

Physiologic factors modulating male sexual arousal

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ABSTRACT Male sexual arousal is inherently linked with the onset of penile tumescence. A change in smooth muscle tone is crucial to the onset and maintenance of erection. Erectile dysfunction affects a significant portion of the male population, increasing in prevalence with age. It is also associated with diabetes, cardiovascular disease, cigarette smoking, and depression. Ongoing research should yield new pharmacotherapeutic strategies that are safe, effective, reliable, noninvasive, easy to administer, and appropriate for a broad range of patients. Recent advances have already had an impact on clinical practice patterns, and primary care physicians are increasingly playing an important role in the delivery of sexual health care. Novel perspectives, the aging process, and the role of androgens in male sexuality are delineated. Knowledge of the physiologic mechanisms regulating male sexual arousal and penile erection suggest new directions for future research and therapies.

Male sexual function is uniquely characterized by a set of coordinated neurohormonal responses to penile erection. Despite redundant mechanisms to preserve this essential biological function, many disorders may compromise erectile function, profoundly affecting an individual's quality of life. Until the 1970s, erectile dysfunction (ED) had been predominantly treated as a psychological condition and classified, along with other disorders leading to compromised sexual function, under the broad term of "impotence." In 1992, a panel at the National Institutes of Health Consensus Conference on Impotence concluded that approximately 75% of erectile disorders originated from organic causes and defined ED as the persistent inability to achieve or maintain an erection for satisfactory sexual function.¹ The advent of the first Food and Drug Administration (FDA) approval of an oral medication for the treatment of ED has resulted in the rapid involvement of primary care physicians in treating patients with erectile disorders. In 1999, a panel of multidisciplinary experts developed a step-wise treatment algorithm for ED, taking into account ease of administration, reversibility, relative invasiveness, and cost.² The panel stressed that physicians must "address the sexual needs of their patients in a sensitive and informed manner,"² without losing sight of the needs and preferences of the patient's partner.

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Practice Tips

- | Address the sexual needs of patients in a sensitive and informed manner, without losing sight of the needs and preferences of the patient's partner.
- | Lifestyle changes that promote general good health and well-being may reduce the risk of sexual dysfunction.
- | For men with high-risk profiles for erectile dysfunction, prophylactic therapies would ultimately be a better choice than seeking treatment after the problem has evolved.
- | Prescribing oral drugs, such as sildenafil or phentolamine, may enhance the total duration of nocturnal penile tumescence and prevent progressive fibrosis of the erectile tissue.

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Risk factors for erectile disorders

Recent epidemiological studies give insight into the prevalence, incidence, and associated risk factors for ED in the United States.^{3,4} Data from the Massachusetts Male Aging Study (MMAS) of men 40 to 70 years old, indicated that ED was self-reported in over half of the respondents; 10% claimed complete dysfunction, while 25% and 17% noted moderate and minimal dysfunction, respectively. The prevalence of ED increased with age, doubling between the ages of 40 and 70 years for moderate ED, and tripling over the same 3-decade time period for complete ED. Although age had the strongest association with ED, other factors were directly correlated with increasing probability of acquiring ED, including diabetes mellitus, heart disease, hypertension, and indices of anger and depression. An inverse correlation was found between ED and serum levels of dehydroepiandrosterone (DHEA) and high-density lipoprotein cholesterol.

Men in the same age group with treated heart disease and hypertension, who began or continued cigarette smoking, had a significantly increased risk of complete ED.

In a follow-up study of the initial MMAS participants (mean of 8.8 years after study entry), the annual incidence of ED was estimated at 26 cases per 1,000 men. Risk for ED was determined to increase with age, lower education, diabetes, heart disease, and hypertension. Similar associations were observed by an analysis of the data from the National Health and Social Life Survey, which indicated an overall prevalence of 31% for sexual dysfunction in men aged 18 to 59 years in the United States. Strong associations were made between sexual dysfunction and previous negative experiences in sexual relationships and overall emotional health. These two studies concluded that sexual dysfunction negatively affects quality of life and is an important health concern.

New perspectives

A new perspective suggests that depression, cardiovascular disease, and ED are interrelated and share many of the same risk factors and etiologies, although they are often treated as separate entities by physicians trained in different disciplines.⁵

It is also now suggested that lifestyle changes that promote general good health and well-being may reduce the risk of sexual dysfunction.⁶ This recent retrospective study determined that men who maintained lifelong physical activity or those who changed from

sedentary to more physically active lifestyles at midlife exhibited the lowest risk for acquiring ED.⁶

Central mechanisms of male sexual arousal

Anatomic considerations of erectile structure and function are discussed in the Figure. The regulation of sexual function by the central nervous system (CNS) is poorly understood. Control of penile erection is organized by a diffuse network of interconnected sites within the CNS and specific neuronal pathways remain largely undefined. However, progress has been made in identifying key central structures that regulate the sexual arousal response in males.^{7,8} A recent study using positron emission tomography (PET) in healthy male subjects has identified specific regions of the brain that are activated in response to visually evoked sexual arousal⁹; these areas are linked to visual association, processing of sensory information and motivational states, and regulation of autonomic and neuroendocrine functions.

Dopamine and oxytocin. Increased levels of dopamine and oxytocin have been associated with sexual activity, and these neurotransmitters are thought to play important roles in mediating the proerectile response in the medial preoptic area and peripheral venous nutrition, respectively.⁷

Serotonin. In contrast, serotonin released from nerves projecting from the nucleus paragigantocellularis to sacral segments of the spinal cord, exerts an inhibitory effect on sexual arousal. This is thought to be the reason why selective serotonin reuptake inhibitors (SSRIs) depress sexual function. The locus coeruleus also exerts inhibitory input via sympathetic nerves that interface with hypothalamic nuclei as well as the spinal cord. Withdrawal of sympathetic input due to suppressed activity of the locus coeruleus during rapid eye movement sleep is thought to lead to episodes of nocturnal penile tumescence.¹⁰

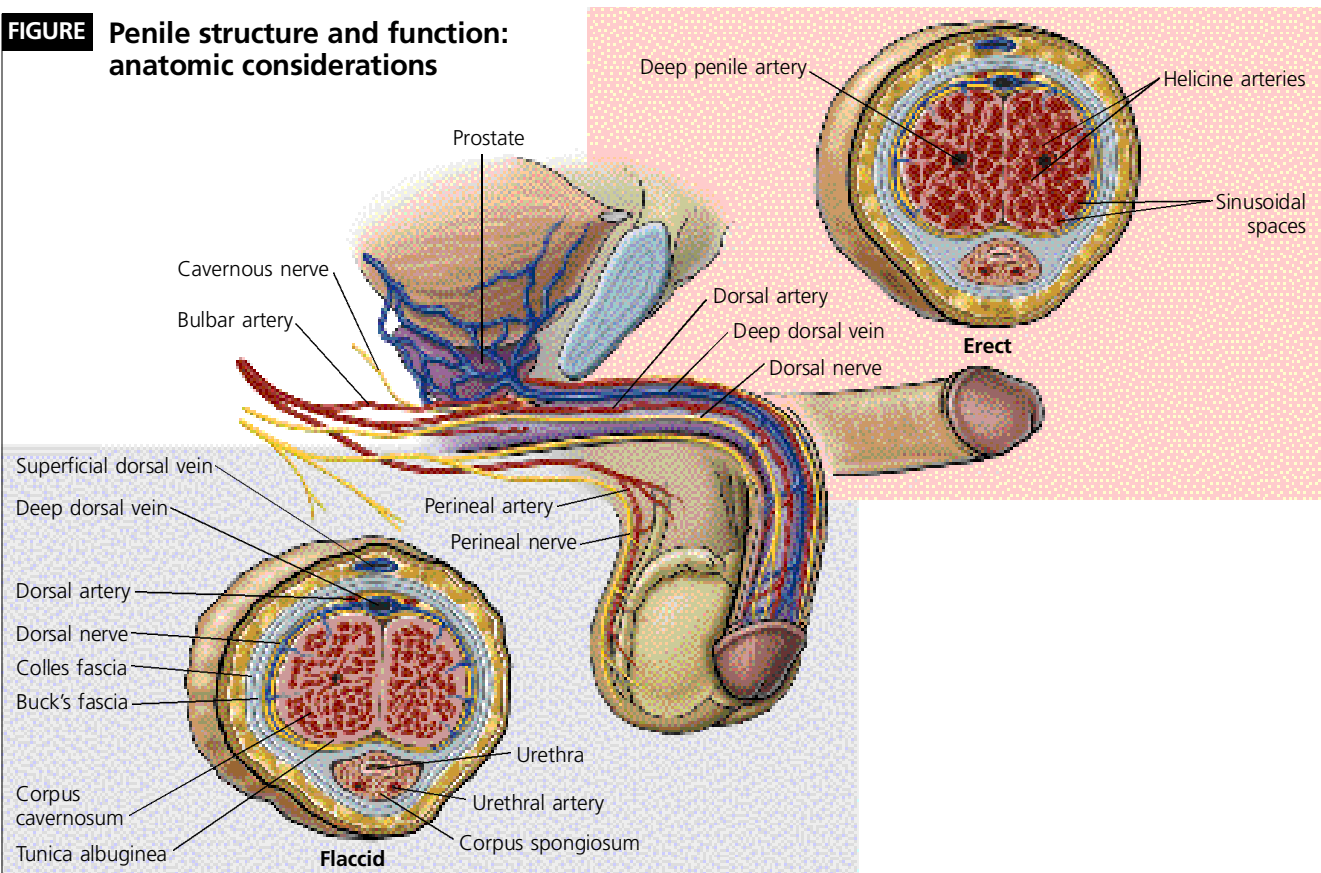
Peripheral (neurogenic) mechanisms

Erectile function in the penis is regulated by autonomic (parasympathetic and sympathetic) and somatic (sensory and motor) pathways. Three sets of peripheral nerves innervate the penis.

Sympathetic nerves. The sympathetic nerves (T10–L2) are responsible for detumescence and maintaining flaccidity. Adrenergic tone is crucial in initiating de-

Men who maintain lifelong physical activity may have the lowest risk of acquiring ED.

FIGURE Penile structure and function: anatomic considerations



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The penis consists of three erectile bodies—the two corpora cavernosa, the key structures mediating penile erection, and the corpus spongiosum. Fibrous tissue plaques in the subtunical layer, known as Peyronie's disease, can result in low compliance of the tunica albuginea, penile curvature, and veno-occlusive dysfunction.¹¹ Along with the nerves that run within Alcock's canal, the blood vessels in the corpus cavernosum are vulnerable to compression injuries, such as may occur during bicycle riding. The dorsal artery interconnects with the cavernosal artery, allowing arterial bypass surgery in the cases of cavernosal artery obstruction.¹² Frequently, the accessory pudendal artery provides additional blood to the corpora cavernosa and has a critical role in men with reduced blood supply via ordinary pudendal arteries, especially in those who have undergone radical pelvic surgery. The venous network connects the corpus spongiosum to the corpora cavernosa, allowing transport of vasodilator substances absorbed through the urethral mucosa into the erectile bodies. This arrangement enables the transurethral delivery of drugs for the treatment of ED. The deep system (ie, cavernous and crural veins) provides the main drainage of the corpora cavernosa and a main source of leakage in venogenic ED.

Under nonpathologic conditions, the tone of the vascular smooth muscle in the corpora cavernosa and the blood vessels feeding this tissue determine the state of penile tumescence or detumescence. The spongelike corpus cavernosum consists of bundles of smooth muscle cells embedded in a matrix of connective tissue and fibroblasts, forming trabeculated structures that define a series of blood-filled lacunar spaces lined with endothelium. Although similar in its cellular constituents to blood vessels, the corpus cavernosum is

unique in its structure and function. Trabecular smooth muscle constitutes approximately 50% of normal erectile tissue. The bulk of the remaining tissue is composed of extracellular matrix, which provides the fibroelastic framework.

In the flaccid state, the trabecular smooth muscle and the central cavernosal and branching helicine arteries are constricted. During the transition to the erect state, sacral parasympathetic stimulation causes dilation of the cavernosal and helicine arteries, enabling a higher rate of blood flow into the penis. Concomitant relaxation of the trabecular smooth muscle greatly increases the compliance of the cavernosal bodies and allows the lacunar spaces to expand and accommodate the enhanced blood flow. The outflow of blood must be reduced to achieve and maintain full tumescence and rigidity. Restriction of venous outflow from the cavernosal bodies is accomplished by elongation and compression of subtunical venules between the expanding trabecular structures and the tunica albuginea—a process known as the veno-occlusive mechanism. Thus, when the trabecular smooth muscle is contracted, there is low resistance to outflow. This permits evacuation of blood from the cavernosal bodies and contributes to the maintenance of penile flaccidity. When the smooth muscle relaxes, the resistance to outflow from the cavernosal bodies greatly increases.

The trabecular smooth muscle cells of the corpus cavernosum form a functional syncytium by virtue of junctional plaques in the plasma membrane, similar to cardiac muscle. This continuity enables a coordinated response to various stimuli, which are not homogeneously distributed throughout the tissue.

tumescence and maintaining the flaccid state of the penis since the smooth muscle of the arteries and cavernosal trabeculae must remain actively contracted. Norepinephrine-induced contraction of cavernosal trabecular smooth muscle is mediated by alpha-1 adrenergic receptors. Alpha-2 adrenergic receptors on adrenergic nerves inhibit neurotransmission and provide a self-regulating negative feedback loop for secreted norepinephrine. Cholinergic nerves also inhibit adrenergic nerve activity.

Adrenergic imbalance favoring vasoconstriction may impair erection. Factors contributing to this imbalance remain unknown, but aging and associated diseases may cause selective upregulation of specific adrenergic receptor subtypes, resulting in greater norepinephrine activity. Since norepinephrine is a key modulator of erectile function, alpha-adrenergic receptor antagonists may prove useful in the treatment of ED.¹³ Drugs such as yohimbine, an alpha-2 adrenergic receptor antagonist, and phentolamine, an alpha-1 and alpha-2 adrenergic receptor antagonist, have varying efficacies for ED.

Parasympathetic nerves. The parasympathetic nerves provide the major excitatory input to the penis and are responsible for vasodilation of the penile vasculature and subsequent erection. These nerves synapse in the pelvic plexus with postganglionic nonadrenergic-noncholinergic (NANC) nerve fibers, which travel within the cavernous nerves to the corpora.

The primary mediator of NANC parasympathetic input is nitric oxide (NO), which is produced by nitric oxide synthase, using the amino acid L-arginine and molecular oxygen as substrates to produce NO and L-citrulline. NO can readily cross plasma membranes to enter target cells and stimulate guanylate cyclase to produce cyclic guanine monophosphate (cGMP). Sildenafil (Viagra®) is a potent selective and reversible inhibitor of phosphodiesterase-type 5 (PDE-5), the major enzyme responsible for cGMP hydrolysis in erectile tissue. Inhibition of PDE-5 increases intracellular cGMP levels and enhances smooth muscle relaxation. This activity may explain sildenafil's success in managing ED.¹⁴

The release of acetylcholine within the corpus cavernosum may coordinate withdrawal of adrenergic input and increase of NANC input by binding to prejunctional muscarinic receptors on adrenergic and NANC nerves.¹⁰ In diseases such as diabetes, the ability of the corpus cavernosum to synthesize and release acetylcholine is diminished,¹⁵ which may be partially respon-

sible for the compromised erectile function. Parasympathetic nerves are also vulnerable in surgical procedures (eg, abdominoperineal rectum resection and radical prostatectomy).

Pudendal nerves. These nerves comprise motor efferent and sensory afferent fibers innervating the ischiocavernosus and bulbocavernosus muscles as well as the penile and perineal skin. The dorsal nerve of the penis emerges as the last branch of the pudendal nerve. It then turns distally along the dorsal penile shaft, lateral to the dorsal artery. Multiple fascicles fan out distally, supplying proprioceptive and sensory nerve terminals to the dorsum of the tunica albuginea and skin of the penile shaft and glans penis.

Nonneuronal modulators of penile erection

Local paracrine or autocrine factors, with vasoactive and/or trophic effects, can also profoundly influence the function of the smooth muscle in the penis. These include endothelins, prostanoids, nitric oxide, and oxygen.

Endothelin-1. A member of the endothelin family of peptides, endothelin-1 (ET-1) is one of the most potent vasoconstrictors. Endothelin produced by the endothelial cells lining vascular compartments may contribute to the maintenance of penile flaccidity by providing sustained tone to the trabecular smooth muscle. Alterations in endothelin production may result in impaired erectile function. Several

endothelin receptor subtype selective antagonists have been developed, but their efficacy and safety in treatment of ED has not been fully evaluated.

Nitric oxide. In addition to the NANC nerves, the vascular endothelium synthesizes and releases NO. Vasodilators such as acetylcholine and bradykinin act by binding their respective membrane receptors and increasing intracellular Ca²⁺ within endothelial cells. Physical stimuli (eg, shear stress) are also known to enhance NO production in endothelium. In the penis, shear-induced NO production by endothelium is most likely to occur during the onset of erection, when blood flow into the cavernosal bodies is rapidly increased.

Prostaglandins. Prostanoids (eg, eicosanoids, prostaglandins) in both endothelial and smooth muscle cells of the corpora cavernosa act locally and exert trophic and tonic effects in an autocrine and paracrine manner. Although the precise role of prostaglandins in penile erection remains poorly defined, they may play an important role in the regulation of extracellular matrix

Adrenergic imbalance favoring vasoconstriction may impair erection.

production. Prostaglandin E₁ (PGE₁) alprostadil is the first FDA-approved intracavernosal injectable drug for the treatment of ED.

Oxygen. Oxygen tension plays an active role in regulating penile erection. Measurements of cavernosal blood P_{O₂} in human volunteers indicate that oxygen tensions change rapidly from venous (~35 mm Hg) to arterial (~100 mm Hg) levels in the transition from the flaccid to the erect state. Maintenance of constant oxygen tension is a critical imperative in most tissues, but the penis is the only organ that changes from venous to arterial oxygen tensions during the course of its normal function. This transition is the basis of a unique regulatory mechanism that takes advantage of key synthetic enzymes that use molecular oxygen as a cosubstrate. NO synthase and prostaglandin synthase are two well-studied examples of a class of enzymes known as dioxygenases. At low oxygen tension, measured in the flaccid state of the penis, the synthesis of NO is inhibited, preventing trabecular smooth muscle relaxation. This inhibition of NO production is probably necessary for the maintenance of penile flaccidity. Following vasodilation of the resistance arteries, the increase in arterial flow raises oxygen tension. In the oxygen-enhanced environment, autonomic dilator nerves and the endothelium are able to synthesize NO, mediating trabecular smooth muscle relaxation.

Novel and potential therapies for ED

The inhibition of PDE-5 by sildenafil has proven to be an effective strategy for treating ED. Because of the multiple etiologies that give rise to this condition, additional noninvasive or minimally invasive treatments are needed. Currently, psychosexual counseling, vacuum constriction devices, and oral sildenafil are the only first-line therapies approved by the FDA for the treatment of ED. Current alternatives consist of intraurethral delivery (MUSE®) or intracavernosal injection (Caverject®, Edex®) and penile prosthesis implantation as secondary and tertiary modes of therapy.

Therapeutic strategies currently in development include novel delivery vehicles for preexisting drugs; centrally acting compounds that may promote sexual arousal and overcome numerous peripheral defects; the introduction of genes that encode for key proteins that regulate erectile tissue; tissue engineering; and multidrug therapy or hybrid molecules with multifunctional effects.

Topical drugs. Several vasoactive compounds in gel or cream—minoxidil (Rogaine®), nitroglycerine (Nitrol®), capsaicin (Zostrix®), papaverine, PGE₁—are in preliminary trials.¹⁶ Applied to the glans penis, these agents have shown varying efficacies in inducing or facilitating erections. The ease of application may be seen as positive, but because of their slow and diffuse delivery, the active compound reaching the erectile tissue and penile arteries may be much less than the applied dose. Thus, topical products may be more effective in men with mild-to-moderate ED. Skin permeabilizing agents or other drug-absorption enhancers may increase the efficiency of percutaneous drug delivery, and topical drugs will likely provide important alternatives to current first-line therapies.

Compounds targeting the CNS. Increasing knowledge of the central neural mechanisms regulat-

ing sexual arousal provides the basis for new therapies. By stimulating the central pro-erectile pathways, compounds targeting the CNS may sometimes be advantageous to drugs that target peripheral biochemical pathways. Apomorphine (Uprima®), a dopamine receptor agonist, is the first example of a centrally acting drug. Initially used to treat neurodegenerative disorders, apomorphine's action has been shown to enhance erectile function in clinical trials,^{17,18} although the FDA has yet to approve it for ED treatment.

Gene therapy. The ability to correct defects in biochemical signaling pathways by genetic manipulation holds promise in treating patients for prolonged periods without the continuous need for medication. Technologies to deliver DNA constructs into cells have developed rapidly. To date, genes for NO synthase and potassium channels as well as vascular endothelial growth factor have been investigated as potential treatments for ED. Such treatments may restore erectile function by overcoming defective biochemical mechanisms that regulate smooth muscle contractility or influence erectile tissue structure. However, the feasibility of such therapies in humans remains to be established and concerns regarding tissue-specific expression, efficiency of gene transfer, and length of expression of introduced genes need to be addressed.

Reconstructed erectile tissue. Although in the past penile prostheses have been a mainstay in treating ED, tissue-engineering techniques may make the recon-

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struction of functional erectile tissue a viable alternative. Resorbable polymers consisting of lactic and glycolic acid have been used to manufacture matrices that provide substrates onto which cells may be seeded and grown. Preliminary experiments have been able to grow human endothelial and smooth muscle cells on biodegradable polymers. Current work is focused on the continued development of engineered tissue substitutes for diseased erectile tissue. Future challenges include functional and biomechanical assessment of engineered tissue and the addition of critical constituents, such as blood vessels and nerves.

Arginase inhibition. The high efficacy of sildenafil emphasizes the importance of the NO pathway in male sexual arousal. Another strategy to enhance NO production is through the inhibition of arginase, an enzyme that catalyzes the hydrolysis of arginine to form ornithine plus urea. Because it shares a common substrate with NO synthase, its activity may influence the arginine bioavailability for NO production. Arginase inhibitors have been shown to enhance the NANC neurogenic relaxation response of gastrointestinal and penile trabecular smooth muscle.¹⁹ Thus, it appears that arginase inhibition enhances NO synthase activity by increasing the substrate pool of arginine that is available for NO biosynthesis. This interaction between arginase and NO synthase may become particularly important in diseases resulting from neuropathies, endothelial dysfunction, and/or compromised smooth muscle responsiveness. Arginase is a potential target for the structure-based design of inhibitors that could be useful for the treatment of ED.

Role of androgens in sexual arousal

The role of androgens in sexual development and their effects on sexual desire and arousal are well documented, but the mechanisms by which androgens modulate erectile tissue structure and function in men is not well understood.²⁰ Using animal models, androgens have been shown to alter NO synthase activity in the brain, adrenergic receptor levels and PDE-5 activity in the penis, and cavernosal smooth muscle and connective tissue content.^{20,21} Autonomic neurons in the lumbosacral spinal cord possess androgen receptors, but their significance remains unclear.⁷ In contrast, no strong correlation exists between plasma androgen levels and erectile func-

tion, as evidenced by hypogonadal men who do not necessarily suffer from ED.²⁰ Also, men with ED do not always regain normal erectile function after testosterone supplementation. Thus, androgens undoubtedly play a significant role in erectile function, but the clinical relevance is yet to be determined.

Aging and sexual function

Understanding the aging process and its influence on male sexual arousal and function may hold the key in preventing ED. Aging is the strongest correlate with ED, but whether this is because of disease states associated with the aging process or whether the process of aging independently affects sexual function is not known. One hypothesis does link the reduction in du-

Adult males undergo three to five erectile episodes per night, with each lasting 20 to 40 minutes.

ration of nocturnal penile tumescence in the aging male with compromised erectile function. Adult males undergo three to five erectile episodes per night, with each lasting from 20 to 40 minutes. The intermittent exposure of the erectile tissue to arterial levels of oxygenation during sleep-related erections is thought to regulate the synthesis of cytokines, growth factors, and prostaglandins that can regulate the structure and cellular composition of the corpora cavernosa.²² Increased connective tissue and decreased smooth muscle content are associated with ED as a result of venous leak.

For men with high-risk profiles for ED, prophylactic therapies would ultimately be a better alternative than seeking treatment after acquiring ED. Oral medications such as sildenafil or phentolamine (Vasomax[®]) may enhance the total duration of nocturnal penile tumescence and prevent progressive fibrosis of the erectile tissue. A pilot study has shown that a 6-week treatment regimen with sildenafil can progressively enhance or fully restore erectile function in men with prostate cancer previously exposed to beam radiation therapy.²³ Since radiotherapy normally results in tissue fibrosis and loss of erectile function, regular use of erectogenic agents in older men may similarly aid in delaying or reversing ED, by increasing tissue oxygenation. Other age-associated alterations may play a role in the loss of erectile function.

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Multidrug therapy

Given the many factors that contribute to ED and the overlapping mechanisms that regulate sexual arousal and

erectile function, it stands to reason that treatment with a combination of drugs may be more effective in cases that are not adequately managed with a single drug. Laboratory studies suggest that forskolin (an adenylyl cyclase activator that is a naturally occurring substance, isolated from the root of the herb *Coleus forskohlii*) and alprostadil act in a synergistic fashion to induce penile erection.²⁴ In one study of men who were nonresponsive to intracavernosal injection with a combination of alprostadil, papaverine, and phentolamine, 61% improved rigidity and/or duration of erection when forskolin was added.²⁴


The use of oral alpha-blockers in conjunction with intracavernosal alprostadil has also been beneficial for patients who do not respond to intracavernosal therapy alone.²⁵ Studies have shown that alpha-adrenergic antagonists enhance the effects of various vasodilators,²⁶ and NO-donor compounds have been shown to interact synergistically with alprostadil.²⁷ The design of novel multifunctional molecules is another possible strategy. Nitrosylated alpha-adrenergic receptor antag-

The suggestion that depression, cardiovascular disease, and ED share many risk factors and etiologies has direct implications on the approach to treatment.

onists may be potential treatments for ED. Acting as both adrenergic receptor antagonists and NO donors, these compounds induce penile erection in animal studies.²⁸ The rationale for multidrug therapy for ED has been developed, but the specific clinical applications require further investigation.

Conclusion

Caring for patients with ED requires a holistic perspective regarding the individual and his partner. Psychosexual counseling should be considered as an integral part of a multidisciplinary treatment approach, and seemingly unrelated conditions in the patient's history should not be ignored. The suggestion that depression, cardiovascular disease, and ED share many risk factors and etiologies and are interrelated has direct implications on the approach to treatment. Incorporating lifelong physical activity regimens will enhance general well-being and may also reduce the risk of sexual dysfunctions. Finally, the dynamics of the relationship should always factor into choosing a course of treatment. Many specialists en-

courage patients to bring their partners with them to office visits. Restoration of erectile function in the absence of a stable and loving relationship may ultimately be unsatisfactory for both the patient and the partner. 

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