

Review Articles

Erectile Dysfunction: Clinical Guidelines (2)

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ABSTRACT

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

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

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

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

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

Treatment of Erectile Dysfunction

The first step in the management of a patient with ED is to facilitate the patient's and his partner's (if available) understanding of the condition, the results of the diagnostic assessment and to identify the patient's and his partner's needs, expectations, priorities, and preferences. The identification and recognition of associated medical and psychological factors in the individual patient must be emphasized. Clearly, the selection of therapy is strongly influenced by personal, cul-

tural, ethnic, religious, and economic (affordability) factors. The presentation and stratification of therapies may therefore vary from individual to individual, culture-to-culture, religious persuasion to religious persuasion, and from one economic tier to another. Sensitivity to these factors is important in determining the long-term success of any selected therapeutic course. Prior to direct intervention, good medical practice recognizes the value of altering modifiable risk factors, and this step alone may be of some value in selected patients.

The patient and his partner (if available) should

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be informed of all of the available and acceptable treatment options applicable to his clinical condition and the related benefits, risks, and costs of each modality. The development of ED can significantly affect the quality of life, but it is not a life-threatening disease. Consequently, it is reasonable to discuss the benefits, risks, and costs of the available treatment strategies with the patient and have the patient actively participate in the choice of therapy (shared decision making). An important issue prior to the institution of any therapy and the subsequent resumption of sexual activity is the overall cardiovascular condition of the patient. Is this patient able to resume the exercise of sexual activity? If not, priority cardiovascular assessment and intervention may be appropriate. The partner's sexual function, if possible, should be considered prior to initiating therapy. The vast majority of patients will need to consider direct treatment options for ED. Only those pharmacological treatments that have been thoroughly tested in randomized clinical trials, with subsequent publication of results in peer-reviewed literature, should be considered for general use. Long-term follow-up of all treatment options must be performed to demonstrate durability and continuous efficacy and safety as well as patient and partner acceptability. Additionally, new treatment options that enter the arena not only will need to meet the above efficacy and safety criteria, but also should be compared to available therapies for cost-effectiveness. The treatment selected by a patient, will be influenced not only by issues such as efficacy and safety, but also by the patient's cultural, religious, and economic background. Additionally, such factors as 1. ease of administration, 2. invasiveness, 3. reversibility, 4. cost and 5. the mechanism of action (peripheral vs. central, inducer vs. enhancer), and 6. availability, may critically influence the individual patient's selection of therapy. As previously mentioned, affordability is a prime factor in influencing patient acceptance and utilization of a specific therapy for ED.⁽¹⁾

Any drugs that might be contributing to ED should be discontinued. In the case of antihypertensive agents, other drugs with a different mechanism of action should be considered.

Five basic types of therapy reported in the literature are potential options for treating organic erectile dysfunction:

1. Oral drug therapy,
2. Vacuum constriction device therapy,

3. Intracavernous vasoactive drug injection and topical therapy,
4. Penile prosthesis implantation,
5. Venous and arterial surgery.

Oral Drug Therapy

There is a wide range of treatments for erectile dysfunction. If organic problems seem to be dominant, the first step is to identify the medical risk factors and correct them, if possible. Plasma glucose must be regulated in men with poorly controlled diabetes. Medications for hypertension must be optimized. Cessation of tobacco abuse is important. Hyperlipidemia must be treated aggressively. Intake of alcohol and illicit drugs should be discontinued. The central issue in understanding the patient with ED is not only understanding ED as a medical condition, but also understanding patient behavior and attitudes. It is important to remember that there is a broader context for treating ED. Physicians need to avoid over-focusing on the genital response and consider the psychosocial consequences and obstacles of ED.

A wide range of oral treatments have been used in men with erectile dysfunction, including sildenafil, apomorphine, oral phentolamine, isoxsuprine, trazodone, and yohimbine.⁽²⁾ New drugs include several new phosphodiesterase type 5 inhibitors and agents with other mechanisms of action.^(3,4)

Sildenafil (Viagra) is now the first choice for treating erectile dysfunction and has helped men with a wide range of conditions.

Pharmacology: Sildenafil facilitates erections associated with sexual stimulation. It will not act if the man is not sufficiently mentally aroused or his peripheral autonomic nerves are absent (e.g. radical prostatectomy). It acts by inhibiting phosphodiesterase isoenzyme 5 (PDE-5), thus prolonging cyclic guanosine monophosphate (cGMP) activity in erectile tissue, and enhancing the vasodilating actions of nitric oxide, which is released in response to sexual stimulation. Sildenafil is rapidly absorbed from the gut peaking 30 to 120 minutes after an oral dose. At peak effect, it lowers mean systolic supine blood pressure (8 mmHg) in healthy volunteers. The drug is eliminated by liver metabolism (CYP3A4) with a half-life of 3 to 5 hours. Half-life is prolonged in patients over 65 years and in patients with renal or hepatic impairment.

Adverse effects: The most common adverse

effects, as absolute risk increase over placebo, were headache at 14%, flushing at 17%, dyspepsia at 4%, rhinitis at 4%, and visual disturbance at 1%. None of the studies assessed the effects of long-term sildenafil use. Such studies are needed, particularly in patients with a history of retinal and cardiovascular disorders. Serious rare side effects include priapism, severe hypotension, heart attack, stroke and death.

Contraindications: Sildenafil is contraindicated in patients taking or at risk of requiring nitrates in any form, patients, in whom sexual activity is inadvisable because of their cardiovascular status (e.g. myocardial infarction or cerebrovascular accident within 6 months, heart failure, unstable angina, hypotension, uncontrolled hypertension, aortic stenosis, etc.), and patients with retinitis pigmentosa, anatomical deformities of the penis, conditions predisposing to priapism (e.g. sickle cell anemia, multiple myeloma), or receiving multiple antihypertensive drugs.

Precautions: There is no safety information on patients excluded from the trials (e.g. patients with alcoholism, active peptic ulcer, proliferative diabetic retinopathy, etc.). Inhibitors of CYP3A4 such as erythromycin, ketoconazole, grapefruit juice, and others would be expected to increase the magnitude and duration of response to sildenafil.

A relatively small number of deaths have been reported in association with sildenafil usage, but the specific relationship to the drug is uncertain. This underscores the need for cardiovascular assessment prior to the treatment of ED and regular follow-up. A small percentage of these deaths occurred with concomitant use of nitrates and are presumed to be due to severe hypotension that may ensue, following this combination.⁽⁵⁾ In addition, patients with possible or active coronary heart disease or other significant cardiovascular diseases such as aortic stenosis should undergo cardiac evaluation and management prior to considering sildenafil usage.⁽⁵⁾ To date, there is no physiological reason to indicate sildenafil exerts a direct effect on the myocardium. In general, sildenafil when prescribed appropriately has demonstrated broad efficacy and an acceptable safety profile.

Dosage and cost: The drug should be taken on an empty stomach 1 hour before intended sexual activity and no more than once daily. Dose range is 25 to 100 mg. As with most drugs start with the lowest dose, 25 mg, and increase only if nec-

essary. Since the cost of each tablet is similar (\$10 to \$12), prescribing the higher dose tablets and dividing them can substantially reduce the cost.

Although sildenafil is currently the most widely used approach and has an excellent overall success rate (60% to 85%), a substantial portion of patients continue to have an inadequate response.⁽⁶⁾ Martinez-Jabaloyas et al⁽⁷⁾ recently evaluated risk factors for treatment failure with sildenafil and noted that diabetes, non-nerve sparing radical prostatectomy and high baseline disease severity, as reflected by Sexual Health Inventory for Men scores, were all predictors of a lower success rate for sildenafil therapy. Oral sildenafil is a moderately effective treatment for erectile dysfunction in men with diabetes. The response rate was lower and cardiovascular events were higher than previously reported in nondiabetic patients.⁽⁸⁾

Currently, two other phosphodiesterase-5 inhibitors are available: tadalafil and vardenafil. Early data indicate that there are differences among sildenafil, tadalafil, and vardenafil in pharmacokinetic properties, efficacy, potency, half-life, and adverse effect profiles.⁽⁹⁾

Tadalafil (Cialis) is the latest of the three to be approved by the Food and Drug Administration (FDA).⁽¹⁰⁾ This medication is a highly selective, potent, reversible inhibitor of phosphodiesterase type 5 (PDE5).^(11, 12) Tadalafil differs from the other two products in that it stays in the body for a longer time, which is an advantage for men with ED.⁽¹⁰⁾ Compared with sildenafil, tadalafil has an extended terminal half life, 17.5 hours⁽¹³⁾ versus 3.7 hours,⁽¹⁴⁾ suggesting a lengthened period of responsiveness compared with sildenafil. The same cautions apply for these agents as they do for sildenafil. Common side effects of this agent are similar to those of sildenafil and include flushing, dizziness, nasal congestion, upset stomach, and vision abnormalities. Success rates have been significant in men suffering from erectile dysfunction of varying severity and from many causes. One study suggested, however, that, as with sildenafil, it may interact with nitrates.

An assessment of the safety and effectiveness of tadalafil in patients older than 65 years of age versus younger patients indicated that it was safe and effective in both groups, with improved erections in up to 81% of men in the combined population.⁽¹⁵⁾

Simultaneous administration of tadalafil and

the alpha-adrenergic antagonists, except for 0.4 mg once-daily tamsulosin, is contraindicated. In a study of drug-drug interactions, 20 mg of tadalafil was administered to healthy subjects taking 8 mg of doxazosin mesylate daily. A significant increase in the blood pressure-lowering effect of doxazosin was observed.⁽¹⁶⁾

The recommended starting dose for most patients is 10 mg, to be taken before anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, depending on the agent's efficacy and patient's tolerability. For most patients, the maximum dosing frequency is once daily. Unlike other available treatments, tadalafil may enable a patient to take a pill on a Wednesday evening and have intercourse with his partner on a Thursday night or a Friday morning. This extended period of responsiveness afforded by tadalafil may lead to a new treatment paradigm for men with ED.^(16,17)

Vardenafil (Levitra), another novel selective phosphodiesterase type 5 inhibitor, has also been shown to be safe and effective for the treatment of erectile dysfunction in a 12-week, multicenter, randomized, double-blind, placebo-controlled trial that included 601 men with mild to severe erectile dysfunction.⁽¹⁸⁾ For most patients, the recommended starting dose of vardenafil is 10 mg, taken orally approximately 60 minutes before sexual activity. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and side effects. The maximum recommended dosing frequency is once per day. Vardenafil can be taken with or without food. Sexual stimulation is required for response to treatment.

Studies evaluating vardenafil have determined it to be safe and effective at doses of 5 mg to 40 mg, including subjects with diabetes mellitus and subjects who have undergone radical prostatectomy. Vardenafil has a pharmacokinetic profile similar to that of sildenafil, with an onset of action and half-life of 0.7 hours and 5 hours, respectively. Vardenafil, like other PDE5 inhibitors, is metabolized hepatically via the cytochrome P-450 system. The drug appears to be well tolerated. In clinical trials, headache, dyspepsia, and flushing were the most common adverse effects reported by subjects taking vardenafil. No adverse hemodynamic or visual effects have been reported during clinical trials of vardenafil; however, further investigation, including post-marketing surveillance, will be required to determine whether var-

denafil will cause these adverse effects. In vivo, vardenafil has been found not to interact with nifedipine, nitroglycerin, digoxin, magnesium hydroxide/aluminum oxide, or ranitidine. Only a small, clinically insignificant interaction was observed when vardenafil was given concurrently with cimetidine.

Further research and clinical experience with the newer PDE-5 inhibitors (vardenafil and tadalafil) will be needed before their roles in the treatment of ED can be determined.

Patients taking nitrate drugs (used to treat chest pain) and those taking alpha-blockers (used to treat high blood pressure and benign prostatic hyperplasia) should not take selective enzyme inhibitors.

Common side effects of selective enzyme inhibitors include headache, reddening of the face and neck (flushing), indigestion, and nasal congestion. Tadalafil may cause muscle aches and back pain, which usually resolve on their own within 48 hours.

Oral Phentolamine. Phentolamine is an agent that has been used in injections for achieving erection. Phentolamine is an α -adrenergic blocking agent with both central and peripheral activity. An oral form of phentolamine (Vasomax) has been developed that may be of some benefit for men with mild impotence. The drug is not as effective as sildenafil and it has more side effects. However, Vasomax works faster and it does not interact with nitrates. Studies suggest that it produces erections within 20 to 40 minutes in 40% to 50% of men with mild to moderate erectile dysfunction. Side effects include nasal congestion, headache, light-headedness, low blood pressure, tachycardia and nausea. These events are minimal at the usual dose of 40 mg.⁽¹⁾

Apomorphine (Spontane, Uprima), which is taken as a tablet under the tongue, causes a sexual signal in the brain to trigger an erection, although it is not an aphrodisiac. Apomorphine is a dopaminergic agonist acting at the central nervous system level. It was initially administered subcutaneously. However intolerable adverse events prompted the development of a sublingual pill.

Apomorphine has shown efficacy in placebo-controlled fixed and dose escalation studies.⁽¹⁹⁾ In responders, erection usually begins within 20 minutes. Its principal adverse effect is nausea, which is usually minimal at lower dosages (2 mg and 4 mg). Other adverse effects are dizziness,

sweating, somnolence and yawning as well as rarely, syncope.⁽¹⁾

Studies report improved erectile function in 40% to 60% of men, with the better results occurring at the higher doses. High doses, however, also cause severe side effects, including nausea (in between 15% to a third of patients), yawning, fatigue, dizziness, sweating, excitability, and aggression. Apomorphine appears to be safe for men with diabetes or stable heart disease, and is well tolerated by men with high blood pressure.

Opioid Antagonists. Opioid antagonists, such as naltrexone (ReVia), are used to help maintain abstinence in alcoholism. Naltrexone may be helpful for erectile dysfunction in men with inhibited sexual desire. The most common side effect of naltrexone is nausea, which is usually mild and temporary. High doses can cause liver damage. The drug should not be administered to anyone who has used narcotics within a week to 10 days.

Angiotensin-receptor blockers. Recent drugs known as angiotensin-receptor blockers (ARBs), also known as angiotensin II receptor antagonists are being used to lower blood pressure in men with hypertension. In one study, after 12 weeks of treatment with an ARB called losartan (Cozaar), 88% of hypertensive males with sexual dysfunction reported improvement in at least one area of sexuality. The number of men reporting impotence declined from 75.3% to 11.8%. Other ARBs include candesartan (Atacand), telmisartan (Micardis), and valsartan (Diovan).

Trazadone, a widely used antidepressant, has been associated with the development of priapism.

Trazodone, a serotonin antagonist and reuptake inhibitor, improved premature ejaculation and erectile function in men with psychogenic ED but had a marginal effect in men with organic ED.⁽²⁰⁾ This side effect has created interest for its potential use in men with impotence. Doses of 150 mg per day have been used in most studies and case reports. The mechanism by which trazodone may help patients with impotence is unclear but is most likely a result of the drug's ability to block both serotonin and α_2 -adrenoreceptors. Whatever the mode of action, recent clinical studies seem to indicate that if trazodone does have a role in the treatment of erectile dysfunction, then its benefit may only be marginal.

Yohimbine, an alkaloid derived from the bark of the Central African yohimbine tree, has been used as folk medicine for many years. The alka-

loid has α_2 -adrenoreceptor blocking activity and produces a rise in sympathetic drive. Yohimbine has no effect on erectile function when administered by intracavernous injection, and its action in relation to erectile dysfunction is thought to be almost entirely central. Traditionally, extracts from the yohimbine bark have been used to treat all forms of impotence.

Most information available on the use of yohimbine comes from isolated reports and uncontrolled trials. Only in the last 15 years have formal clinical studies been undertaken. A review of recent clinical trials indicates that the response rate to yohimbine is only 30-40%. The difference between responders to yohimbine and to placebo has not been clinically significant in many cases. It is clear that some patients, especially those without serious medical problems, demonstrate improvement in the quality, frequency or rigidity of erections but not always enough to restore satisfactory sexual function. Side effects associated with the use of the drug include nausea, insomnia, nervousness, headache, and dizziness. Large doses can increase blood pressure and heart rate but rarely do patients have to discontinue therapy subsequent to adverse effects. Questions about the drugs long-term safety still remain. The most commonly used dose is 5.4 mg three times daily.^(21,22)

Isoxsuprine is a vasodilator, acting by direct relaxation of vascular smooth muscle. Its primary mechanism of action is by stimulation of Beta-adrenergic receptors. The commercially available form is a 10mg tablet. Isoxsuprine is no better than placebo as a first line treatment for mixed type erectile dysfunction.⁽²³⁾

Hormonal Treatment

Endocrine disorders, such as hypogonadism, androgen abnormalities, growth hormone defects, thyroid disease and lipid disorders also play a significant role in ED physiology.⁽¹⁰⁾

Castration reduces intracavernous pressure following intracavernosal administration of adrenomedullin, calcitonin gene-related peptide, vasoactive intestinal polypeptide or nociceptin. All of these compounds lead to increases in cAMP. Moreover, testosterone regulates the expression and activity of NOS in some species. Castration also inhibits the increase in intracavernous pressure following a nitric oxide (NO) donor. These findings suggest that androgens influence the cAMP and cGMP pathways in addi-

tion to NOS. Although androgens may not directly augment the effects of cyclic nucleotides, these data argue that androgen replacement may be a prerequisite for pharmacological therapy to improve ED if an androgen deficiency exists. Thus, in hypoandrogenic patients the combination of testosterone and PDE-5 inhibition or intracavernous activation of adenylate cyclase may be indicated.⁽²⁴⁾

The hypothalamic-pituitary-gonadal axis has been shown to decrease functioning temporarily after acute medical events or surgical procedures; such an occurrence can cause low gonadotropin and testosterone levels. Similarly, a temporary decrease in testosterone levels may occur as a result of less serious circumstances, such as anxiety, excessive intake of alcohol, use of multiple medications, or uncontrolled diabetes. Patients with these causes are less likely to respond to testosterone replacement. Stimulation of gonadotropins with clomiphene citrate and the subsequent increase in testosterone levels emphasize the functional and reversible nature of this phenomenon; short-term therapy with clomiphene citrate may help some patients. If the testicles are intact, testosterone can be stimulated by injections of human chorionic gonadotropin, but this technique is cumbersome and rarely used. Hypogonadism is common in patients with diabetes, many of whom may respond to testosterone treatment.⁽²⁵⁾

Appropriate therapy in the presence of a documented deficiency (e.g. androgen deficiency and hypogonadism), may not necessarily improve ED and thus one may need to consider direct intervention therapy even in this patient population. The issue of androgen replacement therapy is complicated. There is a statistical decline of testosterone levels, particularly free testosterone, in aging men. While this fall is only moderate, aging men show clinical signs of hypogonadism (loss of muscle mass/strength, reduction in bone mass and an increase in visceral fat). Testosterone replacement or supplement therapy may improve bone mass, muscle mass, strength and frequently nocturnal erections as well in this age group. However, the effects on sexual function, mood and cognition are less clear but may be meaningful in certain men. The identification of that segment of the aging male population that might possibly benefit from androgen supplementation remains difficult. Questions still remain regarding the magnitude and longevity of these

potential beneficial effects. More importantly, the long-term risks of androgen therapy in this age group really are now known, especially in the areas of cardiovascular and prostate diseases.⁽²⁶⁾ Despite increasing evidence that patients with subnormal or borderline normal levels of testosterone could be considered as candidates for testosterone treatment, until more information is available, testosterone and androgens in general should not be recommended as supplemental therapy.⁽¹⁾

Testosterone replacement for hypogonadism may also correct sexual dysfunction, unless the patient has other comorbid illnesses. For decades, the standard has been a depot intramuscular injection of testosterone enanthate or cypionate every 2 or 3 weeks (200 mg or 300 mg, respectively). Smaller doses and more frequent injections, however, are better at maintaining circulating testosterone levels of testosterone enanthate or cypionate intramuscularly at 7- to 14-day intervals. An alternative approach is to administer 100 mg on days 1, 11, and 21 of each month, while allowing some flexibility of injection days. If testosterone levels are measured, they should be in the normal range just before the next injection. Other forms of intramuscular testosterone preparations are also being evaluated. Implantable testosterone pellets are now, but they are infrequently prescribed. Oral forms of testosterone are not recommended because of the risk for liver damage when taken for long periods of time.

The US Food and Drug Administration (FDA) have now approved testosterone scrotal and non-scrotal dermal patches. Testosterone absorption is greater through scrotal skin. The scrotal patch was the first to be introduced. These patches are placed on the scrotal skin and are changed daily, in the morning. For many patients, weekly shaving of the scrotum is necessary. The patch increases testosterone levels to the low-normal range, with peak levels achieved 3 to 5 hours after application of the patch. Because 5- α -reductase in scrotal skin is high, the dihydrotestosterone (DHT) level in serum becomes quite high. The role of DHT is currently being investigated. The non-scrotal patch (Androderm), applied daily in the evening, may be worn in various sites on the skin. The manufacturer recommends that it not be used over bony prominences. The levels remain stable in the middle of the normal range, and the DHT levels remain normal. Skin irritation may develop and often responds to applica-

tion of corticosteroid cream. In a certain small percentage of patients, therapeutic blood levels of testosterone may not be achieved. Another non-scrotal patch, Testoderm, was associated with less skin irritation but was more likely to fall off; it has recently been withdrawn from the market. The FDA for use in the United States has recently approved a 1% testosterone gel. It is more expensive than the testosterone patches. The blood levels of testosterone associated with use of the gel are dose dependent and vary less than with the testosterone patches. Care must be exercised because the testosterone can be transferred to another person if skin-to-skin contact occurs.

With any form of testosterone treatment, the patient may have a slow but steady increase in libido and erectile ability during a course of months. If no improvement is noted after three months, the hormone deficiency is probably not the only cause of the sexual dysfunction. A comorbid medical illness might be present, or perhaps performance anxiety is dominant.

Any patient treated with replacement androgens should be reassessed within 1 to 3 months after initiation of therapy and then at 6- to 12-month intervals to ensure that clinical problems have not developed or worsened during such treatment. Prostate cancer and breast cancer are contraindications to androgen therapy, whereas sleep apnea, peripheral edema, erythrocytosis (hematocrit >52%), and benign prostatic Hyperplasia are relative contraindications that may respond to adjustments in the medication or specific treatments (for example, use of continuous positive airway pressure or weight reduction).⁽²⁷⁾

Intracavernous vasoactive drug injection and topical therapies

Intracavernosal Injections. Drugs for ED vary by not only class, but also route of administration. Penile injections have now largely been replaced by oral medications, specifically sildenafil. Nevertheless, injection and topical (skin) therapies employ various agents that have properties that help achieve erection, even in many men who do not succeed with sildenafil.

Alprostadil (Caverject). This is the most widely used agent. Alprostadil is derived from a natural substance, prostaglandin E1, and acts by opening blood vessels. It is an effective treatment for some men. It can be administered in three ways: by injection into the erectile tissue of the penis

(Caverject, Edex), by a device that administers the drug through the urethra (MUSE system), and in a topical cream (Topiglan, Alprox-TD) applied directly to the penis. Regardless of how it is administered, alprostadil works in many men with a wide range of medical disorders related to erectile dysfunction, including the following: diabetes, prostate cancer treatments (early use of alprostadil injections after treatment, particularly when followed by oral sildenafil, may be very helpful for men being treated for prostate cancer), men who are taking nitrates and injury. Alprostadil is not an appropriate choice for the following individuals: men with severe circulatory or nerve damage, men with bleeding abnormalities or men who are taking medications that thin the blood, such as heparin or warfarin and men with penile implants. The drug may have toxic effects if it reaches the fetus in pregnant women, so men should not use alprostadil for intercourse with pregnant women without the use of a condom or other barrier contraceptive device.

It is effective in 70% to 80% of patients and has a low incidence of side effects. Penile pain occurs in 15% to 50% of patients but is often not troublesome. The dose range is 5 to 20 mcg but some physicians will increase it further or use a combination with papaverine and phentolamine. Priapism occurred in about 1% of patients and the incidence of penile fibrosis was 10% in a period of 3 years. About half of the cases with fibrosis resolved spontaneously.

Thymoxamine (moxisylyte hydrochloride) (Erechos, Icacex). This agent, a selective α_1 adrenergic receptor antagonist, has been licensed for use in erectile dysfunction and is used in a dosage of 10-20 mg. It is less effective in initiating erection but with sexual stimulation gives sufficient rigidity in some patients. It has a lower incidence of side effects such as penile pain and prolonged erection.

Papaverine (Pavabid, Cerespan). This was the first agent in general use and had the advantage of being cheap. It is not licensed for the treatment of ED and is not recommended because of the relatively high risk of priapism and penile fibrosis.

Papaverine and Phentolamine Mixtures (Androskat). This is still used in some countries because of its efficacy and relatively low cost. It is more effective than papaverine alone.

Trimix (Papaverine, Phentolamine and Alprostadil). This combination was introduced to

treat those patients who responded poorly to the papaverine/phentolamine mixture or alprostadil. It is unlicensed and is prepared by specialized pharmacies.

Vasointestinal Polypeptide (VIP) and phentolamine (Invicorp). This is another preparation in an advanced phase of clinical development although it is not yet licensed except recently in Denmark. The main side effect is facial flushing and tachycardia but it has the advantage over alprostadil of a lower incidence of pain. Its effectiveness, compared to alprostadil has yet to be determined.⁽²⁸⁾

While intercavernosal injection therapy consistently produces erections in up to 87% of patients, there is a dropout rate of about 50%.⁽²⁹⁾

Intraurethral Suppository. Prostaglandin E1 (alprostadil) (MUSE system), is also available as an intraurethral suppository. Padma-Nathan et al³⁵ reported an at home successful sexual intercourse rate of approximately 60% in a large series of men, 20% of whom had diabetes. Although PGE1 is less invasive and easier to use than intracavernosal injection, it may reduce sexual spontaneity. Men must remain standing after the pellet has been inserted to increase penile blood flow, and the time to erection is 15 to 30 minutes. Patients may complain of penile pain (12%), minor urethral bleeding (5%), testicular pain, and dizziness. Female partners may report vaginal burning or itching (6%) with use of the suppository. Prostaglandin E1 is contraindicated in men with abnormal penile anatomy and those with hyperviscosity syndromes; men cannot take PGE1 if they have intercourse with pregnant women who are not using barrier contraceptives.⁽³⁰⁾

Reported success rates with intraurethral alprostadil have been around 50% but range widely.

Venous and arterial surgery

Impaired arterial inflow has been addressed in select cases by various penile revascularization procedures and attempts to induce neovascularization. Of course, known risk factors, such as smoking, hyperlipidemia, diabetes, hypertension and obesity, should be controlled.

Penile Revascularization. For men whose impotence is caused by damage to the arteries or blood vessels, vascular surgery might be an option. The best candidates for such surgery are young men with discrete blockage of an artery

because of an injury to the crotch or fracture of the pelvis. The procedure is almost never successful in older men with widespread blockage.

Penile revascularization represents the only currently feasible cure of arteriogenic ED.^(31,32) The revascularization procedure usually involves taking an artery from a leg and then surgically connecting it to the arteries at the back of the penis, bypassing the blockages and restoring blood flow. In a related procedure called deep dorsal vein arterialization, a penile vein is used for the bypass. Young men with local sites of arterial blockage or those with pelvic injuries generally achieve the best results. In studies of selected patients there was improvement in erectile dysfunction in 50% to 75% of men after five years. In the Virag type of procedures the epigastric artery is anastomosed to the deep dorsal vein at the base of the penis. Blood flows retrograde through the veins and enters the corpora through the connecting posterior emissary veins.⁽³³⁾ Direct anastomosis of the epigastric artery to the cavernosal artery is feasible but technically challenging.⁽³⁴⁾ Direct epigastric artery to dorsal penile artery anastomosis in various modifications has also been described.^(32,35)

Neovascularization. Neovascularization is another emerging approach to reversal of impaired cavernosal artery flow. Tissue hypoxia and the inflammatory response are major physiological stimuli to angiogenesis. The process is under the control of angiogenic growth factors, small proteins that induce proliferation and migration of endothelial and smooth muscle cells, and branching of the vascular tree. All growth factors are mitogens to endothelial cells and include basic fibroblast growth factor, vascular endothelial growth factor (VEGF) and hypoxia inducible factor. In addition to direct stimulation of endothelial cell growth, some growth factors such as VEGF possess the ability to stimulate production of NO. Intracavernosal injection of VEGF in an ischemic rat model has recently been shown to stimulate endothelial nitric oxide synthase (NOS) and inducible NOS expression.⁽³⁶⁾ Several recent animal studies have shown the feasibility of using local intracavernosal VEGF injection. In vitro VEGF treatment has been shown to ameliorate the effects of hypercholesterolemia on rabbit cavernosal smooth muscle.⁽³⁷⁾ In a rat model using acute arterial ligation, a single intracavernosal bolus of VEGF improved penile erection.⁽³⁸⁾ Regeneration of nerves and endothelial cells

lining the cavernous spaces was seen.⁽³⁸⁾

Venous ligation. Venous leak has been termed an "epiphenomenon" of cavernosal smooth muscle dysfunction.⁽¹⁵⁾ Thus, it does not appear to offer curative potential when addressed as an isolated phenomenon. Venous ligation is performed when the penis is unable to store a sufficient amount of blood to maintain an erection. This operation ties off or removes veins that are causing an excessive amount of blood to drain from the erection chambers. The success rate is estimated at between 40% and 50% initially, but drops to 15% over the long term. It is important to find a surgeon experienced in this surgery. In a variation of this technique called venous ablation, ethanol is injected into the deep dorsal vein, the main vein that drains blood from the penis. The ethanol causes scarring that closes off smaller veins and prevents blood leakage, thereby bolstering erectile function. In a small trial in 10 men with severe impotence, half maintained erectile function two to three years after the procedure.

Recently, improved results were reported when patients were selected according to the presence of mild cavernous leak, more than 30% cavernous smooth muscle content, normal cavernosal electromyography results, and oxygen tension of more than 65 mm Hg during erection, and age younger than 50 years. In this series of 23 men treated with venous ligation 74% had normal erections at 1 year and 50% beyond 1 year. Venous ligation appears to have a role only in highly selected men with minimal cavernosal dysfunction.⁽³⁴⁾

The American Urologic Association stresses that vascular surgery is still investigative.

Vacuum constriction device therapy

Vacuum constrictor device. Any system encouraging blood to flow into and be captured in the penis should produce an erection. This is the principle behind the vacuum constrictor device (VCD) now offered as a noninvasive means of restoring erections for some impotent men. Vacuum devices, or external management systems, are effective, safe, and simple to use for all forms of impotence except when severe scarring has occurred from Peyronie's disease. Vacuum devices rely on first drawing blood into the penis, by means of an externally applied suction pump, and then retaining the resultant erection by means of an elastic ring applied to the base of the penis. Provided it is used properly, the failure rate is very low and serious adverse effects are

rare, although many patients find the method cumbersome. The band may only be kept on for 30 minutes and ejaculation may be obstructed. One small retrospective study shows that 81% of men stopped using the device over a one-year period.⁽³⁹⁾ A second study of 50 men suggested that only 27% preferred the vacuum device to intracavernosal injection therapy.⁽⁴⁰⁾

Not only does vacuum-induced pressure in the VCD cause most men to experience penile discomfort, but the erection achieved by this means is inferior to a spontaneous erection in three significant aspects. Once the vacuum has induced the erection, the rubber bands in place at the base of the penis choke off blood flow into the penis. This causes penile skin temperatures to fall to 35.5-centigrade degree. One-third of the female partners of men using VCDs found the chilled penis displeasing during intercourse. Another drawback is that as the penis becomes engorged and congested by the VCD-induced suction and inhibition of venous outflow, penile circumference increases more than it would during a normal erection. This gives the penis a sausage like appearance. Third, the erection created by the VCD is rigid only from the point at which the rubber bands are affixed. This means that it is not fully upright and rigid like a normal erection, but flexible and capable of swiveling or pivoting at its base. The VCD also does not permit normal ejaculation. Because the rubber bands remain in place throughout the sexual act, semen is trapped in the urethra and can be released only after the bands are removed.

Venous flow controllers. Vacuum-less devices that trap blood within the penis are also available. They are called venous flow controllers or simple constricting devices. These devices are typically rubber or silicone rings or tubes (e.g., Actis) that are placed at the base of the erect penis to trap the erection. Men who can achieve erections but lose them easily can use them. These devices should not be used for longer than 30 minutes or lack of oxygen can damage the penis, and patients who have bleeding problems or are taking anticoagulants should not use them.

Penile prosthesis implantation

Implanted devices, known as prostheses, can restore erection in many men with ED. Possible problems with implants include mechanical breakdown and infection, although mechanical problems have diminished in recent years because of

technological advances.

Malleable implants usually consist of paired rods, which are inserted surgically into the corpora cavernosa. The user manually adjusts the position of the penis and, therefore, the rods. Adjustment does not affect the width or length of the penis.

Inflatable implants consist of paired cylinders, which are surgically inserted inside the penis and can be expanded using pressurized fluid. Tubes connect the cylinders to a fluid reservoir and a pump, which are also surgically implanted. The patient inflates the cylinders by pressing on the small pump, located under the skin in the scrotum. Inflatable implants can expand the length and width of the penis somewhat. They also leave the penis in a more natural state when not inflated.

There appear to be no long-term immune problems related to the silicon or other materials in the devices.

There are potential limitations with these devices. Erectile tissue is permanently damaged when these devices are implanted and procedures are irreversible. Although uncommon, mechanical breakdown can occur, or the device can slip or bulge, especially if the patient coughs or vomits vigorously after the operation. In addition, a less than optimal quality of erection may result. (Using the MUSE system may restore or improve the function of a penile prosthesis in patients with a failed device.)

Infection is the major concern with these devices. Redness and fever often accompany a full-blown

infection. Any intermittent pain that continues to occur after an implant may be an indicator of a low-grade infection. If the infection can be caught early enough, implant failure can be prevented. Most infections are treated with antibiotics for at least 10 to 12 weeks. If antibiotics fail, a surgical exchange, in which the infected implant is simultaneously replaced with a new one, should be considered. This is a complex procedure, but some surgeons have reported a 90% success rate. Coatings with specific antibiotics are being investigated and studies are reporting very low infection rates.

Miscellaneous Therapy

Psychosexual counseling

Although widely recommended, there have been no controlled studies of the use of psychosexual

counseling in erectile dysfunction. One questionnaire survey of 289 sex therapists suggested that they achieved a successful outcome in 25% of patients treated for impotence, although the nature of the patients referred is unclear.⁽⁴¹⁾ In another study, 20 consecutive diabetic men with erectile dysfunction were referred for psychosexual assessment and treatment.⁽⁴²⁾ Three of these achieved long-term improvement in sexual function, although it proved impossible to identify these responders from their pretreatment characteristics. A third study looked at a combination of treatment strategies in 145 men.⁽⁴³⁾ Twenty-one per cent of those studied were able to have intercourse after psychotherapy alone. Interestingly, those with clearly organic impotence benefited almost as much as those with psychogenic impotence (21% versus 32%).

Psychological counseling for patients with or without their partners are helpful in addressing the psychogenic and interpersonal factors associated with erectile dysfunction.⁽⁴⁴⁾ Approaches include techniques to reduce anxiety and to enhance sexual stimulation, desensitization procedures, cognitive-behavioral interventions, and traditional counseling. These approaches may be used alone or in addition to other treatment interventions such as oral medication or the vacuum pump. Such combination therapy may be particularly useful in situations of low sexual desire, problems of sexual initiation, other sexual dysfunction, and significant relationship problems.⁽⁴⁵⁾ Psychosocial factors that contribute to men discontinuing therapy, despite its effectiveness, also can be addressed in psychological counseling or sex therapy sessions.⁽⁴⁶⁾ These factors include emotional readiness of each partner to resume sexual activity, the attitude of each partner toward using a medical intervention, the quality of the sexual relationship, unconventional arousal patterns, and the quality of the couple's sexual life before erectile dysfunction.

Sex Therapy

A significant number of men develop impotence from psychological causes that can be overcome. When a physiological cause is treated, subsequent self-esteem problems may continue to impair normal function and performance. Qualified therapists (e.g. sex counselors, psychotherapists) work with couples to reduce tension, improve sexual communication, and create realistic expectations for sex, all of which can improve erectile function.

Psychological therapy may be effective in conjunction with medical or surgical treatment. Sex therapists emphasize the need for men and their partners to be motivated and willing to adapt to psychological and behavioral modifications, including those that result from medical or surgical treatment.

Lifestyles changes

Staying sexually active can help prevent impotence. Frequent erections stimulate blood flow to the penis. It may be helpful to note that erections are firmest during deep sleep right before waking up. Autumn is the time of the year when male hormone levels are highest and sexual activity is most frequent.

Cigarette smoking has been shown to be an independent risk factor for ED.⁽⁴⁷⁾ In one study the relative risk of developing internal pudendal artery atherosclerosis for each 10 pack-year smoked was 1.⁽⁴⁸⁾ The evidence linking smoking with ED is complex and it has been concluded that an association between smoking and ED is likely.⁽⁴⁹⁾ This finding is supported by some animal⁽⁵⁰⁾ and human⁽⁵¹⁾ studies, which demonstrated a direct inhibitory effect of smoking on erection. However, direct evidence of restoration of erectile ability with smoking cessation is sparse^(52,53) and there may be a point of no return after years of cigarette smoking.

Everyone should eat a diet rich in fresh fruits and vegetables, whole grains, and fiber and low in saturated fats and sodium. Because erectile dysfunction is often related to circulation problems, diets that benefit the heart are especially important. Foods that some people claim to have qualities that enhance sexual drive include chilies, chocolate, licorice, lard, scallops, oysters, olives, and anchovies. No evidence exists for these claims, and eating large amounts of some of these foods, such as licorice and lard, can be dangerous.

Nevertheless, as with hypercholesterolemia, advising our patients who are seeking improvement of erectile function to cease smoking is strongly recommended. Obesity and sedentary lifestyle are also well-recognized risk factors that can be modified in an attempt to improve erectile ability.⁽⁵²⁾ A regular exercise program is extremely important. One study reported that older men who ran 40 miles a week boosted their testosterone levels by 25% compared to their inactive peers. Another study found that men who burned

200 calories or more a day in physical activity (which can be achieved by two miles of brisk walking) cut their risk of erectile dysfunction by half compared to men who did not exercise.

Gene therapy

Defective smooth muscle is seen in the rat model of aging, when the corporal tissue becomes more fibrotic as the animal ages. What has also been shown in this aged animal model is a reduction in NOS activity in the corporal tissue. In an attempt to overcome this dual hit to aged tissue, investigators have searched for ways to either regenerate the relatively noncompliant corporal tissue or to up-regulate the factors that promote smooth muscle relaxation. One of the ways to accomplish this is via the Ca²⁺ sensitive K⁺ channel (maxi-K⁺) that regulates smooth muscle relaxation. Christ et al used naked DNA that encodes the maxi-K⁺ channel for injection into the penises of aged animals and was able to augment their erectile response in this manner. This gene therapy approach to overcome the processes that fail with certain disease states highlights what can be expected in the future for the treatment of patients who have erectile dysfunction that is refractory to medical therapy.⁽⁵⁴⁾

Conclusion

Major advances have been made in the understanding of the pathophysiology of impotence and erectile dysfunction. The ability to relax and contract corporal smooth muscle with pharmacologic agents has led to the development of several new treatment options for men with impotence. The demand for safer and more effective treatments for erectile dysfunction will continue to foster research in this field. Men with erectile dysfunction should be encouraged to overcome their reluctance to seek advice. The standard diagnostic assessment should include a detailed medical and sexual history and clinical examination of the patient.

There are various treatment options available for the management of erectile dysfunction and each is associated with a different profile of efficacy, safety and patient satisfaction. Most patients would prefer to regain their ability to have a normal spontaneous erection. This is however only possible when the problem is mainly psychological, hormonal, drug-dependent or in the rare men where arterial reconstruction is possible. All patients benefit from some psychosexu-

al counseling and it is important to remember that some patients prefer the option of having a satisfactory, non-penetrative, sexual relationship. It is customary to start with a non-invasive type of therapy and limit more invasive treatments to those patients with a special indication, for example arterial reconstruction, or those who do not respond to non-invasive methods by implanting a penile prosthesis.

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