Chapter 1: AUA Guideline on the Management of Erectile Dysfunction: Diagnosis and Treatment Recommendations

Introduction

In 1996, the Erectile Dysfunction Clinical Guideline Panel published the *Report on the Treatment of Organic Erectile Dysfunction* (the 1996 *Report*), an evidence-based guideline for the diagnosis and treatment of erectile dysfunction (ED).[1] Since that time, impotence, more precisely termed "erectile dysfunction," has received increasing attention because of the availability of new treatments approved by the U.S. Food and Drug Administration (FDA). In addition, the overall quality of clinical research and the methods of measuring outcomes have improved substantially. The 1996 analysis was based mainly on the outcomes of clinical series. The randomized, controlled trial has now become the norm.

An Erectile Dysfunction Guideline Update Panel (the Panel) was appointed by the American Urological Association (AUA) Practice Guidelines Committee in the year 2000 to update the existing document. Using a consensus-based approach, the Panel concluded that (1) *informed patient decision making* should remain the standard; (2) no new evidence has suggested that the guideline statements on the diagnostic evaluation should be changed; (3) a psychologic overlay frequently exists in patients with ED; and (4) endocrine disorders are an important consideration in the etiology of ED. Although sex therapy and the diagnosis and treatment of endocrine disorders are important management issues, the Panel agreed that these issues were beyond the scope of the guideline and would, therefore, not be discussed.

The Panel's major focus was to use an evidence-based approach to develop a guideline for the ED treatment modalities that had become available in the United States after publication of the 1996 *Report*. Guideline statements from the 1996 *Report* on previously available therapeutic

modalities were either revised or brought forward unchanged depending on the existing evidence.

All guideline statements were graded according to the degree of flexibility in clinical application: standard, recommendation, or option, with standard being the least flexible and option being the most flexible (Table 1). Grading is based on two characteristics: knowledge of the health outcomes of the alternative intervention and preference for the intervention.

Table 1. Grades of Guideline Statements Based on Levels of Flexibility of Application

Grade	Knowledge of Health Outcomes of the Alternative Interventions	Preference for Intervention
Standard	Sufficiently well known to permit meaningful decisions	Virtual unanimity
Recommendation	Sufficiently well known to permit meaningful decisions	An appreciable but not unanimous majority agrees
Option	Not sufficiently well known to permit meaningful decisions	Unknown or equivocal

The Panel believed that the patient, with physician guidance, must make his own decision in selecting treatment. Outcome estimates derived from review and meta-analysis of evidence provide physicians and patients with scientifically based information to assist them in making appropriate treatment decisions. Thus, a second Panel objective was to determine whether or not there was sufficient evidence for outcomes (both benefits and risks) to be estimated.

Definitions

The National Institutes of Health (NIH) Consensus Development Conference on Impotence (December 7-9, 1992) defined impotence as "male erectile dysfunction, that is, the inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[2] ED is the more

precise term, especially given the fact that sexual desire and the ability to have an orgasm and ejaculate may well be intact despite the inability to achieve or maintain an erection. The recommendations and findings of the Panel were based upon the management of an Index Patient that represents the most prevalent presentation of this disorder since management may vary in atypical patients. ***The Index Patient for this document is defined as a man with no evidence of hypogonadism or hyperprolactinemia who develops, after a well-established period of normal erectile function, ED that is primarily organic in nature.*** This definition is a slightly modified version of the definition used to develop the 1996 *Report.*

Methodology

The Panel's task was to prepare a guideline on therapies for ED that became available after the publication of the 1996 *Report* and to revise those portions that required updating so that patients and physicians could participate in a scientifically based, informed decision-making process. In addition to ED, the Panel elected to address three topics relevant to erection, Peyronie's disease, priapism, and premature ejaculation. Guidelines for priapism and premature ejaculation are currently available: http://www.auanet.org/guidelines/priapism.cfm; http://www.auanet.org/guidelines/pe.cfm.

In the year 2000, MEDLINE® searches of English-language references on human subjects were initiated for each of the four topics. Search strategies ranged from very general to very specific. Citations identified through subsequent targeted searches, such as those specifically focused on individual treatments, and through Panel member suggestions also were added to the database. The ED portion of the searches spanned the years from 1994, when the final literature search for the 1996 *Report* was completed, to February 2004. The Panel continued to scrutinize key references that were identified up until the peer-review process.

Panel chairmen reviewed each citation title and abstract. Papers that presented outcomes data resulting from the evaluation of ED therapies were winnowed from the other publications. Sufficient new evidence was available to update the recommendations for many of the treatments discussed in the 1996 *Report* on ED. The initial plan was to conduct a full review, data extraction, and meta-analysis of the FDA-approved oral agents and alprostadil intra-urethral suppositories. Because of data limitations, varying types of analyses were undertaken for the other treatment modalities.

Data from 112 articles selected by the chairmen were extracted and recorded on a data extraction form. The Panel determined that although there were many different outcome measures used in the studies, only a limited number would be considered adequate for this review: the International Index of Erectile Function (IIEF) (including the erectile function and intercourse satisfaction domains as well as questions 3 and 4 individually) (Appendix 1-A;[3,4]) and the specific measures "ability to have intercourse," “return to normal," and erection grade of 4 or 5 (on a five-point scale). The extracted data were entered into a database, and evidence tables were generated and reviewed by the Panel. Twenty-seven papers were rejected for lack of relevant data or inadequate quality. Of the accepted articles, nine reported the results of two or more trials that were extracted as separate studies. A detailed meta-analysis of study outcomes was attempted. Difficulties were encountered in developing outcome estimates for all therapies because of study inconsistencies in patient selection and outcome measures, the lack of sufficient data, and the reporting of adjusted results. Given these problems with the data, the Panel ultimately decided that meta-analysis was inappropriate.

The Panel performed focused reviews and analyses of the surgical therapies, implantable devices, and vascular surgery. Each topic was assigned to a Panel member for review and

development of evidence tables or reports. The review of implantable devices was restricted to the question of mechanical failure/replacement rates. The review of arterial vascular surgical therapy focused on an Index Patient which differed from the standard Index Patient defined for other treatments. A special review of herbal therapies was performed later in the guideline process since few citations on herbal therapies were initially extracted. The search for herbal therapies included non-English language journals with abstracts written in English. Of the articles on herbal therapies that were identified, only three were randomized controlled trials using objective outcome criteria. The sections on vacuum constriction devices and intracavernous vasoactive drug injection were not updated as no new evidence was found that materially affected the recommendations for these treatments. The Panel also decided against reviewing the data on testosterone as it was beyond the scope of the guideline, and on apomorphine, which was not approved for use in the United States.

As in the 1996 *Report*, the Panel generated guideline statements based on the strength of the evidence and the expected amount of variation in patient preferences for treatments. In some cases, guideline statements were supported solely by the Panel's expert opinion and are designated as such in the text. The Panel also outlined suggestions for future clinical research priorities.

This guideline was drafted, reviewed by the Panel and by 80 peer reviewers, and finally approved by the Practice Guidelines Committee and the Board of Directors of the AUA. A full description of the methodology is presented in Chapter 2.

Diagnostic Evaluation of Erectile Dysfunction

The Panel unanimously agreed that the present update should reflect current practices in the diagnostic evaluation of a new patient with ED. As in the 1996 *Report*, the discussion is based

solely on Panel opinion and is handled similarly herein. The Panel did not conduct a rigorous systematic review of the literature; therefore, the following discussion is not intended to be all-inclusive or limiting with regard to assessment of individual patients.

The typical initial evaluation of a man complaining of ED is conducted in person and includes sexual, medical, and psychosocial histories as well as laboratory tests thorough enough to identify comorbid conditions that may predispose the patient to ED and that may contraindicate certain therapies. History may reveal causes or comorbidities such as cardiovascular disease (including hypertension, atherosclerosis, or hyperlipidemia), diabetes mellitus, depression, and alcoholism. Related dysfunctions such as premature ejaculation, increased latency time associated with age, and psychosexual relationship problems may also be uncovered. Most importantly, a history can reveal specific contraindications for drug therapy. Additional risk factors include smoking, pelvic, perineal, or penile trauma or surgery, neurologic disease, endocrinopathy, obesity, pelvic radiation therapy, Peyronie's disease, and prescription or recreational drug use. Other critical elements are alterations of sexual desire, ejaculation, and orgasm, presence of genital pain, and lifestyle factors, such as sexual orientation, presence of spouse or partner, and quality of the relationship with the partner. Finally, a history of the partner's sexual function may be helpful. Attention is given to defining the problem, clearly distinguishing ED from complaints about ejaculation and/or orgasm, and establishing the chronology and severity of symptoms. An assessment of patient/partner needs and expectations of therapy is equally important.

A focused physical examination evaluating the abdomen, penis, testicles, secondary sexual characteristics and lower extremity pulses is usually performed. Established patients with a new complaint of ED typically are not re-examined. According to the AUA Prostate-specific Antigen

(PSA) Best Practice Policy on early detection of prostate cancer, both digital rectal examination of the prostate and serum PSA measurement should be offered annually in all men over 50 with an estimated life expectancy of more than 10 years.[5] Prostate-specific antigen measurement and rectal examination may assume additional significance when considering the use of testosterone in the management of male sexual dysfunctions. Additional testing, such as testosterone level measurement, vascular and/or neurological assessment, and monitoring of nocturnal erections, may be indicated in select patients.

Initial Management and Discussion of Treatment Options With Patients

Recommended Therapies and Patient Information

Standard: The management of erectile dysfunction begins with the identification of organic comorbidities and psychosexual dysfunctions; both should be appropriately treated or their care triaged. The currently available therapies that should be considered for the treatment of erectile dysfunction include the following: oral phosphodiesterase type 5 [PDE5] inhibitors, intra-urethral alprostadil, intracavernous vasoactive drug injection, vacuum constriction devices, and penile prosthesis implantation. These appropriate treatment options should be applied in a stepwise fashion with increasing invasiveness and risk balanced against the likelihood of efficacy.

[Based on review of data and Panel consensus.]

Currently employed medical interventions for the management of ED include oral therapies that target the penis through phosphodiesterase type 5 (PDE5) inhibition and intrapenile therapies (intra-urethral suppositories and intracavernous injections). The vacuum constriction device is a noninvasive mechanical device. Surgical therapies include implantation of prosthetic devices and vascular surgeries. Psychosexual therapy may be useful in combination with both

medical and surgical treatment for men with ED. For some patients, brief education, support, and reassurance may be sufficient to restore sexual function and for others, referral for more specialized and intensive counseling may be necessary.[6] Endocrine therapy for hypogonadism, hyperprolactinemia, and thyroid disorders is an appropriate intervention for patients with a definite endocrinopathy. The literature on the management of ED in patients with psychosexual etiology or endocrinopathies, though, was not examined by the Panel and will not be reviewed in this guideline. This guideline, except where otherwise noted, is directed at the management of the Index Patient defined earlier in the document.

Standard: The patient and, when possible, his partner should be informed of the relevant treatment options and their associated risks and benefits. The choice of treatment should be made jointly by the physician, patient, and partner, when possible, taking into consideration patient preferences and expectations and the experience and judgment of the physician.

[Based on Panel consensus.]

Erectile Dysfunction and Comorbidities

Modifying Risk Factors for Erectile Dysfunction

Erectile function is the result of a complex interplay between vascular, neurologic, hormonal, and psychologic factors. The attainment and maintenance of a firm erection requires good arterial inflow of blood as well as efficient reduction of venous outflow. Risk factors and disease processes that affect the function of the arterial or venous systems would therefore be expected to have a negative impact on erectile function. Since the risk of developing ED is increased in the presence of diabetes, heart disease, and hypertension, it is logical to conclude that optimal management of these diseases may prevent the development of ED.[7,8,9] It is also logical to

assume that lifestyle modifications to improve vascular function such as avoiding smoking, maintaining ideal body weight and engaging in regular exercise might either prevent or reverse ED, however, only minimal data exists today to support this supposition.[10,11]

Managing Erectile Dysfunction in the Presence of Cardiovascular Disease

Cardiovascular disease and ED may share a common etiology when endothelial dysfunction and atherosclerosis affect both coronary arteries and penile vasculature.[12] Consequently, patients with ED frequently have concurrent cardiovascular disease.[13] Treatment of ED in patients with cardiovascular disease is complicated by a small increase in the risk of myocardial infarction (MI) related to sexual activity in these patients independent of the method of treatment. Sexual activity increases physical exertion levels to 3 to 4 METS (1 MET is the amount of energy used at the resting state associated with oxygen consumption of approximately 3.5 mL/kg/min), and sympathetic activation during sexual activity may increase blood pressure and heart rate more than other types of exercise.[14] Together, these factors result in a 2.5-fold (95% CI, 1.7-3.7) greater relative risk of nonfatal MI following sexual activity in healthy men than during noncoital activities and a 2.9-fold (95% CI, 1.3-6.5) greater risk in men with a history of MI.[14] Even with this effect, however, the absolute risk of MI during and for 2 hours following sexual activity is extremely low — only 20 chances per million per hour in post-MI patients and even less in men without a history of MI.[15] The major risk factors associated with cardiovascular disease are age, hypertension, diabetes mellitus, obesity, smoking, dyslipidemia, and sedentary lifestyle. Patients with three or more of these risk factors[16] are considered to be at increased risk for MI during sexual activity.

Guidelines for managing ED in patients with cardiovascular disease developed by the Princeton Consensus Panel[14] recommend assigning patients to one of three risk levels (high,

intermediate, and low) based on their cardiovascular risk factors. High-risk patients are defined as those with unstable or refractory angina; uncontrolled hypertension; congestive heart failure (CHF; New York Heart Association class III, IV); MI or a cardiovascular accident within the previous 2 weeks; high-risk arrhythmias; hypertrophic obstructive and other cardiomyopathies; or moderate-to-severe valvular disease. The document states that patients at high risk should not receive treatment for sexual dysfunction until their cardiac condition has stabilized. Patients at low risk may be considered for all first-line therapies. The majority of patients treated for ED are in the low-risk category defined as those who have asymptomatic coronary artery disease and less than three risk factors for coronary artery disease (excluding gender); controlled hypertension; mild, stable angina; a successful coronary revascularization; uncomplicated past MI; mild valvular disease; or CHF (left ventricular dysfunction and/or New York Heart Association class I). Patients whose risk is indeterminate should undergo further evaluation by a cardiologist before receiving therapies for sexual dysfunction.

Treatment Guideline Statements

The nonsurgical therapies for ED considered for review by the Panel include the PDE5 inhibitors, sildenafil, tadalafil, and vardenafil; alprostadil intra-urethral suppositories; intracavernous injection with alprostadil, papaverine, or phentolamine or combinations; vacuum constriction devices; trazodone; and herbal therapies including yohimbine. Chapter 3 provides the results of the evidence-based, outcomes analyses of the noninvasive therapies to the extent that the outcomes evidence was available. The following practice guideline statements are specific to the nonsurgical therapies.

Phosphodiesterase Type 5 (PDE5) Inhibitors

Standard: Oral phosphodiesterase type 5 inhibitors, unless contraindicated, should be offered as a first-line of therapy for erectile dysfunction.

[Based on review of data and Panel consensus.]

Sildenafil, tadalafil, and vardenafil are potent, reversible, competitive inhibitors of PDE5. At this time, there is insufficient evidence to support the superiority of one agent over the others. While a comparison of the efficacy and side effects of the PDE5 inhibitors would be very useful for clinicians and patients, such a comparison cannot be done with the presently available data. At the time of our final literature search, studies directly comparing these drugs had not been published. Attempts at developing a comparative outcomes table based on meta-analysis also failed for two reasons. First, studies evaluating vardenafil and tadalafil excluded subjects who did not respond to sildenafil. This specific difference from the sildenafil clinical trials made comparisons invalid. Second, because many of the studies identified through the original literature search used mathematical models to compensate for patient variability in age, race, smoking status, and baseline function, e.g.,[17,18,19,20,21] these data could not be used for valid meta-analysis. Although authors of previously published evidence-based reviews[22,23] had obtained raw data directly from study investigators for meta-analytic purposes, the Panel believed that even if the raw data were obtained, useful comparisons still could not be made due to the incomparable patient populations.

Differences in pharmacokinetic and adverse event profiles do exist. Sildenafil and vardenafil have very similar pharmacokinetic profiles with a time to achieve maximum serum levels (T_{max}) of approximately 1 hour and a serum half-life of approximately 4 hours. In contrast, tadalafil has a T_{max} of approximately 2 hours and a half-life of approximately 18 hours. All three drugs are

metabolized by the liver so the dosage should be adjusted in those patients with altered hepatic function due to disease or medication, especially those that affect cytochrome P450. The side effect profiles of the three drugs are very similar. All three medications have side effects due to peripheral vasodilation such as facial flushing, nasal congestion, headache, and dyspepsia. Both sildenafil and vardenafil, but not tadalafil, have some cross-reactivity with PDE6 and thus may produce visual side effects. Tadalafil exhibits some cross-reactivity with PDE11, but there are no known side effects due to PDE11 inhibition at this time. Back pain has been reported in a limited number of patients, especially those taking tadalafil, and the pathophysiology of this adverse effect is unknown. A mild prolongation of the QT interval has been observed with vardenafil. The FDA-approved product labeling for vardenafil recommends that caution be used when prescribing vardenafil in patients with a known history of QT prolongation or in patients who are receiving agents that prolong the QT interval.

The management of men with ED is often complicated by the concomitant use of antihypertensive and/or lower urinary tract symptom (LUTS) pharmacotherapies. Studies investigating the epidemiology of and risk factors for ED have clearly identified hypertension as a risk for ED and have recently suggested a statistical relationship between ED and LUTS, independent of aging.[13,7,24] When considering PDE5 inhibitors for the management of ED, physicians should be aware that even healthy volunteers may experience mild transient systemic vasodilation; this effect may be aggravated by alpha-blocking therapies. All three medications interact to some degree with alpha blockers, a class of drugs used primarily for the treatment of LUTS in men and, less commonly, for hypertension (for Product Labeling see: http://www.fda.gov/cder/foi/label/1998/viagralabel2.pdf; http://www.fda.gov/cder/foi/label/2003/021368lbl.pdf;

http://www.fda.gov/cder/foi/label/2005/021400s004lbl.pdf). All dosages of vardenafil and tadalafil as well as sildenafil at the 50mg and 100 mg doses should be administered with caution in patients taking alpha blocker medications (see respective PI's for details).

Standard: Phosphodiesterase type 5 inhibitors are contraindicated in patients who are taking organic nitrates.

[Based on review of the Food and Drug Administration approved product labeling and Panel consensus.]

PDE5 inhibitors potentiate the hypotensive effects of organic nitrates and nitrites such as amyl nitrite,[12,25] and therefore their concomitant use is contraindicated (for Product Labeling see: http://www.fda.gov/cder/foi/label/1998/viagralabel2.pdf; http://www.fda.gov/cder/foi/label/2003/021368lbl.pdf; http://www.fda.gov/cder/foi/label/2005/021400s004lbl.pdf). Commonly prescribed nitrates are listed in Appendix 1-B. In an emergent setting (e.g., for presumed MI or ischemia), especially when clinicians are unfamiliar with a patient's drug history, careful questioning may aid in avoiding these combinations. Although a safe time interval between the use of nitrates and PDE5 inhibitors has not been definitively determined, a suggested time interval for nitrate administration during a medical emergency (under close medical supervision and patient monitoring) in patients who have received sildenafil is 24 hours[26] and for tadalafil is 48 hours[27] (http://www.fda.gov/cder/foi/label/2003/021368lbl.pdf). A suggested time interval has not been published for vardenafil, but additional blood pressure and heart rate changes were not detected when vardenafil was dosed 24 hours before nitrate administration (http://www.fda.gov/cder/foi/label/2003/021400lbl.pdf).

Recommendation: The monitoring of patients receiving continuing phosphodiesterase type 5 inhibitor therapy should include a periodic follow-up of efficacy, side effects, and any significant change in health status including medications.

[Based on Panel consensus.]

A patient's medical status and medication use change over time. Thus, it is important to follow-up with each patient to ascertain whether the medication is still effective and that their cardiovascular health has not changed significantly. Typically, this is done at the time of prescription renewal.

Recommendation: Prior to proceeding to other therapies, patients reporting failure of phosphodiesterase type 5 (PDE5) inhibitor therapy should be evaluated to determine whether the trial of PDE5 inhibition was adequate.

[Based on Panel consensus.]

PDE5 inhibitor therapy is not efficacious in all ED patients. However, failure to respond may be due to one or more potentially modifiable factors such as hormonal abnormalities, food or drug interactions, timing and frequency of dosing, lack of adequate sexual stimulation, heavy alcohol use, and the patient's relationship with his partner.[28,29,30] After re-education and counseling, which includes information on patient and partner expectations, proper drug administration, and titration to maximum dosing, evidence has shown that sildenafil therapy becomes successful in some men who were not previously responders.[28,29]

Recommendation: Patients who have failed a trial with phosphodiesterase type 5 (PDE5) inhibitor therapy should be informed of the benefits and risks of other therapies, including the use of a different PDE5 inhibitor, alprostadil intra-urethral suppositories, intracavernous drug injection, vacuum constriction devices, and penile prostheses.

[Based on Panel consensus.]

Once an adequate trial has been completed with one drug and all modifiable risk factors have been addressed, the patient may be treated with a different PDE5 inhibitor or proceed with other, more invasive therapies for ED. Currently, there are not sufficient data to counsel patients on the likelihood of success with a different PDE5 inhibitor if they failed an "adequate" trial with one drug. Still, there are data to support the very realistic chance that more invasive therapies will be successful.

Alprostadil Intra-urethral Suppositories

Standard: The initial trial dose of alprostadil intra-urethral suppositories should be administered under healthcare provider supervision due to the risk of syncope.

[Based on review of the Food and Drug Administration-approved product labeling and Panel consensus.]

Alprostadil, a synthetic vasodilator identical to PGE_1, has been formulated for transurethral delivery as a suppository for the treatment of ED. Despite the significantly greater efficacy of alprostadil intra-urethral suppositories in producing erections when compared to placebo in randomized controlled trials,[31] their use has produced less successful results in postmarketing studies.[32,33] Because hypotension has been reported to occur in approximately 3% of patients after the first dose,[31] it is recommended that the first dose be administered under supervision of a healthcare provider. The efficacy of alprostadil suppositories in combination with other treatment modalities recently has been evaluated. Studies assessing the combination of alprostadil suppositories with either a penile constriction device or oral PDE5 inhibitors have shown increased efficacy over alprostadil alone.[34,35]

Although not as effective, alprostadil intra-urethral suppositories are a less invasive treatment option than penile injection and may be considered for select patients such as men who are either not candidates for or have failed therapy with oral PDE5 inhibitors. The combination of intra-

urethral alprostadil suppositories with other pharmacotherapies or a penile constriction device holds some promise, but additional studies are needed to assess dosing, efficacy, and safety.

Intracavernous Vasoactive Drug Injection Therapy

Intracavernous injection therapy is the most effective nonsurgical treatment for ED; however, it is invasive and has the highest potential for priapism among ED treatments. Alprostadil (PGE_1), papaverine, and phentolamine are the most widely used vasoactive drugs for injection therapy. As monotherapy, alprostadil is the most popular vasoactive agent; however, combination therapy with the other vasoactive drugs (bimix and trimix) can either increase efficacy or reduce side effects. The advantage of monotherapy with either papaverine or alprostadil is that they are readily available at most pharmacies whereas bimix and trimix are only available from pharmacies that offer compounding services. Physician preference guides the initial choice of therapy. Final choice is based on efficacy, side effects, and cost.

Because the Panel believed that the new body of evidence on the efficacy and safety of intracavernous therapy would not substantially change the outcome estimates of the *1996 Report,* the literature on this topic was not reviewed. The co-administration of oral PDE5 inhibitors and intracavernous injection therapy has not been adequately evaluated at this time.

Standard: The initial trial dose of intracavernous injection therapy should be administered under healthcare provider supervision.

[Based on Panel consensus.]

A healthcare provider should be present to instruct patients on the proper technique of intracavernous drug administration, to determine an effective dose, and to monitor patients for side effects, especially prolonged erection. Education of the patient is particularly important to minimize frustration and to decrease the probability of untoward side effects. Effective training

and periodic follow-up will likely decrease the occurrence of improper injection and treatment failure. When appropriate, the patient should be able to adjust within specific bounds the total dose of medication injected to match the specific situation for which it is used. Vasoactive drug injection therapy should not be used more than once in a 24-hour period.

Standard: Physicians who prescribe intracavernous injection therapy should (1) inform patients of the potential occurrence of prolonged erections, (2) have a plan for the urgent treatment of prolonged erections and (3) inform the patient of the plan.

(See AUA guideline on priapism: http://www.auanet.org/guidelines/priapism.cfm)

[Based on Panel consensus.]

Priapism is defined as a prolonged erection lasting greater than four hours. It is important that patients be advised that erections that last 4 hours after an intracavernous injection be reported promptly to the healthcare professional who prescribed intracavernous injection therapy or his surrogate. Priapism should be treated as rapidly as possible to avoid adverse sequelae including corporal tissue damage. The prolonged erections and priapism associated with injection therapy are often readily reversed with nonsurgical measures when intervention occurs early. Thus, it is imperative for the physician to both have a plan in place to manage this complication and to communicate to the patient the seriousness of this complication and the need for rapid intervention.

Vacuum Constriction Devices

Recommendation: Only vacuum constriction devices containing a vacuum limiter should be used whether purchased over-the-counter or procured with a prescription.

[Based on Panel consensus.]

Vacuum constriction devices are often effective, low-cost treatment options for select patients with ED. These devices are available without a prescription. Vacuum limiters avoid injury to the penis by preventing extremely high negative pressures. Because no new evidence on efficacy or safety was found on review of the literature, the Panel decided not to include a detailed discussion of the data in this guideline update. Low patient acceptability limits the application or use of this therapy.

Treatment Modalities With Limited Data

Trazodone

Recommendation: The use of trazodone in the treatment of erectile dysfunction is not recommended.

[Based on review of the data and Panel consensus.]

Trazodone hydrochloride is an oral antidepressant agent with anxiolytic and sedative/hypnotic effects. The mechanism by which trazodone exerts its effect on erectile function may be related to its antagonism of alpha$_2$-adrenergic receptors. In penile vascular and corporal smooth muscle, this may relax the tissues and enhance arterial inflow, producing an erection.[36] Results of a limited number of randomized, placebo-controlled, clinical trials of trazodone evaluating its efficacy and safety in the treatment of ED have been published. Although trazodone appeared to have greater efficacy than placebo in some trials, differences in pooled results were not statistically significant.[36]

Testosterone

Recommendation: Testosterone therapy is not indicated for the treatment of erectile dysfunction in the patient with a normal serum testosterone level.

[Based on Panel consensus.]

Outcome measures used in studies to date are insufficient to evaluate testosterone's efficacy in the treatment of ED in men who have normal serum testosterone levels.[37]

Yohimbine

Recommendation: Yohimbine is not recommended for the treatment of erectile dysfunction.

[Based on review of the data and Panel consensus.]

Yohimbine is an indole alkaloid with a chemical similarity to reserpine. It frequently has been prescribed as an oral treatment for ED prior to the advent of the PDE5 inhibitors. Among its properties is a selective inhibition of alpha$_2$-adrenergic receptors. In humans, yohimbine can cause elevations of blood pressure and heart rate, increased motor activity, irritability, and tremor. [38]

The drug was grandfathered by the FDA in 1976, bypassing controlled trials to demonstrate efficacy in treating ED. Although yohimbine increases sexual motivation in rats, [39] this enhanced libido effect has not been confirmed in humans. There has only been one small study[40] published to date that used acceptable efficacy outcome measures; thus, conclusions about efficacy and safety cannot be made.

Other Herbal Therapies

Recommendation: Herbal therapies are not recommended for the treatment of erectile dysfunction.

[Based on review of the data and Panel consensus.]

Despite the fact that herbal therapies are used extensively worldwide for the treatment of ED,[41] the mechanisms of action, effectiveness, and safety of these agents have not been documented in repeated, randomized clinical trials with independent data monitoring. The literature review of herbal therapies, excluding yohimbine, found three randomized controlled

trials. In only one of these studies did results show benefits that reached statistical significance. The results of this one small randomized controlled trial[42] have suggested that Korean red ginseng may be an effective treatment for ED. Clinical efficacy of Korean red ginseng remains to be validated by larger trials. Based on this insufficiency of data, the Panel cannot make recommendations for the use of herbal therapies.

The lack of regulation for the manufacture and distribution of herbal therapies has permitted disparities in the raw materials used, in variations in manufacturing procedures, and in poor identification of the potentially active agent. Product potency and quality both within and between brands are inconsistent.[43] In addition, one study found deliberate contamination of some herbal products with therapeutic levels of PDE5 inhibitors[44] (U.S. Food and Drug Administration: www.fda.gov/bbs/topics/Answers /2003 /ANS01235.html).

Topical Therapies

Alternative routes of administration of vasoactive drugs for the treatment of ED that are less threatening than injection therapy have been explored. Agents that are approved by the FDA for other indications or other routes of administration, including alprostadil, organic nitrates, minoxidil, papaverine, and yohimbine, have been tested via topical administration to the glans penis or penile shaft. Although these therapies are not currently approved by the FDA, they may be available through compounding pharmacies. A specific literature search was not conducted on this topic due to the lack of both FDA approval and widespread application. Based upon the limited studies available and expert consensus, there does not appear to be significant efficacy beyond that observed with intraurethral administration of alprostadil.

Surgical Therapies

Penile Prosthesis Implantation

Standard: The patient considering prosthesis implantation and, when possible, his partner should be informed of the following: types of prostheses available; possibility and consequences of infection and erosion, mechanical failure, and resulting reoperation; differences from the normal flaccid and erect penis, including penile shortening; and potential reduction of the effectiveness of other therapies if the device is subsequently removed.

[Based on Panel consensus.]

Penile prostheses can be divided into two general types: malleable or noninflatable and inflatable. Noninflatable devices are also commonly referred to as semirigid rod prostheses. The Panel discussion on penile prosthetic implantation was limited to inflatable penile prostheses because recent design changes have improved mechanical reliability. Inflatable penile prostheses provide the recipient with closer to normal flaccidity and erection, but in addition to mechanical failure, they are associated with complications such as pump displacement and auto-inflation. Although design modifications have lowered the 5-year mechanical failure rate of inflatable prostheses to the range of 6% to 16% depending on the type of device, limited information concerning the failure rate beyond 5 years is available.

Infection is a devastating complication of any prosthetic surgery. Currently available inflatable prostheses have been modified in an attempt to reduce the risk of infection. One available device has an antibiotic coating consisting of rifampin and minocycline (American Medical Systems, Minnetonka, MN) and the other has a hydrophilic coating (Mentor Corporation, Santa Barbara, CA). A recently published industry-sponsored study[45] demonstrates a statistically significant reduction of infection rate using the antibiotic-coated device from

1.61% to 0.68% at 180 days. A similar study has been published evaluating the efficacy of a hydrophilic-coated device that is immersed in an antibiotic pre-operatively. At 1-year follow-up, the infection rate for non-coated prosthesis was 2.07% compared to 1.06% for the same prosthesis with hydrophilic coating.[46] Additional data are needed to confirm these initial findings.

Another design modification recently introduced by the Mentor Corporation was the addition of a lockout valve to prevent autoinflation. A study comparing the occurrence of autoinflation in 160 men implanted with the modified Mentor Alpha-1 prosthesis with that in 339 historical controls implanted with the Mentor Alpha-1 prosthesis with no lockout valve found rates of 1.3% and 11%, respectively.[47]

Noninflatable penile prostheses remain legitimate alternatives to inflatable devices with the advantages of lower cost, better mechanical reliability despite the design improvements of the inflatable devices, and ease of use by the patient. Patient education about inflation and deflation techniques is not necessary.

The preliminary literature review found that only evidence on failure rates for inflatables might have yielded changes in the outcome estimates or recommendations of the 1996 *Report.* Hence, these were the only outcomes that were reviewed and updated by the Panel. However, on a more detailed review of the relevant articles, the Panel decided to re-affirm the content of the 1996 guideline. The Panel stresses, though, that it is important for the patient to understand that prosthesis implantation likely will reduce the efficacy of subsequent therapies should they be needed.

Questions often arise concerning the safety of performing magnetic resonance imaging (MRI) in patients with a penile prosthesis. MRI may be utilized to evaluate the status of a penile

implant or may be performed for other indications in a patient who has a penile prosthesis.[48] MRI is contraindicated in patients with a ferromagnetic implant because of the risks associated with movement, dislodgement, induction of electrical current, excessive heating and/or misinterpretation artifacts. An ex-vivo MRI study of nine different types of penile prosthetics found that only the OmniPhase (Dacomed, Minneapolis, MN) device had movement/deflection in an MRI at a field strength of 1.5 Tesla. No movement/deflections were noted with the 3-piece inflatable devices, and MRI has been safely used in this patient population.[49] The OmniPhase prosthesis is no longer marketed. Similarly, the Duraphase prosthesis, previously manufactured by Endocare, is not MRI compatible. Currently in the United States, however, no manufacturer produces penile implants that have MRI contraindications.

Standard: Prosthetic surgery should not be performed in the presence of systemic, cutaneous, or urinary tract infection.

[Based on Panel consensus.]

Preoperative preparation of the implant recipient is directed primarily at reducing the risk of infection. The recipient should be free of urinary tract infection, and he should have no infections elsewhere in the body that might result in bacterial seeding during the healing phase. There should be no dermatitis, wounds, or other cutaneous lesions in the operative area. While better control of diabetes mellitus may reduce risk of infection, the literature fails to demonstrate a consistent benefit.[50,51]

Standard: Antibiotics providing Gram-negative and Gram-positive coverage should be administered preoperatively.

[Based on Panel consensus.]

Based on studies with other surgical procedures and implantable devices, broad-spectrum antibiotics providing both Gram-negative and Gram-positive coverage are administered prophylactically to promote implant survival.[52,53,54] Frequently used agents include aminoglycosides, vancomycin, cephalosporins, and fluoroquinolones. These antibiotics are administered before the incision is made and usually are continued for 24 to 48 hours postoperatively.

The operative area is shaved immediately prior to surgery. If shaving is done earlier, small cuts in the skin may become infected. After the patient is shaved, a thorough skin preparation is performed. Penile prosthesis implantation is usually performed using general, spinal, or epidural anesthesia but has been performed under local anesthesia.[55,56]

Vascular Surgery

Penile Venous Reconstructive Surgery

Recommendation: Surgeries performed with the intent to limit the venous outflow of the penis are not recommended.

[Based on review of the data and Panel consensus.]

Since the publication of the 1992 NIH Consensus Statement and subsequently the 1996 *Report,* there has been no new substantial evidence to support a routine surgical approach in the management of veno-occlusive ED. While the hemodynamics of veno-occlusive ED are recognized, it is difficult to distinguish functional abnormalities (smooth muscle dysfunction) from anatomical defects (tunical abnormality). It also is difficult to determine what percentage of ED is due to veno-occlusive ED independent of general arterial hypofunction, how to accurately diagnose this condition, how often arterial insufficiency coexists, and whether or not there exists a subset of patients with this disorder who would benefit from surgical intervention. Currently, there is no evidence from randomized controlled trials documenting a standardized

approach to diagnosis or the efficacy of treatment for veno-occlusive ED. This lack of new evidence suggests that no changes in the previous guideline statement are warranted.

Penile Arterial Reconstructive Surgery

Surgical intervention for the management of vasculogenic ED has been performed by a variety of procedures for the past 30 years. The efficacy of this surgery remains unproven and controversial, largely because the selection criteria, outcome measurements, and microsurgical techniques have not been objective or standardized. One of the goals of the present Panel was to determine whether there is any objective evidence of efficacy for arterial reconstructive surgery in a subgroup of patients that is likely to respond. The Panel assumed that the patient who is likely to benefit from arterial reconstructive surgery is an otherwise healthy man 55 years old or younger with recently acquired ED due to focal arterial occlusive disease. Therefore, a new Index Patient (Arterial Occlusive Disease Index Patient) definition was created specifically to evaluate the efficacy of the treatment of arterial occlusive disease. The reason for including the criteria of recently acquired onset and the absence of other risk factors such as smoking, diabetes, or others in this definition was to eliminate patients with either diffuse vascular disease or cavernous myopathy due to chronic ischemia.

Initially, 31 papers on penile vascular surgery were identified. After careful review, 27 papers were rejected because they failed to meet the criteria for the Arterial Occlusive Disease Index Patient. A majority of the rejected papers also were excluded for lack of objective outcome criteria. The detailed process of extracting relevant data from the remaining four papers was completed.

While the 31 reports on penile arterial surgery contain hundreds of patients, the four studies that were extracted had only 50 patients that met the criteria. Of these 50, 42 patients had an anastomosis of the inferior epigastric artery to the dorsal penile artery (dorsal artery

arterialization) and eight had an anastomosis of the inferior epigastric artery to the dorsal penile vein (dorsal vein arterialization). Satisfactory outcome, measured by objective criteria, occurred in 36% to 91% of patients.

The Panel consensus is that a patient population of 50 is too small to determine whether arterial reconstructive surgery is efficacious or not. To demonstrate that penile arterial reconstructive surgery is efficacious, a large study of hundreds of patients who meet the demographic, selection, surgical, and outcome criteria of the Arterial Occlusive Disease Index Patient is needed. Such a study should focus on men who meet the criteria listed above, who have failed medical therapy, and who are followed with objective measures of sexual function. In the absence of a control arm for a surgical study, an objective method to document the patency of the vascular anastomosis would help to confirm that a positive functional outcome is due to a physiological response. The following option applies to the Arterial Occlusive Disease Index Patient.

Option: Arterial reconstructive surgery is a treatment option only in healthy individuals with recently acquired erectile dysfunction secondary to a focal arterial occlusion and in the absence of any evidence of generalized vascular disease.

[Based on review of the data and Panel consensus.]

Future Research

Many of the future research needs outlined in the 1996 *Report* have been addressed in the past 8 years. The development of the PDE5 inhibitors has answered the requirement for an oral therapy that has broad-based usage with minimal side effects. While new and better designed studies, i.e., prospective, randomized controlled trials, have allowed fresh insight into the

treatment of ED, drawbacks of the methodologies employed have been identified. Despite these advances, however, many of the issues raised still remain controversial while other knowledge gaps have arisen.

In order to develop new and more effective agents for treatment, research is needed in the areas of pathophysiology, natural history, and epidemiology. Specifically, the Panel recognizes that data concerning the role of hypogonadism in ED are seriously lacking, as are the proportion of men with ED and the prevalence of bothersomeness in men and their partners before and after treatment. The prevalence and severity of ED in men with specific risk factors, such as those with hypertension, hyperlipidemia, diabetes, and smoking, should be identified and compared.

Although diagnostic testing was not evaluated in the guideline, after review of the published clinical trials, the Panel noted that new, clinically applicable instruments are needed to diagnose ED and to assess treatment satisfaction. In addition, a clinically applicable test of neurological function of the corpora cavernosa should be developed. The best measure of venous-occlusive dysfunction must also be determined. Since the advent of oral pharmacotherapy, there has been a shift in the evaluation paradigm for ED away from the objective (evidence-based) toward the subjective (historical) that has impeded our appreciation of the clinical impact of veno-occlusive dysfunction. Evidence-based criteria are needed in order to categorize patients to arterial or venous etiologies.

The therapeutic armamentarium has changed considerably since 1996, and the PDE5 inhibitors are enjoying widespread use. However, many questions still remain unanswered regarding these and other therapeutic modalities:

- Outcomes of oral PDE5 inhibitors should be characterized/stratified based on serum testosterone levels.

- Additional research also is needed to characterize, in greater detail, the adverse events associated with the use of ED therapies such as their duration.
- Effect of lifestyle modification on PDE5 inhibitor use should be clarified.
- The cohort of patients who should not be sexually active with or without PDE5 inhibitors should be identified.
- PDE11 is present in the anterior pituitary and the testes. While studies, to date, have demonstrated no effect on spermatogenesis when PDE5 inhibitors are administered daily for 6 months in healthy individuals, further assessment of the effect of PDE5 inhibitors that cross react with PDE11 in patients with abnormal spermatogenesis is needed.
- The applicability of PDE5 inhibitors after radical prostatectomy needs to be characterized.
- Whether vasoactive intracavernous therapy will cause improvement in spontaneous erectile function needs to be clarified.
- The role of testosterone therapy in men with sexual dysfunction with low, borderline normal, and normal testosterone levels should be better defined.
- Additional randomized controlled trials of various herbal therapies are needed.
- Additional prospective patient-partner satisfaction studies are needed using standardized questionnaires both pre- and post-penile prostheses implantation.
- The role of prophylactic antibiotics in penile prostheses implantation and the use of impregnated prostheses needs to be studied further.
- The efficacy and safety of combining pharmacotherapies and/or mechanical therapies such as oral and intrapenile vasoconstrictive therapies, PDE5 inhibitors and prostheses, or vacuum constriction and vasoconstriction devices should be explored.

- Additional research also is needed to evaluate the efficacy and safety of arterial reconstruction in the treatment of ED.
- No randomized controlled trial to date has addressed the particular efficacy of drugs in the management of veno-occlusive ED or defined those patients thought to have veno-occlusive dysfunction who would benefit from surgical application.
- Cost-effectiveness analyses of the fixed and unfixed costs involved with the various ED treatment modalities need to be undertaken.

Despite the increasing number of properly planned and executed randomized controlled clinical trials in the literature, extraction of data for comparison and meta-analysis remains a challenge. Drawbacks of the methodologies employed have been identified. The Panel now recognizes a need for standardized inclusion and exclusion criteria, as well as outcome measures to be incorporated in future study designs:

- Patients enrolled in these studies have varied in their disease severity and duration, etiology, success with other treatments, and in-office success with therapy. If outcomes are not stratified by patient characteristics, both study and guideline results are biased. A crossover design also may compensate for variation in patient characteristics. While statistically adjusting results can be a useful way to overcome patient differences, reporting results stratified by those characteristics can be more useful for later patient/physician decision making.
- Although the IIEF provides a uniform measure, not all studies use the IIEF and many of those that do report only limited and variable subsets of the IIEF. Many studies still use other measures as well. A standardized measure of patient-partner satisfaction beyond

the IIEF could be developed, for example, in the case of penile prosthesis implantation or in general an instrument to measure sexual desire.

The Panel noted that future research in penile prosthesis implantation should always express survival using Kaplan-Meier methods and include data on the numbers of patients censored.

- Data presentation that facilitates meta-analysis:

  Measures of variance (standard error, standard deviation, confidence interval) are needed to perform meta-analysis on continuous or discrete outcome measures. Change from baseline, mean change, and/or percentage change are frequently the most meaningful outcome measures particularly when patients vary with regard to baseline values. In addition, measures of variance of change and percentage of change are needed to meta-analyze change data.

  While presentation of results adjusted for patient variables compensates for patient differences, meta-analysis is possible only if adjustments are identical. Because investigators do not report details of the adjustment process, raw data should be made available.

  When previously reported study outcomes are regrouped or reanalyzed in a subsequent publication, the investigator should indicate such so that patients will not be counted more than once in a meta-analysis.

Because direct comparisons of the therapies via meta-analyses are not possible with the available data, comparative trials still are required. Trial design should use comparable doses and not use titration-to-response, which can be biased by the available doses. If data presentation

among studies is compatible, one-on-one comparisons for all agents may not be required to produce valid conclusions.

Appendix 1-A: The International Index of Erectile Dysfunction (IIEF) Validation Study (Rosen 1997)

RAPID COMMUNICATION

ELSEVIER

THE INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF): A MULTIDIMENSIONAL SCALE FOR ASSESSMENT OF ERECTILE DYSFUNCTION

RAYMOND C. ROSEN, ALAN RILEY, GORM WAGNER, IAN H. OSTERLOH, JOHN KIRKPATRICK, AND AVANISH MISHRA

ABSTRACT

Objectives. To develop a brief, reliable, self-administered measure of erectile function that is cross-culturally valid and psychometrically sound, with the sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction.

Methods. Relevant domains of sexual function across various cultures were identified via a literature search of existing questionnaires and interviews of male patients with erectile dysfunction and of their partners. An initial questionnaire was administered to patients with erectile dysfunction, with results reviewed by an international panel of experts. Following linguistic validation in 10 languages, the final 15-item questionnaire, the International Index of Erectile Function (IIEF), was examined for sensitivity, specificity, reliability (internal consistency and test-retest repeatability), and construct (concurrent, convergent, and discriminant) validity.

Results. A principal components analysis identified five factors (that is, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) with eigenvalues greater than 1.0. A high degree of internal consistency was observed for each of the five domains and for the total scale (Cronbach's alpha values of 0.73 and higher and 0.91 and higher, respectively) in the populations studied. Test-retest repeatability correlation coefficients for the five domain scores were highly significant. The IIEF demonstrated adequate construct validity, and all five domains showed a high degree of sensitivity and specificity to the effects of treatment. Significant (P values = 0.0001) changes between baseline and post-treatment scores were observed across all five domains in the treatment responder cohort, but not in the treatment nonresponder cohort.

Conclusions. The IIEF addresses the relevant domains of male sexual function (that is, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction), is psychometrically sound, and has been linguistically validated in 10 languages. This questionnaire is readily self-administered in research or clinical settings. The IIEF demonstrates the sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction. UROLOGY **49:** 822–830, 1997.

Erectile dysfunction (ED), defined by a National Institutes of Health (NIH) Consensus Development Conference as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance,[1] is estimated to affect as many as 30 million men in the United States.[2] The problem is strongly age-related, with an approximately twofold to threefold increase in the prevalence of moderate-to-severe ED between the ages of 40 and 70 years.[2] A variety of medical, psychologic, and lifestyle factors have been implicated in the etiology of ED,[2–4] which impacts negatively on self-esteem, quality of life, and interpersonal relationships.[1]

Although laboratory-based diagnostic procedures are available, it has been proposed that sexual function is best assessed in a naturalistic setting with patient self-report techniques.[5,6] For this purpose, multidimensional instruments are more

This research was supported by a grant from Pfizer Inc.

From the Center for Sex and Marital Health, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, New Jersey; Human Sexuality Unit, Harewood House, Springfield University Hospital, London, United Kingdom; Department of Medical Physiology, Panum Institute, University of Copenhagen, Copenhagen, Denmark; and Pfizer Central Research, Sandwich, United Kingdom, and Pfizer Central Research, Groton, Connecticut.

Reprint requests: Raymond C. Rosen, Ph.D., Department of Psychiatry, Robert Wood Johnson Medical School, 675 Hoes Lane, Piscataway, NJ 08854

Submitted: December 11, 1996, accepted (with revisions): February 24, 1997

0090-4295/97/$17.00
PII S0090-4295(97)00238-0

Appendix 1-A: The International Index of Erectile Dysfunction (IIEF) Validation Study (Rosen 1997)

sensitive than unidimensional scales in the evaluation of treatment outcomes, and they are more psychometrically valid.[7] Multidimensional scales also provide greater potential for use in a clinical setting. Self-report methods are preferable to patient interview techniques, particularly in multicenter, multinational clinical trials.

Existing self-report measures of male sexual function[8–11] have several limitations, including excessive length or complexity, unacceptable patient burden, an overly narrow or restrictive focus, and inadequate psychometric, cultural, or linguistic validation. None of the current measures has been demonstrated to have adequate discriminant validity or to provide sufficient sensitivity in evaluating treatment outcomes in multinational clinical trials. Additionally, factor analytic methods were not used in the development of existing measures. Despite these limitations, self-report measures provide essential data on male sexual function in both research and clinical settings.[5] A strong recommendation of the NIH Consensus Conference was to develop better and more reliable methods for assessing the symptoms of ED and relevant treatment outcomes.[1]

The objective of the present research was to develop a brief and reliable measure of erectile function that is culturally, linguistically, and psychometrically valid. State-of-the-art methods for questionnaire development were used, and a multidimensional measure was designed to provide sensitive and specific outcome assessments in clinical trials of ED. Finally, the goal was to develop a self-administered questionnaire that would be suitable for use by clinicians and researchers, one that would be minimally burdensome to patients.

METHODS

Phase 1: Item Selection

Using multiple sources, relevant domains of male sexual function were identified across various cultures. A comprehensive review of the literature was conducted, and existing questionnaire instruments were evaluated. Detailed interviews of male patients with ED (n = 37) and their partners (n = 7) were also conducted in five countries. In this phase, four dimensions of male sexual function were identified: erectile function, orgasmic function, sexual desire, and sexual satisfaction. In a phase II trial of 351 patients with ED, an initial version of the questionnaire was administered and found to have a high degree of internal consistency among items (Cronbach's alpha statistic[12] greater than 0.85) and excellent treatment sensitivity ($P < 0.01$).[13] An exploratory factor analysis was performed that indicated a robust factor structure.[13,14] The results were reviewed by an international panel of experts who made recommendations for item modification and the development of additional items.

Phase 2: Cultural and Linguistic Evaluation

Pilot testing of the instrument was conducted in 14 men with ED in the United Kingdom. All patients completed the International Index of Erectile Function (IIEF) questionnaire in less than 15 minutes and reported little or no difficulty in comprehending the items. Linguistic validation of the instrument was conducted in 10 languages (Danish, Dutch, English [American, Australian, and British], Finnish, French, German, Italian, Norwegian, Spanish, and Swedish)* in 12 countries by the MAPI Research Institute in Lyon, France. This process included forward and back translations of the items and comprehensive testing of the final item pool. International harmonization techniques were used to ensure cross-cultural equivalence of the items in the targeted languages.

Phase 3: Reliability, Construct Validity, and Treatment Responsiveness

The final 15-item questionnaire (see Appendix) was administered in a large-scale clinical trial of patients with ED (study A), a comparison group of functional, age-matched volunteers (study B), and a clinical validation study that included both patients with ED and normal volunteers (study C). The designs of the studies and subject characteristics are summarized in Table I. Each study protocol was approved by the institutional review board at the participating site. All participants in the studies gave written informed consent. Men aged 18 years or older with a clinical diagnosis of ED of broad-spectrum etiology and of at least 6 months' duration (studies A and C) or normal volunteers (studies B and C) were eligible for enrollment. Patients with penile anatomic defects, uncontrolled major medical illnesses or psychologic disorders, or known drug or alcohol dependence were excluded from the studies.

Study A. This study consisted of a 2 to 4-week run-in phase, followed by a 12-week, double-blind, placebo-controlled phase in which 111 patients with ED of broad-spectrum etiology were randomized to receive either placebo or 25 mg (one capsule) of sildenafil (VIAGRA; Pfizer Inc.). Sildenafil is an oral medication that is being evaluated for the treatment of ED.[15,16] The placebo or sildenafil dose could be increased to 50 mg (two capsules) and then to 100 mg (four capsules) if a patient's response was suboptimal. The IIEF was self-administered at the screening visit (week −4 or −2), at the end of the run-in phase (week 0), and at the end of 2, 4, 8, and 12 weeks of double-blind treatment. A global efficacy question ("Did the treatment improve your erections?") was asked at the end of the double-blind treatment phase. The sensitivity, specificity, and reliability (internal consistency and test-retest repeatability) of the 15-item questionnaire were determined as follows. Each patient was designated as a "responder" or "nonresponder," based on his response to the end-of-treatment global efficacy question. Within each cohort, the mean and median baseline-to-end point changes in response values for each question were calculated. The sensitivity of the IIEF was assessed by evaluating the clinical relevance and statistical significance of the changes in the responder cohort. Specificity was assessed in the same manner in the nonresponder cohort. Internal consistency was evaluated by calculating Cronbach's alpha statistic on the item domains and the total scale.[12]

Study B. This study assessed the response to the IIEF questionnaire in 109 male volunteers (controls) without any history of male ED. These volunteers were age-matched to the patients randomized in study A (Table I). The IIEF was self-administered, with the results in these controls compared with those obtained in men with ED in study A using be-

** Additional validation studies of other languages (for example, Arabic, Chinese, Mandarin, and Portuguese, among others) in Asia and Latin America are ongoing.*

Appendix 1-A: The International Index of Erectile Dysfunction (IIEF) Validation Study (Rosen 1997)

TABLE I. ***Study designs and baseline characteristics of individuals enrolled in validation studies***

Study Design	Study A (Patients with ED)	Study B (Controls)	Study C	
			Patients with ED	Controls
Treatments	Sildenafil (25, 50, or 100 mg) or placebo	None	None	
Duration of study	12 weeks	1 day	4 weeks	
Timing of IIEF self-administration	Week −4 or −2, 0, 2, 4, 8, and 12	Day 1	Week 0 and 4	
Other relevant assessments	Global efficacy question: final visit		Clinical interview: Week 0 and 4 Locke-Wallace Scale: Week 0 Marlowe-Crowne Scale: Week 0	
Patient characteristics				
n	111	109	37	21
Mean age, yr (range)	56 (29–89)	55 (29–76)	53 (29–71)	58 (37–76)
Mean duration of ED, yr (range)	4.61 (1–37)	—	5.9 (1–18)	—
Primary etiology*				
Organic	21%	—	14%	—
Psychogenic	40%	—	49%	—
Mixed	37%	—	38%	—
Unknown	3%	—	0%	—

KEY: ED = erectile dysfunction; IIEF = International Index of Erectile Function.
** Percentages do not total 100 due to rounding.*

tween-groups discriminant analysis (analysis of covariance controlling for age) and post hoc comparison of group differences on individual items.

Study C. This 4-week study evaluated the construct validity and test-retest repeatability of the IIEF in 37 patients with male ED and in 21 age-matched controls (Table I). The IIEF was self-administered at week 0 and week 4. In this study, blinded clinical interviews of patients were conducted at week 0 to evaluate the convergent validity of the measure (that is, concordance with an independent method of assessment). In addition, patients completed measures of marital satisfaction (Locke-Wallace scale[17]) and social desirability (Marlowe-Crowne scale[18]) to assess divergent validity (that is, separateness from overlapping or related constructs) at week 0. Test-retest reliability of the total and individual item scores of the IIEF were assessed by calculating the Pearson product-moment correlation coefficient[19] for each group (patients and controls). Internal consistency was evaluated using the Kuder-Richardson formula. Discriminant validity was assessed using repeated-measures analysis of variance, with subject group as the between-groups variable, time (week 0 and week 4) as the repeated-measures factor, and study measure as the outcome variable.

RESULTS

Factor Analysis and Domain Scoring

A principal components analysis (with varimax rotation) was performed to investigate the factor structure of the final 15-item questionnaire (see Appendix). Five factors with eigenvalues† greater than 1.0 were identified (Table II). Final item selection for each factor was based on a combination of statistical and clinical considerations.[20] Based on results of the confirmatory factor analysis, together with clinical interviews and expert panel consultation, the responses to individual items of the questionnaire were assigned to five separate domains of sexual function: (1) erectile function, (2) orgasmic function, (3) sexual desire, (4) intercourse satisfaction, and (5) overall satisfaction. Domain scores were computed by summing the scores for individual items in each domain. The system of domain scoring and resulting interdomain correlations are presented in Table III.

Scale Reliability

Two separate aspects of scale reliability were evaluated, namely, internal consistency and test-retest repeatability. Internal consistency (Cronbach's alpha) was computed separately for the five domains and for all items combined in each of the three test samples. Responses in the erectile and orgasmic function domains were highly consistent, with alpha values greater than 0.90 (Table IV). A satisfactory degree of consistency also was observed for items in the other domains (alpha values greater than 0.70) and for the total scale (alpha values greater than 0.90) in each of the test samples.

Test-retest repeatability was assessed in study C by computing correlations between the domain scores and total scale scores at baseline and week

† *Eigenvalue is a statistical measure of the relative explanatory power of individual factors in a factor analysis.*

TABLE II. ***Principal components analysis with varimax rotation of 15 questions of International Index of Erectile Function: factor loadings****

Item	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
1. Erection frequency	**0.77**	0.03	0.31	0.17	−0.05
2. Erection firmness	**0.92**	0.12	0.20	0.08	0.04
3. Penetration ability	**0.89**	0.16	0.15	0.06	0.14
4. Maintenance frequency	**0.82**	0.26	0.13	−0.02	0.22
5. Maintenance ability	**0.68**	0.39	0.09	0.07	0.41
6. Intercourse frequency	0.10	−0.02	0.11	0.34	**0.79**
7. Intercourse satisfaction	0.61	0.28	0.31	−0.13	**0.48**
8. Intercourse enjoyment	0.53	0.39	0.18	0.01	**0.53**
9. Ejaculation frequency	0.26	0.20	**0.89**	0.10	0.13
10. Orgasm frequency	0.23	0.25	**0.87**	0.18	0.12
11. Desire frequency	0.06	−0.01	0.15	**0.88**	0.16
12. Desire level	0.04	0.26	0.07	**0.87**	0.08
13. Overall satisfaction	0.29	**0.76**	0.28	0.15	−0.01
14. Relationship satisfaction	0.18	**0.83**	0.21	0.14	0.13
15. Erection confidence	**0.65**	0.53	0.01	0.01	0.07
Eigenvalue	4.72	2.22	2.03	1.81	1.47

* *Items with the highest loadings within each factor are boldfaced.*

4 visits. As shown in Table IV, test-retest repeatability was relatively high for the erectile function ($r = 0.84$) and intercourse satisfaction ($r = 0.81$) domains, as well as for the total scale scores ($r = 0.82$). Moderately high correlations were observed for the other domains (r values of 0.64 to 0.77).

Discriminant Validity

Discriminant validity, or the ability of the IIEF scale to discriminate reliably between clinical and nonclinical populations, was assessed by comparing the responses from patients with ED with those from controls in two studies. As shown in Table V, highly significant differences were observed between the the patients with ED and age-matched controls for most domains. Differences between domain scores between these two groups were greatest for the erectile function domain ($P \leq 0.0001$), followed by intercourse satisfaction ($P \leq 0.001$) and overall satisfaction ($P \leq 0.001$). The least degree of difference between patients and controls was seen for the sexual desire domain, with results failing to reach statistical significance in study C. This result is not surprising because all patients were recruited for a clinical trial of ED and were excluded for concomitant sexual disorders, such as hypoactive sexual desire.

Convergent and Divergent Validity

To demonstrate construct validity of a new measure, it is important to show that scale scores are positively correlated with independent measures of the same or similar domains (convergent validity). Conversely, there should be minimal association with measures that do not directly assess the domains in question (divergent validity). In study C, domain scores were compared with blinded, independent clinician ratings of sexual functioning and with scales that measure marital adjustment (Locke-Wallace) and social desirability (Marlowe-Crowne). Significant positive correlations were observed between independent clinician ratings and subscale scores for all five domains (Table VI). In contrast, none of the correlations between domain scores and measures of marital adjustment or social desirability reached statistical significance.

Sensitivity and Specificity

To evaluate the sensitivity of the IIEF, a comparison was made between mean pretreatment and post-treatment domain scores of patients who were self-rated as treatment responders in study A. Specificity was assessed by comparing the pretreatment and post-treatment domain scores in patients rated as nonresponders in the same study. Patients were defined as responders or nonresponders based on their response to the end-of-treatment global efficacy question. All five domains of the IIEF demonstrated a high degree of sensitivity and specificity to the effects of treatment (Table VII). Although the magnitude of change was greatest for the erectile function domain, significant changes were observed across all five domains in the treatment responder group. The lowest magnitude of change was noted for the sexual desire domain. In contrast, none of the comparisons in the treatment nonresponder group approached significance (P values of 0.11 to 0.79).

Appendix 1-A: The International Index of Erectile Dysfunction (IIEF) Validation Study (Rosen 1997)

TABLE III. *IIEF domain scoring and intercorrelations*

Domain	Items	Domain Scoring: Score Range	Minimum Score	Maximum Score
EF	1, 2, 3, 4, 5, 15	0 (or 1)–5	1	30
OF	9, 10	0–5	0	10
SD	11, 12	1–5	2	10
IS	6, 7, 8	0–5	0	15
OS	13, 14	1–5	2	10

	Domain Intercorrelations: EF	OF	SD	IS	OS
EF	1.00				
OF	0.55	1.00			
SD	0.30	0.39	1.00		
IS	0.76	0.47	0.35	1.00	
OS	0.60	0.53	0.37	0.53	1.00

Key: EF = erectile function; IIEF = International Index of Erectile Function; IS = intercourse satisfaction; OF = orgasmic function; OS = overall satisfaction; SD = sexual desire.

COMMENT

A 15-item, self-administered questionnaire scale was developed for the assessment of erectile function. This instrument (the IIEF) was developed in several stages, including initial pretesting with selected patient groups and expert panel consultants, followed by an intensive linguistic validation process. Based on a principal components analysis with varimax rotation, five factors or response domains were identified: (1) erectile function, (2) orgasmic function, (3) sexual desire, (4) intercourse satisfaction, and (5) overall satisfaction. The highest degree of positive correlation was between erectile function and intercourse satisfaction (r = 0.76), with two items (items 7 and 8) showing positive loadings on both factors. This is not surprising because a primary outcome of ED for most patients is the inability to achieve satisfactory sexual intercourse.[1]

Psychometric validation of the final instrument was addressed in three major areas: (1) test reliability, (2) construct validity, and (3) treatment responsiveness. Adequate performance in each of these areas should be demonstrated before a new scale is accepted for general research or clinical use.[21–23] For the IIEF, analyses were performed in each of these areas in two separate samples of patients with ED and age-matched controls. Overall, the IIEF was shown to have strong internal consistency, measured in terms of both the total scale and individual domain scores, and adequate test-retest repeatability. Although some variation in the degree of internal consistency was noted between samples, all of the values obtained were greater than 0.70 and more than half were greater than 0.90. Test-retest repeatability correlation coefficients ranged from 0.64 to 0.84, and all were highly significant.

Construct validity (that is, whether the instrument actually measures what it was designed to assess) is normally accomplished by experimental testing of a priori questions or hypotheses, such as: (1) Will the test reliably differentiate between clinical patients and age-matched controls? (discriminant validity); (2) Can a positive association be shown with alternative measures of the same construct or domains? (convergent validity); and (3) Are the results influenced by related, but conceptually independent, variables? (divergent validity). In the present study, adequate construct validity was established in each of these three areas. Discriminant validity was demonstrated by a comparison of baseline scores between patients and controls. In the larger sample (studies A and B), between-group differences were highly significant (P values ≤ 0.01) for all five domains. In the smaller sample (study C), differences between groups were significant (P values ≤ 0.01) for all domains, with the exception of sexual desire (P = 0.72). In this study, patients and controls were closely matched on sexual desire, perhaps reflecting a high level of sexual motivation in patients seeking treatment in a clinical trial of ED. Tests of convergent and divergent validity were similarly confirmatory. First, a significant positive association was shown with independent clinician ratings for each of the major response domains. As expected, the highest correlation was observed for the domain of erectile function (r = 0.73). This association might have been even higher, except for the fact that clinician interview ratings took

Appendix 1-A: The International Index of Erectile Dysfunction (IIEF) Validation Study (Rosen 1997)

TABLE IV. *IIEF domain characteristics: reliability*

	Internal Consistency*			Test-Retest Repeatability†
	Study A	Study B	Study C	Study C
All items	0.91	0.96	0.91	0.82
Erectile function	0.92	0.96	0.93	0.84
Orgasmic function	0.92	0.99	0.93	0.64
Sexual desire	0.77	0.82	0.91	0.71
Intercourse satisfaction	0.73	0.87	0.88	0.81
Overall satisfaction	0.74	0.87	0.86	0.77

Key: IIEF = International Index of Erectile Function.
** Cronbach's alpha.*
† Pearson product-moment correlation coefficient.

TABLE V. *IIEF domain characteristics: discriminant validity*

	Study A and Study B			Study C		
	Patients	Controls		Patients	Controls	
Domain	Mean ± SD	Mean ± SD	*P* Value*	Mean ± SD	Mean ± SD	*P* Value*
Erectile function	10.7 ± 6.5	25.8 ± 7.6	≤0.0001	13.5 ± 8.1	26.9 ± 5.3	≤0.0001
Orgasmic function	5.3 ± 3.2	8.8 ± 2.9	≤0.001	7.3 ± 3.5	9.5 ± 2.2	≤0.01
Sexual desire	6.3 ± 1.9	7.0 ± 1.8	≤0.01	7.2 ± 1.5	7.0 ± 1.9	0.72
Intercourse satisfaction	5.5 ± 3.0	10.6 ± 3.9	≤0.001	6.0 ± 4.5	10.8 ± 4.8	≤0.0003
Overall satisfaction	4.4 ± 2.3	8.6 ± 1.7	≤0.001	5.5 ± 2.4	9.0 ± 1.6	≤0.0001

Key: IIEF = International Index of Erectile Function.
** P values assessed using repeat-measures, between-groups analysis of variance method.*

TABLE VI. *IIEF domain characteristics: convergent and divergent validity*

	Validation Measure (Study C)					
	Clinical Interview		Marital Adjustment (Locke-Wallace)		Social Desirability (Marlowe-Crowne)	
Domain	Pearson *r*	*P* Value	Pearson *r*	*P* Value	Pearson *r*	*P* Value
Erectile function	0.75	<0.0001	−0.08	0.62	−0.07	0.63
Orgasmic function	0.51	<0.001	−0.21	0.23	−0.13	0.45
Sexual desire	0.61	<0.0001	0.16	0.36	0.24	0.15
Intercourse satisfaction	0.45	<0.005	−0.05	0.89	−0.02	0.78
Overall satisfaction	0.63	<0.001	0.31	0.07	0.17	0.31

Key: IIEF = International Index of Erectile Function.

into account both past history and current sexual performance ratings, whereas the questionnaire assessed only the latter. Second, measures of social desirability and marital adjustment were not significantly correlated with any IIEF domain scores. This suggests that IIEF scores are highly independent of social desirability and marital adjustment influences.

A final area of test validation concerns treatment responsiveness, or the sensitivity and specificity of the instrument, which was evaluated by comparing the change between baseline and end point scores in treatment responders and nonresponders (study A). A high degree of sensitivity and specificity was demonstrated for each of the domains of the IIEF. For the responder group, highly significant changes between baseline and end point scores were observed in each domain. The mean change in scores was highest for the erectile function domain and lowest for the sexual desire domain. These results are not surprising because the study drug, sildenafil, is an agent with a peripheral site of action and proerectile effects.[15,16] Treatment response specificity was demonstrated by the relative lack of change between baseline and end point scores in the nonresponder group. Taken together, these findings indicate that the IIEF is a highly sensitive and specific instrument for de-

TABLE VII. *IIEF domain characteristics: sensitivity and specificity (study A)*

Domain	n	Mean Change*	SEM	*t* Statistic	*P* Value
Treatment responders					
Erectile function	50	12.80	1.2	10.6	≤0.0001
Orgasmic function	50	3.44	0.5	6.4	≤0.0001
Sexual desire	49	1.12	0.3	4.5	≤0.0001
Intercourse satisfaction	48	4.63	0.6	8.4	≤0.0001
Overall satisfaction	49	3.47	0.4	8.4	≤0.0001
Treatment nonresponders					
Erectile function	42	0.88	0.8	1.07	0.67
Orgasmic function	42	0.70	0.6	1.25	0.36
Sexual desire	42	−0.52	0.3	−1.55	0.32
Intercourse satisfaction	42	0.10	0.4	0.27	0.79
Overall satisfaction	42	0.57	0.3	1.65	0.11

KEY: *IIEF = International Index of Erectile Function.*
* *Mean difference between pretreatment score and post-treatment scores.*

tecting changes in erectile function in response to treatment.

Other advantages of this new scale are worth noting. First, all of the major aspects of the NIH definition are addressed by individual items in the erectile function domain. A patient's ability to achieve or maintain an erection sufficient for intercourse are addressed separately (items 3 and 4, respectively), as is the degree of satisfaction achieved (item 7). The IIEF also addresses the ability to achieve erections independent of intercourse (items 1 and 2). Furthermore, the psychologic dimension of erectile confidence is assessed (item 15), which has been shown to be related to treatment outcome in other contexts.[24] Finally, the brevity and ease of comprehension of the measure provide important practical advantages. For example, the IIEF may be ideally suited for use in studies assessing the prevalence of ED in different countries.

Limitations of the instrument are the sole focus on current sexual functioning, the superficial assessment of nonerectile components of sexual response, and the limited assessment of the partner relationship. Although the IIEF provides a broad measure of sexual function across five domains, it should be viewed as an adjunct to, rather than a substitute for, a detailed sexual history. The IIEF was designed as an assessment measure for ED, and it is not intended for use as a primary measure of premature ejaculation or hypoactive sexual desire. Finally, the IIEF has not been evaluated in long-term follow-up studies or in the patient subpopulations that were excluded from the clinical trials described, such as those with anatomic deformities (for example, Peyronie's disease). Thus, further studies would be needed to determine whether this instrument is valid in these instances.

CONCLUSIONS

The IIEF, a 15-item questionnaire, has been developed and validated as a brief and reliable self-administered scale for assessing erectile function. This instrument is psychometrically sound and easy to administer in research and clinical settings. The IIEF currently is available in 10 languages for use in multinational clinical trials, and it demonstrates adequate sensitivity and specificity for detecting treatment-related changes in erectile function in patients with ED.

ACKNOWLEDGMENT. To Drs. Pierre Wicker, Frances Quirk, Mike Hodges, Murray Maytom, David Cox, and Fidela Moreno, and to Mike Smith, Andrew Lee, Michelle Cuddigan, Jennifer Gill, and Claire Hargreaves for their valuable support and contributions, and to Dr. Patricia Leinen for her assistance in the preparation of the manuscript.

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Appendix 1-A: The International Index of Erectile Dysfunction (IIEF) Validation Study (Rosen 1997)

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APPENDIX

Individual items of International Index of Erectile Function Questionnaire and response options (US version)

Question*	Response Options
Q1: How often were you able to get an erection during sexual activity?	0 = No sexual activity 1 = Almost never/never
Q2: When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0 = Did not attempt intercourse 1 = Almost never/never
Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q5: During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q6: How many times have you attempted sexual intercourse?	0 = No attempts 1 = One to two attempts 2 = Three to four attempts 3 = Five to six attempts 4 = Seven to ten attempts 5 = Eleven+ attempts
Q7: When you attempted sexual intercourse, how often was it satisfactory for you?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always

Appendix 1-A: The International Index of Erectile Dysfunction (IIEF) Validation Study (Rosen 1997)

Q8: How much have you enjoyed sexual intercourse?	0 = No intercourse 1 = No enjoyment 2 = Not very enjoyable 3 = Fairly enjoyable 4 = Highly enjoyable 5 = Very highly enjoyable
Q9: When you had sexual stimulation or intercourse, how often did you ejaculate? **Q10**: When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q11: How often have you felt sexual desire?	1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q12: How would you rate your level of sexual desire?	1 = Very low/none at all 2 = Low 3 = Moderate 4 = High 5 = Very high
Q13: How satisfied have you been with your overall sex life? **Q14**: How satisfied have you been with your sexual relationship with your partner?	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
Q15: How do you rate your confidence that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

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

1-B Commonly Used Nitrates/Nitrites

Commonly Used Nitrates/Nitrites

Generic Name	Trade Name*
Amyl nitrite	Various
Erythrityl tetranitrate	Cardilate
Isosorbide dinitrate	Dilatrate & Dilatrate SR Iso-Bid Iso-D Isotrate Isordil Onset-5 Sorbide-10 Sorbitrate & Sorbitrate SR
Isosorbide mononitrate	Imdur Ismo Monoket
Nitroglycerine	Deponit (transdermal) Minitran Transdermal System Nitrek Nitro-Bid Nitrocin (sustained release) Nitrocine Nitrocot Nitroderm (transdermal) Nitrodisc (transdermal) Nitro-Dur Nitrogard Nitroglyn Nitrolingual Spray Nitrol Ointment (Appli-Kit) Nitrong Nitropar Nitrostat Nitro-Time Transderm-Nitro Transdermal NTG Tridil
Pentaerythritol tetranitrate	Cartrax Duotrate Miltrate & Miltrate 10 Papavatral Pennate Penta Cap #1 Pentrate Pentritol Peritrate Tetrate-30
Sodium nitroprusside	Nitropress

*This list is not all inclusive.

