Review Paper

# The Role of Nitric Oxide in Erectile Dysfunction: Implications for Medical Therapy

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*Erectile dysfunction is a common, multifactorial disorder that is associated with aging and a range of organic and psychogenic conditions, including hypertension, hypercholesterolemia, diabetes mellitus, cardiovascular disease, and depression. Penile erection is a complex process involving psychogenic and hormonal input, and a neurovascular nonadrenergic, noncholinergic mechanism. Nitric oxide (NO) is believed to be the main vasoactive nonadrenergic, noncholinergic neurotransmitter and chemical mediator of penile erection. Released by nerve and endothelial cells in the corpora cavernosa of the penis, NO activates soluble guanylyl cyclase, which increases 3',5'-cyclic guanosine monophosphate (cGMP) levels. Acting as a second messenger molecule, cGMP regulates the activity of calcium channels as well as intracellular contractile proteins that affect the relaxation of corpus cavernosum smooth muscle. Impaired NO bioactivity is a major pathogenic mechanism of erectile dysfunction. Treatment of erectile dysfunction often requires combinations of psychogenic and medical therapies, many of which have been only moderately successful in the past. The advent of oral phosphodiesterase type 5 (PDE-5) inhibitors, however, has greatly enhanced erectile dysfunction treatment; patients have demonstrated high tolerability and success rates for improved erectile function. The efficacy of the PDE-5 inhibitors also serves to illustrate the importance of the NO–cGMP pathway in erectile function since these agents counteract the degradation of NO-generated cGMP. Because not all patients respond to PDE-5 inhibitors, additional therapies are being investigated, such as soluble guanylyl cyclase activators and NO donors, which act on NO-independent and NO-dependent pathways, respectively. (J Clin Hypertens. 2006;8(12 suppl 4):53–62)* ©2006 Le Jacq

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Erectile dysfunction (ED) is a common and complex disorder that significantly impacts quality of life and is recognized as an important public health problem.[1–3] Defined as an inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse, ED is associated with aging and an increasing number of common systemic diseases including hypertension, cardiovascular disease (CVD), diabetes mellitus, hypercholesterolemia, and depression, as well as behaviors such as smoking, alcoholism, and drug abuse.[2,4] Evidence suggests that ED may serve as a general marker for occult CVD and as an indicator of general physical and emotional health.[3,5,6]

Estimates of the prevalence of chronic ED in the United States have varied, partly because of differences in methodology and populations in epidemiologic studies.[7] An international study[8] that included 9284 men aged 20–75 years in the United States found that the prevalence of ED in this population was 22% in 2001, which would translate to approximately 20 million men. The Massachusetts Male Aging Study,[9] conducted from 1987–1989 in Boston, showed that the combined prevalence of minimal, moderate, and complete

ED in men aged 40–70 years was 52%, with complete impotence increasing from 5% to 15% from 40–70 years. A larger study, however, of more than 31,000 US health care professionals aged 53–90 years found that the age-standardized prevalence of ED, using conservative criteria of poor to very poor function, was 33%, ranging from about 25% among those younger than 59 years to 61% in individuals older than 70 years.[7] Overall, the prevalence of moderate ED in the United States appears to be about 20% in the total adult male population, 30%–50% in those aged 40–70 years, and >60% in men older than 70. Reflecting the epidemiologic scope of this disorder, more than 23 million men have been prescribed sildenafil citrate since its release in 1998.[10]

Increased study of the epidemiology of ED has been accompanied by significant advances in research in its pathogenesis and treatment.[3,8] Once largely attributed to psychological causes and aging, ED is now understood to have a complex organic etiology in many patients.[4,7,9,11] The considerable evidence linking ED with CVD suggests that both may share the pathogenic pathway of endothelial dysfunction, which is characterized by impaired bioactivity of the nitric oxide (NO) signaling pathway.[7,11] Research has identified NO, a major component of endothelial function, as the primary biochemical mediating erectile function and impairment of NO release or actions as a major pathogenic mechanism of organic ED.[12–14] This article will explore the role of NO in erection physiology and pathophysiology and the potential therapeutic strategies that target NO as a treatment for ED.

## PHYSIOLOGY OF ERECTILE FUNCTION

Penile erection is a remarkably complex process that relies primarily on a neurovascular, nonadrenergic, noncholinergic (NANC) mechanism peripherally, as well as the central nervous system.[2,15] The erectile response is modulated by psychological factors and androgens and may proceed through psychogenic or reflexogenic neuronal pathways.[2,15] Detumescence is controlled by sympathetic responses through release of norepinephrine, which induces smooth muscle constriction, vasoconstriction, and penile flaccidity.[16,17] Therefore, a penile erection occurs when both detumescence is inhibited and erectile response stimulated and when penile blood inflow exceeds outflow.[16,17]

A psychogenic erection is triggered by external erotic input received through the 5 senses or mental fantasies that are processed in the medial preoptic area, including the paraventricular and supraoptic nuclei, of the hypothalamus of the brain.[16,18] In response, the hypothalamus releases multiple amines and neuropeptides, including gonadotropin-releasing hormone, oxytocin, α-melanocyte–stimulating hormone, and substance P, which stimulate the erectile response.[16] These neurohormones then project to the thoracolumbar sympathetic nerve fibers at the $T_{11}$–$L_2$ region and to sacral $S_2$–$S_4$ parasympathetic nerve fibers, which inhibit and stimulate penile erection, respectively.[16]

Stimulation of the sacral parasympathetic nerves is carried through the pelvic plexus and subsequently the cavernous nerves of the corpora cavernosa, which are the 2 parallel columns of erectile tissue of the penis.[2,16] The cholinergic and NANC nerve fibers of the corpora cavernosa, in turn, trigger the release of vasoactive neurotransmitters, including acetylcholine and NO, which promote relaxation of cavernosal trabecular smooth muscle and cause a several-fold increase in blood flow to the corpora cavernosa and expansion of their sinusoids.[16,18] The resultant penile tumescence causes compression of the emissary veins, which run through the tunica albuginea, a sheath-like tissue around the corpora cavernosa; this compression occludes venous drainage, which traps the blood and produces rigidity.[2] In addition, sexual activity triggers the bulbocavernosus reflex, causing the ischiocavernous muscles to forcefully compress the base of the perfused corpora cavernosa, resulting in further, or full, rigidity.[2]

A reflexogenic erection is triggered by direct physical stimulation of the genital organs. While the stimulation sends ascending messages to the brain, it also sends direct messages via a local neural loop involving parasympathetic sacral nerve stimulation from $S_2$–$S_4$ to create the erectile response.[16,18] Nocturnal penile erection, which occurs during rapid eye movement sleep, is poorly understood, but appears to occur through central nervous system mechanisms and involves such neuromediators as serotonin, dopamine, noradrenalin, glutamate, γ-aminobutyric acid, and NO processed in the pontine reticular formation and amygdalae.[18,19]

### NO in Erection Physiology

NO is believed to be the main vasoactive NANC neurotransmitter of erectile action in the corpora cavernosa.[2,4,15] The enzyme NO synthase (NOS), which catalyzes NO from the conversion of L-arginine to L-citrulline, has been localized to neuronal tissue, endothelium, and epithelium within pelvic and urogenital structures of humans and

various animal species.[20,21] The erectile response is triggered with the initial release of NO by the autonomic NANC dilator nerve fibers supplying the corpora cavernosa and the vascular and sinusoidal endothelium.[2] Further NO release from the endothelium results from blood flow shear forces.[22] NO then diffuses across the smooth muscle membrane and activates soluble guanylate cyclase (sGC), which catalyzes the production of 3′,5′-cyclic guanosine monophosphate (cGMP).[2] The increased cGMP activates a protein kinase that phosphorylates specific proteins and ion channels, resulting in the opening of potassium channels and hyperpolarization of the muscle cell membrane.[2,15] These actions lead to the sequestration of intracellular calcium by the endoplasmic reticulum and to blockade of calcium channels and calcium influx, which causes decreased cytosolic calcium levels, relaxation of vascular smooth muscle, and vasodilation.[2,15] Neuronal NO may also mediate the neurotransmission of erectile stimuli from the brain through the spinal cord, although these functions have not been well characterized.[13] The erectile actions of NO have been demonstrated in human penile tissue samples and in a range of experimental in vitro and in vivo animal studies.[23–26]

**Role of NOS Isoforms**

Of the 3 known isoforms of NOS—neuronal NOS, endothelial NOS (eNOS), and inducible NOS—neuronal NOS and eNOS are constitutively present in the corpora cavernosa, although to varying degrees and in different cell types.[4] Neuronal NOS is primarily localized to NANC cells of nerve fibers of the corpora cavernosa although it is also expressed in the paraventricular nucleus of the brain, where it may interact with erectile response neurohormones such as oxytocin, and in the spinal cord, where the mechanisms of NO in erectile function are unclear.[13] eNOS is chiefly found in the endothelium of the vasculature of the penis, although controversy exists over whether it may also be found in cavernosal smooth muscle.[4,13,15,27] Inducible NOS has been detected in the corpora cavernosa, most probably in smooth muscle cells, in association with inflammatory effects or other pathologic changes of the penis.[15,28]

Neuronal NO has been assumed to play the major role, compared with the other NOS isoforms, in facilitating relaxation of the corpora cavernosa and inducing increased blood flow to produce penile erection.[15,29] Increasing evidence suggests, however, that while neuronal NO promotes initial cavernosal relaxation, endothelial NO is essential in facilitating the achievement and maintenance of full erection.[22,30] In vivo studies have shown that intracavernosal administration of an adenovirus containing the eNOS gene to old or diabetic rats with ED significantly improved erectile function, as measured by intracavernous pressure, in response to cavernous nerve stimulation, underscoring the physiologic effects of eNOS in erectile function.[31,32] In addition, intracavernosal administration of vascular endothelial growth factor, which promotes endothelial cell proliferation and migration in vitro and angiogenesis in vivo, has been shown to restore erectile function and endothelium-dependent smooth muscle relaxation in rat and rabbit models of ED.[33–36]

**Modulators of NOS**

Findings from rat studies suggest that NO-mediated cavernosal relaxation in erection physiology is in part regulated by testosterone, of which the active metabolite appears to be dihydrotestosterone.[37,38] Castration in rats has been correlated with a 50% reduction in the erectile response to electrical field stimulation of the cavernous nerve.[37] Conversely, administration of testosterone and dihydrotestosterone to castrated rats has been shown to restore NO-mediated intracavernosal pressure and the erectile response.[37,38] The association of androgens with cavernosal NOS activity in humans is less clear, however.[39] In addition, experimental studies suggest that NO-mediated relaxation of the corpora cavernosa is also related to the physiologic levels of oxygen, and can be inhibited in states of hypoxia.[40,41]

## ERECTILE DYSFUNCTION

Consistent with the complex physiology of penile erection, ED may be caused by 1 or more of a range of psychologic, neurologic, vasculogenic, hormonal, or pharmaceutical factors, and is broadly classified as psychogenic, organic, or mixed (Table I)[2,13]; psychogenic and organic causes of ED are frequently concomitant.[4] Epidemiologic studies have shown that after adjustment for age, ED is significantly associated with CVD, hypertension, diabetes mellitus and associated medications, hypercholesterolemia, metabolic syndrome, obesity, smoking, and lower urinary tract symptoms, as well as anger, depression, and fewer years of education.[8,9,42–46] Neurologic diseases such as Parkinson's disease are also recognized as a cause of ED (Table I).[2] An analysis of data from a managed-care claims database covering 51 health plans and 28 million lives in the United States showed that 68% of all patients with ED (N=272,325) had 1 or more of the following 4

**Table I.** Common Causes of Erectile Dysfunction

| Category of Erectile Dysfunction | Causes of Dysfunction | Characteristics |
|---|---|---|
| Psychogenic | Performance anxiety | Loss of libido, overinhibition, or impaired nitric oxide release |
| | Relationship problems | |
| | Psychological stress | |
| | Depression | |
| | Schizophrenia | |
| Neurogenic | Stroke or Alzheimer's disease | Dysfunction of initial nerve impulse or interrupted neural transmission |
| | Spinal cord injury | |
| | Radical pelvic surgery | |
| | Diabetic neuropathy | |
| | Pelvic injury | |
| Hormonal | Hypogonadism | Loss of libido and inadequate nitric oxide release |
| | Hyperprolactinemia | |
| Vasculogenic (arterial or cavernosal) | Atherosclerosis | Inadequate arterial flow or impaired veno-occlusion |
| | Hypertension | |
| | Diabetes mellitus | |
| | Trauma | |
| | Peyronie's disease | |
| Drug-induced | Antihypertensive and antidepressant drugs | Central suppression |
| | Antiandrogens | Decreased libido |
| | Alcohol abuse | Alcoholic neuropathy |
| | Cigarette smoking | Vascular insufficiency |
| Caused by other systemic diseases and aging | Old age | Usually multifactorial resulting in neural and vascular dysfunction |
| | Diabetes mellitus | |
| | Chronic renal failure | |
| | Coronary heart disease | |

comorbidities: hypertension, hyperlipidemia, diabetes mellitus, or depression.[47]

Among the most common organic risk factors, diabetes mellitus is associated with a particularly high prevalence of ED, with estimates ranging from 27%–75%, and with greater severity than in nondiabetic men. This association may be related to diabetic vasculopathy, neuropathy, or hypogonadism.[6,48–50] A survey found that the rate of hypertension in more than 285,000 men with ED in the United States was 41.2%, compared with 19.2% in more than 1.5 million men without ED, representing an odds ratio of 1.38 for hypertension to be present with ED, after controlling for age and other variables ($P<.0001$).[51] High plasma levels of total and low-density lipoprotein cholesterol were associated with odds ratios for ED of 1.74 ($P=.04$) and 1.97 ($P=.02$), respectively, in men with ED compared with those without ED.[52]

While the pathogenic links between each of these risk factors and ED have been elucidated to varying degrees, they are all strongly associated with CVD.[53] Indeed, a study in 417 men with ED (mean age, 59.1 years) showed that 92.1% had 1 or more risk factors for coronary heart disease (CHD).[54] Furthermore, ED may be an early marker for the presence of CHD among asymptomatic individuals. Studies have found a significantly increased rate of ED among men without symptomatic ischemia but with established CHD markers, such as elevated C-reactive protein, endothelial dysfunction, and angiographic evidence of atherosclerosis.[5,55,56] A study in 300 patients with symptomatic ischemic heart disease (mean age, 62.5 years) found that 49% had ED, of whom 67% reported having experienced ED symptoms before the onset of CHD symptoms.[57] These and other data have led to an increased focus on the neurovascular mechanisms of ED, with a particular emphasis on the role of endothelial dysfunction and impaired NO bioactivity.[58]

**Impaired NO Bioactivity in ED**

Peripheral vascular mechanisms of ED may involve failure of occlusion of the exit veins; inability of the cavernous smooth muscle to relax because of age-related fibrosis; degeneration or dysfunction of gap junctions; insufficient release of NO related

| **Table II.** Specialized Tests for Men With Erectile Dysfunction (ED) | |
|---|---|
| Test | Indications |
| Intracavernous pharmacoerection test | Suspected vasculogenic ED |
| Pharmacopenile duplex ultrasonography (PPDU) | Abnormal penile vasodilation test; suspected veno-occlusive dysfunction or Peyronie's disease |
| Nocturnal penile tumescence and rigidity (NPTR) test | Abnormal PPDU; determine whether psychogenic or organic ED |
| Cavernosometry/cavernosography | Abnormal NPTR; suspected congenital or traumatic venous leakage |
| Pelvic arteriography | Traumatic arterial insufficiency |

to a range of possible organic or psychogenic factors; or deficient vascular communication between the corpora cavernosa and spongiosum or glans, which may be congenital or stem from trauma or penile surgery.[16] Of these pathogenic mechanisms, impairment of NO bioactivity may be most important and offers a viable target for ED therapy.[13] Several animal models of ED have supported the role of impaired endothelium-dependent vasodilation and reduced NO bioavailability.[59,60]

The role of NO in diabetic ED has been the subject of several studies. An early in vitro study found that relaxation of human cavernosal smooth muscle in response to electrical stimulation and to acetylcholine was significantly reduced in tissue samples from diabetic men, compared with the response in tissues from nondiabetic men ($P$=.001 for both), and that this relative impairment increased with the duration of diabetes mellitus ($P$=.007).[61] In animal studies, type 1 and type 2 diabetic rats with ED have been shown to have markedly reduced NOS activity and content, possibly related to corresponding reductions in serum testosterone, compared with nondiabetic control rats.[62] Other rat models have found that diabetes-impaired NO bioactivity stemmed from lack of NOS-stimulating cofactors or presence of inhibitory factors associated with hyperglycemia, rather than reduction in NOS protein content.[63,64]

The role of impaired endothelium-dependent vasodilation and reduced NO bioavailability in ED has also been supported by various animal models of hypertension,[65] hypercholesterolemia,[66] and ischemia.[66,67] Overall, studies have consistently demonstrated the importance of impaired NO bioactivity resulting in reduced cavernosal relaxation as a common pathophysiologic basis for ED. Current studies are underway to clarify the precise mechanisms of impaired NO bioactivity for various disease states and risk factors associated with ED.

## MEDICAL TREATMENT OF ED

Based on the complexity of ED, optimal treatment of this disorder requires a multifactorial approach, including a thorough physical examination, laboratory evaluation, and a complete medical, sexual, and psychosocial history.[2] In addition to laboratory tests recording endocrine and metabolic functions, urologic health, and CVD risk factors, specific tests for erectile function may be appropriate (Table II).[2,16] First-line treatment options for ED fall into 3 major categories: psychologic, medical, and hormonal; a combination of these therapies is often indicated (Table III).[2,68] Until recently, however, most therapies for ED have been cumbersome, uncomfortable, and only moderately effective in some patients.[4,18]

### Oral PDE-5 Inhibitors

Phosphodiesterase type 5 (PDE-5) inhibitors are the first effective oral therapies for ED. These therapies have greatly enhanced ED treatment and are considered first-line therapies for ED regardless of etiology.[18] The 3 PDE-5 inhibitors that have been approved for use in the United States between 1998 and 2003—sildenafil, vardenafil, and tadalafil—have demonstrated similar efficacy in a broad population, including men with CHD, hypertension, diabetes mellitus, or post-radical prostatectomy; psychogenic, organic, or mixed causes of ED; and those with mild-to-severe ED.[18,69,70] Efficacy of PDE-5 inhibitor therapy ranges from 65%–75% for successful intercourse to 80%–85% for significantly improved erections, based on measures of the International Index of Erectile Function, compared with placebo.[18,71–73] These agents do not affect libido, however, which is usually a function of hormonal or psychologic status.[18] Indeed, it is important to note that underlying causes of ED such as depression, diabetes mellitus, or hypogonadism should be investigated and treated in combination with initiation of PDE-5 inhibitor therapy.

The PDE-5 inhibitors are also generally well tolerated, with headache, facial or chest flushing, dyspepsia, and sinusitis being the most commonly reported adverse events, occurring in 5%–40% of patients.[18,71–73] Dose-dependent visual disturbances

**Table III.** Treatment Options for Erectile Dysfunction (ED)

| Treatment | Therapies | General Indications |
|---|---|---|
| Psychosexual therapy | Counseling with sex therapist | First-line treatment |
| Hormonal | Testosterone replacement with intramuscular injection, dermal patches, gel | First-line treatment |
| | Treatment of secondary causes: hyperthyroidism, hypothyroidism, diabetes mellitus | |
| Medical | Treatment and control of ED risk factors: hypertension, dyslipidemia, diabetes mellitus, smoking, cardiovascular disease, and neurologic diseases | First-line treatment |
| Nonspecific | | |
| Oral agents | Phosphodiesterase type 5 inhibitors: sildenafil, vardenafil, tadalafil | First-line treatment |
| Devices | Vacuum constriction devices | Second-line treatment |
| | Venous constriction rings | |
| Implants | Flexible rods | Third-line treatment |
| | Inflatable cylinders | |
| Intracavernosal injections | Prostaglandin $E_1$ | Second-line treatment |
| | Papaverine, phentolamine | |
| | Papavarine, phentolamine prostaglandin $E_1$ | |
| | Potassium channel openers | |
| Intraurethral suppositories | Prostaglandin $E_1$ | Second-line treatment |
| Vascular surgeries | Penile microvascular arterial bypass | Third-line treatment |
| | Penile venous ligation | |

such as color distortion and light sensitivity have been reported in up to 3% of men receiving PDE-5 inhibitor therapy, but these events appear to be transient.[2,71] Since the primary mechanism of action of the PDE-5 inhibitors is arterial vasodilation, the most prevalent concerns regarding use of these agents involve the potential for hypotension and cardiovascular events, particularly in elderly patients and those with CVD.[18] Safety and tolerability data indicate that the risks of myocardial infarction and of mortality from stroke or myocardial infarction in men receiving these drugs are low, with rates comparable to placebo and the general population.[2,18,74]

All of these agents are contraindicated in patients taking nitrates for angina pectoris; addition of a PDE-5 inhibitor greatly compounds the vasodilatory effect of nitrates, and this combination has resulted in severe hypotension and deaths in the United States.[2,18,70] This contraindication underlines the close correlation between the mechanisms of action of PDE-5 inhibitors and NO in erectile function.[75] An in vitro study in isolated vessel rings of rat aorta, however, found that sildenafil did not potentiate the vasodilatory action of the β-blocker nebivolol, which induces endothelium-dependent vasodilation through stimulation of NO release.[76,77] Thus, the interaction between PDE-5 inhibition and organic nitrates may not apply to the NO-stimulating action of nebivolol, and PDE-5 inhibitors appear to be safe to use with this agent.[76]

**PDE-5 Inhibition and NO**

NO promotes penile vasodilation and blood flow by diffusing across the smooth muscle membrane and activating sGC to produce cGMP, resulting in an enzymatic cascade that inhibits calcium influx, lowers cytosolic calcium concentrations, and thus induces relaxation of cavernosal smooth muscle.[2] PDE-5 catalyzes the degradation of cGMP, facilitating smooth muscle contraction.[18,78] PDE-5 is the most important of the PDEs in the corpora cavernosa.[79] By selectively blocking the PDE-5 enzyme, PDE-5 inhibitors thus preserve and sustain the NO-triggered increase in cGMP that promotes cavernosal trabecular smooth muscle relaxation.[18]

Impaired NO bioactivity, as often occurs in diabetes mellitus or advanced CHD or neuropathy, may limit cGMP formation whereby the action of PDE-5 inhibition is inapplicable; this may account for nonresponse to oral ED therapy.[80] In hypercholesterolemic rabbits with reduced cavernosal relaxation in response to sodium nitroprusside,

sildenafil nitrate, an NO-donating derivative of sildenafil, improved erectile function to a greater degree than regular sildenafil, suggesting that the NO-donating component was important in compensating for the impairment of NO bioactivity in hypercholesterolemia and the resulting reduction in cGMP.[81]

Other data, however, suggest that sildenafil at tissue levels approaching millimolar concentrations may act at least in part independently of the NO–cGMP pathway.[82,83] Several agents have also been shown in rat and rabbit models of ED to activate sGC and thus stimulate cGMP production and induce cavernosal tissue relaxation and penile erection independently of NO by binding to a novel allosteric site in the enzyme different from the NO-binding site.[84,85] These sGC activators are under investigation as a possible new class of ED therapies.[84] Nonetheless, the central importance of NO in erectile function was demonstrated in a study showing that the effect on erectile function of the sGC activator BAY 41–2272 alone in conscious rabbits was weak, but it was potentiated by concomitant administration of the NO donor sodium nitroprusside.[86]

### NO-Based Therapies

Although there is a clear rationale for the direct targeting of penile NO in the treatment of ED, development of such therapies is still largely in the preliminary stages, in part owing to the complexity of the multiple physiologic mechanisms of NO.[13,87] Transdermal administration of nitroglycerin, an organic nitrate, via ointment, patch, or plaster has demonstrated only moderate and inconsistent efficacy in improving erectile function, and also has been observed to cause headaches.[13,88] Similarly, oral L-arginine supplements in men with ED have yielded inconclusive results and may only be effective in men with reduced exogenous NO production.[89,90] The NO donor linsidomine chlorhydrate has also been investigated for use in ED therapy, but it has demonstrated only minimal-to-moderate efficacy in clinical trials.[91,92]

New classes of NO donors, including sildenafil nitrate and *S*-nitrosothiols, have demonstrated more promising results in experimental animal models of ED.[93,94] A possible advantage of these new therapies is that they may have minimal hemodynamic effects, resulting in less risk of adverse events.[93] In addition, various combinations of ED therapies, including those targeting NO, are being considered and tested in patients nonresponsive to monotherapies.[95]

## CONCLUSIONS

NO is an essential mediator of erectile function, and impaired NO bioactivity is associated with ED. Treatment of ED often involves a combination of psychogenic and organic therapies. The major first-line oral therapy for ED involves PDE-5 inhibitors, which block an enzyme that degrades cGMP; they have proven to be highly effective and well tolerated in most patients with ED, regardless of etiology. These agents depend on sufficient NO-stimulated production of cGMP, however, which is decreased by severe underlying disease, such as CHD or diabetes mellitus. Alternate therapies for ED may be necessary in some patients, possibly in combination with a PDE-5 inhibitor. Speculative therapies include sGC activators, which act through an NO-independent mechanism, and NO donors, which promote NO-dependent relaxation of cavernosal smooth muscle.

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