history to elicit these possible causes *(25)*. Patients should be queried regarding morning erections, nocturnal erections, erectile quality, and erections during masturbation, and ejaculatory function. Open-ended questions are best for this purpose because they provide the most spontaneous, accurate, and detailed information regarding the current status of erectile function, onset of ED, and surrounding precipitating factors.

Patients who complain of loss of libido or sexual desire may be considered as at risk for hypogonadism. Low libido, however, may be caused by medications, hypochondriasis, stress, anxiety, or depression *(14)*. Low libido clearly requires evaluation to identify those patients with androgen deficiency of the aging male or other causes of hypogonadism. Those patients with chronic renal failure, especially on chronic dialysis, may have low libido caused by low testosterone and high prolactin levels *(19)*. These abnormalities can be treated medically to decrease prolactin and increase testosterone levels.

A history of ejaculatory dysfunction must also be elicited to identify those patients with premature ejaculation or delayed ejaculation. Younger men more often complain of premature ejaculation whereas those in the older age group more often have difficulties with retarded ejaculation or even absent ejaculation. This may be caused by natural aging, lack of androgen, neurologic abnormalities, medications, or pelvic surgery. Patients with retrograde ejaculation must be suspected

Table 2
Modifiable Risk Factors for Erectile Dysfunction

Diabetes mellitus
Cardiovascular disease
Spinal cord injury
Cigarette smoking
Depression
Atherosclerosis
Hypertension
Pelvic surgery/trauma
Medications
Arthritis
Peripheral vascular disease
Renal failure
Substance abuse
Endocrine abnormalities
Peptic ulcer disease

of having diabetes mellitus, may be using α-blocking medication, or may have had previous urologic or neurologic surgery *(20)*.

Medical problems associated with ED may include those listed in Table 2. Each of these should be discussed with the patient during history taking. Any condition associated with cardiac disease, hypertension, diabetes, or lipid abnormalities can be associated with ED. Indeed, atherosclerosis is a risk factor in 70% of men greater than age 60 yr, and ED occurs in diabetic men at 10–15 yr after onset and affects 50% of diabetic men *(16)*. ED in Type 1 diabetes is often of neurogenic etiology, whereas Type 2 diabetics more often have vascular problems or combinations of etiologies.

Medications are also frequently causes of ED. Some of the medications associated with ED are listed in Table 3. Most often, antihypertensives and antidepressant (SSRIs) medications are the culprits. Recreational drugs, such as cocaine, marijuana, alcohol, and tobacco, also have the potential for causing ED.

Additional history should include history of penile trauma, priapism, curvature of the penis from Peyronie's disease, or congenital corporal disproportion. Depression and anxiety can often be identified in this initial phase of the examination.

Physical examination of patients with ED should be focused on the genitalia. A general inspection of body habitus to identify hair distribution, obesity or overweight, and secondary sex characteristics should

Table 3
Medications Associated With Erectile Dysfunction

β-adrenergic antagonists
Thiazide diuretics
Verapamil
Naproxen
Amitriptyline
Digoxin
Phenytoin
Hydralazine
Clofibrate
Indomethacin
Cimetidine
Omeprazole
Metoclopramide
Famotidine
Lithium
Antidepressants (SSRIs)[a]
Antiandrogen hormones
Recreational drugs (marijuana, cocaine, and heroin)

[a]Selective serotonine reuptake inhibitors

be identified. Patients with severe obesity should be suspected of having sleep apnea or high estrogen levels, which may be associated with ED. Testicular size and consistency, as well as penile anatomy, should be examined carefully. Patients with small or soft testes should be suspected of hypogonadism, and lesions of the shaft of the penis can be identified in those patients with Peyronie's disease. A brief neurologic examination should be performed with an evaluation of sensation of lower extremities, deep tendon reflexes, and perineal sensation. A bulbocavernosus or cremasteric reflex as well as sphincter tone on rectal examination can be quantified. Digital rectal examination to identify prostate size, consistency, nodularity, pain, or prostatitis should be conducted. If questions arise regarding penile sensation, biothesiometry of the glans penis and penile shaft can be performed in the office with this vibratory sensation device *(26)*. Results should be compared with an age-adjusted normogram to identify those patients with decreased glans penis sensation.

Once a careful physical examination is completed, laboratory investigation should be tailored to the individual patient and goals of therapy. In patients who have not had recent health evaluation, fasting

blood glucose should be measured to identify patients at risk for diabetes mellitus. This is especially important in those patients with a family history of diabetes or those patients with personal histories of polyuria or polydipsia. In known diabetics, an Hb A1c can evaluate control and medical compliance with diabetic therapy. Similarly, laboratory studies can include a lipid profile to identify those patients with hypercholesterolemia. In those patients with suggestive history, a thyroid profile can be obtained as well. Most importantly, however, is an evaluation of hormone status. Hypogonadism, though only found in a small number of patients, should be evaluated in all patients with ED *(27)*. An initial screening of morning total testosterone should be performed to identify testosterone level. It is important to perform this as a morning evaluation because testosterone concentration peak occurs between 8 and 10 a.m. Repeat testosterone levels with a free testosterone, luteinizing hormone, and prolactin level should be performed if testosterone is suspicious. Buvat and Lemaire reviewed endocrine screening results in 1022 patients with ED and found that limiting testosterone evaluation to those patients with abnormal physical examinations or decreased libido would miss 40% of patients with low testosterone *(27)*. They recommend testosterone determinations for all men over age 50 yr. Other hormonal studies associated with decreased libido and decreased sexual function include dehydroepiandrosterone (DHEA) and DHEA sulfate, which can be evaluated. Reiter et al. demonstrated that replacement of DHEA in patients with low DHEA and normal testosterone may improve sexual desire and libido substantially in addition to improving sexual performance and erectile function *(28)*.

With this basic group of studies, including history, physical examination, questionnaires, and laboratory studies, the majority of patients can be identified as having ED and started on appropriate oral medications for treatment. However, if oral medications are unsuccessful, patients are interested in their underlying ED etiology, or surgical intervention is contemplated, further evaluation may be required (Table 4). This evaluation may include the standard studies of nocturnal penile tumescence monitoring (NPT), arterial and venous studies, including color Doppler arterial studies, and ultimately cavernosography, and selective pudendal arteriography.

NPT monitoring was first described in the 1970s by Fisher for separation of organic and psychogenic ED patients. It is well known that normal men have significant erectile function during rapid eye movement sleep. A total of four to six erections occur during the usual night's sleep with base and tip rigidity greater than 55% and sustained for at

Table 4
Diagnostic Tests for Erectile Dysfunction

Body system	Test
Neurologic testing	Biothesiometry
Somatic nerves	Nerve conduction velocities
	Evoked potentials
Autonomic nerves	Cardiovascular reflex tests
	Sympathetic skin response
	Corpus cavernosum electromyography
	Thermal threshold testing
	Urethroanal reflex latency
	Nocturnal penile tumescence
Vascular testing	Penile brachial index
Arteriogenic	Pharmacopenile duplex
	ultrasonography
	Selective pudendal arteriography
Veno-occlusive	Intracavernous injections
	Pharmacopenile duplex
	ultrasonography
	Dynamic infusion cavernosometry
	and cavernosography
Psychogenic ED	Nocturnal penile tumescence

Abbreviations: ED, erectile dysfunction.

least 10 min. The RigiScan recording device (Timm Medical, Augusta, GA) provides an economical, safe, noninvasive home-monitoring device for screening patients with NPT monitoring studies *(29)*. Although controversy remains regarding the diagnostic accuracy of NPT evaluation, it may be useful in separating patients with organic and psychogenic ED and for use in medical legal situations. False/negative studies may be found in those patients with depression, sleep disorders, sleep apnea, sleep-altering medications, smoking, and caffeine use. The overall accuracy of nocturnal penile tumescence monitoring is approximately 80% *(29)*. An abnormal NPT test should be confirmed with at least two nights of study and subsequent independent validation studies.

Although specific widely available clinical studies for neurogenic testing except for tactile testing have limited availability, such studies as

dorsal nerve conduction velocities and sacral nerve-evoked potentials may be useful in some patients and are available at research institutes and ED centers. Vascular studies to identify functional abnormalities of the arterial and venous systems can be used with accurate determination of vascular function and anatomy. Older studies using hand-held Doppler with penile brachial index identification appear to be inaccurate and poorly reproducible. However, the use of duplex ultrasound color Doppler flow studies with intracavernous injection of vasoactive agents can carefully evaluate both the arterial and venous systems that produce erections in a functional fashion. In 1985, Lue and Broderick reported the combination of intracavernous injections of vasoactive agents with duplex ultrasonography providing high-resolution sonography and pulsed Doppler blood flow analysis to evaluate the penile arteries and provide information regarding venous outflow incompetence. This non-invasive technique measures cavernous arterial diameter, detects abnormalities in cavernous bodies, such as fibrosis and calcifications, and evaluates venous outflow. In 1990, Mueller et al. compared selective internal iliac arteriography with duplex Doppler ultrasound sonography for arteriogenic ED *(30)*. In the 43 men evaluated, selective arteriography and duplex sonography correlated in 91% of cases, with duplex ultrasound providing higher accuracy than selective arteriography for the diagnosis of arteriogenic ED. Duplex ultrasonography can also identify venous leak ED/veno-occlusive dysfunction in an indirect fashion. If veno-occlusive dysfunction is suspected from initial studies, dynamic infusion cavernosography and cavernosometry can be performed to identify areas of veno-occlusive dysfunction and suggests surgical or nonsurgical intervention.

In those patients with suspected traumatic injuries to the arterial supply of the penis, selective pudendal arteriography in combination with intracavernous injection can provide an accurate review of the penile arterial anatomy and identify those patients who are candidates for arterial revascularization. Duplex Doppler studies can identify those patients in whom arteriography may be helpful. Ideal candidates for this procedure include those with a single solitary obstructive lesion of the pudendal arterial system who are less than age 40 yr and non-smokers who have no other significant vascular disease risk factors such as diabetes or hypercholesterolemia.

CONCLUSION

ED is currently treatable with safe effective oral medication that can restore not only erectile function but also quality of life for men with

sexual problems. The most important part of evaluation of patients with ED is asking the patients about their erectile status. Although there are many clinical diagnostic studies, laboratory studies, and possible findings on physical examination, the most important part of evaluation and treatment is taking an adequate history and eliciting an erectile problem from patients. An adequate physician–patient rapport is an important starting point for successful treatment of ED.

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