Oral Pharmacotherapy for Male Sexual Dysfunction

A Guide to Clinical Management

Edited by

Gregory A. Broderick, MD

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Oral Pharmacotherapy for Male Sexual Dysfunction

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Preface

For the generation that reached sexual maturity in the 1960s, the "pill" became synonymous with sexual freedom and started a sexual revolution. For women it meant freedom from the fear of pregnancy, and for men enhanced sexual opportunity. The new era of the pill has nothing to do with fertility, but everything to do with sex. The first orally effective prescription drug for treating erectile dysfunction (ED) was marketed in 1998. Sildenafil (Viagra®) has rejuvenated the aging male veterans of the sexual revolution, forever changed the science of sexual medicine, and transformed society's perspective on aging and sex. This class of drugs, known as oral phosphodiesterase inhibitors (PDE-type 5), is highly effective in the treatment of ED. Since its introduction there has been a much greater awareness of ED, its comorbidities, and its effects on the quality of life. In 1997, while preparing to address the Endocrine Society on the occasion of the 92nd American Urological Association meeting, I first looked at the preclinical studies of sildenafil. I thought "this will change everything" and it clearly has—changing practice patterns in sexual medicine, and the attitudes of patients, potential patients, and their partners. Two new PDE-type 5 inhibitors, tadalafil (Cialis®) and vardenafil (Levitra®), were first approved by the European Committee for Proprietary Medicinal Products and subsequently by the Food and Drug Administration in 2003 and 2004.

The new PDE-5 inhibitors have given health care providers a choice in prescribing therapy for ED, but it remains to be seen whether these or subsequent agents will provide the opportunity to treat more patients or, for that matter, to treat the same patients more effectively and safely. Pharmacological management of ED can now be given as a tablet, as a sublingual preparation, as an intraurethral pellet, as a topical gel, and as an injection. Current lines of study are looking at inhalation as a faster route of treatment delivery. These various drugs work through differing physiological mechanisms: amplifying penile blood flow elicited by sexual stimulation, enhancing neural signaling, and in some instances can even induce erection without sexual stimulation.

The 1970s saw the development of safe and effective surgery; the penile implant was a specific surgical solution addressing only one aspect of male sexual dysfunction. This compendium addresses each aspect of male sexual dysfunction: interest, performance, and orgasm. With the advent of oral

medications, the burden of first evaluation has fallen on the primary care provider. *Oral Pharmacotherapy for Male Sexual Dysfunction* is written for the urologists, family physicians, internists, and residents-in-training who need to be familiar with the diagnostic approaches to male sexual dysfunction and pharmacological strategies for its safe and effective management.

Oral Pharmacotherapy for Male Sexual Dysfunction begins with a review of penile anatomy, physiology, and pharmacology written by Dr. Tom Lue, who first described the hemodynamics of erection, and inspired me some 20 years ago to take up this subspecialty. Dr. John Mulhall of Cornell University addresses common medical risk factors for ED, and the controversial issue of whether lower urinary tract symptoms independent of aging are causally linked to ED? Dr. Irwin Bischoff has devoted a lifetime of effort to pharmaceutical research, and I am grateful that prior to his retirement he accepted this task of summarizing the pharmacology and development of PDE-type 5 inhibitors. Dr. Harin Padma-Nathan has a unique practice devoted to clinical trials, and shares his insights on the preclinical data and five years postmarketing data on sildenafil. Dr. Culley Carson of the Department of Urology at the University of North Carolina has been extensively involved with the design and conduct of US clinical trials of tadalafil. Dr. Ajay Nehra, a consultant for Mayo Clinic, independently reviews the preclinical data on vardenafil. Dr. Louis Kuritzky from the Department of Family Medicine University of Florida, is a lecturer, teacher, and advocate of sexual health in the primary care setting. Dr. Ira Sharlip is a practicing urologist in San Francisco and past president of the Sexual Medicine Society of North America; he addresses who should be referred to a urologist and shares his strategy on how to evaluate and manage men who have atypical presentations that require focused testing. Dr. Robert Kloner of the Keck School of Medicine at the University of Southern California describes how to assess the risk of sexual function in the cardiac patient and just how safe PDE inhibitors are for these men. Dr. Vivian Fonseca of Tulane University tackles the complex pathophysiology of diabetic ED and reviews treatment outcomes in this difficult patient group. Dr. Raymond Rosen, author of a widely used research instrument, the International Index of Erectile Function, specifically looks at the epidemiology of depression and ED, and reviews the mechanisms of antidepressant-associated ED. Dr. Wayne Hellstrom of Tulane University reviews the literature on intracavernous, transurethral therapies, and on topical therapies. Dr. Hellstrom further provides a strategy for using combinations of drugs in refractory patients. Drs. Alvaro Morales, Jeremy Heaton, and Michael Adams of Queens University, Ontario, Canada

together review the impact of androgen deficiencies, the neural regulation of erection, and neuropharmacological therapies for ED. I have asked Dr. Ronald Lewis, of the Division of Urology at the Medical College of Georgia to write the only chapter on vacuum erection devices and surgical implants; despite the abundance of drugs for ED, every clinician should be familiar with these options and outcomes. Every day in my practice I am confronted by patients who self-medicate with dietary supplements; every clinician will appreciate Dr. Mark Moyad's review of this topic and for addressing lifestyle changes in the management of male sexual health. No one in the United States can match the clinical experience of my Australian colleague Dr. Chris McMahon; he reviews the topic of rapid ejaculation and the emerging pharmaceutical therapies for its management. Dr. Andrew McCullough of New York University reviews the literature on prostatectomy; he shares his prospective series on these patients giving us an idea of the pathophysiology, natural rates of recovery, and medical management of post-prostatectomy ED. The last chapter is written by Dr. Ridwan Shabsigh of Columbia University. Female sexual dysfunction (FSD) is emerging as a new subspecialty. I have challenged Dr. Shabsigh to share what is currently known about the types of FSD and its epidemiology, pathophysiology, and current treatments.

I am indebted to all the authors for the year they have spent compiling these reviews and I know the readers will learn much from their various treatment strategies for male sexual dysfunction.

Gregory A. Broderick, MD

Contents

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1 Physiology and Pharmacology of Erectile Dysfunction

Rafael Carrion, MD, Derek Bochinski, MD, Nadeem Rahman, MD, and Tom Lue, MD

CONTENTS

INTRODUCTION

Erectile dysfunction affects a significant proportion of the male population, making it a common urological disorder. It is defined as the inability to obtain or maintain an erection that is sufficient for satisfactory sexual intercourse. Many factors contribute to erectile physiology and pathophysiology. Much of the current understanding of erectile physiology was acquired in the 1980s and 1990s. In addition to the role of smooth muscle in regulating arterial and venous flow, the three-dimensional structure of the tunica albuginea and its role in venous occlusion have been elucidated. Pivotal research identified the importance of nitric oxide (NO), which is the major neurotransmitter for penile tumescence, and its counterpart, the phosphodiesterases (PDEs), which return the penis to a flaccid state. Subsequent studies have shown an important distinction between neurogenic- and endothelial-generated NO, in that the latter essentially helps in maintaining penile erection. Moreover, the role of endothelium in regulating smooth muscle tone and the intercellular link by means of gap junctions have also been uncovered. More recently, research has shown that changes to the

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downstream signaling pathways (RhoA/Rho-kinase pathway) may be of physiological importance in regulating cavernosal smooth muscle tone. In the pathophysiology of erectile dysfunction, the changes in the smooth muscle, endothelium, and fibroelastic framework with hypertension, diabetes, atherosclerosis, and aging have also been identified. The anatomy and physiology of erectile function are discussed in detail in this chapter *(1)*.

ANATOMY OF THE PENIS

The penis is composed of three cylindrical structures: the paired corpora cavernosa and the corpus spongiosum. The urethra traverses the corpus spongiosum. A cross-section of the midpenis depicts the relationship between the various anatomical elements (Fig. 1) *(2)*.

The flaccid length of the penis is controlled by the contractile state of the erectile smooth muscle and varies considerably. Studies have shown that neither age nor the size of the flaccid penis accurately predicts erectile length and that 15% of men have a downward curve during erection *(3,4)*. Regarding penile morphology and erection, a study shows that during erection, the penile buckling forces are dependent not only on intracavernosal pressures but also on penile geometry and erectile tissue properties. Therefore, patients can have inadequate penile rigidity despite having normal penile hemodynamics *(5–7)*.

Tunica Albuginea

The tunica affords great flexibility, rigidity, and tissue strength to the penis *(8)*. The tunical covering of the corpora cavernosa is a bilayered structure with multiple sublayers and is predominantly collagenous. The inner circular layer contains the corpora cavernosa. Radiating from this inner layer are intracavernosal pillars acting as struts, providing essential support to the erectile tissue. Outer-layer bundles are oriented longitudinally, extending from the glans penis to the proximal crura. The corpus spongiosum lacks an outer layer or intracorporeal struts, ensuring a low-pressure structure during erection (Fig. 2) *(1,2,9)*.

The tunica is composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest. The detailed histological composition of the tunica is dynamic, changing with specific anatomical locations. Emissary veins run between the inner and the outer layers for a short distance, often piercing the outer bundles in an oblique manner. The cavernous artery and the communicating arteries between the cavernous and the dorsal artery (both from the common penile artery) take a more direct route and are surrounded by a periarterial soft tissue sheath. The latter structure helps protect the arteries from occlusion by the tunica albuginea during penile tumescence *(10)*.

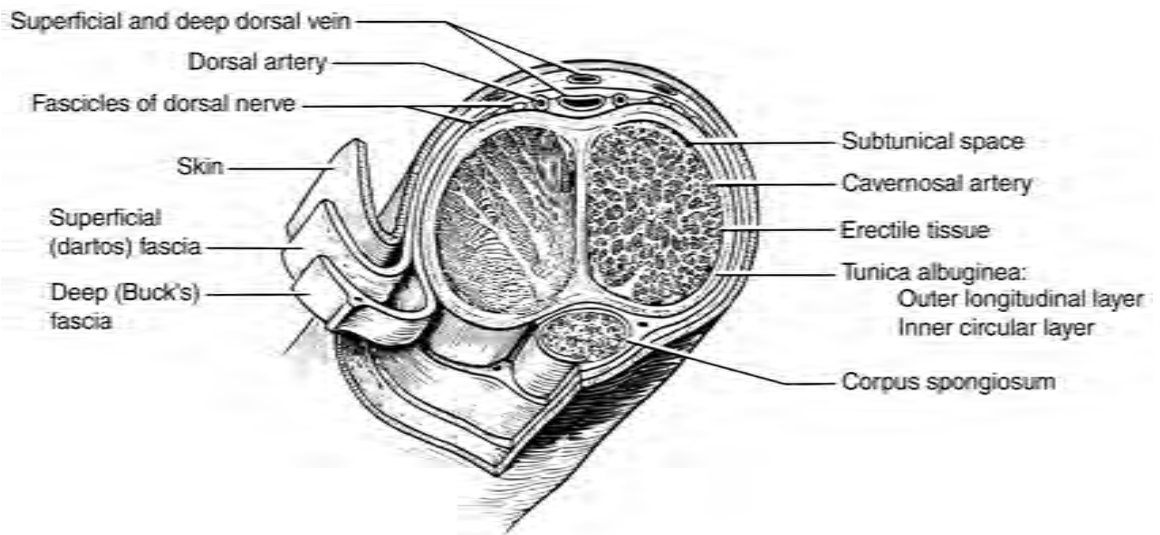


Fig. 1. Cross-section of the penis demonstrating relationships between penile layers and various components.

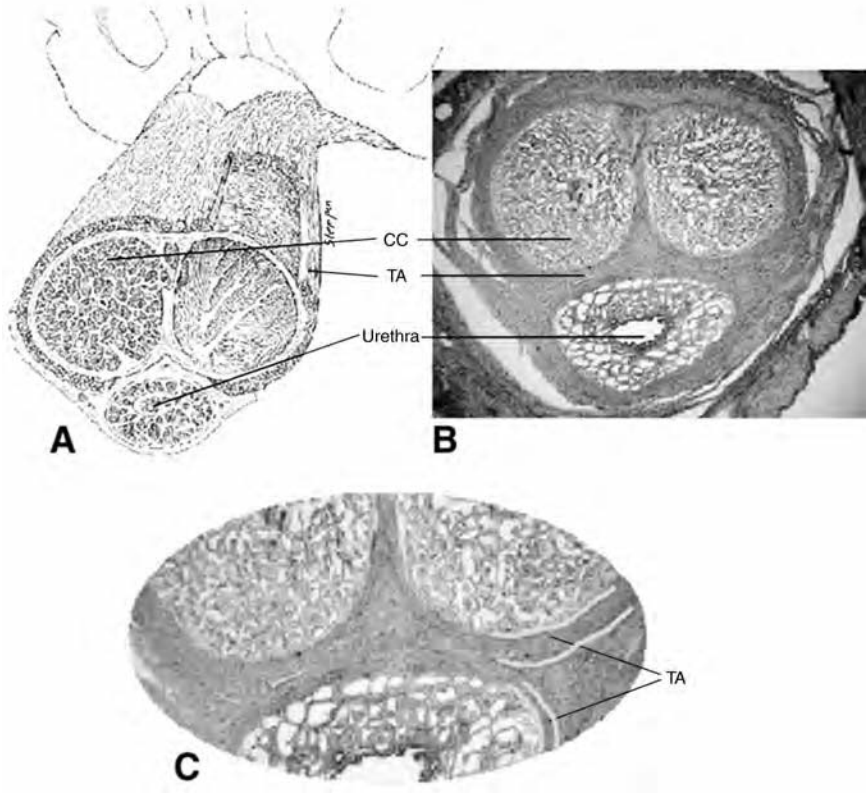


Fig. 2. (A) Schematic displaying a cross-section of the penis with intracavernous pillars supporting the erectile tissue and the inner circular and outer longitudinal layers of the tunica albuginea. **(B)** Transverse section of the penis from a human male specimen at 36 wk of gestation, stained with hematoxylin and eosin. (Courtesy of Dr. Antonio E. P. de Souza, Jr., and Laurence S. Baskin, University of California at San Francisco, Children's Medical Center.) **(C)** Zoom of the center area of the gross picture emphasizing the difference in the thickness of the tunica albuginea around the corpora cavernosa and corpus spongiousum. TA, tunica albuginea; CC, corpora cavernosa.

The outer tunical layer appears to play an additional role in compression of the emissary veins during erection. This important layer essentially determines tunical thickness and strength *(8)*. Studies have shown that the tunica is thickest at the 11- and 1-o'clock positions and thinnest at the 5- and 7-o'clock positions. This results in different corresponding measured stresses on the tunica.

The strength and thickness of the tunica correlate in a statistically significant fashion with location. Predictably, the most vulnerable area is

located on the ventral groove (between the 5- and the 7-o'clock positions), which lacks the longitudinally directed outer-layer bundles discussed earlier. This fact is important because most of the prosthetic extrusions occur here *(8,10)*.

Corpora Cavernosa, Corpus Spongiosum, and Glans Penis

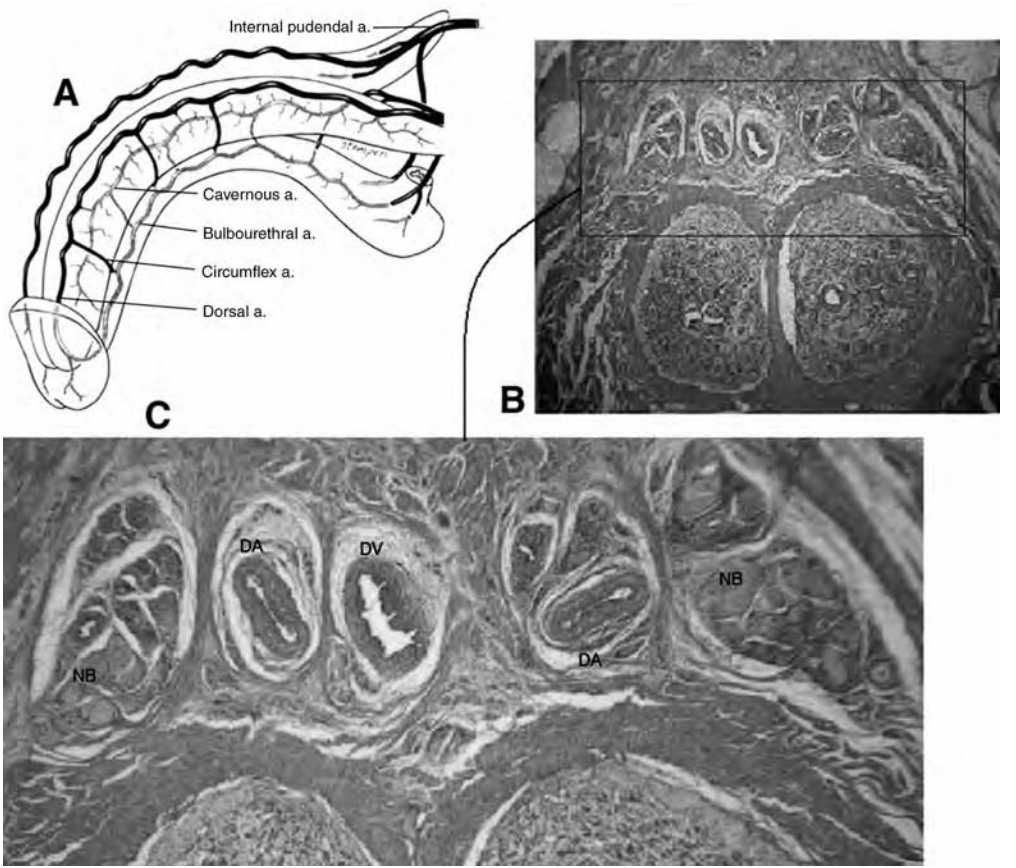
As stated earlier, the corpora cavernosa comprise two spongy, paired cylinders contained in the thick envelope of the tunica albuginea. Their proximal ends—the crura—originate at the undersurface of the puboischial rami as two separate structures but merge under the pubic arch and remain attached up to the glans. The septum between the two corpora cavernosa are typically incomplete but may be functionally complete in some congenital anomalies, such as in epispadias.

The corpora cavernosa are supported by a fibrous skeleton that includes the tunica albuginea, the septum, the intracavernous pillars, the intracavernous fibrous framework, and the periarterial and perineural fibrous sheath *(8,11)*. Some studies have hypothesized that the intracavernous framework adds significant strength to the tunica albuginea *(12)*. Within the tunica are the interconnected sinusoids, which are separated by smooth muscle trabeculae surrounded by elastic fibers, collagen, and loose areolar tissue. The terminal cavernous nerves and helicine arteries are intimately associated with the smooth muscle. Each corpus cavernosum is a conglomeration of sinusoids, larger in the center and smaller in the periphery. In the flaccid state, the blood slowly diffuses from the central to the peripheral sinusoids, and the blood gas levels are similar to those of venous blood. During erection, the rapid entry of arterial blood to both the central and the peripheral sinusoids changes the intracavernous blood gas levels to those of arterial blood. The structure of the corpus spongiosum and the glans is similar to that of the corpora cavernosa, except that the sinusoids are larger. Moreover, as previously discussed, the tunica is thinner in the corporus spongiosum and absent in the glans.

Arterial Supply

The main source of blood supply to the penis typically arises from the internal pudendal artery, which travels through Alcock canal, becomes the common penile artery, and then gives its branches to supply the penis (Fig. 3).

In addition to this rich vascular supply, accessory arteries can exist. These can arise from the external iliac, obturator, vesical, or femoral arteries. Clinically, this becomes important because the accessory blood supply may become the dominant or only arterial supply to the corpus cavernosum *(13)*. Damage to these accessory arteries during radical prostatectomy or


A
Internal pudendal a.
Cavernous a.
Bulbourethral a.
Circumflex a.
Dorsal a.
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C
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cystectomy may result in vasculogenic erectile dysfunction (ED) after surgery *(14,15)*. The three terminal branches of the penile artery are the dorsal, the bulbourethral, and the cavernous arteries. The bulbourethral artery enters proximally to supply the urethra, corpus spongiosum, and glans. The cavernosal artery pierces the corporal body in the penile hilum and subsequently gives off straight and helicine arteries that supply the cavernous sinuses. These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection *(16)*. The dorsal artery courses the dorsal surface of the corpora cavernosa in between the dorsal nerve and vein, and as it travels to the glans it branches to the cavernosum, spongiosum, and urethra. Distally, these three arterial branches join to form a vascular ring near the glans.

Venous Drainage

The venous drainage from the three corpora originates in tiny venules leading from the peripheral sinusoids immediately beneath the tunica albuginea. These venules travel in the trabeculae between the tunica and the peripheral sinusoids to form the subtunical venular plexus before exiting as the emissary veins. Once outside the tunica albuginea, the venous drainage follows one of three patterns:

1. The skin and subcutaneous tissue: Multiple superficial veins run subcutaneously and unite near the root of the penis to form a single (or paired) superficial dorsal vein, which in turn drains into the saphenous veins.
2. The pendulous penis: The emissary veins from the corpus cavernosum and spongiosum drain dorsally to the deep dorsal vein, laterally to the circumflex vein, and ventrally to the periurethral vein. Beginning at the coronal sulcus, the prominent deep dorsal vein is the main venous drainage of the glans penis, corpus spongiosum, and distal two-thirds of the corpora cavernosa. This venous pathway runs upward behind the symphysis pubis to join the periprostatic venous plexus.
3. The infrapubic penis: Emissary veins draining the proximal corpora cavernosa join to form cavernous and crural veins. These veins join the periurethral veins from the urethral bulb to form the internal pudendal veins.

Fig. 3. *(opposite page)* **(A)** Schematic showing the longitudinal view of the penile arterial supply. **(B)** Transverse section of the penis from a human male specimen at 36 wk of gestation, stained with hematoxylin and eosin. (Courtesy of Dr. Antonio E. P. de Souza, Jr., and Laurence S. Baskin, University of California at San Francisco, Children's Medical Center.) **(C)** Magnfication of the penile dorsal area showing the various neurovascular structures. DA, dorsal artery; DV, dorsal vein, NB, nerve bundle.

The veins of the three systems communicate variably with each other. Variations in the number, distribution, and termination of the venous systems are common *(1,17)*.

Nerve Supply of the Penis

The penis is innervated by both the autonomic and somatic nervous systems. Somatic innervation is derived from the S2 to S4 sacral nerve roots and travels via the pudendal nerve. These paired nerves supply the pelvis, perineum, and penis. They terminate as the dorsal nerve of the penis.

The somatosensory pathway originates at the sensory receptors in the penile skin, glans, and urethra and within the corpus cavernosum. The nerve fibers from the receptors converge to form bundles of the dorsal nerve of the penis, which joins other nerves to become the pudendal nerve. The latter enters the spinal cord via the S2 to S4 roots to terminate on spinal neurons and interneurons in the central gray region of the lumbosacral segment *(18)*. Activation of these sensory neurons sends messages of pain, temperature, and touch by means of spinothalamic and spinoreticular pathways to the thalamus and sensory cortex for sensory perception. The dorsal nerve of the penis was previously regarded as a purely somatic nerve; however, nerve bundles testing positive for nitric oxide synthase (NOS), which is autonomic in origin, have been demonstrated *(19,20)*. Thus, the dorsal nerve is a mixed nerve with both somatic and autonomic components, which enable it to regulate both erectile and ejaculatory function.

Onuf's nucleus in the S2 to S4 spinal segments is the center of somatomotor penile innervation. These nerves travel in the sacral nerves to the pudendal nerve to innervate the ischiocavernosus and bulbocavernosus muscles. Contraction of the ischiocavernosus muscles produces the rigid-erection phase. Rhythmic contraction of the bulbocavernosus muscle is necessary for ejaculation.

Studies in animals have identified the medial preoptic area (MPOA) and the paraventricular nucleus of the hypothalamus and hippocampus as important integration centers for sexual function and penile erection *(21)*. Electrostimulation of this area induces erection, and lesions at this site limit copulation. Efferent pathways from the MPOA enter the medial forebrain bundle and the midbrain tegmental region (near the substantia nigra). Pathological processes in these regions, such as Parkinson's disease or cerebrovascular accidents, are often associated with ED.

In the autonomic nervous system, the preganglionic parasympathetic fibers also arise from S2 to S4, then travel to the pelvic plexis (joined with the hypogastric nerves), where they become pelvic nerves and subsequently form three to six trunks that lie deep to the parietal pelvic fascia and cover the piriformis muscle. The sympathetic nerves arise from the

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Fig. 4. The molecular mechanism of penile smooth muscle contraction. Norepinephrine from sympathetic nerve endings and endothelins and prostaglandin $F_{2\alpha}$ from the endothelium activate receptors on smooth muscle cells to initiate the cascade of reactions that eventually result in elevation of intracellular calcium concentrations and smooth muscle contraction. Protein kinase C is a regulatory component of the Ca^{2+}-independent, sustained phase of agonist-induced contractile responses. (From ref. *72*.)

segments T10–L2. They synapse at the sympathetic chain ganglia and then pass along the lumbar splanchnic nerves, superior hypogastric plexus, and finally caudally to the pelvic plexus. Here they intermingle with the parasympathetic fibers. The pelvic plexis innervates the prostate, seminal vesicles, bladder, and rectum. Caudally, fibers from the plexus give rise to the cavernous nerves, which traverse the posterolateral aspect of the prostate to finally supply the corpora cavernosa, corpus spongiosum, and penile urethra *(2,17,22,23)*. Finally, the interactions of the autonomic nervous system, coupled with the mediating transmitters, play an integral role in the contraction and relaxation physiology of the cavernous smooth muscle cell (Fig. 4).

Stimulation of the parasympathetic nerves induces penile tumescence, and stimulation of the sympathetic fibers results in detumescence. Moreover, studies have shown that even with pathological processes that knock off the reflex erectile response (sacral parasympathetic centers), erection can be obtained with stimulation of the MPOA or thoracolumbar sympathetic pathways *(24,25)*. Because the number of synapses between the thoracolumbar outflow and the postganglionic parasympathetic and somatic neurons is less than the sacral outflow, the resulting erection will not be as strong. Hence, many patients with sacral spinal cord injury retain psychogenic erectile ability even though reflexogenic erection is abolished. These cerebrally elicited erections are found more frequently in patients with lower motor neuron lesions below T12 *(26)*. No psychogenic erection occurs in patients with lesions above T9 *(27)*.

In general, there are three types of erections: psychogenic, reflexogenic, and nocturnal. *Psychogenic erection* is a result of audiovisual stimuli or fantasy. Impulses from the brain modulate the spinal erection centers (T11–L2 and S2–S4) to activate the erectile process. *Reflexogenic erection* is produced by tactile stimulation of the genital organs. The impulses reach the spinal erection centers; some then follow the ascending tract, resulting in sensory perception, whereas others activate the autonomic nuclei to send messages through the cavernous nerves to the penis to induce erection. This type of erection is preserved in patients with upper spinal cord injury. *Nocturnal erection* occurs mostly during rapid-eye-movement (REM) sleep. Positron emission tomographic scanning of humans in REM sleep shows increased activity in the pontine area, the amygdalae, and the anterior cingulate gyrus, but decreased activity in the prefrontal and parietal cortices. The mechanism that triggers REM sleep is located in the pontine reticular formation. During REM sleep, the cholinergic neurons in the lateral pontine tegmentum are activated, whereas the adrenergic neurons in the locus caeruleus and the serotonergic neurons in the midbrain raphe are silent. This differential activation may be responsible for the nocturnal erections during REM sleep.

PHYSIOLOGY OF NORMAL ERECTION AND DETUMESCENCE

Penile tumescence results from an interplay of neurogenic, vascular, psychogenic, and hormonal factors *(16,28–31)*. The penile erectile tissue, specifically the cavernous smooth musculature and the smooth muscles of the arteriolar and arterial walls, plays a key role in the erectile process. The phases of penile erection are as follows:

1. Flaccid phase—minimal arterial inflow and venous outflow.

2. Latent phase—stimulation causes initial increase in arterial flow secondary to increased parasympathetic tone.
3. Tumescence phase—penile elongation and expansion. Incoming blood is trapped in the expanding sinusoids because of the compression of the subtunical venular plexus (between the tunica albuginea and peripheral sinusoids).
4. Full erection phase—complete penile expansion, arterial inflow decreasing, venous outflow minimal.
5. Rigid erection phase—ischiocavernosus muscle contraction with further increase in intracavernosal pressure.
6. Detumescence phase—increased venous outflow and decreased arterial inflow *(32,33)*.

Without any stimulation, the penis remains in a flaccid state, where the cavernosal smooth muscles are tonically contracted, allowing only a small amount of arterial inflow for nutritional purposes.

During an erection, the smooth muscle cells of the corpora cavernosa relax and the arterial flow increases; however, the pressure in the corpus spongiosum and glans is only one-third to one-half that in the corpora cavernosa because the tunical covering (thin over the corpus spongiosum and virtually absent over the glans) ensures minimal venous occlusion. During the full-erection phase, partial compression of the deep dorsal and circumflex veins between Buck's fascia and the engorged corpora cavernosa contribute to glanular tumescence, although the spongiosum and glans essentially function as a large arteriovenous shunt during this phase. In the rigid-erection phase, the ischiocavernosus and bulbocavernosus muscles forcefully compress the spongiosum and penile veins, which results in further engorgement and increased pressure in the glans and spongiosum. Ejaculation is facilitated by rhythmic contractions of the bulbocavernosus muscles. Finally, withdrawal of the sexual stimulation results in return of baseline tone and degradation of cyclic guanosine monophosphate (GMP) by PDEs within the trabecular smooth muscle.

NEUROTRANSMITTERS

The sympathetic nervous system with its adrenergic impulses plays an active role during the state of penile detumescence. α-adrenergic nerve fibers and receptors have been demonstrated in the cavernous trabeculae and surrounding the cavernous arteries, and norepinephrine has generally been accepted as the principal neurotransmitter in the control of penile flaccidity and detumescence *(34,35)*. α-Adrenoceptors outnumber β-adrenoceptors 10 to 1 *(36)*; it is suggested that sympathetic contraction is mediated by activation of postsynaptic α_{1a}-, α_{1b}-, and α_{1c}-adrenergic receptors *(37,38)* and modulated by presynaptic α_2-adrenergic receptors *(39)*.

Endothelin, a potent vasoconstrictor produced by the endothelial cells, has also been suggested to be a neurotransmitter for detumescence *(40,41)*. In addition, other vasoconstrictors, such as thromboxane A_2, prostaglandin $F_{2\alpha}$, leukotrienes, and angiotensin II, have been proposed *(42–44)*.

In summary, the maintenance of the intracorporeal smooth muscle in a semicontracted (flaccid) state probably results from three factors: intrinsic myogenic activity, adrenergic neurotransmission, and endothelium-derived contracting factors, such as prostaglandin $F_{2\alpha}$ and endothelins *(45)*.

On the other hand, detumescence after erection may be a result of cessation of NO release, the breakdown of second messengers by PDEs, or sympathetic discharge during ejaculation.

Acetylcholine has been shown to be released with electrical field stimulation of human erectile tissue *(46)*. Although acetylcholine is not the predominant neurotransmitter, it does contribute indirectly to penile erection by the presynaptic inhibition of adrenergic neurons and stimulation of the release of NO from endothelial cells *(47)*.

Most researchers still agree that NO released from nonadrenergic/noncholinergic (NANC) neurotransmission and from the endothelium is the principal neurotransmitter mediating penile erection. NO increases the production of cGMP, which in turn relaxes the cavernous smooth muscle *(48–57)*.

NO was first described in 1979 as a potent relaxant of peripheral vascular smooth muscle, with an action mediated by cGMP *(58)*. Subsequently, endothelium-derived relaxing factor was identified as NO or a chemically unstable nitroso precursor *(59,60)*. NO is synthesized from endogenous L-arginine by NOS, which can be inhibited by N-substituted analogues of L-arginine. NO is inactivated by hemoglobin.

In the penis, the NO that is released from nerve endings or endothelial cells diffuses into smooth muscle cells, where it activates soluble guanylyl cyclase, producing cGMP. The exact mechanism by which intracellular cGMP promotes smooth muscle relaxation has not been defined. The most likely mechanism is the activation of cGMP-specific protein kinase, resulting in the phosphorylation and inactivation of myosin light-chain kinase, thereby causing dissociation of myosin and actin and smooth muscle relaxation *(61)*. Both cGMP and cGMP-specific protein kinase may also activate potassium channels, causing hyperpolarization and closure of voltage-dependent calcium channels and a decrease in the level of intracellular calcium. Independent of cGMP, a study also demonstrated that NO may stimulate the opening of Na-K-ATPase and thus cause hyper-polarization *(62)*. A considerable number of studies suggest that cGMP is a more potent relaxant of smooth muscle than cyclic adenosine monophosphate (cAMP). The increased levels of cGMP in response to neurotransmitters

are caused by activation of soluble or particulate forms of guanylyl cyclase in the cell. A study of cGMP-dependent protein kinase I-deficient mice clearly shows that cGMP/cGMP–protein kinase I is the main physiological signaling pathway for penile erection and cannot be substituted by the cAMP-signaling pathway *(63)*.

Other investigators believe that vasoactive intestinal polypeptide (VIP) may be one of the neurotransmitters responsible for erection. VIP-induced relaxation is reportedly inhibited by the NO synthesis blocker N-α-nitro-L-arginine, which has led some researchers to suggest that NO generation is involved in VIP-stimulated smooth muscle relaxation *(64)*.

In a colocalization study, acetylcholine, VIP, and neuronal NOS appear to be colocalized in parasympathetic neurons *(65)*. Thus, they may act synergistically to induce erection through inhibition of α_1 activity by acetylcholine and release of NO by VIP *(66)*.

Acetylcholine, by acting on the presynaptic receptors on adrenergic neurons, has been shown to modulate the release of norepinephrine *(39)*. The release of norepinephrine can also be inhibited by prostaglandin E_1 *(67)*. Conversely, adrenergic neurons, through prejunctional α_2 receptors, can also regulate the release of NO.

A number of factors have been reported to increase both NOS activity and NO release. These include molecular oxygen, androgen, chronic administration of L-arginine, and repeated intracavernous injection of prostaglandin E_1 *(68–70)*. Conversely, decreased NOS activity has been associated with castration, denervation, hypercholesterolemia, and diabetes mellitus.

For adequate penile tumescence, sinusoidal relaxation, arterial dilatation, and venous compression are required *(1,16)*. The importance of smooth muscle relaxation has been demonstrated in animal and human studies *(47,51,54,71)*. There are a variety of relaxant factors, some of which were already discussed, involved in smooth muscle relaxation, and the balance between these and the contractant factors is what predicts the functional state of the penis (Table 1).

As stated earlier, the relaxation of the corpora cavernosa is mediated by increasing levels of either cGMP or cAMP. These important second messengers activate corresponding protein kinases and result in the phosphorylation of certain proteins and ion channels. This event then leads to the opening of the potassium channels (hyperpolarization), sequestration of intracellular calcium by the endoplasmic reticulum, and inhibition of voltage-dependant calcium channels (which block calcium influx). Myosin is subsequently dephosporylated and detaches from the actin filament, and the muscle relaxes. In smooth muscle contraction, the flux in free Ca^{2+} increases in the cytosole. This calcium will bind to calmodulin and activate

Table 1
Factors Involved in Mediating Relaxation and Contraction of Penile Smooth Muscle [a]

Contraction	Noradrenaline[b]
	Endothelin-1[b]
	Neuropeptide Y
	Prostanoids
	Angiotensin II
Relaxation	Acetylcholine[b]
	Nitric oxide[b]
	Vasoactive intestinal polypeptide
	Pituitary adenylyl cyclase-activation peptide
	Calcitonin gene-related peptide
	Adrenomedullin
	Adenosine triphosphate and adenosine
	Prostanoids

[a] This list shows the various factors involved in mediating the degree of relaxation and contraction of the smooth muscle in the penis.

[b] These factors have major implications in modulating penile erectile tissues.

it. The latter catalyzes the phosphorylation of myosin light chains and subsequently triggers the development of force. The intricate molecular mechanisms involved in penile smooth muscle contraction and relaxation are summarized in detail in Figs. 4 and 5 *(1,16,45,51,54,72–77)*.

Recently, attention has been brought to studying the effects of the RhoA/Rho-kinase signaling pathway and its role in penile smooth muscle physiology. This is a calcium-sensitizing pathway that is activated through agonist activation of heterotrimeric G protein-coupled receptors, activation of RhoA through the exchange of guanosine triphosphate for guanosine diphosphate , and dissociation from a guanine nucleotide dissociation inhibitor. This activated RhoA then activates Rho-kinase, which inhibits myosin light-chain phosphatase. This results in a net increase in myosin phosphorylation and the promotion of cellular contraction (Fig. 6) *(74,78,79)*.

Studies are now showing that antagonism of Rho-kinase may stimulate penile tumescence and hence provide an alternative approach to the management of erectile dysfunction *(80,81)*.

PDE

During the return to the flaccid state, cGMP is hydrolyzed to GMP by the highly specific cGMP-binding PDE type 5 (PDE5). The PDE super-

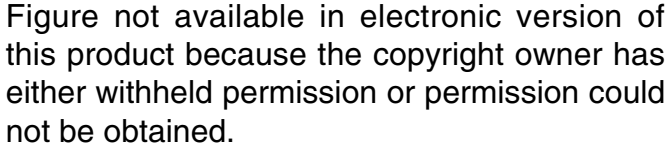

Fig. 5. The molecular mechanism of penile smooth muscle relaxation. The intracellular second messengers mediating smooth muscle relaxation, cyclic adenosine monophosphate and cyclic guanine monophosphate (cGMP), activate their specific kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant fall in intracellular calcium level leads to smooth muscle relaxation. Sildenafil inhibits the action of phosphodiesterase (PDE) type 5 and thus increases the intracellular concentration of cGMP. Papaverine is a nonspecific PDE inhibitor. ATP, adenosine triphosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate. (From ref. *72.*)

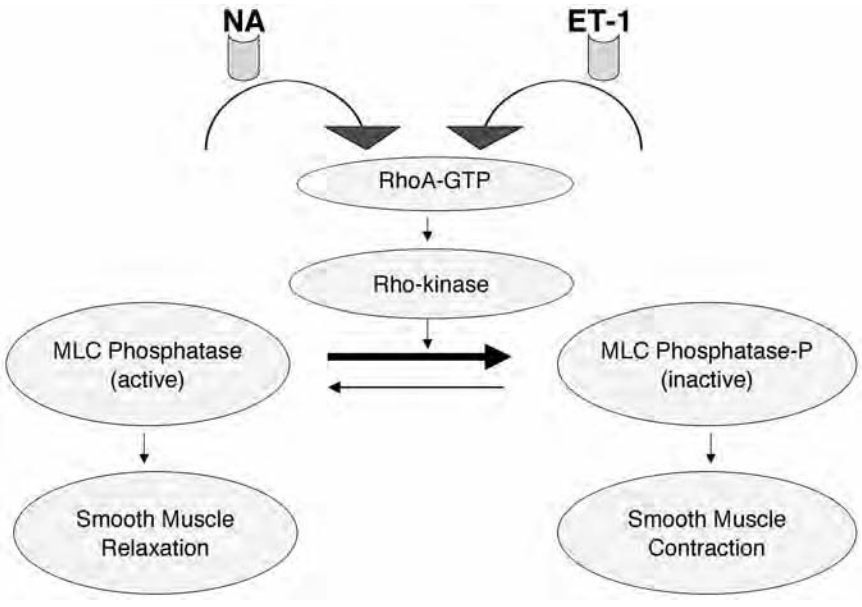

Fig. 6. Simplified flow chart displaying the RhoA/Rho-kinase signaling pathway cascade. Dotted line shows inhibited pathway. ET-1, endothelin-1; MLC, myosin light chain; NA, noradrenaline.

family comprises 11 families of proteins that are encoded by at least 17 genes *(82–84)*. The N-terminal portion contains regulatory domains that 2-, 3, and -4 are also found in the corpus cavernosum, they do not appear to play a significant role in physiological erections when compared with PDE5 *(85)*. The significance and the possible interactions of the PDEs in the penis have yet to be determined, however.

In addition to corpus cavernosum, where three isoforms of PDE5 have been cloned, many other tissues have been reported to express PDE5, including platelet, lungs, cerebellum, spinal cord, skeletal muscle, heart, placenta, pancreas, intestine, aorta, and adrenal gland *(73,86)*. Although one might expect the PDE5 inhibitor sildenafil to have wide-ranging side effects, in clinical trials these have appeared to be limited to the retina (from inhibition of PDE6) and the cardiovascular and gastrointestinal systems (e.g., blurred vision, headache, facial flushing, and indigestion) *(87)*.

Central Neurotransmitters and Neural Hormones

A variety of central neurotransmitters (dopamine, norepinephrine, 5-hydroxytryptamine [5-HT], and oxytocin) and neural hormones (oxytocin,

prolactin) have been implicated in the regulation of sexual function. It is suggested that dopaminergic and adrenergic receptors may promote sexual function and that 5-HT receptors inhibit it *(88)*. Moreover, other substances and hormones, such as endorphins, oxytocin, vasopressin, adrenocorticotropic hormone, and prolactin, also likely participate in the coordinated process of penile tumescence.

Dopamine

There are many dopaminergic systems in the brain with ultrashort, intermediate, and long axons. The cell bodies are located in the ventral tegmentum, substantia nigra, and hypothalamus, one of which—the tuberoinfundibular system—secretes the dopamine into the portal hypophysial vessels to inhibit prolactin secretion. The autonomic and somatic nuclei of the lumbosacral spinal cord are innervated by dopaminergic neurons traveling from the caudal hypothalamus; thus, they potentially participate in the regulation of spinal penile reflexes. There are two main types of receptors associated with erectile function: D1 and D2. D1 receptors predominate in the MPOA (erectile responses), and D2 receptors predominate in the paraventricular nucleus (erections). In men, apomorphine, which stimulates both D1 and D2 receptors, induces penile erection that is unaccompanied by sexual arousal *(89)*. The erectile response induced by injection of apomorphine into the paraventricular area can be blocked by both dopamine receptor blockers and blockers of oxytocin receptors *(90)*. Moreover, NO might be involved as well, because apomorphine given subcutaneously can increase the levels of NOS and NO production in the paraventricular nucleus. Injection of oxytocin into the paraventricular area also induces erection, but this cannot be blocked by dopamine receptor blockers. These findings suggest that dopaminergic neurons activate oxytocinergic neurons in the paraventricular area and that the release of oxytocin produces erection *(91)*. Expectantly, dopamine agonists (apomorphine and pergolide) and dopamine uptake inhibitors (nomifensine and bupropion) have been reported to enhance sexual drive in patients *(92)*.

Serotonin

5-HT-containing neurons have their cell bodies in the midline raphe nuclei of the brainstem and project to a portion of the hypothalamus, the limbic system, the neocortex, and the spinal cord *(93)*. Currently, 5-HT receptors 1–7 have been cloned and characterized. General pharmacological data indicate that 5-HT pathways inhibit copulation but may be facilitatory depending on the action of the amine at different 5-HT receptors in the central nervous system. Studies have summarized the results of the administration of selective agonists and antagonists as follows: 5-HT-1A receptor agonists inhibit erectile activity but facilitate ejaculation; stimu-

lation of 5-HT-2C and 5-HT-1C receptors causes erection; 5-HT-2 agonists inhibit erection but facilitate seminal emission and ejaculation *(45)*.

5-HT is believed to be an inhibitory transmitter in the control of sexual drive *(94)*. Suppressed libido in patients taking fenfluramine, a 5-HT-releasing agent, and elevated libido in patients taking buspirone, a 5-HT neuron suppressor, have been reported *(95)*. Clinically, trazodone (which selectively inhibits central 5-HT uptake) has been reported to enhance nocturnal penile erection and cause priapism in men *(96)*. Its strong sedative effect limits its clinical usefulness, however.

Norepinephrine

Central norepinephrine transmission seems to have a positive effect on sexual function. Animal studies have shown that activation of α_1-adrenoceptors facilitates copulation whereas activation of α_2-adrenoceptors inhibits copulation. Clinically in humans, inhibition of norepinephrine release by clonidine (α_2-adrenergic agonist) is associated with a decrease in sexual behavior, and yohimbine (α_2-receptor antagonist) has been shown to increase sexual activity *(97)*.

Opioid

Endogenous opioids are known to affect sexual function, but the mechanism of action is far from clear. Injection of small amounts of morphine into the MPOA facilitates sexual behavior in rats. Larger doses, however, inhibit both penile erection and yawning induced by oxytocin or apomorphine. It is suggested that endogenous opioids may exert inhibitory control over central oxytocinergic transmission *(98)*.

Oxytocin

Oxytocin is a hormone secreted by the neurons directly into the circulation in the posterior pituitary. Besides the posterior pituitary gland, oxytocin-secreting neurons are also found in the neurons projecting from the paraventricular nuclei to the brainstem and spinal cord; thus, oxytocin can also function as a neurotransmitter. The blood level of oxytocin is increased during sexual activity in humans and animals. It is a potent inducer of penile tumescence when injected into the lateral cerebral ventricle, the paraventricular nucleus, or the hippocampus in laboratory animals. Because neurons in the paraventricular area have been shown to contain NOS, and NOS inhibitors prevent apomorphine- and oxytocin-induced erection, it is suggested that oxytocin acts on neurons whose activity is dependent on certain levels of NO *(99,100)*.

Prolactin

Increased levels of prolactin suppress sexual function in men and experimental animals. In rats, high levels of prolactin decrease the genital reflex

and disturb copulatory behavior. It is suggested that the mechanism of prolactin's action is through inhibition of dopaminergic activity in the MPOA and decreased testosterone level. In addition, prolactin may have a direct effect on the penis through its contractile effect on the cavernous smooth muscle *(101)*.

Adrenocorticotropic Hormone and Related Peptides

Propiomelanocortin gives rise to several peptides, including adrenocorticotropic hormone and α-melanocyte-stimulating (α-MSH) hormone, which are involved in erectile responses. There are five cloned subtypes of melanocortin receptors, which interact differently with α-MSH/adrenocorticotropic hormone peptides. The MC3 receptor shows a high density in the hypothalamus and limbic systems, areas that are important for erectile function. In humans, melanotan (a nonspecific α-MSH analogue) has been reported to initiate erections in men with psychogenic erectile dysfunction *(31)*.

As seen in this chapter, many factors contribute to erectile physiology. There have been significant contributions from both anatomical and physiological areas, which enable us to further comprehend the mechanisms involved in penile tumescence and detumescence. This kind of dedication to research will eventually enable us to understand fully the physiology of penile erections and to optimize our treatment approaches to the various pathological states affecting it.

REFERENCES

1. Lue T. (2002) Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, eds., Campbell's Urology, vol 2, 8th Ed. Philadelphia, PA: WB Saunders Co, pp. 1591–1618.
2. Brooks J. (2002) Anatomy of the lower urinary tract and male genitalia. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, eds., Campbell's Urology, vol 1, 8th Ed. Philadelphia, PA: WB Saunders Co, pp. 72–75.
3. Sparling J. (1997) Penile erections: shape, angle, and length. J Sex Marital Ther 23(3):195–207.
4. Wessells H, Lue TF, McAninch JW. (1996) Penile length in the flaccid and erect states: guidelines for penile augmentation. J Urol 156:995–997.
5. Goldstein I, Udelson D. (1998) Axial penile rigidity: determinants and relation to hemodynamic parameters. Int J Impot Res 10(Suppl 2):S28–S33; discussion S49–S51.
6. Nehra A, Azadzoi KM, Moreland RB, et al. (1998) Cavernosal expandability is an erectile tissue mechanical property which predicts trabecular histology in an animal model of vasculogenic erectile dysfunction. J Urol 159:2229–2236.
7. Udelson D, Nehra A, Hatzichristou DG, et al. (1998) Engineering analysis of penile hemodynamic and structural-dynamic relationships: Part III—Clinical considerations of penile hemodynamic and rigidity erectile responses. Int J Impot Res 10: 89–99.

8. Hsu GL, Brock BG, Martinez-Pineiro L, et al. (1992) The three dimensional structure of the human tunica albuginea: anatomical and ultrastructural levels. Int J Impot Res 4:117–129.
9. Hinman FJ. (1998) Correction of penile defects. In: Hinman FJ, ed., Atlas of Urologic Surgery, 2nd Ed. Philadelphia, PA: WB Saunders Co, pp. 165–166.
10. Brock G, Hsu GL, Nunes L, et al. (1997) The anatomy of the tunica albuginea in the normal penis and Peyronie's disease. J Urol 157:276–281.
11. Goldstein AM, Padma-Nathan H. (1990) The microarchitecture of the intracavernosal smooth muscle and the cavernosal fibrous skeleton. J Urol 144:1144–1146.
12. Bitsch M, Kromann-Andersen B, Schou J, Sjontoft E. (1990) The elasticity and the tensile strength of tunica albuginea of the corpora cavernosa. J Urol 143:642–645.
13. Breza J, Aboseif SR, Orvis BR, et al. (1989) Detailed anatomy of penile neurovascular structures: surgical significance. J Urol 141:437–443.
14. Kim ED, Blackburn D, McVary KT. (1994) Post-radical prostatectomy penile blood flow: assessment with color flow Doppler ultrasound. J Urol 152(6 Pt 2):2276–2279.
15. Aboseif S, Shinohara K, Breza J, et al. (1994) Role of penile vascular injury in erectile dysfunction after radical prostatectomy. Br J Urol 73:75–82.
16. Lue TF, Tanagho EA. (1987) Physiology of erection and pharmacological management of impotence. J Urol 137:829–836.
17. Nitahara KS, Lue TF. (1999) Microscopic anatomy of the penis. In: Carson CC, Kirby RS, Goldstein I, eds., Textbook of Erectile Dysfunction. Isis Medical Media, pp. 31–41.
18. McKenna KE. (1998) Central control of penile erection. Int J Impot Res 10 (Suppl 1):S25–S34.
19. Carrier S, Zvara P, Nunes L, et al. (1995) Regeneration of nitric oxide synthase–containing nerves after cavernous nerve neurotomy in the rat. J Urol 153:1722–1727.
20. Burnett AL, Tillman SL, Chang TS, et al. (1993) Immunohistochemical localization of nitric oxide synthase in the autonomic innervation of the human penis. J Urol 150:73–76.
21. Sachs BD, Meisel RL. (1998) The physiology of reproduction. In: Knobil E, Neill JD, Ewing LL, et al., eds., The Physiology of Reproduction. New York, NY: Raven Press, pp. 1393–1423.
22. Aboseif SR, Tanagno EA. (1999) Anatomy of the penis. In: Hellstrom WJ, ed., The Handbook of Sexual Dysfunction. San Francisco, CA: The American Society of Andrology, pp. 2–6.
23. Burnett A. (1999) Neurophysiology of erectile function and dysfunction. In: Hellstrom WJ, ed., The Handbook of Sexual Dysfunction. San Francisco, CA: The American Society of Andrology, pp. 12–17.
24. Courtois FJ, Macdougall JC, Sachs BD. (1993) Erectile mechanism in paraplegia. Physiol Behav 53:721–726.
25. Paick JS, Lee SW. (1994) The neural mechanism of apomorphine-induced erection: an experimental study by comparison with electrostimulation-induced erection in the rat model. J Urol 152(6 Pt 1):2125–2128.
26. Bors E, Comarr AE. (1960) Neurological disturbances in sexual function with special reference to 529 patients with spinal cord injury. Urol Surv 10:191–222.
27. Chapelle PA, Durand J, Lacert P. (1980) Penile erection following complete spinal cord injury in man. Br J Urol 52:216–219.

28. Rosen RC. (2001) Psychogenic erectile dysfunction. Classification and management. Urol Clin North Am 28:269–278.
29. Nehra AM, Moreland RB. (2001) Neurologic erectile dysfunction. Urol Clin North Am 28:289–303.
30. Morales A, Heaton JP. (2001) Hormonal erectile dysfunction. Evaluation and management. Urol Clin North Am 28:279–288.
31. Andersson KE. (2001) Pharmacology of erectile function and dysfunction. Urol Clin North Am 28:233–247.
32. Junemann KP, Lue TF, Melchior H. (1987) The physiology of penile erection. I. Hemodynamics of penile erection. Urologe A 26:283–288.
33. Russell S, Nehra A. (2003) The physiology of erectile dysfunction. Herz 28:277–283.
34. Hedlund H, Andersson KE. (1985) Comparison of the responses to drugs acting on adrenoreceptors and muscarinic receptors in human isolated corpus cavernosum and cavernous artery. J Auton Pharmacol 5:81–88.
35. Diederichs W, Stief CG, Lue TF, Tanagho EA. (1991) Sympathetic inhibition of papaverine induced erection. J Urol 146:195–198.
36. Levin RM, Wein AJ. (1980) Adrenergic alpha receptors outnumber beta receptors in human penile corpus cavernosum. Invest Urol 18:225–226.
37. Christ GJ, Maayani S, Valcic M, Melman A. (1990) Pharmacological studies of human erectile tissue: characteristics of spontaneous contractions and alterations in alpha-adrenoceptor responsiveness with age and disease in isolated tissues. Br J Pharmacol 101:375–381.
38. Traish AM, Netsuwan N, Daley J, et al. (1995) A heterogeneous population of alpha 1 adrenergic receptors mediates contraction of human corpus cavernosum smooth muscle to norepinephrine. J Urol 153:222–227.
39. Saenz de Tejada I, Kim N, Lagan I, et al. (1989) Regulation of adrenergic activity in penile corpus cavernosum. J Urol 142:1117–1121.
40. Saenz de Tejada I, Carson MP, de las Morenas A, et al. (1991) Endothelin: localization, synthesis, activity, and receptor types in human penile corpus cavernosum. Am J Physiol 261(4 Pt 2):H1078–H1085.
41. Holmquist F, Andersson KE, Hedlund H. (1990) Actions of endothelin on isolated corpus cavernosum from rabbit and man. Acta Physiol Scand 139:113–122.
42. Hedlund H, Andersson KE, Fovaeus M, et al. (1989) Characterization of contraction-mediating prostanoid receptors in human penile erectile tissues. J Urol 141: 182–186.
43. Azadzoi KM, Kim N, Brown ML, et al. (1992) Endothelium-derived nitric oxide and cyclooxygenase products modulate corpus cavernosum smooth muscle tone. J Urol 147:220–225.
44. Kifor I, Williams GH, Vickers MA, et al. (1997) Tissue angiotensin II as a modulator of erectile function. I. Angiotensin peptide content, secretion and effects in the corpus cavernosum. J Urol 157:1920–1925.
45. Andersson KE, Wagner G. (1995) Physiology of penile erection. Physiol Rev 75: 191–236.
46. Blanco R, Saenz de Tejada I, Goldstein I, et al. (1988) Cholinergic neurotransmission in human corpus cavernosum. II. Acetylcholine synthesis. Am J Physiol 254 (3 Pt 2):H468–H472.
47. Saenz de Tejada I, Goldstein I, Azadzoi K, et al. (1989) Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med 320:1025–1030.

48. Pickard RS, Powell PH, Zar MA. (1991) The effect of inhibitors of nitric oxide biosynthesis and cyclic GMP formation on nerve-evoked relaxation of human cavernosal smooth muscle. Br J Pharmacol 104:755–759.
49. Holmquist F, Stief CG, Jonas U, et al. (1991) Effects of the nitric oxide synthase inhibitor NG-nitro-L-arginine on the erectile response to cavernous nerve stimulation in the rabbit. Acta Physiol Scand 143:299–304.
50. Trigo-Rocha F, Aronson WJ, Hohenfellner M, et al. (1993) Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs. Am J Physiol 264(2 Pt 2): H419–H422.
51. Ignarro LJ, Bush PA, Buga GM, et al. (1990) Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem Biophys Res Commun 170:843–850.
52. Rajfer J, Aronson WJ, Bush PA, et al. (1992) Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. N Engl J Med 326:90–94.
53. Knispel HH, Goessl C, Beckmann R. (1992) Nitric oxide mediates neurogenic relaxation induced in rabbit cavernous smooth muscle by electric field stimulation. Urology 40:471–476.
54. Ignarro LJ. (1990) Nitric oxide. A novel signal transduction mechanism for transcellular communication. Hypertension 16:477–483.
55. Burnett AL, Lowenstein CJ, Bredt DS, et al. (1992) Nitric oxide: a physiologic mediator of penile erection. Science 257:401–403.
56. Kim N, Azadzoi KM, Goldstein I, Saenz de Tejada I. (1991) A nitric oxide-like factor mediates nonadrenergic-noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. J Clin Invest 88:112–118.
57. Trigo-Rocha F, Hsu GL, Donatucci CF, Lue TF. (1993) The role of cyclic adenosine monophosphate, cyclic guanosine monophosphate, endothelium and nonadrenergic, noncholinergic neurotransmission in canine penile erection. J Urol 149:872–877.
58. Gruetter CA, Barry BK, McNamara DB, et al. (1979) Relaxation of bovine coronary artery and activation of coronary arterial guanylate cyclase by nitric oxide, nitroprusside and a carcinogenic nitrosoamine. J Cyclic Nucleotide Res 5:211–224.
59. Palmer RM, Ferrige AG, Moncada S. (1987) Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327:524–526.
60. Ignarro LJ, Buga GM, Wood KS, et al. (1987) Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Natl Acad Sci USA 84:9265–9269.
61. Draznin MB, Rapoport RM, Murad F. (1986) Myosin light chain phosphorylation in contraction and relaxation of intact rat thoracic aorta. Int J Biochem 18(10):917–928.
62. Gupta S, Moreland RB, Munarriz R, et al. (1995) Possible role of Na(+)-K(+)-ATPase in the regulation of human corpus cavernosum smooth muscle contractility by nitric oxide. Br J Pharmacol 116:2201–2206.
63. Hedlund P, Aszodi A, Pfeifer A, et al. (2000) Erectile dysfunction in cyclic GMP-dependent kinase I-deficient mice. Proc Natl Acad Sci USA 97:2349–2354.
64. Kim YC, Kim JH, Davies MG, et al. (1995) Modulation of vasoactive intestinal polypeptide (VIP)-mediated relaxation by nitric oxide and prostanoids in the rabbit corpus cavernosum. J Urol 153(3 Pt 1):807–810.
65. Hedlund P, Alm P, Andersson KE. (1999) NO synthase in cholinergic nerves and NO-induced relaxation in the rat isolated corpus cavernosum. Br J Pharmacol 127:349–360.

66. Aoki H, Matsuzaka J, Yeh KH, et al. (1994) Involvement of vasoactive intestinal peptide (VIP) as a humoral mediator of penile erectile function in the dog. J Androl 15:174–182.
67. Molderings G, Malinowska B, Schlicker E. (1992) Inhibition of noradrenaline release in the rat vena cava via prostanoid receptors of the EP3-subtype. Br J Pharmacol 107:352–355.
68. Kim N, Vardi Y, Padma-Nathan H, et al. (1993) Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. J Clin Invest. 91:437–442.
69. Escrig A, Marin R, Mas M. (1999) Repeated PGE1 treatment enhances nitric oxide and erection responses to nerve stimulation in the rat penis by upregulating constitutive NOS isoforms. J Urol 162:2205–2210.
70. Marin R, Escrig A, Abreu P, Mas M. (1999) Androgen-dependent nitric oxide release in rat penis correlates with levels of constitutive nitric oxide synthase isoenzymes. Biol Reprod 61:1012–1016.
71. Vargas HM, Ignarro LJ, Chaudhuri G. (1990) Physiological release of nitric oxide is dependent on the level of vascular tone. Eur J Pharmacol 190:393–397.
72. Lue TF. (2000) Erectile dysfunction. N Engl J Med 342:1802–1813.
73. Lin CS, Lau A, Tu R, Lue TF. (2000) Expression of three isoforms of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in human penile cavernosum. Biochem Biophys Res Commun 268:628–635.
74. Andersson KE. (2003) Erectile physiological and pathophysiological pathways involved in erectile dysfunction. J Urol 170(2 Pt 2):S6–S13; discussion S13–S14.
75. Gold ME, Wood KS, Byrns RE, et al. (1990) L-arginine-dependent vascular smooth muscle relaxation and cGMP formation. Am J Physiol 259(6 Pt 2):H1813–H1821.
76. Hoppner CK, Stief CG, Jonas U, et al. (1996) Electrical and chemical control of smooth muscle activity of rabbit corpus cavernosum in vitro. Urology 48:512–518.
77. Lee SW, Kang TM. (2001) Effects of nitric oxide on the Ca^2-activated potassium channels in smooth muscle cells of the human corpus cavernosum. Urol Res 29: 359–365.
78. Chitaley K, Webb RC, Mills TM. (2001) RhoA/Rho-kinase: a novel player in the regulation of penile erection. Int J Impot Res 13:67–72.
79. Somlyo AP, Somlyo AV. (2000) Signal transduction by G-proteins, rho-kinase and protein phosphatase to smooth muscle and non-muscle myosin II. J Physiol 522 (Pt 2):177–185.
80. Chitaley K, Webb RC, Mills TM. (2003) The ups and downs of Rho-kinase and penile erection: upstream regulators and downstream substrates of rho-kinase and their potential role in the erectile response. Int J Impot Res 15:105–109.
81. Chitaley K, Webb RC, Mills TM. (2001) Rho-kinase as a potential target for the treatment of erectile dysfunction. Drug News Perspect 14:601–606.
82. Wingard CJ, Johnson JA, Holmes A, Prikosh A.(2003) Improved erectile function after Rho-kinase inhibition in a rat castrate model of erectile dysfunction. Am J Physiol Regul Integr Comp Physiol 284:R1572–R1579.
83. Fisher DA, Smith JF, Pillar JS, et al. (1998) Isolation and characterization of PDE9A, a novel human cGMP-specific phosphodiesterase. J Biol Chem 273: 15,559–15,564.
84. Soderling SH, Bayuga SJ, Beavo JA. (1998) Identification and characterization of a novel family of cyclic nucleotide phosphodiesterases. J Biol Chem 273: 15,553–15,558.
85. Fawcett L, Baxendale R, Stacey P, et al. (2000) Molecular cloning and characterization of a distinct human phosphodiesterase gene family: PDE11A. Proc Natl Acad Sci USA 97:3702–3707.

86. Ballard SA, Gingell CJ, Tang K, et al. (1998) Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. J Urol 159:2164–2171.
87. Yanaka N, Kotera J, Ohtsuka A, et al. (1998) Expression, structure and chromosomal localization of the human cGMP-binding cGMP-specific phosphodiesterase PDE5A gene. Eur J Biochem 255:391–399.
88. Goldstein I, Lue TF, Padma-Nathan H, et al. (1998) Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 338:1397–1404.
89. Foreman MM, Wernicke JF. (1990) Approaches for the development of oral drug therapies for erectile dysfunction. Semin Urol 8:107–112.
90. Danjou P, Alexandre L, Warot D, et al. (1988) Assessment of erectogenic properties of apomorphine and yohimbine in man. Br J Clin Pharmacol 26:733–739.
91. Melis MR, Argiolas A, Gessa GL. (1989) Evidence that apomorphine induces penile erection and yawning by releasing oxytocin in the central nervous system. Eur J Pharmacol 164:565–570.
92. Melis MR, Stancampiano R, Gessa GL, Argiolas A. (1992) Prevention by morphine of apomorphine- and oxytocin-induced penile erection and yawning: site of action in the brain. Neuropsychopharmacology 6:17–21.
93. Jeanty P, Van den Kerchove M, Lowenthal A, De Bruyne H. (1984) Pergolide therapy in Parkinson's disease. J Neurol 231:148–152.
94. Ganong WF. (1999) Neural basis of instinctual behavior and emotions. In: Ganong WF, ed., Review of Medical Physiology. Stamford: Appleton & Lange, pp. 244–254.
95. Foreman MM, Hall JL, Love RL. (1989) The role of the 5-HT2 receptor in the regulation of sexual performance of male rats. Life Sci 45:1263–1270.
96. Buffum J. (1982) Pharmacosexology: the effects of drugs on sexual function a review. J Psychoactive Drugs 14:5–44.
97. Saenz de Tejada I, Ware JC, Blanco R, et al. (1991) Pathophysiology of prolonged penile erection associated with trazodone use. J Urol 145:60–64.
98. Clark JT, Smith ER, Davidson JM. (1985) Evidence for the modulation of sexual behavior by alpha-adrenoceptors in male rats. Neuroendocrinology 41:36–43.
99. Argiolas A. (1992) Oxytocin stimulation of penile erection. Pharmacology, site, and mechanism of action. Ann NY Acad Sci 652:194–203.
100. Vincent SR, Kimura H. (1992) Histochemical mapping of nitric oxide synthase in the rat brain. Neuroscience 46:755–784.
101. Melis MR, Argiolas A. (1993) Nitric oxide synthase inhibitors prevent apomorphine- and oxytocin-induced penile erection and yawning in male rats. Brain Res Bull 32:71–74.
102. Ra S, Aoki H, Fujioka T, et al. (1996) In vitro contraction of the canine corpus cavernosum penis by direct perfusion with prolactin or growth hormone. J Urol 156(2 Pt 1):522–525.

2 Epidemiology of Erectile Dysfunction

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CONTENTS

INTRODUCTION

Erectile dysfunction (ED) is a pervasive problem among men worldwide. The National Institutes of Health Consensus Conference defined ED as the "consistent inability to attain or maintain a penile erection, or both, sufficient for adequate sexual relations" *(1)*.

This definition better encompasses the full spectrum of activity that is affected by ED, as opposed to definitions considering only vaginal penetration. Furthermore, it was believed that the term ED was less pejorative than the older term *impotence*. The negative impact of ED on a man is tremendous, including diminishment in self-esteem and sense of well-being, and negative affects on relationships with not only partners, but also acquaintances *(2)*.

Recent data from a longitudinal analysis of the Massachusetts Male Aging Study (MMAS) estimated that up to 600,000 new cases of ED occur annually in the United States *(3)*. This is in addition to a prevalence estimated to be 10 to 20 million American men *(4,5)*. The National Health and Social Life Survey (NHSLS) found that 31% of men have sexual dysfunc-

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tion, which they defined broadly in seven different categories, of which ED was one *(6)*. Furthermore, this study reinforced the notion that sexual function strongly affects a man's global sense of well-being and that sexual dysfunction should be a significant public health concern.

The most recent data suggest that ED increases markedly by decade. A telephone survey of 820 men was conducted who were classified as having ED and admitted that they were sometimes or never able to get or keep an erection satisfactory for sexual intercourse *(7)*. Based on these criteria, the prevalence of ED increases from 8% during the 40s to 19% in the 50s to 39% in men older than 60 yr of age.

This study found ED to be associated with diabetes but not ischemic heart disease, elevated cholesterol, or hypertension.

In the past, studies of male sexual health were poorly constructed and anecdotal, and assessed poorly defined patient populations. Recently, with the publication of data from the MMAS, the NHSLS, the Multinational Survey of the Aging Male in seven countries, and a number of international surveys, robust data now exist defining the epidemiology of ED *(3,6,8–14)*.

EPIDEMIOLOGY OF ED

Kinsey

No chapter pertaining to the epidemiology of male sexual dysfunction would be complete without reference to the classic and ground-breaking work by Kinsey et al. They reported the results of their pioneering study of male sexual function and dysfunction in 1948. Their work clearly documented an increase in ED with age *(15)*. They surveyed 12,000 men and found that the prevalence of ED increased dramatically with age. Men younger than 19 yr of age had a less than 1% risk of ED, compared with less than 3% for men younger than 45 yr of age, 7% in men less than 55 yr of age, and 25% in men age 75 or older. Reanalysis of these data suggested that the original report had underestimated the true prevalence of ED. This reanalysis suggested that as many as 42% of a subset of 5000 of the men reported some erectile difficulty *(16)*.

Massachusetts Male Aging Study

The MMAS was a community-based survey of 1290 men 40 to 70 yr of age from the Boston area that specifically examined, among other items, the prevalence and effects of aging on ED in a cohort of healthy men *(8)*. This study also examined the impact of medical comorbidities on ED. Care was taken to exclude men with significant medical problems and to represent minority populations appropriately in the sample. The survey was composed of 23 questions, nine specifically inquiring about erectile function.

The study found that 52% of the population complained of some degree of ED. The breakdown was mild ED in 17% of men, moderate ED in 25% of men, and severe ED in 10% of men overall. Forty percent of men in their 40s experienced ED, whereas 67% of men experienced ED by 75 yr of age. Complete ED was found in 5% of men by 40 yr of age and in 25% of men by 75 yr of age. When extrapolated to the male population in general, this analysis estimated that 30 million American men and 100 million men worldwide have ED.

In addition to epidemiology, this study also examined risk factors associated with ED. Medical conditions that increased the risk of ED after controlling for age in this study included cardiovascular disease, hypertension, diabetes, depression, anger disorders, and arthritis. Medications associated with ED included vasodilators, oral hypoglycemic agents, and antihypertensives. Several factors were found to be protective against ED. These included high-serum high-density lipoprotein levels, elevated serum dehydroepiandrosterone levels, and dominant personality.

A reanalysis of 847 men 40 to 69 yr old was published more recently *(3)*. The reanalysis followed those men who had no measurable ED symptoms at the beginning of the study. The patients were followed for almost 9 yr, and a 13-question sexual function survey was completed by each of the men. The risk of new-onset ED was 26 cases per 1000 men per year, with the risk increasing by age, presence of heart disease or hypertension, and educational level. Further analysis revealed that lifestyle factors also played a role in the occurrence of ED. Obesity was strongly correlated, and physical activity inversely correlated, with ED *(17)*. The most active men had the lowest risk of developing ED; however, obesity at baseline was still associated with an elevated risk of ED regardless of future weight loss. Interestingly, tobacco and alcohol use were not found to be related to ED risk in this study. Based on these data, Johannes et al. estimate that there are 600,000 cases of ED in the United States annually *(3)*.

National Health and Social Life Survey

The NHSLS was a study that used a 90-min interview to examine the risk of having experienced sexual dysfunction within the preceding 12 mo *(6)*. The interview was conducted by an interviewer of identical gender to the interviewee and was carried out on a population that was representative of the general American population. Seven questions in each of seven areas (libido, experience of ED, orgasm, performance anxiety, premature orgasm, pain during intercourse, and lack of enjoyment during intercourse) were asked during this interview. A large cohort of both men (1410) and women (1749) participated in this study, with an age range of 18 to 59 yr.

In men, the incidence of sexual dysfunction was as follows: premature ejaculation, 21%; ED, 5%; and decreased sexual desire, 5%. Seventy percent of men were not affected by any sexual dysfunction in this survey. Risk factors associated with ED in this study were emotional problems, stress, worsening health status, lower urinary tract symptoms, sexual trauma, and deteriorating economic situation.

Furthermore, ED was found to be associated with lower levels of physical and emotional satisfaction, as well as diminished global happiness. For men, premature ejaculation was not found to be associated with negative physical or emotional satisfaction, nor with low levels of happiness. Men with ED, however, were 4.4, 2.4, and 2.5 times more likely to experience low physical satisfaction level, low emotional satisfaction level, or low general happiness level, respectively, than men without ED. A low level of desire was associated with a 3.1- and a 2.6-fold increased risk of having low levels of physical satisfaction and general happiness, respectively. Women are also significantly affected by sexual dysfunction. Low levels of desire, arousal disorder, and sexual pain were all significantly associated with low physical and emotional satisfaction levels, as well as a low general happiness level, to even larger degrees than men in many cases. Clearly, ED specifically, and sexual dysfunction broadly, are associated with reductions in the quality of life.

International Data

A variety of international surveys have explored the prevalence of ED. Surveys of men in Australia, England, Germany, the Netherlands, and Spain have estimated the prevalence of ED to be 11 to 34% in men aged 16 to 80 yr *(10–14)*.

The Kolner Erhebungsbogen der Erektilen (KEED) study of men in Cologne, Germany, used a validated questionnaire and found a dramatic increase in ED with age *(10)*. The investigators collected 4489 questionnaires from respondents with a mean age of 51.8 yr, 66.1% of whom were either married or involved in a long-term relationship. The overall prevalence of ED was 19.2% in all men. They found a 2.3% prevalence of ED in 30 to 39-yr-old men, 9.5% in men in their 40s, 15.7% in men in their 50s, 34.4% in men in their 60s, and 53.4% in men in their 70s. As described in previous studies, age is the strongest risk factor for ED.

Supporting the findings of the MMAS study, the investigators found that hypertension, diabetes, and previous pelvic surgery were strong risk factors for ED. The reported odds ratios for concurrently having ED if one of these was a comorbid condition were found to be 1:58 with hypertension, 3:95 with diabetes, and 6:03 with previous pelvic surgery, indicating strong, significant relationships. This study also found a 72.2% prevalence

of lower urinary tract symptoms (LUTS) in men with ED, compared with 37.7% in men without LUTS. The odds ratio of having ED if one had LUTS was 2:1 compared with men without LUTS. This finding suggests a strong relationship between the two conditions.

Alcohol and tobacco use were not associated with ED.

A major limitation of the KEED/Cologne study was that the International Index of Erectile Function (IIEF) was not used as the measure of ED. This would have allowed easier comparison to many other studies of ED that more often use the IIEF. Furthermore, the 56% response rate, although respectable, still left open the possibility that nonresponders differed in some significant way from responders, thus biasing the study. Overall, given the strong agreement with other large survey trials, the data support a link between ED and age, hypertension, diabetes, previous pelvic surgery, and LUTS.

Community-based populations in Brazil, Italy, Japan, and Malaysia were randomly sampled to assess ED based on their "ability to maintain an erection satisfactory for sexual intercourse" *(18)*. A total of 600 men who were 40–70 yr old from each country were included in the analysis. Moderate to complete ED was found in 34% of Japanese men, 22% of Malaysian men, 17% of Italian men, and 15% of Brazilian men. Prevalence rates of moderate to severe ED increased with age as follows: 9%, 40 to 44 yr of age; 12%, 45 to 49 yr of age; 18%, 50 to 54 yr of age; 29%, 55 to 59 yr of age; 38%, 60 to 64 yr of age; and 54%, 65 to 70 yr of age. The risk of ED increased by 10% per year.

Factors that increased the risk of ED were diabetes, heart disease, LUTS, tobacco use, and depression *(18)*. Higher educational level, high physical activity, and moderate alcohol consumption were associated with a lower risk of ED.

SUMMARY OF EPIDEMIOLOGICAL DATA

ED is a prevalent problem in men worldwide. The condition increases with age and is found in more than 50% of men older than the age of 65–70 yr in most studies. A variety of medical conditions are associated with an increased risk of ED, including diabetes, vascular disease, and depression, as well as elevated cholesterol levels, arthritis, hypertension, and heart disease. Diseases that impair penile blood flow or innervation will most likely have pathophysiological links to ED, whereas diseases that lower a man's sense of well-being may impair libido and mood, leading to secondary reduction in erectile function.

Most surveys have found that physical activity, higher educational background, and moderate alcohol consumption are associated with a lower risk of ED. Whether these factors modify the pathophysiological develop-

ment of ED, exist in men with a better global mood, or are simply associated with a lower risk of comorbid conditions remains unclear.

RISK FACTORS FOR ED

Vascular Disease

Well-known causes of ED include arterial insufficiency and veno-occlusive dysfunction (venous leak). These conditions are related to generalized vascular disease in many patients with ED. Patients with a previous history of a myocardial infarction, hypertension, or peripheral vascular disease all carry an increased risk of developing ED. In fact, more than half of patients who have either experienced a myocardial infarction (MI) or undergone cardiac bypass surgery experience ED *(19,20)*. A decrease in penile–brachial index (PBI) has also been shown to be associated with future risk of MI. Patients with an abnormal PBI were found to have a 12% incidence of MI, vs only a 1.5% incidence in those with normal PBI in one study *(21)*. Most men (80%) with peripheral vascular disease suffer from ED, and 10% of men with untreated hypertension also have ED *(22,23)*.

A recently advanced hypothesis to explain this relationship centers on endothelial dysfunction *(24)*. Briefly, endothelial dysfunction may impair smooth muscle relaxation by interfering with nitric oxide synthesis or release *(25)*. Generalized vascular disease, specifically cardiovascular disease, is associated with ED, and the link is thought to be via endothelial dysfunction in both cases. In fact, many studies now suggest that ED may serve as a marker for occult cardiovascular disease *(26)*.

Diabetes is another systemic disorder that impairs vasculature, as well as neurological function. One-third to three-quarters of men with diabetes will ultimately experience ED *(23)*. By the time many diabetics are diagnosed, they already have ED. It is estimated that in up to 14% of men diagnosed with diabetes, ED predates the diagnosis of their metabolic condition. Men with insulin-dependent diabetes have a higher incidence of ED than those with noninsulin-dependent diabetes *(27)*. Fifty percent of diabetics develop ED within 10 yr of diagnosis *(28,29)*. The effects of diabetes on erectile function occur over a relatively rapid period of time compared with the end-organ effects of diabetes, such as retinopathy and nephropathy. The risk of ED in diabetic men is increased significantly by the presence of other vascular risk factors, including tobacco use, hypercholesterolemia, and hypertension *(30)*.

The metabolic syndrome is a newly described syndrome encompassing systemic dysfunction characterized by glucose intolerance, hypertension, hyperlipidemia, and central obesity *(31)*. This syndrome is now recog-

nized as a risk factor for ED *(32)*. The previously mentioned data linking endothelial dysfunction to ED is likely the link between the metabolic syndrome and ED, because all of the mentioned pathological processes are associated with endothelial damage and dysfunction *(33)*.

LUTS

LUTS and ED are prevalent problems for the aging male. There is little question that the two conditions are linked, at least insofar as both occur in similarly aged populations. The age relationship between LUTS and ED has been demonstrated in population-based surveys across decades and cultures. These associations have also been strengthened by multivariate analyses showing independent relationships between age and LUTS and age and ED. Data from the Multinational Survey of the Aging Male in seven countries found a very strong relationship between age, LUTS severity, and ED *(9)*. This analysis found that for every decade, the percentage of men with moderate (International Prostate Symptom Score [IPSS] 8–19) or severe (IPSS > 19) LUTS increased, and that for each IPSS grouping (IPSS 0, 1–7, 8–19, >19), the frequency of sexual activity declined with age and the prevalence of ED increased.

Blanker et al. surveyed 1600 men with the IPSS and International Continence Study sex questionnaires to investigate a relationship between age, LUTS, and ED in the same study. A multivariate logistic regression analysis of the data found that age, obesity, and urinary tract symptoms were the most important correlates of significant ED *(11)*. A British study found that rigidity of erection and ejaculate volumes decreased with age. Nine percent of men in their 40s, 79% of men in their 70s, and 86% of men in their 80s reported decreases in rigidity of erection. Reduced ejaculation was also found to increase in prevalence with age. Men with LUTS had a significantly higher odds ratio for sexual dysfunction compared with men without urinary symptoms. Overall, a strong relationship between LUTS and ED was found, but no correlation was found between flow rate and ED *(34)*.

Many investigators have found that LUTS adversely impacts patients' overall quality of life. Impaired quality of life is associated with ED, thus there is the potential for a link. Many studies have documented a very large negative impact on quality of life among men with LUTS. In the Olmsted County study, LUTS was associated with significantly worse physical and mental health overall *(35)*. Men with large prostates were twice as likely to be bothered by their symptoms and also twice as likely to think their symptoms interfered with activities of daily life *(36)*. In another study among men with LUTS, 20% reported that urinary dysfunction impaired at least one daily activity most or all of the time *(37)*.

Important basic science work is examining the impact of bladder obstruction on the corpora. Experimental models were created in animals to test the effect of bladder outlet obstruction on cavernosal smooth muscle. These studies have found alterations in the nitric oxide pathway, changes in the histological structure of erectile tissue, and an altered response of corporal smooth muscle to contractile agents *(38–40)*. Thus, whether the link is a result of age, quality of life, or some other physiological derangement, LUTS is definitely associated with ED.

Endocrine Disorders

As previously mentioned, diabetes is the most prevalent endocrinopathy that causes ED. A variety of other hormones also affect erectile function, however. Testosterone influences libido and contributes to nocturnal tumescence; however, the ultimate role of androgens in ED has not been well defined *(41–45)*. Recent studies demonstrated that correcting the hypogonadal state by giving supplemental testosterone improves response to sildenafil in men with ED and low testosterone level *(46)*. Testosterone clearly plays a role in the level of libido, but the exact role in ED is still debated *(45)*. Hyperprolactinemia, hypothyroidism, hyperthyroidism, and adrenal disorders may either lower serum testosterone level or alter the testosterone:estradiol ratio, thus affecting sexual function. These disorders are the cause of less than 5% of cases of organic ED *(47)*.

Psychological Disorders

Psychological factors definitely play a significant role in erectile function. How a poor quality of life links LUTS to ED was already discussed. Four decades ago, most sexual medicine practitioners believed that ED was a result of psychological disorders in most men. The majority of men with ED are now thought to have organic causes, but many psychiatric and psychological conditions have an impact on erectile function. Furthermore, many men with multiple vascular risk factors and documented organic causes of ED have a secondary sexual psychological component contributing to ED. It is now appreciated that many men have mixed ED *(48)*. The link between depression and ED is well established. Many studies have found an increased incidence of ED in men with depression. Interestingly, men with depressive symptoms and ED note improvements in their depression with successful treatment of the ED *(48–51)*.

Poor overall mood may negatively affect erectile function *(52)*. It is believed that a depressed mood contributes to overall low quality of life, which has been shown to impair erectile function in men. Poor marital relationships also negatively affect erectile function *(53)*.

Shabsigh et al. investigated the incidence of depressive symptoms in men who had ED *(51)*. They examined 120 men with either ED, benign prostatic hypertrophy (BPH), or both. They found that 54% of men with ED and 56% of men with ED and BPH but only 21% of men with BPH alone experienced depression. Men with ED had a 2.6-fold increased risk of depressive symptoms as compared with men with BPH alone, which was statistically significant even after controlling for age, marital status, and comorbidities. Furthermore, patients with depression had a significantly lower libido rating than those without depression. This study also found that depression as a comorbid condition of ED complicated treatment. Although 100% of men with ED who were given treatment remained on the treatment plan, only 38.9% of men with depression and ED remained on an ED therapy plan during the study ($p < 0.0002$). Not only are ED and depression related, but having the two seems to complicate treatment for ED.

Recent data from Nigeria also supports a link between depression and ED *(54)*. The IIEF and the patient health questionnaire were completed by 829 Nigerian men in active military service. They examined the relationship between age, depression, alcohol abuse, and panic disorder to erectile dysfunction.

The mean age of the men was 36.7 yr, and 75% were married. ED was found in 39.6% of all men. Thirty-six percent of men younger than 30 yr of age reported ED, as did 31% of men in their 30s, 46% of men in their 40s, 58% of men in their 50s, and 100% of the two men surveyed who were older than 60. Of men with ED, 10.3% were found to experience depressive symptoms. The degree of depression was not associated with ED. Multivariate analysis found that age and depression were predictors of ED in this study, but not alcohol abuse or panic disorder.

The evidence linking depression directly to ED is somewhat weak. Several additional recent studies have found no link between the two conditions. Araujo et al. examined longitudinal data from the MMAS to study the incidence of ED among men with depression *(55)*. They examined longitudinal data gathered over 8.8 yr from 776 respondents to the MMAS to look for the development of ED among men with several psychological problems. The presence of depressive symptoms (analyzed with the Center for Epidemiologic Studies Depression scale [CES-D]) at study entry was not significantly predictive of developing ED during the study ($p = 0.12$). Among men with baseline depression, 13.2% developed ED, compared with 21.3% of men overall (not significant). One limitation of this study was that depressive symptoms and not a diagnosis of major depressive disorder were used to identify men with depression. Intuitively, more severe depression may be related to ED, or, as the authors point out, the effect of depression may be temporary and may lessen with time.

Other recent studies found no association between current depressive symptoms and moderate to severe ED *(56)*. They received questionnaires from 199 men who completed basic health inventories, the CES-D, and an abbreviated version of the IIEF. Moderate or complete ED was found in 36.4% of men, depression was found in 12.1%, and ED with depression was found in 5.1%. Multivariate analysis found no significant relationship between ED and depression; furthermore, the absolute score on the CES-D questionnaire was not related to the presence of moderate or complete ED. This well-done study gives strong support to the finding that depression and ED are not related. However, the relatively low response rate of the subjects to the survey (59.6%) somewhat weakens the data.

Another recent survey found that men with ED often suffer great distress, but only a few fulfill the clinical criteria for a diagnosis of depression. Only 18.6% of a cohort of depressed men who presented for evaluation reported some degree of sexual dysfunction *(57)*. Some of this variation is explained by differences in the definition of depression. Depressed mood and poor quality of life are very common among men with ED, but clinical depression is not as common. Therefore, until a consistent definition of depression is used and a large sample is followed, any relationship between ED and depression must be regarded with skepticism.

Medications

A plethora of medications have been associated with ED. Studies suggest that as many as one-quarter of patients seen in general medical practices have ED as a result of a medication that they take *(58)*. Many patients who take antihypertensives complain of ED. Although the cause of the ED may be directly related to the medications, some studies suggest that the pathophysiological effect of hypertension on the vasculature may contribute to worsening erectile function. In fact, up to 40% of patients who require antihypertensive medications develop ED *(59–61)*. Antihypertensives in such broad classes as β-blockers, calcium channel blockers, diuretics, and ganglionic blockers have all been implicated in ED. Whether the cause is a diminished blood pressure resulting in insufficient inflow to maintain an erection, direct ganglionic blocking action, or an antiandrogen effect (spironolactone), these medications exert a wide range of effects on the erectile mechanism.

The impact of antihypertensive medication use on ED was carefully evaluated in the Treatment of Mild Hypertension Study *(62)*. This double-blind, randomized trial compared placebo with acebutolol, amlodipine, chlorthalidone, doxazosin, or enalapril in terms of the incidence of sexual dysfunction during the study. Age, baseline hypertension, and previous use of antihypertensive medications were associated with ED. At baseline,

12.2% of men reported ED. Although this finding is lower than expected, men with diabetes, cardiovascular disease, and excess alcohol intake were excluded, so this cohort was probably healthier than the average hypertensive group. The incidence of ED among treatment groups and placebo groups was 6 to 17% at 24 mo and 11 to 18% at 48 mo. Only men taking chlorthalidone had a significantly higher risk of developing ED at 24 mo (15.7%) compared with those taking placebo (4.9%, $p < 0.01$). Men taking doxazosin had a lower rate (2.8%), but this was not significant. At 48 mo, no group differed significantly from the placebo group in the incidence of ED. The authors suggested that new-onset ED developing during treatment for hypertension should not be attributed to medication use generally. Sexual dysfunction may be more related to blood pressure control than medication use *per se*.

These findings agree with those of the MMAS, which found ED to be related to hypertension but also found a relationship between antihypertensive-drug use and ED *(8)*. This study may suggest a relationship between medication use as a marker of hypertension rather than between medication use and ED specifically.

The authors find the data from the randomized, placebo-controlled trial to be convincing and caution anyone from attributing ED to antihypertensive medication use until other risk factors for ED are explored fully.

Antidepressants constitute another class of widely used drugs that are believed to impair erectile function *(63)*. Once again, whether this effect is a direct pharmacological one or is related to the underlying disease process for which the patient is using a psychotropic agent remains unclear. The newer selective serotonin reuptake inhibitors have also been associated with ED that may or may not respond to proerectile medications *(64)*. Overall, the treatment of depression may improve ED symptoms. Antidepressants may exacerbate the condition. ED that persists after a bout of depression must be thoroughly investigated to rule out other causes before pharmacological alterations are begun. Other psychiatric medications, including neuroleptics used to treat schizophrenia, are often associated with ED. Both older (clomipramine) and newer (olanzapine) antipsychotics have been implicated in the development of ED *(65,66)*.

Drugs with endocrine effects may contribute to ED. The most widely used are the luteinizing hormone—releasing hormone agonists for the treatment of advanced and metastatic prostate cancer, which are well known to cause ED. Other drugs, including cimetidine, estrogens, and spironolactone, all have been demonstrated to antagonize androgen production or action and may contribute to ED *(67–69)*. Agents that act on cell membranes may impair tonic excitation or relaxation of smooth muscles, which may lead to ED. For example, digoxin potentiates smooth muscle

contraction via its effect on the sodium–potassium–ATPase pump in smooth muscle cells, eventually leading to increased intracellular levels of calcium *(70)*.

Before any medication is changed or discontinued because of a complaint of ED, a thorough search for other causes must be initiated *(59)*. Many of the conditions for which the abovementioned medications are used also exert progressive negative effects on erectile function.

Systemic Diseases

The literature cites an association between a variety of chronic diseases and ED. Chronic renal insufficiency is often associated with ED. Forty to 80% of men with chronic renal insufficiency or end-stage renal disease have some degree of associated ED *(71,72)*. The causes of ED in renal failure include hypogonadism, hyperprolactinemia, diabetic neuropathy, and vasculopathy, or some combination of these factors *(73)*. ED in patients with renal failure may be improved by transplantation but may also require adjunctive treatment *(74–76)*.

Neurological disorders are also commonly associated with ED. Cerebrovascular accidents, multiple sclerosis, and neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease, are all associated with ED *(77,78)*. Following a cerebrovascular accident, up to 85% of men experience ED, and almost 75% of men with multiple sclerosis experience ED *(79,80)*.

Patients with human immunodeficiency virus and acquired immunodeficiency syndrome may acquire an autonomic neuropathy leading to ED *(81)*.

Other conditions that have been associated with ED include chronic obstructive pulmonary disease *(82)*, systemic sclerosis *(83)*, sleep apnea syndrome *(84),* and liver disease *(85)*.

Trauma

Penile or perineal trauma, usually blunt, and pelvic fracture are associated with ED. Up to 50% of men who experience straddle injuries or prostatomembranous urethral disruption in pelvic fractures develop ED *(86)*. Common penile artery injury is thought to account for the pathophysiology of this type of ED *(87)*.

Treatment of posterior strictures (often resulting from trauma) can also lead to the development of ED *(88)*. The cause of ED in this case is thought to be the interruption of the autonomic nerve fibers that run in close proximity to the posterior urethra, either with initial injury or while dissecting the urethra during repair. The IIEF was examined as a tool to evaluate men after pelvic trauma to identify those with ED *(89)*. Of 77 consecutive men

identified, 46 returned the survey; of these men, 29.7% were found to have some degree of ED. Men with pubic diastasis had a significantly increased risk of decreased erection firmness and a significantly lower degree of erection confidence than did men without diastasis. These authors suggested that cavernosal nerve injury at the time of diastasis may account for the increased risk of ED in these men.

A recent study from Israel identified 25 consecutive patients with posterior urethral strictures secondary to pelvic fracture *(90)*. Eighteen (72%) experienced ED before attempted urethral reconstruction. Thirteen of the men were diagnosed with neurogenic ED—as evidenced by normal vascular response on duplex ultrasound with intracavernous injection—and five were diagnosed with arteriogenic ED—as demonstrated by an abnormal arterial response to intracavernous injection. Cases of secondary arteriogenic ED can be treated by penile revascularization *(91)*.

Posterior urethroplasty for stricture is thought to be associated with a small but significant risk of ED. The data for anterior strictures are much better, with a recent large series reporting only one new onset of ED among 168 consecutive patients who underwent anterior urethroplasty *(92)*.

Surgical trauma is also commonly associated with ED. Radical prostatectomy is probably the most commonly performed urological procedure associated with ED. The cause of ED in this case is likely neurological impairment but may also be associated with vascular disease of the corporal bodies *(93,94)*. Pelvic exenteration for either rectal cancer or bladder cancer is also associated with very high rates of resulting ED *(95)*. The sacral nerve roots that supply the autonomic nervous supply to the cavernous nerve, which mediates erection, may be disrupted during radical pelvic surgery.

Trauma can also occur as a result of vigorous physical activity. Extreme bicycling may be associated with ED *(96)*. Compared with age-matched runners, members of a cycling club had a threefold increased risk of developing ED. A Scandinavian review of 160 cyclists found that of men participating in a 540-km race, 22% reported pudendal or cavernous nerve symptoms after the race, with 33 complaining of penile numbness and 21 complaining of impotence *(97)*.

Mountain biking may be associated with even higher rates of ED. The pathophysiology of this effect is thought to be compression of the common penile arteries against the ischiopubic ramus as a result of an unpadded bicycle seat. Recent studies have measured the transcutaneous oxygen pressure in healthy volunteers without ED *(98)*. They found significant decreases in penile oxygen pressure (which correlates well with arterial and tissue pO_2) regardless of the amount of seat padding. Only wider seats were associated with less of a decrease in pO_2. Although an association has been shown, causation is far from established.

SUMMARY

ED is a highly prevalent worldwide problem. This condition increases with age and is more commonly seen with comorbid medical conditions, including cardiovascular disease, diabetes, and neuropsychiatric disorders. Other associated conditions include trauma, pelvic surgery, and cycling. Recent evidence is accumulating to suggest a robust link between LUTS and ED, which until now was thought to be coincidental. Clearly, ED is a cause of substantial morbidity throughout the world and deserves special consideration during the diagnostic evaluation of any patient, male or female, because ED can have a profound impact on overall mood.

REFERENCES

1. Conference NC. (1993) Impotence. NIH Consensus Development Panel on ED. JAMA 270:83–90.
2. Krane RJ, Goldstein I, Saenz de Tejada I. (1989) Impotence. N Engl J Med 321: 1648–1659.
3. Johannes C, Aranjo A, Feldman H, et al. (2000) Incidence of erectile dysfunction in men 40–69 years old: longitudinal results from the Massachusetts Male Aging Study. J Urol 163:460–463.
4. Furlow WL. (1985) Prevalence of ED in the United States. Med Aspects Hum Sex 19:13–19.
5. Shabsigh R, Fishman IJ, Scott FB. (1999) Evaluation of erectile ED. Urology 32: 83–90.
6. Laumann EO, Edward O, Paik A, Rosen R. (1999) Sexual dysfunction in the United States: prevalence and predictors. JAMA 281:537–544.
7. Carson CC, West SL, Glasser DB, et al. (2002) Prevalence and Correlates of Erectile Dysfunction in a United States Nationwide Population-based Sample: Phase I Results. Presented at the American Urologic Association Annual Meeting, Orlando, FL.
8. Feldman HA, Goldstein I, Hatzichristou DG, et al. (1994) Impotence and its medical and psychological correlates: results of Massachusetts male aging study. J Urol 151:54–61.
9. Rosen R, O'Leary MP, Altwein JE, et al. (2003) LUTS and Male Sexual Dysfunction: The Multi-national Survey of the Aging Male (MSAM-7). Presented at the EAU Annual Meeting, Birmingham, UK, Feb. 24, 2003.
10. Braun M, Wassmer G, Klotz T, et al.(2000) Epidemiology of erectile dysfunction: results of the Cologne Male Survey. Int. J Impot Res 12:305–311.
11. Blanker MH, Bohnen AM, Groeneveld FPMJ, et al. (2001) Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. J Am Geri Soc 49:436–442.
12. Martin-Morales A., Sanchez-Cruz JJ, Saenz de Tejada I, et al. (2001) Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. J Urol 166:569–574.
13. Chew KK, Earle CM, Stuckey BG, et al. (2000) Erectile dysfunction in general medicine practice: prevalence and clinical correlates.Int J Impot Res 12:41–45.
14. Goldmeier D, Keane FE, Carter P, et al. (1997) Prevalence of sexual dysfunction in heterosexual patients attending a central London genitourinary medicine clinic. Int J STD AIDS 8:303.

15. Kinsey AC, Pomeroy WB, Martin CE. (1948) Sexual Behavior in the Human Male. Philadelphia, PA: W.B. Saunders Co.
16. Gebhard PH, Johnson AB. (1972) The Kinsey Data; Marginal Tabulations of the 1938–1963 Interviews Conducted by the Institute for Sex Research. Philadelphia, PA: W.B. Saunders Co.
17. Derby CA, Mohr BA, Goldstein I, et al. (2000) Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk. Urology 56:302–306.
18. Nicolosi A, Moreira ED Jr, Shirai M., et al. (2003) Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology 61:201–206.
19. Wabrek AJ, Burchell RC. (1980) Male sexual dysfunction associated with coronary heart disease. Arch Sex Behav 9:69–75.
20. Gundle GJ, Bozman BR, Tate S, et al. (1980) Psychosocial outcome after aortocoronary artery surgery. Am J Psychiatry 137:1591–1594.
21. Morley JE, Korenman SG, Mooradian AD, Kaiser FE. (1987) Sexual dysfunction in the elderly male. J Am Geriatr Soc 35:1014–1022.
22. Virag R, Bouilly P, Frydman D. (1985) Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. Lancet 1:181–184.
23. Oaks WW, Moyer JH. (1972) Sex and hypertension. Med Aspects Hum Sex 6: 128–135.
24. Goldstein I. (2003) The association of ED (erectile dysfunction) with ED (endothelial dysfunction). Int J Impot Res 15:229–230.
25. Andersson KE. (2003) Erectile physiological and pathophysiological pathways involved in erectile dysfunction. J Urol 170:S6–S13.
26. Solomon H, Man JW, Jackson G. (2003) Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. Heart 89:251–253.
27. Lehman TP, Jacobs JA. (1983) Etiology of diabetic ED. J Urol 129:291–294.
28. Rubin A, Babbott D. (1958) ED and diabetes mellitus. JAMA 168:498–500.
29. Kaiser FEK, Korenman SG. (1988) ED in diabetic men. Am J Med 85:147–152.
30. Shabsigh R, Fishman I, Schum C, Dunn JK. (1991) Cigarette smoking and other vascular risk factors in vasculogenic ED. Urology 38:227–231.
31. Zimmet P, Boyko EJ, Collier GR, de Courten M.(1999) Etiology of the metabolic syndrome: potential role of insulin resistance, leptin resistance, and other players. Ann NY Acad Sci 18:25–44.
32. Deedwania PC. (2003) Mechanisms of endothelial dysfunction in the metabolic syndrome. Curr Diab Rep 3:289–292.
33. McVeigh GE, Cohn JN. (2003) Endothelial dysfunction and the metabolic syndrome. Curr Diab Rep 3:87–92.
34. Frankel SJ, Donovan JL, Peters TI, et al.(1998) Sexual dysfunction in men with lower urinary tract symptoms. J Clin Epidemiol 51:677–685.
35. Roberts RO, Jacobsen SJ, Rhodes T, et al. (1997) Natural history of prostatism: impaired health states in men with lower urinary tract symptoms. J Urol 157:1711–1717.
36. Girman CJ, Jacobsen SJ, Rhodes T, et al. (1999) Association of health-related quality of life and benign prostatic enlargement. Eur Urol 35:277–291.
37. Garraway WM, Kirby RS.(1994) Benign prostatic hyperplasia: effects on quality of life and impact on treatment decisions. Urology 44:629–636.
38. Calvert RC, Khan MA, Thompson CS, et al. (2001) Alterations in nictic oxide signaling provides insight into the pathophysiology of erectile dysfunction associated with benign prostatic hyperplasia. Presented at the American Urological Association Annual Meeting, Anaheim, CA.

39. Chang S, Hypolite JA, Wein AJ, et al. (2001) The effect of bladder outlet obstruction on rabbit corpus cavernosum smooth muscle contractility. Presented at the American Urological Association Annual Meeting, Anaheim, CA.
40. Chang S, Hypolite J, Zderic SA, et al. (2002) Altered contractility of corpus cavernosum smooth muscle: a possible molecular basis for erectile dysfunction associated with partial bladder outlet obstruction resulting from benign prostatic hyperplasia. Presented at the American Urological Association Annual Meeting, Orlando, FL.
41. Foster RS, Mulcahy N, Callaghan JT, et al. (1990) Role of serum prolactin determination in evaluation of the impotent patient. Urology 36:499–501.
42. Korenman SG, Morley JE, Mooradian AD, et al. (1990) Secondary hypogonadism in older men: its relation to ED. J Clin Endocrinol Metab 71:963–969.
43. Bancroft J, Wu FCW. (1983) Changes in erectile responsiveness during androgen replacement therapy. Arch Sex Behav 12:59–66.
44. Mulhall JP. (2000) Current concepts in erectile dysfunction. Am J Manag Care 6: S625–S631.
45. Shabsigh R: Hypogonadism and erectile dysfunction: the role for testosterone therapy. Int J Impot Res 15:S9–S13.
46. Kalinchenko SY, Koslov GI, Gontcharov NP, Katsiya GV. (2003) Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male 6:94–99.
47. Zonszein J. (1995) Diagnoses and management of endocrine disorders of erectile dysfunction. Urol Clin North Am 22:789–802.
48. Seidman SN, Roose SP, Menza MA, et al. (2001) Treatment of erectile dysfunction in depressed men: results of a placebo-controlled trial with sildenafil citrate. Am J Psychiatry 158:1623–1630.
49. Thase ME, Reynolds CF, Jennings JR, et al.(1988) Nocturnal penile tumescence is diminished in depressed men. Biol Psychol 24:33–46.
50. Araujo AB, Durante R, Feldman HA, et al. (1998) The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med 60:458–465.
51. Shabsigh R, Klein LT, Seidman S, et al. (1998) Increased incidence of of depressive symptoms in men with erectile dysfunction. Urology 52:848.
52. Mathew RJ, Weinman ML. (1982) Sexual dysfunction in depression. Arch Sex Behav 11:323–328.
53. Rust J, Golombok S, Collier J. (1988) Marital problems and sexual dysfunction: how are they related? Br J Psychiatry 152:629–631.
54. Okulate G, Psych FMC, Olayinka O, Dogunro AS. (2003) Erectile dysfunction: prevalence and relationship to depression, alcohol abuse and panic disorder. Gen Hosp Psychiatry 25:209–213.
55. Araujo AB, Johannes CB, Feldman HA, et al. (2000) Relation between psychosocial risk factors and incident erectile dysfunction: prospective results from the Massachusetts Male Aging Study. Am J Epidemiol 152:533–541.
56. Kantor J, Bilker WB, Glasser DB, Margolis DJ. (2002) Prevalence of erectile dysfunction and active depression: an analytic cross-sectional study of general medical patients. Am J Epidemiol 156:1035–1042.
57. Strand J, Wise TN, Fagan PJ, Schmidt CW. (2002) Erectile dysfunction and depression: category or dimension? J Sex Marital Ther 28:175–181.
58. Slag MF, Morley JE, Elson JK, et al. (1983) ED in medical clinic outpatients. JAMA 249:1736–1740.

59. Wein AJ, Van Arsdalen KN. (1988) Drug-induced sexual dysfunction. Urol Clin North Am 15:23–31.
60. Goldstein I, Krane RJ. (1983) Drug-induced sexual dysfunction. World J Urol 1:239–242.
61. Seagraves RT, Madsen R, Carter CS, et al. (1985) Erectile dysfunction associated with pharmacologic agents. In Seagraves RT, Schoenberg HW, eds., Diagnosis and Treatment of Erectile Disturbances. New York, NY: Plenum, pp. 22–41.
62. Grimm RH Jr, Grandits GA, Prineas RJ, et al. (1997) Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Hypertension 29:8–14.
63. Mitchell JE, Popkin MK. (1983) Antidepressant drug therapy and sexual dysfunction in men: a review. J Clin Psychopharmacol 3:76–81.
64. Fava M, Rankin M.(2002) Sexual functioning and SSRIs. J Clin Psychiatry 63 (Suppl 5):S13–S17.
65. Yassa R. (1982) Sexual disorders in the course of clomipramine therapy. Can J Psychiatry 27:148–152.
66. Atmaca M, Kuloglu M, Tezcan E. (2002) Sildenafil use in patients with olanzapine-induced erectile dysfunction. Int J Impot Res 14:547–549.
67. Pont A, Williams PL, Azhar S, et al.(1982) Ketoconazole blocks testosterone synthesis. Arch Intern Med 142:2137–2140.
68. Greenblatt DJ, Koch-Weser J. (1973) Gynecomastia and ED: complication of spironolactone. JAMA 223:82–85.
69. Jones CD, Langman MJ, Lawson H, et al. (1985) Post-marketing surveillance of the safety of cimetidine: 12 month morbidity report. Q J Med 54:253–257.
70. Gupta S, Daley J, Pabby A, et al. (1993) A new mechansim for Digoxin-associated ED in vitro and in vivo study. J Urol 155:621A.
71. Abrams HS, Hester LR, Sheridan WF, et al.(1975) Sexual functioning in men with chronic renal failure. J Nerv Ment Dis 160:220–223.
72. Neto AF, de Freitas Rodrigues M, Saraiva Fittipaldi JA, Moreira ED Jr.(2002) The epidemiology of erectile dysfunction and its correlates in men with chronic renal failure on hemodialysis in Londrina, southern Brazil. Int J Impot Res 14(Suppl 2): S19–S24.
73. Kaufman JM, Hatzichristou DG, Mulhall JP, et al. (1994) ED and chronic renal failure. A study of the hemodynamic pathophysiology. J Urol 151:612–618.
74. Glass CA, Fielding DM, Evans C, et al.(1987) Factors related to sexual functioning in males undergoing hemodialysis and with kidney transplants. Arch Sex Behav 16:189–192.
75. Salvatierra O, Fortman JL, Belzer FO. (1975) Sexual function of males before and after renal transplantation. Urology 5:64–69.
76. Barrou B, Cuzin B, Malavaud B, et al. (2003) Early experience with sildenafil for the treatment of erectile dysfunction in renal transplant recipients. Nephrol Dial Transplant 18:411–414.
77. Morley JE. (1985) Impotence. Am J Med 80:897–905.
78. Lilius HG, Valtonen EJ, Wikstrom J. (1976) Sexual problems in patietns suffering from multiple sclerosis. J Chronic Dis 29:643–647.
79. Agarwal A, Jain DC. (1989) Male sexual dysfunction after stroke. J Assoc Physicians India 37:505–507.
80. Goldstein I, Siroky MB, Sax DS, et al.(1982) Neurologic abnormalities in multiple sclerosis. J Urol 128:541–545.
81. Welby SB, Rogerson SJ, Beeching NJ. (1991) Autonomic neuropathy is common in human immunodeficiency virus infection. J Infect 23:123–128.

82. Fletcher EC, Martin RJ. (1982) Sexual dysfunction and erectile ED in chronic obstructive pulmonary disease. Chest 81:413–417.
83. Nowlin NS, Brick JE, Weaver DJ, et al. (1986) ED in scleroderma. Ann Intern Med 104:794–799.
84. Hirshkowitz M, Karacan I, Arcasoy MO, et al. (1990) Prevalence of sleep apnea in men with erectile dysfunction. Urology 36:232–234.
85. Cornely CM, Schade RR, Van Thiel DH, et al. (1984) Chronic advanced liver disease and ED: cause and effect? Hepatology 4:1227–1230.
86. Dhabuwala CB, Hamid S, Katsikas DM, et al. (1990) ED following delayed repair of prostatomembranous urethral disruption. J Urol 144:677–690.
87. Munarriz RM, Yan QR, ZNehra A, Udelson D, Goldstein I. (1995) Blunt trauma: the pathophysiology of hemodynamic injury leading to erectile dysfunction. J Urol 153:1831–1840.
88. Benet AE, Abarbanel J, Lask DM, et al. (1990) Surgical management of long urethral strictures. J Urol 143:917–921.
89. Malavaud B, Mouzin M, Tricoire JL, et al. (2000) Evaluation of male sexual function after pelvic trauma by the international index of erectile function. Urology 55:842–846.
90. Shenfeld OZ, Kiselgorf D, Gofrit ON, et al. (2003) The incidence and causes of erectile dysfunction after pelvic fractures associated with posterior urethral disruption. J Urol 169:2173–2176.
91. Goldstein I. (1986) Arterial revascularization procedures. Semin Urol 4:252–258.
92. Santucci RA, Mario LA, McAninch JW. (2002) Anastomotic urethroplasty for bulbar urethral stricture: analysis of 168 patients. J Urol 167:1715–1719.
93. Mulhall JP, Graydon RJ. (1996) Hemodynamics of erectile dysfunction following nerve-sparing radical retropubic prostatectomy. Int J Impot Res 8:91–94.
94. Meuleman EJ, Mulders PF. (2003) Erectile function after radical prostatectomy: a review. Eur Urol 43:95–101.
95. Lue TF. (1991) ED after radical pelvic surgery: physiology and management. Urol Int 46:259–265.
96. LaSalle M, Wen C, Choi M, et al. (1999) "You don't have to ride in the Tour de France": erectile dysfunction in 81 consecurtive riders. J Urol 161:1041(A).
97. Andersen KV, Bovim G. (1997) Impotence and nerve entrapment in long distance amateur cyclists. Acta Neurol Scand 95:233–237.
98. Schwarzer U, Sommer F, Klotz T, et al. (2002) Cycling and penile oxygen pressure: the type of saddle matters. Eur Urol 41:139–144.

3 Pharmacology of Phosphodiesterase Inhibitors

Erwin Bischoff, PhD

CONTENTS

INTRODUCTION

The second messengers cyclic 3',5' adenosine monophosphate (cAMP) and cyclic 3',5' guanosine monophosphate (cGMP) play a key role in mediating a variety of functional responses to hormones and other cellular transmitters. Phosphodiesterases (PDEs) are intracellular enzymes that specifically catalyze the hydrolysis of these second messengers. By counterbalancing the enzymes adenylyl cyclase and guanylyl cyclase, which catalyze the formation of cAMP and cGMP, respectively, they regulate the intracellular concentration of both second messengers, thereby influencing a broad variety of physiological functions. PDEs belong to a large superfamily (11 different gene families encode for the PDE families PDE1 to PDE11) of structurally related, functionally distinct, and highly regulated enzymes. Owing to their key roles in physiological processes, PDEs are targets for many drugs that are used for different diseases, such as cardiovascular diseases, asthma, erectile dysfunction (ED), and many others. Increasing knowledge of the molecular biology, regulation, and tissue distribution of this class of enzymes has led to a better understanding of the physiological function of cyclic nucleotides and of the

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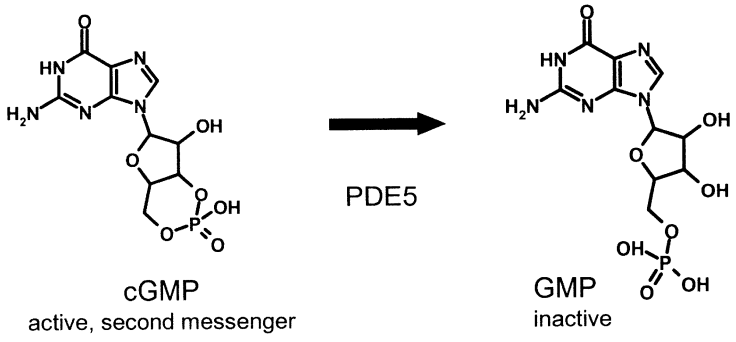


Fig. 1. Phosphodiesterases catalyze the hydrolysis of the phosphodiester bond of cyclic nucleotides cyclic adenosine monophosphate and cyclic guanine monophosphate (cGMP). In this example, phosphodiesterase 5 hydrolyzes active cGMP to the inactive form GMP. PDE5, phosphodiesterase type 5.

regulatory role of PDEs. This progress was supported by the development of potent PDE inhibitors that are highly selective for one PDE family. Prominent examples are the newly developed selective PDE5 inhibitors, which are discussed here, used for the effective oral treatment of ED.

This chapter summarizes the properties and physiological function of the PDE isoenzymes, focusing on the understanding of the role of PDE5 and its inhibitors in regulating smooth muscle tone and penile erection and their roles in the treatment of ED. The pharmacodynamic effects of PDE5 inhibitors are discussed, as well as the parameters influencing their clinical efficacy and side effect profile.

FUNCTION AND PROPERTIES OF PDEs

Signaling pathways include mechanisms for negative feedback control. PDEs are critical homeostatic regulators of intracellular cyclic nucleotide concentrations. By catalyzing the hydrolysis of the diester bond of cAMP and cGMP to their corresponding monophosphates AMP and GMP, they terminate the signaling of cyclic nucleotides. Figure 1 shows the hydrolysis of cGMP by PDE5.

The human genome encodes for 11 families of PDEs localized on 21 PDE genes, which generate multiple protein products *(1)*. Via alternative mRNA splicing or the use of multiple gene promoters or initiation sites, or both, this group of enzymes amounts to a total of at least 60 different PDEs. The knowledge of the relationships between different family members and a better understanding of the regulation and functional characteristics of each have generated a systematic nomenclature *(2)*.

Fig. 2. Schematic representation of the regulatory and catalytic sites of the 11 mammalian phosphodiesterase families *(1)*. CAM, cell adhesion molecule; cGMP, cyclic guanine monophosphate; COOH, carboxylic acid; PAS, *p*-aminosalicylic acid; PDE, phosphodiesterase. (Adapted from ref. *2a*.)

A PDE family is designated by an Arabic numeral followed by a capital letter designating the gene within the respective family. A second Arabic numeral indicates the variant product derived from a single gene (e.g., *PDE4A2* denotes PDE family 4, gene A, splice variant 2).

Mammalian PDEs share a common structural organization, with a conserved catalytic domain located near the C-terminus and divergent regulatory domains and modules mostly near the N-terminus of the protein *(1)*. The catalytic core contains family-specific sequences responsible for differences in substrate specificity, catalytic activities, and sensitivity to inhibitors. The regulatory domain on the N-terminal portion of PDEs is highly divergent. It includes sites and domains that are subject to different modifications (e.g., phosphorylation or interaction with allosteric ligands, such as Ca^{2+} ions, calmodulin, or cGMP), thus regulating the catalytic activity, protein–protein interactions, or subcellular localization. The structural organization of the 11 PDE families is shown in Fig. 2.

The most obvious distinguishing feature between the 11 PDE families is their substrate specificity. Some PDEs specifically hydrolyze cAMP; others are highly specific for cGMP, whereas some are able to hydrolyze both cAMP and cGMP. Most cells contain representatives of multiple gene families but in different amounts, proportions, and subcellular locations, thus forming a complex network among different PDE regulatory pathways. This implies that even highly specific inhibitors of one distinct PDE may influence different physiological processes in different tissues.

The consequences of this on the pharmacodynamic effects of PDE5 inhibitors are discussed later in this chapter. The only PDE that is expressed in a single highly specialized tissue is PDE6, which is involved in the signal transduction of vision in the retina. The most prominent properties of the 11 PDE families and their tissue distribution are summarized in Table 1.

Numerous reviews demonstrate the tremendous increase in knowledge of the structural features, catalytic mechanisms, regulation, physiology, and inhibitors of this fascinating class of enzymes, although many details of their function remain unclear *(1,3–7)*.

PDE INHIBITORS

Based on their central role in regulating the intracellular concentration of cyclic nucleotides, PDEs have been targets for pharmacological interventions. The first clinically available selective PDE inhibitor was the PDE3 inhibitor milrinone, which was used to treat hypertension and certain types of cardiac failure. It is no longer in use, however, owing to its presumed ability to induce life-threatening arrhythmias.

Many efforts are ongoing to develop highly selective PDE4 inhibitors for the treatment of asthma, such as Rolipram or the PDE4A selective inhibitors Roflumilast and Cliomilast.

So far, none of these compounds have made their way to clinical practice.

Natural compounds, such as caffeine or theophylline, that are known to at least partially inhibit PDEs have been in use for centuries. For example, coffee was prescribed to treat asthma in the 19th century, because its active ingredient, caffeine, is a nonselective PDE inhibitor. In addition, caffeine was used in a clinical study for the oral treatment of impotentia erectionis *(8)*. Natural products, together with knowledge of the structure of cGMP itself, served as starting points for the development of more potent or more selective, or both, synthetic PDE5 inhibitors. Zaprinast (M&B 22948) is of special note, because it set a milestone in the development of PDE5 inhibitors. It was synthesized as an antiallergic compound and was proposed as a candidate for clinical use in the treatment of allergic asthma *(9)*. It has some specificity toward PDE5 and was widely used to establish the important role of cGMP as a second messenger in smooth muscle relaxation. In addition, it was used as a pharmacological tool for the evaluation of PDE5 inhibition in various conditions, including ED *(10,11)*.

The awareness of the beneficial pharmacological effects of cGMP (e.g., relaxation of smooth muscle cells [SMC], vasodilation, and inhibition of SMC proliferation) stimulated the search for more powerful inhibitors of cGMP that metabolized PDEs. Increasing understanding of the important role of the nitric oxide (NO) cGMP signaling pathway during sexual stimulation *(12)*, the development of sildenafil citrate (Viagra®) in the early

Table 1
Properties and Tissue Distribution of Phosphodiesterases[a]

Name	*Characteristics*	K_m (μm) *cAMP*	K_m (μm) *cGMP*	*Number of genes*	*Primary tissue distribution*
PDE1	Ca^{++}-CaM-stimulated	1–30	3	3	VSMC, brain, lung, heart.
PDE2	cGMP-stimulated	30–100	10–30	1	Adrenal cortex, brain, heart, liver, corpus cavernosum, olfactory bulbus.
PDE3	cGMP-inhibited	0.1–0.5	0.1–0.5	2	Heart, lung, liver, immunocytes, pancreas.
PDE4	cAMP-specific	0.5–4	>50	4	Immunocytes, lung, brain.
PDE5	cGMP-specific	>40	1.5	1	VSMC, SMC, lung, corpus cavernosum, platelets.
PDE6	Photoreceptor	2000	60	3	Retina.
PDE7	cAMP-high affinity	0.2	>1000	2	Skeletal muscle, T cells.
PDE8	cAMP-high affinity	0.7	>100	2	Widely expressed; most abundant in testes, ovary, intestine color.
PDE9	cGMP-high affinity	>100	0.07	1	Broadly expressed; liver, kidney.
PDE10	Dual substrate	0.5	3	1	Broadly expressed in mice; most abundant in brain, testes.
PDE11	Dual substrate	1	0.5	1	Testes, brain, corpus cavernosum, skeletal muscle, prostate.

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; PDE, phosphodiesterase; SMC, smooth muscle cell; VSMC, vascular smooth muscle cell.

[a] From ref. *3*.

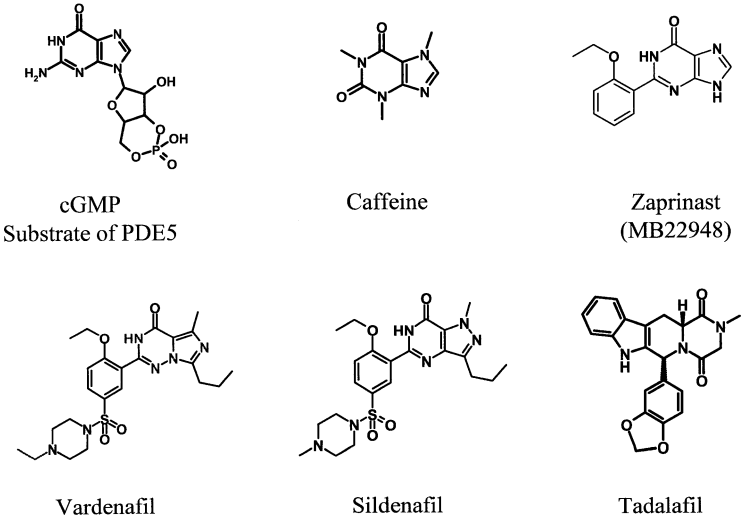


Fig. 3. Chemical structures of the phosphodiesterase type 5 (PDE5) inhibitors that have been developed—caffeine, zaprinast, sildenafil, vardenafil, and tadalafil—and the PDE5 substrate, cyclic guanine monophosphate. cGMP, cyclic guanosine monophosphate; PDE5, phosphodiesterase type 5.

1990s, and its introduction into the market in 1998 as an oral treatment for ED reaffirmed the therapeutic potential of PDE5 inhibitors. Five years later, two more potent PDE5 inhibitors, vardenafil (Levitra®) and tadalafil (Cialis®), came to market. With the addition of these two compounds, further improved therapeutic options for the treatment of ED have been made available. In Fig. 3, the chemical structures of these compounds are shown.

PDE5

PDE5 is known as the cGMP-binding, cGMP-specific PDE and is one of the PDEs that contains allosteric binding sites in their regulatory domains *(1,13)*. PDE5 was first recognized as a cGMP-binding protein in lung tissue, which also possesses cGMP-hydrolyzing activity *(14,15)*. The catalytic and allosteric binding sites of PDE5 are highly specific for cGMP. The catalytic activity of PDE5 is tightly regulated by negative feedback by its own substrate, cGMP, which enhances its own destruction. Binding of cGMP to PDE5 increases the affinity of the catalytic site for cGMP, both by allosteric activation and by activation of protein kinase G (PKG), which in turn phosphorylates the enzyme and increases its activity *(16–18)*.

PDE5 is expressed in a wide variety of tissues as an intracellular cytosolic enzyme. In corpus cavernosum, PDE5 is clearly the most important cGMP-hydrolyzing PDE *(19,20)*, although gene transcripts of nearly all the PDEs could be detected in penile tissue *(21)*. PDE5 enzymatic activity was also detected in the lungs, platelets, the kidneys, the brain, the epithelial cells of pancreatic ducts, and the SMCs, such as vascular SMC and gastric SMC, in a variety of organs, including the esophagus *(13,22–25)*.

The minor activity that was occasionally detected in heart tissue is probably not located in myocardial cells but rather in the SMCs of the blood vessels *(26,27)*. The tissue distribution often coincides with that of PKG, which is not surprising, considering that both of them are regulated by cGMP and PKG is an excellent catalyst of the phosphorylation of PDE5.

The human *PDE5A* gene encodes three isoforms that differ only in the 5'-end of their messenger RNAs and the amino terminus of their proteins *(28,29)*. *PDE5A1* and *PDE5A2* are expressed in most of the tissues mentioned previously, and expression of *PDE5A3* seems to be limited to SMCs. In penile tissue, all isoforms could be detected *(6)*.

The affinity for cGMP is the same for all three subtypes (K_m ~6 μ*M*) and sensitivity to inhibition by sildenafil also seems to be similar for all three subtypes, whereas the PDE5A3 isoform seems to be more resistant.

Therefore, it is questionable whether a subtype-specific PDE5 inhibitor would offer an improved side effect profile.

Why PDE5 is an Ideal Target in the Treatment of ED

Penile erection is a result of the relaxation of arterial and smooth muscle tissue within the penis. Relaxation of arterial smooth muscle is accompanied by increased blood flow to the penile corpora. Trabecular smooth muscle relaxation leads to the opening of the sinusoids in the penile erectile tissue, which is the prerequisite for the initiation of an erection. The state of contractile tone in penile tissue is determined by a dynamic balance of contractile and relaxing mechanisms. Contraction is mediated mostly by adrenergic mechanisms but also by endothelin and certain prostanoids. Relaxation during sexual stimulation is mediated mostly by the NO cGMP signaling pathway but also through peptide hormones such as vasoactive intestinal peptide, calcitonin gene-related peptide, and prostanoids like PGE1. Vasoactive intestinal peptide, calcitonin gene-related peptide, and prostanoids use cAMP as the main second messenger. Effectors of cAMP-mediated relaxation of penile SMCs are described in Fig. 4.

The prominent role of NO as a transmitter during sexual stimulation is the basis for the specificity of PDE5 inhibitors for the treatment of ED.

The mechanism of erection and the physiological background have been extensively studied. Smooth muscle relaxation is mediated by NO. During

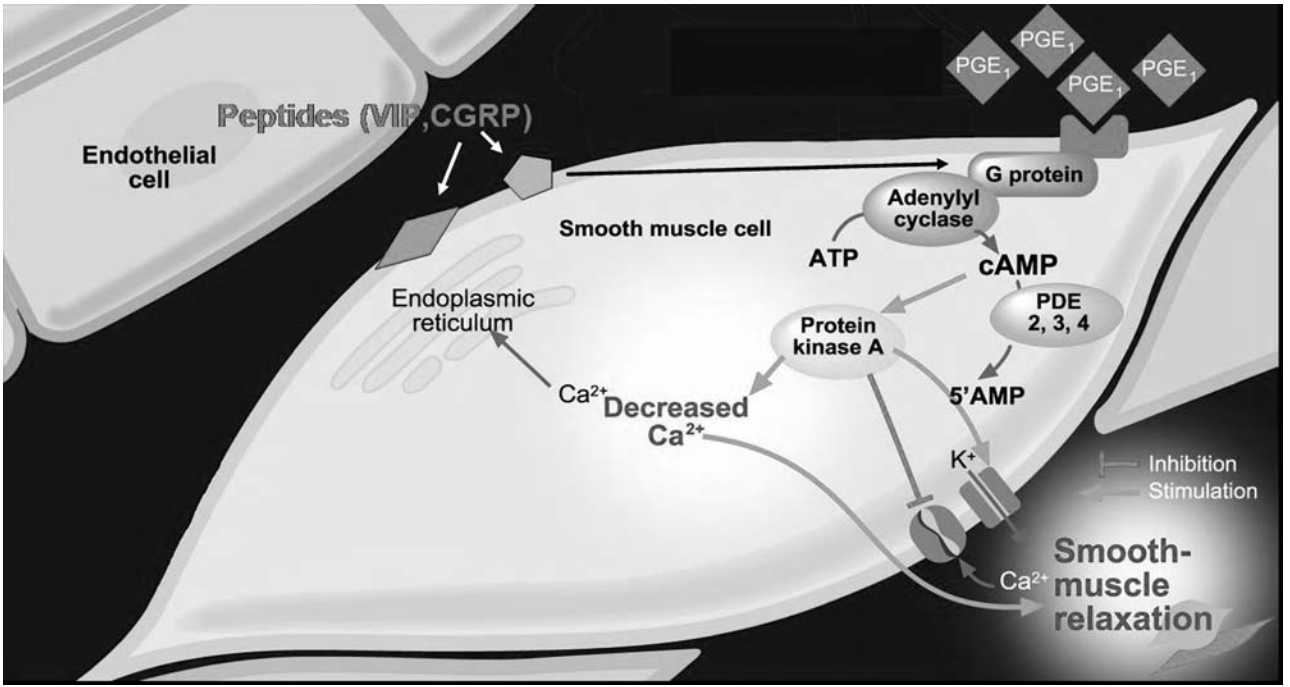


Fig. 4. Role of cyclic adenosine monophosphate signaling in smooth muscle cell relaxation of corpus cavernosum. ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; PDE, phosphodiesterase; PGE_1, prostaglandin E_1; VIP, vaso-active intestinal peptide; cAMP, cyclic adenosine monophosphate.

either direct or psychogenic sexual stimulation, NO is synthesized by neuronal NO synthase in the nerve terminals of parasympathetic and nonadrenergic, noncholinergic neurons in the penis and also by endothelial NO synthase in the endothelial cells of the blood vessels and the lacunar spaces of the corpora cavernosa. NO activates the soluble guanylate cyclase (sGC) of SMCs, resulting in increased intracellular cGMP levels, which leads to relaxation of smooth muscle in the corpus cavernosum and in penile arterioles. The level of cGMP is regulated by its rate of synthesis via sGC and its hydrolysis to the physiologically inactive GMP by the cGMP-hydrolyzing PDEs.

Of all cGMP-hydrolyzing PDEs, PDE5 is the most prominent in the human corpus cavernosum, but some PDE2 activity has also been described *(19)*, as well as significant amounts of the cAMP-metabolizing PDE3 and PDE4 *(20,30)*. Inhibition of PDE5 leads to an increase in the level of cGMP, thus enhancing relaxation of smooth muscle. Consequently, the vascular tone in penile arteries decreases. This causes increased blood flow and an enlargement of the cavernosal tissue, which induces penile erection *(31–33)*. NO-mediated vasorelaxation is the basis for the therapeutic application of PDE5 inhibitors in the treatment of ED. This suggested signaling pathway and the enhancing effect of NO on erectile function was demonstrated in isolated corpus cavernosum *(10)* and in various animal models with different species *(34–38)*. Here also the effects of amplification of NO by administration of PDE5 inhibitors were shown.

The release of NO by nonadrenergic, noncholinergic nerves or the endothelium, or both, is impaired under pathological conditions, such as diabetes or coronary heart disease, hypertension, or spinal cord injury, which consequently leads to reduced cGMP synthesis. Through PDE5 inhibition, sufficient levels of cGMP leading to erection in many patients with ED can still be reached, which is clinically important in patients with a disease, such as diabetes, in which impaired NO release might be the cause of ED.

A prerequisite to PDE5 inhibition as a therapeutic principle for the treatment of ED is sexual stimulation leading to the release of NO, as described earlier. PDE5 is available in many other tissues (*see* Table 1), but the selective induction of vasorelaxation in penile tissue is predominantly based on the increased synthesis of cGMP in the cavernosal tissue in the presence of NO; this occurs only during sexual stimulation. Other tissues do not have this mechanism. This unique situation—increased cGMP concentrations after neural stimulation—contributes more strongly to selective vasodilation in cavernosal tissue than the localization of PDE5 in this tissue *(13,39)*. This provides the basis for the efficacy and favorable therapeutic benefit-vs-side effect ratio that is found

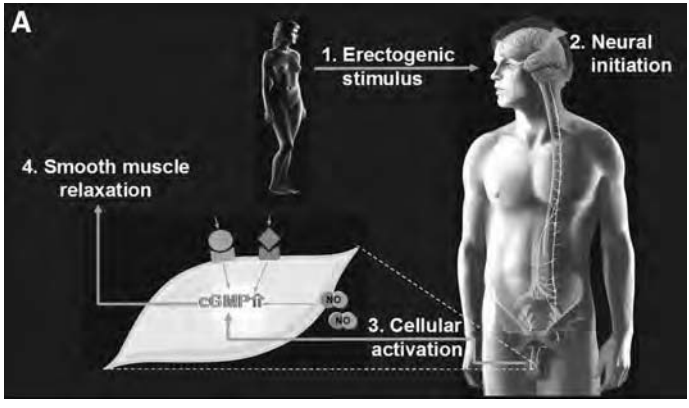


Fig. 5. (A) Mechanism of erection, from neuronal signaling to the cellular mechanism. **(B)** *(opposite page)* Cyclic guanine monophosphate (cGMP) signaling in smooth muscle cells of corpus cavernosum and effect of phosphodiesterase type 5 inhibition on corpus cavernosum cGMP levels. eNOS, endothelial nitric oxide synthase; NO, nitric oxide; GTP, guanosine triphosphate.

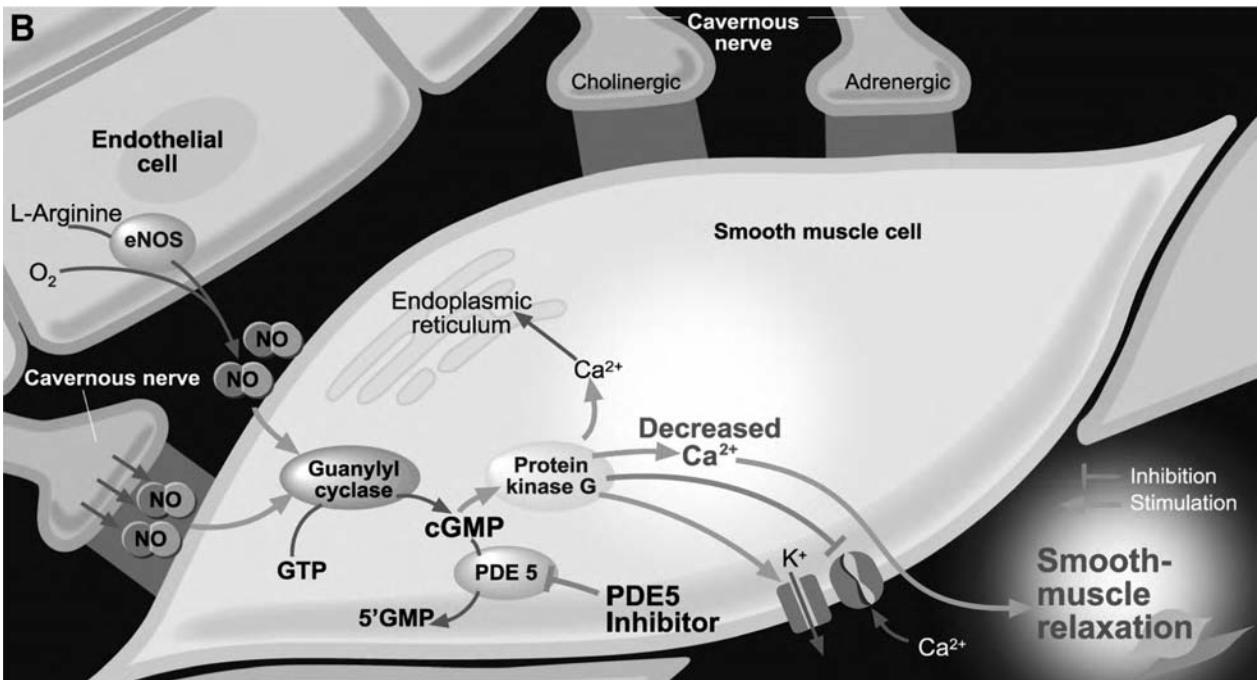
for PDE5 inhibitors in the treatment of ED. Figure 5 shows the steps from neuronal signaling to the cellular mechanism that causes an erection.

The clinical effectiveness of PDE5 inhibition requires at least a minimal NO signal to induce some turnover of cGMP. Otherwise, PDE5 inhibition will not be able to increase intracellular cGMP levels and induce vasorelaxation. Complete destruction of the cavernosal nerves during radical prostatectomy, or severe diabetic neuropathies, could be pathological conditions that principally limit the success of treatment with PDE5 inhibitors.

Other mechanisms, such as increasing intracellular cGMP levels through the stimulation of cGMP synthesis by activators of the cGMP-sGC (BAY 41-7072), could offer an alternative treatment option, principally using the same signaling pathway *(40)*. Because sGC is abundantly distributed in all tissues, however, general vasodilation is a potential drawback of this mechanism. The partial dependency on NO of the activation of sGC by this compound *(41)* may deliver sufficient specificity for penile tissue.

Parameters Determining the Pharmacodynamic Effects of PDE5 Inhibitors

The pharmacodynamic effects of PDE5 inhibitors are determined by their molecular structures, which influences their PDE5 inhibitory potency, and by their selectivity with respect to the other PDEs. The abundant tissue


B
Cavernous nerve
Cholinergic
Adrenergic
Endothelial cell
L-Arginine
eNOS
O_2
NO
NO
Cavernous nerve
NO
NO
Smooth muscle cell
Endoplasmic reticulum
Ca^{2+}
Decreased Ca^{2+}
Guanylyl cyclase
Protein kinase G
cGMP
GTP
PDE 5
PDE5 Inhibitor
5'GMP
K^+
Ca^{2+}
Inhibition
Stimulation
Smooth-muscle relaxation

distribution of PDE5 and the complex network of all other PDEs could be the reason for mechanism-related side effects. Physicochemical properties of PDE5 inhibitors, such as solubility or the capability to permeate cell membranes, may also play a role owing to the intracellular location of PDEs. Furthermore, pharmacokinetic properties related to the compounds' absorption, distribution, metabolism, and excretion play an important role.

Potency

Enzyme inhibitors often mimic the natural substrate of the enzyme and bind reversibly, but more tightly, to the catalytic center than to the natural substrate. Not being hydrolyzed themselves, they act as reversible enzyme inhibitors. The PDE5 inhibitors sildenafil, vardenafil, and tadalafil act through this mechanism.

The higher the affinity of the inhibitor to the PDE, the lower the concentration of the inhibitor needed to inhibit the respective PDE. The lower this concentration, the higher the potency of the drug. High potency does not necessarily translate to higher clinical efficacy; however, because administration of a lower concentration of the drug is possible, the probability of nonspecific interference with other receptors or proteins is lower. Therefore, it is reasonable to assume that such a drug has a greater safety margin for non-PDE-related adverse effects.

The potency of a PDE inhibitor is usually determined in vitro with isolated and purified PDE. It can be expressed by measuring the concentration of the drug necessary to inhibit 50% of the catalytic activity of the enzyme. This median inhibitory concentration is named IC_{50} and is frequently used when comparing the potency of different compounds. As an example, Fig. 6 shows the concentration inhibition dependency and the IC_{50} of vardenafil for PDE5.

The results of IC_{50} measurements depend on assay conditions, such as the source and the quality of the enzyme preparation, the properties of the assay buffer, and the substrate (cGMP/cAMP) concentration. Therefore, a valid comparison of drugs with respect to potency can only be performed under rigorous conditions in the same assay. In comparing published data on the three compounds sildenafil, vardenafil, and tadalafil, there is a wide variation in IC_{50} values *(19,42–50)*. Independent of the different sources, however, vardenafil is the most potent of the group of approved PDE5 inhibitors, followed by sildenafil and tadalafil, as shown in Fig. 7.

All three inhibitors are effective in enhancing cGMP concentration in human penile tissue, as well as in relaxation. Both effects are much more pronounced in the presence of low concentrations of NO donors, such as SNP, which confirms the mode of action of these PDE5 inhibitors in isolated tissues *(45–47)*.

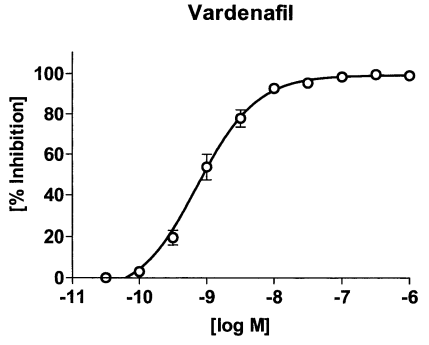


Fig. 6. The inhibitory concentration 50% of the phosphodiesterase type 5 (PDE5) inhibitor vardenafil determined for PDE5 is 0.7 μ*M*. (PDE5 derived from human platelets.) IC_{50}, inhibitory concentration 50%.

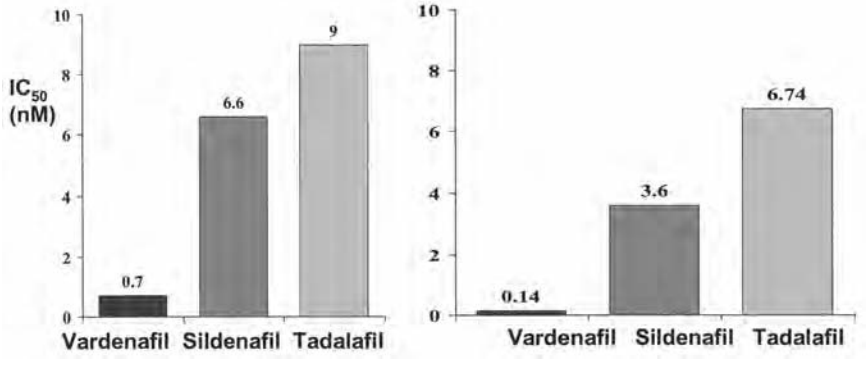


Fig. 7. The in vitro potency of phosphodiesterase type 5 inhibitors: a comparison of published inhibitory concentration data on vardenafil, sildenafil, and tadalafil obtained from different studies *(45,48,50)*. IC_{50}, inhibitory concentration 50%.

Selectivity

The selectivity of an inhibitor for PDE5 is the key determinant in the potential clinical side effect profile of the inhibitor compound. Selectivity describes the balance between the concentrations needed to inhibit the target enzyme PDE5 compared with the concentration needed to inhibit other PDEs. For example, the IC_{50} of vardenafil for PDE5 is 0.7 μ*M (45),* and its IC_{50} for PDE11 is 307 μ*M*, which results in a selectivity ratio of 308/0.7 = 440.

This means that a 440-fold higher concentration of vardenafil is needed to inhibit PDE11 compared with the concentration needed to inhibit PDE5.

The higher this ratio for each of the other PDEs, the smaller the probability that they are affected at concentrations of the drug in the body that can be achieved at therapeutic doses. Therefore, the probability of side effects induced by inhibiting PDE species other than PDE5 is also lower. As an example, the selectivity of the three clinically available drugs is summarized in Table 2.

Inhibition of PDE6 is thought to induce transiently abnormal vision because this enzyme plays a dominant role in the signal transduction of vision. Clinically, this was seen infrequently with vardenafil and rarely with sildenafil *(49)*.

The ratio for tadalafil is very high (300) *(49)*, and no visual side effects have been reported. Tadalafil exerts some nonspecificity with respect to PDE11. This enzyme is expressed in many tissues (*see* Table 1), but neither its physiological function nor the clinical relevance when it is inhibited is understood.

Mechanism-Related Effects of PDE5 Inhibitors

Although PDE5 is the predominant cGMP-metabolizing enzyme in penile tissue, and the specialized signaling that occurs during sexual stimulation makes PDE5 an optimal target for the treatment of ED, PDE5 is present in many other tissues, and its coexpression with other PDEs within the same cells forms a complex network of crosstalk among different PDE-regulatory pathways. Owing to the latter, some mechanism-related side-effects are induced just by inhibiting PDE5.

In penile tissue, PDE2 enzymatic activity was detected, as well as significant amounts of PDE3 and PDE4 *(19,30)*. Indeed, sildenafil has been shown to increase cAMP levels in isolated cavernous strips, although it does not inhibit any of these enzymes *(51)*. This effect is thought to be the result of the increased cGMP levels induced by sildenafil, which in turn prevents cAMP degradation by inhibiting PDE3. Therefore, it cannot be excluded that an elevated cAMP level also contributes to the erectogenic effect of sildenafil. Increased cAMP levels were also found in human cardiac auricle when treated with sildenafil *(51)*; this could be a potential risk owing to the chronotropic effects of cAMP. However, it was demonstrated that PDE5 is not expressed in human myocardial cells *(26,27)* but is expressed in SMCs of blood vessels of the heart. Therefore, crosstalk between PDE5 as a cGMP-elevating principle and the cGMP-inhibited PDE3 in myocardial cells in this tissue seems to be unlikely. Furthermore, it has been shown that PDE5 is not expressed in the human cardiac His-Purkinje system, and so a direct ionotropic or chronotropic effect is also unlikely, and direct mechanism-related effects of PDE5 inhibition on the myocardium are not probable.

Table 2
Selectivity of PDE5 Inhibitors Against All PDE Families [a]

	IC_{50} (nM)											
Compound	*PDE1*	*PDE2*	*PDE3*	*PDE4*	*PDE5*	*PDE6 rod*	*PDE6 cone*	*PDE7*	*PDE8*	*PDE9*	*PDE10*	*PDE11*
Sildenafil	281	<30,000	16,200	7680	3.5	37	34	21,300	29,800	2610	9800	2730
	(80)	(>8750)	(4630)	(2190)		(11)	(10)	(6100)	(8500)	(750)	(2800)	(780)
Vardenafil	70	6200	>1000	6100	0.14	3.5	0.6	>30,000	>30,000	580'	3000	162
	(500)	(44,290)	(>7140)	(43,570)		(25)	(4)	(>241,000	(214,000)	(4150)	(21,200)	(1160)
Tadalafil	>30,000	>100,000	>100,000	>100,000	6.74	1260	1300	>100,000	>100,000	>100,000	>100,000	37
	(>4450)	(>14,800)	(>14,800)	(>14,800)		(187)	(193)	(>14,800)	(>14,800)	(>14,800)	(>14,800)	(5)

PDE, phosphodiesterase.

[a] From ref. *49*.

Localization of PDE5 in all SMCs and consequently in all vascular tissues is thought to be the reason for another mechanism-related side effect. All PDE5 inhibitors exert a transient vasodilatory effect, including occasional reports of symptoms, such as facial flushing, headache, and/or stuffy nose. Dyspepsia is also occasionally reported as a side effect of all PDE5 inhibitors. It can be attributed to the high expression of PDE5 in the lower esophagus, which may induce reflux *(52)*.

Potentially severe interactions between organic nitrates and this group of compounds are related to their mechanism of action and have led to the establishment of a contraindication to the combined use of nitrates and PDE5 inhibitors. Organic nitrates release NO systemically, which in turn stimulates cGMP synthesis and therefore may amplify the minor systemic vasodilation induced by PDE5 inhibition and induce severe systemic decreases in blood pressure. Expression of all three PDE5 isoforms is regulated by isoenzyme-specific gene promotors. These promotors exhibit, at least in in vitro assays, activity dependent on increasing concentrations of cAMP and cGMP *(28)*.

Binding studies with radiolabeled sildenafil suggest that the elevated intracellular cGMP level induced by the PDE5 inhibitor causes further increases in sildenafil concentration in the corpus cavernosum. This positive feedback, which should also occur with the other PDE5 inhibitors, could lead to an effective concentration of the inhibitors in cells containing high levels of PDE5 and should be slowly cleared.

This could have an impact on the duration of action of these compounds, which may be much longer than suggested by the plasma levels *(53)*. In an animal study with rabbits, it was shown that vardenafil was effective for at least four times the half-life of the compound in this species *(54)*.

Influence of Pharmacokinetic Properties

Pharmacokinetic properties have a decisive impact on the pharmacodynamic properties of a drug. They describe the absorption, the distribution, the metabolism, and the excretion of a drug. The basis for determination of these parameters is the measurement of the concentration of the drug after administration, as shown in the pharmacokinetic profile of vardenafil in Fig. 8.

Three key parameters are used to characterize pharmacodynamic properties: C_{max}, $T_{max,}$ and $T_{1/2}$. C_{max} indicates the maximum plasma concentration obtained at a given dose. At $C_{max,}$ the maximal effect is expected. C_{max} allows for an estimate of whether PDEs other than PDE5 will be inhibited at therapeutic concentrations. T_{max} reflects the absorption and indicates the time necessary to reach C_{max}. The shorter the T_{max}, the faster the maximal concentration is expected to be reached, but this does not nec-

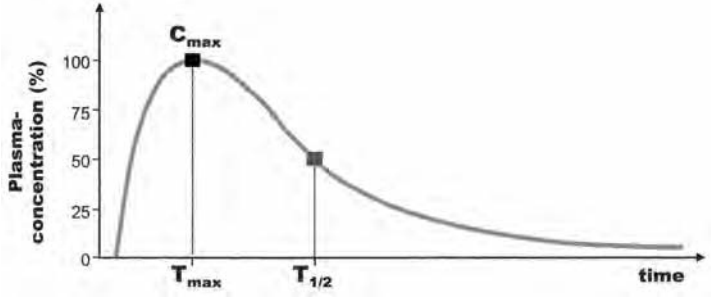


Fig. 8. Key parameters of vardenafil plasma concentration curve.

Table 3
Pharmacokinetic Profiles

	Vardenafil 20 mg	*Sildenafil 100 mg*	*Tadalafil 20 mg*
T_{max}, h	0.8	1.16	2.0
$T_{1/2}$, h	4.7	3.82	17.5
C_{max}, µg/L	31.8	327	378
AUC, µg × h/L	96.3	1963	8066

Data derived from separate studies, values shown as means.
AUC, area under the curve.

essarily coincide with onset of action. $T_{1/2}$ describes the time needed to decrease the plasma concentration to 50% of C_{max}. The longer the $T_{1/2,}$ the longer the duration of action expected, but as mentioned previously, $T_{1/2}$ is not necessarily an exact measure of the duration of action.

These parameters can be influenced by many additional factors, such as food intake or comedication with other drugs. For example, when the inhibitors are metabolized by the same cytochrome P450 system or, even worse, when this system is inhibited by a concomitantly administered drug, C_{max} can be significantly increased. Another important parameter is absolute bioavailability, which is the amount of the orally administered drug available in the body; this has an impact on its efficacy. The most important pharmacokinetic data for all three PDE5 inhibitors are summarized in Table 3.

The attractive mechanism of PDE5 inhibition for the treatment of ED, as well as other possible therapeutic options for these type of inhibitors, such as the treatment of female sexual dysfunction *(55,56)* or the treatment

Table 4
PDE5 Inhibitors Currently Undergoing Clinical Development[a]

Compound name	*Company*	*Development status*
Sildenafil/Viagra	Pfizer	Launched 1998
UK 114542	Pfizer	Phase I[b]
UK 357903	Pfizer	Phase II[b]
Vardenafil/Levitra	Bayer	Launched in 2003
Tadalafil/Cialis	Icos/Lilly	Launched in 2003
E8010	Esai	Phase I
DA8159	Dong A (Korea)	Phase I
TA-1790	Tanabe Seiyaku (License Vivus)	Phase I
EMD-221829	Merck KgaA	Phase II[c]
UK 369003	Pfizer	Phase II

[a] At least nine other compounds are reported to be in preclinical development.
[b] No further clinical development reported.
[c] Development has been terminated.

of pulmonary hypertension *(57,58),* has stimulated the search for more highly specific inhibitors. Many of these are in the preclinical phase of development or have just entered clinical trials for sexual dysfunction *(3,59)*. The most relevant are summarized in Table 4.

CONCLUSIONS

Owing to their key physiological roles, PDEs are interesting targets in the treatment of many maladies. The special signal transduction during sexual stimulation makes PDE5 an ideal target in the treatment of ED. PDE5 inhibitors used for the treatment of ED have to be as selective as possible in order to minimize undesired side effects by inhibiting other PDEs. The expression of PDE5 in all SMCs, often together with other PDEs, and the complex regulation of the PDEs by their own substrates lead to several mechanism-related side effects, even with highly selective inhibitors. Concomitant use with NO-releasing compounds (e.g., nitrates) is not allowed with all PDE5 inhibitors based on their mechanism of action.

REFERENCES

1. Francis S H, Turko IV, Corbin JD. (2001) Cyclic nucleotide phosphodiesterases: relating structure and function. Prog Nucleic Acid Res Mol Biol 65:1–52.
2. Beavo JA, Conti M, Heaslip RJ. (1994) Multiple cyclic nucleotide phosphodiesterases. Mol Pharmacol 46:399–405.
2a. Conti M. (2000) Phosphodiesterases and cyclic nucleotide signaling in endocrine cells. Mol Endocrinol 14:1317–1327.

3. Haning H, Niewohner U, Bischoff E. (2003) Phosphodiesterase type 5 (PDE5) inhibitors. Prog Med Chem 41:249–310.
4. Mehats C, Andersen CB, Filopanti M, et al. (2002) Cyclic nucleotide phosphodiesterases and their role in endocrine cell signaling. Trends Endocrinol Metab 13:29–35.
5. Manganiello V. (2003) Cyclic nucleotide phosphodiesterase 5 and sildenafil: promises realized. Mol Pharmacol 63:1209–1211.
6. Lin CS, Xin ZC, Lin G, et al. (2003) Phosphodiesterases as therapeutic targets. Urology 61:685–691.
7. Soderling SH, Beavo JA. (2000) Regulation of cAMP and cGMP signaling: new phosphodiesterases and new functions. Curr Opin Cell Biol 12:174–179.
8. Rytter M. (1973) Impotentia erectionis—therapeutic attempt using bamethan sulfate, synephrine, and coffeinum purum. Z Haut Geschlechtskr 48:481–486.
9. Broughton BJ, Chaplen P, Knowles P, et al. (1974) New inhibitor of reagin-mediated anaphylaxis. Nature 251:650–652.
10. Rajfer J, Aronson WJ, Bush PA, et al. (1992) Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. N Engl J Med 326:90–94.
11. Bush PA, Aronson WJ, Buga GM, et al. (1992) Nitric oxide is a potent relaxant of human and rabbit corpus cavernosum. J Urol 147:1650–1655.
12. Ignarro LJ, Bush PA, Buga GM, et al. (1990) Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem Biophys Res Commun 170:843–850.
13. Corbin JD, Francis SH. (1999) Cyclic GMP phosphodiesterase-5:target of sildenafil. J Biol Chem 274:13,729–13,732.
14. Francis SH, Lincoln TM, Corbin JD. (1980) Characterization of a novel cGMP binding protein from rat lung. J Biol Chem 255:620–626.
15. Davis CW, Kuo JF. (1977) Purification and characterization of guanosine 3':5'-monophosphate-specific phosphodiesterase from guinea pig lung. J Biol Chem 252:4078–4084.
16. Mullershausen F, Russwurm M, Thompson WJ, et al. (2001) Rapid nitric oxide–induced desensitization of the cGMP response is caused by increased activity of phosphodiesterase type 5 paralleled by phosphorylation of the enzyme. J Cell Biol 155:271–278.
17. Rybalkin SD, Rybalkina IG, Feil R, et al. (2002) Regulation of cGMP-specific phosphodiesterase (PDE5) phosphorylation in smooth muscle cells. J Biol Chem 277:3310–3317.
18. Rybalkin SD, Rybalkina IG, Shimizu-Albergine M, et al. (2003) PDE5 is converted to an activated state upon cGMP binding to the GAF A domain. EMBO J 22:469–478.
19. Boolell M, Allen MJ, Ballard SA, et al. (1996) Sildenafil: an orally active type 5 cyclic GMP–specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. Int J Impot Res 8:47–52.
20. Taher A, Stief C, Raida M, et al. (1992) Cyclic nucleotide phosphodiesterase activity in human cavernous smooth muscle and the effect of various selective inhibitors. Int J Impot Res 4(Suppl 2):11.
21. Kuthe A, Wiedenroth A, Magert HJ, et al. (2001) Expression of different phosphodiesterase genes in human cavernous smooth muscle. J Urol 165:280–283.
22. Kuthe A, Montorsi F, Andersson KE, et al. (2002) Phosphodiesterase inhibitors for the treatment of erectile dysfunction. Curr Opin Invest Drugs 3:1489–1495.
23. Stief CG. (2000) Phosphodiesterase inhibitors in the treatment of erectile dysfunction. Drugs Today (Barc) 36:93–99.

24. Giordano D, De Stefano ME, Citro G, et al. (2001) Expression of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in mouse tissues and cell lines using an antibody against the enzyme amino-terminal domain. Biochim Biophys Acta 1539: 16–27.
25. Kotera J, Fujishige K, Omori K. (2000) Immunohistochemical localization of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in rat tissues. J Histochem Cytochem 48:685–693.
26. Moreland RB, Goldstein II, Kim NN, et al. (1999) Sildenafil citrate, a selective phosphodiesterase type 5 inhibitor. Trends Endocrinol Metab 10:97–104.
27. MacGrouther C, Charlton R, Thompson L, et al. (2000) Biochemical In Situ Hybridisation and Immunohestochemical Characterisation of Phosphodiesterase Type 5 Expression in Human Corpus Cavernosum and Cardiac Tissue. Presented at the 9th World Meeting in Impotence Research. Int J Impot Res 27.
28. Lin CS, Chow S, Lau A, et al. (2002) Human PDE5A gene encodes three PDE5 isoforms from two alternate promoters. Int J Impot Res 14:15–24.
29. Loughney K, Hill TR, Florio VA, et al. (1998) Isolation and characterization of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3',5'-cyclic nucleotide phosphodiesterase. Gene 216:139–147.
30. Taher A, Meyer M, Stief CG, et al. (1997) Cyclic nucleotide phosphodiesterase in human cavernous smooth muscle. World J Urol 15:32–35.
31. Schultheiss D, Stief CG. (1999) Physiology and pathophysiology of erection: consequences for present medical therapy of erectile dysfunction. Andrologia 31 (Suppl 1):59–64.
32. Saenz de Tejada I, Blanco R, Goldstein I, et al. (1988) Cholinergic neurotransmission in human corpus cavernosum. I. Responses of isolated tissue. Am J Physiol 254:H459–H467.
33. Lue TF, Takamura T, Umraiya M, et al. (1984) Hemodynamics of canine corpora cavernosa during erection. Urology 24:347–352.
34. Trigo-Rocha F, Aronson WJ, Hohenfellner M, et al. (1993) Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs. Am J Physiol 264: H419–H422.
35. Bischoff E, Schneider K. (2001) A conscious-rabbit model to study vardenafil hydrochloride and other agents that influence penile erection. Int J Impot Res 13:230–235.
36. Giuliano F, Bernabe J, Alexandre L, Niewoehner U, Haning H, Bischoff E. (2003) Proerectile effect of vardenafil: in vitro experiments in rabbits and in vivo comparison with sildenafil in rats. Eur. Urol 93:605–608.
37. Goldstein I, Lue TF, Padma-Nathan H, et al. (1998) Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 338:1397–1404.
38. Holmquist F, Stief CG, Jonas U, et al. (1991) Effects of the nitric oxide synthase inhibitor NG-nitro-L-arginine on the erectile response to cavernous nerve stimulation in the rabbit. Acta Physiol Scand 143:299–304.
39. Murray K. (1993) Phosphodiesterase V inhibitors. Drugs News Perspect 3:150–156.
40. Bischoff E, Schramm M, Straub A, et al. (2003) BAY 41-2272: a stimulator of soluble guanylyl cyclase induces nitric oxide–dependent penile erection in vivo. Urology 61:464–467.
41. Stasch JP, Becker EM, Alonso-Alija C, et al. (2001) NO-independent regulatory site on soluble guanylate cyclase. Nature 410:212–215.
42. Corbin J D, Turko IV, Beasley A, et al. (2000) Phosphorylation of phosphodiesterase-5 by cyclic nucleotide–dependent protein kinase alters its catalytic and allosteric cGMP-binding activities. Eur J Biochem 267:2760–2767.

43. Turko IV, Ballard SA, Francis SH, et al. (1999) Inhibition of cyclic GMP-binding cyclic GMP-specific phosphodiesterase (type 5) by sildenafil and related compounds. Mol Pharmacol 56:124–130.
44. Gibson A. (2001) Phosphodiesterase 5 inhibitors and nitrergic transmission-from zaprinast to sildenafil. Eur J Pharmacol 411:1–10.
45. Saenz de Tejada I, Angulo J, Cuevas P, et al. (2001) The phosphodiesterase inhibitory selectivity and in vivo potency of the new PDE5 inhibitor vardenafil. Int J Impot Res 13:282–290.
46. Angulo J, Gadau M, Fernandez A. (2001) IC351 enhances nitric oxide mediated relaxation of human arterial and trabecular penile smooth muscle. Diabetologia 44: 259.
47. Ballard SA, Gingell CJ, Tang K, et al. (1998) Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. J Urol 159:2164–2171.
48. Bischoff E, Niewöhner U, Haning H, et al. (2001) The inhibitory selectivity of vardenafil on bovine and human recombinant phosphodiesterase isoenzymes. Int J Impot Res 13:41.
49. Corbin JD, Francis SH. (2002) Pharmacology of phosphodiesterase-5 inhibitors. Int J Clin Pract 56:453–459.
50. Gbekor E, Bethell S, Fawcett L, et al. (2002) Selectivity and other phosphodiesterase type 5 (PDE5) inhibitors against all human phophodiesterase families. Eur Urol Suppl 1:63.
51. Stief CG, Uckert S, Becker AJ, et al. (2000) Effects of sildenafil on cAMP and cGMP levels in isolated human cavernous and cardiac tissue. Urology 55:146–150.
52. Bortolotti M, Mari C, Giovannini M, et al. (2001) Effects of sildenafil on esophageal motility of normal subjects. Dig Dis Sci 46:2301–2306.
53. Corbin JD, Blount MA, Weeks JL II, et al. (2003) [3H]sildenafil binding to phosphodiesterase-5 is specific, kinetically heterogeneous, and stimulated by cGMP. Mol Pharmacol 63:1364–1372.
54. Bischoff E, Mondritzki T, Niewoehner U, et al. (2002) Vardenafil improved erections in rabbits longer than expected from plasma half-life. Int J Impot Res 14 (Suppl 4):S7–S42.
55. Berman JR, Berman LA, Lin H, et al. (2001) Effect of sildenafil on subjective and physiologic parameters of the female sexual response in women with sexual arousal disorder. J Sex Marital Ther 27:411–420.
56. Basson R, McInnes R, Smith MD, et al. (2002) Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. J Womens Health Gend Based Med 11:367–377.
57. Wilkens H, Guth A, Konig J, et al. (2001) Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. Circulation 104: 1218–1222.
58. Ghofrani HA, Wiedemann R, Rose F, et al. (2002) Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. Ann Intern Med 136:515–522.
59. Zhihua S. (2003) Phosphodiesterase-5 inhibitors for male erectile dysfunction. Expert Opin Ther Patents 13:1373–1388.

4 Sildenafil Citrate, the Classic PDE5 Inhibitor

A Five-Year Review of Its Efficacy and Safety in the Arena of Erectile Dysfunction

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CONTENTS

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INTRODUCTION

In 1988, a new class of drugs was heralded by the release of sildenafil citrate, an orally administered, potent, and selective phosphodiesterase type 5 (PDE5) inhibitor.

Initially a candidate antianginal agent, it has now become the global cornerstone of medical therapy for erectile dysfunction (ED). PDE5 is found in the trabecular smooth muscle of the corpora cavernosa, as well as in the smooth muscle of arteries and veins. It is not found in cardiac myocytes or the cells of the conducting system. The mechanism of action of sildenafil, as well as other PDE5 inhibitors, is to enhance the endogenous signal transduction process. Initially, with sexual simulation, efferent neurotransmission in the cavernous nerves that innervate the trabecular smooth muscle of the corpora cavernosa releases nitric oxide, a fleeting neurotransmitter that diffuses into the smooth muscle cell and activates guanylate cyclase, which in turn increases the production of cyclic GMP (cGMP). cGMP produces, through the intracellular sequestration and extracellular translocation of calcium, smooth muscle relaxation with subsequent increased arterial inflow and veno-occlusion. Thus, cGMP mediates the events of sexual stimulation. These events may be amplified pharmacologically, through sildenafil, by decreasing the degradation of cGMP through the inhibition of the enzyme that breaks down cGMP, PDE5. Herein lies the means to understanding the mechanism of the organic nitrate interaction with PDE5 inhibitors—the only absolute contraindication to sildenafil therapy. Organic nitrates are nitric oxide donors that convert a local phenomenon into a systemic event with potential for significant vasodilation and hypotension. This nitrate contraindication is a class effect.

Sildenafil citrate, the first orally delivered selective PDE5 inhibitor, was approved by the United States Food and Drug Administration (FDA) as a treatment for ED in March of 1998.

To date, there have been more than 2000 peer-reviewed journal articles, published abstracts, and medical reviews related to sildenafil, including more than 500 peer-reviewed papers and nearly 100 cardiovascular-related publications. Recently, three review articles have been published that summarize the efficacy and safety of sildenafil citrate over time *(1,2)* in selected clinical populations *(1)* and in multiple racial and ethnic groups *(3)*. These data provide clear support for sildenafil's safety and long-term efficacy in the management of ED.

INDICATIONS AND CONTRAINDICATIONS

At present, PDE5 inhibitors are approved only as on-demand (not chronic) therapy for the treatment of ED. PDE5 is found not only in the

smooth muscle of the corpora cavernosa but also in arterial and venous smooth muscle. Consequently, if nitric oxide is made available systemically in the presence of a PDE5 inhibitor, systemic vasodilation and potentially significant drops in blood pressure may occur. As a result, all PDE5 inhibitors are absolutely contraindicated in men receiving organic nitrates or other nitric oxide donors. The greatest period of risk for an interaction between a PDE5 inhibitor and a nitrate may be at most 2 h after dosing with sildenafil and 48 to 72 h after dosing with tadalafil *(4,5)*.

PHARMACOKINETICS AND PHARMACODYNAMICS

The three PDE5 inhibitors are separable into two groups—fast-onset (sildenafil and vardenafil) and long-duration (tadalafil) *(6–11)*. In addition to the biochemical properties discussed earlier, pharmacokinetic properties and effects of PDE5 inhibitors (ingestion or food interaction, first-pass metabolism in the liver, tissue uptake, elimination) have an impact on efficacy. There are several common pharmacokinetic parameters that can be measured and quantified that describe distribution and availability of a PDE5 inhibitor *(6–8)*.

The bioavailability, maximum plasma concentration (C_{max}), time (T_{max}) required for attaining C_{max}, and time ($T_{1/2}$) required for elimination of one-half of the inhibitor from plasma are all such factors. Bioavailability is the ultimate percentage of an orally administered drug that is found in the circulation compared with an injected dose. It is a reflection of absorption and the effects of first-pass hepatic metabolism. Lower bioavailability can affect inter- and intrapatient variability in efficacy and may result in drug–drug interactions. Sildenafil has 40% bioavailability vs 15% for vardenafil. Tadalafil has not yet been formulated for intravenous administration, and therefore bioavailability data are not available. Sildenafil and vardenafil have broadly similar T_{max}, but the C_{max} of vardenafil is significantly lower than that for either of the other two inhibitors. This might be expected based on the lower bioavailability. Onset of activity is faster for sildenafil and vardenafil than it is for tadalafil. Sildenafil has the fastest onset of action of any PDE5 inhibitor, and it may be effective as quickly as within 14 min in 35% of responders, and within 20 min in more than half of all responders *(12)*.

The duration of action is probably about three half-lives of a PDE5 inhibitor. The half-life of sildenafil is 3 to 5 h; therefore, sildenafil efficacy may be seen 8 to 12 h beyond administration. The $T_{1/2}$ of tadalafil is considerably longer than that of the other two PDE5 inhibitors—17.5 h for men younger than 60 yr of age and 21 h for men older than 60 yr of age *(13)*.

The extended exposure of tadalafil is overall, 105 h, or five half-lives, in men older than 60 yr of age and 87.5 h in men younger than 60 yr of age.

ONSET OF ACTION OF SILDENAFIL

Data from a recent study of the minimum time to onset of erection after dosing with 100 mg of sildenafil reveal that the drug's onset of action may be significantly quicker than the commonly perceived 30–60 min (time to reach T_{max}) *(9)*. In this double-blind trial, 228 men with ED who had been successfully treated with sildenafil for more than 12 mo were randomly assigned to receive 100 mg of sildenafil ($n = 115$), or placebo ($n = 113$) for 4 wk. Patients recorded the time (via stopwatch) needed to obtain an erection sufficient for sexual intercourse (as verified by diary data) after administration of the study drug in the fasted state (>2 h). Nearly 35% of sildenafil-treated patients reported more than one erection leading to successful intercourse within 14 min of dosing, whereas 51% reported more than one erection leading to successful intercourse within 20 min of dosing ($p < 0.05$). This time to onset of erection is substantially shorter than the 1 h assumed by most physicians and is more rapid than the onset time obtained for vardenafil (16 min) or any other PDE5 inhibitor to date.

LONG-TERM EFFICACY AND SAFETY DATA

A recent analysis of pooled data from 11 double-blind, placebo-controlled, flexible-dose studies of sildenafil in men with ED ($n = 2667$) revealed that sildenafil significantly improved erectile function compared with placebo ($p < 0.02 – p < 0.0001$), regardless of patient age, race, body mass index, the presence of various comorbidities, or the etiology, severity, or duration of ED *(1)*. Efficacy evaluations included the International Index of Erectile Function (IIEF), a global efficacy question (GEQ) (GEQ: "Did treatment improve your erections?"), and patient-recorded event logs of sexual activity *(1)*. Significantly, the efficacy of sildenafil was maintained with long-term therapy. Few patients discontinued sildenafil owing to inadequate response, and few required a higher dose adjustment to sustain response. Of 2618 men with ED who participated in three 1-yr, open-label extension studies, 89% continued to receive sildenafil at the end of 1 yr. Satisfaction with the treatment's effect on erections was reported by 96% of these patients and was associated with an improved ability to engage in sexual activity in 99% of patients. Less than 2% of patients discontinued use owing to insufficient response. Of patients who were followed for an additional 2 yr, satisfaction with the treatment's effect on erections and improved ability to engage in sexual activity was consistently reported by 95% or more patients at each yearly assessment. Over the 3-yr study period, 32% of patients discontinued medication; however, of these discontinuations, only 6.7% were considered to be treatment related *(1)*.

A recent 4-yr update on the safety of sildenafil provided additional evidence of sildenafil's positive safety profile *(2)*. This extensive review summarized the general, cardiovascular, and ophthalmological adverse event profile of sildenafil in more than 7000 men with more than 13,000 person-years of exposure.

The authors concluded that sildenafil has an excellent safety profile, noting that field experience in more than 20 million men also strongly supports the drug's record of high efficacy and safety. The most common adverse events are most commonly mild to moderate in intensity and rarely cause dropout. These adverse events include headache (13–16%), flushing (10%), and dyspepsia (7%). Myalgia occurs in less than 1% of men taking sildenafil.

EFFICACY AND SAFETY IN SELECTED PATIENT GROUPS

Diabetes (1)

Four 12-week, double-blind, placebo-controlled trials have evaluated sildenafil in men with ED and underlying diabetes mellitus *(1)*. In the first two of these trials, 259 and 261 patients were randomly assigned to receive placebo or sildenafil, respectively. Approximately 20% of patients had type 1 diabetes, and 80% had type 2 diabetes. In these studies, 51–56% of sildenafil-treated patients reported improved erections, compared with 10–12% of patients receiving placebo. The remaining studies evaluated sildenafil in men with type 2 diabetes separately from those with type 1 diabetes. The type 2 diabetes study included 219 patients randomly assigned to receive sildenafil ($n = 110$) or placebo ($n = 109$). After 12 wk of treatment, mean scores for GEQ, IIEF question (Q)3 and Q4, and erectile function domain had significantly improved in the sildenafil-treated group, as had the percentage of successful intercourse attempts reported. These improvements were statistically significant as compared with placebo ($p < 0.0001$). Moreover, sildenafil was effective in improving erectile function even in cases of poor glycemic control or multiple chronic complications. Efficacy was similar in a double-blind, placebo-controlled study of 188 men with type 1 diabetes and ED.

Ischemic Heart Disease (1)

In a double-blind, placebo-controlled trial of sildenafil in men with cardiovascular disease who were receiving one or more of either α-blockers, angiotensin-converting enzyme inhibitors, or calcium-channel blockers, sildenafil produced a significant improvement in erectile function (GEQ and IIEF Q3 and Q4, $p = 0.0001$) *(1)*.

Hypertension (1)

A recently completed, double-blind, placebo-controlled trial assessed the efficacy of sildenafil in 562 men with ED who were taking two or more antihypertensive agents (two agents, $n = 324$; ≥ 3, $n = 235$; unspecified, $n = 3$) *(1)*. Mean scores on IIEF Q3 and Q4 and erectile function domain improved significantly in sildenafil-treated patients compared with placebo-treated patients. In addition, significantly more sildenafil-treated patients reported improved erections (71% vs 18% in the placebo group), and significantly more intercourse attempts were successful in the sildenafil group (62% vs 26% in the placebo group) ($p < 0.0001$).

Treated Prostate Cancer (1,11,14)

In the 11 pooled trials, response rates to sildenafil were lower in men with ED who had previously undergone radical prostatectomy compared with men with other comorbidities. The radical prostatectomy subgroup included a mix of men who had undergone nerve-sparing and nonnerve-sparing surgeries. Several studies have now shown that the response to sildenafil in men with ED who have undergone radical prostatectomy varies with the number of neurovascular bundles spared during surgery. Reported response rates to sildenafil have ranged from 33 to 80% for bilateral nerve-sparing surgery, from 0 to 80% for unilateral nerve-sparing surgery, and from 0 to 20% for nonnerve-sparing surgery. Other factors associated with sildenafil response in men with ED after prostatectomy include pretreatment erectile function, patient age, and recovery time after surgery. In general, studies have concluded that response to sildenafil was poor during the first 6 to 9 mo following surgery *(11)*. An improvement in treatment satisfaction from 26%, when sildenafil was tried during the first 6 mo after prostatectomy, to 60%, for treatment at 18 mo to 2 yr after surgery, was observed in one study *(14)*. In studies assessing the effectiveness of sildenafil in men with postradiotherapy ED, sildenafil improved erectile function in 71% (15 of 21), 45% (27 of 60 vs 8% [5 of 60] with placebo), 77% (23 of 30), 70% (16 of 23), and 74% (37 of 50) of patients. Similar response rates have been reported with transperineal ultrasound-guided prostate brachytherapy with or without moderate-dose external beam radiation, with 62% (52 of 84) and 81% (50 of 62) reporting a positive outcome with sildenafil *(1)*.

THE PREVENTION OF ED IN THE PATIENT UNDERGOING NERVE-SPARING PROSTATECTOMY *(15)*

A recent double-blind, placebo-controlled prospective study of 76 men with normal preoperative erectile function who underwent a bilateral nerve-

sparing radical retropubic prostatectomy (NSRRP) performed by an experienced surgeon was the first prospective examination of the impact of sildenafil on the return of normal erections in this population. It is also the first such prevention study in this field *(15)*. "Normal" erectile function was defined as a combined score of greater than or equal to eight for Q3 and Q4 of the IIEF and normal nocturnal penile tumescence (NPT) testing (10 continuous min of $\geq$ 55% base rigidity).

Four weeks after undergoing NSRRP, patients were randomly assigned to receive nightly dosing with either sildenafil (50 mg, $n = 23$; 100 mg, $n = 28$) or placebo ($n = 25$) for 36 wk. Erectile function was assessed 8 wk after discontinuation of drug treatment (week 48) by asking the question, "Over the past 4 wk, have your erections been good enough for satisfactory sexual activity?" and by IIEF and NPT assessments. Patients with a combined score of greater than or equal to eight for IIEF Q3 and Q4 and a positive response to the abovementioned question were classified as treatment responders. Fourteen of 51 (27%) patients receiving sildenafil demonstrated a return of spontaneous erectile function, compared with one of 25 (4%) in the placebo group ($p = 0.0156$). Postoperative NPT assessments were supportive. There were no treatment-related serious adverse events reported; two patients discontinued because of treatment-related adverse events.

This study demonstrates that nightly administration of sildenafil for 9 mo after NSRRP was well tolerated and significantly increased the return of spontaneous erections (off drug) compared with placebo. Possible mechanisms for this effect include sildenafil-induced improvement in oxygenation at the time of nocturnal erections or postoperative neuronal regeneration, or both. These results support the consideration of this treatment regimen as an adjunct to postoperative care for NSRRP. Such findings have not been demonstrated with the other PDE5 inhibitors.

Black and Hispanic Patients (3)

A total of 246 black and 197 Hispanic-American men were randomly assigned to receive 50 mg of sildenafil, adjustable to 25 or 100 mg ($n = 124$ and $n = 99$, respectively) or matching placebo ($n = 122$ and $n = 98$, respectively). After 6 wk of treatment, patients were given the option of switching to the other blinded treatment for the following 6 wk. Twelve weeks of double-blind treatment were followed by 12 wk of open-label extension. Despite intergroup differences in the prevalence of hypertension, diabetes mellitus, hyperlipidemia, and use of antihypertensive agents, sildenafil treatment was both effective and well tolerated. The proportion of patients switching to the other treatment after 6 wk was significantly higher in the placebo group (71–85%) than in the sildenafil group (27–28%). The most common adverse events included headache and vasodilation *(3)*.

THE CARDIOVASCULAR PROFILE OF SILDENAFIL

During routine outpatient cardiology visits, Kloner et al. administered a validated five-question questionnaire, the Sexual Health Inventory for Men (SHIM), based on the IIEF questionnaire, to 76 male patients aged 40 to 82 yr old (mean age 64 yr old) with chronic stable coronary artery disease (CAD) *(16)*.

Most of these men had not previously discussed ED with their cardiologists. In this population, 47% of the men were on β-blockers, 92% were on statins, and 28% were on diuretics. Fifty-three of 76 (70%) had a SHIM score of less than 21, which is indicative of ED.

The questionnaire results demonstrated that 57 of 76 (75%) of these men had ED or recent histories of ED. On sildenafil treatment, their SHIM scores were 23 to 25. This score indicates near normalization of erectile function. Clearly, ED is extremely common in the population of men with chronic CAD who are routinely seen in cardiologists' offices—affecting approx 75% of men—yet most cardiologists do not ask about it. Successful treatment of this population is readily possible using sildenafil. These efficacy results mirror the success rates previously demonstrated in larger studies of patients with CAD.

The cardiovascular characterization of sildenafil through Pfizer-sponsored and independent studies has enabled a large degree of clinical comfort in its use. Recently, Padma-Nathan et al. reviewed and graded the English language-based peer-reviewed publications on oral therapies for ED *(13)*.

Of the nearly 95 such publications, more than 90 were related to sildenafil, with the majority being graded as high-level scientific evidence. In summary, sildenafil is a modest peripheral vasodilator that causes mean maximal drops in systolic blood pressure of less than 8 mmHg, and diastolic blood pressure decreases of less than 6 mmHg. It is interesting that there is no dose-related decrease in blood pressure associated with sildenafil. Additionally, sildenafil does not produce a reflex increase in heart rate. Because PDE5 is not found in cardiac myocytes or cells of the conducting system, it is not surprising that sildenafil does not change cardiac contractility or myocardial oxygen consumption. It has no effect on pulmonary hemodynamics in the patient with normal pulmonary artery pressure *(12)*.

Clinical trials are an excellent source of data for rates of myocardial infarction and all-cause mortality. In the more than 13,000 men who have received sildenafil in more than 130 ongoing or completed phase II–IV clinical trials, the incidence of both myocardial infarction and all-cause mortality has been statistically the same in the sildenafil and placebo groups (more than 7000 of these men were in placebo-controlled trials) *(2)*. It

should be noted, however, that the men in clinical trials are often low to moderate risk, and men in clinical practice who seek ED therapy may represent a slightly higher risk population. To address this difference, independent, as well as regulatory-based, surveillance systems exist worldwide. The most extensive such study of more than 22,000 men (with more than 30,000 patient-years of exposure) from the National Health System in the United Kingdom demonstrated no increased signal for cardiovascular morbidity or mortality when compared with the age-matched male population *(17)*.

There has been much misplaced concern regarding the safety of using sildenafil in patients receiving multiple antihypertensive medications. In a randomized, double-blind, placebo-controlled 6-wk study of the efficacy and safety of sildenafil in men receiving multiple antihypertensives (two or more, $n = 307$; 222 of which were receiving three or more antihypertensives), Pickering and coinvestigators have clearly demonstrated greater than 70% efficacy and, more important, an associated safety profile comparable to that seen in men not taking medications for hypertension *(18,19)*.

Recently, an interaction between α-blockers and all PDE5 inhibitors has been noted *(20–22)*. Although many (possibly millions) men have been prescribed sildenafil and an α-blocker without reports of adverse events, a drug–drug interaction study has demonstrated that two of 20 men simultaneously receiving both 50 mg of sildenafil and 4 mg of doxazosin demonstrated symptomatic hypotension. No such interaction was seen with the 25-or 100-mg dose of sildenafil. Additionally, the interaction was not seen after 4 h or more of separation in administration. The current labeling change indicates that doses of 50 or 100 mg of Viagra should not be taken within 4 h of α-blocker administration. A 25-mg dose of Viagra may be taken at any time. There are α-blocker interactions and contraindications related to vardenafil (as a class) and tadalafil (excluding the 0.4-mg dose of tamsulosin) *(21,22)*.

In a recent report to the FDA advisory panel on the effects of vardenafil on QTc prolongation, an executive summary report was submitted to the committee regarding the QT/QTc interval data on sildenafil *(23)*. To date, no cases of QTc prolongation or torsades de pointes have been identified in a review of clinical trials and postmarketing surveillance data in more than 20 million men. The published independent nonclinical data consistently demonstrate the lack of prolonging effect on cardiac repolarization by sildenafil up to the highest concentration tested (0.9 μ*M*). The QT/QTc data from the relevant sildenafil phase I, II, and III studies provide no evidence that up to 800 mg of sildenafil induces arrhythmias.

The major risk factors for ED include age, chronic cardiovascular diseases (heart disease, hypertension, diabetes, and hyperlipidemia with or

without depression), medications (antihypertensives and antidepressants), and lifestyle (stress, alcohol or drug abuse, and smoking). Obviously, significant overlap exists between the populations of men with ED and those with CAD. In fact, the initial diagnosis of ED may help uncover clinically silent CAD. Therefore, selection of ED therapies frequently must take into consideration the cardiovascular risk profile of the patient. Even in healthy individuals, sexual activity raises the relative risk of myocardial infarction. However, the absolute risk remains exquisitely low. Most patients with CAD can be effectively and safely treated for ED by employing PDE5 inhibitors, particularly sildenafil. Clearly, it is important to understand the hemodynamic effects of PDE5 inhibitors in the patient with CAD when selecting an ED therapy. These hemodynamic effects, with respect to sildenafil, have been examined in a number of landmark studies, including the following:

1. Invasive hemodynamic assessment of sildenafil in patients with severe CAD at cardiac catheterization.
2. An investigation of the effects of sildenafil on coronary and peripheral circulation and on myocardial ischemia in patients with CAD.
3. Exercise treadmill or ergometric bicycle testing in men with reproducible angina receiving sildenafil.

HEMODYNAMIC ASSESSMENT OF SILDENAFIL IN PATIENTS WITH SEVERE CAD *(12)*

In a landmark lead article in the New England Journal of Medicine, Herrmann et al. examined the effects of 100 mg of oral sildenafil in men with severe CAD at the time of cardiac catheterization and planned subsequent angioplasty *(12)*. Study subjects included 14 men with stable angina, at least one of whom had a severely stenosed (>70% of the vessel diameter) coronary artery, who had been referred for percutaneous revascularization. Nitrates were discontinued at least 24 h before the start of the study. Hemodynamic measurements included arterial blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and right atrial pressure. Heart rate and cardiac output were determined by thermodilution. Systemic and pulmonary vascular resistances and their indexes were calculated. Angiography was performed. Average peak velocity and coronary flow reserve at baseline were measured before and after intracoronary administration of adenosine. After baseline measurements were completed, 100 mg of sildenafil was administered; all measurements were repeated 45 min later. Percutaneous coronary vascularization was performed at the end of the study. For the 14 patients (mean age ± standard deviation [SD] was 61 ± 11 yr), the mean ± SD degree of stenosis of at least one coronary artery was 78 ± 7%. Among these men, 57% were smokers, 57% had hypertension, 43% had diabetes, and 36% had a previous myocardial infarction.

Results

Small decreases (<10%) were observed in arterial systolic, diastolic, and mean blood pressure and in systolic and mean pulmonary pressures. There were no significant changes in pulmonary capillary wedge pressure, right atrial pressure, heart rate, cardiac output, cardiac index, or calculated systemic and pulmonary vascular resistances and their indexes. The double product (heart rate × systolic blood pressure) also decreased.

Sildenafil produced no significant changes in average peak velocity at baseline, coronary artery diameter, coronary blood flow, or coronary vascular resistance. The hyperemic average peak velocity and coronary flow reserve increased 13% after administration of sildenafil, however; the effect was consistently observed in both stenosed and reference arteries. In the 11 men in whom measurements were made in both a stenosed and a reference artery, relative coronary reserve (ratio of coronary flow reserve in diseased vs reference vessels) was unchanged by sildenafil (0.57 ± 0.14 at baseline vs 0.57 ± 0.15 after sildenafil, $p = 0.90$).

Conclusion

No adverse cardiovascular effects of oral sildenafil were detected in men with severe CAD. These findings support the American College of Cardiology/American Heart Association consensus position that sildenafil is safe for patients with stable CAD who are not taking nitrates.

THE EFFECTS OF SILDENAFIL ON CORONARY AND PERIPHERAL CIRCULATION AND ON MYOCARDIAL ISCHEMIA IN PATIENTS WITH CAD *(24)*

The effect of sildenafil on resting coronary vascular tone and on endothelium-dependent and -independent function and platelet activation was measured in 24 men in this study *(24)*. In addition, 24 other men with CAD and ischemia during exercise and 12 control subjects received either 100 mg of sildenafil, 10 mg of isosorbide dinitrate (ISDN), or placebo during exercise on three separate days in a randomized, double-blind manner. Flow-mediated dilation of the brachial artery was measured, and patients with CAD underwent exercise treadmill testing (ETT).

Results

Sildenafil vasodilated epicardial coronary arteries ($+6.9\% \pm 1.3\%$, $p < 0.0001$). Coronary epicardial and microvascular responses with acetylcholine and cold pressor testing improved, with greater enhancement in patients with CAD and endothelial dysfunction. Verapamil responses were unchanged. Both resting and adenosine diphosphate-stimulated

platelet IIb/IIIa receptor activation was inhibited by sildenafil ($p < 0.05$). Brachial arteries dilated in response to sildenafil in controls. Peak flow-mediated dilation was similar, but the duration of hyperemia was prolonged after sildenafil administration ($p < 0.001$). Compared with placebo, ISDN improved myocardial ischemia during ETT ($p < 0.05$), whereas the effect of sildenafil was intermediate between the two.

Conclusion

Sildenafil dilates epicardial coronary arteries, improves endothelial dysfunction, and inhibits platelet activation in patients with CAD. It has an intermediate effect on myocardial ischemia compared with ISDN and placebo.

THE EFFECT OF SILDENAFIL ON EXERCISE-INDUCED ANGINA *(25,26)*

Arruda-Olson et al. published a randomized, double-blind, placebo-controlled, crossover trial involving 105 men older than 40 yr of age with ED and known or highly suspected CAD *(25)*. CAD was defined as having any of the following:

1. More than 50% diameter stenosis of a major epicardial artery or one of its major branches.
2. A history of myocardial infarction.
3. A prior positive stress imaging result.
4. Previous coronary artery bypass surgery or angioplasty.
5. A high (>70%) pretest probability of CAD according to the presence of typical angina pectoris.

Major exclusion criteria were asthma, severe aortic stenosis, hypertrophic obstructive cardiomyopathy, unstable angina, recent myocardial infarction (<1 mo), congestive heart failure, or a systolic blood pressure of less than 90 mmHg. Long-acting nitrates were discontinued 2 h before testing. The sildenafil dose was 50 mg unless a different dose was recommended by the patient's physician.

All patients underwent two symptom-limited exercise electrocardiograms (EKGs) separated by 1 to 3 d; all cardioactive medications were continued. Subjects were randomly assigned in a double-blind crossover design, to 50 mg of sildenafil or to placebo, to be taken 1 h before the exercise test. Baseline EKG images were obtained, and the test was repeated 1 h after drug administration. Overall, 54 and 52 men performed the exercise test after receiving sildenafil first and second, respectively, whereas 54 and 53 men performed the exercise test after receiving placebo first and second, respectively. Exercise EKGs were performed on a supine bicycle attached to a table tilted 30–45° to the left. Subjects began exercising at 25 W with

a 25-W increase at 2-min intervals. EKG imaging was performed continuously during each stage of the exercise protocol. The criteria for test termination included development of symptoms, including fatigue; a decrease in systolic blood pressure of greater than10 mmHg; ventricular dilation or global reduction of systolic function; and significant arrhythmia.

Results

Of 110 men, 105 (sildenafil, $n = 53$; placebo, $n = 52$) were included in the analysis. The mean age was 66 yr; 89% of men had known CAD, and 28% had typical angina pectoris. A total of 92% of men received the 50-mg dose of sildenafil, and 7% received the 100-mg dose. The baseline EKG result was abnormal in 56% of patients, and resting wall-motion abnormalities were present in 57% of patients. The mean resting ejection fraction was 56%. Resting heart rate and diastolic blood pressure did not change significantly after sildenafil administration; systolic blood pressure showed a mean decrease of 7 mmHg ($p < 0.001$) with sildenafil and 3 mmHg with placebo ($p = 0.08$). The rate of decrease from peak exercise was similar in the sildenafil and placebo groups for heart rate (3%/min and 1%/min, respectively), systolic blood pressure (3.6 mmHg/min and 3.3 mmHg/min, respectively), and diastolic blood pressure (1.0 mmHg/min and 0.9 mmHg/min, respectively). Resting wall motion (wall motion score index) did not change significantly after sildenafil administration. Exercise-induced wall motion abnormalities developed in a similar number of men with sildenafil ($n = 84$) or placebo use ($n = 86$), and the wall motion score index at peak exercise was similar after sildenafil or placebo use. Symptoms of dyspnea or angina developed in 69 men from the sildenafil group and 70 men from the placebo group. There were no deaths, acute myocardial infarctions, or episodes of ventricular fibrillation associated with exercise studies.

Conclusion

In this prospective, randomized, crossover study of men with ED and known or probable CAD, sildenafil administered 1 h before exercise testing was well tolerated and did not change the onset, extent, or severity of ischemia.

In the second study, Fox et al. examined the effect of sildenafil on exercise-induced angina in men at the time of a treadmill test *(26)*. This was a double-blind, parallel-group, placebo-controlled, multicenter study in men with ED and chronic stable angina, assessing the effect of sildenafil on time to onset of limiting angina during incremental ETT. Patients with reproducible exercise-induced angina received a 100-mg dose of sildenafil or placebo 1 h before treadmill exercise. The primary end point was time to limiting angina; secondary end points included time to angina, time to

1-mm ST-segment depression, total exercise time, blood pressure, heart rate, and rate pressure product.

Results

In the evaluable patients, sildenafil ($n = 56$) significantly increased the time to onset of limiting angina and angina, as well as exercise duration, compared with placebo ($n = 52$). Adjusted treatment differences (sildenafil minus placebo) were 19.9 ± 9.6 s (confidence interval [CI], 0.9–38.9; $p = 0.04$), 31.7 ± 10.7 s (CI, 10.5–53.0; $p = 0.0039$), and 19.5 ± 9.8 s (CI, 0.04–38.9; $p = 0.05$), respectively.

Blood pressure after exercise was similar in the two treatment groups; rate pressure product was lower after drug administration in the sildenafil group at rest, during exercise, and throughout the recovery period. There were no serious treatment-related adverse events.

Conclusion

Sildenafil did not adversely affect any exercise parameter in men with severe CAD and ED; the time to limiting angina was improved by 9.8% and 4.7% with sildenafil and placebo, respectively.

COMPARATIVE PHARMACOLOGY OF PDE5 INHIBITORS

An Evidence-Based Review

The introduction of sildenafil citrate has dramatically altered the management of ED. To date, it remains the standard-bearer for PDE5 inhibitors, owing in large part to a significant body of data supporting its efficacy, safety, and excellent cardiovascular profile, as well as an enormous field experience in more than 25 million men. Two new potential members of the class of PDE5 inhibitors have joined sildenafil in the armamentarium of ED treatment.

The European Commission recently issued marketing authorizations for tadalafil and vardenafil *(27,28)*, and both have recently been approved by the FDA *(21,22)*. Although pharmacologically members of the same class of drugs, these new molecules have unique and different chemical, pharmacokinetic, efficacy and safety profiles.

Potency, Selectivity, and Cardiovascular Profile

Similar to sildenafil, vardenafil and tadalafil are potent PDE5 inhibitors. Biochemical potency is described by the IC_{50}—the concentration of the enzyme inhibitor needed to inhibit 50% of the activity of the enzyme. This is a test-tube measure, and the IC_{50} of all three drugs is within the range of 1 to 10 n*M*, although vardenafil appears to be more potent within this

range *(29)*. Clinical efficacy does not appear to be different within this potency range. In fact, existing data indicate that all three drugs have similar clinical efficacy; furthermore, in head-to-head trials, neither tadalafil nor vardenafil appears to have reached statistical noninferiority to sildenafil *(27,29)*. This reflects the fact that clinical efficacy is driven by factors other than potency (including bioavailability and dosage).

Selectivity is the differential ability to inhibit PDE5 as opposed to the other 10 members of the PDE family. In addition to their PDE5 inhibitory activity, both sildenafil and vardenafil appear to inhibit PDE6 at high doses. PDE6 is the one PDE that is localized to a single organ, the eye (rods and cones). Although PDE6 inhibition is associated with transient visual disturbances, data on sildenafil indicate that this inhibition is not associated with significant acute or chronic effects in men with normal visual function or in men with macular degeneration, treated glaucoma, or nonproliferative diabetic retinopathy *(2,30)*. Tadalafil does not inhibit PDE6; however, it has been shown to inhibit PDE11, a dual substrate (cGMP and cAMP) found in the anterior pituitary, testes, prostate, cardiac myocytes, and cells of the conducting system of the heart *(31)*. The localization and the implied functional role of PDE11 are clear, but the functional significance of pharmacological PDE11 inhibition is unknown and unclear. The safety implications are fairly significant but unresolved. The effect of PDE11 inhibition on sperm count and more particularly function (particularly in subfertile men) remains unclear, as does its effect on inotropism and myocardial oxygen consumption. Also unknown is the potential impact of PDE11 inhibition on myocardial cAMP. It is conceivable that PDE11 inhibition can lead to elevations in myocardial cAMP that may increase the risk of cardiac events in men with compromised left ventricular function, as has been seen with PDE3 inhibitors, such as milrinone. These patients, however, have not been examined in clinical trials. To date the effects of tadalafil and vardenafil on cardiac contractility are unknown.

The European Agency for the Evaluation of Medicinal Products (EMEA) analyzed data related to timing and period of responsiveness. Despite inferences to the contrary from investigators and the sponsor (in European marketing), the EMEA concluded that there was "no evidence of 'spontaneous' drug taking not being linked to sex" and "no evidence of 'weekend use patterns' in subsequent days post dosing" *(27)*.

Comparative Efficacy and Safety

Vardenafil has demonstrated efficacy in general, diabetic and post-prostatectomy-related ED *(32,33)*. Tadalafil has demonstrated efficacy in general and diabetic ED *(34)*. In head-to-head trials performed and

released by the EMEA, however, neither drug met statistical noninferiority criteria compared with sildenafil *(1,2)*. Comparative head-to-head study results made public by the EMEA indicate that tadalafil was not as effective as sildenafil. Specifically, the 5- and 10-mg doses did not reach noninferiority vs 50 and 100 mg, respectively, of sildenafil. The EMEA also concluded that noninferiority could not be established for the 20-mg dose vs 50- or 100-mg doses of sildenafil, owing to the following issues:

1. Approximately half of study subjects had mild erectile dysfunction, "and it seems there were patients included that did not suffer from erectile dysfunction according to baseline IIEF scores."
2. The exclusion of prior sildenafil nonresponders and of patients with severe ED would lead to higher success rates for tadalafil.
3. Sildenafil was recommended to be taken 1 to 5 h before sexual activity—a window that was too large and that may have diminished the efficacy of sildenafil in the comparator trials

The EMEA also noted that in studies in which safety was analyzed, most patients received doses of less than 20 mg. In phase III studies, total patient exposure was only 949, of which less than a third (311 patients) received the 20-mg dose.

In general, all PDE5 inhibitors have similar adverse effects as a result of PDE5 inhibition—headaches, flushing, and dyspepsia (PDE5 inhibition in lower esophageal sphincter with resultant gastroesophageal reflux disease). Although myalgia, back pain, and pain in the extremities may also be class effects, they are only seen in the presence of high prolonged serum levels and as such are seen only with tadalafil *(27)*. Myalgia may occur with tadalafil in about 12 to 16% of men, but the incidence may be as high as 40% in younger men *(27)*. Myalgia was indicated to be severe in 16% of cases *(27)*. The US label indicates that overall, tadalafil is associated with a less than 5% incidence of myalgia when one includes all trials, including those employing lower does than are approved in the US *(22)*. On the US label, it is indicated that the myalgia may last up to 48 h and may rarely require a mild narcotic analgesic for treatment. To date, this myalgia is not associated with rhabdomyolysis, although it is not clinically differentiable from the life-threatening myalgia associated with statins.

In reviewing preclinical toxicology data, EMEA noted findings of degeneration, vacuolation, and atrophy of seminiferous tubular epithelium in mouse and dog and noted, "the clinical relevance of these findings has not been addressed." Data from two studies conducted in humans that involved only two spermatogenic cycles did not "provide enough reassurance for daily use in man for more than six months" *(27)*.

Vardenafil has recently been approved for use in the United States by the FDA *(21)*. On the US label, an absolute contraindication to using vardenafil

exists for both organic nitrates and all α-blockers. Vardenafil, 10 or 20 mg, was given either simultaneously or 6 h after 10 mg of terazosin. With simultaneous dosing of 10 mg of vardenafil and terazosin, six of eight subjects had hypotension (standing systolic blood pressure of less than 85). With simultaneous dosing of 20 mg of vardenafil and terazosin, two of nine subjects had hypotension (standing systolic blood pressure of less than 85). When 20 mg of vardenafil was separated in dosing from terazosin by 6 h, seven of 28 subjects had hypotension (standing systolic blood pressure of less than 85).The administration of lower doses of vardenafil with α blockers has not been examined. Such studies are currently planned *(21)*.

Despite only minor QT prolongation (<10 ms), the label indicates that vardenafil should be "avoided in patients with congenital QT prolongation or in those taking Class IA (e.g., quinidine or procainamide) or Class III (e.g., amiodorone, sotalol) antiarrhythmic medications." Further drug–drug interaction studies of QT have been requested postapproval *(21)*.

OTHER PDE5 INHIBITORS

Nearly half a dozen PDE5 inhibitors are in preclinical or early clinical development. One particular PDE5 inhibitor that offers a unique selectivity profile (similar to sildenafil) and the potential for both rapid onset (T_{max}, 1 h) and longer duration ($T_{1/2}$, 11 h) is DA8159 (DongA Pharmatech, Seoul, Korea). This compound does not have an excessive half-life and therefore can be used for both chronic dosing for ED and daily dosing for such entities as pulmonary artery hypertension.

CONCLUSION

Sildenafil has demonstrated unsurpassed efficacy, tolerability, and cardiovascular safety in both clinical trials and clinical practice. Evidence-based medicine would support it as the first-line PDE5 inhibitor for the management of ED.

REFERENCES

1. Carson CC, Burnett AL, Levine LA, et al. (2002) The efficacy of sildenafil citrate (Viagra®) in clinical populations: an update. Urology 60(Suppl 2B):12–27.
2. Padma-Nathan H, Eardley I, Kloner R, et al. (2002) A four-year update on the safety of sildenafil citrate (Viagra). Urology 60(Suppl 2B):67–90.
3. Young JM, Bennett C, Gilhooly P, Wessells H, Ramos DE. (2002) Efficacy and safety of sildenafil citrate (Viagra) in black and Hispanic American men. Urology 60(Suppl 2B):39–48.
4. Oliver JJ, Bell K, Leckie SM, et al. (2002) Interaction between Glyceryl Trinitrate and Sildenafil Citrate May Last Less Than Four Hours. Paper presented at the 10th World Meeting on Impotence Research. International Society for Sexual and Impotence Research, Montreal, Canada, Sept.

5. Kloner RA, Hutter AM, Emmick JT, Mitchell MI, Denne J, Jackson G. (2003) Time course of the interaction between tadalafil and nitrates. J Am Coll Cardiol 42:1855–1860.
6. Muirhead GJ, Rance DJ, Walker DK, et al. (2002) Comparative human pharmacokinetics and metabolism of single-dose oral and intravenous sildenafil citrate. Br J Clin Pharmacol 53(Supp 1):13S–20S.
7. Rajagopalan P, Mazzu A, Xia C, et al. (2003) The effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. J Clin Pharmacol 43:1–8.
8. Patterson. (2002) Presented at European Society for Sexual and Impotence Research (ESSIR), Rome.
9. Padma-Nathan H, Stecher V, Sweeney M, et al. (2003) Minimal time to successful intercourse after sildenafil citrate: results of a randomized, double-blind, placebo-controlled trial. Urology 62:400–403.
10. Porst H, Padma-Nathan H, Giuliano F, et al. (2003) Efficacy of tadalafil in the treatment of erectile dysfunction at 24 and 36 h after dosing: a randomized clinical trial. J Urol 62:121–125; discussion, 125–126.
11. McCullough AR. (2001) Prevention and management of erectile dysfunction following radical prostatectomy. Urol Clin North Am 28:613–627.
12. Herrmann HC, Chang G, Klugherz BD, et al. (2000) Hemodynamic effects of sildenafil in men with severe coronary artery disease. N Engl J Med 342:1622–1626.
13. Wyllie MG. (2003) The Second International Consultation on Erectile Dysfunction. BJU Int 92(6):645–646..
14. Hong EK, Lepor H, McCullough AR. (1999) Time dependent patient satisfaction with sildenafil for erectile dysfunction (ED) after nerve-sparing radical retropubic prostatectomy (RRP). Int J Impot Res 11(Suppl 1):S15–S22.
15. Padma-Nathan H, McCullough A, Giuliano F, et al. (2003) Postoperative Nightly Administration of Sildenafil Citrate Significantly Improves the Return of Normal Spontaneous Erectile Function after Bilateral Nerve-Sparing Radical Prostatectomy (abstract). Paper presented at the American Urological Association Annual Meeting, Chicago, IL, April 27.
16. Kloner RA, Mullin SH, Shook T, et al. (2003) Erectile function in the cardiac patient: how common and should we treat? J Urol 170:S46–S50.
17. Shakir SAW. (2002) ESSIR Annual Meeting. Hamburg, Germany.
18. Mancia G, Pickering TG, Glasser D, et al. (2002) Efficacy of Viagra (Sildenafil Citrate) in Men with Erectile Dysfunction and Hypertension Who Are Taking Multiple Antihypertensive Medications. Paper presented at the American Society of Hematology Annual Meeting, New York, NY.
19. Pickering TG, Mancia G, Glasser D, et al. (2002) Safety of Viagra (Sildenafil Citrate) in Men with Erectile Dysfunction and Hypertension Who Are Taking Multiple Antihypertensive Medications. Paper presented at the American Society of Hematology Annual Meeting, New York, NY.
20. Viagra, USPI Labeling, September 2002.
21. Levitra, USPI Labeling, 2003.
22. Cialis, USPI Labeling, November 2003.
23. Pfizer (2003) Overview of relevant sildenafil data: absence of adverse outcomes potentially related to QT prolongation—five yr of post-marketing experience. Executive summary. Paper presented to the Cardiovascular and Renal Drugs Advisory Committee, May 29.

24. Halcox JPJ, Nour KRA, Zalos G, et al. (2002) The effect of sildenafil on human vascular function, platelet activation and myocardial ischemia. J Am Coll Cardiol 40:1232–1240.
25. Arruda-Olson AM, Mahoney DW, Nehra A, et al. (2002) Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. JAMA 287:719–725.
26. Fox KM, Thadani U, Ma PT, et al. (2001) Time to onset of limiting angina during treadmill exercise in men with erectile dysfunction and stable chronic angina: effect of sildenafil citrate (in press; presented AHA 2001, Anaheim, CA).
27. European Agency for the Evaluation of Medicinal Products (EMEA). (2002) Committee for Proprietary Medicinal Products European Public Assessment Report: Cialis—international non-proprietary name: tadalafil (CPMP/3960/02). London, UK: European Agency for the Evaluation of Medicinal Products.
28. European Agency for the Evaluation of Medicinal Products (EMEA). (2003) Committee for Proprietary Medicinal Products European Public Assessment Report: Levitra—international non-proprietary name: vardenafil (CPMP/6210/02). London, UK: European Agency for the Evaluation of Medicinal Products, 2003.
29. Bischoff E, Niewohner U, Haning H, et al. (2001) The inhibitory selectivity of vardenafil on bovine and human recombinant phosphodiesterase isoenzymes (Poster 113). Int J Impot Res 13(Supp l4):41.
30. Laties A, Zrenner E. (2002) Viagra (sildenafil citrate) and ophthalmology. Prog Retin Eye Res 21:485–506.
31. Fawcett L, Baxendale R, Stacey P, et al. (2000) Molecular cloning and characterization of a distinct human phosphodiesterase gene family: PDE11A. Proc Natl Acad Sci USA 97:3702–3707.
32. Porst H, Rosen R, Padma-Nathan H, et al. (2001) The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 13:192–199.
33. Hellstrom WJG, Gittleman M, Karlin G, et al. (2002) Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 23: 763–771.
34. Brock GB, McMahon CG, Chen T, et al. (2002) Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of an integrated analysis. J Urol 168:1332–1336.

5 Tadalafil

Clinical Trials Experience

Culley C. Carson III, MD

CONTENTS

INTRODUCTION

Tadalafil (Cialis®) is an oral medication indicated for the treatment of erectile dysfunction (ED). This chapter reviews the current state of knowledge of the pharmacodynamics, pharmacokinetics, effectiveness, and safety of tadalafil. Data are derived from clinical trials involving more than 5700 men with mild to severe ED of various causes regardless of the presence of major comorbidities, such as diabetes and hypertension.

In clinical studies, tadalafil has been shown to have a unique pharmacokinetic profile, which includes a long duration of action, up to 36 h *(1)*. This has the potential to provide couples with increased flexibility by minimizing the need to schedule sexual activity around time of day. Additionally, one study has shown that the rate and extent of tadalafil absorption is not affected by the presence of high-fat food, which also

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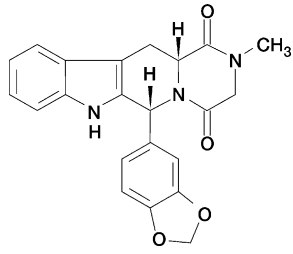

Fig. 1. Tadalafil is a selective inhibitor of the enzyme phosphodiesterase type 5 (PDE5), one of a family of 11 PDEs that degrade cyclic guanosine monophosphate or cyclic adenosine monophosphate, or both. Tadalafil has the empirical formula of $C_{22}H_{19}N_3O_4$, representing a molecular weight of 389.41. Compared with other PDE5-inhibiting agents, tadalafil has a unique structure (*see* ref. *5*).

translates into increased flexibility for couples by minimizing the need to schedule sexual activity around mealtimes *(2)*.

PHARMACODYNAMICS AND PHARMACOKINETICS

Site and Mechanism of Action

Tadalafil is a selective inhibitor of the enzyme phosphodiesterase type 5 (PDE5), one of a family of 11 PDEs that degrade cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine monophosphate (cAMP). Compared with other agents in the class of PDE5 inhibitors, tadalafil has a unique chemical structure (Fig. 1).

Tadalafil is also considered to be highly selective for PDE5 and is more selective for PDE5 than for any other PDEs *(3–5)*. For example, tadalafil is more than 10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscles, and other organs. In addition, tadalafil is 9000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10 and 14-fold more potent for PDE5 than for PDE11A1, an enzyme found in human skeletal muscle. The physiological role and clinical relevance of PDE11 inhibition in humans, however, have not been determined *(4–6)*.

PDE5 is found in high concentrations in the corpus cavernosum of the penis and, to a lesser extent, in vascular smooth muscle cells. Because PDEs are found in a variety of tissues and are implicated in a broad range of cellular functions, the selectivity for PDE5 over other PDEs may have clinical relevance for adverse events. For example, tadalafil is a weak inhibitor of PDE6, which is found in high concentrations only in

the photoreceptors of the retina. This lower affinity of tadalafil for PDE6 may explain the low incidence of visual adverse effects reported in clinical trials in patients receiving the drug. Inhibition of PDE6 is thought to underlie the visual disturbances sometimes reported by patients taking PDE5 inhibitors, such as sildenafil *(7)*.

The mechanism by which tadalafil inhibits PDE5 and improves erections in men with ED requires an understanding of the physiology of the erectile response to sexual stimulation *(8,9)*. During sexual stimulation, nitric oxide (NO) released from nonadrenergic, noncholinergic (NANC) neurons and endothelial cells stimulates guanylate cyclase to produce cGMP, which in turn decreases intracellular calcium levels. This ultimately results in the relaxation of the vascular smooth muscle and increased blood flow into the corpus cavernosa, followed by penile erection *(8,9)*.

Tadalafil augments this naturally occurring NO-cGMP pathway by inhibiting PDE5-induced cGMP degradation, thereby increasing levels of cGMP and ultimately enhancing erectile function *(4)*. This has been demonstrated in vitro using tissue taken from men with ED undergoing surgery for penile implantation *(3)*. Consistent with increased cGMP levels, tadalafil, like other PDE5 inhibitors, also enhances sodium nitroprusside (SNP)-induced relaxation of corpus cavernosum and penile arterial tissues, as well as relaxation induced by NO stimulation and by acetylcholine *(10)*. In vivo, this process results in penile erection in the presence of sexual stimulation. Because sexual stimulation is required to initiate the local release of NO, the inhibition of PDE5 has no effect in the absence of sexual stimulation *(5,9)*.

Absorption, Distribution, Metabolism, and Excretion

Pharmacokinetic studies conducted in healthy subjects show that tadalafil is rapidly absorbed, with mean peak plasma levels observed between 30 min and 6 h (median time of 2 h) after single oral-dose administration *(5,11–13)*. Tadalafil exhibits linear pharmacokinetics over the dosage range of 2.5 to 20 mg, and steady-state plasma concentrations are attained within 5 d of once-daily dosing, with exposure approx 1.6-fold greater than after a single dose *(5)*. At therapeutic concentrations, 94% of tadalafil in plasma is protein bound, but, as indicated by its large apparent volume of distribution, tadalafil is widely distributed in tissues *(5,14)*. In vitro studies indicate that tadalafil is metabolized via cytochrome P450 3A4 (CYP3A4), but tadalafil itself is neither an inhibitor nor an inducer of CYP3A4. This has been confirmed by clinical pharmacology studies of tadalafil given in combination with other substrates (lovastatin, midazolam) for CYP3A4, or with an inhibitor (ketoconazole) or inducer (rifampin) of CYP3A4 *(15)*. No dosing adjust-

ment of tadalafil is warranted when taken in combination with CYP3A4 inducers *(5)*. Studies have shown that drugs inhibiting CYP3A4 can increase tadalafil exposure. Based on study results, in patients taking concomitant potent CYP3A4 inhibitors, the dose of tadalafil should not exceed 10 mg, and the dose should not be taken more frequently than once every 72 h *(5)*.

Notably, tadalafil has an elimination half-life of 17.5 h, considerably longer than the half-lives of the other drugs in this class (i.e., sildenafil [3–5 h] and vardenafil [4–5 h]) *(1,16,17)*. With respect to metabolism, no active metabolites of tadalafil have been identified. Tadalafil is excreted predominantly as inactive metabolites mainly in the feces (61% of the dose) and, to a lesser extent, in the urine (36% of the dose) *(5)*.

Clinical pharmacology studies have examined the effects of tadalafil on pharmacokinetics in special populations (i.e., elderly patients and those with diabetes, renal impairment, or hepatic insufficiency). For healthy, elderly male subjects (65 yr or older), a lower oral clearance of tadalafil was observed, resulting in 25% higher exposure (area under the dose-response curve [AUC]) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 yr of age. No dose adjustment is warranted based on age alone; however, greater sensitivity to medications in some older individuals should be considered *(2,5)*.

In the case of patients with mild or moderate hepatic impairment, the maximum dose should not exceed 10 mg, and use in patients with severe hepatic impairment is not recommended. No dose adjustment is required in patients with diabetes or with mild renal insufficiency. For patients with moderate renal insufficiency, tadalafil should be limited to 5 mg not more than once daily, with the maximum dose limited to 10 mg not more than once every 48 h. In patients with severe renal insufficiency or end-stage renal disease, tadalafil should be limited to 5 mg not more than once daily *(5)*. Likewise, common extrinsic factors appear to exert no influence on tadalafil's pharmacokinetics. For instance, the presence of high-fat food affects neither the rate nor the extent of tadalafil absorption; thus, tadalafil may be taken with or without food (Fig. 2) *(2,5)*.

Although previous studies showed no pharmacodynamic interactions between tadalafil and alcohol *(2,12)*, recent studies show that both alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *(5)*.

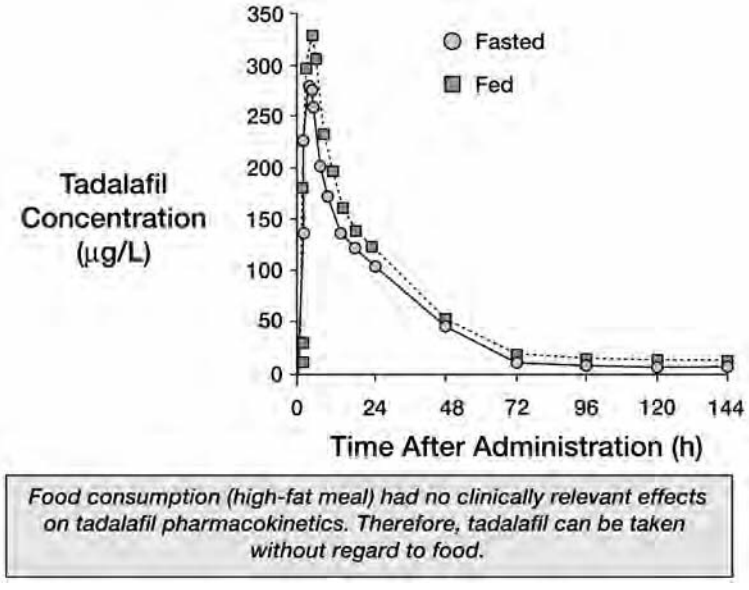

Fig. 2. Common extrinsic factors appear to exert no influence on the pharmacokinetics of tadalafil. For example, the presence of high-fat foods affects neither the rate nor the extent of tadalafil absorption; thus, tadalafil may be administered with or without food. (From ref. *2*.)

Onset and Duration of Action

In one study, significantly greater penile rigidity (as measured by RigiScan® [Timm Medical Technologies, Eden Prairie, MN] and compared with placebo) was observed at an average of 45 min after subjects took a single 10-mg dose of tadalafil. Achievement of erection was observed as early as 16 min after subjects took a single 20-mg dose *(13)*.

Although tadalafil has a relatively fast onset of action, comparable with that of other PDE5 inhibitors, its long half-life and consequent prolonged duration of action sets it apart from other drugs in this class. Several studies have been conducted to determine whether tadalafil's rapid appearance in the blood and long half-life translate into a quick onset of action and prolonged period of responsiveness in terms of erectile function *(1,6,13,18)*.

One multicenter, randomized, double-blind, placebo-controlled study to determine the duration of action of tadalafil was divided into two 4-wk intervals of treatment. Men with mild to severe ED were provided with two 20-mg doses of tadalafil for at-home use and, in one 24-h treatment interval, were asked to attempt sexual intercourse. In a separate 36-h treatment

interval, men were also asked to attempt intercourse *(1)*. In response to Question (Q) 3 of the Sexual Encounter Profile (SEP) (i.e., "Did your erection last long enough to have successful intercourse?"), more than 60% of men taking tadalafil reported having successful intercourse at 24 h and 64% at 36 h after dosing ($p < 0.001$). Tadalafil was effective for 36 h, with 59% of sexual intercourse attempts at 36 h being successful in patients randomly assigned to receive the 20-mg dose, compared with 28% for placebo (Table 1) *(1)*.

The integrated analysis of trials in which patients took tadalafil without restriction on food or alcohol intake also showed that 79–80% of attempts at sexual intercourse made between 4 and 36 h after tadalafil dosing were successful *(18)*. A subsequent analysis of 11 clinical trials involving more than 2000 men with ED confirmed the long period of responsiveness with tadalafil, with the mean-per-patient rate of successful intercourse attempts ranging from 65.5% (at 30 min–1 h) to 73.4% (at 24–36 h) after a single 20-mg dose of tadalafil *(19)*.

The long period of responsiveness to tadalafil allows couples to take full advantage of the long duration of effectiveness associated with ED medication *(20)*. In another study assessing the period of responsiveness after taking tadalafil, 82% of men with ED attempted sexual intercourse at least once in the 4 to 36 h after dosing. As many as 59% of men in this study attempted intercourse between 12 and 36 h *(20)*. Clearly, tadalafil represents a new step forward in the pharmacotherapy of ED by removing restrictions associated with other PDE5 inhibitors on the timing of sexual activity. The pharmacokinetic profile of tadalafil has the potential to allow couples increased flexibility, reducing the need to plan and schedule sexual activity under time constraints. This is a key consideration for couples seeking real-life sexual effectiveness.

EFFICACY OF TADALAFIL IN THE TREATMENT OF MEN WITH ED

Effectiveness in the General Population

Tadalafil significantly improves erectile function (EF), as assessed by a variety of determinants of efficacy, including the following: the EF domain of the International Index of Erectile Function (IIEF), which classifies erectile function into five levels ranging from normal (26–30) to severe ($\leq$10) *(21)*; SEP Q2 and Q3 *(22)*; and the global assessment questions (GAQ) *(18,23–25)*.

The SEP Q2 asks patients, "Were you able to insert your penis into your partner's vagina?" The SEP Q3 offers the key question, "Did your erection last long enough for you to have successful intercourse?"

Table 1
Successful Intercourse Attempts Maintained With Tadalafil Up to 36 h [a]

	Placebo (n = *173*)			*20 mg Tadalafil* (n = *175*)			
Duration	*Attempts*	*Successes*	*Patients* [b]	*Attempts*	*Successes*	*Patients* [b]	p *Value*
24 h	247	72 (29.1%)	36.8%	227	120 (52.9%)	60.9%	<0.001
36 h [c]	212	60 (28.3%)	35.2%	223	132 (59.2%)	64.1	<0.001

[a] *n* = 348.
[b] Based on SEP Q3 responses.
[c] Mean value (range 34–38 h).
From ref. *1*.

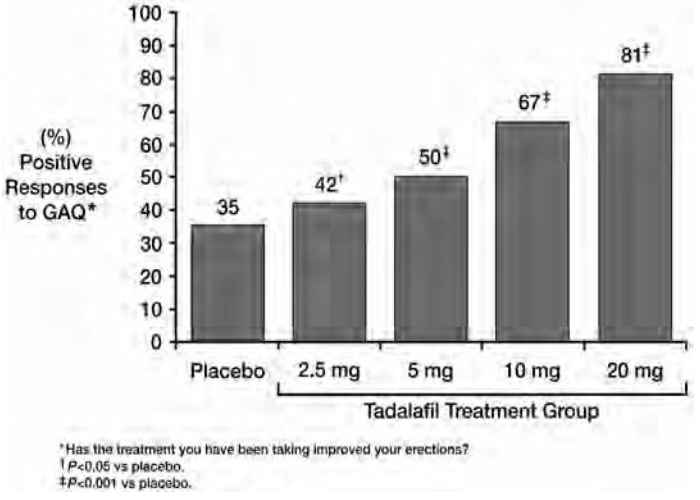

Fig. 3. At the 12-wk end point, a statistically significant response to the global assesment question, "Has the treatment you have been taking improved your erections?" was achieved by men who received 2.5 mg ($p < 0.05$) through 20 mg ($p < 0.001$) of tadalafil *(18)*. GAQ, global assessment question.

The GAQ 1 and 2 are self administered at the end of the treatment period during efficacy studies. For the GAQ 1, the patient is asked, "Has the treatment you have been taking during the study improved your erections?" GAQ then follows with Q2, "If 'yes,' has the treatment improved your ability to engage in sexual activity?" *(22)*. Using these assessment tools, several studies have been conducted to determine the effectiveness of tadalafil. Clinical trials have supported its efficacy and tolerability in a broad population of men with ED *(6)*.

The integrated analyses of randomized, double-blind, placebo-controlled trials confirm the efficacy of tadalafil, particularly at doses of 10 and 20 mg, according to a variety of end points *(18,19,23,26)*. One integrated analysis consisted of five trials including 1112 men, some with comorbidities of hypertension or diabetes, and most with ED of more than 1-yr duration. After a 4-wk, no-treatment baseline period, patients received fixed daily doses of tadalafil (2.5–20 mg) or placebo in an at-home setting for the next 12 wk. Patients were instructed to take the study medication as needed before sexual intercourse, without restriction on food, alcohol use, or timing of sexual activity. At the end point of these studies, the men responded to the GAQ, which asked whether the treatment had improved their erections. Results showed that the majority of men who received 10 or 20 mg of tadalafil felt that treatment had improved their erections ($p < 0.001$) (Fig. 3).

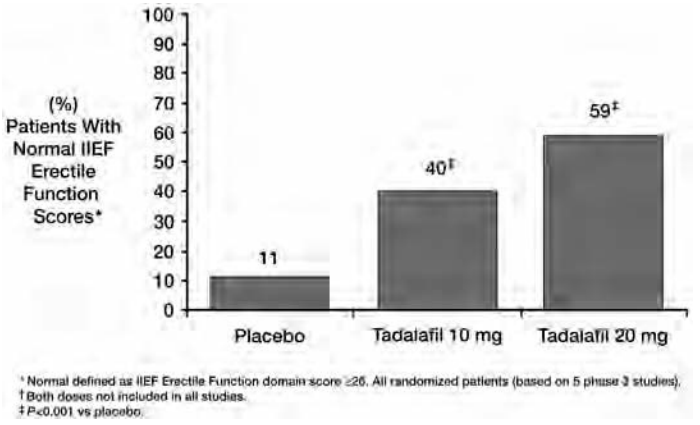

Fig. 4. Normal erectile function at end point (defined by an International Index of Erectile Function Erectile Function domain score of 26 or more out of a possible 30) was attained by 59% of men taking 20 mg of tadalafil and 40% of men receiving 10 mg of tadalafil vs 11% receiving placebo ($p < 0.001$). IIEF, International Index of Erectile Function *(18)*.

Lower doses of tadalafil were less effective than 10 or 20 mg but still elicited significantly more positive responses than placebo *(18)*.

When EF was assessed by the EF domain of the IIEF, significant improvement was observed at all doses of tadalafil ($p < 0.001$ vs placebo) *(18)*. Importantly, by the end point of the studies, normal erectile function (defined by an IIEF EF domain score of 26 or more out of a possible 30) was attained by 59% of men receiving 20 mg of tadalafil and 40% of men receiving 10 mg of tadalafil, compared with 11% of those receiving placebo ($p < 0.001$) (Fig. 4).

A subsequent analysis of 11 randomized, double-blind, 12-wk efficacy trials conducted in more than 2000 patients indicated that tadalafil is effective regardless of the baseline severity of ED. Thus, normal erectile function was attained with 20 mg of tadalafil by 40% of men who had severe ED at baseline (vs 3% for placebo control, $p < 0.001$) *(26)*.

In the integrated analysis of five trials, improved EF as measured by SEP diary was accompanied by an increased number of successful attempts at vaginal penetration (SEP Q2) and completion of intercourse (SEP Q3) *(18)*. In this study, 57 to 80% of attempts at penetration were successful in men receiving 5 to 20 mg of tadalafil, compared with 48% in men receiving placebo ($p < 0.001$). More than twice the attempts at intercourse were successful in men taking 20 mg of tadalafil than in men

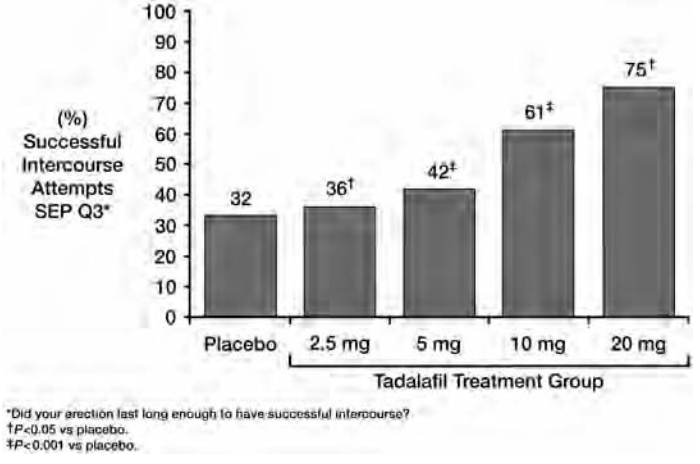

Fig. 5. In the integrated analysis of five trials, the percentage of successful intercourse attempts, as measured by Sexual Encounter Profile Question 3, was reported by 75% of men taking 20 mg or less of tadalafil vs 32% of men taking placebo ($p < 0.001$). SEP, Sexual Encounter Profile; Q, question *(18)*.

taking placebo (75% vs 32%, $p < 0.001$), with lower doses also being effective (Fig. 5) *(18)*.

In addition, the majority of men experienced successful intercourse after taking their very first dose of tadalafil, 10 or 20 mg (56% and 67%, respectively, vs 31% for placebo, $p < 0.001$). Moreover, even men with severe ED experienced a 46 to 68% success rate for intercourse through the first four doses of 10 or 20 mg of tadalafil (vs 20% for placebo, $p < 0.001$) *(27)*.

Overall, studies conducted in clinical settings that mimic real-life situations, without restriction on food, alcohol, or timing of sexual activity, show that tadalafil provides effective early treatment of ED irrespective of its cause or severity. In addition, factors, such as age and ethnicity, do not appear to influence the response to tadalafil. In the integrated analysis of five randomized trials, the efficacy of tadalafil was similar in patients older than 65 yr and in their younger counterparts *(18)*. Tadalafil was similarly effective in a study conducted in the United States and Puerto Rico, which included men of diverse ethnic origin (73% white, 13% Hispanic, 13% black, and 1% Asian) *(28)* and in two primary US efficacy and safety trials (78% white, 14% black, 7% Hispanic, and 1% other ethnicities) *(5,29)*.

Effectiveness in Men With Comorbid Diabetes

Diabetes is a common comorbidity in men with ED. Several studies have explored the effectiveness of tadalafil in this patient population. One

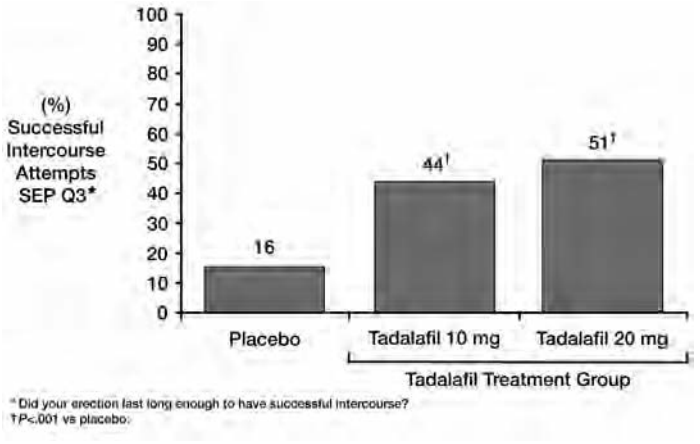

Fig. 6. The percentage of successful intercourse attempts (Sexual Encounter Profile Question 3) reported in patients with type 1 or type 2 diabetes was 51% for men taking 20 mg of tadalafil and 44% for men taking 10 mg of tadalafil, compared with 16% for placebo ($p < 0.001$). SEP, Sexual Encounter Profile; Q, question *(10)*.

study investigated men ($n = 216$) with type 1 or type 2 diabetes. Most men in this study had moderate to severe ED (72%) and a diagnosis of type 2 diabetes (>90%), with more than 80% having only fair ($HbA_{1C} > 7.0$–9.5%) to poor ($HbA_{1C} > 9.5\%$) diabetes control. Nearly 40% of the patients also had hypertension; 22% had microvascular complications, including retinopathy or neuropathy; and 18% had hypercholesterolemia. Patients were eligible whether or not they had responded to previous ED therapy, including sildenafil *(30)*.

As in studies of the general population of men with ED, studies of men with comorbid diabetes ($n = 216$) benefited from using tadalafil. The erectile function in most men improved significantly, with more than a six-point (with 10 mg) or seven-point (with 20 mg) increase in scores for the EF domain of the IIEF (compared with a 0.1 increase for placebo [$p < 0.001$]) at end point. Both doses of tadalafil, 10 and 20 mg, were superior to placebo in improving successful vaginal penetration (SEP Q2). The end points (change from baseline) were 30% (–4%), 57% (22%), and 54% (23%) for placebo, 10 mg of tadalafil, and 20 mg of tadalafil, respectively *(5)*.

Similarly, end-point scores for successful intercourse attempts (SEP Q3) were more pronounced in patients receiving 20 mg of tadalafil, (51%) or 10 mg (44%), vs 16% for those taking placebo ($p < 0.001$) (Fig. 6) *(10)*.

By the end of the 12-wk treatment period, 56% and 64% of men taking 10 and 20 mg, respectively, of tadalafil, compared with 25% receiving

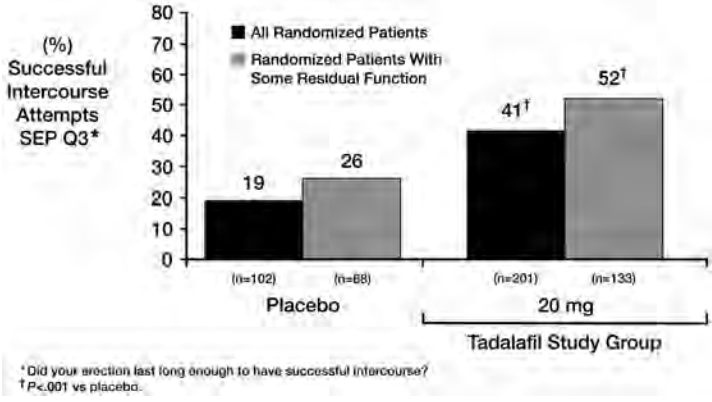

Fig. 7. By the end of the 12-wk treatment period, patients after bilateral nerve-sparing radical retropubic prostatectomy who were receiving 20 mg of tadalafil had significantly better rates of successful intercourse attempts (41%) than those receiving placebo (19%) ($p < 0.001$). BNRRP, bilateral nerve-sparing radical retropubic prostatectomy; SEP, Sexual Encounter Profile; Q, question *(32)*.

placebo, responded positively to the GAQ ($p < 0.001$). These benefits were observed irrespective of the level of diabetes control *(30)*. Many of the patients in this study had long-standing, fairly advanced diabetes, and, given the level of morbidity of the patient population, the effects of tadalafil were clinically noteworthy.

Effectiveness in Men After Postprostatectomy

ED is a frequent complication of radical prostatectomy. Despite improvements in surgical techniques used in prostatectomy, trauma to neurovascular bundles leaves many patients with ED. In fact, more than 50% of patients who undergo prostatectomy procedures will have ED *(31)*. In one study, the effects of tadalafil were examined in men who had developed ED after bilateral nerve-sparing radical retropubic prostatectomy (BNRRP). After a 4-wk no-treatment baseline period, patients received 20 mg of tadalafil or placebo as needed for the next 12 wk. Patients who received tadalafil had significantly improved EF, with a five-point increase in scores for the EF domain of the IIEF (compared with a one-point increase for placebo [$p < 0.001$]). (An increase of just five points in the IIEF EF domain is consistent with an improvement, such as moving from severe to moderate ED or from moderate to mild ED). By the end of the 12-wk treatment period, the group of all randomized patients receiving 20 mg of tadalafil after BNRRP had significantly better rates of successful intercourse attempts (41%) than those receiving placebo (19%) ($p < 0.001$) (Fig. 7) *(32)*.

Table 2
Tadalafil Tolerability[a]

	Patients reporting event (%)	
Adverse event	*Placebo (n = 308)*	*20 mg Tadalafil (n = 804)*
Headache	6	14
Dyspepsia	2	10
Back pain	5	6
Mylagia	2	5
Nasal congestion	4	5
Flushing	2	4

[a] Phase II/III: adverse events ≥2%.
From ref. *18*.

All randomized patients responded positively to the GAQ (62% with 20 mg of tadalafil vs 23% with placebo; $p < 0.001$). Additionally, encouraging results for patients with this type of ED were observed in a subgroup of men who exhibited at least some erection or tumescence at baseline and experienced an even better response to tadalafil than subjects in a separate study. Another study showed that after nerve-sparing surgery, the highest dose of a PDE5 inhibitor, such as tadalafil, is usually the most efficacious dose, and that best results are seen 12 mo after surgery *(32)*.

Dosage and Administration

The recommended starting dose of tadalafil in most patients is 10 mg, taken before anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg once per day, based on individual efficacy and tolerability. No dose adjustment of tadalafil is required in patients older than 65 yr age, in patients with diabetes, or in patients with mild renal insufficiency *(5)*.

SAFETY OF TADALAFIL IN THE GENERAL POPULATION OF MEN WITH ED

Safety in Clinical Trials

Clinical trials conducted with tadalafil show it to be safe and generally well tolerated. The most common treatment-emergent adverse events reported in men receiving 20 mg of tadalafil are headache and dyspepsia, which are mild or moderate in severity and transient in nature *(18)*. Flushing and myalgia have also been reported to occur with somewhat greater frequency among men taking tadalafil than among those receiving placebo *(1)*, but the incidence of flushing and myalgia among 804 men taking up to 20 mg of tadalafil was 5% or less (Table 2) *(18)*.

A similar profile of adverse events was observed in men with comorbid diabetes. In these men, only dyspepsia occurred with significantly greater frequency in men taking tadalafil (11%) than in men taking placebo (0%) ($p < 0.005$) *(30)*. No clinically significant changes in the electrocardiogram, vital signs, or blood chemistry have been observed with tadalafil. Notably, there has been only one report of visual disturbance, consisting of abnormal color vision, among men receiving tadalafil *(18)*. As discussed earlier, tadalafil lacks selectivity for the PDE6 isoenzyme, which may explain the low incidence of visual disturbances. For this reason, tadalafil as a therapy for ED has been suggested as an option in patients with retinopathy *(33)*. In addition, no visual disturbances were reported among men with comorbid diabetes, including those with diabetic retinopathy *(30)*.

Lack of Adverse Effects on Spermatogenesis

Studies conducted in 421 men, either healthy or with mild ED, have found no evidence that tadalafil has adverse effects on spermatogenesis. Tadalafil had no clinically relevant effect on sperm concentration, sperm count per ejaculate, sperm motility, or sperm morphology. Similarly, tadalafil has no effect on serum levels of testosterone, luteinizing hormone, or follicle-stimulating hormone *(5,34)*.

Drug–Drug and Drug–Food Interactions

Common extrinsic factors appear to exert no influence on the pharmacokinetics of tadalafil. For example, in a clinical pharmacology study conducted in 18 healthy subjects, on the effect of food on tadalafil absorption, the mean plasma tadalafil concentration was similar among subjects who received a single 20-mg dose of tadalafil after eating a high-fat meal and among subjects who fasted, indicating that tadalafil may be taken with or without food. This study also demonstrated that the presence of high-fat food affects neither the rate nor the extent of tadalafil absorption *(2)*.

Other drug interactions do exert influence on the pharmacokinetics of tadalafil. For example, since tadalafil is metabolized predominantly by CYP3A4 in the liver, the dosage should be limited to 10 mg not more than once every 72 h in patients taking potent inhibitors of CYP3A4, such as ritonavir and ketoconazole. In addition, drugs that induce CYP3A4, such as rifampin (600 mg daily), reduce tadalafil exposure. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted, however *(5)*.

In addition, tadalafil did not potentiate the increase in bleeding time caused by aspirin. Simultaneous administration of an antacid (magnesium

hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure AUC to tadalafil, and no dose adjustment is warranted *(5)*.

Long-Term Safety

The long-term safety of tadalafil has been assessed in 1173 patients enrolled in an ongoing, international, open-label study. Of the patients enrolled, most (870) had been exposed to 10 or 20 mg of tadalafil daily for at least 1 yr, with 991 being exposed to these dosages for more than 6 mo. Adverse events experienced by patients in the long-term study generally reflected those observed in the shorter-term studies. Headache and dyspepsia were the most frequently reported treatment-emergent adverse events, with incidence rates of 15% and 11%, respectively. Other adverse events reported with a frequency of 6 to 10% included infection, back pain, rhinitis, flu syndrome, pain, and a need for surgical procedures.

Overall, tadalafil was associated with good safety and tolerability for the treatment of ED in a broad range of patients using the drug for periods up to 1 yr. Few subjects in this study discontinued use because of adverse events *(35)*.

SAFETY OF TADALAFIL IN MEN WITH CARDIOVASCULAR DISEASE

PDE5 is found in the smooth muscle cells of systemic arteries and veins, and inhibitors of this isoenzyme act as mild vasodilators. Through relaxation of vascular smooth muscle, the hemodynamic effects of the PDE5 inhibitors can have major implications for the treatment of ED, especially in patients with comorbid cardiovascular conditions, such as coronary artery disease (CAD) and hypertension. Because patients with cardiovascular disease (CVD) typically receive multiple drug regimens to control angina, hypertension, and other cardiac conditions, potential drug interactions between PDE5 inhibitors and agents used for management of these conditions are particularly important *(36,37)*.

Effects of Tadalafil on Blood Pressure

Study results consistently show that tadalafil treatment has little effect on systemic arterial pressure. This is supported by data reported on more than 5700 subjects treated with tadalafil in more than 22 clinical trials *(5,38,39)*. One study, conducted in 80 healthy subjects, showed that single doses of 10 or 20 mg of tadalafil have only modest effects on systolic blood pressure (SBP) or diastolic blood pressure (DBP) (Fig. 8) *(38)*.

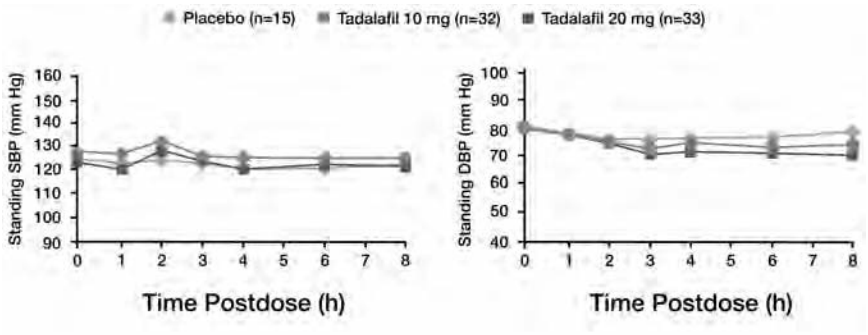

Fig. 8. Study results consistently show that tadalafil treatment has little effect on systemic systolic blood pressure (SBP) and diastolic blood pressure (DBP), supported by data reported in more than 5700 subjects treated with tadalafil over 22 clinical trials. One study, conducted in 80 healthy subjects, showed that single doses of 10 or 20 mg of tadalafil have only modest effects on SBP or DBP. (From ref. *38*. Copyright © 2002, with permission from European Society of Cardiology.)

Continued dosing once a day for 10 d revealed no clinically significant changes in standing or supine SBP or DBP or in heart rate. Additionally, 20 mg of tadalafil, administered to healthy male subjects produced no significant difference compared with placebo in supine SBP and DBP (difference in the mean maximal decrease of 1.6 and 0.8 mmHg, respectively) and in standing SBP and DBP (difference in the mean maximal decrease of 0.2 and 4.6 mmHg, respectively). In addition, there was no significant effect on heart rate *(5,38,39)*.

The modest hemodynamic effects of tadalafil in healthy subjects are reflected in the analyses of five placebo-controlled studies in a general population of men with ED and of one in men with comorbid diabetes. Men with significant CVD (for example, history of myocardial infarction, unstable angina, uncontrolled hypertension) were excluded from these studies. Blood pressure and heart rate were measured at baseline and at monthly intervals until the end of the 12-wk treatment period. No clinically or statistically significant effects on SBP or DBP or heart rate were observed over a range of doses of tadalafil (2.5–20 mg) compared with placebo ($p \geq 0.300$) *(38,39)*.

Incidence of Adverse Cardiovascular Effects in Clinical Trials

Patients receiving tadalafil would appear to be at no greater risk for cardiovascular-related side effects, including flushing, dizziness, hyper-

tension, and syncope, than are patients taking placebo because the incidence of these adverse events is low (0.1–3.7%) and not statistically significantly different among the two patient populations *(39)*. Importantly, the rate of myocardial infarction among patients taking tadalafil (0.43 per 100 patient-years) was no greater than that among a group of age-standardized men (Table 3) *(5,38,40)*.

Despite these assurances from the clinical trial database, the potential cardiac risk of sexual activity in patients with pre-existing CVD should be considered *(5,38)*.

Effects of Tadalafil on Exercise Tolerance

Because ED and CAD may often coexist, a study was conducted in men with stable CAD who demonstrated ischemia during a screening exercise test to examine the effects of tadalafil on physical exercise at a workload similar to that experienced during sexual activity *(41)*. The study was a randomized, double-blind, two-way crossover design in which patients (aged 53–75 yr) received 10 mg of both placebo and tadalafil on separate occasions approx 2 to 2.5 h before exercise. As assessed by the primary end point of time to limiting ischemia, tadalafil did not affect the exercise time or time to ischemia in these men. The mean difference in total exercise time was 3 s (10 mg of tadalafil minus placebo), which represented no clinically meaningful difference (Table 4) *(5,41)*.

Effects of Tadalafil on Cardiac Electrophysiology

The effect of a single 100-mg dose of tadalafil on QT interval, which represents ventricular depolarization and repolarization, was evaluated at the time of peak tadalafil concentration in a randomized, double-blind, placebo- and active (intravenous ibutilide)-controlled crossover study in 90 healthy males 18 to 53 yr of age. The mean change in QTc (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 ms (two-sided 90%, confidence interval = 1.9, 5.1). The mean change in QTc (individual QT correction) for tadalafil, relative to placebo, was 2.8 ms (two-sided 90%, confidence interval = 1.2, 4.4). A 100-mg dose of tadalafil (five times the recommended dose) was chosen because this dose yields exposures covering those observed on coadministration of tadalafil with potent CYP3A4 inhibitors. In this study, the mean increase in heart rate associated with a 100-mg dose of tadalafil compared with placebo was 3.1 beats per min. These changes are not likely to be clinically relevant *(5,38)*.

Drug Interactions Between Tadalafil and Nitrates

Like other PDE5 inhibitors, clinical pharmacology studies show that tadalafil (5–20 mg) potentiates the hypotensive effect of nitrates. This is

Table 3
Tadalafil: Incidence of MI Across All Studies

			Tadalafil-treated patients		
	Age-standardized male population	*Placebo-treated patients*	*Double-blind studies*	*Open-label safety studies*	*All studies*
Total no. of patients	—	1437	3666	1707	4196
Total patient exposure as patient years	—	334.5	791.7	1786.2	2578.0
No. of patients with MI	—	2	2	9	11
Rate of MI/100 patient-years flushing	0.60	0.60	0.25	0.50	0.43

MI, myocardial infarction.
From refs. *38* and *40*.

Table 4
Tadalafil: Total Exercise Time/Time to Ischemia [a]

	Placebo (n = 23) (min:sec)	*10 mg Tadalafil (n = 23) (min:sec)*	*Mean difference* [b] *(min:sec)*	*Lower 95% CI for the mean difference* [c] *(min:sec)*
Mean ± SD	13:31 ± 2:08	13:36 ± 1:59	0:03	–0:14
Minimum	9:12	9:19	0:03	(noninferior
Maximum	17:15	16:36	0:03	to placebo)

[a] 1.5-mm change from baseline to ST segment depression.
[b] Mean difference between tadalafil, 10 mg, and placebo in the least squares method.
[c] Mean difference between tadalafil, 10 mg, and placebo.
In patients with coronary artery disease, tadalafil, 10 mg, did not reduce total exercise time/time to ischemia during exercise stress testing when compared with placebo. CI, confidence interval; SD, standard deviation.
From ref. *41*.

thought to result from the combined effects of nitrates and tadalafil on the NO-cGMP pathway. Therefore, administration of tadalafil to patients who are using any form of organic nitrates, either regularly or intermittently, is contraindicated *(5,36,42)*.

Results of a recent placebo-controlled study to assess the degree of interaction between nitroglycerin and tadalafil showed that 20 mg of tadalafil enhanced the hypotensive effects of sublingual nitroglycerin (NTG) for up to 24 h after tadalafil dosing. In this study, a significant interaction between tadalafil and NTG was observed at each time point up to and including 24 h. At 48 h, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared with those receiving placebo experienced a decrease in blood pressure at this point in time. After 48 h, the interaction was not detectable. In emergency situations in which nitrate administration is deemed medically necessary, at least 48 h should elapse after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision and patient monitoring *(5,36,42,43)*.

Drug Interactions Between Tadalafil and α-Blockers

Another potential drug interaction exists between PDE5 inhibitors and α blockers. In a drug-interaction study, when 20 mg of tadalafil was administered to healthy subjects taking doxazosin (8 mg daily), an α_1-adrenergic blocker, there was a significant augmentation of the blood pressure-lower-

ing effect of doxazosin. When 20 mg of tadalafil was administered to healthy subjects taking 0.4-mg once-daily tamsulosin, a selective α_{1A}-adrenergic blocker, no significant decreases in blood pressure were observed. Therefore, administration of tadalafil to patients taking any α-blocker other than 0.4 mg of once-daily tamsulosin is contraindicated in the United States *(5)*.

Drug Interactions Between Tadalafil and Other Antihypertensives

Although tadalafil, like other PDE5 inhibitors, is a vasodilator that may augment the blood pressure-lowering effects of antihypertensive agents, recent data show that tadalafil is safe in patients receiving two or more concomitant antihypertensive agents *(38,43)*. According to an analysis of data from six placebo-controlled phase III studies of interactions between tadalafil and commonly prescribed antihypertensive agents, a comparison of patients receiving and not receiving antihypertensive therapy showed comparable incidence rates of cardiovascular events. No statistically significant differences were observed between tadalafil and placebo in the mean changes in blood pressure from baseline in patients taking concomitant antihypertensive therapy. Hypotension or postural hypotension was not reported in any tadalafil-treated patients, compared with a report of each in the placebo-treated patients. Additionally, syncope was reported in one tadalafil-treated patient (0.1%) who was not receiving concomitant antihypertensive medication and in two patients (1.9%) who received placebo with concomitant antihypertensive agents. In clinical pharmacology studies evaluating the combined efforts of tadalafil and various antihypertensive agents on blood pressure, the additional blood pressure reduction observed was generally mild, and there was no increase in hypotensive symptoms. In addition, the studies demonstrated no difference in adverse events in patients taking tadalafil with or without antihypertensive medications *(38,43)*.

SUMMARY AND CONCLUSIONS

Tadalafil is a highly selective PDE5 inhibitor that is safe and efficacious for the treatment of ED. Clinical evidence generally demonstrates the favorable safety and efficacy profiles of the PDE5 inhibitors in most patient populations, including men with stable ischemic heart disease and those receiving therapy with antihypertensive agents (other than α-blockers). These general properties also hold true for tadalafil, which provides clinical benefits regardless of the cause or severity of ED and may be safely used in men with comorbid conditions, such as diabetes and hypertension in men following prostatectomy.

In both healthy men and those with cardiovascular disease, PDE5 inhibitors generally produce only mild vasodilation and minimal hemodynamic effects and are not associated with increases in myocardial infarction or death rates in controlled clinical trials. Clinical evidence with tadalafil is consistent with this general statement, and it is important to note that the majority of patients assessed at low cardiovascular risk may be safely treated with tadalafil. Tadalafil is not associated with serious cardiovascular adverse events, although, like other PDE5 inhibitors in its class, its use is contraindicated in patients taking any form of organic nitrates. When chest pain occurs more than 48 h after tadalafil administration, however, nitrates may be used under close medical supervision. In addition, tadalafil is contraindicated with the use of α blockers other than 0.4 mg of once-daily tamsulosin because of the potential for additive hypotensive effects. There are no reports of increased risk of cardiovascular mortality or morbidity after use of tadalafil, and the drug does not affect exercise tolerance or time to ischemia during physical activity.

With its pharmacokinetic properties, which include a long duration of action (up to 36 h), tadalafil represents a distinctly unique profile in the pharmacotherapy of ED. The 36-h duration of action of tadalafil may provide couples with increased flexibility by minimizing the need to schedule sexual activity, thereby potentially increasing patient–partner satisfaction. Additionally, the fact that neither the rate nor the extent of tadalafil absorption is affected by the presence of high-fat food also translates into increased flexibility for couples concerned about delayed onset of action or reduced efficacy.

REFERENCES

1. Porst H, Padma-Nathan H, Giuliano F, et al. (2003) Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. Urology 62:121–126.
2. Patterson B, Bedding A, Jewell H, et al. (2001) The effect of intrinsic and extrinsic factors on the pharmacokinetic profile of tadalafil (IC351). Poster presented at the Fourth Congress [Biennial Meeting] of the European Society for Sexual and Impotence Research. Rome, September 30–October 3.
3. Angulo J, Gadau M, Fernandez A, et al. (2001) IC351 enhances NO-mediated relaxation of human arterial and trabecular penile smooth muscle (abstract). Eur Urol 39(Suppl 5):106.
4. Corbin JD, Francis SH. (2002) Pharmacology of phosphodiesterase-5 inhibitors. Int J Clin Pract 56:453–459.
5. Cialis® (tadalafil) prescribing information. (2003) Indianapolis, IN, and Bothell, WA: Lilly ICOS LLC. Available at Website: http://www.fda.gov/cder/foi/label/2003/021368lbl.pdf.
6. Padma-Nathan H. (2003) Efficacy and tolerability of tadalafil, a novel phosphodiesterase 5 inhibitor, in treatment of erectile dysfunction. Am J Cardiol 92(Suppl): 19M–25M.

7. Osterloh IH, Collins M, Wicker P, Wagner G. (1999) Sildenafil citrate (Viagra): overall safety profile in 18 double-blind, placebo controlled, clinical trials. Int J Clin Pract Suppl 102:3–5.
8. Jardin A, Wagner G, Khoury S, et al. (2000) Recommendations of the First International Consultation on Erectile Dysfunction. In: Jardin A, Wagner G, Khoury S, et al., eds., Erectile Dysfunction. Plymouth, U.K: Health Publication Ltd, pp. 711–726.
9. Lue TF. (2000) Erectile dysfunction. N Engl J Med 342:1802–1813.
10. Saenz de Tejada I, Emmick J, Anglin G, Fredlund P, Pullman WE. (2001) The Effect of IC351 Taken as Needed for Treatment of Erectile Dysfunction in Men with Diabetes. Poster presented at 16th Congress of the European Association of Urology, Geneva, Switzerland, April 7–10.
11. Curran MP, Keating GM (2003) Tadalafil. Drugs 63:2203–2212.
12. Giuliano F, Varanese L. (2002) Tadalafil: a novel treatment for erectile dysfunction. Eur Heart J Suppl 4(Suppl H):H24–H31.
13. Padma-Nathan H, Rosen RC, Shabsigh R, Saikali K. (2001) Cialis (IC351) provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction (ED) J Urol 165(Suppl 5):224 (abstract 923).
14. Patterson B, Bedding A, Jewell H, Payne C, Mitchell M. (2001) Dose-normalized pharmacokinetics of tadalafil (IC351) administered as a single dose to healthy volunteers. Int J Impot Res 13(Suppl 5):S63–14 (abstract 14).
15. Patterson BE, Mitchell MI, Bedding AW, et al. (2003) Tadalafil and inducers, inhibitors, and substrates of cytochrome P450 isoenzymes 3A4 (CYP3A4) Int J Impot Res 15(Suppl 5):S173 (abstract 26).
16. Viagra® (sildenafil) prescribing information. (2003) New York, NY: Pfizer Inc. Available at Website: http://www.fda.gov/cder/foi/label/1998/viagralabel2.pdf.
17. Levitra® (vardenafil) prescribing information. (2003) West Haven, CT: Bayer Pharmaceuticals Corp. Available at Website: http://www.fda.gov/cder/foi/label/2003/021400lbl.pdf.
18. Brock GB, McMahon CG, Chen KK, et al. (2002) Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of an integrated analysis. J Urol 168:1332–1336.
19. Eid JF, Hatzichristou DG, Whitaker S, et al. (2003) Tadalafil is effective for 36 hours in men with erectile dysfunction—results from an 11-study integrated analysis Int J Impot Res 15(Suppl 5):S175 (abstract 30).
20. Shabsigh R, Eardley I, Whitaker S, Denne J, Ahuja S. (2003) Time distribution of sexual intercourse attempts after taking tadalafil or placebo Int J Impot Res 15 (Suppl 5):S17 (abstract 36).
21. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. (1997) The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49:822–830.
22. Mulhall JP. (2003) Deciphering erectile dysfunction drug trials. J Urol 170: 353–358.
23. Holmes S. (2003) Tadalafil: a new treatment for erectile dysfunction. Br J Urol 91:466–468.
24. Porst H, Rosen RC, Padma-Nathan H, Varanese S, Anglin G, Giuliano F. (2002) Tadalafil allows men with erectile dysfunction to have successful intercourse up to 36 hours post dose. J Urol 167(Suppl):177 (abstract 709).
25. Padma-Nathan H, McMurray JG, Pullman B, et al. (2001) On-demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. Int J Impot Res 13:2–9.

26. Carson C, Porst H, Kaufman JM, et al. (2003) Tadalafil is effective in treating mild to severe erectile dysfunction. Int J Impot Res 15(Suppl 5):S174 (abstract 28).
27. Kaufman JM, Ahn T-Y, Schulman CC, Shen W. (2003) Tadalafil allows for early success and maintenance of successful intercourse in men with erectile dysfunction Int J Impot Res 15(Suppl 5):S176–S177 (abstract 35).
28. Seftel AD, Wilson SK, Knapp PM, Shin J, Wang C, Ahuja S. (2003) Efficacy and safety of tadalafil in US men with erectile dysfunction. Int J Impot Res 15 (Suppl 5):S172–S173 (abstract 25).
29. Seftel AD, Wilson SK, Knapp P, Shin J, Wang WC, Ahuja S. (2003) Efficacy and safety of tadalafil in US men with ED J Urol 169:376 (abstract 1404).
30. Saenz de Tejada I, Anglin G, Knight JR, Emmick JT. (2002) Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 25:2159–2164.
31. McCullough AR. (2001) Prevention and management of erectile dysfunction following radical prostatectomy. Urol Clin North Am 28:612–627.
32. Montorsi F, McCullogh A, Brock G, et al. (2003) Tadalafil in the treatment of erectile dysfunction following bilateral nerve-sparing radical retropubic prostatectomy. Int J Impot Res 15(Suppl 5):S170–S171 (abstract 21).
33. Vickers MA, Satyanarayana R. (2002) Phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction in patients with diabetes mellitus. Int J Impot Res 14:466–471.
34. Hellstrom WJG, Overstreet JW, Yu A, et al. (2003) Tadalafil has no detrimental effect on human spermatogenesis or reproductive hormones. J Urol 170:887–891.
35. Montorsi F, Verheyden B, Junemann K-P, et al. (2003) Long-term safety experience with tadalafil. J Urol 169(Suppl 4):245 (abstract 947).
36. Kloner RA, Mitchell MI, Bedding A, Emmick J. (2002) Pharmacodynamic interactions between tadalafil and nitrates compared with sildenafil. J Urol. 167(Suppl): 176–177 (abstract 708).
37. Kloner RA, Mitchell M, Emmick JT. (2003) Cardiovascular effects of tadalafil in patients on common antihypertensive therapies. Am J Cardiol 92(Suppl):47M–57M.
38. Emmick JT, Stuewe SR, Mitchell M. (2002) Overview of the cardiovascular effects of tadalafil. Eur Heart J 4(Suppl H):H32–H47.
39. Kloner RAWatkins VS, Costigan TM, et al. (2002) Cardiovascular profile of tadalafil, a new PDE5 inhibitor. J Urol 678(Suppl 4):176 (abstract 707).
40. Sadovsky R, Miller T, Moskowitz M, Hackett G. (2001) Three-year update of sildenafil citrate (Viagra®) efficacy and safety. Int J Clin Pract 55:115–128.
41. Patterson D, McDonald TM, Effron M, Emmick JT, Mitchell MI, Kloner RA. (2002) Tadalafil does not affect time to ischemia during exercise stress testing in patients with coronary artery disease. Circulation 106(Suppl II):II-330 (abstract 1650).
42. Kloner RA, Mitchell MI, Bedding A, Emmick J. (2002) Pharmacodynamic interactions between tadalafil and nitrates compared with sildenafil. J Urol 167 (Suppl 4):176–177 (abstract 708).
43. Kloner RA, Hutter AM, Emmick JT, Mitchell MI, Denne J, Jackson G. (2003) Time course of the interaction between tadalafil and nitrates. J Am Coll Cardiol 42:1855–1860.

6 Vardenafil Clinical Trials Experience

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CONTENTS

INTRODUCTION

The Place of PDE5 Inhibitors in the Treatment of Erectile Dysfunction

There can be little doubt that the introduction into clinical practice of oral phosphodiesterase type 5 (PDE5) inhibitors has had a major and positive impact on the quality of life in men with erectile dysfunction (ED) of various causes. PDE5 inhibitors have largely supplanted less subjectively appealing local treatments for ED, such as vacuum constriction devices, penile self-injection therapy, transurethral alprostadil, and inflatable penile prostheses, as first-line therapy in the majority of men seeking treatment for ED. The first of these PDE5 inhibitors was sildenafil (Viagra™). In spite of the benefits of sildenafil, its ocular effect, which manifests as dose-related changes in blue-tinted vision in some patients, reflects its weak inhibition of PDE6 and lack of selectivity.

Furthermore, the Men's Attitude Towards Life Events and Sexuality (MALES) study *(1,2)* has indicated that many patients remain dissatisfied or apprehensive about treatment, indicating the need for a continuing search for viable alternative approaches to the treatment of ED by PDE5 inhibition.

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The MALES Study

To evaluate the prevalence of self-reported sexual dysfunction, a representative sample of 27,838 adult males (aged 20–75 yr) in eight countries across Europe and North and South America* were interviewed between February and April of 2001 using a standard questionnaire *(1)*. As such, it is the largest survey about ED yet conducted. Overall, the prevalence of self-reported ED in this population was 16%. In European and South American countries, the prevalence of ED was similar and ranged between 10 and 14%, but the prevalence was higher in the United States (22%). This may be related to the higher prevalence of diabetes and depression in the US, both of which are risk factors for ED.

Of the total cohort, 4422 men self-reported ED (16%); approximately half of these indicated that they had never sought treatment for ED. Of the population of 3291 men with self-reported ED who participated in phase II of the study, 28% of respondents had tried a PDE5 inhibitor† at least once, and about a quarter (23% of 749) respondents expressed dissatisfaction with it. Commonly cited reasons for such dissatisfaction and abandonment of use of a PDE5 inhibitor were suboptimal hardness of erection (34% of 255 respondents), complete failure of therapy (34%), and lack of reliability of therapy (22%). When asked what they were seeking in ED therapy, reliability was the most important concern, cited by 47% of respondents. Of those subjects with ED who had never used a PDE5 inhibitor, or had used it only once, 42% of 2542 respondents cited safety concerns as the reason for avoiding its use.

Thus, the MALES study has shown the following:

- ED is an undertreated condition.
- Men with ED were not wholly satisfied with treatment with a PDE5 inhibitor at the time of the study.
- Patients with ED need to be counseled to overcome safety concerns about PDE5 inhibitors.
- Those with ED represent a population of subjects with unmet need.
- There is an ongoing need for effective and reliable PDE5 inhibitor treatment.
- Rapid onset and reliability are important treatment attributes.

Furthermore, in a sample of 2912 men with ED *(2)*, the perceived severity of self-reported ED strongly correlated with both the perception that the condition is permanent and a reduction in sexual activity ($p < 0.0001$). The perceived severity, however, did not correlate with the temporal duration of ED. Analysis of these data also indicates that men who self-report mild ED

*United States, $n = 6162$; United Kingdom, $n = 3024$; Germany, $n = 3163$; France, $n = 3018$; Italy, $n = 3249$; Spain, $n = 3121$; Mexico, $n = 3046$; Brazil, $n = 3055$.

†At the time of the survey, only one PDE5 inhibitor (sildenafil) was available.

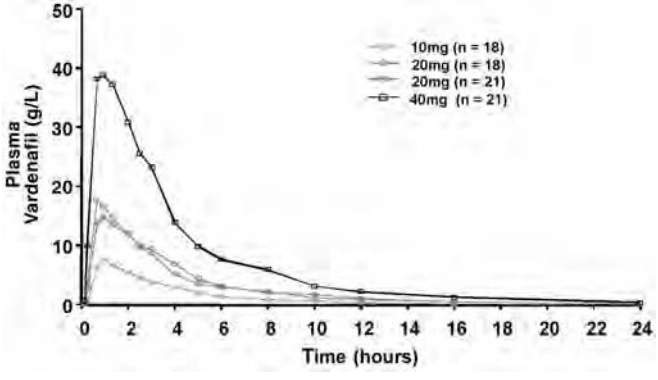

Fig. 1. Mean plasma concentration-time curves for vardenafil after a single dose of 10-, 20-, and 40 mg in men with erectile dysfunction. Data from two studies *(3)*.

are more likely to describe their problem as a temporary one of maintaining an erection. Those who self-report moderate ED are more likely to cite difficulties achieving a sufficiently good erection, and about half believe that the problem is temporary. In contrast, men who self-report severe ED are more likely to report being unable to achieve an erection at all and that the problem is permanent, with a substantial loss of their previous level of sexual activity.

These data collectively provide an insight into the perceptions that patients with ED have of their condition that may be of value to clinicians in their understanding of the treatment-seeking behavior of men with ED. These findings also support the contention that new treatment options are needed. A number of alternative PDE5 inhibitors have been identified that aim to build on the attributes of PDE5 inhibition as the first-line treatment of ED, while limiting the drawbacks, both real and perceived, as well as enhancing patient choice. One of these, vardenafil (Levitra®), a highly selective (and the most potent in vitro) PDE5 inhibitor that is currently available, has been extensively evaluated in a comprehensive clinical development program. This chapter reviews the evidence gathered from this program.

CLINICAL PHARMACOKINETICS AND METABOLISM OF VARDENAFIL

Pharmacokinetic Studies

Single-Dose Pharmacokinetics

Pharmacokinetic studies in men with ED (age range, 22–59 yr) have shown that oral vardenafil is rapidly absorbed, with peak plasma concentrations (C_{max}) occurring approx 45 min (t_{max}) after dosing (Fig. 1; Table 1) *(3)*.

Table 1
Single-Dose Pharmacokinetic Profile of Vardenafil
After 10-, 20-, and 40 mg in Men with ED (Mean ± SD)

	Vardenafil			
Parameter	*10 mg* (n = *18*)	*20 mg* (n = *18*)	*20 mg* (n = *21*)	*40 mg* (n = *21*)
t_{max} (h) (range)	0.9 (0.3–2.5)	0.7 (0.4–3.0)	0.7 (0.3–2.6)	0.7 (0.3–3.0)
C_{max} (µg/L)	9.0 ± 1.7	19.4 ± 1.8	19.3 ± 1.7	50.8 ± 1.7
$C_{max,norm}$ (10^3 kg/L)	69.0 ± 1.7	73.7 ± 1.8	79.7 ± 1.8	105.0 ± 1.8
AUC (µg·h/L)	33 ± 1.6	73 ± 1.9	70 ± 1.8	164 ± 1.5
AUC_{norm} (10^3·kg·h/L)	249 ± 1.6	276 ± 1.9	288 ± 1.9	335 ± 1.5
$t_{1/2}$	4.3 ± 1.3	3.9 ± 1.3	4.4 ± 1.3	4.8 ± 1.2

Data from two studies *(3)*.
AUC, area under the curve; ED, erectile dysfunction.

C_{max} and the area under the time-concentration curve (AUC) are linearly dose related between 10 and 20 mg of vardenafil, such that $C_{max,norm}$ and AUC_{norm} are similar for both doses, although dose linearity is lost at 40 mg. The maximum recommended dose of vardenafil is 20 mg.

The elimination of vardenafil is monophasic and rapid (*see* Fig. 1), with a plasma half life ($t_{1/2}$) of 4 to 5 h (*see* Table 1).

Multiple-Dose Pharmacokinetics

A multiple-dose evaluation of 40 mg/d of vardenafil over 14 d in seven healthy male volunteers showed a similar pharmacokinetic profile to that seen after a single dose, with no evidence of accumulation *(4)*.

Effect of Age on the Pharmacokinetics of Vardenafil

The effect of age on the pharmacokinetics of vardenafil has also been evaluated *(5)*. In a comparison of a single oral dose of 40 mg of vardenafil in fasted healthy men aged 18 to 45 yr ($n = 8$) and older than 65 yr ($n = 9$), t_{max} was similar in both groups (0.6 and 0.5 h, respectively), although the plasma half-life ($t_{1/2}$) was slightly longer in the older group (6 h) than in the younger group (4.8 h). C_{max} and AUC values for men older than 65 yr were 134% and 152% respectively, of those for men younger than 45 yr, suggesting that a starting dose of 5 mg of vardenafil would be appropriate in an elderly population with uptitration to 10 or 20 mg as needed.

Effect of Food and Alcohol

The effect of food on the pharmacokinetics of vardenafil has been evaluated in a single-dose study of 20 mg of vardenafil in 25 healthy adult males in a four-way crossover study *(6)*. Vardenafil was administered in the morning after an overnight fast, after a high-fat breakfast, on an empty stomach in the evening, and after a moderate-fat evening meal. Results showed that although a high-fat meal may alter C_{max} slightly and delay t_{max} for up to 1 h compared with fasting conditions, a moderate-fat meal had no clinically relevant effect on the pharmacokinetics of vardenafil.

A three-way, placebo-controlled crossover study of the effect of alcohol (given as ethanol, 0.5 g/kg of body wt) on the pharmacokinetics of a single dose of 20 mg of vardenafil in 12 healthy male subjects showed that the profile of each is unaffected *(7)*. There were no changes in vital signs (systolic and diastolic blood pressure and heart rate) during their concomitant administration beyond those seen with alcohol alone.

Given that subsequent phase III clinical trials, which were not specific in terms of food or alcohol intake, showed good clinical efficacy across a spectrum of men with ED (discussed in detail later) without unexpected sequelae, dose modifications of vardenafil on the basis of food or alcohol intake are not warranted.

Distribution and Metabolism of Vardenafil

Vardenafil and its major metabolite (M1) are highly protein bound in plasma (93–95%), and the volume of distribution of vardenafil (208 L) suggests widespread tissue distribution.

Vardenafil undergoes extensive first-pass metabolism in the liver by the cytochrome P450 system, primarily by the CYP3A4 isoform, to the major metabolite M1, which is active and contributes about 7% of the pharmacological activity of vardenafil. After oral dosing, vardenafil and its metabolites are primarily eliminated fecally (91–95%) and to a lesser extent in the urine (2–6%) *(8)*.

Vardenafil in Impaired Renal Function

The effect of renal impairment on the pharmacokinetics of a single oral dose of 20 mg of vardenafil has been evaluated in 32 fasted male Caucasians aged 30 to 75 yr with normal renal function (creatinine clearance [CR_{CL}] >80 mL/min; $n = 8$) and in patients with renal impairment that was mild (CR_{CL} >50–80 mL/min; $n = 8$), moderate (CR_{CL} >30–50 mL/min; $n = 8$) or severe ($CR_{CL} \leq 30$ mL/min, but not on dialysis; $n = 8$) *(9)*. Plasma levels of vardenafil were only slightly higher (21–31%) in patients with moderate or severe renal impairment, with no statistically significant association between pharmacokinetic parameters and CR_{CL} values. Although renal clearance was reduced in more severe cases of

renal impairment, less than 1% of drug was excreted in the urine, consistent with biotransformation and subsequent predominant biliary and fecal excretion. Based on these pharmacokinetic data, it is unlikely that men with mild or moderate renal impairment who are taking vardenafil for ED would require dose adjustment. In patients with severe renal impairment, a starting dose of 5 mg should be considered, with uptitration to 10 or 20 mg based on tolerability and efficacy.

Drug Interactions

Because vardenafil is extensively metabolized hepatically by the P450 enzyme system, concomitant administration of vardenafil with drugs that are potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, indinavir, or ritonavir, can be expected to produce markedly increased plasma levels of vardenafil. For concomitant use with ritonavir or indinavir, a maximum single dose of 2.5 mg of vardenafil should not be exceeded. Because ritonavir prolongs vardenafil elimination half-life five- to sixfold, no more than a single 2.5-mg dose of vardenafil should be taken in a 72-h period by patients also taking ritonavir. Patients taking indinavir should not exceed a vardenafil dosage of 2.5 mg once daily. If a 2.5-mg dose of vardenafil is not available, concomitant use of vardenafil and ritonavir or indinavir is contraindicated.

If used in combination with ketoconazole and itraconazole, a maximum dose of 5 mg of vardenafil should not be exceeded. For patients taking ketoconazole or itraconazole in a dosage of 200 mg daily, a single dose of 5 mg of vardenafil should not be exceeded in a 24-h period. Patients taking 400 mg of ketoconazoledaily, or 400 mg of itraconazole daily, should not exceed 2.5 mg of vardenafil once daily. If a 2.5-mg dose is not available, vardenafil must not be taken with doses of ketoconazole and itraconazole higher than 200 mg. A maximum dose of 5 mg of vardenafil should not be exceeded if used in combination with erythromycin.

A comprehensive series of drug interaction studies have been conducted with vardenafil (refer to the Summary of Product Characteristics for vardenafil).

To date, interaction studies with antacids, cimetidine, ranitidine, digoxin, nifedipine, nitroglycerin, and low-dose aspirin have been published and are summarized in Table 2.

Summary of the Pharmacokinetics of Vardenafil

- Vardenafil is rapidly absorbed, with peak plasma concentrations (C_{max}) occurring approx 45 min (t_{max}) after oral dosing.
- Vardenafil is rapidly eliminated, with a plasma half-life ($t_{1/2}$) of 4–5 h. The principal route of elimination is the fecal route, and there is no accumulation when vardenafil is taken once daily.

Table 2
Published Drug Interaction Studies With 10–20 mg of Vardenafil

Interaction study with	*Summary of findings*	*Reference*
Antacids		
Mg hydroxide/Al oxide (10 mL)	No effect on the oral bioavailability or absorption of 20 mg vardenafil	*10* *11*
Cimetidine (400 mg twice daily for 7 doses)		
Ranitidine (150 mg twice daily for 7 doses)		
Cardiovascular drugs		
Digoxin (0.375 mg/d)	Vardenafil has no clinically significant effect on digoxin plasma concentrations or clearance.	*12*
Nifedipine (30 or 60 mg/d)	A single 20-mg dose of vardenafil caused no clinically significant alteration of the hemodynamic effects of nifedipine in patients with essential hypertension.	*13*
Nitroglycerin (0.4 mg, sublingual)	Although a single 10-mg dose of vardenafil did not potentiate the hypotensive response to sublingual nitroglycerin taken 1 h after vardenafil in healthy subjects 4, 8, or 24 h postdose, the vasodilatory properties of PDE5 inhibitors could result in exaggerated reductions in blood pressure during the concomitant administration of nitrates. Therefore, the use of PDE5 inhibitors with nitrates, or nitric oxide donors in any form, is contraindicated within 24 h (US guidelines) or 1 wk (UK Consensus Statement) of the last dose of either drug.	*14*
Low-dose aspirin (mean 81 mg bid)	10 mg of vardenafil does not potentiate the increase in bleeding time associated with acetylsalicylic acid.	*15*

- Although a high-fat meal may reduce C_{max} and delay t_{max} slightly, food does not appear to affect the efficacy of vardenafil.
- Vardenafil and alcohol do not potentiate the effects of each other.
- Dose adjustment of vardenafil is unlikely to be needed in most patients with renal impairment.
- The metabolism of vardenafil is cytochrome P450-dependent, so the concomitant use of potent CYP34A inhibitors should be avoided.
- A comprehensive series of interaction studies has, to date, revealed no areas of particular concern, although, in common with all PDE5 inhibitors, concomitant use of nitrates is a class-related absolute contraindication.

PHASE III CLINICAL TRIALS WITH VARDENAFIL IN ED

Vardenafil in a Broad Population of Men With ED

The North American Pivotal Trial

The North American pivotal trial *(16)* reported that in a broad population of men with various causes and severity of ED, vardenafil in general safely, substantially, and consistently improved erectile function (EF) regardless of baseline severity.

Subjects and Methods

This 26-wk, randomized, placebo-controlled, parallel-group trial of three fixed doses of vardenafil (5, 10, or 20 mg) was conducted at 54 investigational sites across the United States and Canada and recruited 805 eligible men with ED of various causes and severity. To be eligible, adult men were required to have experienced at least a 50% failure rate in maintaining an erection sufficient to achieve satisfactory intercourse on at least four separate attempts over a previous 4-wk treatment-free period, for reasons that were not attributable to anatomical, surgical, or traumatic causes.

The demographic and baseline ED characteristics of the trial subjects were well matched across each randomized group in terms of age (57–58 yr), race, (77–82% caucasian), duration of ED from the time of diagnosis (2.9–4.2 yr), and severity of ED. Thirty to 45% reported severe ED (as measured by the International Index of Erectile Function [IIEF] questionnaire) *(17)* (EF score <10), and 22 to 37% reported ED of moderate severity (IIEF EF score of 11–16) at baseline. In more than half the subjects in all groups (54–61%), there was an organic cause of ED, and there was a psychogenic cause in only 7 to 9%; the remainder was of mixed etiology. Medical comorbidity was common across each of the groups and included hypertension, prostatic hyperplasia, diabetes, depression, and previous myocardial infarction. The majority (66–77%) of subjects had used

sildenafil previously. Thus, this was a broad population of men that may typically present with ED in a normal clinical practice setting.

Of the 805 eligible subjects, 197 were randomly assigned to receive placebo, 205 were assigned to receive 5 mg of vardenafil, 206 were assigned to receive 10 mg of vardenafil, and 197 were assigned to receive 20 mg of vardenafil. Subjects were instructed to take their randomized medication (no more than one dose per calendar day) approx 1 h before intended sexual intercourse, with no special instructions regarding food intake and alcohol consumption to reflect a normal living situation as much as possible. Subjects continued treatment for 26 wk.

Overall, 295 subjects (37%) discontinued study treatment before 26 wk, comprising 54% of placebo-treated subjects (most commonly a result of insufficient therapeutic effect [20%]) and 31% of subjects treated with vardenafil. In the vardenafil groups, the most common causes of discontinuation were insufficient therapeutic effect in the 5-mg group (13%), "lost to follow-up" in the 10-mg group (10%), and adverse events of any cause in the 20-mg group (8%). Of the 805 randomized subjects, 749 were eligible for analysis of efficacy and 762 for safety evaluations in that they had received at least one dose of study medication and had had at least one postbaseline assessment.

Efficacy Measures

The primary efficacy measures in this trial were the EF domain score (questions (Q) 1–5 and 15 of the IIEF questionnaire) after 12 wk and the subjects' response to the Sexual Encounter Profile (SEP) Q2 ("Were you able to insert your penis into your partner's vagina?") and Q3 ("Did your erection last long enough to have successful intercourse?") *(18)*.

Secondary efficacy end points were these outcome measures after 4, 8, 18, and 26 wk of treatment, as well as the responses at wk 12 and 26, to the Global Assessment Questionnaire (GAQ) question, "Has the treatment you have been receiving over the past 4 wk improved your erections?"

Improvements in EF Domain Scores

All doses of vardenafil consistently and significantly improved all three primary efficacy outcomes. Moreover, these benefits were sustained to 26 wk, demonstrating the reliability of continuing treatment with vardenafil. The significant improvements in EF from baseline compared with placebo are shown in Fig. 2, which also illustrates a dose-response relationship for EF domains.

At wk 12, compared with the scores of subjects who were randomly assigned to receive the 5-mg dose, EF domain scores were significantly higher in subjects receiving vardenafil at doses of 10 mg ($p < 0.01$) and

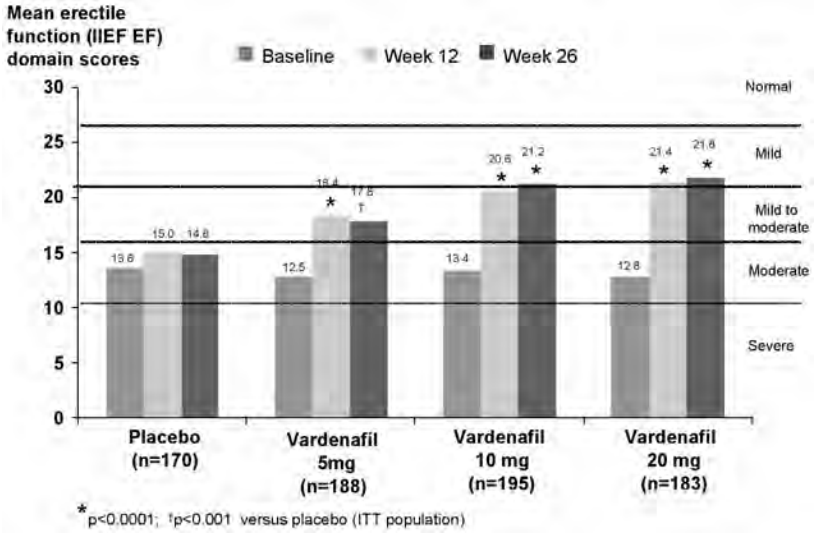

Fig. 2. Improvements in erectile function (International Index of Erectile Function) domain scores in subjects with erectile dysfunction after 12- and 26-wk treatment with 5, 10, and 20 mg of vardenafil compared with placebo. IIEF, International Index of Erectile Function; ITT, intent-to-treat.

20 mg ($p < 0.001$). The dose superiority of 10 and 20 mg of vardenafil over the 5-mg dose also persisted at wk 26 ($p < 0.0001$).

In addition, the ability of vardenafil to normalize EF (EF domain score $\geq$26) was correlated with the baseline severity of ED. In subjects with mild ED at baseline (EF domain score of 22–25), 89% ($n = 9$) and 79% ($n = 14$) of subjects achieved a normalized EF score with 10 and 20 mg of vardenafil, respectively.

This contrasts with 21% ($n = 14$) who received placebo. In subjects with severe ED at baseline (EF domain score $\leq$ 10), 40% ($n = 76$) of subjects achieved a normalized EF score with 20 mg of vardenafil, compared with only 4% who received placebo.

Improvements in SEP Scores

Improvements in SEP scores were concordant with improvements in EF domain scores. The mean success rates for vaginal penetration (SEP Q2) and maintenance of erection to completion of intercourse (SEP Q3) after 12 wk of treatment were significantly superior to the rates for placebo at all doses of vardenafil ($p < 0.0001$) (Fig. 3A,B).

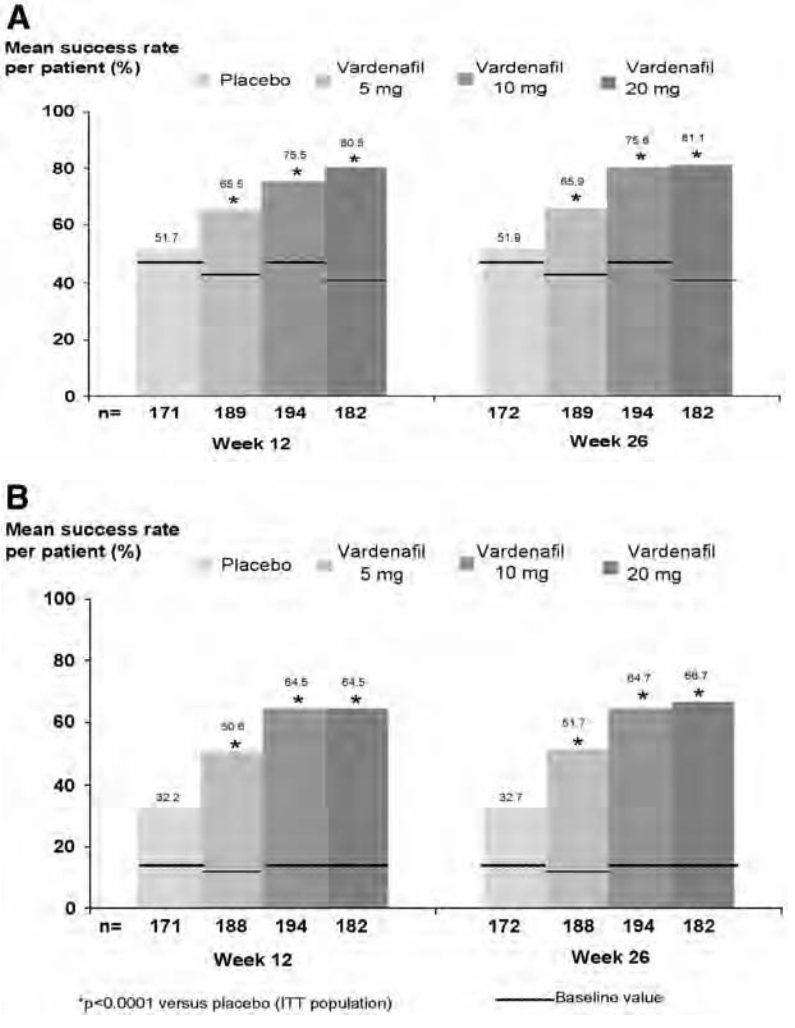

Fig. 3. Improvements in Sexual Encounter Profile (SEP) items question (Q)2 and Q3 in subjects with erectile dysfunction after 12- and 26-wk treatment with 5, 10, or 20 mg of vardenafil compared with placebo. **(A)** The proportion of subjects responding affirmatively to SEP Q2, showing improvements in the rate of successful vaginal penetration. **(B)** Proportion of subjects responding affirmatively to SEP Q3, showing improvements in the maintenance of an erection to successful completion of intercourse. ITT, intent-to-treat.

For both SEP Q2 and SEP Q3, the improvements were also dose-related, and the superiority of vardenafil over placebo for these outcome measures at 12 wk was maintained at 26 wk.

Although SEP Q2 scores changed little from baseline with placebo, there was a 1.5- to twofold increase over baseline in the success rate of vaginal penetration with vardenafil (*see* Fig. 3A). Similarly, the change from baseline in the rate of successful intercourse (SEP Q3) was greater with vardenafil (a 3.6- to 4.5-fold increase) than with placebo (*see* Fig. 3B). These benefits of vardenafil were apparent at both wk 12 and 26.

Time Course of Improvements

The principal efficacy measure of treatment with vardenafil in the North American pivotal trial was the difference from results with placebo in IIEF EF domain scores and SEP Q2 and SEP Q3 scores at wk 12. To gain a broader picture of the time course of improvements in these outcome parameters before wk 12 (and between wk 12 and 26), the scores for these parameters at 4, 8, and 18 wk have been examined *(19)*. This analysis has shown that treatment with all doses of vardenafil resulted in significantly greater improvements than placebo at wk 4 in the IIEF EF domain score ($p \leq 0.0017$), as well as in SEP Q2 ($p = 0.007$), and SEP Q3 ($p = 0.014$) scores. Moreover, the improvements at wk 8 were comparable with those at wk 4 and at wk 12 and beyond. This analysis, therefore, has shown that not only is the efficacy of vardenafil durable, but its desirable effects also occur early in the course of treatment.

Improvements in GAQ

The proportion of affirmative ("yes") responses to the GAQ item ("Has the treatment you have been receiving over the past 4 wk improved your erections?") was significantly higher in subjects receiving any dose of vardenafil compared with placebo at both 12 and 26 wk ($p < 0.0001$) (Fig. 4).

Up to 85% of subjects treated with vardenafil reported an improvement in erections. Again there was an apparent dose–response relationship with a greater proportion of subjects (80.9%) receiving 20 mg of vardenafil giving an affirmative response to this GAQ item at 12 wk than those receiving 5 mg (64.5%).

Satisfaction With Treatment

In addition to the primary and secondary objective measures of the success of treatment just described, additional efficacy analyses were conducted based on responses to subjective diary questions about erection quality, satisfaction with the sexual experience, and ability to ejaculate. As well as the EF domain scores of the IIEF questionnaire, which formed the primary efficacy outcome measure of this study, data collected from the IIEF Intercourse Satisfaction Domain (Q 6–8) and the Orgasmic Function Domain (Q 9 and 10) have also been reported (Table 3) *(20)*.

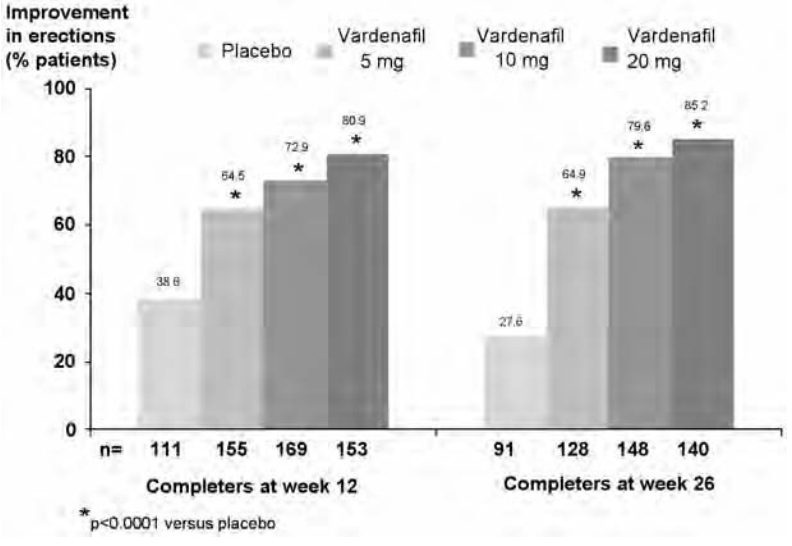

Fig. 4. Proportion of subjects with erectile dysfunction who completed 12 and 26 wk of treatment with 5, 10, or 20 mg of vardenafil or placebo and responded affirmatively to the Global Assessment Question, "Has the treatment you have been receiving over the past 4 weeks improved your erections?"

Vardenafil improved parameters associated with the subjective perceptions of sexual intercourse, with the 10- and 20-mg doses being consistently significantly superior to placebo for all parameters ($p < 0.01$). Overall, compared with placebo, treatment with all doses of vardenafil resulted in up to a threefold increase in satisfaction with erection hardness ($p < 0.01$), a more than twofold increase in satisfaction with the sexual experience ($p < 0.01$), and a significant increase in the ability to ejaculate ($p < 0.01$). Moreover, all doses of vardenafil significantly improved IIEF domain scores for intercourse satisfaction ($p < 0.01$), and doses of 10- and 20 mg significantly improved orgasmic function ($p < 0.01$) compared with placebo.

Summary of the Findings of the North American Pivotal Trial

- In men with ED of various causes and severity, vardenafil (compared with placebo) achieved clinically meaningful and statistically significant dose-dependent improvements in erectile function (IIEF EF scores), successful vaginal penetration (SEP Q2), and maintenance of erection to successful completion of intercourse (SEP Q3) from 4 wk, which was sustained to 26 wk with continued treatment.

Table 3
Improvements in Patient Satisfaction With Erection Hardness, Orgasmic Function, and Sexual Experience in Subjects With ED Treated With 5, 10, or 20 mg of Vardenafil or Placebo for 26 Wk

			Vardenafil		
		Placebo	*5 mg*	*10 mg*	*20 mg*
Diary questions (ITT)	*n*	172	188	194	182
Satisfaction with erection hardness (per patient rate, %)	Baseline	4.4	5.3	6.1	3.4
	wk 26	17.6	38.0[a]	52.0[a]	58.5[a]
Satisfaction with sexual experience (per patient rate, %)	Baseline	10.8	12.4	9.9	12.2
	wk 26	23.1	44.9[a]	57.7[a]	62.0[a]
Ability to ejaculate (% yes)	Baseline	36.2	31.5	36.2	34.1
	wk 26	42.2	55.7[a]	65.5[a]	67.6[a]
IIEF domains (LOCF)	*n*	170	188	195	183
Intercourse satisfaction (IIEF Q 6–8)	Baseline	6.7	6.8	6.8	6.8
	wk 26	7.7	8.9[a]	10.3[a]	10.3[a]
Orgasmic function (IIEF Q 9, 10)	Baseline	4.8	4.9	5.0	5.0
	wk 26	5.3	5.6	7.1[a]	6.9[a]

[a] $p < 0.01$ vs placebo.
IIEF, International Index of Erectile Function; ITT, intent-to-treat; LOCF, last observation carried forward.

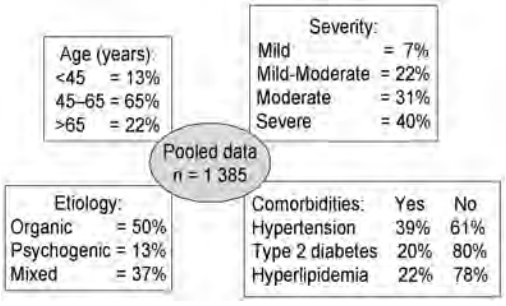

Fig. 5. Subpopulation variables examined in the pooled analysis.

- Normal erectile function was restored in up to 89% of men with mild ED and in 39% of men with severe ED treated with vardenafil, as measured by the IIEF EF domain scores, compared with only 21% and 4%, respectively, in subjects receiving placebo. Compared with baseline, treatment with vardenafil resulted in a 1.5- to twofold improvement in the success rate of vaginal penetration (SEP Q2) and a 3.6- to 4.5-fold improvement in successful completion of intercourse (SEP Q3) in men with ED. Corresponding changes with placebo were substantially lower.
- Vardenafil improved erections and satisfaction in up to 85% of men with ED at 26 wk as measured by the GAQ, compared with 28% of men who received placebo.
- Responses to diary questions revealed that significantly greater improvements in subjective perceptions of sexual intercourse occurred in men with ED who were treated with vardenafil, in terms of satisfaction with erection hardness, sexual experience, and ability to ejaculate, compared with placebo.
- IIEF domain scores for intercourse satisfaction and orgasmic function were improved with vardenafil significantly more so than with placebo.

Vardenafil in Subpopulations of Men With ED

To evaluate the potential influence of some common variables on the efficacy of vardenafil in men with ED, an analysis of data, pooled from two prospective, randomized, double-blind, placebo-controlled trials of similar design, was conducted at 12 wk postbaseline. The variables investigated were age, cause of ED, severity of ED at baseline, and coexisting significant comorbidities (specifically, the concomitant use of antihypertensive medication and the presence of hyperlipidemia and type 2 diabetes) (Fig. 5).

In this analysis, pooled data from 1385 eligible men with ED of more than 6 mo duration who received 5 mg of vardenafil (n = 346), 10 mg

($n = 353$), 20 mg ($n = 349$), or placebo ($n = 337$) showed that none of these variables had a significant confounding effect on the outcome of treatment of ED with vardenafil.

Effect of Age

In the pooled population, the majority of subjects were between 45 and 65 yr of age (*see* Fig. 5). In the older population (>65 yr), the mean baseline EF scores were generally lower than in the younger group (<45 yr), suggesting that men older than 65 yr of age had more severe ED than those younger than 45 yr. Nevertheless, compared with placebo, all doses of vardenafil significantly improved EF irrespective of age when measured in terms of the IIEF EF domain scores, SEP Q2, SEP Q3, and GAQ (Table 4) *(21,22)*.

With 20 mg of vardenafil, the older age group achieved a degree of EF that was similar to that in the younger group. Although baseline vaginal penetration rates (SEP Q2) generally decreased with increasing age, vardenafil significantly improved this outcome measure compared with placebo, irrespective of age. The GAQ confirmed these findings: 20 mg of vardenafil improved erections in older, more difficult-to-treat subjects (71%) in a proportion similar to that seen in younger subjects with less severe ED (75%). Thus, age has no substantial influence on the benefits of vardenafil.

Influence of the Cause of ED

The majority of subjects in the pooled population had an organic or mixed organic and psychogenic cause of ED (87%) (*see* Fig. 5). Psychogenic factors as the sole cause of ED were, therefore, much less frequent in this population. All doses of vardenafil improved outcome measures of treatment in subjects with any cause of ED (*see* Table 4) *(23)*. Differences from placebo were always significant at all doses regardless of the cause of ED.

Baseline Severity of ED

At baseline, 71% of the subjects in the pooled analysis had moderate or severe ED (*see* Fig. 5). Compared with placebo, vardenafil significantly improved EF and other outcome parameters in subjects with all degrees of ED severity (*see* Table 4) *(23)*. The difference from placebo was, not surprisingly, lower in the subjects with mild ED and greatest in subjects with severe ED. Subjects with mild baseline ED regained almost normal EF, and those with more challenging, severe ED improved to a mild-to-moderate category. Thus, compared with placebo, treatment with vardenafil significantly improves ED regardless of baseline severity.

Table 4
Analysis of the Effect of Variables on the Efficacy of Vardenafil at 12 Wk From Data Pooled From Two Randomized, Double-Blind, Placebo-Controlled Studies in Men With ED

				Vardenafil								
Efficacy at 12 wk	*Placebo*			*5 mg*			*10 mg*			*20 mg*		
Age (yr) (22)	*<45*	*45–65*	*>65*	*<45*	*45–65*	*>65*	*<45*	*45–65*	*>65*	*<45*	*45–65*	*>65*
IIEF EF score	16.1	14.0	13.5	20.3[g]	19.6[e]	16.3[g]	3.5[e]	20.5[e]	19.6[e]	21.5[e]	22.0[e]	19.8[e]
SEP Q2[†] (% success)	58.2	46.8	46.2	75.2[f]	71.3[e]	51.5	78.9[e]	75.4[e]	72.7[e]	81.5[e]	79.4[e]	75.4[e]
SEP Q3[‡] (% success)	38.5	27.5	24.8	54.7[h]	56.7[b]	35.6[h]	72.4[b]	62.7[b]	53.9[b]	65.6[b]	66.3[b]	54.4[b]
GAQ (% yes)	34.2	24.6	23.4	71.4[e]	67.6[e]	50.7[e]	85.1[e]	70.6[e]	67.2[e]	75.0[e]	75.5[e]	71.4[e]
Etiology of ED (23)	*Org*	*Psych*	*Mixed*	*Org*	*Psych*	*Mixed*	*Org*	*Psych*	*Mixed*	*Org*	*Psych*	*Mixed*
IIEF EF score	14	15	15	19[a]	22[a]	19[a]	20[a]	23[a]	21[a]	21[a]	22[a]	22[a]
SEP Q3 (% success)	25	34	30	49[e]	57[e]	54[e]	58[e]	72[e]	64[e]	60[e]	65[e]	67[e]
Severity of ED (24)	*Mild*	*M-M*	*Mod*	*Sev*	*Mild*	*M-M*	*Mod*	*Sev*	*Mild*	*M-M*	*Mod*	*Sev*	*Mild*	*M-M*	*Mod*	*Sev*
IIEF EF score	21	18	16	9	24	22[e]	21[e]	15[e]	26[g]	23[e]	22[e]	17[e]	26[g]	24[e]	23[e]	18[e]
SEP Q3 (% success)	40	35	32	17	67[f]	62[a]	57[a]	39[a]	73[f]	68[a]	67[a]	53[a]	67[f]	70[a]	69[a]	54[a]

Continued

Table 4 *(Continued)*

Efficacy at 12 wk	*Placebo*			*Vardenafil* 5 mg			10 mg			20 mg		
Age (yr) (22)	*<45*	*45–65*	*>65*	*<45*	*45–65*	*>65*	*<45*	*45–65*	*>65*	*<45*	*45–65*	*>65*
Antihypertensive medication (24)	*None*	*Yes*		*None*	*Yes*		*None*	*Yes*		*None*	*Yes*	
IIEF EF score[i]	13.9	14.8		19.2[a]	18.7[e]		21.3[a]	19.8[a]		21.8[a]	20.7[a]	
SEP Q3 (% success)[j]	27	31.3		52.9[e]	50.3[e]		65.3[e]	56.7[e]		66.2[e]	58.1[e]	
Hyperlipidemia (25)	*None*	*Yes*		*None*	*Yes*		*None*	*Yes*		*None*	*Yes*	
IIEF EF score[k]	14.2	14.3		19.2[d]	18.3[d]		21.1[d]	19.8[d]		21.6[d]	20.7[d]	
SEP Q3 (% success)[k]	29	27		54[d]	45[d]		65[d]	56[d]		64[d]	61[d]	
Diabetes (25)	*None*	*Yes*		*None*	*Yes*		*None*	*Yes*		*None*	*Yes*	
IIEF EF score[l]	14.1	14.4		19.7[e]	16.2		21.4[e]	18.3[e]		22.2[e]	18.5[e]	
SEP Q3 (% success)[m]	28	28		56[c]	34		65[c]	52[c]		68[c]	48[c]	

[†] Vaginal penetration success.

[‡] Erection maintenance success.

[a] $p < 0.0001$; [b] $p < 0.0002$; [c] $p < 0.005$; [d] $p < 0.003$; [e] $p < 0.001$; [f] $p < 0.01$; [g] $p < 0.03$; [h] $p < 0.04$ (all vs placebo); [i] $p = 0.0571$; [j] $p = 0.0611$ for patients not taking hypertensive medication vs those taking hypertensive medication; [k] not significantly different for those with and without hyperlipidemia; [l] $p = 0.018$; [m] $p = 0.0013$ for nondiabetics vs diabetics.

ED, erectile dysfunction; EF, erectile function; IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile; GAQ, Global Assessment Question; Q, question; Org, organic; Psych, psychogenic; M-M, mild to moderate severity; Mod, moderate severity; Sev, severe.

Effect of Comorbidities

The comorbidities examined in the pooled population of men with ED were the use of antihypertensive medication (39% subjects), the presence of hyperlipidemia (22% subjects), and the presence of type 2 diabetes (20% subjects) (*see* Fig. 5). The potential influence of each of these comorbidities on the effect on vardenafil in ED was evaluated.

Influence of Hypertensive Medication

Efficacy variables and safety parameters were assessed in patients with EF who did and did not take antihypertensive medication *(24,25)*. In terms of EF outcome measures (IIEF EF domain, SEP Q2 and SEP Q3 scores), all doses of vardenafil were associated with significant improvements compared with placebo irrespective of the use of antihypertensive medication, although in this analysis the treatment effects of vardenafil were somewhat higher in subjects who were not taking antihypertensives (*see* Table 4).

Subjects With Hyperlipidemia

Twenty-two percent of the pooled population were hyperlipidemic, based on history and defined by International Classification of Diseases, 9th edition (ICD-9) codes (*see* Fig. 5). In this patient population, all doses of vardenafil improved EF relative to placebo, with no significant difference in the therapeutic effect of vardenafil in subjects with and without hyperlipidemia (*see* Table 4) *(25)*.

Subjects With Type 2 Diabetes

In the 20% of subjects who had a diagnosis of type 2 diabetes at baseline (*see* Fig. 5), vardenafil was effective in improving EF, with the 10- and 20-mg doses being significantly superior to placebo in these patients. In contrast, all doses of vardenafil were significantly better than placebo in improving EF in the nondiabetic population (*see* Table 4) *(25),* confirming that diabetic patients with ED present a more challenging population to treat for ED.

No Influence of Ethnicity

Studies have been undertaken to evaluate the efficacy of vardenafil in adult men with ED from different ethnic populations. In all populations studied, vardenafil was effective and generally well tolerated.

Caucasian, African-American, and Hispanic Populations

In an open-label multicenter study, the efficacy of a flexible dose of vardenafil (5–20 mg) was compared after 10 wk of treatment in Caucasian (n = 153), African-American (n = 136), and Hispanic (n = 102) subjects

with ED *(26,27)*. Improvements in IIEF EF domain scores brought 59 to 74% of subjects into the normal EF range (>26) from a baseline mean score of 9.7 to 10.9 (severe to moderate) irrespective of ethnicity.

The Mexican Population

In 176 Mexican subjects with ED who were treated with 20 mg of vardenafil for 12 wk *(28)*, the baseline IIEF EF score improved from 14.8 (moderate ED) to 25.5 (near-normal erectile function), and SEP Q2 response improved from 17.3% at baseline to 80.5% after treatment with vardenafil. Furthermore, 93% of subjects reported improved erections (GAQ) after 12 wk. The authors concluded that treatment with vardenafil was effective and well tolerated in Mexican men with ED.

The Japanese Population

A 12-wk, prospective, double-blind clinical trial was undertaken in 283 Japanese men with ED *(29)*, in which subjects were randomly assigned to receive 5, 10, or 20 mg of vardenafil or placebo. All three doses resulted in improved scores for Q3* and Q4† of the IIEF questionnaire at 12 wk, significantly more than placebo ($p < 0.0001$). In addition, up to 86% of patients achieved improved erections when evaluated by GAQ. The authors concluded that vardenafil is an effective and well-tolerated treatment for ED in Japanese men.

Onset of Action of Vardenafil

The earliest time to onset of therapeutic effect of vardenafil was investigated in a randomized, double-blind, parallel-group, placebo-controlled trial in a broad population of 471 men with mild to severe ED (mean baseline IIEF EF score was 12.2) *(30)*. Using a stopwatch in an at-home setting, the men recorded the earliest time after dosing that they perceived an erection adequate for intercourse completion (SEP Q3).

The earliest time that an affirmative response to SEP Q3 was achieved was 10 min (21% success in men taking 10 mg of vardenafil, 11% success rate in men taking 20 mg of vardenafil vs 14% in men on placebo; $p < 0.05$). At 25 min after dosing, this relative difference in SEP Q3 success rates was greater (53/50% in men taking 10/20 mg of vardenafil compared with 26% in men taking placebo; $p < 0.001$) (Fig.6).

The authors concluded that the onset of action of vardenafil leading to the completion of intercourse occurred as early as 10 min after ingestion. This

*Q3 of the IIEF asks, "When you attempted sexual intercourse (vaginal penetration), how often were you able to penetrate your partner?"

†Q4 of the IIEF asks, "During sexual intercourse (vaginal penetration), how often were you able to maintain your erection after you have penetrated (entered) your partner?"

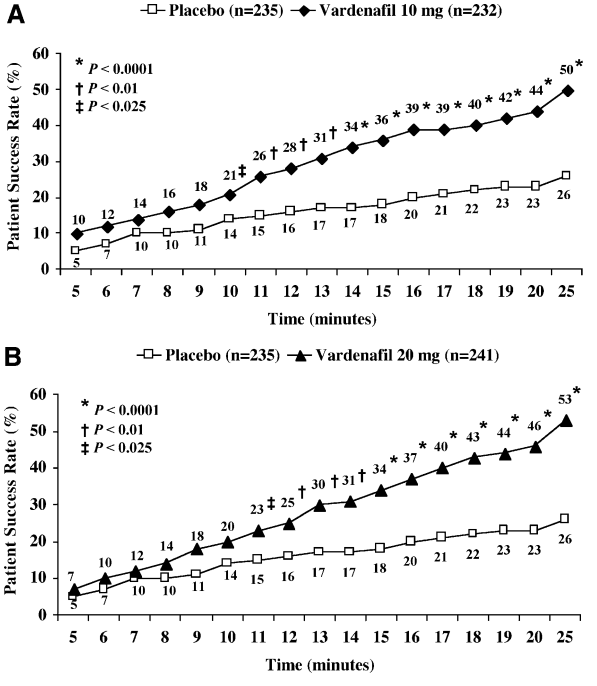

Fig. 6. Success rates of attaining an erection adequate for completion of intercourse, measured by Sexual Encounter Profile Question 3, at 5–25 min after dosing with vardenafil or placebo. PLA, placebo; ITT, intent-to-treat.

suggests that the therapeutic effect of vardenafil is expressed before maximal plasma concentrations are achieved.

Sustained Long-Term Efficacy With Vardenafil

After 1 Yr

The long-term efficacy of vardenafil has been investigated in a broad population of men with ED. One thousand twenty men with ED of broad etiology and severity were randomly assigned to receive either 10 mg ($n = 514$) or 20 mg ($n = 506$) of vardenafil, to be taken as needed for up to 52 wk *(31)*. The mean baseline IIEF EF domain score in each study population was 13.0, which is indicative, on average, of a moderate severity of ED. Clinically relevant improvements over baseline in this score to near-normal EF levels (22.6 and 23.9 in the 10- and 20-mg groups, respectively), achieved at the week 4 assessment interval, were sustained at all subsequent assessment timepoints (wk 8, 13, 26, 39) up to wk 52. Similarly, the mean SEP Q3 score improved from baseline values of a 14.2% intercourse success rate in the group taking 10 mg and 15.6% in the group

taking 20 mg to 82% and 85.6%, respectively, at wk 52. Also at wk 52, a "yes" response to the GAQ was given by 79 and 82% of subjects in the 10- and 20-mg dose groups, respectively. These data (last observation carried forward [LOCF] analysis) have shown that with continued use over 1 yr, treatment of ED with vardenafil, 10 or 20 mg, resulted in sustained near-normal EF and a quadrupled intercourse success rate and maintained improvements in erection quality in the majority of men with mild to severe ED.

After 2 Yr

Of the 755 subjects (74%) who completed the 1-yr study, 566 continued to receive double-blinded medication (10 mg of vardenafil, $n = 272$; 20 mg, $n = 294$) for an additional 52 wk *(32)*. Of these, 479 subjects (85%) completed this extended study period. In this cohort who had received treatment with vardenafil over a continuous 2-yr period, near-normal EF was maintained throughout this time in both dose groups. The mean IIEF EF domain score at baseline in this 2-yr cohort was similar in the 10- and 20-mg dose groups (13.4 and 13.8, respectively). Clinically important improvements in this score at wk 104 (LOCF) were also similar (24.7 and 25.7, respectively). Mean SEP Q3 values also maintained the pattern of improvement over the extended study period. SEP Q3 values improved from a 15.9% successful intercourse rate at baseline to 86.5% at 2 yr in the 10-mg group, and from 17.4 to 89.3% in the 20-mg group at the 2-yr end point. An affirmative GAQ response was maintained at 90 to 92% at 2 yr after the start of treatment. The authors concluded that vardenafil provides and maintains excellent efficacy (and tolerability) for up to 2 yr.

Flexible-Dose Studies

Although fixed-dose clinical trials are important to distinguish between the efficacy and tolerability of different doses of any medication, in a "real world" situation, subjects may elect to titrate doses to achieve an optimal balance between efficacy and tolerability. Two studies have been reported that focus on a flexible dose regimen of vardenafil, ranging from 5 to 10 to 20 mg, in subjects with a broad etiology and severity of ED.

In one 10-wk study *(33)*, 398 subjects were permitted to titrate their starting dose of 10 mg of vardenafil up to 20 mg or down to 5 mg based on efficacy and tolerability at assessment intervals of 2 and 6 wk. Dose increases to 20 mg were reported in 63.3% of subjects at any time during the study, and dose decreases to 5 mg occurred in only 6.3% of subjects. At the end point, 104 subjects had chosen to remain on the 10-mg baseline dose throughout the study, whereas 180 patients had used the vardenafil 10/20/20-mg dosing regimen, and 29 had used the 10/10/20-mg regimen.

At wk 10, the mean IIEF EF domain score was in the range of normal EF in men who chose to remain on 10 mg of vardenafil throughout the study period. Subjects who chose 20 mg of vardenafil after either 2 or 6 wk of treatment with 10 mg achieved a clinically meaningful additional increase in treatment benefit on uptitration, with patients on a 10/20/20-mg treatment regimen showing a mean EF domain score of 27.5 at wk 10. At the end of the study period, normal EF ($\geq$26) was achieved by 70% of evaluable subjects (n = 347) on any dose of vardenafil.

Overall, the mean SEP Q2 success rate was 90.4% (LOCF), that for SEP Q3 was 81.1%, and for GAQ, the affirmative response rate was 91.8%. Similar improvements were evident at both 6 and 10 wk.

In a separate study *(34)*, subjects were randomly assigned to receive either placebo (n = 148) or 10 mg of vardenafil (n = 150), to be taken as needed. After 4 wk on vardenafil, subjects could elect to uptitrate the dose to 20 mg or downtitrate to 5 mg. After an additional 4 wk, another opportunity to adjust the dose was made available. The baseline IIEF EF domain scores indicated, on average, ED of moderate severity (12.6 in the vardenafil group and 13.1 in the placebo group). At 12 wk, the mean IIEF EF domain score in all vardenafil-treated subjects improved to 22.9 (LOCF), which was significantly superior to that with placebo (15.4) ($p <$ 0.01). Overall, in this flexible-dose regimen, 86% of subjects taking vardenafil reported improved erections at wk 12, compared with 36% taking placebo. The final vardenafil dose choices were as follows: 68% of subjects elected to take the 20-mg dose, 28% chose 10 mg, and only 3% took 5 mg. In subjects who chose to remain on 10 mg of vardenafil, the proportion of affirmative responders to the GAQ was 96% at wk 4, 100% at wk 8, and 92% at wk 12. In subjects electing to uptitrate to 20 mg at wk 4, the proportion of men responding affirmatively to the GAQ was 70% at wk 4 (when they were taking 10 mg), 83% at wk 4, and 82% at wk 12, indicating an improved response with the increased dose in subjects who perceived the need for such.

Because men with ED would normally be expected—in consultation with their physician—to adjust the dose of vardenafil according to the subjective balance between efficacy and tolerability, these studies show that subjective choice of the dose of vardenafil enables the outcome to be optimized.

Reliability of Vardenafil

Reliability of treatment in ED is closely linked with patient satisfaction with that treatment and as such is an important influence on the patients' choice to continue with the treatment. The reliability of vardenafil has been evaluated in two retrospective analyses of SEP items

Table 5
Reliability of Vardenafil in ED Measured as Success Rates of Vaginal Penetration (SEP Q2), Successful Intercourse (SEP Q3), and Overall Satisfaction (SEP Q5) at the First Attempt Compared With Subsequent Attempts up to Wk 12 in Patients Successful at First Attempt

	Vardenafil							
	Placebo		*5 mg*		*10 mg*		*20 mg*	
	First	*Subs*	*First*	*Subs*	*First*	*Subs*	*First*	*Subs*
Ref. *(35)*								
(n)	*(171→76)*		*(189→125)*		*(194→149)*		*(182→135)*	
SEP Q2 (% success)	46→77%		67→80%		77→85%		74→91%	
(n)	*(171→47)*		*(189→95)*		*(194→134)*		*(182→114)*	
SEP Q3 (% success)	28→57%		51→75%		69→76%		61→85%	
(n)	*(171→35)*		*(189→92)*		*(194→114)*		*(182→102)*	
SEP Q5 (% success)	21→50%		49→66%		59→72%		56→80%	
Ref. *(36)*								
(n)	*(317→140)*		*(339→239)*		*(347→264)*		*(339→258)*	
SEP Q2 (% success)	44→74%		71→82%		76→86%		76→91%	
(n)	*(317→80)*		*(339→173)*		*(347→225)*		*(339→201)*	
SEP Q3 (% success)	25→56%		51→76%		65→78%		59→84%	
(n)	*(317→59)*		*(339→162)*		*(347→193)*		*(339→190)*	
SEP Q5 (% success)	19→48%		48→68%		56→72%		56→79%	

First, successful first attempt; Subs, successful subsequent attempts up to wk 12 in subjects with a successful first attempt. Intent-to-treat patients with at least two valid diary entries. ED, erectile dysfunction; Q, question; SEP, Sexual Encounter Profile.

(SEP Q2, vaginal penetration; SEP Q3, intercourse success; SEP Q5, satisfaction with the overall sexual experience) from two pivotal phase III trials in a broad spectrum of patients with ED. Reliability was evaluated for each SEP item in terms of the per-patient success rate at wk 12 in patients who were successful at the first attempt after the start of treatment *(35,36)*. For subjects achieving success at the first attempt, vardenafil consistently improved each SEP item response in subsequent attempts through wk 12. More placebo-treated patients discontinued the trial owing to insufficient therapeutic effect than did those on vardenafil (Table 5).

Vardenafil in Diabetic Men With ED

ED is a common complication of diabetes, and more than 50% of diabetic men develop ED within 10 yr of diagnosis of diabetes. In addition, the incidence of ED increases with duration of diabetes, poor glycemic control, and diabetic complications such as vascular and microvascular disease and neuropathies. For these reasons, diabetic men represent a particularly challenging population to treat for ED *(37,38)*.

A randomized, multicenter, double-blind, fixed-dose, parallel-group trial was conducted in 452 patients with a clinical diagnosis of type 1 or type 2 diabetes (glycosylated hemoglobin A_{1c} [HbA_{1c}] $\leq$12%) who had experienced ED for more than 6 mo *(39)*.

These diabetic patients with ED were randomly assigned to receive placebo (n = 150), 10 mg of vardenafil (n = 153), or 20 mg of vardenafil (n = 149) for 12 wk. The mean age of this trial population was 57 yr, and most patients (88%) had type 2 diabetes with poor glycemic control. The mean duration of ED was 3.5 yr. The majority of men (55%) reported severe ED. Primary efficacy variables were the IIEF EF domain score and responses to SEP Q2 and SEP Q3 in 430 evaluable patients (95%). GAQ was also recorded.

At 12 wk, changes from baseline IIEF EF domain scores were significantly greater in the vardenafil-treated diabetic patients than in the group receiving placebo ($p < 0.0001$), with a dose-response pattern being apparent for vardenafil in this domain ($p = 0.03$) (Fig. 7).

Improvements in SEP Q2, SEP Q3, and GAQ were also significantly greater in the vardenafil-treated diabetic men than those treated with placebo ($p < 0.0001$) (*see* Fig. 7).

Given that more than half of these diabetic patients had severe ED at baseline, SEP Q3 was also evaluated based on the severity of ED at baseline. In this group, the low rate of successful intercourse before treatment (0.9–2.5%) significantly improved to 40% in the group receiving 20 mg of vardenafil, compared with 11% in the group receiving placebo group ($p < 0.0001$). Even though the diabetic patients with mild ED at baseline had a greater baseline success rate (35–47%), the average success rate at 12 wk improved to 75% in the group receiving 20 mg of vardenafil, compared with 47% in the group receiving placebo ($p < 0.009$). The study also showed that there was no clear relationship between the response to vardenafil and the level of glycemic control *(39,40)*. The authors concluded that vardenafil significantly improves EF in diabetic men at each level of baseline severity of ED, and that this effect is independent of glycemic control and irrespective of the type (1 or 2) of diabetes. Moreover, vardenafil was generally well tolerated in this difficult-to-treat group of subjects.

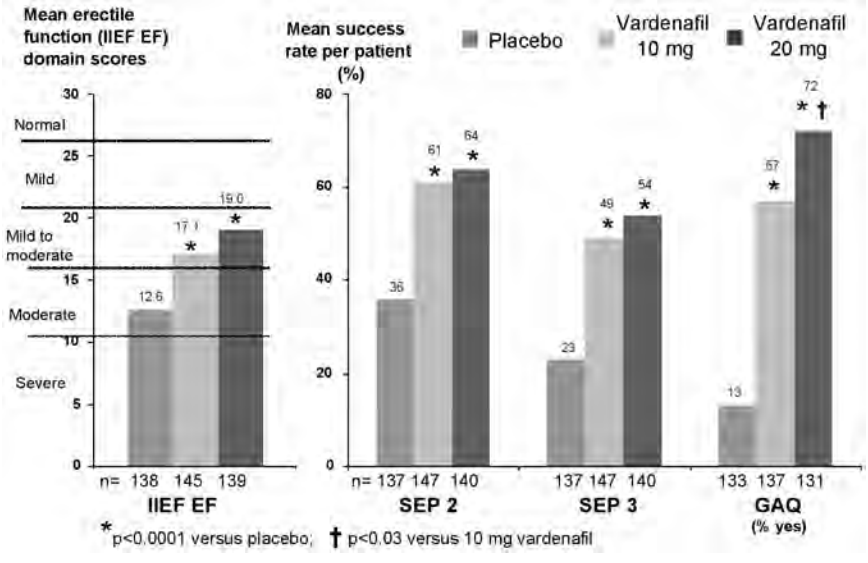

Fig. 7. Changes in efficacy variables in diabetic patients with erectile dysfunction treated with vardenafil or placebo for 12 wk. GAQ, Global Assessment Question; IIEF EF, International Index of Erectile Function, Erectile Function domain; SEP, Sexual Encounter Profile.

An analysis of other secondary efficacy variables conducted at 12 wk in this population of diabetic men with ED showed that the rate of satisfaction with erection hardness was more than three times greater with 20 mg of vardenafil (44.9% satisfaction), compared with placebo (12.0%) ($p <$ 0.0001) *(41)*. In addition, the overall satisfaction with sexual experience, ability to ejaculate, and IIEF domains of intercourse satisfaction (IIEF Q6 and Q7) and orgasmic function (IIEF Q9 and Q10) were also significantly improved with both doses of vardenafil compared with placebo ($p <$ 0.0001). Of the vardenafil-treated diabetic men in this study, 234 elected a 3-mo extension, maintaining their randomized dose such that their total vardenafil treatment time was 6 mo *(42,43)*. In this extension trial, patients receiving placebo ($n = 106$) were randomly assigned to receive 10 or 20 mg of vardenafil for 3 more mo. For all three primary variables, efficacy was sustained at 6 mo in the patients who had received vardenafil from the start. For those who were converted from placebo, improvements in EF at 3 mo were similar to the results seen in those who had received 6 mo of treatment. Overall, in this extension study, vardenafil demonstrated sustained efficacy and good tolerability, with 73% of diabetic patients reporting improved erections with the 20-mg dose.

Vardenafil After Prostatectomy

Even with careful nerve-sparing radical retropubic prostatectomy (NSRRP) for prostate cancer, over one-third of men experience postsurgical ED. ED of this cause presents a particularly challenging population to treat. Although the PDE5 inhibitor sildenafil has been evaluated in patients after NSRRP, the evidence for its efficacy has been derived from relatively small-scale studies *(44–46)*. In a randomized, double-blind, placebo-controlled study in 440 men (mean age, 60 yr) who had developed ED 6 mo to 5 yr (mean, 1.7 yr) after bilateral (73%) or unilateral NSRRP *(47)*, 10 and 20 mg of vardenafil were evaluated using the IIEF EF domain score, SEP Q2, and SEP Q3 as primary efficacy variables after 12 wk of treatment, and GAQ as a secondary outcome variable.

An assessment of IIEF EF domain score showed that 6 mo before surgery, these patients had mild ED (EF domain scores, 22.7–22.9), whereas at trial entry, severe ED was evident (mean EF domain scores, 9.0–9.1). The randomized groups in this study were well matched for demographic and baseline clinical variables and for the pattern of ED-specific symptoms, with 88t o 91% of patients unable to achieve an erection and 90 to 94% unable to maintain an erection to completion of intercourse. Overall, 80% of this population reported previous use of sildenafil, and the majority of these patients (96%) claimed some erectile improvement at some time.

After 12 wk of treatment with vardenafil (10 and 20 mg), all primary efficacy variables and GAQ results were improved significantly more so than with placebo (<0.0001) (Fig. 8).

The efficacy responses to vardenafil were related to the baseline severity of ED, but even in the group with severe ED (the majority, $n = 282$ of 403 evaluable patients [70%]), 28% were able to successfully complete intercourse (SEP Q3), compared with only 4% of those on placebo. In the group with the least severe disease at baseline (mild to moderate, $n = 51$ [13%]), success rates for SEP Q3 at 12 wk were 70, 74, and 49% in the groups receiving 10 mg of vardenafil, 20 mg of vardenafil, and placebo, respectively.

In the relatively large group who had undergone bilateral NSRRP, significant improvements in EF were experienced by 60 and 71% of patients treated with 10 and 20 mg, respectively, of vardenafil compared with only 12% of those who took placebo ($p < 0.0001$). In the smaller cohort with unilateral NSRRP, improvements in erections, measured by GAQ, were experienced by 64, 55, and 15%, respectively ($p < 0.05$ vardenafil vs placebo). Previous sildenafil use did not appear to influence the efficacy of vardenafil relative to PDE5-inhibitor naive patients.

Other secondary efficacy variables in this 12-wk study included diary questions regarding subjective satisfaction with erection hardness, as well

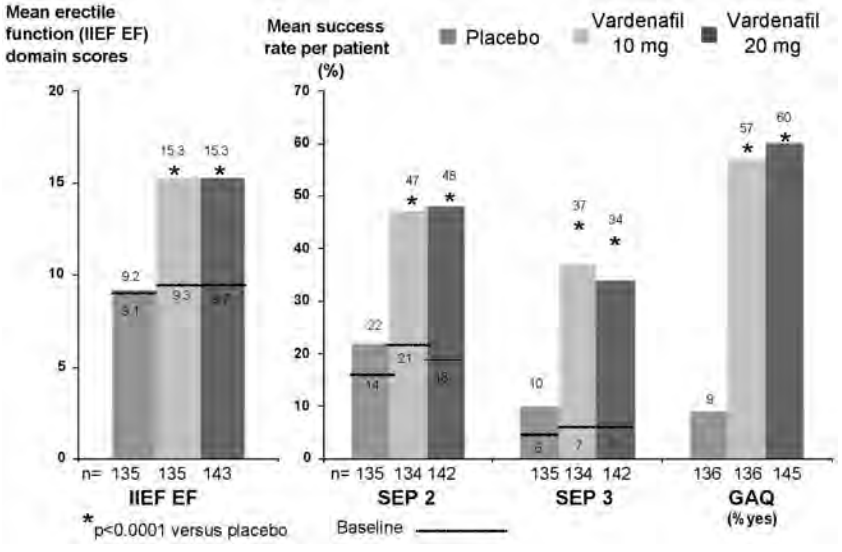

Fig. 8. Changes in efficacy variables in prostatectomy patients with erectile dysfunction treated with vardenafil or placebo for 12 wk. GAQ, Global Assessment Question; IIEF EF, International Index of Erectile Function, Erectile Function domain; SEP, Sexual Encounter Profile.

as IIEF responses regarding intercourse satisfaction, orgasmic function, and overall satisfaction *(48)*. Analysis of these variables indicates that both doses of vardenafil significantly improved the per-patient satisfaction rate for all these variables compared with placebo. In this patient group, satisfaction with erection hardness was very low at baseline in all three groups (0.1, 1.0, and 1.4% of patients in the groups receiving placebo, 10 mg, and 20 mg of vardenafil, respectively). By 12 wk, these rates had increased to 8, 28, and 24%, respectively ($p < 0.002$ for vardenafil vs a dose of placebo) such that the satisfaction with erection hardness was three times greater with vardenafil than with a dose of placebo. Also at 12 wk, the IIEF intercourse satisfaction domain had improved from a baseline score across the groups of 5.0 to 5.4 to 7.7 in the group receiving 10 mg of vardenafil and 7.2 in the group receiving 20 mg. No such improvement occurred with placebo (5.1–5.2); this difference between vardenafil and placebo at 12 wk was significant ($p < 0.002$). A similar pattern was seen for the IIEF orgasmic function domain score and the overall satisfaction score ($p < 0.002$ for each vardenafil dose vs placebo at 12 wk).

Thus, in this challenging population of men with ED after NSRRP, vardenafil not only improved objective outcome measures of EF but also improved key aspects of the subjective sexual experience that are so

important to improving the overall quality of life.In addition, although most patients in this study were not mentally depressed, as measured by the Centre of Epidemiologic Studies Depression Scale , in the subgroup of men with scores indicative of depression at baseline, treatment with 20 mg of vardenafil, (n = 14) resulted in significantly improved depression scores compared with placebo (n = 10) ($p < 0.001$) *(49)*.

Vardenafil in Nonresponders to Sildenafil

In a multicenter double-blind study (the Patient Response with Vardenafil in Sildenafil Nonresponders [PROVEN] study) *(50)*, 463 men with moderate to severe ED who had a documented history of nonresponse to sildenafil according to historical questions were randomly assigned to receive placebo or 10 mg of vardenafil. After 4 wk, subjects were given the option to titrate their dose up to 20 mg or down to 5 mg during a 12-wk study period. Mean IIEF EF domain scores were indicative of severe ED at baseline in both randomized groups (9.3–9.7). By 12 wk, statistically significant and clinically relevant improvements in the IIEF EF domain, SEP Q2 and SEP Q3 scores, and GAQ responses were seen in the vardenafil-treated subjects, compared with those treated with placebo (all $p < 0.001$).

The change from baseline to 12 wk in the IIEF EF scores was 9.7 to 10.5 in the placebo-treated group of sildenafil nonresponders, whereas in the vardenafil-treated sildenafil nonresponders, the change from baseline was 9.3 to 17.6 at 12 wk ($p < 0.001$ vs placebo). Similarly, for SEP Q2, the changes from baseline to 12 wk were 31.7 to 29.9% with placebo and 28.5 to 62.3% with vardenafil ($p < 0.001$ vs placebo). For SEP Q3, the changes were 11.6 to 16.1% with placebo and 14.7 to 61.8% with vardenafil ($p < 0.0001$ vs placebo). At the study's end point, affirmative responses to the GAQ were 14.7% in placebo-treated patients and 61.8% in subjects treated with vardenafil ($p < 0.001$ vs placebo).

Thus, in subjects with ED who were by history nonresponders to sildenafil, vardenafil resulted in a fourfold improvement in successful intercourse completion rates over baseline and brought mean IIEF EF scores from the severe range into the mild-to-moderate range.

Summary of the Efficacy Findings in Subpopulations of Men With ED Treated With Vardenafil

- Vardenafil is effective in improving EF in a broad population of subjects with ED, irrespective of age, cause and severity of ED, and the presence of significant comorbidities.
- Ethnicity is not a confounder to the efficacy of vardenafil. Studies have shown significant benefit in broad populations of Caucasian, African-American, Hispanic, Mexican, and Japanese men with ED.

- The onset of action of vardenafil is rapid. The earliest time that subject erectile benefit was detected that was significantly different from placebo was 16 min.
- Vardenafil provides and maintains long-term efficacy in men with ED with no apparent tolerance to its use over a 2-yr period, the maximum period evaluated so far in clinical trials with vardenafil.
- In flexible-dose studies, in which subjects with ED (in consultation with their physicians) choose the most appropriate dose of vardenafil (5, 10, or 20 mg) for their needs in a real-world setting, more than two-thirds prefer the 20-mg dose.
- The reliability of vardenafil, measured in terms of the consistency of its proerectile effect each time it is used, has been demonstrated.
- In diabetic patients with ED, traditionally a more difficult-to-treat subject group, vardenafil has shown efficacy at all levels of baseline severity whether glycemic control is good or poor.
- In men with severe ED after NSRPP, vardenafil significantly improved key indices of EF.
- Vardenafil can produce significant and clinically meaningful improvements in EF in men with severe ED who have a documented nonresponse to sildenafil by history.

SAFETY AND TOLERABILITY OF VARDENAFIL IN ED

Data from five randomized, double-blind, placebo-controlled phase III trials of 12- to 26-wk duration have been pooled to enable the safety and tolerability profile of vardenafil in subjects with ED to be characterized *(51)*.*

*In evaluating the safety and tolerability profile, the exclusion criteria used in the five phase III trials need to be borne in mind. These were subjects who had a history of unstable angina, myocardial infarction, stroke, electrocardiographic ischemia (except for stable angina), atrial tachyarrhythmia, or life-threatening arrhythmia within the preceding 6 mo. Subjects were also excluded if they had significant chronic hematological disease, a history of significant peptic ulcer disease within 1 yr, resting or symptomatic postural hypotension or hypertension within 6 mo, or uncontrolled diabetes mellitus (HbA_{1C} >12%). Prohibited concomitant medications were nitric oxide donors, anticoagulants, androgens, ketoconazole, itraconazole, ritonavir, sildenafil, or other ED therapy within 7 d of the first visit, or other investigational drugs within 30 d of the first visit. Subjects were excluded if their serum creatinine concentration was >2.5 mg/dL, if their total testosterone level was below normal, if they had a history of severe migraine headaches, or if they had previously discontinued sildenafil owing to adverse events or lack of efficacy (in three of the five studies). Hypersensitivity to any medication component, planned or current radiation therapy, or planned or current hormone therapy also constituted exclusion criteria.

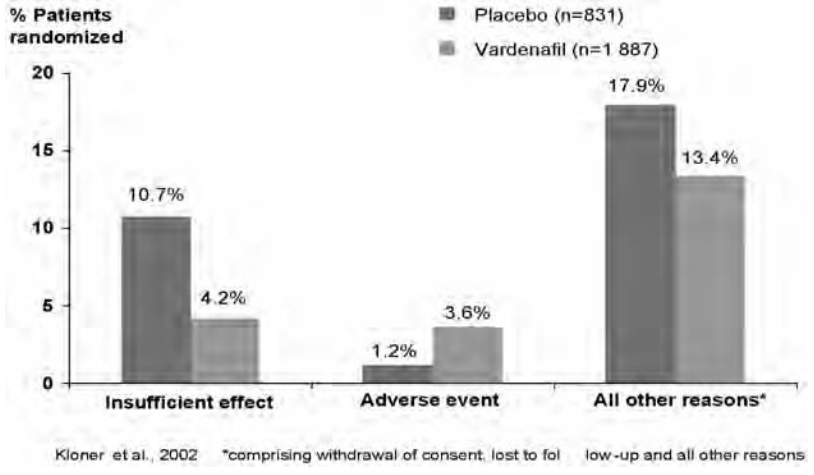

Fig. 9. Reasons for premature discontinuation from five randomized, placebo-controlled trials in subjects with erectile dysfunction treated with vardenafil (5–20 mg) for up to 12 or 26 wk.

Premature Discontinuations

Of 1887 subjects with ED randomly assigned to receive vardenafil in doses of 5, 10, or 20 mg, 78.8% completed their respective trial period, compared with 70% of 831 subjects who received placebo. A greater proportion of subjects receiving placebo prematurely discontinued the trials, largely owing to insufficient therapeutic effect (Fig. 9).

A slightly greater proportion of subjects discontinued vardenafil because of adverse events compared with placebo, although the overall incidence of withdrawal for this reason was low (<4%) (*see* Fig. 9).

The more common adverse events resulting in discontinuation of vardenafil were consistent with this class of drugs and included headache (0.7%), flushing (0.4%), rhinitis (0.4%), tachycardia, nausea, abnormal liver function test results, dizziness, and hypotension, each resulting in the withdrawal of 0.2% of subjects.

Treatment-Emergent Adverse Events

Overall, vardenafil was generally well tolerated. The incidence and nature of treatment-emergent adverse events reported in subjects with ED treated with at least one dose of vardenafil and who had at least one safety assessment during five placebo-controlled trials of 12- and 26-wk duration are consistent with the pharmacological profile of a PDE5 inhibitor. The incidence of back pain was similar to that seen with placebo (Table 6).

Table 6
Incidence of Treatment-Emergent Adverse Events
in More Than 2% of Vardenafil-Treated Subjects
With ED That Were More Frequent Than Placebo Reported
During Five Double-Blind Trials of 12- and 26-Wk Duration

	Placebo (n = *793*)		*Vardenafil* (n = *1812*)	
Adverse event	n	%	n	%
Headache	44	5.5	282	15.6
Flushing	5	0.6	212	11.7
Rhinitis	30	3.8	186	10.3
Dyspepsia	6	0.8	70	3.9
Accidental injury	19	2.4	58	3.2
Sinusitis	6	0.8	56	3.1
Flu syndrome	18	2.3	49	2.7
Dizziness	7	0.9	43	2.4
Nausea	6	0.8	41	2.3
Creatine kinase increase	9	1.1	36	2.0
Arthralgia	8	1.0	36	2.0
Back pain	19	2.4	39	2.2

Adverse events are not mutually exclusive. ED, erectile dysfunction.

Abnormal vision was reported by two subjects taking placebo (0.3%) and 11 subjects taking vardenafil (0.6%) *(51)*.

Serious treatment-emergent adverse events occurred in 3.3% of placebo-treated subjects and in 2.7% of subjects taking vardenafil. One patient in the placebo group and none in the vardenafil group reported dizziness as a serious adverse event. During the course of the trials, one death occurred in the placebo group; there were no deaths, from any cause, in subjects receiving vardenafil in any dose (5, 10, or 20 mg).

Cardiovascular Safety

Cardiovascular Events and Hemodynamics

There were very few cardiovascular events in the pooled safety population. The incidence of those that occurred with vardenafil was broadly similar to that seen with placebo (Table 7) *(52)*.

In addition, there were no notable differences between vardenafil and placebo in relation to treatment-emergent electrocardiographic results (rhythm, conduction, and ischemia-related findings).

Table 7
Treatment-Emergent Cardiovascular Adverse Events Reported During Five Double-Blind Trials of 12- and 26-Wk Duration Comparing Vardenafil and Placebo

	Placebo (n = *793*)		*Vardenafil* (n = *1812*)	
Adverse event	n	%	n	%
Hypertension	9	1.1	33	1.8
Tachycardia	2	0.3	14	0.8
Palpitation	2	0.3	10	0.6
Peripheral edema	1	0.1	10	0.6
Syncope	1	0.1	2	0.1
Hypotension	0	0	2	0.1
Angina pectoris	2	0.3	1	<0.1
Atrial arrhythmia	0	0	1	>0.1
Myocardial infarction	1	0.1	1	>0.1
Stroke	1	0.1	0	0

Vardenafil did not significantly alter mean blood pressure (BP) or heart rate (HR) relative to placebo. From 11 min to 5 h after dosing, mild reductions in supine and standing systolic and diastolic BP (–4.6 and –4.8 vs –3.9 and –3.2 mmHg, respectively) and a small increase in HR (two beats per minute) were recorded. Three of 511 subjects taking vardenafil (0.6%) had a standing systolic BP less than or equal to 90 mmHg and a decrease from baseline of at least 20 mmHg, whereas none of the placebo-treated subjects exhibited this change *(52)*.

One or more antihypertensive medications were used concomitantly by 40% of subjects taking placebo and 42% of subjects taking vardenafil. Although there were no consistent changes in BP and HR in those receiving vardenafil plus antihypertensive medication, minimal additional reductions in systolic and diastolic BP were observed that were generally similar for all types of antihypertensive medications (anticholinerastase inhibitors, calcium channel antagonists, α- or β-blockers, diuretics, and angiotensin receptor blockers) *(52)*.

These data indicate that vardenafil exhibits a favorable cardiovascular safety profile in the pooled data of broad and challenging subjects with ED. The overall incidence of cardiovascular-related adverse events with vardenafil was similar to that with placebo. Vardenafil, though, may be associated with small, transient decreases in BP and small changes in HR relative to placebo.

Table 8
No Adverse Influence of Vardenafil on Treadmill Exercise Time, Time-to-Onset of Angina, or Ischemic Threshold in Men With Ischemic Coronary Heart Disease

	Placebo	*Vardenafil 10 mg*	*Placebo*	*Vardenafil 20 mg*
Number of patients	41		39	
Mean age (yr)	61.9		63.8	
Total exercise time (s)	427	433	411	414
Time to angina awareness (s)	292	291	347	354
Time to ischemic threshold (s)	334	384[a]	366	364

[a] $p = 0.0004$ vs placebo.

Exercise Tolerance in Patients With Coronary Artery Disease Taking Vardenafil

ED is common among men with coronary artery disease (CAD). Although sexual activity can trigger the onset of myocardial infarction, the absolute risk is low *(53)*. Nevertheless, it is a consideration when physicians are selecting the best course of treatment for ED in patients with CAD *(54)*. Two double-blind, placebo-controlled, single-dose crossover studies have been conducted in men with reproducible stable exertional angina because of ischemic CAD to examine the effect of vardenafil (10 and 20 mg) on symptom-limited exercise time, time to first awareness of angina, and time to ischemic threshold, measured as ST segment depression greater than or equal to 1 mm from baseline. In both studies, the effect on exercise tolerance was tested at the time of maximum plasma concentrations of vardenafil.

In one study *(55)*, 41 men (mean age, 61.9 yr) with ischemic CAD received a morning dose of vardenafil, 10 mg, followed 1 h later by exercise tolerance testing.* In those patients who routinely used sublingual nitrate, this was not permitted for at least 24 h before or after the exercise study days.

The second study, in 39 men (mean age, 63.8 yr), mirrored the first except that these men received a single 20-mg dose of vardenafil *(56)*.

The results indicate that relative to placebo, vardenafil did not adversely affect total treadmill exercise time, time-to-onset of angina, or ischemic threshold (Table 8).

*Using the standard Bruce protocol, exercise was conducted to a level of 5–10 metabolic equivalents (METS) on the basis that completed sexual intercourse typically expends around 3 METS.

The finding that 10 mg of vardenafil significantly increased the ischemic threshold by about 15% relative to placebo is interesting in that it implies that vardenafil-treated patients with CAD were able to exercise for a longer period before manifesting electrocardiographic evidence of cardiac ischemia. There were no differences between either dose of vardenafil and placebo in HR, BP, or the rate product (HR × systolic BP).

These studies support the contention that 10- and 20 mg of vardenafil, does not alter the ability of patients with CAD to complete an exercise tolerance test at a level that meets or exceeds the level of exertion typically required to complete sexual intercourse.

QTc Interval

Drug-induced prolongation of the QT/corrected (QTc) QT interval is a risk factor for the development of the ventricular tachyarrhythmia known as torsades de pointes. Although a QT threshold value for risk of torsades de pointes has not been established, most reported cases occur in individuals with a measured QTc value exceeding 500 ms *(57)*.

The effect of vardenafil on the QTc interval has been evaluated at a therapeutic dose (10 mg) and a supratherapeutic dose (80 mg) in a double-blind, placebo-controlled crossover study in 58 men (mean age, 53 yr) using a 12-lead digital electrocardiogram *(58)*. Two sildenafil doses (50 and 400 mg) were evaluated in a similar way, and an active control (moxifloxacin) was used. Electrocardiograms were analyzed in a fashion that was blinded to treatment, and the Fridericia correction (QTcF) was used in the comparisons of QTcF changes between baseline and 1 h postdose to coincide with t_{max}. For placebo, there was no change from baseline in QTcF. Both doses of vardenafil and of sildenafil produced no increase over baseline in absolute QT interval and similar small increases in QTcF (6–10 ms), which are considered to be clinically insignificant.

Concomitant Use of Nitrates

Pharmacodynamic studies in healthy middle-aged subjects have evaluated the potentiation of blood pressure-lowering effects and increases in heart rates that occur with administration of sublingual nitrates (0.4 mg) 1 and 4 h after a 20-mg dose of vardenafil *(14)* (*see* section entitled "Drug Interactions").

Potentiation of the hypotensive effects of nitrates in patients with ischemic heart disease has not been evaluated. Concomitant use of vardenafil and nitrates is contraindicated, however, in line with the expert consensus recommendations of the American College of Cardiology/American Heart Association based on the use of the first PDE5 inhibitor, sildenafil, in patients with cardiovascular disease *(59)*.

Summary of the Safety and Tolerability Profile of Vardenafil

- The rate of discontinuation of vardenafil owing to adverse events is low and occurs with a frequency that is only less than 3% higher than with placebo.
- Vardenafil is generally well tolerated. The most common reasons for discontinuation owing to adverse events are headache, flushing, and rhinitis (collectively <1.5%).
- The most common treatment-emergent adverse events that did not result in discontinuation of vardenafil were also headache (10% more than placebo), flushing (11% more than placebo), and rhinitis (7% more than placebo).
- There were few cardiovascular events associated with vardenafil that were different from those occuring with placebo.
- Vardenafil may be associated with small, transient decreases in BP and HR.Vardenafil does not exacerbate angina during exercise and has no clinically significant effects on the QT interval.
- Concomitant use of nitrates with vardenafil remains an absolute class contraindication.

SUMMARY AND CONCLUSIONS

Vardenafil is a potent, selective PDE5 inhibitor that has a rapid onset of action and provides consistent, reliable, and sustained efficacy, as demonstrated in long-term studies for up to 2 yr. Vardenafil is effective and generally well tolerated in the broad population of men with ED, as well as in those considered characteristically challenging to treat, including diabetics and men who have undergone radical prostatectomy. In addition to improving EF, vardenafil improves those parameters important to quality of life and satisfaction with the sexual experience. Vardenafil also displays efficacy in patients previously unresponsive to sildenafil. Collectively, therefore, the findings from a comprehensive clinical trials program demonstrate that vardenafil will contribute to the clinical armamentarium available to optimize treatment in men with ED.

REFERENCES

1. Eardley I, Rosen R, Fisher W, et al. (2003) Attitudes toward treatment of erectile dysfunction: results from the MALES study. Eur Urol Suppl 2:97.
2. Fisher W, Eardley I, Rosen R, et al. (2003) The Men's Attitudes to Life Events and Sexuality (MALES) Study-II: Correlates of Self-Reported Disease Severity among Men with Erectile Dysfunction. Prog Urol 13(Suppl 2):32.
3. Sachse R, Rohde G, Stark S, et al. (2000) Safety, tolerability and pharmacokinetics of BAY 38-9456 in patients with erectile dysfunction. J Urol 163:204.
4. Sachse R, Rohde G. (2000) Safety, tolerability and pharmacokinetics of multiple dose treatment with the new PDE-5 inhibitor Bay 38-9456. Eur Urol 37:321.

5. Porst H, Steidle C, Hollister A, et al. (2001) Vardenafil demonstrated similar efficacy and tolerability among older and younger patients with marginal differences in PK characteristics between age groups. Int J Impot Res 13:45.
6. Rajagopalan P, Mazzu A, Xia C, et al. (2003) Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. J Clin Pharmacol 43:260–267.
7. Bauer R-J, Rohde G, Wensing G. (2002) Evaluation of the interactions of alcohol and PDE5 inhibitor, vardenafil. Int J Impot Res 14(Suppl 4):S22–S59.
8. Radtke M, Karl W, Seidel D, et al. (2001) Biotransformation of [14C]-vardenafil in man. Drug Metab Rev 33(Suppl):114.
9. Klotz T, Bauer RJ, Rohde G. (2002) Effect of renal impairment on the single-dose pharmacokinetics of vardenafil 20 mg, a novel PDE5 inhibitor, for the treatment of erectile dysfunction. Pharmacotherapy 22:418.
10. Rohde G, Wensing G, Sachse R. (2001) The pharmacokinetics of vardenafil, a new selective PDE5 inhibitor, are not affected by the antacid, Maalox 70. Pharmacotherapy 21:1254.
11. Rohde G, Wensing G, Unger S, et al. (2001) The pharmacokinetics of vardenafil, a new highly selective PDE5 inhibitor, is minimally affected by coadministration with cimeditine or ranitidine. Pharmacotherapy 21:1254.
12. Rohde G, Bauer R-J, Unger S, et al. (2001) Vardenafil, a new selective PDE5 inhibitor, produces no interaction with Digoxin. Pharmacotherapy 21:1254.
13. Rohde G, Jordaan P. (2002) Influence of vardenafil on blood pressure and pharmacokinetics in hypertensive patients on nifedipine therapy. Pharmacotherapy 22:418.
14. Mazzu A, Nicholls A, Zinny M. (2001) Vardenafil, a new selective PDE-5 inhibitor, interacts minimally with nitroglycerin in healthy middle-aged male subjects. Int J Impot Res 13(Suppl 5):S64.
15. Mazzu A, Rajagopalan P, Xia C, et al. (2003) Vardenafil does not alter aspirin-induced prolongation of bleeding time in normal healthy volunteers: a phase I study. Pharmacotherapy 23:399–400.
16. Hellstrom WJ, Gittelman M, Karlin G, et al. (2002) Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 23:763–771.
17. Rosen RC, Riley A, Wagner G, et al. (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49:822–830.
18. Rosen R, Bennett A, Ferguson D, et al. (2000) Standards for clinical trials in erectile dysfunction: research designs and outcomes assessment. In: Jardin A, Wagner G, Khoury S, et al., eds., Erectile Dysfunction. Health Publications Ltd., p. 660.
19. Hellstrom W, Gittelman M, Karlin G, et al. (2003) Sustained efficacy and tolerability of vardenafil (Levitra), a highly potent, selective phosphodiesterase-5 inhibitor, in men with erectile dysfunction: results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. Urology 61(4 Suppl 1): 8–14.
20. Donatucci C, Pommerville P, Niederberger C, et al. (2003) Vardenafil improved patient satisfaction with erection hardness, orgasmic function, and sexual experience in men with erectile dysfunction. J Urol 169:246.
21. Breuil T. (2002) Does the age of patients have an impact on the efficacy and safety of vardenafil in the treatment of erectile dysfunction? Andologia 34:282–283.
22. Donatucci C, Karlin G, Goldfischer E, et al. (2002) Influence of age on the efficacy and safety of vardenafil, a novel phosphodiesterase-5 inhibitor, for the treatment of erectile dysfunction. J Am Geriatr Soc 50:S107.

23. Donatucci C, Eardley I, Thibonnier M, et al. (2002) Vardenafil improves erectile function regardless of etiology or baseline severity in men with erectile dysfunction. J Urol 167(Suppl): 178.
24. Porst H, Padma-Nathan H, Thibonnier M, et al. (2002) Efficacy and safety of vardenafil, a selective phosphodiesterase 5 inhibitor, in men with erectile dysfunction on antihypertensive therapy. Eur Urol 1(Suppl):152.
25. Goldfischer E, Eardley I, Segerson T, et al. (2002) Vardenafil improves erectile function in men with significant comorbidities associated with erectile dysfunction. J Urol 167(Suppl):178.
26. Bennett J, Trujillo A, for the Vardenafil Study Group (2003) Vardenafil improves erectile function in African-American, Hispanic, and Caucasian men with erectile dysfunction (ED). National Medical Association.
27. Bennett J, Trujillo A, for the Vardenafil Study Group (2003) Vardenafil provides for reliable successful intercourse in African-American, Hispanic, and Caucasian men with erectile dysfunction (ED). National Medical Association.
28. Sotomayor M, Rubio E, Tapia R, et al. (2002) Vardenafil improved erectile function in Mexico: a 3-month open-label study. Int J Impot Res 14 (Suppl 3):S88.
29. Nagao K, Ishii H, Kamidono S, et al. (2004) Safety and efficacy of vardenafil (Levitra) in patients with erectile dysfunction: result of a bridging study in Japan. Int J Urol 11:515–524.
30. Montorsi F, Padma-Nathan H, Buvat J, et al., for the Vardenafil Study Group. (2004) Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind, placebo-controlled trial. J Sex Med 1:168–178.
31. Sáenz de Tejada I, Geina S, Becher E, et al. (2002) Vardenafil exhibits long-term efficacy and safety for up to 52 weeks. Int J Impot Res 14:S35.
32. Stief C, Porst H, Saenz de Tejada I, et al. (2003) Sustained efficacy and tolerability of vardenafil over two years in men with erectile dysfunction. Prog Urol 13(Suppl 2):100–103 (abstract).
33. Potempa A-J, Bernard I, Ulbrich E. (2002) Vardenafil improved erectile function in a "real world" flexible regime. Int J Impot Res 14(Suppl 4):S37–S61.
34. Hatzichristou D, Montorsi F, Porst H, et al. (2003) A flexible dose regimen of vardenafil for erectile dysfunction: a placebo-controlled trial. Eur Urol 43 (Suppl 2):176.
35. Valiquette L, Hellstrom W, Gittelman M, et al. (2002) Vardenafil provides reliable efficacy over time in men with erectile dysfunction. Int J Impot Res 14(Suppl 3): S88.
36. Montorsi F, Hellstrom W, Valiquette L, et al. (2003) Reliable efficacy over time of vardenafil, a potent, highly selective PDE-5 inhibitor in men with erectile dysfunction: a retrospective analysis of two pivotal phase III studies. Prog Urol 13(Suppl 2):31
37. Vinik A, Richardson D. (1998) Erectile dysfunction in diabetes. Diabet Rev 6:16–33.
38. Fedele D, Coscelli C, Santeusanio F, et al. (1998) Erectile dysfunction in diabetic subjects in Italy. Gruppo Italiano Studio Deficit Erettile nei Diabetici. Diabetes Care 21:1973–1977.
39. Goldstein I, Young JM, Fischer J, et al. (2003) Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 26: 777–783.
40. Goldstein I, Young J, Segerson T, et al. (2002) Influence of HbA1c on the efficacy and safety of vardenafil for the treatment of erectile dysfunction in men with diabetes. Diabetes 51:A98.

41. Young J, Goldstein I, Fischer J, et al. (2003) Vardenafil (Levitra) improved patient satisfaction with erectile hardness, orgasmic function, and sexual experience in men with diabetes with erectile dysfunction. Diabetes 52:A16.
42. Young J, Goldstein I, Taylor T. (2001) Long-term efficacy and safety of vardenafil in diabetic men with erectile dysfunction. Diabetologia 45(Suppl 2):A334–A335.
43. Goldstein I, Young J, Segerson T, et al. (2002) Long-term efficacy and safety of vardenafil in diabetic men with erectile dysfunction. Diabetes 51:A98.
44. Zippe CD, Kedia AW, Kedia K, et al. (1998) Treatment of erectile dysfunction after radical prostatectomy with sildenafil citrate (Viagra). Urology 52:963–966.
45. Zippe CD, Jhaveri FM, Klein EA, et al. (2000) Role of Viagra after radical prostatectomy. Urology 55:241–245.
46. Vale J. (2000) Erectile dysfunction following radical therapy for prostate cancer. Radiother Oncol 57:301–305.
47. Brock G, Lipshultz L, Karlin G, et al. (2003) Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction subsequent to radical retropubic prostatectomy. J Urol 170:1278–1283.
48. Brock G, Vezina JG, Nehra A, et al. (2003) Vardenafil Improved Patient Satisfaction with Erection Hardness, Orgasmic Function, and Sexual Experience in Men with Erectile Dysfunction Following Nerve-Sparing Radical Prostatectomy. Prog Urol 13(Suppl 2):32 (abstract 104).
49. Brock G, Nehra A, Lipshultz L, et al. (2002) Influence of Vardenafil on Erectile Dysfunction (ED) and Depressive Symptoms Post-Radical Prostatectomy. AUA—South Central Section Annual Meeting, Colorado Springs, CO: October 5–9, 2002.
50. Carson C, Hatzichristou D, Carrier S, et al. (2003) Vardenafil exhibits efficacy in men with erectile dysfunction unresponsive to prior sildenafil therapy: results of a phase III clinical trial—Patient Response with Vardenafil in Sildenafil non-responders (PROVEN). Int J Impot Res 15(Suppl 5):S175.
51. Kloner R, Mohan P, Norenberg C, et al. (2002) Cardiovascular safety of vardenafil, a potent, highly selective PDE-5 inhibitor in patients with erectile dysfunction; an analysis of five placebo-controlled clinical trials. Pharmacotherapy 22:1371.
52. Carrier S, Herschorn S, Elhilali M, et al. (2003) Cardiovascular safety of Levitra (vardenafil) in patients with erectile dysfunction: an analysis of five placebo-controlled clinical trials. Can J Urol 10:1826.
53. Muller JE, Mittleman A, Maclure M, et al. (1996) Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Investigators. JAMA 275: 1405–1409.
54. DeBusk R, Drory Y, Goldstein I, et al. (2000) Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. Am J Cardiol 86:62F–68F.
55. Thadani U, Smith W, Nash S, et al. (2002) Effect of vardenafil on the cardiovascular responses to exercise in men with coronary artery disease. J Am Coll Cardiol 40:2006–2012.
56. Thadani U, Chrysant S, Mazzu A, et al. (2003) The effect of vardenafil, a selective PDE5 inhibitor, on ischemic threshold, exercise tolerance, and circulatory responses during treadmill exercise in men with stable angina pectoris. J Am Coll Cardiol 41:336A.
57. Makkar RR, Fromm BS, Steinman RT, et al. (1993) Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 270: 2590–2597.

58. Morganroth J, Ilson BE, Shaddinger BC, et al. (2004) Evaluation of vardenafil and sildenafil on cardiac repolarization. Am J Cardiol 93:1378–1383.
59. Cheitlin MD, Hutter AM Jr, Brindis RG, et al. (1999) ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/American Heart Association. J Am Coll Cardiol 33:273–282.

7 Erectile Dysfunction Assessment and Management in Primary Care Practice

Louis Kuritzky, MD, and Martin Miner, MD

CONTENTS

INTRODUCTION

Appropriate management of erectile dysfunction (ED) is the same for providers of all specialties. With the advent of oral agents as first-line therapy for the treatment of ED, the path to discussion of ED and its treatment often winds through the primary care clinician's office. (The term primary care clinician [PCC] is intended to include physicians, nurse practitioners, and physician's assistants who provide primary care services to patients.) Indeed, on a national basis, approximately two-thirds of prescriptions for PDE5 inhibitors are written by PCCs. Because of the issues particularly pertinent to primary care, such as time constraints, multiple

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competing problems, long-term relationship with the patient, potential inclusion of the partner as a patient as well, an efficient and yet thorough management plan is essential.

What are the themes that are consistently pertinent to the management of ED by the PCC?

1. PCCs are the usual source of initial contact for management of ED.
2. PCCs are often responsible for detection and management of ED and concomitant comorbidities (e.g., depression, cardiovascular disease, dyslipidemia, diabetes, lower urinary tract symptoms, and relationship issues).
3. Partner involvement in the ED management process has been shown to have a critical impact on outcome. Because both the patient and his partner often have an established relationship with the PCC, a greater opportunity for optimizing treatment of ED exists.
4. The longitudinal nature of the relationship between PCC and patient lends itself to disclosure of issues of intimacy.
5. The sheer epidemiological prevalence of ED (more than half of men older than the age of 40 yr manifest some degree of ED, according to the Massachusetts Male Aging Study [MMAS]) provides compelling motivation for attention to this problem in the primary care setting.

The following topics are addressed in this chapter:

- ED and its relationship to men's health.
- ED and the primary care workup.
- Best approach to ED in the primary care setting and the barriers to this.
- Reasons to treat ED: the relationship of sexual function to vital comorbid disease states in men.
- Oral agents for ED.
- Cardiovascular concerns for primary care regarding PDE5 inhibitors.
- Reimbursement for treating male sexual dysfunction and concluding thoughts.

In the United States, popular philosophy, with its inordinate focus on youthfulness, has fostered long-held beliefs that sexual activity becomes less important to the aging male and his partner. Sexuality at midlife and beyond is rarely dealt with in either popular film or other media. There are a dearth of media images exemplifying the positivity of sexuality at midlife and beyond. Indeed, the persistence of sexual activity in aging adults appears to be a topic that we may not openly acknowledge, or even discourage! Yet studies consistently report that 80 to 90% of men between the ages of 40 and 50 yr have sex at least twice weekly, whereas 70% of men in their 70s still have sex at least weekly *(1–3)*. Clearly, sexual activity and function are of great importance to the midlife and more mature male.

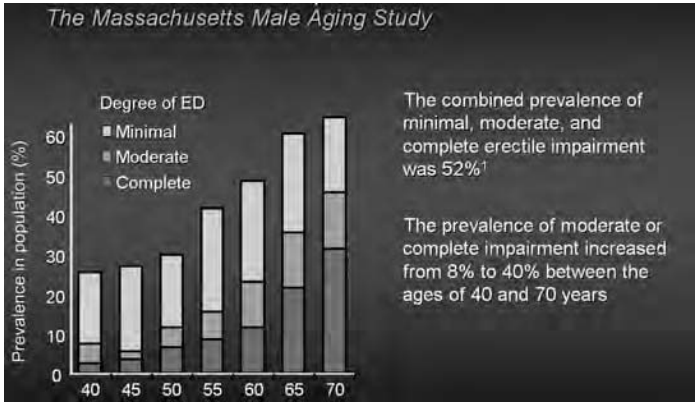


Fig. 1. The prevalence of erectile dysfunction. It is intuitive that ED increases with age. Clinicians are sometimes surprised to learn that "mild" ED is not what increases over time, but rather it is the moderate to complete ED that becomes ever more commonplace. Note also that in this analysis ($n \geq 1000$), literally one-quarter of men by age 40 yr experienced some degree of ED. ED, erectile dysfunction. Adapted from ref. *8*.

It is evident that the potential causes of ED include a myriad of organic factors—vascular (e.g., arterial flow, endothelial function, venous competence), endocrine (e.g., diabetes, hypogonadism, and pituitary abnormalities), neurogenic (e.g., neuropathy, demyelinating disorders, and spinal cord injury), mechanical (e.g., elite-level bicycling) *(4)*, medication-induced (e.g., thiazides, selective serotonin uptake inhibitors, β-blockers, phenothiazines, and surgical follow-ups [SFUs]) *(5,6)*, local disorders of the genitourinary system (e.g., prostate disease), and postsurgical (e.g., prostatectomy, and colectomy).

Erectile function is a high priority for men, regardless of age. It affects as many as 40 million men in the United States *(7)*. In addition to deserving attention in its own right, ED merits evaluation because it may indicate the presence of a serious underlying comorbid medical disorder. Because the most common cause of ED is endothelial cell dysfunction, which is induced most often by the well-recognized endothelial cell toxins (diabetes, dyslipidemia, smoking, obesity, hypertension, and hyperhomocysteinemia), every man with ED merits consideration for evaluation of the cardiovascular risk factor burden. In the MMAS *(8)*, after adjusting for age, there was a 39% incidence of ED in men with cardiovascular disease, a 29% incidence in diabetic men in good control (46% in those with poor control), up to 90% incidence in depression, and 60 to 90% association with dyslipidemias. In the same study, the overall prevalence of ED (minimal to severe), irrespective of age, was 52% (Fig. 1) *(9)*.

Fig. 2. An oft-missed opportunity: the clinical sexual health conversation. Despite the knowledge that a majority of patients consider discussions of sexual health pertinent to clinical encounters, only a very small number of consultations evidence inquiry into sexual health. ED, erectile dysfunction; PCP, primary care physician.

The association of ED with aging primarily reflects the cumulative burden of cardiovascular disease risk factors (i.e., as men reach midlife, the degree of endothelial dysfunction attributed to acknowledged risk factors, such as hypertension, lipids, smoking, and sedentary lifestyle becomes magnified) *(10)*.

There is a distressing discordance between the prevalence of ED, the readily available and highly efficacious treatments, and the relative infrequency with which clinicians actually address the problem (Fig. 2).

Studies note that sexual issues are documented in as few as 2% of primary care provider charts *(11)*.

Yet more than 70% of adult patients consider sexual matters to be an appropriate topic to be raised by the primary care physician *(12)*. Given that ED compromises multiple aspects of the lives of patients and their partners, the challenge is to lessen this disparity.

It has been demonstrated that if providers do not ask, patients will not be likely to initiate discussions of a sexual problem. In one study, 71% of patients thought the physician would dismiss their sexual concerns, 68% feared that the clinician would be embarrassed, and 76% thought that there would be no medical treatment *(12)*.Obviously, barriers to communication between clinicians and their patients remain significant but offer much opportunity for positive resolution.

In summary, the PCC is in an opportune position to identify and manage patients with ED, through both the patient and (often) his partner. Owing to the nature of the breadth of primary care, PCCs are also the appropriate source for the evaluation of cardiovascular risk factor burden in this population. Although there are exceptions, most patients believe that it is appro-

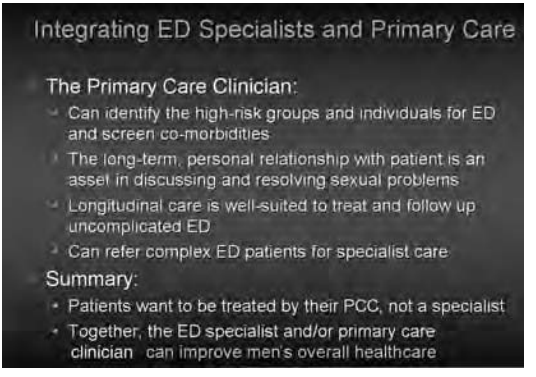


Fig. 3. Rational for erectile dysfunction management in primary care. ED, erectile dysfunction; PCC, primary care clinician.

priate to share issues of intimacy with their PCC. Occasionally, patients would rather have some degree of anonymity when they discuss issues like sexuality. Because of the long-term relationship often established, the clinician and patient might be members of the same golf club, religious institution, or other social organization. In such circumstances, patients may wish to seek a provider with whom they do not have an ongoing relationship, and it is not unheard of for patients to seek consultation with a subspecialist in this setting—not because of the need for specialty care, but because of the desire for a less personal relationship.

The longitudinal care model of primary care practice is well-suited to treating and following uncomplicated ED. PCCs can refer patients with complex ED to either a urologist or another ED specialist. In our experience, however, most patients prefer to be treated by their primary care provider (Fig. 3).

THE PATHOPHYSIOLOGY OF ORGANIC ED AND THE WORKUP IN THE PCC SETTING

Whereas a decade ago most ED was felt to be psychogenic in origin, new insights have shown that the vast majority of ED (at least 70%) is a result of vasculopathy, with the remaining organic causes relating to pharmacological, operative, neurogenic, and hormonal influences (Fig. 4) *(13–17)*.

Even when men suffer from purely organic ED, it should be anticipated that there will essentially always be important emotional consequences of ED that merit consideration, including counseling by a sex therapist or other individual experienced in helping men who suffer from sexual dysfunction and their partners.

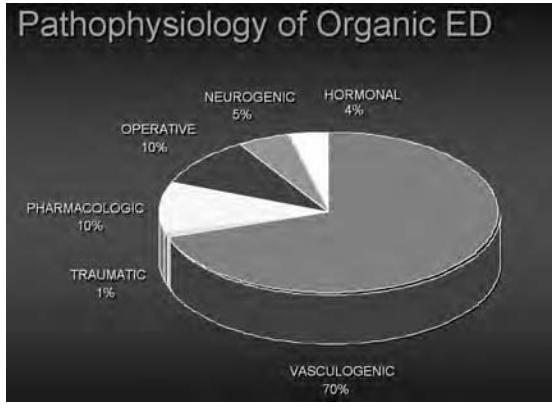


Fig. 4. Pathophysiology of organic ED. ED is most often a vasculopathy. Although a decade ago, most ED was considered psychogenic in origin, the majority of persons with ED manifest endothelial dysfunction because of a variety of cardiovascular risk burdens, such as hypertension, obesity, dyslipidemia, glucose intolerance, sedentary lifestyle, and smoking. ED, erectile dysfunction

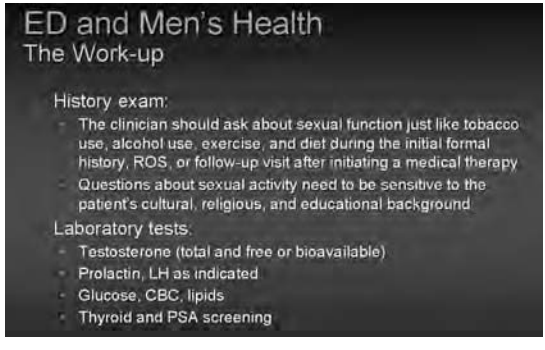
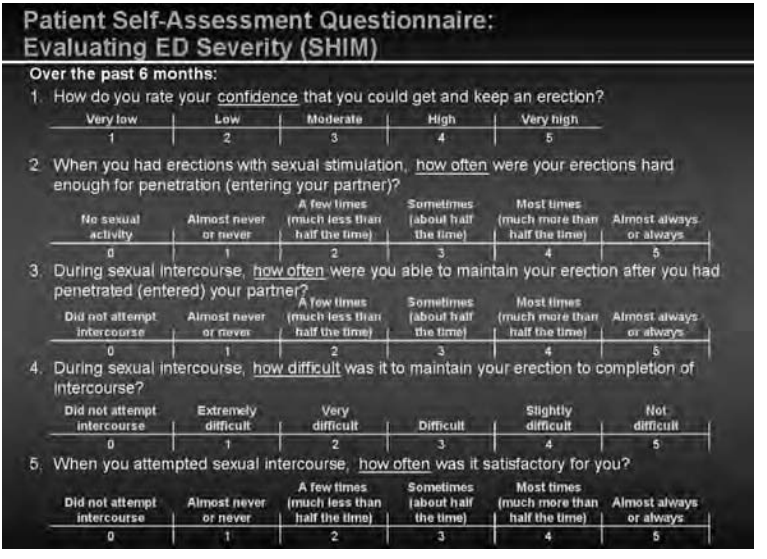


Fig. 5. Successfully addressing erectile dysfunction. History and lab clinicians are encouraged to address issues of sexual health more routinely; and traditional laboratory investigation is aimed at detecting subnormal testosterone, diabetes, and other disorders potentially leading to endothelial dysfunction. CBC, complete blood count; ED, erectile dysfunction; LH, luteinizing hormone; PSA, prostate-specific antigen; ROS, review of systems.

Inquiring about sexual function should not be considered a "special circumstance" but rather a routine part of health surveillance, as normal as asking about tobacco use, alcohol use, exercise, and diet. Some clinicians prefer to ask these questions during the formal review of systems. We prefer to do so during the social and lifestyle history component of the examination (Fig. 5) or when a pertinent clinical syndrome may dictate the appropriate



Patient Self-Assessment Questionnaire: Evaluating ED Severity (SHIM)

Over the past 6 months:

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

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

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

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

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

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

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

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

5. When you attempted sexual intercourse, how often was it satisfactory for you?

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

Fig. 6. Office questionnaires. The Sexual Health Inventory for Men use of an office questionnaire may be useful as an "icebreaker," and may also help to quantify degree and quality of sexual dysfunction. High scores (>17), mild or no ED; Low scores(<11), moderate or severe ED. ED, erectile dysfunction; SHIM, Sexual Health Inventory for Men.

inclusion of sexuality-related information (e.g., penile lesion, dysuria, urethral discharge, or perineal dermatitis).

Sometimes clinicians find additional value in using questionnaires that patients are to fill out before the visit, including the SHIM (Sexual Health Inventory for Men) (Fig. 6) *(18)*.

A special merit of direct provider inquiry is that even if the response is a brief, "it's fine," you have validated sexual function as an appropriate topic for discussion in a future visit. It is equally wise to ask about sexual function after initiating a regimen of medications that might be anticipated to have adverse sexual effects, especially antihypertensives and antidepressants. However one may ask, such inquiries need to be sensitive to the patient's cultural, religious, and educational background.

It is important to recognize that we have evolved from including sexual function inquiries based primarily on the risk for sexually transmitted diseases to including such questioning based on the concept that, not only should sexual function be one of the vital signs of lifestyle, but also an important potential indicator of cardiovascular comorbidity. Especially since the advent of highly effective oral agents, it is appropriate to inquire,

"Are you satisfied with your sexual function?" How we do this reflects our own level of comfort in these matters, and we might use any of the following questions: "Are you satisfied with your sexual functioning?"; "How is your sex life?"; "Are you experiencing any problems with your sexual function?"; or "Many men with diabetes (or hypertension, or coronary artery disease [CAD], or midlife changes, etc.) notice changes in their sexual function. Has this been an issue for you?"

Many men experience mixed sexual dysfunction, which may include issues of libido and orgasmic difficulties. Although this discussion is focused on ED, the frequency with which other types of sexual dysfunction are mistakenly identified by the patient as ED (e.g., disorders of ejaculation or desire) requires clear elucidation of the mechanics of the dysfunction: Is there a problem with erection hardness, durability, pain, or ejaculation? "Distress" is an essential part of the therapeutic decision process, in that any patient who has a demonstrated dysfunction that does not cause distress to him or his partner does not merit intervention.

Once the problem is identified, the medical history should highlight the following *(13,16)*:

- List of current medications taken, including over-the-counter and herbal drugs.
- Family history of premature cardiovascular disease (CVD) or prostate cancer.
- Salient partner issues (e.g., menopause, pain, relationship conflicts, sexual abuse history).
- Tobacco, alcohol, and illicit drug use.
- Pelvic trauma or genital or pelvic surgery.
- Past medical history, noting the presence of diabetes, hypertension, and thyroid or other endocrine disorders.
- History of depression or anxiety.
- Sleep history to exclude sleep apnea as a contributing cause.

Physical examination should highlight the following:

- Blood pressure.
- Vascular examination, noting the presence or absence of pulses and bruits.
- Neurological examination for peripheral neuropathy (e.g., rectal examination).
- Endocrine examination for signs and symptoms of thyroid or adrenal disease, hypogonadism, gynecomastia, atrophic testes (<2.5 cm), absent body hair, or thyromegaly.

Penile examination should focus on the following:

- Loss of elasticity of penile shaft, nodularity, or plaques suggesting Peyronie's disease. The patient with Peyronie's disease will typically

describe a history of penile curvature, pain with erections, or difficulty with intromission. Peyronie's disease generally requires a referral to a urologist.

Laboratory tests should include measurement of the following:

- Glucose.
- Low-density lipoproteins (LDL) and high-density lipoproteins (HDL) and triglycerides.
- Testosterone:
  - ◇ Initial screen: Total morning testosterone.
  - ◇ Follow-up with total and free testosterone if initial total testosterone level is low or borderline.
- Prolactin (and luteinizing hormone (LH) if total testosterone is low, especially in an individual younger than the age of 50).
- Thyroid-stimulating hormone.
- Prostate-specific antigen.

Because ED is a harbinger for disproportionate cardiovascular risk-factor burden (or established CVD), the physical and laboratory screening should focus on the presence or absence of these disease states. Of 521 patients with ED examined for comorbidities in a large sexual dysfunction clinic, 39% had hypertension, 37% were found to be hypogonadal, and 34% experienced medication-related ED; 68% were thought to have primarily organic causes, 8% psychogenic, and 24% mixed. Of men with hypogonadism, 99% had other comorbidities that could also contribute to or independently cause ED *(19)*.

PRIORITIZATION OF ED TREATMENT IN PRIMARY CARE: THE RELATIONSHIP OF ED TO COMORBIDITIES

In addition to the well-described risk factors for ED (diabetes, prostate disease, atherosclerotic cardiovascular disease, peripheral vascular disease, cigarette smoking, hypertension, obesity, sedentary lifestyle, and depression), obstructive sleep apnea and debilitating neurological disorders (e.g., Parkinson's disease, multiple sclerosis, and dementia) can be added to the list. The common denominator for the majority of disorders associated with ED appears to be endothelial cell dysfunction. It is well-established that dyslipidemia, hypertension, hyperglycemia, hyperhomocysteinemia, central obesity, smoking, and sedentary lifestyle are associated with endothelial dysfunction. Encouragingly, improvements in endothelial function attendant to improvements in these disease processes has been documented, but unfortunately it has not been conclusively demonstrated that management of cardiovascular risk factors will result in meaningful improvement in ED. Some preliminary data suggest that opti-

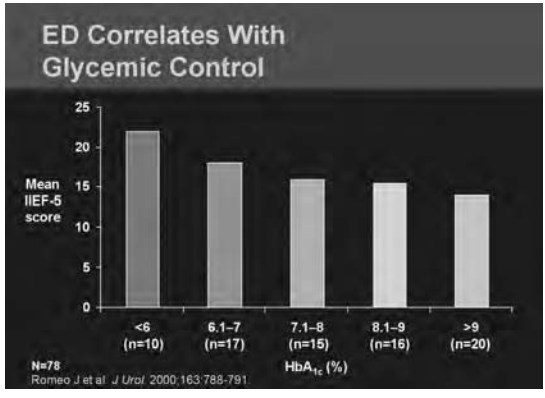


Fig. 7. Severity of sexual dysfunction correlates with degree of glucose impairment. Studies of sexual function scores among persons with various degrees of glucose perturbation have shown that worse deviation from normal glucose levels are associated with poorer sexual function. To date, it is unknown whether restoration of euglycemia will improve sexual function in these individuals. IIEF, International Index of Erectile Function. Adapted from ref. *21*.

mized endothelial function, through optimized disease management (diabetes, hypertension, and so forth), results in improved sexual function in men with ED *(20,21)*.

Diabetes Mellitus and ED

The estimated ranges of moderate to severe ED in the diabetic male are 25 to 70% *(22,23)*. Diabetes is a documented correlate of ED in the MMAS and is reported to account for as much as 40% of organic ED in this population. The etiological mechanisms of ED in the diabetic male include vasculopathy (macrovascular disease, as well as endothelial dysfunction) and autonomic dysfunction. Diabetic individuals also appear to experience perturbations in the nitric oxide secondary messenger *(23)*. Although glycemic control does correlate with severity of ED (Fig. 7) *(24)*, it remains to be demonstrated whether glucose control will improve suboptimal erectile function.

ED and Depression

Depression often is characterized by decreased quality of life, altered relationship dynamics, and increased sympathetic tone (Fig. 8).

The pharmacotherapy of depression is associated with ED, especially in regard to selective serotonin reuptake inhibitors, although other agents can also produce sexual dysfunction. Specifically, phenothiazines may produce ED, most prominently by elevating levels of prolactin. Fortunately,

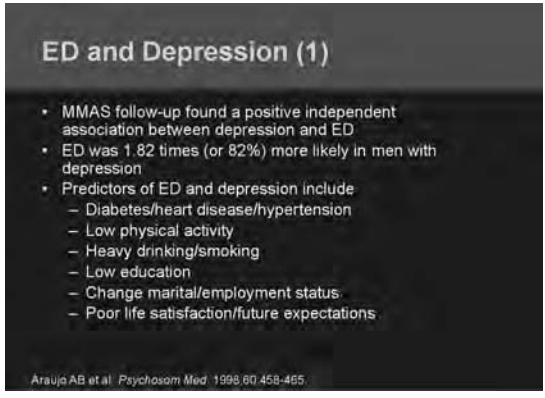


Fig. 8. Depression and erectile dysfunction (ED) are often comorbid. In addition to the recognition that depression causes ED, ED is also a cause of depression. Fortunately, the literature provides support for the beneficial impact of successful ED treatment on depression. ED, erectile dysfunction; MMAS, Massachusetts Male Aging Study.

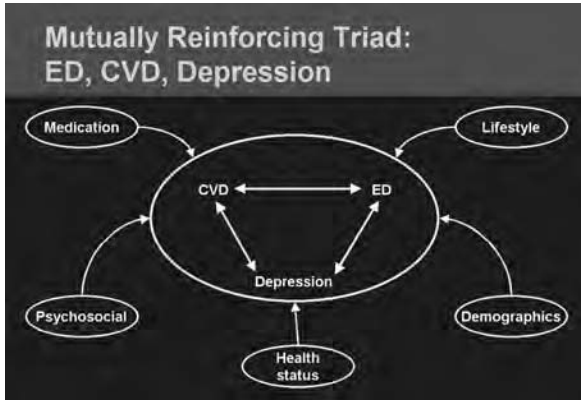


Fig. 9. The mutually reinforcing triad. CVD, cardiovascular disease; ED, erectile dysfunction. Adapted from ref. *25*.

reduction in prolactin levels with use of agents, such as bromocriptine, or alteration of the therapeutic regimen to another agent, is usually successful. ED and depression have a reciprocal relationship: ED alone may be a cause of depression, and depression may result in ED.

Of great interest is the relationship between cardiovascular disease, ED, and depression. As noted, these variables are a mutually reinforcing triad (Fig. 9) *(25)*.

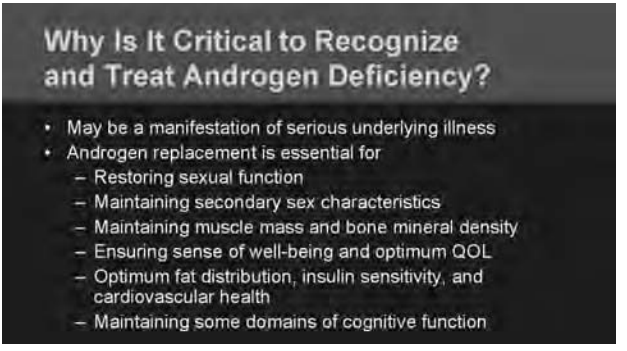


Fig. 10. Androgen deficiency. Although androgen deficiency is an uncommon cause of erectile dysfunction (ED) (because it is fully correctable), many experts recommend routine screening for testosterone in men reporting ED. ED, erectile dysfunction. QOL, quality-of-life. Adapted from refs. *29,31*.

Neurological Disease and ED

ED may also be associated with other neurological diseases, including multiple sclerosis, Parkinson's disease, and peripheral neuropathies. Patients with upper motor neuron spinal cord injuries appear to respond well to PDE5 inhibitors. PDE5 unresponsiveness may be indicative of lower motor neuron lesions. Neurological risk factors for ED include diabetes, cerebrovascular accident, lumbar disk disease, multiple sclerosis, pelvic surgery, pelvic radiation therapy, and peripheral neuropathy *(26)*.

Endocrine ED and Hypogonadism

Overall, it is estimated that only 5% of men with ED have a subnormal testosterone level as the cause of ED *(27)*. The signs and symptoms of a low testosterone level may include loss of libido, ED, depression, lethargy, osteoporosis, loss of muscle mass and strength, and possible regression of secondary sexual characteristics, including pubic hair and testicular size (Fig. 10).

Low serum testosterone levels are noted in up to 36% of patients with ED. The correction of sexual dysfunction in this population with testosterone replacement is surprisingly low, however (approx 35%) *(27)*.

Changes in behavior may include an inability to concentrate, diminished interest in activities, sleep disturbance, and depressed mood. It is obvious that many of these symptoms can be overlooked or misattributed to other agendas in midlife. Because clinically relevant low testosterone levels are most commonly reflected by low libido, there has been some support in the literature for restricting testosterone measurement to those men who

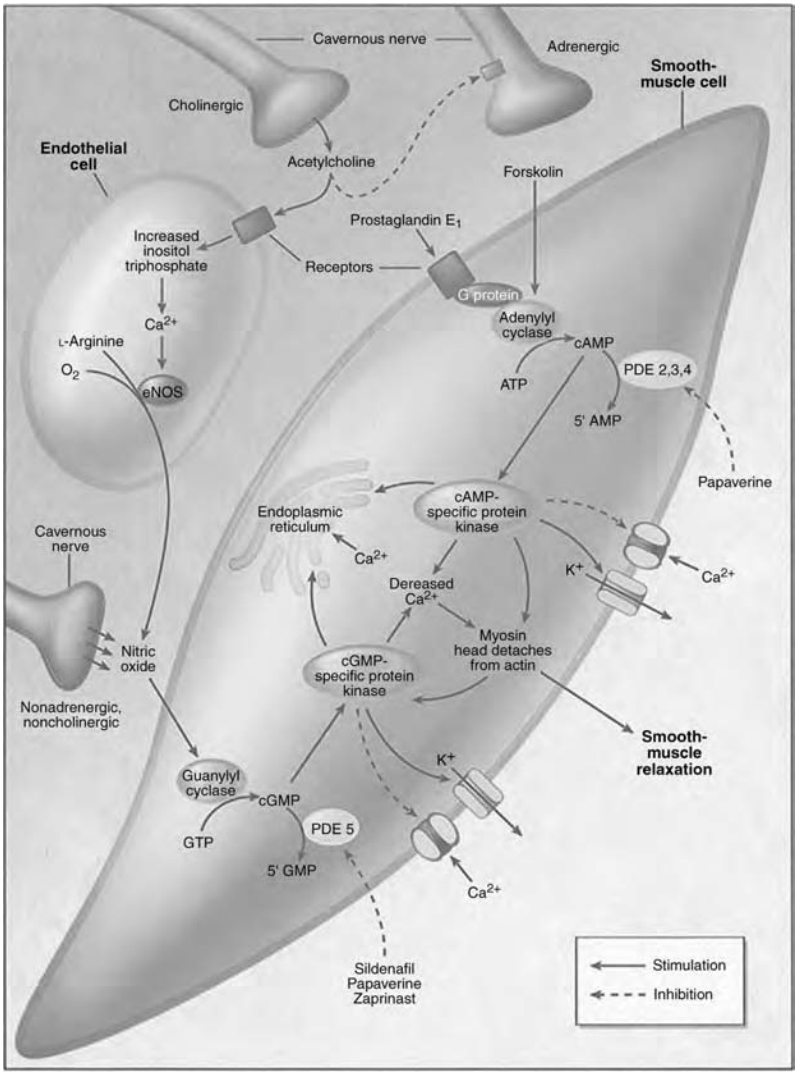


Fig. 5. The molecular mechanism of penile smooth muscle relaxation. The intracellular second messengers mediating smooth muscle relaxation, cyclic adenosine monophosphate and cyclic guanine monophosphate (cGMP), activate their specific kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant fall in intracellular calcium level leads to smooth muscle relaxation. Sildenafil inhibits the action of phosphodiesterase (PDE) type 5 and thus increases the intracellular concentration of cGMP. Papaverine is a nonspecific PDE inhibitor. ATP, adenosine triphosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate. (From ref. *72*.)

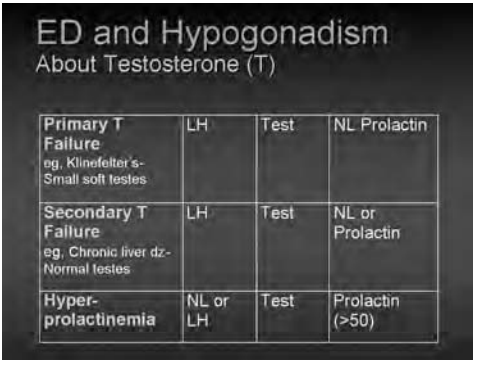


Fig. 12. Confirmatory laboratory in hypogonadism. Once hypogonadism is confirmed, evaluation of luteinizing hormone and prolactin can confirm primary vs secondary hypogonadism. LH, luteinizing hormone; NL, normal; dz, disease.

a low-normal level of testosterone, it is possible that he previously functioned with a mid- or high-normal level; hence, his current low-normal is insufficient for him) *(29)*. A number of systemic illnesses (e.g., cirrhosis, chronic renal failure, sickle cell anemia, thalassemia, hemochromatosis, human immunodeficiency virus infection, amyloidosis, chronic obstructive pulmonary disease, rheumatoid arthritis, chronic infections, and inflammatory or debilitating conditions) may suppress levels. Hypogonadism may be central (hypothalamic or pituitary) or testicular in origin. Therefore, after a low testosterone level has been determined, serum LH and prolactin levels should be measured, especially in men younger than 50 yr of age (Fig. 12) *(30)*.

Those men with a subnormal LH level or an elevated prolactin level, or both, should be further evaluated with magnetic resonance imaging to visualize both the hypothalamus and the pituitary gland.

Treatment options are noted in Fig. 13 *(31,32)*.

The absolute contraindications to TRT include documented prostate cancer, existing or previous history of breast cancer, and hematocrit greater than 55%. Relative contraindications include hematocrit greater than 52%, untreated sleep apnea, severe obstructive symptoms of benign prostatic hypertrophy, and advanced congestive heart failure (Fig. 14).

Data regarding the long-term risks and benefits of TRT are limited.

Before the implementation of TRT, baseline measurements of hematocrit and prostate-specific antigen (PSA) and a digital rectal examination (DRE) of the prostate are performed. Efficacy and adverse effects are assessed at 6 to 12 wk after initiation of TRT, at 6 mo (Fig. 15), and then annually *(33)*.

Fig. 13. Commercially available testosterone (T) preparations. All testosterone formulations are efficacious. Therapeutic choice is based on the patient's personal preference, cost, ease of administration, and dosing frequency, and hence, must be individualized. Adapted from refs. *31,32*.

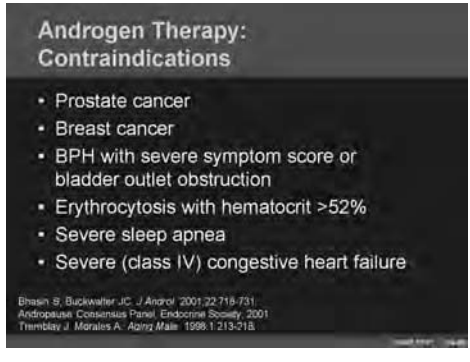


Fig. 14. Contraindications to androgen therapy. BPH, benign prostatic hyperplasia.

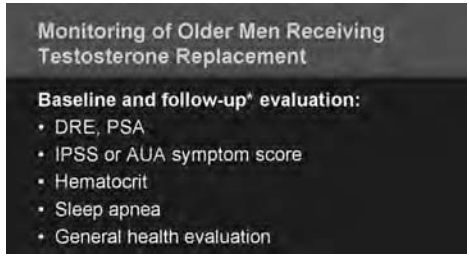


Fig. 15. Monitoring testosterone replacement. AUA, American Urological Association; DRE, digital rectal exam; IPSS, International Prostate Symptoms Score; PSA, prostate-specific antigen. * Three and six months, and annually thereafter.

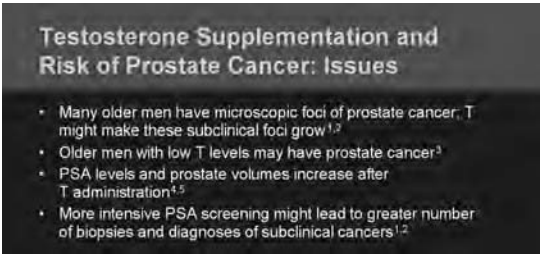


Fig. 16. Prostate risks of testosterone replacement. Because of the trophic effects of testosterone on the prostate, caution is necessary in men with benign prostatic hyperplasia. It remains uncertain whether testosterone replacement alters risk of prostate cancer. T, testosterone; PSA, prostate-specific antigen. Adapted from refs. *29,30,34–36*.

This includes evaluation of the clinical response (which may include the validated Androgen Deficiency in the Aging Male questionnaire); testosterone levels, with a goal of midnormal range; hematocrit; PSA; and DRE at 6 mo *(30)*.

The issues of prostate cancer risk and testosterone repletion are summarized in Fig. 16 *(29,30,34–36)*.

TRT does not cause prostate cancer but may accelerate the growth of occult prostate cancer. Therefore, the management of TRT includes periodic DRE and PSA analysis. A PSA velocity of greater than 0.075 ng/mL per year should arouse suspicion of a neoplastic origin, and appropriate action should be taken (Fig. 17) *(37,38)*.

Whether TRT improves the efficacy of oral PDE5 inhibitors remains unclear, although two studies recently noted improved efficacy of these agents during testosterone repletion in hypogoanadal men.

ED and Sleep Disorders

Forty-eight percent of men with sleep disorders have ED *(39,40)*; correspondingly, 50% of men with decreased nocturnal erectile activity have some form of sleep disorder *(41)*. Treatment of the sleep apnea syndrome may also lead to improvement in erectile function *(52)*.

ED and Vascular Disease

The association between ED and CVD is greater than would be expected on the basis of age and gender alone. In the MMAS, ED was associated with increasing age and several risk factors for atherosclerotic vascular disease: An elevated LDL level or a low HDL level, diabetes mellitus, hypertension, or smoking at entry into the prospective cohort study was

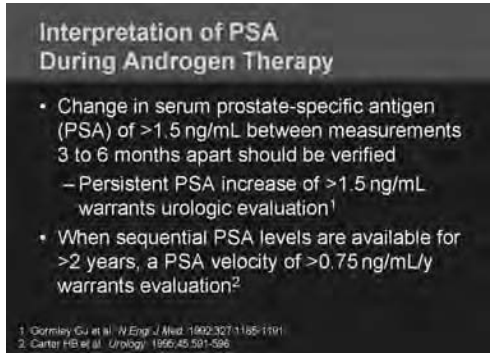


Fig. 17. Testosterone (T) replacement: monitoring prostate-specific antigen (PSA). Because T replacement may enhance prostate growth, monitoring of PSA levels is appropriate, with referral for persistent increases or velocity enhancement greater than 0.75 ng/mL/yr. PSA, prostate-specific antigen; T, testosterone.

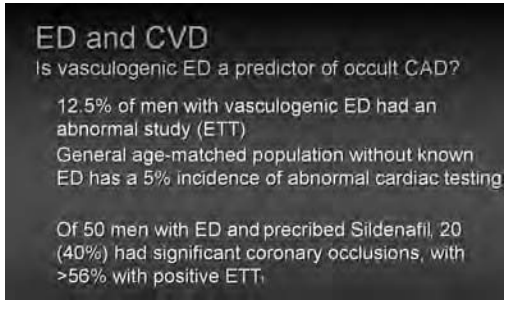


Fig. 18. Erectile dysfunction (ED) may signal vasculopathy. Studies of men with ED corroborate the vasculopathic nature of the disorder; a disproportionate number of men with ED harbor other vasculopathies. CAD, coronary artery disease; CVD, cardiovascular disease; ED, erectile dysfunction; ETT, exercise tolerance testing. Adapted from ref. *52*.

associated with a nearly fourfold increase in the risk of developing ED (for any single factor present) with a greater likelihood of developing ED if multiple risk factors were present. In essence, the risk factors for ED are the same as those for CAD *(7,8,15)*.

Several studies have examined whether the presence of vasculogenic ED can serve as a predictor of asymptomatic ischemic heart disease. Clearly, the reverse assumption is true—the greater the extent of heart disease, the greater is the likelihood of ED (Fig. 18).

Dhabuwala et al. noted that 42% of their male patients who had had a myocardial infarction reported ED *(43)*. Morley and others observed that ED is present in two-thirds of men at the time of myocardial infarction. This incidence of penile vascular impairment has been repeatedly demonstrated in patients with coronary artery disease and other vascular risk factors *(44)*. Shabsigh et al. have consistently noted that the rate of ED was found to be higher in patients with one vascular risk factor than in those with none, and that the severity of ED (as noted by the proportion of abnormal vascular findings) significantly increased as the number of risk factors increased *(45)*. More recently, Greenstein et al. reported the outcome of a study, the first of its kind, demonstrating that self-reported erectile function correlated with the number of afflicted coronary vessels in 40 men undergoing coronary angiography owing to ischemic symptoms *(46)*. Men with multivessel CAD were more likely to experience ED than were men with single-vessel disease. Solomon and others also assessed the prevalence and severity of ED in a cohort of men who underwent coronary angiography *(47)*. In this cross-sectional study of 132 men with angio-graphic coronary disease, 65% showed objective evidence of ED on the International Index of Erectile Function. The erectile function score correlated with the cardiovascular risk factors and with the atherosclerotic disease burden, as assessed by the Gensini score, even after allowance for drug therapies associated with ED. Clearly demonstrated is a correlation between the degree of ischemic heart disease and the degree of ED.

Thus, CVD is a predictor of ED. More than 60% of men with a history of myocardial infarction have ED, and more than 66% of men have ED after coronary artery bypass grafting *(8)*. In selected cases, i.e., young men with very localized vascular diseases, pelvic vascular surgery and angioplasty have been documented to improve erectile function.

ED is a predictor of occult dyslipidemias. Men presenting with ED have a significant risk of dyslipidemia. Billups found that of 57 men 23 to 64 yr of age who had undergone penile Doppler ultrasonography and lipid screening, 60% had abnormal total cholesterol levels, including 89% with abnormal LDL level (Fig. 19) *(48)*.

Together, these data beg the question, "Is vasculogenic ED a predictor of occult CAD (not known to the patient or the physician)?" Is ED the tip of the iceberg in regard to systemic vascular disorders *(49)*? The incidence of occult CAD increases with age, and studies of CAD by nuclear imaging have suggested that by the age of 70, more than 33% of CAD is occult *(50)*. In this context, the physician treating ED will confront CVD as a comorbidity in a significant number of patients.

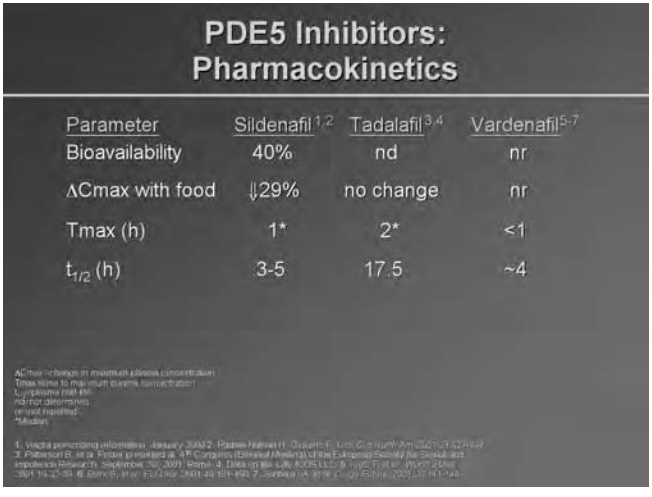


Fig. 19. Phosphodiesterase type 5(PDE5) comparisons. Vardenafil andsildenafil are very similar agents. The very long half-life of tadalafil allows for the long "window of opportunity" (36 h) for restoration of sexual function. PDE5, phosphodiesterase type 5.

Of 50 men with ED who were prescribed sildenafil, 20 (40%) had significant coronary occlusions, with more than 56% of these men having a positive exercise tolerance test *(51)*.

Kim, Paick, and others also examined potential predictors of asymptomatic ischemic heart disease in patients with vasculogenic ED and have replicated these findings *(52)*. In almost 100 patients who were given pharmacological erection tests and then classified into two groups, responders and nonresponders, 50% of the nonresponders had two or more cardiovascular risk factors. Of these, approx 16% experienced ischemic changes on the exercise tolerance test (Fig. 20).

Should all asymptomatic men who present with ED undergo noninvasive cardiac testing? Clearly, we cannot yet make that argument. These men should undergo thorough cardiovascular risk assessment, however, including evaluation for hyperlipidemia, hypertension, diabetes mellitus, and peripheral vascular disease. Further testing can thus be individualized based on the number of cardiovascular risk factors and cardiovascular symptoms.

Finally, regarding the issue of a potential tachyphylaxis effect of long-term sildenafil use, it is thought that the majority of men who initially

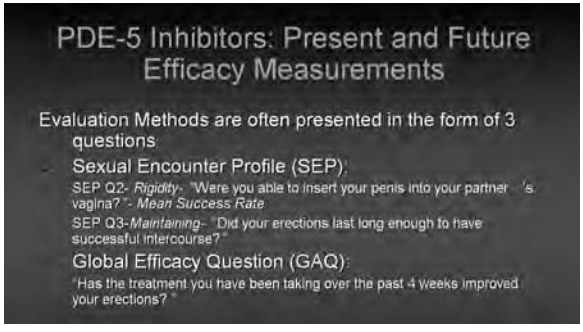


Fig. 20. Evaluating phosphodiesterase type 5 efficacy. When comparing pharmacotherapies, it is important to understand which metric is being utilized. The most stringent criterion is the Sexual Encounter Profile question 3: were you able to complete successful intercourse?

respond well to sildenafil but on follow-up report a decrease in erectile function have worsening vascular disease or other increasing burden of endothelial toxicity (e.g., worsening diabetes, worsening hyperlipidemia). Many of these same men who report decreased efficacy also have poorly controlled lifestyle issues or ED risk factors, such as smoking, obesity, or sedentary behavior *(53)*.

In summary, it is the authors' belief that clinicians should view ED as one of the earliest and most useful clinical indicators of potentially disproportionate cardiovascular risk burden available.

TREATMENT OF ED: THE NEW ORAL AGENTS

The availability of sildenafil citrate (Viagra®), a PDE5 inhibitor and the first effective oral agent for ED, has dramatically increased the number of men seeking treatment and shifted much of the management for ED to PCCs. At present, two other agents have received Food and Drug Administration approval in the United States: vardenafil (Levitra®) and tadalafil (Cialis®). Despite the common belief that PDE inhibition is a new topic, clinicians have been manipulating PDE for decades: Caffeine also is a weak PDE5 inhibitor. Anecdotal reports even suggest that caffeine improves erectile function *(54)*. Aminophylline is a nonspecific PDE inhibitor, and cilosatzol (Pletal) is a PDE3 inhibitor. On the therapeutic horizon are PDE4 inhibitors with demonstrated usefulness in asthma.

PDE5 inhibitors inhibit PDE5 at low concentrations, thereby preventing it from destroying cyclic guanine monophosphate (cGMP), the ultimate mediator of erection. cGMP is released after guanylate cyclase,

induced by nitric oxide (NO), converts guanosine triphosphate (GTP) to cGMP. Because men with vasculopathy of any origin are not efficient in the production of NO, they are less capable of producing cGMP and hence less able to achieve erection. PDE5 inhibitors do not stimulate erection; rather, by blocking degradation of cGMP, they enhance and prolong the activity of whatever cGMP the patient can produce. Because PDE5 inhibitors require sufficient sexual stimulation to release NO, it is not surprising that there is a learning effect in some patients who are reinitiating sexual activity. Although about two-thirds of men respond within the first two doses, the rest only begin to respond on subsequent dosing, reaching a maximum threshold of response after six to eight doses. (These data are based on sildenafil use; although we have no tadalafil or vardenafil data for comparison, it is anticipated that similar responsiveness would be seen) *(55)*.

Vardenafil (Levitra) is a PDE5 inhibitor with a pharmacokinetic profile and molecular configuration nearly identical to that of sildenafil. The other approved PDE5 inhibitor is tadalafil (Cialis), which has a unique chemical structure and pharmacokinetic profile that differs from both sildenafil and vardenafil.The release of these new PDE5 inhibitors greatly expands the PCC's choices for first-line ED therapy and, in addition, raises important questions. First, how do we choose between these three drugs? Second, how do the new drugs differ from sildenafil, the established benchmark in the past 5 yr of oral ED treatment?

More than 11,000 patient-years of experience with sildenafil exists, as well as a tremendous amount of reassuring safety and efficacy data. Although response rates to sildenafil are high, depending on the underlying cause of ED, up to 20 to 40% of patients may fail to respond to PDE5 inhibition *(56)*. Twelve percent of men may discontinue the drug owing to lack of efficacy within 2 yr, yet it remains uncertain whether this is caused by an actual loss of efficacy, inadequate follow-up, or a worsening underlying comorbid disease state. In controlled clinical studies, discontinuation rates because of insufficient clinical response over 2 to 3 yr are reported to be only 2.1% *(57)*. Only 1 to 3% of men discontinue sildenafil because of side effects *(58)*. Clearly, current pharmacological treatment of ED can be improved on and individualized with regard to efficacy, pharmacokinetics, and side effects. A significant amount of attention must be given to the overall management of the ED patient, however, to allow such therapies to deliver optimal outcomes.

To understand these new oral agents in the absence of controlled head-to-head trials, it is important to examine some of their distinguishing features, including selectivity, onset and duration of action, safety, and efficacy in disease states commonly seen by the primary practitioner.

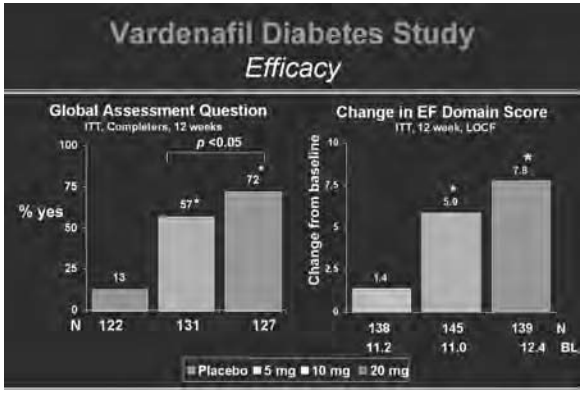


Fig. 21. Diabetes and erectile dysfunction. Although patients with diabetes do not have the same degree of responsivity to phosphodiesterase type 5 inhibitors as other populations, medication is still highly effective. EF, erectile function; ITT, intent-to-treat; LOCF, last observation carried forward. *$p < 0.0001$ vs placebo. Adapted from ref. *71*.

Selectivity and Potency

Selectivity is an important issue because there are no pure PDE5 inhibitors. In addition to inhibiting PDE5, both sildenafil and vardenafil produce modest receptor crosstalk; within the therapeutic range, they can also produce effects of PDE6 inhibition (i.e., PDE6 inhibition affects the cones of the retina, thereby resulting in the blue vision experienced by some users of sildenafil and vardenafil) *(58),* whereas these effects are absent with tadalafil. In contrast, only tadalafil has definite PDE11 inhibition at therapeutic doses, although this significance is not yet clear. PDE11 is present in the pituitary, heart, testes, and corpus cavernosum. Inhibition does not appear to lower sperm counts.

The potency of enzyme inhibitors is often documented in terms of 50% inhibitory concentration (IC_{50}), which is defined as the concentration of the compound required to produce 50% inhibition of the enzyme.

The lower the IC_{50}, the higher the biochemical potency of the compound. The IC_{50} of vardenafil is 0.7 n*M*, vs 6.7 n*M* for sildenafil and 9.0 n*M* for tadalafil *(59)*. This implies that it takes 1/90 of the same amount of vardenafil to achieve the same PDE5 inhibition as sildenafil. How this translates to clinical efficacy remains unclear at this time. Biochemical potency should not be confused with clinical potency, because many other factors, such as drug absorption, distribution, and elimination, also contribute to potency (Fig. 21) *(60)*.

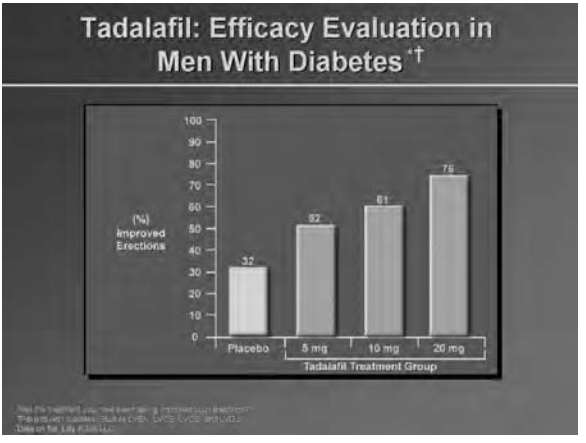


Fig. 22. Diabetes and erectile dysfunction. Although patients with diabetes do not have the same degree of responsivity to phosphodiesterase type 5 inhibitors as other populations, medication is still highly effective. *Has the treatment you been taking imnproved your erection? †Patients with diabetes. Studies LVBN, LVCE, LVCO, and LVDJ. Adapted from ref. *63*.

Onset of Action

None of these agents works immediately or without sexual stimulation. Most studies suggest that these agents have an onset of action of 30 to 60 min (Fig. 22), although there have been reports that some individuals become responsive with any of the three available agents in less than 20 min.

For the clinician, however, it is more germane to know when the majority of potential users will respond. In general, the onset of action varies from individual to individual and may be lengthened (for both sildenafil and vardenafil) if taken with food, high-fat food in particular. Tadalafil appears to act independently of food absorption *(61–65)*.

Clinicians can be confident in advising patients that by 1 h after ingestion on an empty stomach, all currently available PDE5 inhibitors are efficacious.

Duration

The reported half-lives ($t_{1/2}$) of sildenafil (3.5 h) and vardenafil (4.5 h) generally provide for a window of opportunity for initiating sexual intercourse of approx 4 to 5 h. The $t_{1/2}$ of tadalafil is between 17 and 21 h (*see* Fig. 22).

Indeed, trials examining drug efficacy show that intercourse response rates were undiminished 36 h after administration compared with the first few hours after administration. In theory, men could use this long-

acting agent on an every-other-day basis and initiate intercourse at any time they wish without having to interrupt the spontaneity of sexual energy by preparing for sex, as they would with either of the shorter-acting agents.

Although tadalafil may give some men greater confidence about their erectile function without regard to time and may allow for greater spontaneity, the implications of prolonged PDE5 inhibition remain uncertain. The longer the duration of PDE5 inhibition, the longer that nitroglycerin is proscribed. On the other hand, clinicians should recognize that nitroglycerin provides symptomatic relief only and is not a disease-modifying agent (i.e., since the thrombolytic era, data have not shown a survival benefit for recipients of nitroglycerin). Persons who suffer chest pain acutely and require medical intervention can be given traditional analgesics (e.g., morphine) for pain relief.

The adverse effect profile of tadalafil appears comparable to that of the other PDE5 inhibitors. Current thinking suggests that symptoms may be more directly related to maximum concentration than to steady state, explaining the rapid disappearance of adverse effects, in a parallel fashion to that seen with sildenafil and vardenafil.

Safety and Adverse Effects

Safety and adverse effects are clearly important concerns given that many of the men treated for ED have risk factors identical to those for CVD. A careful assessment of cardiovascular status before prescribing treatment for ED or advising the resumption of sexual activity is recommended *(66)*. To date, there is no evidence that any of the PDE5 inhibitors have direct adverse cardiovascular effects. In fact, the reverse may be true, because recent studies suggest that sildenafil may delay exercise-induced ischemia and angina *(67)*.

Population-based studies indicate that the rate of myocardial infarction among those taking PDE5 inhibitors is less than that seen in age-matched populations who do not take these agents. Perhaps this should not be surprising when one considers that the original rationale in the development of PDE5 inhibitors was the belief that they might enhance coronary circulation and hence be useful as antianginal agents.

Overall, PDE5 inhibitors are well-tolerated agents that have similar mild-to-moderate adverse affects, which seem to diminish with use. The most common adverse events are headache, nasal congestion, facial flushing, and dyspepsia. There appears to be a greater incidence of myalgia and low back pain with tadalafil, although the cause of this myalgia remains unclear. The only absolute contraindication to all of the PDE5 inhibitors is concomitant use of organic nitrates (i.e., nitroglycerin and related

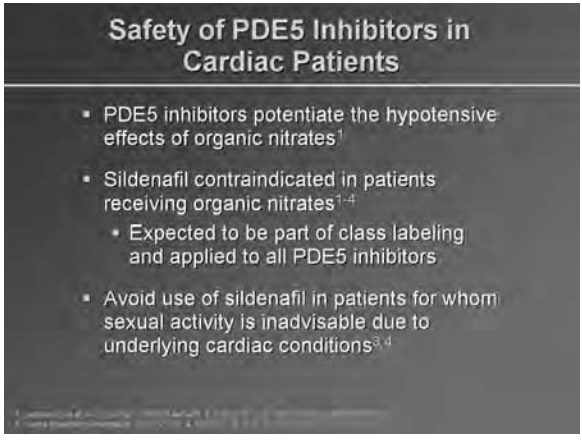


Fig. 23. Phosphodiesterase type 5 (PDE5) and safety. The cardiovascular safety profile of PDE5 inhibition is excellent. Sexual activity, like any other vigorous activity, may induce myocardial ischemia in men with compromised vascular supply. There is no evidence to suggest that PDE5 inhibitors have a deleterious impact on this risk. PDE5, phosphodiesterase type 5.

chemicals). All PDE5 inhibitors potentiate nitrate-induced vasodilation, resulting in potentially disastrous hypotension.

Because concomitant α-blockers–PDE5 inhibitors can produce hypotension, clinicians need to be aware of contraindications. With vardenafil, there is an absolute contraindication to the concomitant use of any α-blockers (i.e., doxazosin, terazosin, tamsulosin, alfuzosin). The use of tadalafil contraindicates the administration of α-blockers other than 0.4 mg of tamsulosin; and caution should be exercised in the coadministration of sildenafil doses of more than 25 mg within 4 h of an α-blocker.

Efficacy

In one placebo-controlled study, a baseline 51% placebo penetration rate (Sexual Encounter Profile [SEP] question (Q) 2: "Were you able to insert your penis into your partner's vagina?") improved to 76 and 81% with 10 and 20 mg of vardenafil, respectively, at 12 wk, without change at 26 wk *(68)*. In the same study, the maintenance rate (SEP Q3: "Did your erections last long enough to have successful intercourse?") improved from 30% with placebo to 65% in both the 10- and 20-mg groups at 12 wk (Figs. 23 and 24).

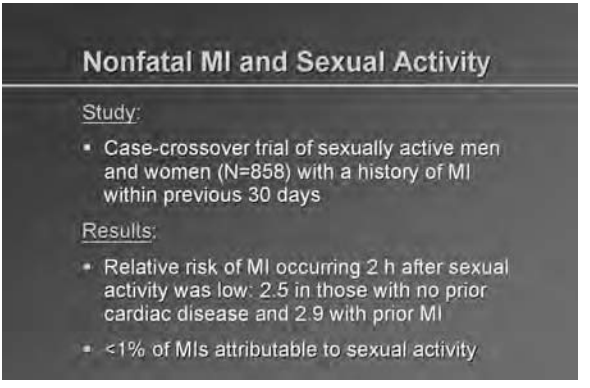


Fig. 24. Sexual activity and cardiovascular risk. MI, myocardial infarction. Adapted from ref. *78*.

Finally, a phase III multicenter trial evaluated the efficacy of vardenafil at doses of 5, 10, and 20 mg vs placebo in 508 patients with hypertension, benign prostatic hypertrophy, and diabetes *(69)*. The response to the general assessment question (GAQ), "Has the treatment you have been taking over the past 4 wk improved your erections?" was assessed. After 12 wk of treatment, 65% of patients in the 5-mg treatment group responded positively, as did 72% in the 10-mg group and 81% in the 20-mg group, in contrast to placebo response rates of 39%.

The GAQ data gleaned from the Vardenafil Prostatectomy Study rose from 12.5% with placebo to 65.2% with 20 mg of vardenafil at 12 wk, and in the Vardenafil Diabetes Study rose from 13% with placebo to 72% at 20 mg for 12 wk (Fig. 25) *(70,71)*.

For tadalafil, Padma-Nathan and others found the following in response to the GAQ at 12 wk, with a 35% response to placebo: 42% improvement with 2.5 mg, 50% improvement with 5 mg, 67% improvement with 10 mg, and 81% improvement with 20 mg *(72)*. The efficacy rates are also comparable with those seen with vardenafil in response to the GAQ in the diabetic population: 32% with placebo, 52% with 5 mg, 61% with 10 mg, and 76% with 20 mg (Fig. 26).

The response rate to SEP Q3 (successful intercourse) was also high with tadalafil. This percentage of successful intercourse attempts ranged from 32% with placebo to 61% with 10 mg and 75% with 20 mg.

In contrast, the efficacy of 50 mg of sildenafil at 12 wk is 70%, vs 16% for placebo *(73)*. When comparing the efficacy data of these PDE5 inhibi-

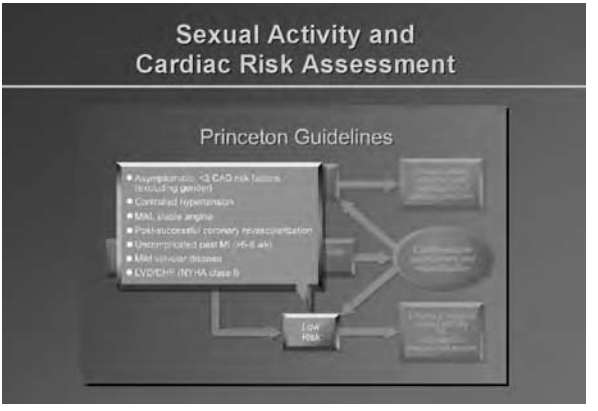


Fig. 25. Sexual activity and cardiovascular risk. For clinicians who wish to risk-stratify patients prior to sexual activity, guidelines, such as the Princeton Guidelines, may be useful. The United States Preventative Services Task Force has indicated that there is no evidence that exercise testing in asymptomatic men improves outcomes. CAD, coronary artery disease; CHF, congestive heart failure; LVD, left ventricular dysfunction; MI, myocardial infarction; NYHA, New York Heart Association. Adapted from ref. *66*.

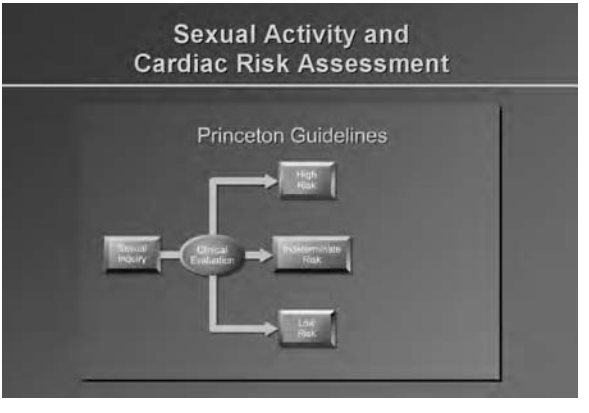


Fig. 26. Risk stratification: Princeton guidelines. Adapted from ref. *66*.

tors, one must use caution, given that there are no head-to-head comparative trials and that different patient populations may affect treatment outcomes.

The most common adverse affects again appear to be class related for the PDE5 inhibitors: headache, flushing, rhinitis, and dyspepsia.

CVD and PDE5 Inhibitors

In placebo-controlled and open-label phase II/III clinical trials including men with ischemic heart disease, the following points can be made:

- There was no evidence of an increase in myocardial infarction or other serious cardiovascular events in patients treated with sildenafil, compared with those using placebo *(74)*. Furthermore, the number of spontaneous reports of death among sildenafil users falls within the mortality rates for heart disease described in epidemiological studies.
- Oral sildenafil, when given to those men undergoing coronary angiography, produced only a small decrease in systemic arterial pressure (<10%) and had no effect on pulmonary capillary wedge pressures, heart rate, or cardiac output *(67)*. It was not found to induce a steal syndrome by diverting blood flow from occluded to nonoccluded vessels.
- Sildenafil may dilate epicardial coronary arteries, improve endothelial cell function, and inhibit platelet activation in patients with established coronary disease *(75)*.
- In a retrospective analysis of 357 men reporting a history of stable ischemic heart disease, 70% reported improved erections (SEP Q2) while taking sildenafil, vs 20% with placebo *(76)*.
- The effects of sildenafil in men with severe CAD have been evaluated using hemodynamic monitoring. The medication exerted no effect on heart rate, cardiac output, or other central cardiac parameters. Coronary blood flow reserve increased by 13% in both stenosed and nonstenosed arteries after treatment with PDE5 inhibitors *(67)*.
- In those men with CAD assessed by stress echocardiography after administration of sildenafil, an average reduction of 7 mmHg in the systolic blood pressure was noted, with no change in exercise capacity or hemodynamic response to exercise *(77)*.

The implications of these data are as follows(Fig. 27):

- No significant additional risk exists with the use of PDE5 therapy in men with stable cardiac disease.
- Modest reductions in blood pressure occur with PDE5 therapy, with no clinically relevant orthostatic effects.
- The coadministration of organic nitrates and PDE5 inhibitors produces a synergistic effect in lowering blood pressure to a potentially serious degree.
- A slight risk of developing ischemia or infarction is associated with sexual activity, as noted in the Myocardial Infarction Onset Study. This study concluded that the relative risk of a myocardial infarction in the 2 h after sexual activity was 2.5 (Fig. 28), a risk less than that associated with anger and unaccustomed physical exercise *(78)*.

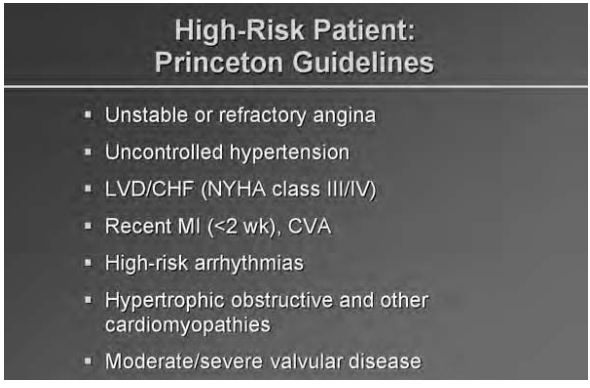


Fig. 27. High-risk patients: Princeton Guidelines. CHF, congestive heart failure; CVA, cerebrovascular accident; LVD, left ventricular dysfunction; NYHA, New York Heart Association.Adapted from ref. *66*.

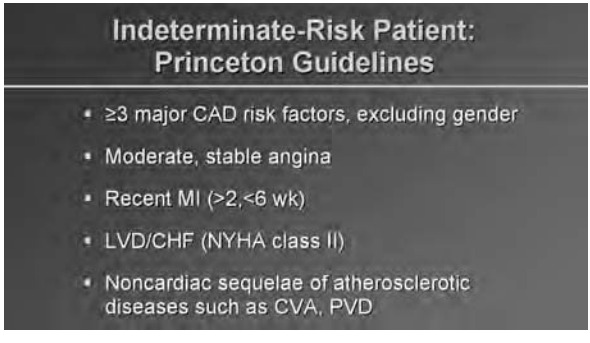


Fig. 28. Intermediate-risk patients. Definition of intermediate-risk patients according to the Princeton Guidelines. CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; LVD, left ventricular dysfunction; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease. Adapted from ref. *66*.

In summary, these drugs are highly efficacious and safe in the cardiac patient, as determined through extensive study and experience with sildenafil. There is no information to suggest that sexual activity differs from other activities that require similar expenditure of energy as far as cardiovascular risk is concerned *(78)*. Sexual activity is generally recognized to require 3 to 5 metabolic equivalents of physical activity.

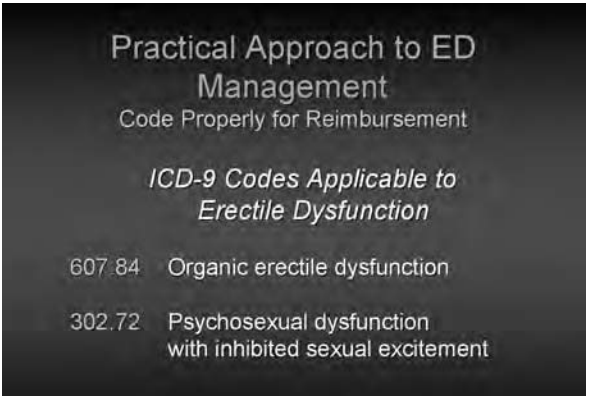


Fig. 29. Codes for sexual dysfunction. ED, erectile dysfunction; ICD-9, International Classification of Diseases of the World Health Organization, 9th Edition.

A man who can walk a mile in 15 min (i.e., 4 mph) has essentially performed the equivalent of a stress test to four metabolic equivalents and can thus successfully engage in intercourse. Although special risk stratification guidelines for persons with ED have been published (Figs. 29) *(62)*, there is no evidence that men who are asymptomatic for CAD derive any benefit from stress testing, except for the identification of an accurate target exercise heart rate.

In essence, if the clinician believes that the patient will require exercise testing before beginning any exercise, then the patient will similarly require such exercise testing before engaging in sexual activity.

CONCLUSION

There are compelling reasons why primary care practitioners should be interested in diagnosing and treating ED. They are often the first to address the topic with their patients. ED is a sign and symptom of common comorbid disease states in men. Patients are often grateful after discussions about sexual matters and show that gratitude with increased enthusiasm for better health and increased confidence and loyalty to the physician.

In reality, there is only a minimal increase in the time required to manage these issues if they are raised in the settings described previously. Patients are more satisfied with their appointments and attend more regularly. Management of ED is reimbursable, by coding for organic ED.

Finally, treatment of this condition blends the art of medicine with the physiology of a domain very important to most individuals—sexual function and emotional intimacy—with evidence-based science.

It is our experience that by raising issues of sexual health, we can establish improved rapport and obtain an additional venue to achieve global improvements in the health of male patients. Such efforts translate into improved satisfaction among our male patients and their partners.

REFERENCES

1. Pfeiffer E, Verwoerdt A, Wang HS. (1968) Sexual behavior in aged men and women. I. Observations on 254 community volunteers. Arch Gen Psychiatry 19: 753–758.
2. Janus SS, Janus C. The Janus Report on Sexual Behavior. Hoboken, NJ: John Wiley and Sons.
3. Keil JE, et al. (1992) Self-reported sexual functioning in elderly blacks and whites: the Charleston Heart Study experience. J Aging 4:12.
4. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. (2000) Epidemiology of erectile dysfunction: results of the "Cologne Male Survey." Int J Impot Res 12:305–311.
5. Finger WW, Lund M, Slagle MA. (1997) Medications that may contribute to sexual disorders. A guide to assessment and treatment in family practice. J Fam Pract 44:33–43.
6. Brock GB, Lue TF. (1993) Drug-induced male sexual dysfunction. An update. Drug Saf 8:414–426.
7. NIH Consensus Conference. (1993) Impotence. NIH Consensus Development Panel on Impotence. JAMA 270:83–90.
8. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. (1994) Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 151:54–61.
9. Laumann EO, Paik A, Rosen RC. (1999) Sexual dysfunction in the United States: prevalence and predictors. JAMA 281:537–544.
10. Solomon H, Man JW, Jackson G. (2003) Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. Heart 89:251–253.
11. Phillips NA. (2000) Female sexual dysfunction: evaluation and treatment. Am Fam Physician 62:127–136.
12. Marwick C. (1999) Survey says patients expect little physician help on sex. JAMA 281:2173–2174.
13. Burnett AL. (1998) Erectile dysfunction: a practical approach for primary care. Geriatrics 53:34–35.
14. Davis-Joseph B, Tiefer L, Melman A. (1995) Accuracy of the initial history and physical examination to establish the etiology of erectile dysfunction. Urology 45:498–502.
15. DeWire DM. (1996) Evaluation and treatment of erectile dysfunction. Am Fam Physician 53:2101–2108.
16. The Process of Care Consensus Panel. (1999) The process of care model for evaluation and treatment of erectile dysfunction. Int J Impot Res 11:59–74.

17. Miller TA. (2000) Diagnostic evaluation of erectile dysfunction. Am Fam Physician 61:95–104.
18. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49:822–830.
19. Guay AT, Velasquez E, Perez JB. (1999) Characterization of patients in a medical endocrine-based center for male sexual dysfunction. Endocrine Pract 5:314–321.
20. Guay AT. (1998) Treatment of erectile dysfunction in men with diabetes. Diab Spectr 11:101–111.
21. Romeo JH, Seftel AD, Madhun ZT, Aron DC. (2000) Sexual function in men with diabetes type 2: association with glycemic control. J Urol 163:788–791.
22. Cummings MH, Alexander WD. (1999) Erectile dysfunction in patients with diabetes. Hosp Med 60:638–644.
23. Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. (2000) Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 56:302–306.
24. The Diabetes Control and Complications Trial Research Group. (1995) The effect of intense diabetes therapy on the development and progression of neuropathy. Ann Intern Med 122:561–568.
25. Goldstein I. (2000) The mutually reinforcing triad of depressive symptoms, cardiovascular disease, and erectile dysfunction. Am J Cardiol 86:41F–45F.
26. Nehra A, Moreland RB. (2001) Neurologic erectile dysfunction. Urol Clin North Am 28:289–308.
27. Matasumoto AM. (2002) Andropause: clinical implications of the decline of serum testosterone levels with aging in men. J Gerant Biol Sci Med Sci 57:76–99.
28. Guay AT, Bansal S, Heatley GJ. (1995) Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. J Clin Endocrinol Metab 80:3546–3552.
29. Bhasin S, Buckwalter JG. (2001) Testosterone supplementation in older men: a rational idea whose time has not yet come. J Androl 22:718–731.
30. The Endocrine Society. Summary from the Second Annual Andropause Consensus Meeting. Available at Website: http://www.endo-society.org/membersonly/summarypdf.pdf. Accessed on November 6, 2002.
31. Morales A, Heaton JP, Carson CC 3rd. (2000) Andropause: a misnomer for a true clinical entity. J Urol 163:705–712.
32. Wang C, Swedloff RS, Iranmanesh A, et al. (2000) Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. J Clin Endocrinol Metab 85:2839–2853.
33. Guay AT, Nankin HR, and Committee. (1998) AACE Clinical Practice Guidelines.
34. Morgentaler A, Bruning CO 3rd, DeWolf WC. (1996) Occult prostate cancer in men with low serum testosterone levels. JAMA 276:1904–1906.
35. Meikle AW, Arver S, Dobs AS, et al. (1997) Prostate size in hypogonadal men treated with a nonscrotal permeation-enhanced testosterone transdermal system. Urology 49:191–196.
36. Behre HM, Bohmeyer J, Nieschlag E. (1994) Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. Clin Endocrinol (Oxf) 40:341–349.

37. Gormley GJ, Stoner E, Bruskewitz RC, et al. (2002) The effect of finasteride in men with benign prostatic hyperplasia. J Urol 167(2 Pt 2):1102–1107; discussion 1108.
38. Carter HB, Pearson JD, Waclawiw Z, et al. (1995) Prostate-specific antigen variability in men without prostate cancer: effect of sampling interval on prostate-specific antigen velocity. Urology 45:591–596.
39. Guilleminault C, Eldridge FL, Tilkian A, Simmons FB, Dement WC. (1977) Sleep apnea syndrome due to upper airway obstruction: a review of 25 cases. Arch Intern Med 137:296–300.
40. Schmidt HS, Wise HA 2nd. (1981) Significance of impaired penile tumescence and associated polysomnographic abnormalities in the impotent patient. J Urol 126:348–352.
41. Hirshkowitz M, Karacan I, Arcasoy MO, Acik G, Narter EM, Williams RL. (1990) Prevalence of sleep apnea in men with erectile dysfunction. Urology 36:232–234.
42. Karacan I, Karatas M. (1995) Erectile dysfunction in sleep apnea and response to CPAP. J Sex Marital Ther. 21:239–247.
43. Dhabuwala CB, Kumar A, Pierce JM. (1986) Myocardial infarction and its influence on male sexual function. Arch Sex Behav 15:499–504.
44. Morley JE, Kaiser FE. (1989) Sexual function with advancing age. Med Clin North Am. 73:1483–1495.
45. Shabsigh R, Fishman IJ, Schum C, Dunn JK. (1991) Cigarette smoking and other vascular risk factors in vasculogenic impotence. Urology 38:227–231.
46. Greenstein A, Chen J, Miller H, Matzkin H, Villa Y, Braf Z. (1997) Does severity of ischemic coronary disease correlate with erectile function? Int J Impot Res 9:123–126.
47. Solomon H, Man JW, Wierzbicki AS, Jackson G. (2003) Relation of erectile dysfunction to angiographic coronary artery disease. Am J Cardiol 91:230–231.
48. Rubanyi GM. (1993) The role of endothelium in cardiovascular homeostasis and diseases. J Cardiovasc Pharmacol 22(Suppl 4):S1–S14.
49. Billups KL, Tsai M. (2000) Fasting lipid values and Doppler ultrasound testing in men with erectile dysfunction and no other medical co-morbidity. In abstracts of the American Urological Association 95th Annual Meeting; April 29–May4, 2000; Altanta, GA. J Urol 163(4 Suppl):S147.
50. Montorsi P, Montorsi F, Schulman CC. (2003) Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? Eur Urol 44:352–354.
51. Muller JE. (2000) Triggering of cardiac events by sexual activity: findings from a case-crossover analysis. Am J Cardiol 86:14F–18F.
52. Pritzker MR. (1999) The penile stress test: a window to a man's heart? 72nd Scientific Sessions of the American Heart Association, November (abstract 104561).
53. Kim SW, Paick J, Park DW, Chae I, Oh B. (2001) Potential predictors of asymptomatic ischemic heart disease in patients with vasculogenic erectile dysfunction. Urology 58:441–445.
54. Billings K. (2001) Letter to the Editor. Re: Long-term efficacy of sildenafil and tachyphylaxis effect. El-Galley R, Rutland H, Talic R, Keane T, Clark H. J Urol 166:927–931
55. Kongkanand A. (2000) Prevalence of erectile dysfunction in Thailand. Thai Erectile Dysfunction Epidemiological Study Group. Int J Androl 23(Suppl 2):77–80.

56. McCullough AR, Siegel RL, Shpilsky AB. (2001) Intercourse success rates with sildenafil citrate. J Urol 165(Suppl):170 (abstract no. 699).
57. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. (1998) Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 338:1397–1404.
58. Padma-Nathan H, Earley I, Maytom M. (2001) Long-term efficacy of Viagra (sildenafil citrate): results after 2–3 years of treatment. Abstract presented at the 4th Congress of the European Society of Sexual and Impotence Research, Rome, Italy, September 30–October 3.
59. Prior J. (2001) Vardenafil: update on clinical experience. Int J Impot Res 13: S1–S5.
60. Bischoff SS, Saenze de Tejada, et al. (2001) Data on file. Bayer AG.
61. Corbin JD. (2002) Pharmacology and mechanisms of action. CME Booklet: treating Erectile Dysfunction: advances in PDE-5 inhibitors. May 9–12.
62. Viagra (2000) Package insert. New York, NY: Pfizer Pharmaceuticals.
63. Lilly ICOS LLC (2001) Data on file. Indianapolis, IN: Lilly ICOS LLC.
64. Klotz T, Sachse R, Heidrich A, et al. (2001) Vardenafil increases penile rigidity and tumescence in erectile dysfunction patients: a RigiScan and pharmacokinetic study. World J Urol 19:32–39.
65. Porst H. (2002) IC351 (tadalafil, Cialis): update on clinical experience. Int J Impot Res 14(Suppl 1):S57–S64.
66. DeBusk R, Drory Y, Goldstein I, et al. (2000) Management of sexual dysfunction in patients with cardiovascular disease: recommendations of The Princeton Consensus Panel. Am J Cardiol 86:175–181.
67. Hermann HC, Chang G, Klugherz BD, Mahoney PD. (2000) Hemodynamic effects of sildenafil in men with severe coronary artery disease. New Engl J Med 342: 1622–1626.
68. Porst H, Rosen R, Padma-Nathan H, et al. (2001) The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 13: 192–199.
69. Hellstrom WJG, Gittleman MC, Shapiro J, et al. (2001) Vardenafil improved erectile dysfunction in men with a broad range of erectile dysfunction etiologies and severities: a phase III trial. Charleston, SC: Sexual Medicine Society of North America, Fall Meeting, December.
70. Brock G Taylor T, Seger M, and the Vardenafil PROSPECT Group. (2002) Efficacy and tolerability of vardenafil in men with erectile dysfunction following radical prostatectomy. In press.
71. Goldstein I, Young JM, Fischer J, et al. (2001) Vardenafil, a new highly selective PDE-5 inhibitor, improves erectile dysfunction in patients with diabetes mellitus. Diabetes 50(Suppl):A56.
72. Padma-Nathan H, McMurray JG, Pullman WE, Whitaker JS, Saoud JB, Ferguson KM, Rosen RC; IC351 On-Demand Dosing Study Group. (2001) On-demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. Int J Impot Res 13:2–9.
73. Pfizer Inc. Data on file. New York, NY: Pfizer Inc.
74. Kloner RA. (2000) Cardiovascular risk and sildenafil. Am J Cardiol 86:57F–61F.

75. Halcox JP, Nour KR, Zalos G, et al. (2002) The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia. Am Coll Cardiol 40:1232–1240.
76. Conti CR, Pepine CJ, Sweeney M. (1999) Efficacy and safety of sildenafil citrate in the treatment of erectile dysfunction in patients with ischemic heart disease. Am J Cardiol. 83:29C–34C.
77. Arruda-Olson AM, Mahoney DW, Nehra A, Leckel M, Pellikka PA. (2002) Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. JAMA 287:719–725.
78. Muller JE, Mittleman A, Maclure M, Sherwood JB, Tofler GH. (1996) Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Investigators. JAMA 275:1405–1409.

8 When to Refer the Patient With Erectile Dysfunction to a Specialist

Ira D. Sharlip, MD

CONTENTS

INTRODUCTION

Since the introduction of effective oral therapy for erectile dysfunction (ED) in 1998, there has been a marked change in diagnostic and treatment patterns among physicians who see patients with ED. Initially after the approval of sildenafil, the great majority of prescriptions were written by urologists. Now, as primary care physicians have become increasingly sophisticated in their knowledge of ED, they, along with their nurse practitioners and physician's assistants, account for about two-thirds of prescriptions written for phosphodiesterase (PDE) inhibitors.

The great majority of men with ED are initially seen, evaluated, and treated by primary care physicians. Although about two-thirds of men with ED are satisfactorily treated by oral PDE inhibitors *(1)*, one-third are not.

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This means that primary care physicians should understand when to refer their patients to specialists in sexual medicine for additional diagnostic tests or treatment, or both.

To understand the indications for referral from primary care physicians to specialists in sexual medicine, it is necessary to have a basic understanding of the causes of ED, the types of ED that can be reversed with cause-specific therapy, the diagnostic modalities available for evaluating ED, and the range of treatment options beyond first-line oral therapy. This chapter discusses these topics and concludes with the indications for referral from primary care physicians to sexual medicine specialists.

CAUSES OF ED

To aid in understanding the mechanisms by which ED may occur, the causes may be categorized into four pathogenic groups. The four organ systems that must be functioning for a man to experience a normal erection are the vascular, neurological, psychological, and endocrine systems. In addition, the smooth muscle cells of the corpora cavernosa must function adequately. All of the causes and risk factors associated with ED can be categorized into dysfunction of one or more of these systems.

Vascular Conditions Associated With ED

Erection is largely a vascular phenomenon. Conditions that impede the arterial blood flow into the corpora cavernosa or interfere with the mechanism of trapping blood within the corpora cavernosa during erection often cause ED.

The most common conditions associated with ED are the same as the risk factors for endothelial dysfunction. These include smoking, hypertension, diabetes, dyslipidemia, peripheral vascular disease, and coronary vascular disease *(2)*.

Age has been identified as an independent risk factor for ED. The mechanisms by which age causes ED are not completely understood, but vascular, as well as neurological and hormonal dysfunction, is certainly among them. Also, changes in the function of the smooth muscle cells of the corpora cavernosa may result from the aging process *(3)*.

Diabetes, which is associated with an acceleration of endothelial dysfunction, causes vasculogenic forms of ED. In addition, diabetic neuropathy involving the cavernous nerves is associated with ED.

Many prescription, as well as illegal, drugs are associated with ED. Antihypertensive agents, diuretics, and antidepressants are the types of drugs that are most commonly associated with sexual side effects. Although the precise mechanism by which many drugs cause ED is not clear, in the case

of α-and β-blocking agents and diuretics, a reduction in penile arterial blood flow is likely to be involved.

An uncommon cause of vasculogenic ED is pelvic or perineal trauma, which may injure the internal pudendal or penile arteries, causing penile arterial insufficiency.

Neurological Conditions Associated With ED

Erection is also a neurological phenomenon. Several common neurological conditions may be associated with ED. One of the most common of these is diabetes. In addition to causing premature or accelerated vascular disease, diabetic peripheral neuropathy may cause ED. This is, in fact, a common cause of ED in diabetic men.

Several other causes of peripheral neuropathy are associated with a high incidence of ED. These include alcoholism, human immunodeficiency virus infection, and administration of a variety of medications, including antiviral agents. In addition to peripheral neuropathy, other neurological conditions may be associated with ED. Among these are multiple sclerosis, Parkinson's disease, spinal cord injury, spinal cord tumor, and syringomyelia.

The risk of ED in men who have had significant pelvic or perineal trauma is high. Pelvic and perineal trauma cause ED either by compromise of the pudendal or penile arteries, or both, or by injury to the cavernous or other pelvic nerves.

Treatment of cancer of the rectum, bladder, or prostate by radical pelvic surgery, external-beam radiation therapy, or interstitial brachytherapy carries a significant risk of ED. The pathogenesis of ED associated with treatment of pelvic cancer is multifactorial and may be vasculogenic, psychological, or neurogenic. When neurogenic, ED is a result of surgical or radiation injury to the cavernous nerves.

Endocrine Conditions Associated With ED

The endocrine conditions associated with ED are those conditions that cause hypotestosteronemia, such as testicular atrophy and hypopituitarism. The precise mechanism by which hypotestosteronemia causes ED is not clear. In fact, most experts believe that hypotestosteronemia is more likely to cause decreased sexual interest than it is to cause ED. Nevertheless, ED in hypogonadal men can be ameliorated by testosterone replacement therapy *(4)*.

Psychological Conditions Associated With ED

In virtually all men with ED, there is a significant psychological component. The psychological component may be primary, but even in cases

of primarily organic ED, frequently there is a secondary psychogenic component.

There is a strong association between ED and clinical depression. Men with ED are more likely to be depressed, and men with depression are more likely to have ED *(5)*. Similarly, successful treatment of depression is likely to ameliorate ED, and successful treatment of ED is likely to ameliorate depression *(6)*.

There is a high prevalence of ED in alcoholism and other forms of drug abuse, including abuse of street drugs, such as cocaine and heroin. It is not clear whether ED associated with alcoholism and drug abuse is purely psychogenic, whether there are direct effects of these drugs on sexual function, or whether there are other comorbidities that cause the ED. In alcoholic men with cirrhosis, ED is often a result of low blood levels of testosterone and high blood levels of estrogen.

Lower Urinary Tract Symptoms Associated With ED

In the past few years, epidemiological studies have shown a relationship between ED and lower urinary tract symptoms (LUTS).

One large epidemiological study clearly documents that erectile function declines with increasing severity of LUTS independent of age. The same study shows that ejaculatory function also declines with increasing severity of LUTS independent of age *(7)*. Therefore, LUTS, such as urinary frequency, urgency, nocturia, restricted flow, double voiding, and urinary hesitancy are risk factors for both erectile and ejaculatory dysfunction. The mechanism responsible for this relationship is not understood at the present time.

Chronic Diseases Associated With ED

Several other chronic disease states are associated with a significant risk of developing ED. The most common of these are chronic renal failure, chronic hepatic failure, and chronic pulmonary disease. The precise mechanism by which these chronic conditions cause ED is not known. Multiple factors are probably involved; these include vasculogenic, neurogenic, and endocrine factors, often combined with markedly decreased sexual interest.

REVERSIBLE CAUSES OF ED

Of the various causes of ED, it is important to understand that there are only four that may be reversible with cause-specific therapy. These four causes are (1) predominantly psychogenic ED; (2) arteriogenic ED owing to pelvic and/or perineal trauma; (3) ED owing to hypotestosteronemia; and (4) neurogenic ED owing to reversible peripheral neuropathy.

In men whose ED is predominantly psychogenic, psychotherapy has the potential to be curative. These patients should be referred for psychological or psychiatric evaluation and treatment.

In young men who have had pelvic fractures as a result of trauma, ED may result from injury to the internal pudendal or common penile arteries. Penile arterial reconstruction or bypass surgery can be very effective in this very small group of men. These patients should be referred to a specialist in sexual medicine for vascular evaluation, which may lead to penile microvascular surgery.

Rarely, ED is associated with reversible peripheral neuropathies, such as pernicious anemia and vitamin B deficiency. The ED resulting from these reversible neuropathies can be cured by successful treatment of the neuropathy.

ED resulting from low testosterone levels and often associated with decreased sexual desire, can be eliminated by testosterone replacement therapy.

Thus, it is important for the primary care physician to identify patients in these four categories and then to either initiate specific therapy, such as testosterone replacement therapy, or refer the patient to an appropriate expert, such as a psychotherapist, microvascular surgeon, or neurologist.

Other than these four causes of ED, which can be reversed by specific therapy, all other therapies for ED are nonspecific and can be used for almost every patient regardless of the cause of the ED.

DIAGNOSIS OF ED

Psychogenic ED

It is impossible to objectively identify which patients have predominantly or purely psychogenic ED. However, it is important to diagnose patients in this category because these patients should be treated with psychotherapy. Various tests can be used to aid in the diagnosis of psychogenic ED, but all of the tests for psychogenic ED lack specificity and sensitivity.

Nocturnal erections are associated with the rapid eye movement phases of sleep. It is normal for a man to have two to five erections per night, each erection lasting from 1 to 30 min or more. Patients in whom the cause of ED is predominantly psychogenic usually have a normal pattern of nocturnal erections, whereas patients who have organic causes of ED usually have abnormal nocturnal penile tumescence and rigidity (NPTR).

Monitoring of NPTR is most commonly done with a device called the RigiScan monitor (Timm Medical Technologies, Eden Prairie, MN) *(8)*. This consists of a pair of loops that are placed at the tip and the base of the

penis and then connected to a computer. The patient wears the computer on his thigh for two or three nights. The loops measure penile circumference and radial rigidity. RigiScan testing can be conducted in the home setting or in a sleep laboratory. In the sleep laboratory, NPTR is continuously monitored, along with electroencephalography and electrooculography. Although studies in a sleep laboratory are very expensive, they do provide the most objective testing, because rapid eye movement sleep can be shown to be present or absent.

RigiScan monitoring of erections can also be undertaken in a laboratory setting using erotic audiovisual sexual stimulation. Many experts believe that the erectile response to erotic audiovisual stimulation more closely simulates psychogenic erectile function than does monitoring of nocturnal erections.

Monitoring of NPTR is fraught with false-negative results but can be very useful, particularly in men who claim to have totally absent conscious erectile function but who have completely normal nocturnal erections. For this reason, RigiScan studies are much more meaningful when they are normal than when they are abnormal.

Psychometric tests, such as depression scales and personality questionnaires, have been used to evaluate patients for psychogenic ED but have been largely abandoned for lack of specificity. Psychological or psychiatric opinion, as subjective as it may be, is often the final determining factor in identifying men whose ED is predominantly psychogenic.

Neurogenic ED

Neurogenic ED is easy to recognize in men who have peripheral neuropathy, such as diabetic neuropathy or that associated with human immunodeficiency virus infection. However, there is still no specific clinical test for neurological function of the corpus cavernosum. Testing methods for peripheral and autonomic neuropathies may be used as surrogates for the neurological function of the corpora cavernosa. These include tests of penile dorsal nerve conduction velocity and of sensation of the genitalia. Biothesiometry has been used as a measure of the vibration threshold of the penis. Bulbocavernosus reflex latency time has also been used for this purpose, as have genitocerebral-evoked responses *(9)*. None of these tests, however, directly measures the sensory or motor component of the autonomic nerves involved in the erection reflex. They provide only indirect evidence of peripheral neuropathy.

ED of Endocrine Origin

There is no consensus among experts regarding which is the best endocrine blood test to identify clinically significant hypotestosteronemia.

Some experts recommend testing of total serum testosterone level, whereas others recommend testing of free testosterone or bioavailable testosterone. The testing for hypogonadism, specifically for hypotestosteronemia, is important because treatment of ED as a result of this condition is simple and effective.

Vasculogenic ED

Many tests have been developed for identifying the presence of arteriogenic, venogenic, or mixed ED.

A test that can be performed as an office procedure to screen for vasculogenic factors is the intracavernous injection test of vasoactive drugs. Typically, 10 to 20 μg of alprostadil is administered, although other agents and combinations of agents may be used.

The erectile response to such injections is assessed over about 30 min. If the erectile response is incomplete, self-stimulation, erotic audiovisual videotape stimulation, or a second injection may be administered. A continued poor response to large doses of drugs suggests either vasculogenic ED or inhibition of the response because of anxiety. Because the intracavernous injection test may have false-negative responses because of anxiety or psychological factors, it is not considered highly reliable and is not used frequently. However, a good erectile response to the intracavernous injection test can be useful in selecting patients who are good candidates for self-injection therapy, even though it does not rule out the presence of mild penile arterial insufficiency *(10)*.

For studying the arterial side of the penile circulation, color duplex Doppler ultrasonography of the corpus cavernosum is the most commonly used test *(11)*. In this test, a 5- to 10-MHz ultrasound probe is placed on the penis before and after intracavernous injection of a vasoactive drug, such as alprostadil, papaverine, or phentolamine. The technique provides real-time images of the cavernous arteries and measurements of the diameter and blood flow velocity in these arteries. Normal results are homogeneity of the cavernous tissue, peak blood flow velocity in the cavernous arteries of more than 30 mL/s, and an increase in diameter of the cavernous arteries after intracavernous injection of vasoactive drugs of greater than 70% over baseline *(12)*.

For identifying abnormal function of the venous side of the circulation of the corpora cavernosa, there is a relatively simple test that can identify corporovenous occlusive dysfunction. In this test, a 19-gage butterfly needle is placed into the corpus cavernosum on one side. A large dose of vasoactive drug is administered through the needle. Five minutes later, when a partial erectile response should have started to occur, heparinized saline is injected into the corpus cavernosum through the butterfly needle to create a full and rigid erection. Then the rate of injection needed to maintain the

erection is measured. The flow rate needed to maintain the erection is equivalent to the rate at which blood is leaving the corpora cavernosa. Sometimes the flow-to-maintain rate is referred to as the venous leak rate. In a normal male, the maintenance flow rate is less than 5 to 10 mL/min. Standards of flow-to-maintain rates in men with veno-occlusive dysfunction have not been defined. It seems reasonable to say that rates of 10 to 20 mL/min suggest mild corporovenous occlusive dysfunction, 20 to 40 mL/min suggest moderate corporovenous occlusive dysfunction, and greater than 40 mL/min suggest severe corporovenous occlusive dysfunction. Sophisticated pumps and pressure measurements using advanced technology have been developed for controlling the rate of infusion of heparinized saline into the corpora cavernosa and for measuring the intracavernous pressure. These are used in referral clinics specializing in sexual medicine.

Penile arteriography can be used to demonstrate the anatomy of the penile blood flow *(13)*. This rarely performed test produces anatomical but not functional information about penile blood flow. It requires superselective catheterization of the internal pudendal or penile arteries with concomitant intracavernous injection of vasoactive drugs. The contrast agent used for the arteriogram should be mixed with vasodilating drugs. The timing of obtaining the radiographic images and the positioning of the patient require special attention and experience to achieve optimum results. Penile arteriography is indicated only in preparation for penile arterial revascularization, a microvascular procedure used exclusively in young men with ED after pelvic or perineal trauma.

The clinical value of diagnostic testing for arteriogenic, venogenic, or mixed ED is limited. The majority of men with erectile dysfunction respond to first-line therapy and do not need to be tested for vasculogenic factors, even if they are present. Testing for vasculogenic factors as a cause of ED should be limited to young men with ED owing to severe pelvic or perineal trauma, men with a lifetime history of ED, and men who have a genuine psychological need to know whether the cause of their dysfunction is psychogenic or organic.

OPTIONS FOR THE TREATMENT OF ED

Oral therapy with a PDE inhibitor is the first-line therapy for the majority of men with ED. Oral therapy with PDE inhibition is most commonly prescribed by primary practitioners. Other first-line therapies apply only to special situations. These include psychotherapy for men with predominantly psychogenic ED and testosterone therapy for men with hypotestosteronemia. The former is administered by psychotherapists or psychiatrists, and the latter is administered by primary practitioners, internists, endocrinologists, or urologists.

More advanced therapies for ED generally require greater time and supervision from the prescribing physician than does oral therapy. They are usually administered by a physician with a specific interest in sexual medicine, although some primary care physicians who have a special interest in ED also administer more advanced treatments. Second-line therapies include the intraurethral application of alprostadil; intracavernous injection therapy using alprostadil or a combination of alprostadil, papaverine, and phentolamine; and vacuum therapy. Third-line therapy consists of penile prosthesis implantation.

Intraurethral alprostadil therapy is administered by the insertion of a 1×3-mm pellet into the distal urethra. The alprostadil is absorbed through the urethral wall. Some of it is transferred through small vascular communications to the corpora cavernosa *(14)*. In clinical practice, this therapy provides a satisfactory solution to the problem of ED for only about one-third of men who use it.

Intracavernous injection therapy is administered by the percutaneous injection of papaverine, alprostadil, or phentolamine in various doses into the corpora cavernosa. This therapy is effective for about two-thirds to three-fourths of men with ED *(15)*. There is a high dropout rate because of the inconvenience of intracavernous injection.

Vacuum erection therapy is effective in about three-fourths of men as well *(16)*. As is the case with intracavernous therapy, there is a high dropout rate with vacuum therapy, because the equipment required may be awkward or inconvenient to use.

Despite their drawbacks, these second-line therapies are very good methods of dealing with ED for some, if not many, men.

Penile prosthesis implantation is the most reliable method of treating ED and the most invasive. More than 85% of men who use a penile prosthesis and their partners report satisfaction with this modality of therapy *(17)*. Penile prosthesis implantation should be offered as an option to all men with ED in whom first-line treatment with PDE inhibition is intolerable, unsuccessful, or contraindicated.

Clinical use of these second- and third-line therapies almost always requires referral of patients from the primary care arena to a specialist in sexual medicine.

A PRACTICAL APPROACH TO THE DIAGNOSIS AND TREATMENT OF ED BY THE PRIMARY CARE PHYSICIAN

For the primary care physician, the basic evaluation of patients with ED should consist of a careful psychosexual history, a general medical history, a focused physical examination, and basic laboratory tests.

The psychosexual history is the single most important part of the diagnostic evaluation of patients with ED. An excellent method of giving the patient permission to discuss his sexual dysfunction is to say, "Many men of your age experience sexual difficulty. Has this happened to you?" This discussion should be conducted in an environment that is comfortable for the patient. This requires the physician to be nonjudgmental, open, and frank. It requires the use of language that the patient understands. For some patients, this language may include "street" or vulgar terms.

Validated sexual surveys and questionnaires may be helpful in following a patient's progress. One such questionnaire is the Sexual Health Inventory for Men (SHIM). It consists of five questions about sexual function. Briefly, the questions ask the following:

1. How often is the patient able to get an erection with sexual activity?
2. How often are the patient's erections hard enough for penetration?
3. How often is the patient able to penetrate with sexual activity?
4. How often is the patient able to maintain his erection after penetration?
5. How difficult is it to maintain the erection to completion of intercourse?

Each question can be scored from 1 to 5, giving a maximum score of 25. Patients scoring a total of 22 to 25 points are considered to have normal erectile function. Scores of 17 to 21 indicate mild ED, scores of 12 to 16 indicate mild-to-moderate ED, scores of 8 to 11 indicate moderate ED, and scores of 7 or less indicate severe ED. Printed pads of the SHIM are available and make administration of the SHIM an easy waiting-room activity.

The general medical history should include questioning designed to elucidate the presence of major risk factors for ED.The physical examination should focus on endocrine, genitourinary, vascular, and neurological systems. The screening physical examination for ED can be done in a short period of time. Physical examination rarely contributes significantly to understanding the cause of ED.

Laboratory screening should include a complete blood count, urinalysis, general chemical analysis, lipid profile, serum testosterone level, and evaluation for occult coronary or peripheral vascular disease when there is a suspicion that such may be present.

After the basic evaluation, a trial of an oral PDE inhibitor is indicated. If treatment with an oral PDE inhibitor is successful, the treatment should be continued, and the patient does not need referral to a sexual medicine specialist.

WHEN TO REFER THE PATIENT WITH ED TO A SPECIALIST

In addition to first-line oral therapy with PDEinhibition, it is appropriate and common for primary care physicians to treat uncomplicated endocrine

disorders, such as primary hypogonadism and simple psychological problems that may respond to reassurance and encouragement. The conditions and situations that usually require referral from the primary care physician to a specialist include the following:

- ED that is predominantly psychogenic.
- Complicated psychological or psychiatric disorders.
- Complex relationship problems.
- ED complicated by sexual dysfunction in the partner.
- Lifelong history of ED.
- Complicated endocrinopathies.
- Failure to respond to oral PDE inhibitors.
- Bothersome side effects from oral PDE inhibitors.
- Noncandidates for oral PDE inhibitors.
- ED owing to a reversible peripheral neuropathy.
- ED resulting from severe pelvic or perineal trauma.
- Abnormal prostate-specific antigen test in patients who are candidates for testosterone replacement therapy.
- Peyronie's disease.
- Reluctance of the health care provider to deal with sexual dysfunction.
- Request by the patient or his partner for a referral to a sexual medicine specialist.

Most, but not all, specialists in sexual dysfunction are urologists or psychologists. The primary care physician should refer the patient with one of the listed conditions or situations to the most appropriate specialist.

Men with problems that are predominantly psychological or psychiatric should be referred to a psychologist or psychiatrist with experience and interest in the treatment of psychogenic sexual dysfunction. In this category are patients whose ED is predominantly psychogenic, patients with complicated psychological or psychiatric disorders, patients with complex relationship problems, patients whose ED is complicated by sexual dysfunction in the partner, and patients who have a lifelong history of ED.

Patients with complicated endocrine disorders should be referred to an endocrinologist.

Patients whose ED may be related to a reversible peripheral neuropathy should be managed by the primary care physician in conjunction with a neurologist.

Patients who fail to respond to oral PDE inhibitors, who have bothersome side effects from oral PDE inhibitors, who are not candidates for oral PDE inhibitors, whose ED is a result of pelvic or perineal trauma, who have hypotestosteronemia with an abnormal prostate-specific antigen level, or who have Peyronie's disease should be referred to a urologist for further care.

CONCLUSION

About two-thirds of patients with ED can be managed successfully by primary care physicians. The remaining one-third require more advanced diagnosis and/or management than is available in most primary care settings. Patients who require advanced care can be reassured by their initial caregivers that the chance for resumption of satisfactory sexual function can be as high as 85% if they are willing to try all available second- and third-line therapies. Although some men with ED choose not to undertake second- or third-line therapies, those who do are likely to have pleasurable sexual activity for the duration of their lives.

REFERENCES

1. Carson CC, Burnett AL, Levine LA, Nehra A. (2002) The efficacy of sildenafil citrate (Viagra) in clinical populations; an update. Urology 60(Suppl 2B):49.
2. Kloner RA. (2003) Introduction: erectile dysfunction and cardiovascular risk factors. Am J Cardiol 92(9A):1M–2M.
3. Bacon CG, Mittleman MA, Kawachi I, et al. (2003) Sexual function in men older than 50 years of age: results from the Health Professionals Follow-up Study. Ann Intern Med 139:161–168.
4. Kim YC, Buvat J, Carson CC, et al. (2000) Endocrine and metabolic aspect including treatment. In: Jardin A, Wagner G, Khoury S, et al., eds., Erectile Dysfunction. Plymouth, UK: Health Publications Ltd, pp 224–225.
5. Shabsigh R, Klein RT, Seidman S, et al. (1998) Increased incidence of depressive symptoms in men with erectile dysfunction. Urology 52:848–852.
6. Nurnberg HG, Seidman SN, Gelenberg AJ, et al. (2002) Depression, antidepressant therapies, and erectile dysfunction: clinical trials of sildenafil citrate (Viagra) in treated and untreated patients with depression. Urology 60(Suppl 2B):58–66.
7. Rosen R, Altwein J, Boyle P, et al. (2004) Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male (MSAM-7). Eur Urol 44:637–649.
8. Levine LA. (1999) Nocturnal penile tumescence and rigidity monitoring for the evaluation of erectile dysfunction. In: Carson C, Kirby R, Goldstein I, eds., Textbook of Erectile Dysfunction. Oxford, UK: Isis Medical Media Ltd., pp. 267–277.
9. Beck R, Fowler CJ. (1999) Neurophysiological testing in erectile dysfunction. In: Carson C, Kirby R, Goldstein I, eds., Textbook of Erectile Dysfunction. Oxford, UK: Isis Medical Media Ltd., pp. 257–266.
10. Pescatori ES, Hatzichristou DG, Namburi S, et al. (1994) A positive intracavernous injection test implies normal veno-occlusive but not necessarily normal arterial function: a hemodynamic study. J Urol 151:1209–1216.
11. Broderick GA. (1999) Non-invasive vascular imaging for erectile dysfunction. In: Carson C, Kirby R, Goldstein I, eds., Textbook of Erectile Dysfunction. Oxford, UK: Isis Medical Media Ltd., pp 233–256.
12. Lee B, Sikka SC, Randrup ER, et al. (1993) Standardization of penile blood flow parameters in normal men using intracavernous prostaglandin E1 and visual sexual stimulation. J Urol 149:49–52.
13. Wahl SI, Rubin MB, Bakal CW. (1997) Radiologic evaluation of penile arterial anatomy in arteriogenic impotence. Int J Impot Res 9:93–97.

14. Padma-Nathan H, Hellstrom WJG, Kaiser FE, et al. (1997) Treatment of men with erectile dysfunction with transurethral alprostadil. N Engl J Med 336:1–7.
15. Spahn M, Manning M, Jeunemann KP. (1999) Intracavernosal Therapy. In: Carson C, Kirby R, Goldstein I, eds., Textbook of Erectile Dysfunction. Oxford, UK: Isis Medical Media Ltd., pp. 345–353.
16. Cookson MS, Nadig PW. (1993) Long term results with vacuum constriction device. J Urol 149:290–294.
17. Carson CC, Mulcahy JJ, Govier FE, et al. (2000) Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. J Urol 164:376–380.

9 Erectile Dysfunction

Assessing Risk and Managing the Cardiac Patient

Thorsten Reffelmann, MD
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CONTENTS

ERECTILE DYSFUNCTION: AN ARTERIAL DISORDER?

"Is impotence an arterial disorder?" When Virag et al. *(1)* asked this question in their *Lancet* article in 1985, an important association between atherogenic risk factors and erectile dysfunction (ED) was brought to our attention. In 440 men with ED, atherogenic risk factors were significantly more common than in a male population of similar age. Smoking (64%), diabetes mellitus (30%), and hyperlipidemia (34%) were the most common risk factors associated with ED.

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The Massachusetts Male Aging Study estimated an annual incidence of ED of 26 new cases per 1000 men in their population (40- to 69-yr-old men). However, the incidence increased markedly with each decade of life. Clearly, heart disease, diabetes, and hypertension were identified as major risk factors in this prospective study *(2,3)*.

A recent investigation reported a prevalence of 44% for hypertension, 23% for diabetes mellitus, 16% for tobacco use, 79% for obesity, and 74% for elevated low-density lipoprotein cholesterol levels (>120 mg/dL) among men with ED *(4)*.Thus, even if various causes and factors—including endocrine disorders, renal and hepatic dysfunction, side effects of several medications, and psychiatric and psychogenic causes—are to be considered in any patient presenting with ED, atherogenic risk factors and arterial disease will play a prominent role. A recent study estimated that 75% of patients attending routine outpatient cardiology visits had chronic stable coronary artery disease, as well as ED, as evaluated by means of a standardized questionnaire *(5)*.

Consequently, any patient who is under medical treatment for ischemic heart disease should be given an opportunity to mention and discuss potential problems regarding sexual function. In many cases, the primary care physician or cardiologist might be the first health care worker to initiate such a discussion. Depending on the patient's willingness and readiness to discuss these problems, the physician should proceed with a nonjudgmental but forthright evaluation of the problem, respecting cultural and personal characteristics *(6)*. Indeed, a recent study emphasized that many patients with ED do not take the initiative of telling their physician or even their urologist about the problem because of embarrassment or other causes *(7)*. This study also stressed that the majority of their patient population would have liked their primary care physician to have initiated a discussion of these problems during routine visits.

The first presentation of ED in a patient may also signal serious underlying diseases, including diabetes mellitus, hypertension, and cardiovascular disease, or it could be a predictor of various manifestations of atherosclerosis. O'Kane et al. recently reported a series of patients who had visited their doctors because of ED but soon thereafter developed an acute myocardial infarction or were diagnosed with severe three-vessel coronary artery disease *(8)*. Therefore, the presence of ED could prompt further investigations that eventually lead to diagnosis of ischemic heart disease, other manifestations of atherosclerosis, or identification of major risk factors *(9–13)*.

Table 1, a synopsis of various references, summarizes the main risk factors for and frequent causes of ED *(9–22)*. Looking at this table, it becomes clear that "managing the cardiac patient" is likely to be a frequent task for any doctor involved in the treatment of ED. Because of the high

Table 1
Risk Factors and Causes of ED[a]

Vascular factors	• Risk factors associated with atherosclerosis ◇ Smoking ◇ Diabetes mellitus ◇ Hypertension ◇ Low levels of high-density lipoproteins/high levels of low-density lipoproteins ◇ Sedentary lifestyle ◇ Genetic predisposition to atherosclerosis ◇ Obesity • Atherosclerosis, vascular surgery
Neurogenic factors	• Neuropathies ◇ Diabetic and others • Other neurological disorders ◇ Spinal cord injury, cerebrovascular insult, multiple sclerosis, nerve damage resulting from prostate surgery, and others
Various medical diseases	• Renal failure • Dialysis • Abnormal liver function • Endocrine disorders ◇ Hypogonadism ◇ Hyperprolactinemia ◇ Hypo- and hyperthyroidism • Sickle cell anemia
Drug treatment (selection)	• Antihypertensives, thiazide diuretics, spironolactone, digoxin, antidepressants, β-blockers, centrally acting antihypertensives, phenothiazines, carbamazepine, phenytoin, risperidone, fibrates, statins, histamine-2 receptor antagonists, allopurinol, indomethacin, tranquilizers, disulfiram, levodopa, chemotherapeutics, and others
Drug abuse	• Alcohol • Other abuses
Anatomic-structural abnormalities	• Peyronie's disease • Priapism • Trauma
Psychogenic/ psychiatric	• Depression • Anxiety disorder • Problems or changes in relationship

[a] Adapted from refs. *9–22*.

prevalence of ED in patients with heart disease, the complex concurrent cardiovascular medications (which may also contribute to ED), and various psychological implications of heart disease, special considerations and recommendations are required in evaluating the cardiac patient.

THE PATIENT PRESENTING WITH ED: A CARDIAC PATIENT?

As discussed in other chapters of this book, any patient presenting with ED needs to supply a detailed medical history, including sexual and psychosocial history, and a complete list of any drugs he is taking. In addition, the evaluation of anginal or other symptoms potentially related to ischemic heart disease, a check of a potential genetic predisposition for atherosclerosis or diabetes, a careful clinical examination including genitourinary examination, and complete cardiovascular, pulmonary, and neurological examinations, are indispensable. A working hypothesis regarding the most likely causes of ED should be the result. In some cases, laboratory tests, as well as further technical workup, may be required *(9)*.

It is important to mention that oral treatment strategies, namely phosphodiesterase-5 (PDE5) inhibitors, are highly effective in the treatment of ED of a broad spectrum of causes *(9)*. This efficacy should not give rise to the impression that a search for specific causes is not necessary, however. The relatively large chance of detecting potentially serious underlying diseases warrants these further investigations *(23–25)*.

Any patient without an obvious cause for ED, such as structural anatomical causes, neurological disorders, or endocrine factors, should be evaluated for risk factors and potential vascular or arterial diseases *(26)*. In a substantial number of patients with apparently obvious reasons for ED, atherogenic risk factors might further contribute to the symptoms of ED in a synergistic manner *(27)*.

We suggest the following evaluation for these patients (Fig. 1): blood glucose fasting, arterial blood pressure measurement, cardiac examination, examination of peripheral pulses, analysis of cholesterol level (total, low-density lipoprotein, and high-density lipoprotein), and resting electrocardiography. A simple urinary dipstick test for glucosuria will miss the diagnosis of diabetes mellitus in a high percentage of patients *(25)*. If any of these tests is abnormal and the patient has a history of cigarette smoking or a genetic predisposition for atherosclerosis, an exercise test and, in some cases, a Doppler ultrasonographic evaluation of the carotid arteries and lower extremity arteries may be considered (*see* Fig. 1).

If the results suggest that this patient with ED might have or be at a high risk for cardiovascular disease, a referral to a cardiologist seems to be reasonable before initiation of specific treatment for ED.

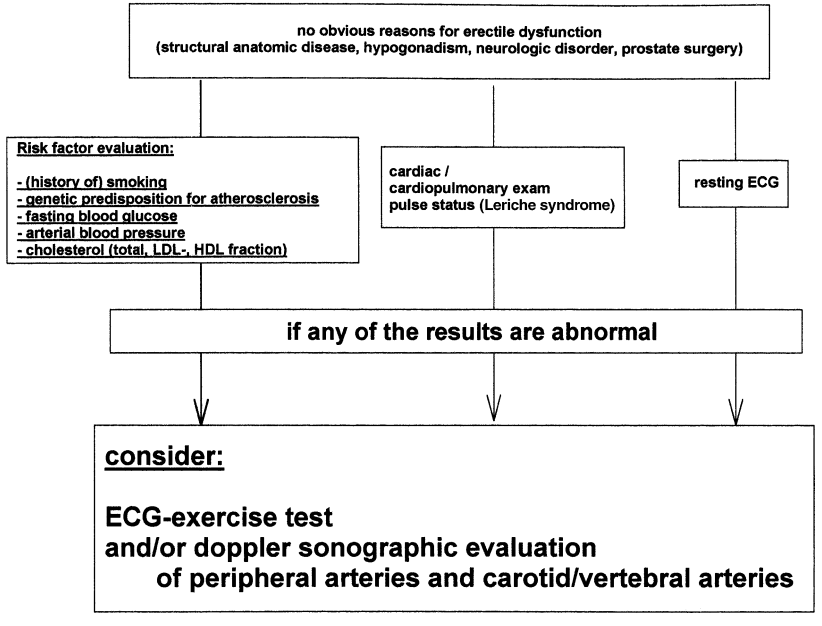

Fig. 1. Erectile dysfunction: warning for severe underlying disease? ECG, electrocardiogram; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

IS TREATING RISK FACTORS AN ADEQUATE TREATMENT FOR ED?

The strong association between atherogenic risk factors and ED may suggest that reducing these risk factors (at least those that can be modified) could favorably influence the severity or progression of symptoms or even lead to reversal of ED. For most risk factors, it is not undoubtedly established that risk factor modification bears the potential of reversing ED, but it seems to be very suggestive that a potential progression of ED could at least be attenuated by risk factor modification. In either case, the strong association between risk factors and ED should be brought to the patient's attention. In some cases, this association with ED might be a more convincing motivation for the patient to modify these risk factors, change his lifestyle, or quit smoking than is the more abstract association of risk factors with heart disease and arterial disorders.

Smoking

Cigarette smoking and ED are both closely related to endothelial dysfunction, suggesting that smoking cessation might improve erectile function in cigarette smokers *(28,29)*. Most of the studies revealed a 1.5- to twofold

increased risk for ED in smokers in comparison with nonsmokers *(16,28)*. McVary stated that the prevalence of ED in former smokers was not different from that in individuals who had never smoked *(16)*, suggesting that cessation of tobacco use might reverse ED. In contrast, Mirone et al. did not find a difference between current smokers (odds ratio 1,7 in comparison with those who had never smoked) and ex-smokers (odds ratio 1,6) *(30)*.

Nonetheless, it might be regarded as self-evident that smoking cessation will more likely be associated with improved sexual function than will continued smoking. Even if a therapeutic effect is not undoubtedly documented, any patient suffering from ED should be encouraged to quit cigarette smoking.

Diabetes Mellitus

The best possible control of blood glucose levels should be achieved in any patient with diabetes mellitus irrespective of cardiovascular complications or the presence of ED. Even if convincing data on reversal of ED after initiation of antidiabetic treatment are lacking, a strong association between the prevalence of ED and the level of glycemic control, measured as hemoglobin A_{1c} levels, is well established *(31)*. Whether this might imply an improvement of sexual function with optimal blood glucose control is not irrefutably proven, but these considerations should be reviewed with the patient to further motivate him and to stress blood glucose control.

Hypertension

Whether treatment of hypertension can reduce the risk of developing ED, as suggested from animal investigations *(32)*, is difficult to answer, because many antihypertensive agents are regarded as potential causes of ED as a drug-specific side effect. It is important to emphasize that the development of side effects of antihypertensive agents should not result in discontinuation of effective control of arterial blood pressure. Especially with the currently available broad spectrum of antihypertensive agents, it should be possible to find a hypertensive medication that is both effective in controlling arterial blood pressure and has minimal side effects.

It is necessary to estimate the risk of ED associated with various drugs. For example, β-blocking agents are most often mentioned in any discussion of drug-induced ED. Thiazide diuretics are associated with a higher percentage of drug-induced ED, however, than are β-blocking agents *(22)*. Although the mechanisms are unknown, this side effect of thiazide diuretics seems to be reversible or attenuated in a high percentage by a simple weight-loss diet *(33)*.

Table 2 gives some suggestions how to modify antihypertensive treatment when considering ED as a potential side effect *(18,20,21)*. Overall,

Table 2
Drugs Associated With ED (Selection) and Potential Alternatives [a]

Class of drug	*Potential alternative*[b]	*Comments*
Thiazide diuretics	Loop diuretics	In special cases, a weight-loss diet in combination with thiazides might prevent/reverse ED associated with thiazide diuretics.
Potassium-sparing diuretics	Loop diuretics and potassium supplementation	—
Aldosterone antagonists (spironolactone)	Depending on indication: as diuretics, *see* above; for treatment of heart failure, ?	In case of heart failure, beneficial effects on prognosis of aldosterone antagonists may not allow discontinuation of these drugs *(41,42)*.
β -Blockers	Angiotensin-converting enzyme inhibitors, calcium channel blockers, α-adrenergic blockers, angiotensin receptor blockers	After myocardial infarction and in the treatment of heart failure, discontinuation of β-blockers might not be warranted owing to prognostic benefit.
Lipid-lowering fibrates (gemfibrozil, clofibrate, and so forth)	Statins, niacin	—
Angiotensin-converting enzyme inhibitors	Angiotensin receptor blockers	Angiotensin receptor blockers may even slightly improve sexual function *(35)*.
Histamine-2 receptor antagonists	Proton pump inhibitors	—

[a]Adapted from refs. *18,20,21,33–40*.
[b]Alternatives listed in this table are only meant as guidelines, and may not be applicable in certain patients.

angiotensin-converting enzyme inhibitors seem to carry a low risk of causing ED as a side effect *(34)*. Angiotensin receptor antagonists might even slightly improve sexual function in hypertensive patients *(35)*. Calcium antagonists are also associated with a rare incidence of ED (however, sometimes they increase prolactin levels, which could lead to ED). We stress that Table 2 is only meant to be a general guideline of how to modify treatment; in many cases, other considerations apart from ED will be important as well, and may dictate the choice of medication.

Lipid Disorders

Whether cholesterol-lowering interventions or treatment of hyperlipidemia is capable of reversing or at least attenuating the progression of ED is not well documented. It should be mentioned, however, that lipid-lowering drugs, especially fibrates, can also induce ED *(36–39)*. Although it has not been systematically investigated, statins seem to be associated with a lower incidence of ED (*see* Table 2) *(36)*.

Physical Exercise, Obesity, Lifestyle

The systematic prospective investigations by Derby et al. clearly identified sedentary lifestyle as an important variable in the development of ED. Initiation of physical activity significantly reduced the risk of developing ED *(40)*. These changes in lifestyle might also be applicable to most patients with cardiovascular disease, even if special recommendations with regard to physical activity might be necessary according to severity and stage of disease. On the other hand, Derby et al. also reported that weight loss, reduction of alcohol consumption, and smoking cessation had few beneficial effects on ED when initiated at an older age. Correction of lifestyle once atherosclerosis has developed may be too late to reverse ED, but it might prevent its progression to severe ED. As a consequence, any patient should be advised to correct his lifestyle as early as possible.

In summary, modifiable atherogenic risk factors should be treated aggressively. When specific drug therapy is required, in most cases a treatment regimen associated with a low incidence of ED as a side effect ought to be possible. After being informed of the association between risk factors and ED, the patient should be strongly encouraged to reduce his own specific risk with regard to atherosclerosis and ED.

THE KEY QUESTION: DOES SEXUAL INTERCOURSE BEAR THE RISK FOR A CARDIAC EVENT?

Sexual activity significantly contributes to quality of life, and this is of particular importance for patients after myocardial infarction or other car-

diac events, and chronic heart diseases *(43,44)*. When evaluating the cardiac patient, the key question will be whether this patient can be recommended to have sexual intercourse or whether sexual activity is associated with increased risk. Which of the treatment options for ED might be the best for this individual patient and consideration of the contraindications, side effects, and drug interactions are secondary questions, however, to be posed after stratification of the patient to a specific risk category.

Energy Expenditure During Sexual Intercourse

With regard to its effects on the cardiovascular system, sexual intercourse can be interpreted as physical activity or exercise similar to other activities in daily life. Thus, the level of exercise or the metabolic expenditures associated with sexual activity may be used to estimate the cardiovascular risk of sexual intercourse, similar to considerations for other forms of physical activity *(45)*. In general, the risk of an effort-induced cardiac event is reduced by optimizing therapy with β-blockers, aspirin, and lipid-lowering therapy, which should likewise apply to exercise during sexual intercourse *(45,46)*.

Metabolic expenditures during sexual intercourse vary depending on several variables. In a laboratory setting, Bohlen et al. measured a peak heart rate of 110 to 127 beats per min in healthy males during intercourse with their usual female partner *(47)*.To quantify the level of physical exertion, usually the metabolic equivalent of energy expenditure at the resting state (MET), which is approx 3.5 mL/kg/min of oxygen consumption, is used for various physical activities in everyday life *(48)*. As a rule of thumb, briskly climbing two flights of stairs equals 3 METs, and digging in the garden equates to 5 METs. Measuring oxygen uptake, Bohlen et al. found that 2.5 to 3.3 METs are attained during sexual stimulation and orgasm, whereas the variation among individuals was relatively high (2.0–5.4 METs) *(47)*. In general, the upper range appears to be 5 to 6 METs during sexual intercourse. Historically, the stair-climbing test was introduced to simulate the level of physical activity during intercourse by Larson et al., who demonstrated an increased heart rate of 115 ± 7 beats per min and a systolic blood pressure of 164 ± 7 mmHg during sexual intercourse, and a heart rate of 118 ± 6 beats per min and a systolic blood pressure of 144 ± 6 mmHg with stair climbing in patients with coronary artery disease *(49)*. In these investigations, 10 min of brisk walking were followed by stair climbing, which equals approx 5 to 6 METs and may provide a general impression of the level of energy expenditure during sexual intercourse. Nevertheless, some excess sympathetic activation during sexual activity in comparison with other exercise at the same MET level may occur *(48)*.

In conclusion, an exercise test can approximately gauge the potential cardiac stress of sexual activity. If a patient achieves 5 to 6 METs on

exercise testing without signs of ischemia or arrhythmias, the patient is not likely to be at risk of developing ischemia or arrhythmia during intercourse *(50)*. Nonetheless, in some circumstances, emotional stress before and during sexual intercourse may be excessive, especially in patients who have not performed sexual activity in some time and resume intercourse with initiation of treatment for ED. This stress itself may promote myocardial ischemia, and these patients should be advised to use common sense and appropriately moderate their physical activity *(50)*.

The Statistical Risk

Patients with different types and stages of heart disease, especially those who have been sexually inactive and now want to resume sexual activity (and also their partners), might be concerned about a potentially life-threatening cardiac event during sexual intercourse. These patients and any patient with cardiovascular disease asking for treatment of sexual dysfunction should be given a realistic estimate of the risk of a cardiac event during sexual intercourse. After stratification of the individual patient to a specific risk category (*see* Subheading entitled "Risk Stratification"), in many circumstances it will be possible to emphasize how low the risk of a cardiac event during sexual activity is for that patient. This might help the couple in coping with unfounded fears. Another opportunity is to explain the predictive value of an exercise test, as mentioned previously. Perhaps the physician might propose that the partner who is concerned about the potential perils of sexual intercourse observe the patient performing the exercise test. This may reassure the couple about the safety of their sexual relationship. Some facts that can provide the patient with a realistic estimate of the risk of sexual activity follow.

In general, fewer than 1% of myocardial infarctions occur during sexual intercourse. A coital death is very rare, encompassing only 0.6% of sudden deaths *(51)*. A 50-yr-old man in the United States has a baseline annual risk of myocardial infarction of 1.00%, which increases to 1.01% as a consequence of sexual activity *(52)*. In a patient with a previous myocardial infarction, the annual risk increases to 1.10%. These data illustrate that the absolute risk of a myocardial infarction in temporal connection with sexual intercourse is very low.

When estimating the relative risk of sexual activity, Muller et al. included all myocardial infarctions occurring during sexual intercourse and in a 2-h period thereafter and compared them with the overall incidence of myocardial infarction *(53)*. In these investigations, using a case-crossover method, the relative risk of coition-induced myocardial infarction was estimated as 2.5-fold higher than during noncoitive activities *(53)*. In patients with known coronary artery disease, the relative risk of sexual activity with respect to

myocardial infarction was similar (2.1-fold). Thus, sexual activity can be regarded as an established trigger for myocardial infarction; however, the absolute risk is very low *(54)*. Importantly, in patients with known coronary artery disease, the relative risk is not further increased *(45)*, and the risk might further be reduced by a physical exercise program *(55)* and risk factor modification *(54)*. Patients who have undergone successful revascularization by percutaneous transluminal angioplasty or coronary artery bypass grafting do not have an increased risk for a cardiac event during sexual intercourse in comparison with the general population *(56)*.

Risk Stratification According to the Princeton Consensus Panel (52)

Based on available data with respect to statistical risk and physiological changes during sexual intercourse, the Princeton Consensus Panel issued guidelines on risk stratification of cardiac patients, leading to recommendations for the treatment of ED *(52)*. In addition, an American College of Cardiology/American Heart Association expert consensus document was published in 1999, which provided detailed recommendations on the use of sildenafil in patients with cardiovascular disease *(50)*. According to the Princeton Consensus Panel, patients with cardiovascular disease should be divided into three groups with low, intermediate, or high risk of a cardiac event during sexual intercourse.

The High-Risk Group

The high-risk group (Table 3) consists of patients with cardiovascular disease that require either stabilization or a detailed diagnostic workup before any sexual activity is advisable. This usually means referral to a cardiologist or even hospital admission based on the specific condition. Treatment of ED needs to be deferred until stabilization.

Unstable or refractory angina is characterized by new-onset, accelerated, or refractory chest pain or angina at rest. The functional cardiac reserve in these patients might be exceeded by mild physical activity and also physical activity during coition.

Poorly controlled hypertension also belongs to the high-risk group, because an acute cardiac event, as well as stroke, might be triggered by sexual activity.

Congestive heart failure with symptoms at rest or at lowest levels of activity (New York Heart Association [NYHA] III and IV) should also give rise to further evaluation and stabilization before treatment of ED, because sexual intercourse can result in acute cardiac decompensation.

In addition, patients with high-risk arrhythmia need a detailed diagnostic workup and adequate treatment before sexual activity can be recommended.

Table 3
Risk Stratification According to the Princeton Consensus Panel[a]

High-risk group
Patients with the following: • Unstable angina/refractory angina • Uncontrolled arterial hypertension • Congestive heart failure (NYHA III–IV) • Myocardial infarction (within the last 2 wk)[b] • Recent stroke • Moderate to severe valvular heart disease or hypertrophic obstructive cardiomyopathy • High-risk arrhythmia
Intermediate or undetermined risk group
Patients with the following: • Three or more atherogenic risk factors • Moderate, stable angina • Myocardial infarction (2–6 wk after the acute event[b]) • Congestive heart failure (NYHA II) • Stroke, peripheral vascular disease
Low-risk group
Patients with the following: • Fewer than three atherogenic risk factors • Controlled hypertension • Mild, stable angina (consider exercise test in some cases) • Post successful coronary revascularization (without remaining ischemia) • Post uncomplicated myocardial infarction[b] • Mild valvular disease • Congestive heart failure (NYHA I)

[a] Modified according to ref. *52*.

[b] For most oral treatment options for ED, a period of 90 d or more after myocardial infarction is suggested.

NYHA, New York Heart Association.

After myocardial infarction, a period of at least 2 wk without sexual activity is recommended, owing to the risk of coition-induced arrhythmia *(57)*, reinfarction, or cardiac rupture. According to the Princeton Consensus Conference, however, patients may be at a slightly increased risk up to 6 wk after myocardial infarction. In addition, guidelines and recommendations for the use of sildenafil emphasize that conclusive data regarding the cardiovascular risk within the first 6 mo of myocardial infarction are lacking, and therefore special caution during this period is mandatory *(50,58)*.

Finally, the Princeton Consensus Panel recommended caution in patients with hypertrophic obstructive cardiomyopathy and moderate or severe valvular disease, in particular aortic stenosis. Although little evidence is documented regarding the risk of sexual intercourse in these patients, it is known that exercise, as well as vasodilating interventions, may be detrimental in some cases.

The Intermediate-Risk or Indeterminate-Risk Group

Patients in this group require further diagnostic testing to be reclassified into the high- or low-risk group. In many cases, an exercise test is appropriate.

According to the Princeton Consensus Conference, patients with moderate stable angina belong to this category, which may, depending on the result of exercise testing, prompt intensified medical treatment or coronary angiography with subsequent angioplasty or bypass grafting.

Congestive heart failure of NYHA classification II, with three or more atherogenic risk factors (i.e., age, hypertension, diabetes mellitus, obesity, cigarette smoking, dyslipidemia, or sedentary lifestyle), and noncardiac manifestations of atherosclerosis (e.g., stroke, transient ischemic attacks, or peripheral arterial disease) are also reasons for stratification as intermediate risk. In addition, patients are at intermediate risk if they have experienced a myocardial infarction 2 to 6 wk previously. These conditions may require intensified treatment, and in many cases an exercise test will be needed to decide whether energy expenditure during coition may be tolerated *(59)*. Even though the Princeton Consensus Panel has assigned patients who experienced an acute myocardial infarction 2 to 6 wk previously to this intermediate group, it seems to be advisable for these patients to be careful. Especially if (1) no revascularization of the infarct-related artery by thrombolysis, percutaneous interventions, or bypass grafting was performed, (2) a large part of the myocardial wall has become necrotic, or (3) significant arrhythmias were recorded, one might rather recommend a step-by-step increase in physical activity and allow sexual intercourse only after an appropriate exercise test.

The Low-Risk Group

Finally, the low-risk group comprises the remaining patients with cardiovascular disease with asymptomatic coronary heart disease or mild stable angina. Patients who have experienced acute myocardial infarction are considered to be at low risk after 6 to 8 wk provided that a stress test result is negative. Importantly, patients are also placed into this group after successful revascularization, percutaneous coronary interventions, or coronary artery bypass grafting. Exercise testing may be helpful in assessing potential residual ischemia. This group usually contains the majority of

patients, and they can safely be encouraged to engage in sexual activity. Discussing the low statistical risk of a cardiac event may be important for many patients who are afraid of serious consequences of sexual intercourse and thereby experience psychological encroachment upon their sex life.

TREATMENT OPTIONS FOR ED: SPECIAL CONSIDERATIONS FOR THE PATIENT WITH CARDIOVASCULAR DISEASE

Several treatment options for ED are currently available, and it is important to find the appropriate therapy for the individual patient. The discovery of the PDE5 inhibitor sildenafil in 1989 has revolutionized treatment of ED. Now additional treatment options, including other PDE5 inhibitors and dopamine agonists, are being considered for patients seeking help for their problem *(9)*. When specific causes of ED have been identified, such as neurological and anatomical problems, causal treatment is also required in patients with cardiovascular disease. For instance, for patients with cardiovascular disease with known hypogonadism and testosterone deficiency, testosterone replacement therapy is certainly first-line therapy, although this is a rare cause of ED and this therapy should be used very selectively *(9)*. (Hematocrit, prostate-specific antigen, and lipid profile should be reassessed during such treatment.)

For all treatment strategies, psychosocial counseling is an important factor, and it should accompany all other treatments. In many cases, assessing coexistent problems, treating depression, if indicated, and discussing factors that create a normal sexual response with the couple might be performed by the primary care physician, sometimes in cooperation with the specialist. In selected cases, however, professional psychotherapy may be necessary.

PDE5 Inhibitors

As outlined in Chapters 4 to 6 of this book, PDE5 inhibitors, namely sildenafil, tadalafil, and vardenafil, have become first line-treatment for many patients with ED, including the patient with cardiovascular disease.

Efficacy has been demonstrated for a broad spectrum of causes and accompanying factors of ED, including diabetes and hypertension *(9)*. Early after the approval of sildenafil for the treatment of ED, reports of adverse cardiac events posed questions regarding the safety of PDE5 inhibition in patients with cardiovascular disease *(60–63)*. These reports triggered a substantial body of clinical, statistical, and basic science research. Several concepts could in theory explain a lowered threshold for arrhythmia or reduced tolerance to ischemia *(64,65)*. However, none of them has ever been shown to lead to an increased risk in clinical

circumstances. Indeed, randomized trials *(66)* and retrospective analyses *(67)* did not report an increased cardiac risk for patients on sildenafil in comparison to what would have been expected for a patient population of similar age characterized by several atherogenic risk factors. Overall, the cardiovascular risk of PDE5 inhibition, especially of sildenafil treatment, has been extensively reviewed *(62,63)*, and detailed guidelines on the use of sildenafil in cardiovascular diseases are available *(50)*. The overall profile of side effects seems to be very similar for tadalafil and vardenafil, although the experience with these agents is based on a smaller number of patients *(68–70)*. Side effects are mainly characterized by symptoms related to vasodilation.

For the patient with cardiovascular disease, the most important contraindication to the use of sildenafil or any other PDE5 inhibitor is concurrent medication with a nitric oxide donor (e.g., nitroglycerin). Because inhibitors of the enzyme PDE5 slow the breakdown of cyclic guanosine monophosphate , the concurrent administration of a nitric oxide donor can lead to accumulation of cyclic guanosine monophosphate with subsequent severe hypotension. Any patient who suffers from chronic stable angina that may require treatment with nitroglycerin should not be given sildenafil, tadalafil, or vardenafil. For PDE5 inhibitors to be administered, a stable cardiac condition, including determination of appropriate exercise tolerance, needs to be achieved with antianginal therapy other than nitrates. Any patient who is on nitrates must not take sildenafil or any other PDE5 inhibitor because the combination can lead to life-threatening hypotension *(50)*. Notably, any patient who is prescribed PDE5 inhibitors must be informed about this contraindication. Recent guidelines suggest a 24-h interval between the use of sildenafil and any nitric oxide donor, and vice versa. Cheitlin et al. *(50)* list representative organic nitrates.

Sildenafil has a half-life of about 4 h, and six half-lives (24 h) were recommended to allow adequate tissue washout before administration of a nitrate in an emergency situation. Vardenafil has a similar half-life, so that this interval probably will be 24 h for vardenafil as well. Tadalafil has a 17.5-h half-life, however; thus, the interval between administration of tadalafil and safe administration of any nitric oxide donor drug will be longer. A preliminary study suggests that this interval will be at least 48 h.

Figure 2 provides an algorithm of how to treat hypotension in patients who have received a combination of PDE5 inhibitors and nitric oxide donors by mistake *(50)*.

Blood pressure-lowering effects of PDE5 inhibitors, as long as they are not combined with a nitric oxide donor, are moderate. Zusman et al. reported a nondose-dependent reduction in arterial blood pressure to 7 to 10 mmHg after sildenafil was administered*(61)*. In hypertensive patients,

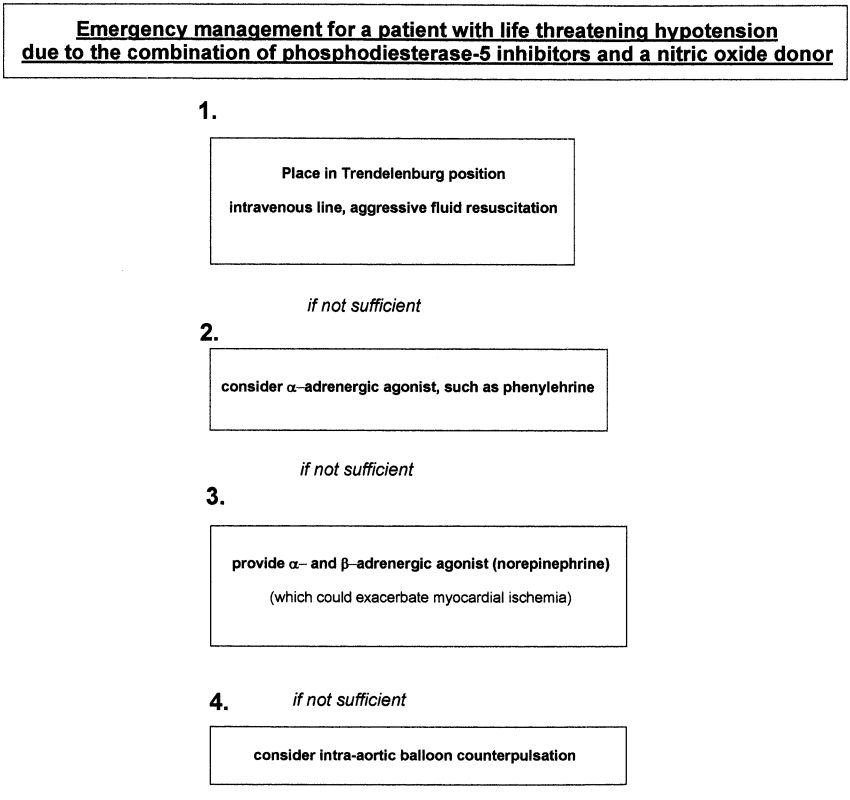

Fig. 2. Algorithm for the emergency treatment of patients with life-threatening hypotension owing to a combination of phosphodiesterase-5 inhibitors and nitric oxide donor. (Adapted from ref. *50.*)

effects on blood pressure were also relatively small *(71)*; importantly, combination with a wide range of blood pressure-lowering drugs, including angiotensin-converting enzyme inhibitors, calcium channel blockers, or β-blockers, seems to be well tolerated *(72)*. Nonetheless, a patient with a resting blood pressure of 90/50 mmHg or lower should not be given a PDE5 inhibitor. Similarly, patients taking sildenafil should not receive doxazosin at the same time because some patients will exhibit orthostatic hypotension. In our opinion, in patients with aortic stenosis or hypertrophic obstructive cardiomyopathy, one should also refrain from prescribing PDE5 inhibitors owing to the vasodilating effect.

Within 90 d of myocardial infarction and within 6 mo of a stroke, tadalafil, sildenafil, or vardenafil should not be used or used cautiously to treat ED.

For sildenafil, the absolute bioavailability amounts to 41% and is mainly determined by a hepatic first-pass effect *(73)*. It is metabolized by the cytochrome P4503A4 pathway, which is inhibited by a number of commonly prescribed drugs *(50)*. As a consequence, in older patients, patients with hepatic dysfunction, patients with renal dysfunction, or those taking concomitant medication, lower doses of sildenafil (starting with 25 mg) should be prescribed initially *(74)*.

The presence of PDE5 in platelets is consistent with observations that sildenafil potentiates the inhibitory effects of a nitric oxide donor on adenosine diphosphate -induced platelet aggregation in vitro. In healthy subjects, sildenafil alone or in combination with warfarin or aspirin did not affect bleeding time or prothrombin time *(50)*.However, in a recent study, a transient prolongation of bleeding time 1 h after administration of 100 mg of sildenafil was demonstrated *(75)*. Therefore, we recommend special caution in patients at risk of bleeding complications (e.g., peptic ulcers), especially when they are taking multiple anticoagulant and antiplatelet drugs (e.g., ticlopidine, clopidogrel, aspirin, or warfarin), which is relatively common in patients with cardiovascular disease.

Dopamine Agonists

Sublingual apomorphine has been shown to be effective in the treatment of ED, even if efficacy rates appear to be lower compared with sildenafil. Recent studies demonstrate its therapeutic potential in many male patients, including those with cardiovascular disease and diabetes *(76)*. These investigators also reported that combination with a wide range of antihypertensive agents is possible, and, most important, nitrates or other nitric oxide donors do not represent an absolute contraindication *(77)*. Baseline hypotension however, is a contraindication to the use of sublingual apomorphine.

Main side effects are related to the increased vagal tone, which might lead to nausea, bradycardia, sinus pauses, or even orthostatic syncope. We suggest caution in patients with cardiovascular disease with a history of syncope, sinus bradycardia, or atrioventricular conduction disturbances. Nonetheless, these agents may be an alternative for patients with cardiovascular disease, especially when the use of nitrates is necessary.

Vacuum Pump

The vacuum pump is an established choice in the treatment of ED. It may also be helpful for the patient with cardiovascular disease. No specific contraindications need to be considered except for general risk stratification according to the Princeton Consensus Panel, as outlined previously *(9)*.

Intracavernosal Self-Injection, Intraurethral Alprostadil, and Penile Protheses

The intracavernosal injection of vasodilating agents (e.g., alprostadil, which has a high efficacy) with orally available therapy has become a second-line treatment. This also applies to the intraurethral application of alprostadil. With respect to the patient with cardiovascular disease, the general consideration of whether sexual intercourse is advisable or not apply. A penile prothesis is certainly one of the last choices. For the patient with heart disease, the risk of surgery and anesthesia may dictate whether it is applicable *(9)*. Again, these treatment options may also be employed in the patient with cardiovascular disease after appropriate risk stratification, according to the abovementioned guidelines.

SUMMARY

Atherogenic risk factors are extremely common in the patient population with ED; therefore, a high percentage of patients with various forms and stages of heart disease and arterial disease also have ED. Presentation of a patient with ED might therefore prompt further investigations with respect to risk factors for atherosclerosis and the presence of silent ischemic heart disease. Any patient with ED ought to be encouraged to minimize his atherogenic risk through lifestyle changes and, in some cases, medical therapy. A drug regimen with a low incidence of ED as a side effect should be sought. Sexual activity can be regarded as an established trigger for a cardiac event, even if the absolute statistical risk is very low and definite. Therefore, in any patient with cardiovascular disease seeking treatment for ED, the first question should be whether sexual intercourse can safely be recommended. The Princeton Consensus Conference's *(52)* risk stratification guidelines for patients with heart disease are our preferred method of classifying patients with cardiovascular disease.

In many cases, an exercise test may be required to decide whether the patient is able to tolerate physical exercise during coition without evidence of ischemia or arrhythmia. These energy expenditures have been estimated as being equal to approx 5 to 6 METS at the upper range and 3 to 5 METS at the lower end.

For patients having a low risk, treatment of ED may be initiated by use of orally effective agents as first-line therapy, such as PDE5 inhibitors or apomorphine, taking into account specific contraindications. Most importantly, PDE5 inhibitors must not be combined with any nitric oxide donor owing to potentially life-threatening hypotension. Vacuum pumps and second-line treatment for ED may also be considered in some patients.

REFERENCES

1. Virag R, Bouilly P, Frydman D. (1985) Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. Lancet 1:181–184.
2. Johannes CB, Araujo AB, Feldman HA, et al. (2000) Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study. J Urol 163:460–463.
3. Feldman HA, Goldstein I, Hatzichristou DG, et al. (1994) Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 151:54–61.
4. Walczak MK, Lokhandwala N, Hodge MB, et al. (2002) Prevalence of cardiovascular risk factors in erectile dysfunction. J Gend Specif Med 6:19–21.
5. Kloner RA, Mullin SH, Shook T, et al. (2003) Erectile dysfunction in the cardiac patient: how common and should we treat? J Urol 170:S46–S50.
6. Levine LA, Kloner RA. (2000) Importance of asking questions about erectile dysfunction. Am J Cardiol 86:1210–1213.
7. Baldwin K, Ginsberg P, Harkaway RC. (2003) Under-reporting of erectile dysfunction among men with unrelated urologic conditions. Int J Impot Res 15:87–89.
8. O'Kane PD, Jackson G. (2001) Erectile dysfunction: is there silent obstructive coronary artery disease? Int J Clin Pract 55:219–220.
9. Levine LA. (2000) Diagnosis and treatment of erectile dysfunction. Am J Med. 109:3S–12S.
10. Benet AE, Melman A. (1995) The epidemiology of erectile dysfunction. Urol Clin North Am 22:699–709.
11. Greiner KA, Weigel JW. (1996) Erectile dysfunction. Am Fam Physician 54:1675–1682.
12. Kloner RA, Speakman M. (2002) Erectile dysfunction and atherosclerosis. Curr Atheroscler Rep 4:397–401.
13. Nicolosi A, Moreira ED, Shirai M, et al. (2003) Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology 61:201–206.
14. NIH Consensus Development Panel on Impotence. (1993) Impotence. JAMA 270: 83–90.
15. Nusbaum MR. (2002) Erectile dysfunction: prevalence, etiology, and major risk factors. J Am Osteopath Assoc 102:S1–S6.
16. McVary KT, Carrier S, Wessells H, Subcommittee on Smoking and Erectile Dysfunction Socioeconomic Committee, Sexual Medicine Society of North America. (2001) Smoking and erectile dysfunction: evidence based analysis. J Urol 166: 1624–1632.
17. Brock GB, Lue TF. (1993) Drug-induced male sexual dysfunction. An update. Drug Saf 8:414–426.
18. Keene LC, Davies PH. (1999) Drug-related erectile dysfunction. Adverse Drug React Toxicol Rev 18:5–24.
19. Nurnberg HG, Hensley PL, Gelenberg AJ, et al. (2003) Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. JAMA 289:56–64.
20. Roth A, Kalter-Leibovici O, Kerbis Y. et al. (2003) Prevalence and risk factors for erectile dysfunction in men with diabetes, hypertension, or both diseases: a community survey among 1412 Israeli men. Clin Cardiol 26:25–30.
21. Moulik PK, Hardy KJ. (2003) Hypertension, anti-hypertensive drug therapy and erectile dysfunction in diabetes. Diabet Med 20:290–293.

22. Kloner RA, Jarow JP. (1999) Erectile dysfunction and sildenafil citrate and cardiologists. Am J Cardiol 83:576–582.
23. Kim SW, Paick J, Park DW, et al. (2001) Potential predictors of asymptomatic ischemic heart disease in patients with vasculogenic erectile dysfunction. Urology 58:441–445.
24. Solomon H, Man J, Wierzbicki AS, et al. (2003) Erectile dysfunction: cardiovascular risk and the role of the cardiologist. Int J Clin Pract 57:96–99.
25. Sairam K, Kulinskaya E, Boustead GB, et al. (2001) Prevalence of undiagnosed diabetes mellitus in male erectile dysfunction. BJU Int 88:68–71.
26. Boyce EG, Umland EM. (2001) Sildenafil citrate: a therapeutic update. Clin Ther 23:2–23.
27. Levine SB. (2003) Erectile dysfunction: why drug therapy isn't always enough. Cleve Clin J Med 70:241–246.
28. Dorey G. (2001) Is smoking a cause of erectile dysfunction? A literature review. Br J Nurs 10:455–465.
29. Jeremy JY, Mikhailidis DP. (1998) Cigarette smoking and erectile dysfunction. J R Soc Health 118:151–155.
30. Mirone V, Imhimbo C, Bortolotti A, et al. (2002) Cigarette smoking as risk factor for erectile dysfunction: results from an Italian epidemiological study. Eur Urol 41:294–297.
31. Romeo JH, Seftel AD, Madhum ZT, et al. (2000) Sexual function in men with diabetes type 2: association with glycemic control. J Urol 163:788–791.
32. Hale TM, Okabe H, Heaton JP, et al. (2001) Antihypertensive drugs induce structural remodeling of the penile vasculature. J Urol 166:739–745.
33. Langford HG, Rockfold RW, Wassertheil-Smoller S, et al. (1989) Effect of weight loss on thiazide produced erectile problems in men. Trans Am Clin Climatol Assoc 101:190–194.
34. Carvajal A, Lerida MT, Sanchez A, et al. (1995) ACE inhibitors and impotence: a case series from the Spanish drug monitoring system. Drug Saf 13:130–131.
35. Llisterri JL, Lozano Vidal JV, Aznar Vicente J, et al. (2001) Sexual dysfunction in hypertensive patients treated with lorsatan. Am J Med Sci 321:336–341.
36. Ralph D, McNicholas T, for Erectile Dysfunction Alliance. (2000) UK management guidelines for erectile dysfunction. BMJ 321:499–503.
37. Rizvi K, Hampson JP, Harvey JN. (2002) Do lipid-lowering drugs cause erectile dysfunction? A system review. Fam Pract 19:95–98.
38. Schachter M. (2000) Erectile dysfunction and lipid disorders. Curr Med Res Opin 16:S9–S12.
39. Bruckert E, Giral P, Heshmati HM, et al. (1996) Men treated with hypolipidaemic drugs complain more frequently of erectile dysfunction. J Clin Pharm Ther 21: 89–94.
40. Derby CA, Mohr BA, Goldstein I, et al. (2000) Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 56:302–306.
41. Pitt B, Remme W, Zannad F, et al. (2003) Eplerone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 348:1309–1321.
42. Pitt B, Zannad F, Remme WJ, et al. (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 341:709–717.
43. Laumann EO, Paik A, Rosen RC, et al. (1999) Sexual dysfunction in the United States: prevalence and predictors. JAMA 281:537–544.
44. Sjorgen K, Fugl-Meyer AR. (1983) Some factors influencing quality of sexual life after myocardial infarction. Int Rehabil Med 5:197–201.

45. Jackson G. (2000) Sexual intercourse and stable angina pectoris. Am J Cardiol 86: 35F–37F.
46. Jackson G. (1997) Stable angina: drugs, angioplasty or surgery? Eur Heart J 18: B2–B10.
47. Bohlen JG, Held JP, Sanderson MO, et al. (1984) Heart rate, rate-pressure product and oxygen uptake during four sexual activities. Arch Intern Med 144:1745–1748.
48. DeBusk RF. (2000) Evaluating the cardiovascular tolerance for sex. Am J Cardiol 86:30F–56F.
49. Larson JL, McNaughton MW, Kennedy JW, et al. (1980) Heart rate and blood pressure response to sexual activity and a stair-climbing test. Heart Lung 9:1025–1030.
50. Cheitlin MD, Hutter AM, Brindis RG, et al. (1999) Use of sildenafil (Viagra) in patients with cardiovascular disease. J Am Coll Cardiol 33:273–282.
51. Ueno M. (1963) The so-called coition death. Jpn J Leg Med 17:330–335.
52. DeBusk R, Drory Y, Goldstein I, et al. (2000) Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. Am J Cardiol 86:175–181.
53. Muller JE, Mittleman MA, Maclure M, et al. (1996) Triggering myocardial infarction by sexual activity. JAMA 275:1405–1409.
54. DeBusk RF. (1996) Sexual activity triggering myocardial infarction: one less thing to worry about. JAMA 275:1447–1448.
55. Stein RA. (1977) The effect of exercise training on heart rate during sexual activity in the post-myocardial infarction patient. Circulation 55:738–740.
56. Jackson G. (1999) Erectile dysfunction and cardiovascular disease. Int J Clin Prac 53:363–368.
57. Drory Y, Fisman EZ, Shapira Y, et al. (1996) Ventricular arrhythmias during sexual activity in patients with coronary artery disease. Chest 109:922–924.
58. Kloner RA. (2000) Sex and the patient with cardiovascular risk factors: focus on sildenafil. Am J Med 109:13S–21S.
59. Arruda-Olson AM, Pellikka PA. (2003) Appropriate use of exercise testing prior to administration of drugs for treatment of erectile dysfunction. Herz 28:291–297.
60. Feenstra J, van Drie-Pierik RJ, Lacle CF, et al. (1998) Acute myocardial infarction associated with sildenafil. Lancet 352:957–958.
61. Zusman RM, Morales A, Glasser DB, et al. (1999) Overall cardiovascular profile of sildenafil citrate. Am J Cardiol 83:35C–44C.
62. Kloner RA. (2000) Cardiovascular risk and sildenafil. Am J Cardiol 86:57F.
63. Padma-Nathan H, Eardley I, Kloner RA, et al. (2002) A 4-year update on the safety of sildenafil citrate (Viagra®). Urology 60:67–90.
64. Reffelmann T, Kloner RA. (2003) Therapeutic potential of phosphodiesterase 5 inhibition for cardiovascular disease. Circulation 108:239–244.
65. Reffelmann T, Kloner RA. (2003) Effects of sildenafil on myocardial infarct size, microvascular function, and acute ischemic left ventricular dilation. Cardiovasc Res 59:441–449.
66. Morales A, Gingell C, Collins M, et al. (1998) Clinical safety of oral sildenafil citrate (Viagra) in the treatment of erectile dysfunction. Int J Impot Res 10:69–73; discussion 73,74.
67. Wysowski DK, Farinas E, Swartz L. (2002) Comparison of reported and expected deaths in sildenafil (Viagra) users. Am J Cardiol 89:1331–1334.
68. Kloner RA, Mohan P, Norenberg C, et al. (2002) Cardiovascular safety of vardenafil, a potent, highly selective PDE-5 inhibitor in patients with erectile dysfunction: an analysis of five placebo-controlled clinical trials. Pharmacotherapy 22:1371–1376.

69. Gresser U, Gleiter CH. (2002) Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil. Review of the literature. Eur J Med Res 7:435–446.
70. Corbin JD. (2002) Pharmacology of phosphodiesterase-5 inhibitors. Int J Clin Pract 56:453–459.
71. Vardi Y, Klein L, Nassar S, et al. (2002) Effects of sildenafil citrate (Viagra) on blood pressure in normotensive and hypertensive men. Urology 59:747–752.
72. Kloner RA, Brown M, Prisant LM, et al. (2001) Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. Am J Hypertens 14:70–73.
73. Nichols DJ, Muirhead GJ, Harness JA, et al. (2002) Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. Br J Clin Pharmacol 53:5S–12S.
74. Muirhead GJ, Wilner K, Colburn W, et al. (2002) The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil. Br J Pharmacol 53: 21S–30S.
75. Berkels R, Klotz T, Sticht G, et al. (2001) Modulation of human platelet aggregation by the phosphodiesterase 5 inhibitor sildenafil. J Cardiovasc Pharmacol 37: 413–421.
76. Montorsi F. (2003) Tolerability and safety of apomorphine SL (Ixense). Int J Impot Res 15:S7–S9.
77. Fagan TC, Buttler S, Marbury T, et al. (2001) Cardiovascular safety of sublingual apomorphine in patients on stable doses of oral antihypertensive agents and nitrates. Am J Cardiol 88:760–766.

10 Is Diabetic Erectile Dysfunction More Difficult to Treat?

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and Vivian A. Fonseca, MD

CONTENTS

INTRODUCTION

Approximately 35 to 75% of men with diabetes mellitus (DM) have erectile dysfunction (ED). ED occurs about 5 to 10 yr earlier in men with diabetes than in age-matched controls *(1)*. In a cross-sectional survey of 541 men with diabetes at a community-based clinic, the prevalence of ED increased progressively with age, from 6% in men aged 20 to 24 yr to 52% in those aged 55 to 59 yr *(2)*. After the age of 60, 55 to 95% of men with diabetes are affected by ED, compared with approx 50% in an unselected population in the Massachusetts Aging Male Survey *(3,4)*. In another cohort of patients who had type 1 diabetes for at least 10 yr, ED was reported in 1.1% of men aged 21 to 30 yr, 55% of men aged 50 to 60 yr, and 75% of men older than 60 yr *(5)*.

ED in men with diabetes is correlated with glycosylated hemoglobin A (A_{1c}), but it is not known whether improving control of this factor will improve ED. The presence of peripheral neuropathy also increases the risk of ED, possibly as a result of undiagnosed autonomic neuropathy. (Almost 100% of patients with diabetic neuropathy will have ED.)

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Table 1
Pathophysiology and Factors Complicating Diabetic ED

- Glycation of elastic fibers caused by hyperglycemia and increasing age, with failure of relaxation of the corpora cavernosa *(37)*.
- Multiple drug treatments associated with erectile dysfunction—diuretics, β-blockers.
- Dyslipidemia.
- Endothelial dysfunction of the sinusoidal endothelial cells resulting in a decrease in nitric oxide (NO) release and impaired vasodilatation.
- Peripheral vascular disease resulting in reduced arterial and arteriolar inflow *(42)*.
- Increase in reactive oxidizing substances and reduction in NO production caused by advanced glycation end products *(39,43)*.
- Failed neural signal transmission to and from the spinal cord due to diabetic neuropathy *(44)* and reduced production of neuronal NO synthase *(45)*; reduced levels of neuronal NO released to the cavernosal smooth muscle.
- Hypogonadotrophic hypogonadism *(29,30)*.

There have been major advances in the treatment of ED. Some data suggest that patients with diabetes do not respond to treatment as successfully as do nondiabetic men. In this review, we examine the evidence for this assertion, as well as review the potential pathophysiological reasons for this phenomenon.

PATHOPHYSIOLOGY OF ED IN DM

ED in diabetes has a multifactorial etiology. It is the result of a combination of impairments in nearly every step responsible for the production of penile erection.

Table 1 lists these impairments and other indirectly acting mechanisms responsible for diabetic ED. Patients with diabetes often suffer from hypertension, obesity, and dyslipidemia.

The clinician must consider these etiological factors when treating ED in men with diabetes. In addition, a comprehensive evaluation should include assessment of gonadal function, medication, and drug history along with psychological and marital status *(6)*.

The risk factors for ED are the same as those for cardiovascular disease and are listed in Table 2.

ED is often the first warning sign of underlying cardiovascular problems, which are more common in persons of either sex affected by diabetes.

Table 2
Risk Factors for ED

Risk factor	*Percent risk for ED*
Diabetes mellitus	23
Hypertension	44
Hyperlipidemia (low-density lipoprotein >120 mg/dL)	74
Hypogonadism	36
Increased weight (body mass index >26.9)	79

Fortunately, the treatment options for ED have expanded in recent years, especially with the introduction of phosphodiesterase-5 (PDE5) inhibitors. However, a significant proportion of men with diabetes and ED are still frustrated by poor responses to the available treatment modalities *(7,8)*. This often leads to noncompliance and increasing psychological distress as patients run out of therapeutic options.

It is the multifactorial etiology that makes ED in diabetes harder to treat, and most treatments deal with only one part of the ED equation. This leads to partial or poor responses. Ongoing research is looking at agents, or combinations thereof, that will deal with all aspects of diabetic ED. The most promising therapeutic agents available so far are the PDE5 inhibitors.

Endothelial Dysfunction

The endothelium is important in the maintenance of vascular health. It is a critical determinant of vascular tone and patency, reactivity, inflammation, vascular remodeling, and blood fluidity. The importance of endothelial dysfunction in the pathogenesis of cardiovascular disease in diabetes has only recently been recognized *(9)*.

A link between erectile and endothelial dysfunction was suggested in a study by De Angelis et al. *(10)*. Thirty men with diabetes and symptomatic ED were matched for age and disease with 30 potent men with type 2 diabetes. The decrease in blood pressure and platelet aggregation in response to L-arginine was lower in patients with ED ($p < 0.05$–0.02). Soluble thrombomodulin, P-selectin, and intercellular adhesion molecule-1 (ICAM-1) concentrations were higher. Indices of coagulation activation (F1 and 2, D-dimers) and reduced fibrinolysis (plasminogen activator inhibitor-1 [PAI-1]) were also found to be higher in the men with ED ($p < 0.05$–0.02).

The investigators concluded that ED in men with diabetes correlates with endothelial dysfunction.

The same vascular and endothelial injuries that occur in the coronary arteries likely occur in the cavernosal arteries, the primary vessels supplying penile erectile tissue *(11)*.

Nitric oxide (NO) is the most potent known vasodilator and is secreted by the endothelium. It is synthesized from L-arginine by the endothelial enzyme NO synthase (eNOS). The bioavailability of NO can be decreased by various mechanisms—decreased production by eNOS, enhanced NO breakdown owing to increased oxidative stress, or both. eNOS deactivation is often associated with an increase in plasma levels of its endogenous inhibitor, asymmetrical dimethyl-L-arginine (ADMA) *(12)*.

Increased levels of ADMA are associated with endothelial dysfunction and increased risk of cardiovascular disease. Increases in plasma ADMA concentrations may contribute to the endothelial dysfunction observed in insulin-resistant individuals and also to macrovascular disease in diabetes.

It is not clear why the ADMA level is higher in subjects with type 2 diabetes. A recent animal study suggests that this is a direct effect of glucose on dimethylarginine dimethylaminohydrolase (DDAH) activity. This enzyme is responsible for ADMA breakdown. Diabetic rats had reduced levels of DDAH activity (not expression), and this was negatively correlated with their plasma ADMA levels. DDAH activity was significantly reduced in vascular smooth muscle cells and human endothelial cells exposed to high glucose levels. The impairment of DDAH activity in vascular cells was associated with an accumulation of ADMA and a reduction in cyclic GMP (cGMP) synthesis *(13)*.

There is a growing body of evidence that ED correlates with the level of glycemic control. In animal experiments, glycated hemoglobin significantly impairs endothelial NO-mediated corpus cavernosal relaxation in vitro. This is partly because of the generation of superoxide anions and the extracellular inactivation of NO *(14)*. A retrospective analysis of a cohort of men with type 2 diabetes demonstrated that A_{1c} was an independent predictor of erectile function score *(1)*. No large scale, well-designed human studies are available to confirm that improvement in glycemic control results in improved ED. Given the association of A_{1c} with microvascular disease, improved glycemia should, at least, slow down progression of ED.

Endothelial dysfunction and NO are also linked to microvascular complications of diabetes, including neuropathy. The role of neuronal nitric oxide synthase (nNOS) was studied in rats with uncontrolled diabetes. These rats had decreased expression of nNOS in the dorsal root ganglia and diminished withdrawal responses to noxious mechanical stimuli. cGMP levels paralleled nNOS expression. Insulin treatment led to improved nerve conduction and increased nNOS expression. This suggests that a decreased

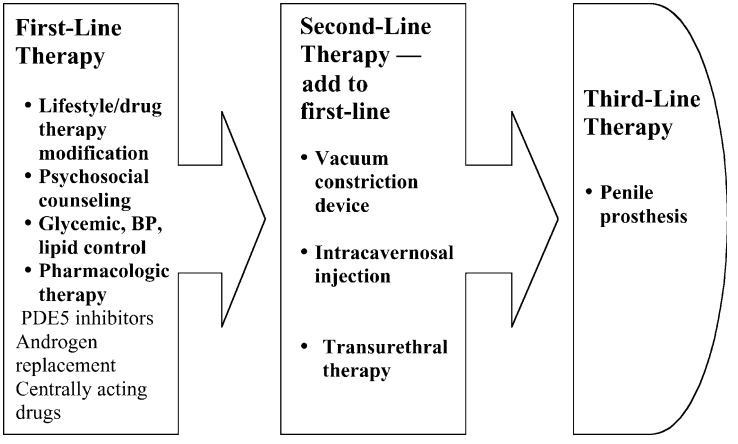

Fig.1. Proposed step-care approach to diabetic ED therapy.

nNOS–cGMP system in the dorsal root ganglion may play a role in the pathogenesis of diabetic neuropathy *(15)*. It might provide a link between diabetic neuropathy and endothelial dysfunction in patients with diabetes and ED.

The ability to increase blood flow depends on an intact neurogenic vascular response. Diabetic autonomic neuropathy leads to impaired endothelium-dependent and endothelium-independent vasodilatation, even in the absence of clinical macrovascular disease *(16)*. The interaction between endothelial dysfunction and autonomic neuropathy results in an inability to increase blood flow under conditions of stress or increased demands.

Efficacy of Treatment for ED in Patients With DM

Figure 1 suggests a stepped-care approach to treatment of ED in men with diabetes.

Table 3 summarizes the data available for the different treatment options in ED. It also shows comparisons of success rates in men with and without diabetes, supporting the hypothesis that patients with diabetes have a lower rate of efficacy with treatment of ED.

PDE5 Inhibitors

In 1999, the Food and Drug Administration approved sildenafil citrate for clinical use in the treatment of ED. Tadalafil and vardenafil are the newer generation of agents in this class. These are potent and selective inhibitors of cGMP-specific PDE5. They prevent breakdown of cGMP and prolong and improve smooth muscle relaxation.

Table 3
Treatment Options for ED and Percentage Response (Improved Erections)

		Response (%)	
Treatment modality		*Diabetic ED*	*Nondiabetic ED*
PDE5 inhibitors:	Sildenafil	59 *(46)*[a]	74 *(50)*
		64 *(47)*[b]	—
	Tadalafil	64 *(48)*	81 *(18)*
	Vardenafil	72 *(49)*	85 *(51)*
Intracavernosal PGE_1 derivative (alprostadil)		80–85	
Intraurethral PGE_1 (MUSE)		70 *(23)*	
Vacuum devices		75 *(24)*	
Surgical implants		86 *(25)*	
Androgen therapy		17	—
Combination injection therapy		84 *(52)*	—

[a] Type 1 diabetes mellitus.
[b] Type 2 diabetes mellitus.
DM, diabetes mellitus; MUSE, Medicated Urethral System for Erection; PDE phosphodiesterase; PGE_1, prostaglandin E_1.

A meta-analysis of 11 randomized, double-blind, placebo-controlled trials of sildenafil citrate in patients with diabetes reported improved erections in 59% of those with type 1 diabetes and in 63% of those with type 2 diabetes *(7)*. Improvement was noted regardless of age, race, ED severity and duration, or the presence of various comorbidities *(17)*. The response rate in men with diabetes is less than the 83% improvement seen in nondiabetic individuals with ED. Discontinuation rates range from 5 to 17%, primarily because of insufficient clinical response *(8)*.

For tadalafil, 76% of men with diabetes taking the 20-mg dose had improved erections, and 58% of the total group had satisfactory erections to complete intercourse (data on file Lilly ICOS, LLC, Indianapolis, IN).

In nondiabetic men, the rates were 81% and 75%, respectively *(18)*. Vardenafil led to similar results in nondiabetic men, with a 71 to 75% improvement in erections with 5-, 10-, and 20-mg doses. In men with diabetes, the response to the 10-mg dose was 57%, and the response to the 20-mg dose was 72% *(19)*.

It is possible that this lower response rate in men with diabetes is related to their impaired endothelial function *(10)*. This causes a decrease in NO release. Because PDE5 inhibitors enhance the downstream effect of NO, if NO production is very low, they are unlikely to be effective.

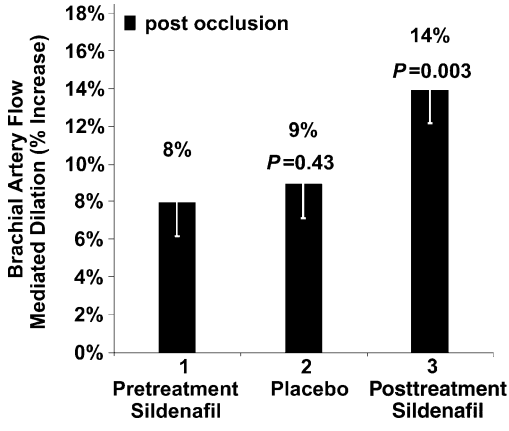

Fig. 2. Effect of chronic sildenafil citrate on flow-mediated arterial dilatation. (Reproduced with permission from ref. *20.* Copyright © 2002 American Diabetes Association.)

Recent studies show that both acute and chronic sildenafil citrate therapy improves brachial artery flow-mediated dilatation, an effect of intrinsic endothelial NO release (Fig. 2) *(20)*.

This enhanced dilatation suggests that sildenafil citrate directly improves endothelial function. Similar findings were noted in another study *(21)*. In addition, sildenafil citrate dilates epicardial coronary arteries and inhibits platelet activation in patients with coronary artery disease *(22)*. Other studies are under way to test the hypothesis that chronic sildenafil use improves biochemical markers of endothelial dysfunction.

Based on these findings, men with diabetes and ED may benefit from daily dosing with sildenafil citrate at the onset of treatment to allow better response with subsequent use. This "priming" phase of therapy could restore endothelial function secondary to PDE5 inhibition. Preliminary confirmation of this hypothesis comes from *post hoc* analysis of small studies (personal communication, Pfizer Inc.). Confirmation from a large randomized clinical trial is needed.

Lack of sexual activity because of ED decreases testosterone levels through a central effect on the hypothalamic–pituitary axis. A recent study looked at the effect of different PDE5 inhibitor treatments for ED on the reversibility of the endocrine pattern. This was an open-label, retrospective study of 74 consecutive patients who were treated on demand with 50 mg of sildenafil and 20 mg of tadalafil. The success in sexual intercourse was recorded and total and free testosterone levels were studies before and after

3 mo of treatment. Basal levels of total and free testosterone were at the bottom of the normal range and luteinizing hormone (LH) levels were at the top of the high normal range. After treatment, this pattern was reversed in both groups. However, the testosterone increase in sildenafil-treated patients was significantly lower than in tadalafil-treated patients (47 ± 2.7 vs 5.1 ± 0.9, $p < 0.001$). Free testosterone levels followed a directly proportional patter, whereas the inverse was found when LH production was studied. The intercourse rate reflected this effect as the sildenafil group showed a 4.9 ± 2.9/mo full sexual intercourse rate, whereas the tadalafil group had a higher rate of sexual intercourse (6.9 ± 4.6/mo, $p = 0.04$). Drug consumption was comparable between the groups (sildenafil, 4.9 ± 2.9 vs tadalafil, 4.4 ± 2.8 pills/mo, $p = 0.72$). Because it is unlikely that the two drugs have a different effect on the pituitary–testicular axis, this effect is probably a result of the higher frequency of full sexual intercourse in the tadalafil-treated group. This could be attributed to the drug's longer half-life *(23)*.

Intracavernosal Therapy

Several vasoactive substances can be used to stimulate the erectile process. These can be delivered directly into the corpora cavernosa by injection. Papaverine (a nonspecific PDE) and alprostadil (a prostaglandin E1 [PGE_1] derivative) relax the smooth muscle of the corpora cavernosa. Phentolamine, a competitive inhibitor of α-adrenergic receptors, reduces sympathetic tone. Urologists have also combined these three agents.

Alprostadil is a synthetic prostaglandin related to PGE_1. It has α-blocking properties, is a vasodilator, and directly relaxes smooth muscle via a prostacyclin receptor. A number of studies have been reported of the use of alprostadil in men with diabetes and ED. The largest study included 577 men. Sixty-nine percent of these men completed the 6-mo injection therapy study. Eighty-seven percent reported satisfactory sexual function. The 31% of study noncompleters complained of pain at the injection sites and lack of efficacy. Of all the studies, 50% of men complained of pain at injection sites.

Although intracavernosal therapy has a success rate of 80 to 90% in neuropathic ED and 70% in vasculopathic ED, half of the men eventually discontinue the treatment because of pain, loss of efficacy, or lack of interest.

Because diabetic complications, including poor visual acuity from retinopathy and decreased manual dexterity, increase with age, it is not uncommon that diabetic men are excluded from this therapy or have a poor response.

Intraurethral Prostaglandin Therapy

An intraurethral alprostadil suppository system (Medicated Urethral System for Erection [MUSE]) was developed in an attempt to avoid the problems and issues of injection therapy *(24)*. This is less effective and may cause urethral pain in 30% of users but it avoids the side effects of injection therapy. It is not effective in men who fail injection therapy. In the largest published study, 70% of men with diabetes were able to achieve an erection satisfactory for intercourse in 70% of the attempts. Only 2.4% discontinued the drug because of pain *(24)*.

Combination therapy could be used to augment the effect of MUSE. No clinical trial data support these combinations, but such treatment is available.

Vacuum-Constriction Devices

Vacuum tumescence devices work irrespective of the underlying cause of ED. Reported success in men with diabetes is 75% *(25)*. Most find the technique acceptable, especially if they tried oral or injection therapy and it failed. Some individuals consider it cumbersome, but other couples treat the application of the device as a form of sexual foreplay and therefore are more acceptable of its use. It can also be added to one of the other treatment modalities to enhance a partial response.

Surgery

Penile prostheses are rarely recommended now that penile injection and vacuum therapy are widely available. However, there is an 86% success rate at 5 yr, and 91% of attainable erections are suitable for coitus *(26)*. Men with diabetes are particularly prone to prosthesis-associated infection, which often necessitates prosthesis removal and possible worsening of the primary problem.

Rarely, a severely compromised blood flow could be the reason for treatment failure. Revascularization might help some of these individuals, but it is difficult to select patients with a predictable good outcome. Revascularization is contraindicated in men with diabetes *(27)*. In other patients, venous incompetence prevails, and ligation of the deep dorsal vein and any incompetent circumflex veins can improve venous leakage.

Unfortunately, the complexity of ED, such as underlying endothelial dysfunction and neuropathy, and the extent of vascular disease in patients with diabetes lead to less successful outcomes for these surgical procedures. Surgery should be reserved for clear-cut cases of vascular or venous insufficiency in young patients with recent-onset diabetes.

α-Blockers

Yohimbine and phentolamine are α-adrenergic blockers. They have modest efficacy in treating ED but are not widely used, especially in the United States, because of lack of availability or side effects, including palpitations and hypertension. In a recent study in 18 nonsmoking males with ED, there was a 50% success rate (completion of intercourse) in more than 75% of attempts. The responders tended to have less severe ED *(28)*. A meta-analysis of yohimbine use found it to be more effective than placebo *(29)*.

Androgen Therapy

Investigation of ED should always include obtaining a plasma testosterone level. If this is low, a prolactin level should be checked to rule out a central problem. Screening the serum testosterone levels of 105 consecutive patients with impotence showed that 37 patients had previously unsuspected disorders of the hypothalamic–pituitary–gonadal axis. Twenty had hypogonadotropic hypogonadism, seven had hypergonadotropic hypogonadism, eight had hyperprolactinemia, and two had occult hyperthyroidism. Once the specific defect was defined and treated, potency was restored in 33 patients *(30)*.

Obese men with type 2 diabetes are more prone to hypogonadotropic hypogonadism *(31)*. This is attributed to elevated levels of estrone and estradiol produced by the aromatase enzyme in adipose tissue derived from adrenal (androstenedione) and testicular (testosterone) androgen. Aging is also associated with a progressive decline in androgens *(32)*. Serum testosterone concentration is inversely associated with carotid atherosclerosis in men with type 2 diabetes *(33)*.

It is uncertain if either of these factors contribute to ED, but they must be recognized and, if severe, treated with androgen replacement.

Testosterone monotherapy has had quite poor results in treatment of ED. Long-term sexual function improved in only 17% of 78 obese men with type 2 diabetes when they were placed on testosterone enanthate.

In a smaller study of 17 patients with ED as a result of secondary hypogonadism, patients received clomiphene citrate or placebo for 2 mo each (crossover design). LH, follicle-stimulating hormone, and total and free testosterone levels showed significant elevation in response to clomiphene citrate over the response to placebo. However, sexual function as monitored by questionnaires and nocturnal penile tume-scence and rigidity testing, did not improve except for some limited parameters in younger and healthier men. The results confirmed that there can be a functional secondary hypogonadism in men on an outpatient basis, but correction of the hormonal status does not universally reverse the associated ED to normal.

Thus, closer scrutiny of claims of cause and effect relationships is required between hypogonadism and ED *(34)*.

The use of testosterone in men with normal testosterone levels is not recommended. Replacement therapy should be reserved for those who are androgen deficient, and especially if contemplating the use of a PDE5 inhibitor. These agents require the presence of NO if they are to work because neural NO production is androgen-dependent.

Statin Therapy

Total cholesterol and high-density lipoprotein (HDL) cholesterol are important predictors of ED. In a study of 3250 men (mean age, 51 yr) followed for a mean of 22 mo, 71 developed ED during follow-up. Those subjects with total cholesterol greater than 240 mg/dL had a 1.83-fold increased risk of ED. An HDL level of greater than 60 mg/dL meant a 0.30-fold risk for ED. This suggests that a high total cholesterol level and a low HDL cholesterol level are risks for ED *(35)*.

Given the correlation between hyperlipidemia and ED, a recent small study showed improvement in ED by lowering cholesterol using atorvastatin daily for 4 mo. It is unclear whether this is a direct effect of lipid lowering or an indirect effect from improved endothelial dysfunction (*36*).

Other Management Strategies

There are several over-the-counter herbal remedies but there are no adequate scientific data to support their safety or efficacy *(37)*.

Medication history is very important to consider, especially in men with diabetes, who are often on multiple drugs to treat hypertension, dyslipidemia, depression, glaucoma, neuropathic pain, and diabetes itself. The major culprits are antihypertensives, especially nonselective β-blockers, sympatholytics, and diuretics (Table 4).

The main problem in diabetes is that often these agents cannot be replaced. β-blocker therapy is essential in patients with coronary artery disease or heart failure; depression and painful conditions should be adequately treated. All these problems are very real to the patient and may exacerbate ED if not adequately managed. The clinician should try to optimize therapy using agents that are least likely to cause ED. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, and thiazolidinediones either enhance NO levels or block production of oxygen radicals, which quench NO and prevent vasodilation *(10,38–42)*. Other studies suggest that angiotensin-converting enzyme inhibitors increase the incidence of ED (relative risk [RR] 2.78). This is still less than with diuretic therapy (RR 3.86).

Table 4
Investigation of Nonresponders

Medication history[a]

- Antihypertensives: β-blockers, thiazide diuretics, clonidine, spironolactone, methyldopa (angiotensin-converting enzyme inhibitors and α-blockers are agents of choice).
- Agents acting on the central nervous system: tricyclic antidepressants, selective serotonin reuptake inhibitors, phenothiazines, butyrophenones, atypical antidepressants (trazodone is agent of choice when indicated).
- Agents affecting the endocrine system: antiandrogens, gonadotropin-releasing hormone agonists and antagonists, estrogens, cimetidine, metoclopramide, fibric acid derivatives, alcohol, marijuana. (consider proton-pump inhibitors, statins when indicated).

Hormonal status

- Total testosterone.
- Luteinizing hormone, follicle-stimulating hormone, prolactin.
- Ferritin.

Autonomic neuropathy

- Electrocardiogram (R-R variability); heart rate variability.
- Orthostatic blood pressure readings.
- Tilt-table studies.

Vascular disease

- Doppler studies of penile blood flow.
- Pharmacodynamic testing using vasoactive compounds.
- Pudendal angiography and cavernosometry.

Psychosocial assessment

- Combine with nocturnal penile tumescence test.
- Marital counseling.

[a] Change agents that could contribute to the problem
R-R, distance between subsequent R-waves of an electrocardiogram.

Animal experiments have recently shown that NOS can be restored by gene transfer techniques and can physiologically improve erectile function *(43)*. This is an exciting field that could lead to the development of more therapeutic options in the treatment of ED.

CONCLUSION

The cause of ED in patients with diabetes is multifactorial. Every effort should be made to correct or improve all causes of ED, whether organic, psychogenic, or iatrogenic. A multidisciplinary approach is recommended

to deal with comorbidities to ensure the best possible outcomes for patients with ED and diabetes.

Diabetes is a complex chronic disorder associated with various factors that could exacerbate ED: obesity, poor glycemic control, dyslipidemia, micro- and macrovascular disease, and autonomic neuropathy. All interact to some degree and exacerbate erectile failure. Endothelial dysfunction is probably the major underscoring factor that makes diabetic ED more difficult to treat.

More research is needed in this exciting field to develop more effective therapies to improve the quality of life for patients with diabetes and their loved ones.

REFERENCES

1. Romeo JH, Seftel AD, Madhun ZT, et al. (2000) Sexual function in men with diabetes type 2: association with glycemic control. J Urol 163:788–791.
2. McCulloch DK, Campbell IW, Wu FC, et al. (1980) The prevalence of diabetic impotence. Diabetologia 18:279–283.
3. Feldman HA, Goldstein I, Hatzichristou DG, et al. (1994) Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 151:54–61.
4. Kaiser FE. (1999) Erectile dysfunction in the aging man. Med Clin North Am 83: 1267–1278.
5. Klein R, Klein BE, Lee KE, et al. (1996) Prevalence of self-reported erectile dysfunction in people with long-term IDDM. Diabetes Care 19:135–141.
6. Richardson D, Vinik A. (2002) Etiology and treatment of erectile failure in diabetes mellitus. Curr Diab Rep 2:501–509.
7. Fink HA, Mac DR, Rutks IR, et al. (2002) Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med 162:1349–1360.
8. Guay AT, Perez JB, Velasquez E, et al. (2000) Clinical experience with intraurethral alprostadil (MUSE) in the treatment of men with erectile dysfunction. A retrospective study. Medicated urethral system for erection. Eur Urol 38:671–676.
9. Calles-Escandon J, Cipolla M. (2001) Diabetes and endothelial dysfunction: a clinical perspective. Endocr Rev 22:36–52.
10. De Angelis L, Marfella MA, Siniscalchi M, et al. (2001) Erectile and endothelial dysfunction in type II diabetes: a possible link. Diabetologia 44:1155–1160.
11. Levine LA, Kloner RA. (2000) Importance of asking questions about erectile dysfunction. Am J Cardiol 86:1210.
12. Theuma P, Fonseca VA. (2003) Novel cardiovascular risk factors and macrovascular and microvascular complications of diabetes. Curr Drug Targets 4: 477–486.
13. Lin KY, Ito A, Asagami T, et al. (2002) Impaired nitric oxide synthase pathway in diabetes mellitus: role of asymmetric dimethylarginine and dimethylarginine dimethylaminohydrolase. Circulation 106:987–992.
14. Cartledge JJ, Eardley I, Morrison JF. (2000) Impairment of corpus cavernosal smooth muscle relaxation by glycosylated human haemoglobin. BJU Int 85: 735–741.
15. Sasaki T, Yasuda H, Maeda K, et al. (1998) Hyperalgesia and decreased neuronal nitric oxide synthase in diabetic rats. Neuroreport 9:243–247.

16. Veves A, Akbari CM, Primavera J, et al. (1998) Endothelial dysfunction and the expression of endothelial nitric oxide synthetase in diabetic neuropathy, vascular disease, and foot ulceration. Diabetes 47:457–463.
17. Carson CC, Burnett AL, Levine LA, et al. (2002) The efficacy of sildenafil citrate (Viagra) in clinical populations: an update. Urology 60:12–27.
18. Brock GB, McMahon CG, Chen KK, et al. (2002) Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol 168: 1332–1336.
19. Porst H, Rosen R, Padma-Nathan H, et al. (2001) The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 13: 192–199.
20. Desouza C, Parulkar A, Lumpkin D, et al. (2002) Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilatation in type 2 diabetes. Diabetes Care 25:1336–1339.
21. Katz SD, Balidemaj K, Homma S, et al. (2000) Acute type 5 phosphodiesterase inhibition with sildenafil enhances flow-mediated vasodilation in patients with chronic heart failure. J Am Coll Cardiol 36:845–851.
22. Halcox JP, Nour KR, Zalos G, et al. (2002) The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia. J Am Coll Cardiol 40:1232–1240.
23. Carosa E, Martini P, Brandetti F, et al. (2004) Type V phosphodiesterase inhibitor treatments for erectile dysfunction increase testosterone levels. Clin Endocrinol (Oxf). 61:382–386.
24. Padma-Nathan H, Hellstrom WJ, Kaiser FE, et al. (1997) Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. N Engl J Med 336:1–7.
25. Price DE, Cooksey G, Jehu D, et al. (1991) The management of impotence in diabetic men by vacuum tumescence therapy. Diabet Med 8:964–967.
26. Carson CC, Mulcahy JJ, Govier FE. (2000) Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. AMS 700CX Study Group. J Urol 164:376–380.
27. Benet AE, Sharaby JS, Melman A. (1994) Male erectile dysfunction assessment and treatment options. Compr Ther 20:669–6673.
28. Guay AT, Spark RF, Jacobson J, et al. (2002) Yohimbine treatment of organic erectile dysfunction in a dose-escalation trial. Int J Impot Res 14:25–31.
29. Ernst E, Pittler MH. (1998) Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. J Urol 159:433–436.
30. Spark RF, White RA, Connolly PB. (1980) Impotence is not always psychogenic. Newer insights into hypothalamic-pituitary-gonadal dysfunction. JAMA 243: 750–755.
31. Tan RS, Pu SJ. (2002) Impact of obesity on hypogonadism in the andropause. Int J Androl 25:195–201.
32. Leifke E, Gorenoi V, Wichers C. et al. (2000) Age-related changes of serum sex hormones, insulin-like growth factor-1 and sex-hormone binding globulin levels in men: cross-sectional data from a healthy male cohort. Clin Endocrinol (Oxf) 53: 689–695.
33. Fukui M, Kitagawa Y, Nakamura N, et al. (2003) Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes. Diabetes Care 26:1869–1873.

34. Guay AT, Bansal S, Heatley GJ. (1995) Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. J Clin Endocrinol Metab 80: 3546–3552.
35. Wei M, Macera CA, Davis DR, et al. (1994) Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. Am J Epidemiol 140:930–937.
36. Saltzman EA, Guay AT, Jacobson J. (2004) Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. J Urol 172:255–258.
37. Moyad MA, Hathaway S, Ni HS. (1999) Traditional Chinese medicine, acupuncture, and other alternative medicines for prostate cancer: an introduction and the need for more research. Semin Urol Oncol 17:103–110.
38. Colberg SR, Stansberry KB, McNitt PM, et al. (2002) Chronic exercise is associated with enhanced cutaneous blood flow in type 2 diabetes. J Diabetes Complications 16:139–145.
39. Jiaan DB, Seftel AD, Fogarty J, et al. (1995) Age-related increase in an advanced glycation end product in penile tissue. World J Urol 13:369–375.
40. Plante GE. (2002) Vascular response to stress in health and disease. Metabolism 51:25–30.
41. Seftel AD, Vaziri ND, Ni Z, et al. (1997) Advanced glycation end products in human penis: elevation in diabetic tissue, site of deposition, and possible effect through iNOS or eNOS. Urology 50:1016–1026.
42. Xie Y, Garban H, Ng C, et al. (1997) Effect of long-term passive smoking on erectile function and penile nitric oxide synthase in the rat. J Urol 157:1121–1126.
43. Bivalacqua TJ, Usta MF, Champion HC, et al. (2003) Gene transfer of endothelial nitric oxide synthase partially restores nitric oxide synthesis and erectile function in streptozotocin diabetic rats. J Urol 169:1911–1917.
44. Jevtich MJ, Edson M, Jarman WD, et al. (1982) Vascular factor in erectile failure among diabetics. Urology 19:163–168.
45. Burchardt T, Burchardt M, Karden J, et al. (2000) Reduction of endothelial and smooth muscle density in the corpora cavernosa of the streptozotocin induced diabetic rat. J Urol 164:1807–1811.
46. Bemelmans BL, Meuleman EJ, Doesburg WH, et al. (1994) Erectile dysfunction in diabetic men: the neurological factor revisited. J Urol 151:884–889.
47. Vernet D, Cai L, Garban H, et al. (1995) Reduction of penile nitric oxide synthase in diabetic BB/WORdp (type I) and BBZ/WORdp (type II) rats with erectile dysfunction. Endocrinology 136:5709–5717.
48. Stuckey BG, Jadzinsky MN, Murphy LJ, et al. (2003) Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. Diabetes Care 26:279–284.
49. Boulton AJ, Selam JL, Sweeney M, et al. (2001) Sildenafil citrate for the treatment of erectile dysfunction in men with type II diabetes mellitus. Diabetologia 44: 1296–1301.
50. Saenz de Tejada I, Anglin G, Knight JR, et al. (2002) Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 25:2159–2164.
51. Goldstein I, Young JM, Fischer J, et al. (2003) Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 26: 777–783.

52. Padma-Nathan H, Steers WD, Wicker PA. (1998) Efficacy and safety of oral sildenafil in the treatment of erectile dysfunction: a double-blind, placebo-controlled study of 329 patients. Sildenafil Study Group. Int J Clin Pract 52:375–379.
53. Hellstrom WJ, Gittelman M, Karlin G, et al. (2002) Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 23:763–771.
54. Valdevenito R, Melman A. (1994) Intracavernous self-injection pharmacotherapy program: analysis of results and complications. Int J Impot Res 6:81–91.

11 Depression and Antidepressant-Associated Erectile Dysfunction

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CONTENTS

INTRODUCTION

Erectile dysfunction (ED) is a highly prevalent disorder in aging men, with multiple associated risk factors and comorbidities *(1–4)*.

Epidemiological studies have highlighted the prevalence of psychosocial factors in addition to organic causes in the etiology of ED. In the Massachusetts Male Aging Study (MMAS) *(5)*, ED was significantly associated with self-reported depressive symptoms (odds ratio [OR] = 2.88), pessimistic attitudes (OR = 3.89), or a negative outlook on life (OR = 2.30). Depressed mood was found to be a significant predictor of ED, even after potential confounding factors had been controlled *(6)*. Similar findings were reported for the National Health and Social Life Survey *(7)*, in which ED was significantly associated with self-reported emotional stress (OR = 3.56) and a history of sexual coercion (OR = 3.52). Socioeconomic factors, including a decrease in household income over the past 5 yr, was also significantly associated with the incidence of ED

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in this study. In the recent multinational Men's Attitudes to Life Events and Sexuality (MALES) study of more than 20,000 men worldwide, self-reported depression was a highly significant risk factor for ED in men of all ages. Overall, these studies underscore the independent and interactive effects of psychosocial factors in general, and depression in particular, in the etiology of ED.

The relationship between ED and depression is complex and multifactorial. Men with ED typically have increased rates of depression compared with men with normal sexual function, although depression may serve as a consequence, as well as a cause, of ED. The psychosocial distress that often accompanies ED may cause depressive illness in susceptible individuals, or ED can be one of the symptoms of major depressive disorder, which is associated with decreased libido, diminished erectile function (EF), and decreased sexual activity *(8)*. An increased prevalence of sexual dysfunction has been noted in association with both treated and untreated depression, because commonly used antidepressant medications, such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), can cause sexual side effects, including ED. Depression and ED may be indirect effects of a chronic illness, such as congestive heart failure, a chronic psychiatric disorder (e.g., alcoholism or substance abuse), or other chronic life stresses. In addition, the use of antidepressants has been linked to problems with ejaculation, orgasm, desire, and erections *(9–11)*. A subgroup of men with major depressive disorder developed a reversible loss of nocturnal penile tumescence *(12)*, suggesting that depression can directly affect the erectile process. Finally, hormonal changes in the aging male, such as a reduction of circulating testosterone level, or cardiovascular disease, may cause both conditions, or alternatively, both conditions can coexist but be etiologically unrelated. The following case vignette illustrates the often complex interplay between medical illness, depression, and ED in patients with chronic disease.

Case Vignette 1

Fred C. is a 62-yr-old married hospital administrator with end-stage renal disease. Mr. C. has been treated with kidney dialysis for the past 2 yr and has been hospitalized several times in the past year for his illness. He suffers from chronic fatigue, muscle weakness, and moderate depression. Mr. C. has had increasing difficulty in achieving erections during the past year and has not initiated sexual intercourse for several months. His libido is also significantly reduced. His wife, Martha, is in good overall health and continues to be sexually interested and available. The couple, who has three grown children, has enjoyed a close and affectionate marriage for the past 34 yr.

Fred has major difficulty adjusting to his illness in several areas. Previously a physically active man, he now tires easily with minimal exertion. He experiences unpleasant side effects from several medications he takes daily and is sometimes noncompliant with his medication regimen. He is socially withdrawn and frequently noncommunicative and depressed. His physician has recommended consideration of a kidney transplant, but Fred is reluctant to undergo surgery and has been postponing the decision for several weeks.

He feels embarrassed about his sexual difficulty and has been avoiding the issue with his wife. On questioning, he reveals that he misses their sexual relationship greatly and that his inability to perform sexually contributes significantly to his depression.

This chapter considers various aspects and implications of the relationship between ED and depression. In the first section, we consider the role of depression as a significant risk factor or predictor of ED in both treated and untreated men. Next, we review the effects of ED therapy with current oral agents on concomitant depression and other quality of life outcomes. Finally, we discuss the clinical implications and the need for clinicians to consider depression as an important etiological determinant or treatment outcome associated with common ED therapies.

DEPRESSION AND ED: A BIDIRECTIONAL RELATIONSHIP

Epidemiological studies have demonstrated a strong and consistent association between ED and depression, independent of age or the presence of other comorbidities *(1,5,6)*. In the MMAS, for example, men with depression had a 1.8 times higher chance of developing ED than did those without depression, and the prevalence rates of ED increased as the severity of depression increased *(5)*. In a Brazilian study of sexual behavior, a bivariate age-adjusted analysis showed a significant association between a history of depression and an increased prevalence of ED *(13)*. In the recent MALES study, a multinational study of 27,839 men in eight countries aged 20 to 75 yr, depression was a significant predictor of ED, after controlling for the effects of age and other comorbid health conditions. Twenty-five percent of men with ED in this large multinational study reported symptoms of depression, compared with only 13% ($p < 0.0001$) of men without ED *(1)*.

In two studies of men with major depressive disorder (MDD) that assessed the occurrence of sexual dysfunction (SD) before antidepressant therapy, 46% of men reported an inability to sustain an erection *(14)* and 65% reported some SD at baseline *(15)*. In a randomized controlled trial of 90 men with MDD, the baseline prevalence of some degree of ED was

reported to be 87%. In addition, the mean number of sexual problems reported by these men was 3.6, emphasizing that in depression, single sexual complaints are rare *(16)*.

Other studies have shown an increased rate of depression in men with ED compared with other urological disorders. These studies suggest that depression may be an important consequence or sequela of ED as much as a cause of the condition. As described later, recent studies have shown that effective treatment of ED in these patients can result in clinically significant improvements in depression, further supporting the bidirectional relationship frequently observed between ED and depression. The following case vignette illustrates this relationship in clinical practice.

Case Vignette 2

William P. is a 54-yr-old married accountant in good physical health. He has a history of mood disorder and psychological adjustment difficulties since the death of both parents in an automobile accident in 1987. William was an only child and very close to both parents. Since that time, Mr. P has received psychotherapy intermittently and antidepressant medications (fluoxetine, sertraline) for the past 8 yr. Before entering treatment, he experienced severe sleep-onset insomnia, loss of appetite and interest in social activities, and occasional suicidal thoughts. The patient has had a chronic loss of libido and intermittent ED for the past 10 yr. He reports that his wife is supportive and reassuring of his sexual difficulties, and the couple enjoys a positive marital relationship. Owing to a continuing loss of appetite and weight loss, the patient was started on paroxetine (20 mg/d) within the past 6 mo. Since that time, he has experienced further loss of libido and increased erectile difficulties.

The physical examination and laboratory tests are all within normal limits. The patient was given sildenafil (50 mg) to be taken approx 1 h before sexual intercourse. After 2 mo, he reported significant improvement in erection and a mild improvement in libido.

ED AND ANTIDEPRESSANT THERAPY

ED is frequently associated with either mood or other psychiatric disorders or with the medications commonly used in the treatment of these disorders. A worsening of pre-existing ED has been reported with various agents from all antidepressant classes, including monoamine oxidase inhibitors, tricyclic antidepressants, and SSRIs *(9)*. Although SSRIs have transformed the treatment of depression since their release in the late 1980s and are now the most commonly prescribed antidepressants worldwide *(10)*, sexual function disturbances associated with these agents have been prevalent (Table 1).

Table 1
Prevalence of ED Associated With SSRIs

Reference	*Type of study*	*SSRI used*	*Men* (n)	*Overall SD%*	*ED%*
Ashton, 1997 *(17)*	Retrospective	Fluoxetine, paroxetine, sertraline, venlafaxine	167	23.4	10.0
Jacobson, 1992 *(18)*	Prospective	Fluoxetine	160	34	13
Montejo-Gonzales, 1997 *(19)*	Prospective	Fluoxetine	152	58 (14)[a]	16
		Fluvoxamine			9.5
		Paroxetine			34
		Sertraline			16
Labbate, 1998 *(20)*	Prospective	Fluoxetine	12	ND	58[b]
		Sertraline			38[b]
		Paroxetine			
Fava, 1998 *(21)*	Double-blind, placebo-controlled	Paroxetine	63	25	
		Fluoxetine		7	
Clayton, 2002 *(22)*	Cross-sectional, observational	Citalopram	183	30	
		Venlafaxine		30	
		Sertraline		27	
		Paroxetine		27	
		Fluoxetine		24	
		Bupropion		7	
		Overall		24	ND

[a] Number in parentheses indicates percentage of patients reporting sexual or erectile dysfunction without prompting.
[b] 58 and 38% of patients had decreased erection scores after 1 and 2 mo of SSRI therapy, respectively.
ED, erectile dysfunction; ND, not determined; SD, sexual dysfunction; SSRI, selective serotonin reuptake inhibitor.

Postmarketing surveillance and clinical trials have shown the high prevalence of SD associated with SSRI use generally, although specific drugs, such as paroxetine, have been associated with a higher rate of sexual side effects. For example, a cohort study by the Drug Safety Research Unit of the United Kingdom comparing antidepressants found that ED was reported significantly more often with paroxetine than with the other SSRIs *(11)*. Similarly, in a comparison of the postmarketing safety profiles of antidepressants using the spontaneous adverse drug reaction reports of the United Kingdom Committee on Safety of Medicines, reports of ED were higher for paroxetine compared with other SSRIs *(10)*.

Prerelease and early clinical studies rarely reported any SSRI-associated SD; in fact, the initial incidence of SD with fluoxetine in controlled trials was reported to be 1.9%, probably owing to the fact that no structured or validated questionnaires were used. A large-scale, nonrandomized, retrospective study of 167 men using one of four SSRIs (fluoxetine, paroxetine, sertraline, or venlafaxine) for 6 mo or more showed that 23% reported overall SD and 10% reported ED specifically *(17)*. In a prospective study of fluoxetine in 160 outpatients, 13% of patients reported decreased sexual response *(18)*. Similarly, in another prospective multicenter study of 152 male outpatients taking one of four SSRIs, the incidence of ED ranged from 10% (fluvoxamine) to 34% (paroxetine), depending on the SSRI used *(19)*. Labbate et al. reported reduced erection scores in 12 patients with MDD after 1 and 2 mo of antidepressant use compared with baseline values *(20)*, and Fava et al. demonstrated a 25% and 7% incidence of SD with paroxetine and fluoxetine, respectively, in a double-blind study involving 63 men *(21)*. More recently, a cross-sectional, observational study conducted in more than 1000 United States primary care clinics involving more than 1700 male outpatients receiving antidepressant therapy concluded that in a subpopulation (n = 795) unlikely to have predisposing factors for SD, the prevalence of SD ranged from 7 to 30%, depending on the antidepressant used *(22)*.

ED may occur as a direct or an indirect effect of antidepressant therapy. It is well known that many antidepressants, including Ssris, cause a number of other disturbances in SD, such as delayed ejaculation, anorgasmia, or decreased libido *(10,11)*. Montejo-Gonzalez's report of 344 patients showed a high incidence of loss of libido (40–58%), delayed orgasm or ejaculation (46–59%), or anorgasmia (31–48%), depending on the SSRI taken *(19)*. These results are in agreement with other studies in patients taking antidepressants *(20–22)*.

Because the link between depression and SD is complex, it is possible that antidepressant-associated ED is a consequence of other comorbid forms of SD. For example, on detailed inquiry, patients have revealed that

their antidepressant-induced ED is associated with the inability to sustain an erection long enough to achieve orgasm and ejaculation *(17)*; thus, it may be considered that ED in those men occurs secondarily to prolonged ejaculatory latency *(10)*. Similarly, because desire is the first step in the sexual response cycle and is intimately connected with sexual arousal, its absence may preclude men from engaging in sexual activity and achieving erections. Therefore, ED in this situation may be labeled as secondary to hypoactive sexual desire.

MECHANISMS OF ANTIDEPRESSANT-ASSOCIATED ED

The neurochemistry of sexual function involves multiple integrated systems. Although the precise mechanisms mediating SSRI-associated SD are not understood well, based on evidence from case reports, uncontrolled studies, and conclusions drawn from sexual side effects observed with the use of psychotropic drugs, a number of pathways have been implicated in this process. These include serotonergic, dopaminergic, and cholinergic systems, as well as prolactin and nitric oxide *(10,24)*.

Given the wide distribution and numerous serotonin receptor families located both centrally and peripherally, it is no surprise that serotonin mediates a number of aspects of the sexual response cycle. In general, serotonin exerts an inhibitory role on sexual function; thus, drugs causing an increase in serotonergic activity, such as SSRIs, lead to some form of SD *(24)*. In the brain, there is evidence that serotonin causes a decrease in dopamine levels (a neurotransmitter-enhancing sexual function) in animal models. Peripherally, inhibition of α-adrenergic and cholinergic receptors in the genitourinary tract also impairs sexual function; cholinergic fibers aid blood flow in the corpora cavernosa, whereas α_1-receptors aid in the detumescence process *(25)*. Sexual side effects have consistently been observed with SSRI use but not with serotonin (5-hydroxytryptamine [5-HT_{1A}]) agonists. Apparently, activation of 5-HT_{1A} receptors may facilitate sexual behavior in rats, whereas activation of 5-HT_2 receptors may be inhibitory *(10)*.

Dopamine neurotransmission has been reported to play a role in sexual function (i.e., libido, psychological arousal, and erection) *(25)*. Agents that are potent SSRIs but lack any effect on dopamine uptake inhibition, such as paroxetine, have an apparently greater incidence of SD than other agents with a more balanced profile *(26,27)*. In animal models, dopamine agonists have been linked to a decreased ejaculatory threshold, whereas removal of dopaminergic neurons is associated with increased ejaculatory latency *(28)*. Supporting these in vitro results are reports that dopamine antagonists (i.e., antipsychotics) are associated with a high incidence of ED *(29)*.

Although the currently available evidence does not support a direct role for acetylcholine in sexual function, antidepressants with potent anticho-

linergic activity, such as tricyclic antidepressants, and those SSRIs with greater affinity for the cholinergic receptor (e.g., paroxetine) have shown a marked incidence of SD *(30,31)*.

The role of prolactin in the sexual response cycle remains uncertain. Because serotonergic stimulation increases prolactin release from the hypothalamus and dopamine is the prolactin-inhibiting factor, any disturbance of the hypothalamic–pituitary–dopaminergic pathway is likely to affect prolactin secretion *(24)*. Hyperprolactinemia, which can be a consequence of SSRI use *(32)*, is associated with a marked negative effect on sexual desire and performance in men. Consistent with these findings, studies have shown that paroxetine, a potent SSRI lacking an effect on dopamine uptake inhibition, can cause marked increases in plasma prolactin levels in healthy volunteers and patients *(33,34)*.

Another possible explanation for the increased incidence of SD with SSRIs is suggested by recent findings that certain SSRIs are potent inhibitors of nitric oxide synthase both in vitro and in vivo *(35)*; nitric oxide is a critical element in the signal transduction cascade mediating penile erection.

TREATMENT OF ED AND COMORBID DEPRESSION

Several clinical trials have demonstrated that ED can be successfully treated in men with comorbid depression whether or not they are taking concomitant antidepressant medications *(36–39)*. In the first study of this kind (Seidman et al. *[36]*), men with ED and mild to moderate depression were treated for 12 wk with either flexible-dose sildenafil or placebo. The clinical questions to be addressed in this study were:

1. Does the presence of depression affect ED treatment response to sildenafil?
2. Does efficacious treatment of ED indirectly affect the symptoms of depression?

To address these questions, Seidman et al. *(36)* conducted a 12-wk randomized, double-blind, placebo-controlled, multicenter trial in men with ED and mild to moderate depression ($n = 152$), defined by criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (depressive disorder, not otherwise specified [NOS]) and a score of 12 or less on the 24-item Hamilton Rating Scale for Depression (HAM-D). Patients were randomly assigned to receive sildenafil ($n = 74$) or placebo ($n = 78$) for 12 wk of treatment. Efficacy was assessed using a number of interviewer-rated and self-administered questionnaires: Change in EF was evaluated using the International Index of Erectile Function (IIEF), among others; depression was evaluated using the HAM-D and Beck Depression Index.

After 12 wk of treatment, mean scores on the IIEF had improved significantly among patients who had received sildenafil compared with scores among those who had received placebo. Thus, sildenafil was efficacious in treating ED among men with minor depression. Of the 136 patients evaluable for efficacy, 73% of patients (48 of 66) who received sildenafil and 14% (10 of 70) who received placebo were classified as ED treatment "responders." Of note, improvements in ED were highly correlated with improvements in depressive symptoms and quality of life measures, irrespective of the treatment received (i.e., sildenafil or placebo). That is, responders showed statistically significantly greater reductions in mean HAM-D (10.6) and Beck Depression Index scores (10.7) compared with treatment nonresponders.

This widely cited study was the first to demonstrate that sildenafil treatment significantly improves EF in men with both ED and untreated comorbid depression. Moreover, the results suggest that patients who responded to treatment, regardless of the treatment received, showed significant improvements in depressive symptoms compared with patients who did not respond to treatment. Thus, successful treatment of ED in men with symptoms of depression can lead to marked improvements in these symptoms.

More recently, the author reported results of a similar double-blind study of vardenafil (5–20 mg) and placebo in the treatment of men with ED and untreated mild depressive disorder. In this multicenter, flexible-dose, parallel-group, double-blind study, 280 men with mild MDD as assessed by DSM-IV and HAM-D_{17} score (between 11 and 17) who were not on psychotherapy or antidepressant medication were randomly assigned to receive placebo or flexible-dose vardenafil (5–20 mg) for 12 wk of treatment.

Primary end points included the IIEF-EF domain score and the HAM-D_{17}. Secondary end points included penetration (sexual encounter profile [SEP] question 2 [Q2]), maintenance (SEP Q3), global assessment question , and Rosenberg Self-Esteem Scale scores. Results indicated significant changes in all measures of EF and both HAM-D_{17} and self-esteem scores. A high level of treatment responsiveness was noted in the vardenafil arm, approx equivalent to the improvement in erection observed in the previous study with sildenafil. Marked improvements in mood and self-esteem were associated with the changes in ED.

Taken together, these two studies provide strong evidence of the efficacy of PDE5 inhibitors in patients with both ED and symptoms of mild to moderate depression. A high level of treatment responsiveness was observed in patients receiving active drug vs placebo in both studies, despite the presence of comorbid depression in all patients. The rate of adverse events was also comparable to other clinical trials with both drugs,

and no significant increases in psychiatric adverse events were noted. Clinically significant improvements in mood were also observed, which were associated with positive changes in EF in both studies. Finally, significant changes in self-esteem and other aspects of quality-of-life were observed in association with changes in EF and mood resulting from treatment. Overall, these studies provide strong support for the safety and clinical effectiveness of PDE5 therapy in men with ED and comorbid depression.

PDE5 INHIBITORS IN PATIENTS RECEIVING ANTIDEPRESSANT THERAPY

As noted by Nurnberg et al. *(16)*, the sexual side effects associated with medication treatment of depression, hypertension, and other illnesses frequently lead to noncompliance. Overall, treatment-emergent events, such as ED, weight gain, and sleep disturbance, account for a significant proportion of treatment discontinuations, which in turn may lead to a relapse or recurrence or an increase in the morbidity associated with depression *(40,41)* or cardiovascular disease *(42–44)*. Even when MDD is recognized and treated, up to 70% of patients taking antidepressants are prematurely noncompliant *(45)*, with side effects reported as the principal reason for discontinuation of therapy *(46)*. Given the high prevalence and strong association between ED, depression, and other chronic conditions, a correct differential diagnosis is essential, albeit difficult. For ED and MDD, it is imperative that clinicians accurately diagnose the primary disorder and secondary condition so that treatment can be optimized and the risk of developing complications or missing treatment of the primary disorder is minimized.

Given the strong association between the use of antidepressant medication and SD, several studies have addressed the efficacy of PDE5 therapy in male patients with ED being treated concomitantly with SSRIs or other antidepressant drugs. Nurnberg et al. *(16)* conducted a prospective, randomized, double-blind, placebo-controlled, multicenter trial in men with MDD in remission. MDD was diagnosed according to the DSM-IV criteria *(47)* and monitored using the 17-item HAM-D *(48)*.

Patients were required to have been taking an SSRI for 12 wk or more, to have been experiencing SSRI-induced ED for 4 wk or more, and to have had satisfactory sexual function before the onset of MDD or SSRI treatment. Thus, in this study, the patients' depression status (i.e., MDD in remission) and cause of ED (i.e., SSRI treatment) were prescribed by the inclusion criteria. In this case, the clinical question of interest was whether sildenafil was efficacious in treating SSRI-induced ED.

Male patients with a primary complaint of ED ($n = 67$) were randomly assigned to receive sildenafil ($n = 35$) or placebo ($n = 32$) for 6 wk of

treatment. Efficacy was assessed by the change in IIEF mean scores from baseline to end of treatment. Results indicated that sildenafil-treated patients showed statistically significant improvements in mean scores on Q3 and Q4 compared with those in placebo-treated patient. At baseline, HAM-D scores were in the normal range (5.4 in the sildenafil group and 4.7 in the placebo group) and were similarly low at the end of treatment (3.3 and 5.4, respectively), indicating that MDD in remission was maintained for the duration of the study. The most common adverse effect was headache (21% sildenafil vs 10% placebo), followed by facial flushing (17% vs 3%), dyspepsia (7% vs 0%), nasal congestion (12% vs 3%), and transient visual disturbances (12% vs 5%). These results suggest that sildenafil was efficacious and well-tolerated for the treatment of ED associated with SSRI therapy for MDD. Thus, sildenafil treatment of SSRI-induced ED may reduce the likelihood of antidepressant discontinuation because of the sexual side effects, which in turn may reduce the likelihood of depression relapse or recurrence.

Similarly, Tignol and Benkert conducted a randomized, double-blind, placebo-controlled, multicenter trial of sildenafil of ED in men with MDD in remission *(37)*.

Men were eligible to participate if the ED was a presenting symptom when the depression was diagnosed but was refractory to successful treatment of the depression. In contrast to the study by Nurnberg et al. *(16)* , not all patients were required to be taking SSRIs. In fact, at entry into the study, 47 and 41% of patients randomly assigned to take sildenafil and placebo, respectively, were taking antidepressant medication. Those who were taking antidepressants were required to have been on a stable dose for 8 wk or more. Depression in remission was assessed and monitored using the 10-item Montgomery-Asberg Depression Rating Scale (MADRS) *(50)*.

Patients were randomly assigned to receive to sildenafil (n = 83) or placebo (n = 85) for 12 wk of treatment. Efficacy was evaluated using the IIEF questionnaire.

After 12 wk of treatment, patients randomly assigned to receive sildenafil showed statistically significant improvements in mean Q3 and Q4 scores compared with patients taking placebo.

In addition, total MADRS scores did not change significantly from an overall baseline score of 6.3; end-of-treatment scores were 6.6 and 6.2 in sildenafil- and placebo-treated patients, respectively. Adverse effects were mild to moderate in severity, and only one patient discontinued because of an adverse effect. Thus, like the results reviewed previously, these findings suggest that sildenafil was an efficacious and well-tolerated treatment for ED in men with MDD in remission, whether treated with an antidepressant or not.

Overall, these findings provide strong support for the safety and benefits of treating antidepressant-associated ED with PDE5 therapy. Although other treatment options are available (e.g., use of buproprion, dose reduction, or "drug holidays"), these alternatives each have significant disadvantages compared PDE5 inhibitors, which are safe and effective in this context. Further studies are indicated to investigate the long-term benefits of ED therapy in this context.

SUMMARY AND CONCLUSION

In summary, ED and other forms of male SD are commonly associated with depression and the use of antidepressant medications. A number of direct and indirect mechanisms have been proposed to account for this association. The relationship between ED and depression is bidirectional in that depression may occur as a consequence of ED, as well as serving as a causal or risk factor for ED. Men with ED frequently show signs of mild or moderate depression, which may resolve with effective treatment of their SD. Conversely, patients with major depression or bipolar mood disorder should be carefully screened for the presence and severity of these disorders before initiation of ED treatment. If necessary, a referral for specialized psychiatric management should be made. In most cases, however, the combined treatment of ED and concomitant mood disorders can be safely and effectively initiated. Based on the studies reviewed in this chapter, it appears that male patients with ED and concomitant mild to moderate depression are ideal candidates for treatment with a PDE5 inhibitor, either alone or in conjunction with their ongoing psychotropic medication. When indicated, primary care physicians or ED specialists should seek specialized consultation in these cases from a psychiatrist or other mental health specialist.

REFERENCES

1. Rosen R, Fisher W, Eardley I, Niederber C, Nadel A, Sand M. (2004) The multinational men's attitudes of life events and sexuality (MALES) study: prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin 20:607–617.
2. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. (2000) Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey.' Int J Impot Res 12:305–311.
3. Mak R, De Backer G, Kornitzer M, De Meyer JM. (2002) Prevalence and correlates of erectile dysfunction in a population-based study in Belgium. Eur Urol 41: 132–138.
4. Nicolosi A, Moreira ED, Shirai M, Ismail Bin Mohd Tambi M, Glasser DB. (2003) Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology 61: 201–206.

5. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. (1994) Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 151:54–61.
6. Araujo AB, Durante R, Feldman HA, et al. (1998) The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med 60:458–465.
7. Laumann EO, Paik A, Rosen RC. (1999) Sexual dysfunction in the United States: prevalence and predictors. JAMA 281:537–544.
8. Mathew RJ, Weinman ML. (1982) Sexual dysfunctions in depression. Arch Sex Behav 11:323–328.
9. Margolese HC, Assalian P. (1996) Sexual side effects of antidepressants: a review. J Sex Marital Ther 22:209–217.
10. Rosen R, Lane R, Menza M. (1999) Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 19:67–85.
11. Rosen R, Marin H. (2003) Prevalence of antidepressant-associated erectile dysfunction. J Clin Psych 64:5–10.
12. Roose SP, Glassman AH, Walsh BT, et al. (1982) Reversible loss of nocturnal penile tumescence during depression: a preliminary report. Neuropsychobiology 8:284–288.
13. Moreira ED Jr, Abdo CH, Torres EB, Lobo CF, Fittipaldi JA. (2001) Prevalence and correlates of erectile dysfunction: results of the Brazilian study of sexual behavior. Urology 58:583–588.
14. Kennedy SH, Dickens SE, Eisfeld BS, et al. (1999) Sexual dysfunction before antidepressant therapy in major depression. J Affect Disord 56:201–208.
15. Zajecka J, Dunner DL, Gelenberg A, et al. (2002) Sexual function and satisfaction in the treatment of chronic major depression with nefazodone, psychotherapy, and their combination. J Clin Psychiat 63:709–716.
16. Nurnberg HG, Hensley PL, Gelenberg AJ, et al. (2003) Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. JAMA 289:56–64.
17. Ashton AK, Hamer R, Rosen RC. (1997) Serotonin reuptake inhibitor-induced sexual dysfunction and its treatment: a large-scale retrospective study of 596 psychiatric outpatients. J Sex Marital Ther 23:165–175.
18. Jacobsen FM. (1992) Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. J Clin Psychiatry 53:119–122.
19. Montejo-Gonzalez AL, Llorca G, Izquierdo JA, et al. (1997) SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. J Sex Marital Ther 23: 176–194.
20. Labbate LA, Grimes J, Hines A, et al. (1998) Sexual dysfunction induced by serotonin reuptake antidepressants. J Sex Marital Ther 24:3–12.
21. Fava M, Amsterdam JD, Deltito JA, et al. (1998) A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. Ann Clin Psychiatry 10:145–150.
22. Clayton AH, Pradko JF, Croft HA, et al. (2002) Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 63:357–366.
23. Haensel SM, Klem TM, Hop WC, et al. (1998) Fluoxetine and premature ejaculation: a double-blind, crossover, placebo-controlled study. J Clin Psychopharmacol 18:72–77.
24. Halaris A. (2003) Neurochemical aspects of the sexual response cycle. CNS Spectr 8:211–216.

25. Segraves RT. (1989) Effects of psychotropic drugs on human erection and ejaculation. Arch Gen Psychiatry 46:275–284.
26. Hyttel J .(1994) Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). Int Clin Psychopharmacol 9(Suppl 1):19–26.
27. Kugaya A, Seneca NM, Snyder PJ, et al. (2003) Changes in human in vivo serotonin and dopamine transporter availabilities during chronic antidepressant administration. Neuropsychopharmacology 28:413–420.
28. Bitran D, Hull EM. (1987) Pharmacological analysis of male rat sexual behavior. Neurosci Biobehav Rev 11:365–389.
29. Sullivan G, Lukoff D. (1990) Sexual side effects of antipsychotic medication: evaluation and interventions. Hosp Community Psychiatry 41:1238–1341.
30. Richelson E. (1994) The pharmacology of antidepressants at the synapse: focus on newer compounds. J Clin Psychiatry 55(Suppl A):34–39.
31. Stanton T, Bolden-Watson C, Cusack B, et al. (1993) Antagonism of the five cloned human muscarinic cholinergic receptors expressed in CHO-K1 cells by antidepressants and antihistaminics. Biochem Pharmacol 45:2352–2354.
32. Davies PH. (1997) Drug-related hyperprolactinaemia. Adverse Drug React Toxicol Rev 16:83–94.
33. Cowen PJ, Sargent PA. (1997) Changes in plasma prolactin during SSRI treatment: evidence for a delayed increase in 5-HT neurotransmission. J Psychopharmacol 11:345–348.
34. Amsterdam JD, Garcia-Espana F, Goodman D, et al. (1997) Breast enlargement during chronic antidepressant therapy. J Affect Disord 46:151–156.
35. Finkel MS, Laghrissi-Thode F, Pollock BG, et al. (1996) Paroxetine is a novel nitric oxide synthase inhibitor. Psychopharmacol Bull 32:653–658.
36. Seidman SN, Roose SP, Menza MA, et al. (2001) Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. Am J Psychiatry 158:1623–1630.
37. Tignol JL, Benkert O. (2001) Sildenafil citrate effectively treats erectile dysfunction in men who have been successfully treated for depression. New Orleans, LA: American Psychiatric Association Annual Meeting, 2001.
38. Nurnberg HG, Hensley P, Lauriello J, et al. (2001) Sildenafil citrate for the treatment of sexual dysfunction associated with serotonergic reuptake inhibitors. Int J Impot Res 13:S49.
39. Nurnberg HG, Gelenberg A, Hargreave TB, et al. (2001) Efficacy of sildenafil citrate for the treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Am J Psychiatry 158:1926–1928.
40. American Psychiatric Association. (2000) Practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry 157:1–45.
41. Greden JF. (2001) The burden of disease for treatment-resistant depression. J Clin Psychiatry 62:26–31.
42. Slag MF, Morley JE, Elson MK, et al. (1983) Impotence in medical clinic outpatients. JAMA 249:1736–1740.
43. Benet AE, Melman A. (1995) The epidemiology of erectile dysfunction. Urol Clin North Am 22:699–709.
44. Keene LC, Davies PH. (1999) Drug-related erectile dysfunction. Adverse Drug React Toxicol Rev 18:5–24.
45. Katon W, von Korff M, Lin E, et al. (1992) Adequacy and duration of antidepressant treatment in primary care. Med Care 30:67–76.
46. Lin EH, Von Korff M, Katon W, et al. (1995) The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 33:67–74.

47. American Psychiatric Association. (1994) Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association.
48. Hamilton MA. (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.
49. Montgomery S, Asberg M. (1979) A new depression scale designed to be sensitive to change. Brit J Psychiatry 134:382–389.

12 Intracavernous, Transurethral, and Topical Therapies for Erectile Dysfunction in the Era of Oral Pharmacotherapy

Salvaging First-Line Therapy Failures With Combination Therapies

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CONTENTS

INTRODUCTION

It is estimated that 20 to 30 million American men suffer from some degree of erectile dysfunction (ED) *(1)*. As the male population ages and awareness of the problem increases, this number is expected to at least double by 2025 *(2)*.

Current therapies may be grouped into four general categories:

1. Psychosexual counseling and education.
2. Pharmacological therapy.

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Table 1
Management of ED
Gradual Therapeutic Options

First-line therapy
- Lifestyle/drug therapy modification
- Psychosocial counseling
- Androgen replacement therapy
- Oral therapy

Second-line therapy
- Vacuum tumescence device
- Intracavernosal injection
- Transurethral therapy
- Topical therapy

Third-line therapy
- Penile prosthesis
- Penile vascular surgeries

3. Mechanical devices.
4. Surgical approaches.

Pharmacological treatment for ED includes oral, sublingual, intracavernosal, transurethral, and topical administration of erectogenic drugs. First-line therapy includes orally and sublingually administered drugs, whereas intracavernosal and transurethral treatments are considered second-line therapy. Table 1 shows the therapeutic options of first-, second-, and third-line therapy according to the "process of care" model published by Rosen et al. in 1999 for evaluation and treatment of ED *(3)*.

Local treatments for ED continue to be an expanding area for new research. As new pathways for the mechanism of erection are elucidated, therapeutic innovations will follow. Although oral treatment for ED is expanding, second-line treatment options, including viable combination therapies (such as oral medication), will most likely maintain an important position in the clinician's therapeutic armamentarium, especially for patients who have not had success with oral therapies.

INTRACAVERNOSAL, TRANSURETHRAL, AND TOPICAL DRUGS

Patients who do not respond to oral therapy are considered for second-line treatments; it is now rare to initially prescribe one of the second-line therapies when deciding on a treatment. This was more common when sildenafil was the only oral drug available on the market, because there was

a definite contraindication to the use of sildenafil in patients using nitrate medications. Beyond this, the only other group requiring second-line therapy might be those requesting a faster onset of response (>15 min), which cannot be obtained with oral phosphodiesterase-5 (PDE5) inhibitors.

Topical administration of vasoactive agents represents a potentially reliable option that is appealing to many patients because of its direct action on the penis, lack of systematic influence, and rapid effect *(4)*.

When counseling patients with ED on available treatment options, every alternative needs to be extensively detailed, including the side effects, which are more common and more severe in intracavernosal and transurethral approaches than in oral therapies.

Intracavernous Injection Therapy

In the early 1980s, researchers endeavored to understand the physiology of erection after demonstrating that injecting vasoactive agents intracorporeally could produce an erection sufficient for successful sexual intercourse. In 1982, Virag reported that a nonselective PDE inhibitor, papaverine hydrochloride, caused penile erection after hypogastric infusion during vascular reconstructive surgery *(5)*. The first clinical report about self-injection of erectogenic agents was published by Brindley in 1983 *(6)*. He used the α-adrenergic blocker phenoxybenzamine. In 1985, Zorgniotti and Lefleur were the first researchers to use a combination of papaverine and the α-adrenergic blocker phentolamine to improve the erectogenic effect. This was followed by several studies by Ishii introducing prostaglandin E_1 (PGE_1), a smooth muscle relaxant and vasodilator, for the treatment of ED in 1986 *(7,8)*.

There are a number of other agents that are available or currently undergoing evaluation for use as intracavernosal agents. The ideal agent needs to be widely available, user-friendly, and inexpensive. It also should have an excellent response rate with minimal side effects in patients with varying causes of ED. The target is to produce an ample erection suitable for sexual intercourse, lasting about 1 h.

Patient Selection

When a patient is considered as a potential candidate for intracavernosal therapy, the characteristics and adverse effects of the treatment, such as priapism, painful erection, and fibrosis, are explained clearly, along with a discussion of other alternatives. Patients with a history of hemoglobinopathy, bleeding diathesis, Peyronie's disease, or idiopathic priapism are excluded from this treatment option. Patients who may be poor candidates for intracavernosal injection therapy are those who are morbidly obese, have poor hand dexterity or serious psychiatric disorders, lack a partner

Fig. 1. Intracorporeal self-injection technique. The needle is directed into the lateral aspect of the corpora at a 90°; angle to the skin, taking care to avoid the superficial veins, dorsal neurovascular bundle, and urethra.

willing to assist with injections, or might misuse or abuse this therapy. Patients must be able to understand the importance of proper administration and the importance of timely intervention when a side effect, such as priapism, occurs.

The Trial Injection

Many authorities believe that if a first-line oral treatment fails in a young or middle-aged patient, a workup for organic impotence using penile duplex Doppler ultrasonography is indicated. Information gained in this way can be valuable in directing future interventions (e.g., adding the use of a constriction band if a patient has a significant venous leak). The duplex study can be performed using intracavernosally administered alprostadil (Caverject; Upjohn, North Peapack, NJ), and some centers redose if necessary. This maneuver may also serve as a patient's trial teaching injection.

If duplex Doppler ultrasonography is not readily available or not covered by medical insurance, a trial injection alone in the office may be sufficient. A relaxed atmosphere with visually stimulating material is helpful, providing that the patient has no personal or religious aversion to erotic material. The patient is instructed to stand in order to augment blood flow to the pelvis, and is encouraged to self-stimulate. Injections are directed along the lateral aspect of the penis and at a 90° angle to the skin, taking care to avoid the superficial veins, dorsal neurovascular bundle, and urethra, respectively (Fig. 1).

Immediately after drug administration, the injection site should be compressed firmly between thumb and index finger for 5 to 10 min to prevent subsequent development of intracavernosal hematomas. In the meantime, the base of the penis is squeezed using a rubber band to block the drug from entering the systemic blood circulation. Patients are then left alone to watch an erotic video and asked to stimulate themselves, and the erectile response is assessed by the physician and the patient. The dose of the injected drug or mixture is considered adequate when it produces an erection that is equal to 50 to 70% of the maximum erectile response by the patient. If the patient reaches a maximal rigid erection, a lower dose is suggested for home use because the erectile effect induced by the drug is usually greater than under laboratory conditions.

Patients are instructed to limit the use of injections to three times a week, with no more than one injection in any 24-h period. They are also taught to inject the right and left cavernosal bodies alternately and must recognize the importance of medical follow-up and intervention if an erection lasts more than 4 h.

Routine Follow-Up

Once the physician feels comfortable that the patient has attained an appropriate level of competence with a given regimen, injections at home may begin. The patient should be seen in the office within several weeks or months of starting home therapy for a physical examination of the penis and inspection for any signs of improper technique or early fibrotic changes. After this examination, office visits one or two times per year are reasonable for most individuals.

Agents Used for Intracavernosal Therapy

Papaverine

Papaverine hydrochloride is a nonopiate derivative of the poppy plant (*Papaver somniferum*) and the first agent widely used for intracavernosal self-injection. Papaverine inhibits PDE nonspecifically, preventing breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which leads to a decrease in intracellular calcium level, corporal smooth muscle relaxation, and penile tumescence.

A pilot study by Virag et al. in 1982 demonstrated rigid erections in normal potent volunteers and subjects with psychogenic impotence *(5)*. Kapoor et al. showed a satisfactory response in 44% of patients with a 7.5-mg dose and in another 41% taking 10 to 15 mg *(9)*. Reported efficacy rates with doses between 30 and 110 mg varied between 27 and 78% and were dependent on dose and the patient population. A literature analysis of 19 publications, which included 2181 patients overall, demonstrated

that papaverine induced an average response rate of 61% during in-office testing *(10)*.

Although papaverine is inexpensive and effective and does not require refrigeration, it has a number of well-recognized adverse effects. Specifically, the incidence of priapism from the use of papaverine as monotherapy has ranged from 15 to 18%, occurring most commonly in men with neurogenic or psychogenic ED *(11)*. This can be explained by its longer half-life relative to other intracavernosal agents. The development of painless fibrotic nodules within the corpora cavernosa may lead to penile curvature. This problem has been reported in 1.5 to 60% of patients treated for 1 yr *(12)*.

Montorsi et al. found that most of the fibrotic nodules occurred in patients who injected themselves very frequently (multiple trauma to the corporeal tissue) and who did not compress the injection site for a sufficient period after each use, which led to the subsequent development of intracavernosal hematomas. Local hematomas, burning, pain after injection, urethral damage, cavernositis, or local infections have also been reported. Because of these safety concerns, monotherapy with papaverine is not considered by most authorities as the treatment of choice.

Phentolamine

In 1976, Domer et al. reported the effect of α-adrenergic agonists and antagonists on the internal urethral sphincter of cats *(13)*. These investigators also documented that intravenous administration of phentolamine induced penile erection. Phentolamine is a nonselective inhibitor of α-adrenergic receptors. It inhibits smooth muscle contraction directly and has been used in both oral and intravenous approaches for the management of hypertension and pheochromocytoma. Although phentolamine alone is poor at inducing an erectile response in humans, it is known to act synergistically with other vasoactive agents. Therefore, its clinical use is mostly limited to combination approaches.

Combination Product: Bimix

The combination of papaverine hydrochloride and phentolamine mesylate by Zorgniotti and Lefleur in 1985 significantly increased success rates for pharmacological therapy. Their success rate was 71% in 250 patients *(7)*. Numerous follow-up reports confirmed the efficacy and safety of this mixture *(14–19)*. The success rates for bimix are as high as those reported for the most common intracavernosal agent in the United States, PGE_1 *(20)*. When the side effects of prostaglandin and bimix are compared, the latter is associated with a decreased incidence of penile pain but can cause fibrosis and priapism.

Because of its relatively low cost, the combination of papaverine and phentolamine continues to be a popular method of intracavernosal therapy.

Prostaglandins

The history of prostaglandin therapy dates back to the 1930s, when the relaxation of uterine smooth muscle in response to exposure to semen was observed *(10)*.

Soon after, Euler reported the hypotensive effect of a substance he called "prostaglandin" because it was found in the prostatic fluid and was thought to originate from the prostate gland (although in fact it derives from the seminal vesicles).

PGE_1 modulates adenyl cyclase to increase cAMP concentrations in the corpus cavernosum. This leads to a decrease in intracellular free calcium, which induces smooth muscle relaxation, resulting in erection. It is rapidly metabolized in the lungs and is excreted by the kidney. There are no reports of any significant systemic accumulation of PGE_1.

In the United States, alprostadil (a prostaglandin derivate) is available as Caverject (Pharmacia and Upjohn Co., Bridgewater, NJ) and EDEX (Schwarz Pharma, Milwaukee, WI). Caverject has been marketed since 1996, whereas EDEX has been marketed since 1997.

In 1983, Adaikan et al. described the strong relaxing effect of PGE_1 on smooth muscle *(21)*. The first report on intracavernosal injection of PGE_1 for therapy of ED was published by Ishii and coworkers in 1986 *(8)*. In a study of 447 patients, a response rate of 72% to PGE_1 was published by Porst *(22)*. Large prospective trials have since documented even higher success rates *(23–25)*.

Alprostadil, the synthetic formulation of PGE_1, is well established as a monotherapy for ED, with efficacy rates greater than those associated with papaverine alone. It is also the most widely used component in multidrug combination vasoactive mixtures; its use allows for reductions in the doses of other single agents, thus improving the adverse effect profile.

The most frequently reported adverse effect of PGE_1 intracavernous injections is local corporeal discomfort, which occurs in more than 25% of the patients *(24,26)*.

Some researchers believe that coinjection with lidocaine, sodium bicarbonate, or other anesthetics may reduce pain, but this is debatable *(27)*. Another common side effect is prolonged erection, which occurs in 4% of patients. Compared with papaverine and the bimix combination, however, PGE_1 is associated with a lower incidence of prolonged erections and corporal fibrosis but has the disadvantages of penile pain and higher cost.

The use of alprostadil is to be avoided in any patient with a history of anticoagulant therapy, bleeding disorders, polycythemia, sickle cell dis-

ease, thrombocytosis, or multiple myeloma. PGE_1 or alprostadil can also be exploited for topical and transurethral use of alprostadil.

An interesting concept is the increase in the frequency of spontaneous erections and the decreased need for treatment after follow-up with long-standing intracavernosal vasoactive injection therapy. PGE_1 intracavernosal injections can markedly improve cavernosal artery function, as shown by penile duplex Doppler ultrasonography *(28)*.

This may be a result of significant changes in intracavernosal structure (e.g., microvascularization or hypertrophy of the sinusoidal smooth muscles at the ultrastructural level). Brock et al. *(29)* reported a return of spontaneous erections in 85% of attempts in 54 men during long-term intracavernosal alprostadil therapy. The issue remains controversial. In another study, nocturnal penile tumescence activity remained unchanged after the long-term use of intracavernosal injections *(30)*. Potential explanations for these opposing results may be the methods used to evaluate ED.

Combination Product: Trimix

The combination of papaverine, phentolamine, and PGE_1, known as *trimix*, has become popular owing to its high efficacy, lower incidence of pain, and lower cost per dose. Combination therapy was first introduced in 1991 by Bennet and coworkers, with a reported success rate of 92% in 116 patients *(31)*. A crossover study by McMahon comparing PGE_1 alone with the three-drug regimen in 228 patients also showed increased efficacy with the trimixture in patients with arterial insufficiency and with mild-to-moderate venous insufficiency *(32)*. Many clinicians reserve the trimix regimen for men with vascular ED in whom therapy with PGE_1 or the bimix combination failed, or for patients who experience severe penile pain with PGE_1 injections. A prospective study by Bechara et al. found that the trimixture is more effective than high-dose PGE_1 in achieving suitable erection and that there is a lower incidence of pain during injection or erection *(33)*. The rates of priapism were essentially the same.

The rationale for the use of multiple vasoactive drugs is the synergistic action resulting from the different mechanisms of action of the drugs involved, producing erectogenic effects. Unfortunately, none of the drugs mentioned herein is guaranteed to produce an erectile response in all types of ED patients participating in pharmacological injection programs. Patients with severe penile vascular impairments, especially those with marked veno-occlusive dysfunction of the corpora cavernosa, are usually poor responders to single-drug injections. In addition, adverse effects observed during intracavernous pharmacotherapy are mainly drug related (i.e., they are a result of the chemical composition of the drug itself, to the total dose of the drug used for a single injection, or to the total volume

injected). The combination of multiple vasoactive drugs can produce a full erectile response in more than 90% of patients.

Vasoactive Intestinal Polypeptide

Vasoactive intestinal polypeptide (VIP) is a neurotransmitter that acts through stimulation of adenyl cyclase and does not appear to act through the release of nitric oxide.

Specific VIP receptors are present in cavernosal smooth muscle cells and mediate smooth muscle relaxation by increasing concentrations of cAMP. In vitro studies on canine models demonstrated modest increases in arterial inflow and more pronounced effects on decreasing venous outflow. As a single-agent therapy, VIP fails to produce erection sufficient for sexual intercourse *(34)*. Its efficacy has been proposed in intracavernosal combination therapy, and it has the recognized benefit of not inducing penile pain.

A recent study of intracavernosal therapy failures revealed that the combination of VIP and phentolamine caused sufficient erections *(35)*. Sandhu and coworkers, using VIP in combination with phentolamine, reported an 82% response rate in 183 patients in whom other ED therapies had failed. Minor side effects, including facial flushing, bruising, and pain at the injection site, occurred in less than 3% of the patients, and only 0.5% of the patients developed priapism *(36)*.

Further trials with VIP in combination with other agents are in progress.

Nitrodonors: Linsidomine and Nitroprusside

Linsidomine is the active metabolite of the antianginal drug molsidomine and is thought to liberate nitric oxide nonenzymatically. Nitric oxide is recognized as the primary mediator of penile erection *(37)*. Various studies in the early 1990s reported promising results with few side effects. A follow-up, single-blind crossover study by Wegner and coworkers comparing linsidomine chlorhydrate and PGE_1 injections in 20 patients demonstrated a superior response to prostaglandin in every case *(38)*. Although linsidomine seems to be safe, it does not exhibit superior results compared with other current intracavernosal therapy options.

A comparative study of nitroprusside and PGE_1 revealed that 20 µg of PGE_1 induced better responses overall than 300 to 400 µg of nitroprusside. Furthermore, nitroprusside induced systemic hypotension in 15% of patients. Despite lower costs, decreased pain, and shorter activity compared with PGE_1, nitroprusside has never entered into any multicenter trials *(39)*. Further research using linsidomine and other nitric oxide donors is still in order.

Forskolin

Forskolin (an alkaloid from the plant *Coleus forskohlii*) induces smooth muscle relaxation by direct activation of the catalytic domain of the enzyme adenylate cyclase. In contrast, PGE_1 and VIP indirectly stimulate adenylate cyclase by interacting with specific G protein-coupled receptors. Mulhall et al. *(40)* revealed that forskolin acts synergistically with PGE_1 to increase cAMP levels and induce smooth muscle relaxation. In 31 patients with ED who were poor responders to the trimix combination of papaverine, phentolamine, and PGE_1, the response rate improved rising to 61% with the addition of forskolin.

Although promising, no follow-up studies examining the efficacy and the potential toxicity of forskolin have been undertaken.

Potassium Channel Openers

Myogenic activity is intimately related to fluctuations in calcium concentrations across the cell membrane. Calcium influx is controlled through voltage-sensitive channels. Maintaining smooth muscle relaxation in the corpus cavernosum through membrane hyperpolarization by opening potassium channels is currently an area of intense interest. In vitro and in vivo animal studies using intracavernosal potassium channel openers may represent tomorrow's pharmacological breakthrough.

Calcitonin gene-related peptide (CGRP) is a potassium channel opener. The use of CGRP, 5 μg together with 10 μg PGE_1 in patients who did not respond to a bimix of papaverine and phentolamine caused full erections in 70% of patients with no significant complications *(41)*. Higher doses (25 μg) are known to cause facial flushing and hypotension.

In the future, CGRP may be considered when intracavernosal PGE_1 or other drugs alone fail to produce a full erectile response *(42)*.

Moxisylyte

Moxisylyte (thymoxamine) is a selective α_1-receptor blocker. It clearly decreases the spontaneous activity, amplitude, and tone of contractions of cavernous smooth muscle in dogs in vivo and relaxes norepinephrine-contracted corporeal smooth muscle strips in vitro *(43)*.

Doses of 10 to 30 mg are able to induce a erection satisfactory for sexual intercourse in 85% of patients *(44)*. In comparison to PGE_1, moxisylyte causes less penile pain, a similar incidence of prolonged erection, and cavernosal fibrosis. PGE_1 has a higher success rate, however, and results in better penile rigidity *(45)*.

Atropine

The use of atropine sulfate in pharmaceutical erection programs was first reported by Virag et al. *(46)*. In low doses, atropine blocks muscarinic

receptors, thereby diminishing cholinergic inhibition of the adrenergic and cholinergic excitation of the nonadrenergic, noncholinergic neuroeffector systems that control neurogenic corporeal smooth muscle relaxation. In large doses, atropine releases an endothelium-derived relaxing factor that has recently been identified as a neurotransmitter involved in penile erection. Atropine is often included in multidrug mixtures for intracavernosal injection *(47)*.

Oral Treatment vs Intracavernosal Injection Therapy

In March 1998, sildenafil citrate, a selective PDE5 inhibitor, became the first approved oral drug for the treatment of ED in the United States. Its advent revolutionized the clinical management of ED. Because of its acceptable mode of administration, many patients who were using intracavernous injection therapy voluntarily converted to oral sildenafil therapy. Intracavernosal therapy remains a second-line treatment for patients who do not respond to oral therapy or for whom it is contraindicated.

Hatzichristou et al. *(48)* switched patients with ED who had been using intracavernous alprostadil successfully for at least 6 mo to sildenafil with an individually titrated dose. Sixty-four percent of the patients responding to oral therapy preferred to continue with oral medication at the end of a 12-wk period; 33% chose injection therapy; and 3% continued to use both treatments alternately. Validated questionnaires have demonstrated a higher rate of erections resulting in sexual intercourse with alprostadil injections, but patients who respond to both options prefer to use oral medication. There is a subset of patients who decide to use injection therapy because of its better efficacy and earlier onset of erection.

An interesting issue relates to patients who do not respond to PDE5 inhibitors. Shabsigh et al. *(49)* treated 67 patients with ED with escalating does of sildenafil over a 4-wk period. Nonresponding patients were evaluated with the International Index of Erectile Dysfunction (IIEF) questionnaire and entered into an alprostadil alfadex in-office titration phase to determine the optimal dose up to 40 μg, followed by a 6-wk at-home treatment phase. This resulted in improvements in questions 3 and 4 of the IIEF in 90 and 85% of the patients, respectively. The most common side effect was penile pain in 30%. Hence, intracavernosal alprostadil therapy is efficacious and safe in men in whom initial therapy with sildenafil fails.

Another open-label multicenter study investigated the efficacy and safety of alprostadil in 195 sildenafil (Viagra) nonresponders *(50)*. Intracavernous Caverject administration led to a response rate of 81% and an overall success rate of 66% in patients not responding to oral sildenafil. Reasons for withdrawal included lack of efficacy, minor adverse effects, and partner issues.

Combination therapy was demonstrated by McMahon et al. *(51)*, who studied 93 patients not responding to a home trial with high-dose alprostadil or trimix. Thirty-four percent of these patients had a sufficient erection with sildenafil alone, whereas 47.5% responded to the sildenafil-plus-injection combination.

Hence, salvage of nonresponding patients with ED works in a significant proportion of those in whom injections alone fail. This is because different mechanisms of action for PGE_1 and PDE5 inhibitors are operative, namely, the nitric oxide cGMP and cAMP systems.

Transurethral Therapy

Background

Although intracavernous injection of vasoactive agents is the most effective pharmacological therapy for ED, there is a 31 to 80% dropout rate. This is despite its high safety, efficacy, and short onset time *(10)*. Reasons for dropout include penile pain, loss of effectiveness, concomitant illness, aversion to self-injection, and fear of self-injection with a needle *(52,53)*.

A number of researchers and entrepreneurs sought alternative routes for delivering vasoactive agents to treat ED. Oral PGE_1 failed to induce rigid erections *(54)*. Transcutaneous therapies, such as nitroglycerin *(55)*, minoxidil *(56)*, yohimbine ointment, PGE_1 *(57)*, and papaverine topical gel *(58)*, demonstrated few side effects but also failed to induce penile erection sufficient for satisfactory intercourse in most patients.

A novel approach involved transurethral drug delivery, which allows the transfer of drugs through the urethra directly into the cavernosal tissues. Retrograde urethrography with contrast media performed with the proximal urethra constricted demonstrated vascular communications between the spongiosal and cavernosal compartments *(59)*.

Transurethral Alprostadil

Transurethral application of alprostadil (PGE_1) has been developed and marketed by VIVUS (Mountain View, CA). The Medicated Transurethral System for Erection (MUSE) consists of a polypropylene applicator with a hollow stem 3.2 cm in length and 3.5 mm in diameter. The tip (measuring 3 or 6 mm in length) contains a semisolid pellet of medication, available in doses of 125, 250, 500, and 1000 μg. The stem is inserted fully into the urethra, a button is depressed to dispense the pellet, and the applicator is removed (Fig. 2).

It is important to instruct the patients to urinate immediately before application, because residual urine in the urethra helps facilitate insertion of the applicator and helps disperse the medicine. After the applicator is removed, massaging the penis for 30 to 60 s while standing allows the compound to disperse and be fully absorbed.

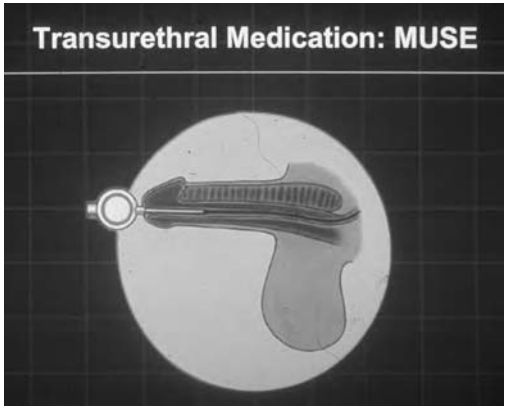

Fig. 2. Intraurethral technique. After voiding, the patient gently passes the applicator stem into the distal urethra to allow for deposition of the alprostadil pellet. MUSE, Medical Transurethral System for Erection.

One study showed that 49% of 68 men with long-standing ED of primarily organic origin achieved an erection sufficient for sexual intercourse *(60)*. Another multicenter study reported that more than 60% of men using MUSE in the office achieved erections rigid enough for penetration *(61)*. Results with home use were defined as successful penetration occurring at least once during the trial. This occurred in 65 to 70% of those using MUSE vs 10 to 20% of those on placebo *(61)*. The onset time was rapid, averaging about 7 min, and duration of erection was dose-dependent, ranging from 67 to 79 min *(62)*.

Most patients responded to 500- and 1000-µg doses; for this reason, most patients are started with 500-µg dose *(63)*. In special patient categories, such as those with spinal cord injury or men who have undergone radical prostatectomy, MUSE achieved erection rates lower than those seen in the general population of men with ED *(64,65)*.

Better erections were achieved by using the adjustable external penile band, or ACTIS (Virus Inc., Mountain View, CA) at the base of the penis.

This device is placed snugly around the base of the penis immediately before MUSE application to facilitate medication exposure, blood entrapment within the penis, and better erections. The band is gradually loosened and removed within 10 min.

Adverse Reactions

Although alprostadil is a vasodilatory agent, it exhibits few systemic effects. Adverse reactions are more frequent with intravenous administra-

tion. Nevertheless, local penile pain has been reported as the most common side effect (29–41%) *(61,66,67)*, as it is for intracavernous and topical administration.

Alprostadil sensitizes the sensory nerve fibers to noxious stimuli through interactions with specific prostaglandin receptors. Procaine, lidocaine, and sodium bicarbonate plus PGE_1 have been reported to alleviate penile pain with intracavernous injection studies *(68–70)*. However, no such clinical study has been reported for the transurethral route.

Other side effects from transurethral administration include urethral bleeding in about 5% of men and dizziness in 2 to 14% *(61,66,70)*. Priapism has rarely been reported in the literature.

Fulgham and coworkers *(66)* reported that a significant proportion of treated patients showed a decrease in both systolic and diastolic blood pressure after the administration of MUSE. A total of 20% of patients experienced at least one adverse effect. These authors reported that less than 30% of patients at any given time, using any dose, achieved erections sufficient for intercourse during in-office testing. Because of this limited efficacy, discomfort, and cost, more than 80% of the patients did not continue with MUSE at home *(66)*.

Trials Comparing Transurethral and Oral Therapy

Mydlo et al. *(71)* showed that most patients who did not respond to MUSE did respond to sildenafil, whereas patients in whom sildenafil failed responded to MUSE in less than 1% of cases.

Trials Comparing Transurethral and Intracavernosal Alprostadil

Shabsigh and coworkers *(72)* performed a crossover, randomized, open-label multicenter study in 111 patients with ED, comparing efficacy, safety, and patient preference of intracavernous injections of EDEX with MUSE plus optional ACTIS.

Intracavernosal injections produced better results than transurethral application, with sufficient erections in 83% vs 53%, respectively. Significantly more patients using EDEX achieved at least one erection sufficient for sexual intercourse (93% with EDEX vs 62% with MUSE). Patient and partner satisfaction was greater with EDEX, whereas the overall number of adverse effects was similar with both treatments. Furthermore, Porst reported similar results in 1997 *(73)*. The finding that intracavernosal alprostadil is able to produce erections with better rigidity compared with transurethral alprostadil has been also confirmed by other investigators *(74,75)*. MUSE has been reported to be effective in 58% of patients who had not responded to intracavernosal injections with alprostadil, however *(76)*.

TOPICAL PHARMACOLOGICAL THERAPY

General Principles

Transdermal application of medications is a well-established technology that provides durable and constant plasma levels of drugs, such as hormones, narcotics, and vasodilators. Penile topical therapy invokes certain issues regarding its unique anatomy and physiology. There are numerous fascial layers between the penile skin and the corpora cavernosa. The tunica albuginea is presumed to be difficult to penetrate because of its thick layers of collagen. Thus, topical treatment trials have focused on exposure to the glans penis, because it has direct venous communication to the corpus spongiosum, which bridges the drug transfer through the tunica albuginea. Investigators have used permeation enhancers to facilitate the transfer of drug to the corporal smooth muscle. The penile and scrotal skin are the most permeable of all anatomical locations tested. An additional factor confounding the effective delivery of drugs is the rich vasculature of the deep dermis, which may drive a certain amount of the drug into systemic circulation.

In pilot studies, transcutaneous therapies, such as nitroglycerin *(55)*, minoxidil *(56)*, yohimbine ointment, PGE_1 *(57)*, and papaverine topical gel *(58)*, demonstrated few side effects but failed to induce rigid erections, apparently because of insufficient transfer of the vasoactive agent through penile skin without the aid of permeation enhancers. Borges *(77)* tried to overcome the presumed permeation problem by performing a surgical procedure, creating a 1-cm square window in Buck's fascia and the tunica albuginea of impotent men and covering the defect with a patch of deep dorsal vein. The intention was to apply local nitroglycerin cream on the skin right above the defect. The concept did not progress further, perhaps because of failure of the patch, inherent absorptive tissues in the skin, or failure in the formulation of the topical agent.

Most of the delivery systems currently in use for topical therapy are intended for slow and steady release of medication, such as those used in hormonal, analgesic, or narcotic patches. This slower process is not effective as an erection initiator because the drug transfer is likely to be slow. The formulation used needs to have a sufficient penetration enhancer to help transfer the active agent and release it at the site of action.

A well-established agent that enhances the transport of a variety of drugs through human or porcine skin in vitro is soft enhancer of percutaneous absorption (SEPA) (2-nonyl-1,3-dioxolane) *(78)*. Because of its amphiphilic structure, it causes a temporary reversible modification in the stratum corneum that provides diffusion of drugs at a much higher rate than normal.

Topical PGE_1

McVary et al. *(79)* evaluated and compared the use of SEPA in a gel formulation containing alprostadil for systemic effects, local tolerance of the penis, and effectiveness in inducing erections in patients with ED. Application of the PGE_1 correlated positively with erectile response in a majority of patients on active drug: 67 to 75% of the patients achieved an erection sufficient for intercourse compared with 17% in the control group. This represented an advance in topical administration studies. With audiovisual or tactile stimulation, the response to the drug was greatly augmented, suggesting the role of topical gels in facilitation rather than initiation of erection. No serious side effects were reported except for minimal skin discomfort. Systemic drug interactions are unlikely because of the low systemic absorbance and the short half-life of topical prostaglandin.

Goldstein et al. reported that 40% of patients treated with topical PGE_1/SEPA were able to get a satisfactory erection without significant changes in systemic vital signs *(80)*.

The first at-home phase II study was published by Padma-Nathan in 2003 *(81)*. He included a broad range of ED severities, as determined by the IIEF, and described a clinically meaningful improvement in this domain. In conclusion, these studies support the rationale for phase III studies, which are currently ongoing.

A different agent for topical penile therapy was explored recently: PGE_1 ethyl ester, a prodrug of PGE_1 that improves transdermal permeation because of esterification. Schanz et al. reported both good efficacy and few adverse effects. A further evaluation of this route is in progress using higher doses in a placebo-controlled trial *(82)*.

Topical Minoxidil

Minoxidil is an antihypertensive agent that primarily acts by opening potassium channels in the membrane of vascular smooth muscle cells. Although little can be said about its role in regard to ED, there is extensive literature on its use as an antihypertensive medication. Because of its potency and the adverse reactions it causes, oral minoxidil is used mainly for patients with severe drug-resistant forms of hypertension.

Minoxidil does not have a direct vasodilatory effect on arterial smooth muscle. It is converted to minoxidil *O*-sulfate by a hepatic enzyme, however, which does have a direct vasodilatory effect on arterial smooth muscle. Minoxidil-induced delay in the hydrolysis of cAMP via the inhibition of PDE may contribute to the drug's vasodilatory action as well.

Conflicting results have been reported regarding its erectogenic effects. Under laboratory conditions, application of 1 mL of a 2% minoxidil solu-

tion to the glans penis caused greater change in penile tumescence and rigidity and in arterial function than did administration of 2.5 g of 10% nitroglycerin ointment and placebo *(83)*.

When the same doses of minoxidil were used in a clinical setting, however, this drug appeared to be of minimal usefulness in improving sexual activity *(84,85)*. This striking difference may be a result of different criteria used to assess the erectile response; that is, in the clinical studies, only the patients achieving erections adequate for vaginal penetration were considered responders.

The adverse reaction profile for minoxidil depends on its use. Systemic adverse reactions are unlikely to occur from topical administration.

Topical Papaverine

The use of topical papaverine was reported by Kim et al. in a phase I/II single-blinded placebo-controlled trial in 20 patients with organic impotence *(58)*. After the application of the gel to the penis, scrotum, and perineum, a dose-dependent hemodynamic effect was found during duplex ultrasonography. Full clinical erections were present in only 15% of patients, however, which was also reported for the group receiving placebo. Papaverine gel is not as effective as intracavernous injection therapy but could be promising at higher concentrations or in combination with other skin enhancers.

Topical Nitroglycerin

The use of topical nitroglycerin is a standard treatment for unstable angina pectoris and Raynaud's disease because predictable blood levels of this drug can be achieved. The use of nitroglycerin ointments, pastes, plasters, and patches for the treatment of ED has been tried in several studies. A measurable vasodilatory response to nitroglycerin ointment has been shown by color Doppler ultrasonography, and a definite relaxation of strips of penile cavernous tissue induced in vitro by nitroglycerin has also been demonstrated *(86,87)*.

The most frequent adverse reaction is headache, occurring in 2% of patients. Other reactions, occurring in less than 1%, are tachycardia, nausea, vomiting, restlessness, palpitations, dizziness, and abdominal pain. Cutaneous flushing, weakness, drug rash, and allergies to adhesives used with the nitroglycerin have also been reported.

Conclusion

Because of its safety, efficacy, and simple administration, topical PGE_1 application is a viable second-line agent for the treatment of ED and may become an option for patients who are unresponsive to oral PDE5 inhibi-

tors or in whom they are contraindicated. For patients who are unable to perform local intracavernosal injection owing to bodily inadequacy, such as patients with Parkinson's disease or spinal injuries, as well as morbidly obese patients, it is a welcome therapy.

Further studies regarding different topically administered agents are in progress.

COMBINATION THERAPIES

In March 1998, sildenafil citrate, a selective PDE5 inhibitor, became the first approved oral drug for ED in the United States. Its advent revolutionized the management of ED. Clinical trials documented efficacy and safety in patients of all ages and with ED of various causes and degrees of severity. Despite its efficacy, determined in clinical trials conducted with healthy volunteers and subsequently with patients with minimal or moderate ED, general urological practice outcomes are usually less than expected.

Efficacy rates of the PDE5 inhibitors in urological practice range from 50 to 70%, depending on the severity of ED and underlying diseases.

This raises the issue of how we can best help the other 30 to 50% of patients who have an unsatisfactory response to first-line oral monotherapy. Motivated patients should proceed to second-line therapies, such as transurethral application of alprostadil, intracavernosal injection of alprostadil, or a trimixture combination. In many cases, however, this is not a cure-all. The initial success of transurethral MUSE has been difficult to duplicate in an office setting and intracavernous injections often have severe side effects.

Another currently uninvestigated approach is the use of combination therapies. Similar to cancer therapy, an ideal combination therapy would combine drugs with:

1. Different mechanisms acting at different targets.
2. Durable efficacy.
3. Nonoverlapping adverse effects *(88)*.

The cost of combination therapy may be prohibitive, however. The simplest combination therapy may be a single agent plus brief psychotherapy or counseling. In addition, behavioral modifications may be effective, because patients with diabetes, hypertension, and coronary artery disease are often affected by ED.

The concept of combination drug therapy for ED is appealing and has been used since the 1980s in the form of intracavernous injection therapy. The impetus was to reduce the incidence of adverse effects and to improve efficacy. The emergence of oral agents with efficacy in the treatment of ED led to pilot studies using a wide array of drug combinations. These studies mixed agents with different mechanisms of action and alternate routes of

Table 2
Drug Combination Strategies

cAMP + α-adrenergic blocker:	ICI PGE_1 + doxazosin
cAMP + cGMP:	ICI PGE_1 + sildenafil MUSE PGE_1 + sildenafil
cGMP + α-adrenergic blocker:	sildenafil + phentolamine sildenafil + doxazosin
Central + peripheral:	apomorphine + alfuzosin apomorphine + sildenafil apomorphine + α_{1D}-antagonist

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanine monophosphate; ICI, intracavernous injection; MUSE, Medical Transurethral System for Erection; PGE_1, prostaglandin E_1.

administration. For example, substances that use cAMP have been combined with those that antagonize α-adrenergic receptors or that increase cGMP levels. Similarly, drugs that increase cGMP levels have been used with those that antagonize α-adrenergic receptors or elevate cAMP levels.

Another approach has been to use centrally-acting dopamine agonists and agents that increase cGMP levels or block α-adrenoceptors. The reluctance to perform intracavernous injections along with the emergence of approved oral agents for ED has led to the use of oral combinations.Before the release of PDE5 inhibitors, an oral α_1-adrenergic blocker plus intracavernous therapy had been used. Kaplan et al. examined 38 men in whom intracavernous alprostadil was ineffective *(89)*. The combination of doxazosin and intracavernous alprostadil resulted in an overall 55.7% improvement on the global efficacy questionnaire. Nevertheless, this study was open label and nonrandomized, raising questions regarding applicability.

Benign prostatic hyperplasia is often treated with oral α-adrenergic blockers. Not unexpectedly, many men also using sildenafil because of ED noticed an enhanced response to sildenafil when combined with oral doxazosin.

After the approval of sildenafil, clinicians empirically tried combination therapies as a salvage treatment for patients in whom monotherapy failed. The two most popular approaches have been the use of sildenafil plus transurethral application of alprostadil or intracavernous injection of alprostadil (Table 2).

The efficacy of sildenafil plus transurethral alprostadil was reported by Nehra and coworkers *(90)*. Twenty-eight patients, 17 with a history of radi-cal prostatectomy and 11 with a diagnosis of organic ED, were

included in this study. In all these patients, monotherapy with either 100 mg of sildenafil citrate or 1000 μg of MUSE had failed. After initiating combination therapy, all 28 patients reported erections sufficient for vaginal penetration at 30 mo, with 3.6 intercourse episodes per month. None of the patients switched to the use of intracavernosal therapy or penile prosthesis.

As mentioned previously, McMahon et al. reported that combining sildenafil and intracavernosal injection therapy may be a salvage treatment for a significant proportion of patients in whom oral monotherapy and injections alone fail *(51)*.

These combinations raise the possibility that a sildenafil-plus-alprostadil regimen may act as a rescue treatment for those in whom monotherapies fail. Yet the true safety and efficacy remain to be tested in a double-blind, placebo-controlled, randomized trial.

CONCLUSION

At present, oral pharmacotherapy represents the first-line option for most patients with ED. Patients who do not respond to oral therapy or those who are not eligible for this treatment are appropriately considered for second-line treatments, which include intracavernosal injections, transurethral suppositories, and topical agents. Currently, intracavernosal injection therapy is associated with the highest efficacy within this group. The major limitation of this approach is represented by its high attrition rate. In addition, intraurethral administration of alprostadil may have a more limited role in the future in view of the advent of novel, safe, and effective oral drugs. Topical agents remain an attractive option with the potential to become a first-line treatment, if an effective system to facilitate skin and tunica transfer can be identified.

Preliminary investigations regarding combination therapies suggest avenues for further research and offer the potential for a convenient, noninvasive treatment for patients with ED who do not respond to PDE5 inhibitor monotherapy.

These reports must be viewed with some degree of skepticism because of the lack of randomized comparative drug trials with sufficient numbers of patients. Furthermore, in designing such studies, it is difficult to control the placebo effect when two routes of administration or two agents with different adverse effects are used.

Because of the lack of control data and the potential for significant safety issues, it would make sense to recommend a combination of pharmacological and sex therapy or psychological therapy first before moving into combination therapies. Lifestyle modification would most likely contribute to therapeutic success.

REFERENCES

1. Benet AE, Melman A. (1995) The epidemiology of erectile dysfunction. Urol Clin North Am 22:699–709.
2. Aytac IA, McKinlay JB, Krane RJ. (1999) The likely worldwide increase in erectile dysfunction between 1995 an 2025 and some possible policy consequences. BJU Int 84:50–56.
3. Rosen R, Goldstein I, Heiman J, et al. (1999) The process of care model for evaluation and treatment of erectile dysfunction. Int J Impot Res 11:59–74.
4. Montorsi F, Guazzoni G, Rigatti P, Pozza G. (1995) Pharmacological management of erectile dysfunction. Drugs 50:465–479.
5. Virag R. (1982) Intracavernous injection of papaverine for erectile failure. Lancet 2:938.
6. Brindley GS. (1983) Cavernosal alpha-blockade: a new technique for investigating and treating erectile impotence. Br J Psychiatry 143:332.
7. Zorgniotti AW, Lefleur RS. (1985) Auto-injection of the corpus cavernosum with a vasoactive drug combination for vasculogenic impotence. J Urol 133:39–41.
8. Ishii N, Watanabe H, Irisawa C, et al. (1986) Studies on male sexual impotence. Report 18. Therapeutic trial with prostaglandin E_1 for organic impotence. Jpn J Urol 77:954–962.
9. Kapoor VK, Chahal AS, Jyoti SP, et al. (1995) Intracavernous papaverine for impotence in spinal cord injured patients. Paraplegia 31:675–680.
10. Porst H. (1996) The rationale for PGE_1 in erectile failure: a survey of world-wide experience. J Urol 155:802–815.
11. Lomas T, Jarow J. (1992) Risk factors for papaverine-induced priapism. J Urol 147:1280.
12. Leungwattanakij L, Flynn V, Hellstrom WJG. (2001) Intracavernosal injection and transurethral therapy for erectile dysfunction. Urol Clin North Am 28:343–354.
13. Domer F, Wessler G, Brown R, et al. (1978) Involvement of the sympathetic nervous system in the urinary bladder internal sphincter and in penile erection in the anaesthetized cat. Investig Urol 15:404–407.
14. Padma-Nathan H, Goldstein I, Payton T, et al. (1987) Intracavernosal pharmacotherapy: the pharmacologic erection program. World J Urol 5:160.
15. Robinette M, Moffat MJ. (1986) Intracorporeal injection of papaverine and phentolamine in the management of impotence. Br J Urol 58:692–695.
16. Sidi A, Chen K. (1987) Clinical experience with vasoactive intracavernous pharmacotherapy for treatment of impotence. World J Urol 5:156.
17. Nellans RE, Ellis LR, Kramer-Levien D. (1987) Pharmacological erection: diagnosis and treatment applications in 69 patients. J Urol 138:52–54.
18. Gasser TC, Roach RM, Larsen EH, et al. (1987) Intracavernous self-injection with phentolamine and papaverine for the treatment of impotence. J Urol 137:678–680.
19. Keogh EJ, Watters GR, Earle CM, et al. (1989) Treatment of impotence by intracavernosal injections. A comparison of papaverine and papaverine and phentolamine: a double-blind crossover trial. J Urol 142:726–728.
20. Bechara A, Casabe A, Cheliz G, et al. (1997) Comparative study of papaverine plus phentolamine versus prostaglandin E_1 in erectile dysfunction. J Urol 157(6):2132–2134.
21. Adaikan P, Karim S, Kottegoda S, et al. (1983) Cholinoreceptors in the corpus cavernosum of the human penis. J Auton Pharmacol 3:107–111.
22. Porst H. (1989) Prostaglandin E_1 bei erektiler Dysfunktion. Urologe A 28:94.

23. Porst H, Buvat J, Meulemann E, et al. (1996) Final results of a prospective multicenter study with self-injection therapy with PGE_1 after 4 years of follow-up. Int J Impot Res 8:D118.
24. Linet OI, Ogrinc FG, Alprostadil Study Group. (1996) Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. N Engl J Med 334:873–877.
25. Lea AP, Bryson HM, Balfour JA. (1996) Intracavernous alprostadil. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in erectile dysfunction. Drugs Aging 8(1):56–74.
26. Sato Y, Suzuki N, Adachi H, et al. (1996) Effect of neurotropin for penile pain induced by intracavernous injection of prostaglandin E_1. Int J Impot Res 8:139.
27. Earle CM, Chew KK, Stuckey BGA, Keogh EJ. (1996) Pain with intracavernosal therapy. Int J Impot Res 8:114.
28. Marshall GA, Breza J, Lue TF. (1994) Improved hemodynamic response after long-term intracavernous injection for impotence. Urology 43:844–847.
29. Brock G, Mai Tu L, Linet O. (2001) Return of spontaneous erection during long-term intracavernosal alprostadil (Caverject) treatment. Int J Impot Res 57:536–541.
30. Maniam P, Seftel A, Corty E. (2001) Nocturnal penile tumescence activity unchanged after long-term intracavernous injection therapy. J Urol 165:830–833.
31. Bennet AH, Carpenter AJ, Baranda JH. (1991) An improved vasoactive drug combination for a pharmacological erection program. J Urol 146:1564–1565.
32. McMahon CG. (1991) A comparison of the intracavernosal injection of a combination of papaverine and phentolamine, prostaglandin E_1, and a combination of all three agents in the management of impotence. Int J Impot Res 3:113.
33. Bechara A, Casabe A, Cheliz G, et al. (1996) Prostaglandin E_1 versus mixture of prostaglandin E_1, papaverine and phentolamine in nonresponders to high papaverine plus phentolamine doses. J Urol 155:913–914.
34. Roy JB, Petrone RL, Dais SI. (1990) A clinical trial of intracavernous vasoactive intestinal polypeptide to induce penile erection. J Urol 143:302.
35. Gerstenberg TC, Metz P, Otteson B. (1992) Intracavernous self-injection with vasoactive intestinal polypeptide and phentolamine in the management of erectile dysfunction. J Urol 147:1277–1279.
36. Sandhu D, Curless E, Dean J, et al. (1999) A double blind, placebo controlled study of intracavernosal vasoactive polypeptide and phentolamine mesylate in a novel auto-injector for the treatment of non-psychogenic erectile dysfunction. Int J Impot Res 11:91.
37. Steif CG, Homlquist F, Djamilian M, et al. (1992) Preliminary results with the nitric oxide donor linsidomine chlorhydrate in the treatment of human erectile dysfunction. J Urol 148:1437.
38. Wegner HE, Knispel HH, Klan R, et al. (1994) Prostaglandin E_1 versus linsidomine chlorhydrate in erectile dysfunction. Urol Int 53:214.
39. Martinez-Pineiro L, Lopez-Tello J, Dorrego J. (1995) Preliminary results of a comparative study with intracavernous sodium nitroprusside and prostaglandin E_1 in patients with erectile dysfunction. J Urol 153:1487–1490.
40. Mulhall JP, Daller M, Traish A, et al. (1997) Intracavernosal forskolin: role in management of vasculogenic impotence resistant to standard 3-agent pharmacotherapy. J Urol 158:1752.
41. Truss MC, Becker AJ, Thon WF, et al. (1994) Intracavernous calcitonin gene-related peptide plus prostaglandin E_1: possible alternative to penile implants in selected patients. Eur Urol 26:40–45.

42. Montorsi F, Salonia A, Zanoni M, et al. (2002) Current status of local penile therapy. Int J Impot Res 14(Suppl 1):70–81.
43. Imagawa A, Kimura K, Kawanishi Y. (1989) Effect of moxisylyte hydrochloride on isolated human penile corpus cavernosum tissue. Life Sci 44:619–623.
44. Costa P, Sarrazin B, Bressolle F, et al. (1993) Efficiency and side effects of intracavernous injections of moxisylyte in impotent patients: a dose-finding study versus placebo. J Urol 149:301–305.
45. Buvat J, Costa P, Morlier D, et al. (1998) Double-blind multicenter study comparing alprostadil alpha-cyclodextrin with moxisylyte chlorohydrate in chronic organic erectile dysfunction. J Urol 159:116–119.
46. Virag R, Shoukry K, Floresco J, et al. (1991) Intracavernous self-injection of vasoactive drugs in the treatment of impotence: 8-year experience with 615 cases. J Urol 145:287–292.
47. Sogari PR, Teloken C, Vargas Souto CA. (1997) Atropine role in the pharmacological erection test: study of 228 patients. J Urol 158:1760–1763.
48. Hatzichristou D, Apostolidis A, Tzortzis V, et al. (2000) Sildenafil versus intracavernous injection therapy: efficacy and preference in patients on intracavernous injection for more than 1 y. J Urol 164:1197–1200.
49. Shabsigh R, Padma-Nathan H, Gittleman M, et al. (2000) Intracavernous alprostadil alfadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). Urology 55:477–480.
50. Padma-Nathan H, Shabsigh R, Weiss RE, et al. (2000) Efficacy and safety of alprostadil in sildenafil failures. J Urol 166:201–202A.
51. McMahon CG, Samali R, Johnson H. (1999) Treatment of intracorporeal nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy. J Urol 162:1992–1998.
52. Irwin MB, Kata EJ. (1994) High attrition rate with intracavernous injection of prostaglandin E_1 for impotence. Urology 48:84.
53. Valdevenito R, Melman A. (1994) Intracavernous self-injection pharmacotherapy program: analysis of results and complications. Int J Impot Res 6:81.
54. Kawanishi Y, Kimura K, Iriguchi H, et al. (1992) Double-blind trial of oral PGE_1 on impotence. Nippon Hinyokika Gakki Zasshi 83:1655.
55. Gramkow J, Lendorf A, Zhu J, et al. (1999) Transcutaneous nitroglycerine in the treatment of erectile dysfunction: a placebo controlled clinical trial. Int J Impot Res 11:35.
56. Cavallini G. (1994) Minoxidil versus nitroglycerine: a prospective double-blind, controlled trial in transcutaneous erectile therapy for organic impotence. Int J Impot Res 6:205.
57. Kim ED, McVary KT. (1995) Topical PGE_1 for the treatment of erectile dysfunction. J Urol 153:1828.
58. Kim ED, el-Rashidy R, McVary KT. (1995) Papaverine topical gel for treatment of erectile dysfunction. J Urol 153:361.
59. Vardi Y, Sàenz de Tejada I. (1997) Functional and radiologic evidence of vascular communications between the spongiosal and cavernosal compartments of the penis. Urology 49:749–752.
60. Hellstrom WJ, Bennett AH, Gesunheit N, et al. (1996) A double-blind placebo controlled evaluation of the erectile response to transurethral alprostadil. Urology 48:851.
61. Padhma-Nathan H, Hellstrom WJG, Kaiser FE, et al. (1997) Medicated Urethral System for Erection (MUSE) Study Group: treatment of men with erectile dysfunction with transurethral alprostadil. N Engl J Med 336:1.

62. Peterson CA, Bennet AH, Hellstrom WJG, et al. (1998) Erectile response to transurethral alprostadil, prazosin and alprostadil-prazosin combinations. J Urol 159:1523.
63. Ekman P, Sjogren L, Englund G, Persson BE. (2000) Optimizing the therapeutic approach of transurethral alprostadil. BJU Int 86:68–74.
64. Bodner D, Haas CA, Krueger B, Seftel AD. (1999) Transurethral alprostadil for treatment of erectile dysfunction in patients with spinal cord injury. Urology 53: 199–202.
65. Costabile RA, Spevak M, Fishman IJ, et al. (1998) Efficacy and safety of transurethral alprostadil in patients with erectile dysfunction following radical prostatectomy. J Urol 160:1325–1328.
66. Fulgham PF, Cochran JS, Denman JL, et al. (1998) Disappointing initial results with the transurethral alprostadil for erectile dysfunction in a urology practice setting. J Urol 160:2041.
67. Labasky RC, Spivack AP. (1998) Transurethral alprostadil for the treatment of erectile dysfunction: two-year safety update. J Urol 159(Suppl 5):907A.
68. Kattan S. (1995) Double-blind randomized crossover study comparing intracorporeal prostaglandin E_1 with a combination of prostaglandin E_1 and lidocaine in the treatment of organic impotence. Urology 45:1032.
69. Moriel EZ, Raijfer J. (1993) Sodium bicarbonate alleviates penile pain induced by intracavernous injections for erectile dysfunction. J Urol 149:1299.
70. Schramek P, Pals EG, Hubner WA, et al. (1994) Intracavernous injection of PGE_1 plus procaine in the treatment of erectile dysfunction. J Urol 152:1108.
71. Mydlo JH, Volpe MA, Machia RJ. (2000) Initial results utilizing combination therapy for patients with a suboptimal response to either alprostadil or sildenafil monotherapy. Eur Urol 38:30–34.
72. Shabsigh R, Padma-Nathan H, Gittleman M, et al. (2000) Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over transurethral alprostadil plus optional ACTIS: a comparative, randomised, crossover, multicenter study. Urology 55:109–113.
73. Porst H. (1997) Transurethral alprostadil with MUSE vs intracavernous alprostadil, a comparative study in 103 patients with erectile dysfunction. Int J Impot Res 9: 187–192.
74. Shokeir AA, Alserafi MA, Mutabagani H. (1999) Intracavernosal versus transurethral alprostadil: a prospective randomised study. Br J Urol 83:812–815.
75. Werthman P, Raijfer J. (1997) MUSE therapy: preliminary clinical observations. Urology 50:809–811.
76. Engel JD, McVary KT. (1998) Transurethral alprostadil as therapy for patients who withdrew from or failed prior intracavernous injection therapy. Urology 51:687–692.
77. Borges FD. (1994) A new approach to the pharmacologic treatment of impotence. Int J Impot Res 6:137.
78. Samour CM, Donaruma LG, Daskalakis S, et al. (1989) A new class of percutaneous absorption enhancers. Proc Intern Symp Control Rel Bioact Mater 16:183.
79. McVary KT, Polepalle S, Riggi S, Pelham RW. (1999) Topical PGE_1/SEPA gel for the treatment of erectile dysfunction. J Urol 162:726.
80. Goldstein I, Payton TR, Scheichter PJ. (2001) A double-blind, placebo-controlled, efficacy and safety study of topical gel formulation of 1% alprostadil (Topiglan) for the in-office treatment of erectile dysfunction. Urology 57:301–305.
81. Padma-Nathan H, Steidle C, Salem S, et al. (2003) The efficacy and safety of a topical alprostadil cream, Alprox-TD, for the treatment of erectile dysfunction: two phase 2 studies in mild-to-moderate and severe ED. Int J Impot Res 15:10–17.

82. Schanz S, Hauswirth U, Ulmer A, Fierlbeck G. (2002) Prostaglandin E_1 ethyl ester, a new agent for topical penile therapy. Int J Impot Res 14:317–318.
83. Cavallini G. (1991) Minoxidil versus nitroglycerin: a prospective double-blind controlled trial in transcutaneous erection facilitation for organic impotence. J Urol 146:50–53.
84. Radomski SB, Herscorn S, Rangaswamy S. (1994) Topical minoxidil in the treatment of male erectile dysfunction. J Urol 151:1225–1226.
85. Chancellor MB, Rivas DA, Panzer DE, et al. (1994) Prospective comparison of topical minoxidil to vacuum constriction device and intracorporeal papaverine injection in treatment of erectile dysfunction due to spinal cord injury. Urology 43: 365–369.
86. Anderson DC, Seifert CF. (1993) Topical nitrate treatment of impotence. Ann Pharmacother 27:1203–1205.
87. Owen JA, Saunders F, Harris C, et al. (1989) Topical nitroglycerine: a potential treatment for impotence. J Urol 141:546–548.
88. Steers WD. (2003) Viability and safety of combination drug therapies for erectile dysfunction. J Urol 170:20–23.
89. Kaplan SA, Reis RB, Kohn IJ, et al. (1998) Combination therapy using oral alpha-blockers and intracavernosal injection in men with erectile dysfunction. Urology 52:739.
90. Nehra A, Blute ML, Barrett DM, Moreland RB. (2002) Rationale for the combination therapy of transurethral prostaglandin E_1 and sildenafil in the salvage of erectile dysfunction patients desiring noninvasive therapy. Int J Impot Res 14(Suppl 1):S38.

13 Androgen Deficiency in the Aging Male

Enhancing Erectile Response to Oral Pharmacotherapy

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CONTENTS

INTRODUCTION

A rekindling of interest in androgen supplementation therapy has occurred in the last decade. Undoubtedly this is a result of the increasing recognition and acceptance of issues of men's health, which in many ways are closely related to the aging process. This interest has not been limited to health care professionals and the pharmaceutical industry but

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has extensively included the lay press and the general public. In addition, long-established concepts related to hormone replacement therapy in women have been vigorously challenged, and some of the new findings were, erroneously and baselessly, extrapolated to androgen replacement therapy (ART) in men.

GENERAL CONCEPTS OF HORMONES AND SEXUAL FUNCTION

This chapter deals exclusively with hormonal alterations naturally developing in the adult male; congenital anomalies and hypogonadism occurring as a consequence of medical intervention (i.e., surgical or medical castration for the treatment of advanced prostate carcinoma) are excluded. In men, gonadal function is affected in a slow, progressive way as part of the normal aging process *(1)*. Although the age-related decrease in androgen production has been clinically documented and categorized for more than 50 yr *(2)*, only recently has significant and sustained interest in this condition developed. It is variously known as male climacteric, andropause, or, more appropriately, androgen decline in the aging male or late-onset hypogonadism (LOH). The term *andropause* is biologically wrong and clinically inappropriate, but it adequately conveys the concept of emotional and physical changes that (although related to aging in general) can also be associated with significant hormonal alterations. The inappropriateness of the term is based on the fact that in women, the reproductive cycle invariably ends with ovarian failure. In men, this process is not universal, and, when it occurs, it is normally subtle in its clinical manifestations.

LOH is relatively common. It is important to differentiate between symptomatic LOH , which requires treatment, and the incidentally found low level of testosterone in a man without symptoms. The former may require treatment, while the latter does not. The prevalence of LOH throughout the world is not known. Table 1 shows estimates of prevalence from three separate North American studies *(3)*.

The International Society for the Study of the Aging Male has recommended a definition for the condition resulting from the decline in androgen production in the adult *(4)*. This definition was modified to focus more directly on sexual function at the Second Consultation on Sexual Medicine and now offers the most explicit and acceptable definition useful for clinicians. It reads as follows: "Adult onset hypogonadism is a clinical and biochemical syndrome frequently associated with advancing age and characterized by a deficiency in serum androgen levels, with or without changes in receptor sensitivity to androgens. It may affect the function of multiple organ systems and result in significant detriment in the quality of life, including major alterations in sexual function."

Table 1
Prevalence of Hypogonadism in Older Males (%)

Age (yr)	*Baltimore Longitudinal Study* [a]	*Mayo Clinic* [b]	*Canadian MDs* [b]
40–49	2	2	5
50–59	9	6	30
60–69	34	20	45
70–79	68	34	70
80+	91	—	—

[a] Based on a free androgen index.
[b] Based on bioavailable testosterone.
Adapted from ref. *3*.

It is worth mentioning that endocrinopathies resulting from the normal process of aging in men are not exclusively centered on sex steroids. Although hypotestosteronemia is the most widely recognized and investigated hormonal alteration associated with sexual performance, the production of several other hormones (e.g., growth hormone, dehydroepiandrosterone [DHEA], and melatonin) is also profoundly affected by age and may have direct and indirect implications in sexual function.

CORRELATES OF HYPOGONADISM AND SEXUAL FUNCTION

Convincing and well-recognized epidemiological studies have found age to be the most important factor associated with erectile dysfunction (ED) *(5,6)*. Traditionally, it was thought that a variety of vascular and neurological problems developing during the aging process acted together to cause frequent and severe disruption of the peripheral erectile mechanisms. Undoubtedly, there is an immediate relationship between the neurovascular alterations and the sexual response. However, more recent research offers new perspectives that need to be taken into consideration for their potential clinical implications.

Evidence for Direct Transsynaptic Neural Phalloencephalic Connection

Our understanding of the neurological control of a major portion of the sexual response has been greatly enhanced by techniques capable of mapping central nervous system (CNS) circuitry via transneuronal tracing studies. These techniques permit delineation of the CNS and its connections with specific peripheral organs. Thus, through a number of elegant animal experiments using a pseudorabies virus capable of transsynaptic transport

and amplification, Marson et al. *(7)*, among others, have documented consistent labeling of the following portions of the forebrain within a day of injection of pseudorabies virus into the penis: the paraventricular nucleus (PVN), the medial preoptic area (MPOA), and the supraoptic nucleus. Such findings clearly support the view that these high locations of the CNS have a direct connection to the genitals and are fundamental in the control of sexual behavior and function.

In addition to the ever-important anatomical links, further evidence has been provided of a direct functional relationship via the induction of penile erections with either electrical stimulation or the injection of the dopaminergic agonist apomorphine directly into the MPOA and PVN *(8)*. Taken together, these studies offer solid and convincing evidence of a major central neurological contribution to the erectile mechanisms. *See* Chapters 1 and 14 regarding a thorough explanation of the role of the CNS in the mechanisms of erectile function.

The Role of Sex Steroids

The extent to which the changes in the hormonal milieu that develop as life progresses contribute to the appearance and persistence of ED remains speculative. It is known, however, that hypogonadism is associated with a decrease in sexual interest and deterioration in the quality of erectile function. Both these situations can be improved with androgen supplementation therapy. The therapeutic response has been explained as being the result of the combined central and peripheral activity of androgens. The latter appear to be fundamental in the signaling process leading to the adequate production of nitric oxide (NO) concentrations in the smooth muscle of the penile corpora through the activity of NO synthase (NOS).

The Integrated System

Basic animal research is providing important clues to the integration of the concepts of decreased sexual function and hormonal alterations in the aging male. At the peripheral level, it is believed that testicular function deteriorates on the basis of decreased gonadal perfusion, leading to a loss in the population of Leydig cells. The causes may be more fundamental and complex than that, however. Chen and Zirkin *(9)* postulated that a cause was deterioration of Leydig cell function as a result of accumulation of free radical damage, which could be prevented by placing the Leydig cells in a state of steroidogenesis "hibernation." This is an interesting concept that unfortunately largely lacks usefulness in humans. Wang et al. *(10)* has shown, in a series of investigations in rodents, that hypothalamic-pituitary functional alterations may not be the only, or even the major, cause of male gonadal dysfunction. They reported evidence of a significant increase in

apoptosis in both the hypothalamus and the gonads, a dual alteration that may explain in a more integral way the relationship between hypogonadism and the appearance of sexual dysfunction.

Interestingly enough, the areas of the forebrain closely linked to the decrease in gonadotropin-releasing hormone resulting from this apoptotic process are the same (MPOA and arcuate nucleus) or are intimately related to the areas controlling the penile erection process (MPOA and PVN) and the synthesis and release of oxytocin (PVN and supraoptic nucleus), a neurotransmitter fundamental in human sexuality. Peptides normally characterized by their ability to release growth hormone (GH) were found to be capable of inducing penile erections when injected into the PVN of experimental animals. GH production, which also declines with age, has not been known to play a role in human sexuality, although only limited research has been conducted in this area. Despite the fact that these findings are of obvious interest, they remain speculative and, for the moment, are not clinically relevant; however, they are worth additional research.

PHYSIOLOGICAL ASPECTS OF HORMONES INVOLVED IN SEXUAL FUNCTION

Gonadotropins and Androgens

The hypothalamic–pituitary–gonadal system is a closed-loop feedback control mechanism directed at maintaining normal reproductive function *(11)*. The gonadal hormones have inhibitory effects on the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Although testosterone, the major secretory product of the testes, is a primary inhibitor of LH secretion in men, other testicular products, including estrogens and other androgens, also inhibit LH secretion. The inhibitory effects of testosterone are produced both by testosterone itself and indirectly through aromatization to estradiol. Dihydrotestosterone (DHT), a nonaromatizable androgen, also inhibits LH secretion.

Testosterone

Testosterone exerts a variety of effects on organ systems of the body. These include formation of the male phenotype during the period of sexual differentiation; regulation of gonadotropin secretion; initiation and maintenance of spermatogenesis; promotion of sexual maturation at puberty; control of sexual drive; and facilitation of penile erections. Regarding sexual function, adequate levels of testosterone are necessary for the maintenance of normal libido, several aspects of ejaculatory function, and the normal cycle of spontaneous erections during sleep and wakefulness. There is a threshold, with marked interindividual variation, below which sexual function is impaired *(12)*.

Table 2
Relative Activity of Androgens

Dihydrotestosterone	300
Testosterone	100
Androstenedione	10
DHEA, DHEAS	5

DHEA, dehydroepiandrosterone; DHEAS, dehydrepiandrosterone sulfate.

In the same context of sexual function and the understanding of sexual dysfunction, it has been reported that androgens are important in the expression of neuronal NOS and in phosphodiesterase-5 (PDE5) gene expression *(13)*.

More recently, compelling evidence has been elicited by Traish et al. in a series of well-designed studies in rabbits.

They clearly establish that profound hypogonadism achieved by surgical or medical means profoundly affects penile hemodynamics in the absence of relevant changes in the activities of NOS or arginase *(14)*.

The effect of testosterone, however, is not limited to the peripheral mechanisms. Wu et al. *(15)*, whereas investigating the relevance of NO as one of the neurotransmitters in the PVN, found that penile erections, readily induced by infusion of L-arginine into the PVN, are dependent on the androgen milieu. These views further support the integral concept of neuroendocrine system involvement in the adequate functioning of many aspects of human sexuality.

Adrenal Androgens

The adrenal androgens are DHEA, its sulfate (DHEAS), and androstenedione. Their androgenic action is much weaker than that of testosterone, which in turn is weaker than DHT. The relative potency of DHEA in relation to other sex steroids is illustrated in Table 2.

Although there is no credible evidence that any of the adrenal androgens play a pivotal role in sexual function, there are a number of reasons to consider them potentially active compounds. First, they undergo conversions to other sex steroids, such as testosterone, but their contribution to circulating levels of testosterone in adult men is insufficient to prevent hypogonadism in cases of gonadal failure. Second, they are capable of interacting with different classes of hormone receptors *(16)*, although it is believed that they lack a true hormonal effect on their own. More recently, a specific receptor for DHEA (a prerequisite for hormonal effects) has been described. Third, the effect of DHEA on the vascular system may turn out to be its major influence on erectile function (*vide infra*).

The finding of a putative specific DHEA receptor on the plasma membrane of bovine aortic endothelial cells *(17)* may radically change our understanding of the role of DHEA/DHEAS in many functions, particularly regarding the vascular system of the penis. Recent studies show that the receptor is functionally coupled to the G protein family, primarily to Gα12 and Gα13 subtypes. Activation of these G proteins promotes the production of endothelial nitric oxide synthase (eNOS). Although the proposed DHEA receptor resembles the plasma membrane estrogen receptor, neither estrogens nor antiestrogens alter the binding of DHEA to the receptor or its effects on eNOS production.

This discovery led to the concept of an intracellular receptor, because all major steroid hormones in which plasma membrane receptors have been reported also have well-characterized intracellular receptors. A further recent study by Williams et al. *(18)* produced evidence supporting the existence of a DHEA-specific receptor in human vascular smooth muscle cells. Additional evidence of the vascular role of DHEA was published recently in two separate studies by Kawano et al. *(19)* and by Simoncini *(20)*, that documented an improvement in vascular endothelial function in middle-aged men with a variety of vascular problems.

Neither study, however, specifically assessed erectile function. Taken together, all these findings, when and if they are replicated and confirmed, have direct and significant implications for the mechanisms of erectile function of the penis. We may, therefore, find a dual role for DHEA in sexual activity: an indirect endocrinological role and a direct vascular one.

DHEA is also a neurosteroid, suggesting the possibility that specific effects on the nervous system are exerted by nongenomic mechanisms *(21)*. It has been shown that hypothalamic and cortical astrocytes convert DHEA into testosterone and estradiol *(22)*. The role of DHEA in the CNS, however, remains to be elucidated. That DHEA and DHEAS are fertile fields for research in human sexuality is self-evident.

If sex steroids play such a crucial role in overall sexual function, what is the clinical relevance, and what should the physician know about their assessment and therapeutic use?

THE ROLE OF HORMONAL SCREENING IN MEN WITH ED

The role of hormonal screening in men with ED has been a controversial topic in the literature. Some have argued that the prevalence of hormonal abnormalities is so low that it does not justify the expense and effort of studying them. We, and others, have argued for years to the contrary.

There are several reasons that rationalize the need for hormonal evaluation in men with ED, as follows:

1. The manifestations of hypogonadism may not be clinically evident and can easily escape a proper history and physical examination.
2. It is not possible to know what levels of serum testosterone are needed for optimal sexual functioning on an individual basis.
3. Failure to respond to initial treatment (e.g., sildenafil) may discourage the patient from following additional investigations or treatment in the presence of a significant hormonal abnormality.
4. Among the basic investigations for ED, a testosterone level determination is one of the most readily obtained, least expensive, and most reliable.
5. The etiological diagnosis of ED and the therapeutic plan for a man with the condition is based not on a single test but is generally the product of a comprehensive assessment of numerous causes, among which hormonal factors play an important role.

Perhaps the most compelling reason is the increasingly recognized importance of an adequate hormonal milieu in the response to medical treatment with PDE inhibitors. The early evidence cited previously strongly advocates for, at the very least, a testosterone level determination as part of the initial evaluation, regardless of the amount of sexual interest reported by the patient. The increasing importance of the endocrinological aspects of sexual function is reflected in the recommendations of the World Health Organization Consultation on Sexual Function, which took place in the summer of 2003. The specific recommendation indicated that assessment of the hormonal environment is indicated initially in all men with ED. A decision tree, shown in Fig. 1, is taken from the report of this meeting.

EFFICACY OF VARIOUS ANDROGENS IN THE TREATMENT OF SEXUAL DYSFUNCTION

Testosterone

In clinical practice, it is common and appropriate to judge the efficacy, adequacy, and need for testosterone treatment not only according to the biochemical changes in the serum but also according to the improvements in general well-being, mood, sexual interest, and sexual performance. When testosterone is used to treat sexual dysfunction, the effects are evident in a relatively short period. A different story occurs when testosterone is the primary agent for treatment of osteoporosis or sarcopenia, for which a longer period of observation is needed. If after a short trial of exogenous testosterone (usually around 12 wk) there is no evident improvement in sexual function, it becomes mandatory to seek out comorbidities that are not uncommonly associated with hypogonadism.

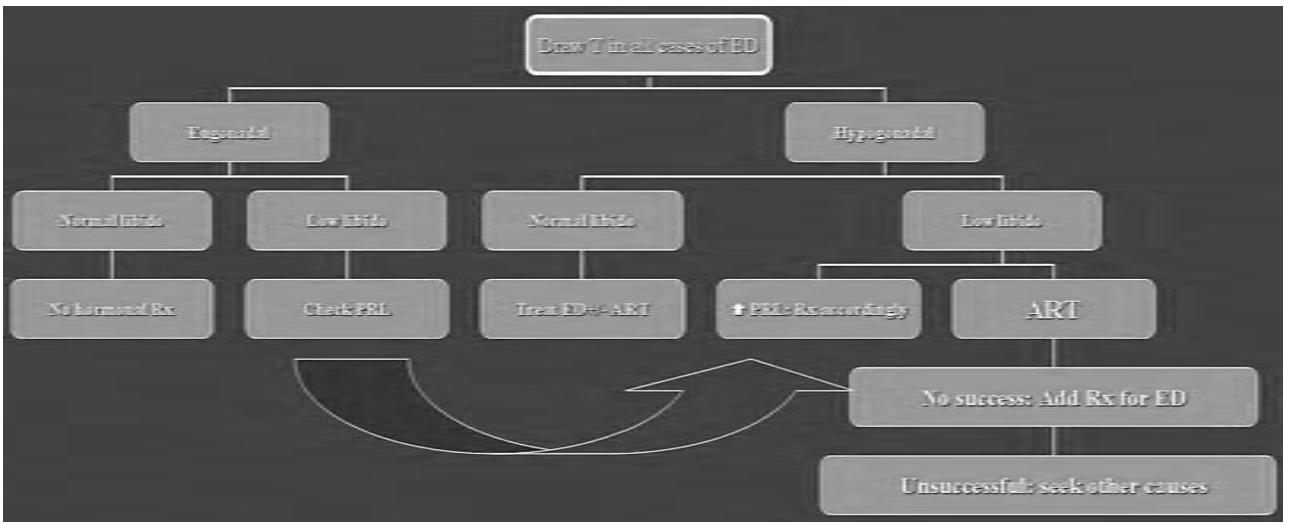

Fig. 1. Algorithm for the treatment of hypogonadal men with erectile dysfunction . ART, androgen replacement therapy; PRL, prolactin; T, testosterone.

The efficacy of testosterone administration in men with sexual dysfunction needs to be discussed in two different areas: sexual desire and erectile function.

Sexual Desire

Hypogonadal men frequently experience hypoactive sexual desire. The threshold of serum androgen levels for adequate libido exhibits large interindividual variability and is largely dependent on a number of intrapsychical and environmental factors. It is evident that associated causes of the alterations in desire require consideration and may be an indication for simultaneous treatment. As monotherapy, testosterone administration is successful in a majority of patients *(23)* but is far from a universal solution. Part of the problem resides in the difficulty in assessing outcomes of sexual interest and the lack of large controlled studies in this area. It is, however, widely recognized that hypoactive sexual desire and low serum testosterone levels are a clear indication for therapy. As mentioned earlier, the response is frequently satisfactory *(24)* but heavily influenced by situational and environmental aspects, which should not be ignored.

ED

When testosterone is used as monotherapy, only a minority of patients with ED respond to treatment *(23)*. This is explained by the myriad of comorbidities that are detrimental to the erectile process in the age group (>50 yr) presenting with the combination of ED and hypotestosteronemia. As mentioned previously, an adequate amount of testosterone is essential for the cascading of mechanisms driving the penile erectile response: the production of NOS, the release of NO, and the augmentation of the synthesis of cyclic guanine monophosphate, leading to arteriolar dilatation and relaxation of the corporeal smooth muscle. When a critical low androgen milieu is reached, this complex process is blunted or fails altogether. The critical androgen level for the adequate maintenance of the process remains to be determined, but, undoubtedly, it exhibits large interindividual (and possible some intraindividual) inconsistency. For this reason, in the presence of a combination of erectile insufficiency and hypotestosteronemia, a trial of supplemental androgen is justified. A relatively low response is expected from this approach. If no success is evident, other causes need to be explored. If additional causes are documented or the decision is made to treat empirically (e.g., administering sildenafil), the maintenance of androgen administration is generally necessary.

Synergism of Testosterone With PDE5 Inhibitors

Relevant evidence is emerging from various quarters supporting isolated observations from most clinicians treating men with ED: that a

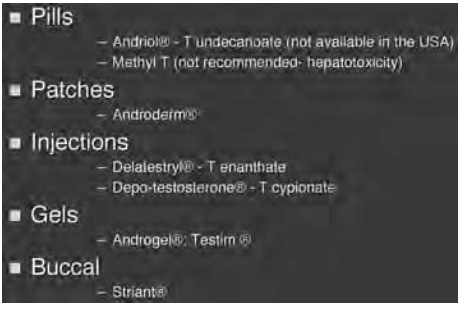

Fig. 2. Testosterone preparations available in North America.

multiprong pharmacological approach is more effective, in some cases (i.e., the most severe ones), than single-agent management. Specifically, in cases of ED and hypogonadism, the available evidence is encouraging and, obviously, deserving further assessment. Aversa et al. *(25)* showed in a small controlled, randomized study that hypogonadal patients in whom sildenafil failed could be rescued by the administration of testosterone (Fig. 2).

The proposed mechanism of action in the study was vascular, owing to increased arterial dilatation, as documented by Doppler ultrasonography. These findings have been supported by the preliminary report of Shabsigh et al. *(26)*. Further corroborative evidence is available from a study by Kalichenko et al. *(27)*, who treated a group of patients with type II diabetes with sildenafil. Those responding to treatment were eugonadal. In the group of hypogonadal patients in whom a trial of sildenafil alone failed initially, 70% responded to the combination of sildenafil and oral testosterone undecanoate, as judged by improvement in several domains of the International Index of Erectile Function (IIEF). A small observational study *(28)* added further support to these investigations. It is evident that further exploration of a number of well-established class agents, such as the PDE5 inhibitors sildenafil, vardenafil, and taladafil, as well as dopaminergic agonists in combination with androgens needs to be pursued vigorously. Various groups are working in this area; more discriminating results are anticipated for the near future.

DHEA

A great deal of enthusiasm was generated following a randomized, placebo-controlled crossover trial of a small group of men and women with low levels of DHEA to whom either 50 mg of DHEA or a placebo was

administered nightly for a period of 3 mo *(29)*. In the subjects receiving DHEA, the serum levels of this hormone, as well as testosterone, reached levels in the young adult range. Clinically, there was an increase in the sense of well-being reported by most (>60%) subjects after 12 wk of DHEA administration, whereas less than 10% reported any change after placebo. No changes were evident in the domain of sexual interest, however. Another placebo-controlled study of 39 men receiving 100 mg of DHEA daily for 3 mo resulted in no effect on well-being and sexual function *(30)*. Artl et al. *(31)*, in a controlled trial, did not find significant differences in well-being or sexual function between those receiving 50 mg of DHEA for 4 mo and those on placebo. It should be noted, however, that none of these patients had sexual dysfunction, a somewhat unusual situation considering that they were all older than 50 yr of age. The largest controlled study available is the one conducted by Beaulieu et al. *(32)* (140 men and 140 women), in which they did not detect a difference in sexual function between men receiving DHEA and those receiving placebo. This contrasted somewhat with the effect of the hormone in the female counterparts.

In focusing specifically on ED (as opposed to sexual dysfunction in general), the effect of DHEA remains obscure. DHEAS was the only one of 17 hormones that strongly and inversely correlated with the prevalence of ED in the Massachusetts Male Aging Study (MMAS) *(5)*. These findings were partly confirmed in a study by Reiter et al. *(33)*, who found DHEAS levels to be significantly lower in otherwise healthy men with ED with respect to age-matched normal controls, but only in those younger than the age of 50. The same authors evaluated the effects of DHEA replacement (50 mg daily) in 40 men with ED in a double-blind placebo-controlled study *(34)*. DHEA treatment was associated with higher mean scores for all five domains of the IIEF, but it is unclear whether the difference reached statistical significance. Regardless, it is obvious that these results need to be confirmed. Currently, there is no convincing evidence of the involvement of DHEA in ED, although the recent data (cited earlier) supporting the probability of DHEA-specific receptors on vascular endothelial and smooth muscle cells allow speculation of a possible involvement of DHEA in the vascular mechanisms of erection alone or in combination with endocrine (hormonal) effects.

It is important to emphasize here that exogenous DHEA is readily and extensively metabolized into other sex steroids. This process seriously interferes with the accuracy of determining the efficacy of DHEA *per se* as opposed to the effect of its converted metabolites. Clinically, this is not a major concern, but it contributes to the confusion that exists regarding the true value of DHEA in sexual function. In addition, its biological effects may

be exerted locally in tissues by DHEA or its metabolites, under the mechanisms appropriately designated as *intracrinology* by Labrie et al. *(35)*.

DHT

The available studies in hypogonadal men show that DHT maintains sex characteristics, increases muscle mass, and improves sexual function without significant increases in prostate size *(36)*. In fact, in elderly men, DHT administration resulted in a 15% decrease in prostate size *(37)*. This effect was ascribed to the lack of aromatization of DHT to estradiol, therewith reducing the hypothesized synergism between androgens and estrogens on the prostate. In a more recent study, in which percutaneous DHT was administered to aging men for 3 mo *(38)*, no effect on circulating estradiol levels was noted. Prostate disease markers, such as serum prostate-specific antigen (PSA), the prostate symptom score, and prostate volume, assessed with sonography, showed no changes after DHT replacement. In another recent trial *(39)*, DHT was also administered by the transdermal route for 6 mo to a group of aging men. In this study, a reduction of plasma estradiol level was noted, but again effects on the prostate were not observed. Neither were detrimental effects on lipid profiles noted. Erectile function was improved in the active compound group, as detected by the IIEF. On the basis of these findings, DHT cannot be dismissed as a potentially useful androgen for the aging male; however, a number of the same issues raised previously in regard to testosterone have to be addressed in future studies. For instance, DHT could be used as a single agent instead of testosterone on hypogonadal men with ED or in combination with other drugs, as discussed earlier.

DHT gel is available in a dosage of 125 to 250 mg/d, which yields plasma DHT levels comparable with physiological testosterone levels. More recently, it has been shown that in healthy elderly males, a lower dose of 32 to 64 mg/d yields comparable levels.

Prolactin

Although not a steroid hormone, prolactin needs to be mentioned among the hormones to be considered in the assessment of men with sexual dysfunction. There are two reasons for this: Prolactin itself is a relatively frequent cause of hypoactive sexual desire, and its overproduction is commonly associated with hypogonadism, which may or may not resolve after adequate treatment of the hyperprolactinemic state. If low levels of testosterone and clinical manifestations of hypogonadism persist after successful treatment of prolactinoma, testosterone supplementation is indicated.

TREATMENT OF ENDOCRINE ABNORMALITIES EXCLUDING DIABETES MELLITUS

The algorithm shown in Fig. 1 provides a guide to when testosterone replacement is indicated. Under ideal circumstances, testosterone replacement therapy would employ the same molecule as the natural hormone, with a dose schedule that mimics physiological hormone levels over a 24-h period. Currently, it is not known whether the molecule or the circadian rhythmicity produced by some of the commercially available exogenous testosterone preparations carries clinical significance.

The production of testosterone by the testicles is pulsatile and follows a circadian rhythm. (It may also exhibit a seasonal rhythm.) Although the availability of new forms of testosterone delivery represent an important improvement in the pharmacokinetics and pharmacodynamics of therapeutic androgen substitution, none of these can replicate the patterns of androgen production by the testis. This situation may have a bearing on some of the adverse effects of testosterone supplementation. Such side effects may be a result of the appearance of unphysiologically high or low levels of testosterone, overreduction into 5α-DHT, or the aromatization of testosterone into estrogen. Of course, a combination of these factors or their relative ratios may also play a role.

The route of administration also matters; transdermal administration of testosterone is associated with high DHT levels. This is also the case with the oral testosterone undecanoate. This oral androgen circumvents a first pass through the liver through its absorption from the gut, along with fats, via the thoracic duct. Probably a fair amount of testosterone still arrives via the portal vein in the liver and causes a significant decline in the production of sex hormone-binding globulin *(40)*. Although it is documented much more clearly for estrogens, it seems likely that androgens also exert different metabolic effects depending on their route of administration.

COMMERCIAL PREPARATIONS

With the notable exception of the 17-α-alkylated preparation, currently available preparations generally are (with some peculiar variations) safe and effective. The choice depends primarily on perceived safety, efficacy, cost, convenience, and patient's and physician's choice (*see* Fig. 2). Each preparation offers advantages and drawbacks.

Injectables have the longest history of use and are the least expensive. They are, however, inconvenient, frequently produce a "roller-coaster" effect, and are more prone to induce polycythemia.

The oral testosterone undecanoate is safe and effective, although it may require doses greater than manufacturers' recommendations. It needs to be

taken with food (to avoid first passage through the liver) and is not available in the United States. Other oral preparations (the alkylated ones) exhibit a potential for liver toxicity and have been banned from many countries, although they are still available in the United States.

Testosterone patches are also safe and effective. They must be applied in the evening but have a tendency to produce skin irritation in a significant number of patients. In addition, they are visible, a drawback that some men find unacceptable.

There are several testosterone gels available. They circumvent the problem of skin irritation, but precautions need to be taken to avoid passage to a second party through skin contact.

Buccal preparations are the newest in the North American market. Satisfactory levels of serum testosterone are achieved. Our experience with this delivery form is still very limited.

It needs to be emphasized that exogenous administration of androgens directly affects the feedback mechanisms of the hypothalamus–pituitary–gonadal axis. Chronic testosterone supplementation will eventually translate in a shutting off of endogenous androgen by the gonads. Therefore, even in cases of partial androgen production—as seen with the aging process—full therapeutic substitution is usually required.

RECOMMENDATIONS

The Second Consultation on Sexual Dysfunction produced a series of recommendations for the use of androgen replacement in men with ED. It appears eminently practical to include them in this chapter.

Definition

Adult-onset hypogonadism is a clinical and biochemical syndrome frequently associated with advancing age and characterized by a deficiency in serum androgen levels, with or without changes in receptor sensitivity to androgens. It may affect the function of multiple organ systems and result in significant detriment in the quality of life, including major alterations in sexual function.

Clinical Diagnosis

The clinical manifestations of adult hypogonadism are not specific. Sexual dysfunction (decrease in sexual interest and quality of erections) is prominent and often the presenting symptom. Depression, irritability, and diminished cognition and sleep, as well as diminished strength and endurance, may also be present. The physical examination is frequently unhelpful. Alterations in testicular size and consistency, hair distribution, muscle mass and body shape, and sequelae of osteoporosis can be detected. Not all

the manifestations need to be evident simultaneously, and their intensity shows marked interindividual variability.

Biochemical Diagnosis

In patients with sexual dysfunction, the following biochemical investigations are recommended: First, a blood sample for testosterone level determination between 8:00 and 11:00 am. The most accessible and reliable assays to establish the presence of hypogonadism are the measurement of bioavailable testosterone or the calculated free testosterone . Assays for total testosterone, particularly in the elderly, may not reflect the true androgenic status. If testosterone levels are below or at the lower limit of the accepted normal values, it is prudent to confirm the results with a second determination, together with assessment of LH, FSH, and prolactin.

Prolactin

Hyperprolactinemia is an uncommon cause of ED.However, determination of serum prolactin level is recommended in cases associated with diminished sexual interest and when biochemical hypogonadism has been documented.

Other Hormonal Alterations Beside Sex Hormones

It is recognized that significant alterations in other endocrine systems occur in association with aging, but the significance of these changes is not well understood, particularly in relation to sexual function. In general terms, determinations of estradiol, DHEA, DHEAS, melatonin, GH, and insulin-like growth factor I are not indicated in the uncomplicated evaluation of hypogonadism. Under special circumstances or for well-defined clinical research, however, assessment of these and other hormones may be warranted.

Diabetes

Diabetes mellitus is a frequent endocrinological cause of ED. It should be ruled out in men complaining of sexual inadequacy. Appropriate glycemic control is fundamental before consideration of any other hormonal treatment in men with ED.

Lipids

A lipid profile should be considered a relevant option in the initial assessment of men with ED.

Indications for Therapy

A clear indication (a clinical picture together with biochemical evidence of hypogonadism) should exist before initiation of androgen therapy.

Age

In the absence of defined contraindications, age is not a limiting factor to the initiation ofART in aged men with hypoandrogenism.

Sexual Function

Hypogonadal men with specific sexual dysfunctions (e.g., ED or diminished interest, or both) are candidates for androgen therapy. Absence of an adequate response after appropriate testosterone treatment calls for further investigation to rule out associated comorbidities.

Combined Treatment for ED

Evidence is emerging suggesting a therapeutic synergism with the combined use of testosterone and PDE5 inhibitors in hypogonadal or borderline eugonadal men. These observations are very preliminary and require additional study. The combination treatment can be considered in patients in whom adequate treatment with PDE inhibitors alone fails. No credible evidence for or against the use of other drugs in combination with androgens exists.

Testosterone Commercial Formulations

Currently commercially available preparations of testosterone (with the exception of the alkylated ones) are safe and effective. The treating physician should have sufficient knowledge and adequate understanding of the advantages and drawbacks of each preparation. The patient should be given the opportunity to actively participate in the choice of androgen formulation.

Serum Levels

The purpose of ART is to bring serum testosterone levels within the physiological range and maintain them there. Supraphysiological levels are to be avoided. Although it may appear to be desirable, no evidence exists for or against the need to maintain a circadian rhythm in serum testosterone levels.

Other Androgens

The use of DHEA and DHT has not been proven to be effective, specifically in male sexual dysfunction. Current evidence on DHT efficacy is also insufficient. There is a need for additional studies aimed expressly at investigating the effects of these hormones on sexual function.

Androgen Abuse

Androgens should be used only when specific indications exist. Their (ab)use for performance enhancement, in the absence of hypogonadism, is to be condemned in the strongest terms.

Monitoring the Liver

Currently available testosterone preparations are largely free of hepatic toxicity. (Methylated forms are an exception.) Liver function studies are advisable before the onset of therapy. Periodic assessment during treatment may be considered. Despite the lack of evidence, commercial manufacturers (for regulatory purposes) include warnings about hepatic risks in their product inserts.

Monitoring Lipids

A fasting lipid profile is recommended before initiation of treatment, if not done as part of the initial evaluation. Reassessment 3 or 6 mo after onset of testosterone administration is also recommended.

Monitoring the Prostate

In men older than 40 yr of age, digital rectal examination and determination of serum PSA level are mandatory as baseline measurements of prostate health before therapy with androgens, every 3 to 6 mo for the first 12 mo, and yearly thereafter. Transrectal ultrasound-guided biopsies of the prostate are indicated only if the digital rectal examination or the PSA levels are abnormal.

Prostate and Breast Safety I

Androgen administration is absolutely contraindicated in men suspected of harboring carcinoma of the prostate or breast.

Prostate Safety II

Men successfully treated for prostate cancer and suffering from symptomatic hypogonadism may become candidates for androgen therapy after a prudent interval if there is no evidence of residual cancer. The risk and benefits must be clearly understood by the patient, and the follow-up must be particularly careful. No reliable evidence exists in favor of or against this recommendation. The clinician must exercise good clinical judgment, together with demonstrating adequate knowledge of the advantages and drawbacks of androgen therapy, in this situation.

Prostate Safety III

Androgen supplementation is contraindicated in men with severe bladder outlet obstruction owing to an enlarged, clinically benign prostate. Moderate obstruction represents a partial contraindication to ART. After successful treatment of the obstruction, the contraindication can be lifted.

Monitoring Mood

ART normally results in improvements in mood and well-being. The development of negative behavioral patterns (aggressiveness, hypersexuality) during treatment calls for dose modifications or discontinuation of therapy.

Monitoring Hematology

Polycythemia may develop during ART. Periodic hematological assessment is indicated. Dose adjustments, change of preparation, periodic phlebotomy, or discontinuation of treatment may be necessary.

Monitoring Sleep Apnea

Exacerbation of sleep apnea may occur during testosterone supplementation therapy. Proper assessment and treatment of the sleep apnea are indicated during testosterone supplementation. Careful consideration should be given to the need for testosterone treatment if the sleep disturbances deteriorate.

Physician's Responsibilities

ART normally continues for life. This demands a lifetime commitment for follow-up. The treating physician must be familiar with the diagnostic, therapeutic, and monitoring aspects of androgen therapy. Good clinical judgment is equally important. Inadequate therapeutic response or the appearance of significant adverse effects call for reassessment of treatment indications.

REFERENCES

1. Kaufman JM. (1999) Hypothalamic-pituitary-gonadal function in aging men. Aging Male 2:157–165.
2. Werner AA. (1946) The male climacteric: report of two hundred and seventy three cases. JAMA 132:188–183.
3. Morley J, Perry HM 3rd. (2003) Andropause: an old concept in new clothing. Clin Geriatr Med. 19:507–528.
4. Morales A, Lunenfeld B. (2002) Investigation, treatment and monitoring of late onset hypogonadism in males. Aging Male 5:74–86.
5. Feldman HA, Goldstein I, Hatzichristou, et al. (1994) Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. J Urol 151:54–61.
6. Braun M, Wassmer G, Klotz T, et al. (2000) Epidemiology of erectile dysfunction: results of the Cologne Male Survey. Int J Impot Res 12:305–311.
7. Marson L, McKeena KE. (1996) CNS cell groups involved in the control of the ischiocavernosus and bulbospongiosus muscles: a transneuronal tracing study using pseudorabies virus. J Comp Neurol 374:161–169.

8. Ferrini M, Wang C, Swerdloff RS, et al. (2001) Aging-related increased expression of inducible nitric oxide synthase and cytotoxic markers in rat hypothalamic regions associated with male reproductive function. Neuroendocrinology 74: 1–12.
9. Chen H, Zirkin BR. (1999) Long term suppression of Leydig cell steroidogenesis prevents Leydig cell aging. Proc Natl Acad Sci USA 96:14,877–14,885.
10. Wang C, Hikim AS, Ferrini M, et al. (2002) Male reproductive aging: using the Brown Norway rat as a model for man. In: Endocrine Facets of Aging. Novartis Foundation Symposium 242. London, UK: Wiley, pp. 82–97.
11. Veldhuis JD. (1997) Male hypothalamic-pituitary-gonadal axis. In: Lipshultz LA, Howards SS, eds., Infertility in the Male, 3rd Ed. St. Louis, MO: Mosby-Year Book, pp. 23–58.
12. Carani C, Bancroft J, Granata A, et al. (1992) Testosterone and erectile function, nocturnal penile tumescence and rigidity and response to erotic stimuli in hypogonadal and eugonadal men. Neuropsychoendocrinology 17:647–654.
13. Traish AM, Park K, Dhir V, et al. (1999) Effects of castration and androgen replacement on erectile function in a rabbit model. Endocrinology 140:1861–1866.
14. Traish AM, Munarriz R, O'Conell L, et al. (2003) Effects of medical or surgical castration on erectile function in an animal model. J Androl 24:381–386.
15. Wu XH, Hu LQ. (2002) Effect of androgen on penile erection induced by L-arginine in the paraventricular nucleus Natl J Andrology 8:270–274.
16. Hinson JP, Raven PW. (1999) DHEA deficiency syndrome: a new term for old age? J Endocrinol 163:1–4.
17. Liu D, Dillon JS. (2002) Dehydroepiandrosterone activates endothelial cell nitric-oxide synthase by a specific plasma membrane receptor couplet to Gα(i2,3). J Biol Chem 277:21,379–21,387.
18. Williams MRI, Ling S, Dawood T, et al. (2002) Dehydroepiandrosterone inhibits human vascular smooth muscle cell proliferation independent of ARs and ERs. J Clin Endocrinol Metab 87:176–181.
19. Kawano H, Yasue H, Kitagawa A, et al. (2003) Dehydroepiandrosterone supplementation improves endothelial function and insulin sensitive in men. J Clin Endocrinol Metab 88:3180–3187.
20. Simoncini T, Manella P, Fornari L, et al. (2003) Dehydroepiandrosterone modulates endothelial nitric oxide synthesis via direct genomic and nongenomic mechanisms. Endocrinology 144:34–41.
21. Baulieu EE. (2001) Neurostéroides, leur rôle dans le fonctionnement du cerveau: neurotrophicité, mémoire, vieillissement. Bull Acad Natle Méd 185:349–356.
22. Zwain IH, Yen SSC. (1999) Dehydroepiandrosterone (DHEA): biosynthesis and metabolism in the brain. Endocrinology 81:233–242.
23. Morales A, Johnson B, Heaton JPW, Lundie M. (1997) Testosterone supplementation in hypogonadal impotence: assessment of biochemical measurements and therapeutic outcomes. J Urol 157:849–854.
24. Morley JE. (2003) Testosterone and behavior. Clin Geriatr Med 19:605.
25. Aversa A, Isidori AM, Spera G, et al. (2003) Androgens improve vasodilation and response to sildenafil in patients with erectile dysfunction. Clin Endocrinol (Oxf) 58:632–636.
26. Shabsigh R, Kaufman JL, Steidle C. (2003) Testosterone replacement therapy with testosterone gel 1% converts sildenafil non-responders to responders in men with hypogonadism and erectile dysfunction who failed prior sildenafil therapy. J Urol 169:247 (abstract 954).

27. Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. (2003) Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male 6:94–99.
28. Rosenthal B, Ginsberg PC, Metro M, Hacaway RC. (2003) The addition of testosterone to treat erectile dysfunction after failure of sildenafil alone in men with acquired androgen deficiency syndrome . J Urol 169:377 (abstract 1408).
29. Morales AJ, Haubrich RH, Hwang JY, et al. (1998) The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. Clin Endocrinol 49:421–426.
30. Flynn MA, Weaver-Osterholtz D, Sharpe-Timms KL, et al. (1999) Dehydroepiandrosterone replacement on aging humans. J Clin Endocrinol Metab 84: 1527–1532.
31. Artl W, Callies F, Koehler I. (2001) Dehydroepiandrosterone supplementation in healthy men with an age-related decline of dehydroepiandrosterone secretion. J Clin Endocrinol Metab 86:4686–4693.
32. Baulieu EE, Thomas G, Legrain S, et al. (2000) DHEA, DHEA sulfate and aging: contribution of the DHEA age study to a sociobiomedical issue. Proc Nat Acad Sci USA 97:4279–4288.
33. Reiter WJ, Pycha A, Schatzl G, et al. (2000) Serum dehydroepiandrosterone sulfate concentrations in men with erectile dysfunction. Urology 55:755–759.
34. Reiter WJ, Pycha A, Schatzl G, et al. (1999) Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study. Urology 53:590–594.
35. Labrie F, Diamond P, Cusan L, Candes B. (1997) Effect of 12 month dehydroepiandrosterone replacement therapy on bone, vagina, and endometrium in postmenopausal women. J Clin Endocrinol Metab 82:3498–3506.
36. Schaison G, Couzinet B. (1998) Percutaneous dihydrotestosterone (DHT) treatment. In: Nieschlag E, Behre HM, eds., Testosterone: Action, Deficiency, Substitution. Berlin, Germany: Springer Verlag, pp. 423–436.
37. de Lignieres B. (1993) Transdermal dihydrotestosterone treatment of "andropause." Ann Med 25:235–241.
38. Ly LP, Jimenez M, Zhuang TN, et al. (2001) A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. J Clin Endocrinol Metab 86:4078–4085.
39. Kunelius P, Lukkarinen O, Hannuksela ML, et al. (2002) The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab 87(4):1467–1472.
40. Conway AJ, Boylan LM, Howe C, et al. (1998) Randomized clinical trial of testosterone replacement therapy in hypogonadal men. Int J Androl 11:247–253.

14 Central Activation of Erection and Clinical Experience

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CONTENTS

INTRODUCTION

Success in developing an understanding of the vascular and neural biology of the penis and its pathology has shaped modern sexual medicine. The most recent and pervasive contribution to this progression has been the rise of the phosphodiesterase (PDE) inhibitors as a highly successful therapeutic strategy. The extrapenile tissues of the neurovascular-genital axis (NVGA), also known as the cerebroneurogenital axis, have received notably less attention, and correspondingly there has been less success in designing a drug to target them. Extrapenile problems encompass a large group of sexually relevant disorders, including the entire spectrum of female sexual difficulties, desire disorders, ejaculatory disorders, and interpersonal and relationship issues. Understanding the central control of erection and sexual activity is also an extrapenile consideration.

The importance of the central nervous system (CNS) within the NVGA is unquestioned, but its complexity has been a hindrance to harnessing it

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successfully for therapeutic ends. Furthermore, the power to change the penis by remote actuation (e.g., using neural connections) is limited in comparison with the power of direct vascular intervention. In fact, it is probable that the efficacy of interventions to improve erections diminishes with each generation of development: Prostheses are more effective than intracavernous injection, which is more effective than oral PDE inhibitors, which in turn are more effective than CNS agents. It may also be true that the impact ranking would be reversed if the focus of development of new treatments were broadened to include the whole spectrum of conditions needing management in sexual medicine; that is, the CNS must be the target for many other aspects that may strongly influence the quality of sexual health, such as desire, orgasm, and reward, whereas penocentric treatment would have little benefit on those endpoints.

As a consequence of the inability of the human brain to understand its details and complexities, much of what we know about the central control of erection comes from animal experiments. Technical experimental tools, such as microdialysis, stereotactic brain lesioning, iontophoretic drug infusion, and focal electrical stimulation, as well as tracing of neural tracks, have provided a wealth of information. In addition, experimentally there has been freedom to use new chemical entities in fully instrumented animals or in complex mating paradigms, which provides a glimpse of the importance of functional pathways, thereby providing therapeutic possibilities for CNS manipulation. Despite best efforts, however, the complexity of man's sexuality compared with the experimental paradigms has made clinical trial observation and patient-based reporting the only true yardsticks of effect. Even the dynamic imaging techniques of positron emission tomography (PET) and functional magnetic resonance imaging have only served to illustrate generalities. Animal-derived understanding has been put to the test as the predominantly D_2 receptor agonist apomorphine and melanocortin receptor agonists have been tried. The data in men and women show that there is real but underdeveloped potential for pharmacological intervention involving the CNS with respect to managing sexual health.

CONCEPTUAL ORGANIZATION OF CENTRAL CONTROL OF ERECTION

Male sexual activity is normally focused on the genitals, but it must be recognized that it is also rich in imagery (i.e., characterized by desire, cognitive and sensory arousal, erection, climax [seminal emission and ejaculation and orgasm], and detumescence). These aspects of the overall sexual response are under the control of a complex interplay of the central and peripheral neural systems. In the male, the end-point experience of a satisfactory erectile response must involve these systems appropriately as

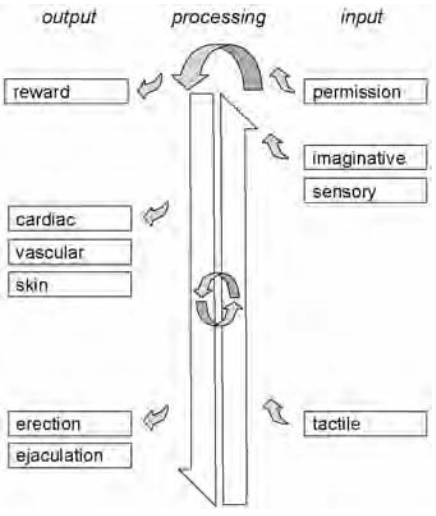

Fig. 1. A schematic representation of the neurovascular–genital axis, conceptualizing the interaction of central and peripheral neural elements vital to a sexual erection and the overall sexual response.

local and central participants in a cycle of input/processing/output functions within the NVGA. The development of a normal erection is dependent on various sensory inputs, brain processing, and neurally controlled, mainly vascular outputs. In general, the initial erection is mainly derived from visual and sensual stimuli. The enjoyment of the accompanying sexual activity draws on a broader range of inputs, but the final experience and the reward in humans are wholly achieved through the CNS (Fig. 1).

ROLE OF THE CNS

As discussed, the understanding of CNS control of sexual function is less complete than the understanding of the processes regulating local penile vascular, physiological, biochemical, and genomic responses. There are established parallels between peripheral vascular problems and erectile dysfunction (ED) and their common origin in endothelial disease. The importance of this association has become increasingly evident, such that it is now being used to guide overall management of patients presenting with either vascular condition. What is somewhat surprising is that it has taken more than 10 yr for these parallels to reach the mainstream of thinking. Similarly, although it has long been known that diseases of the neural system (e.g., depression and Parkinson's disease) negatively affect erectile function, little consideration is presently given to the deteriora-

tion of erectile function associated with subclinical or unrecognized CNS disease.

An important step in determining the basis of the disorder is recognizing that when vascular problems cannot fully explain the lack of response to conventional therapy, it is probable that the additional disease burden is based in CNS or neural dysfunction. The understanding of extrapenile NVGA contributions to erection and other essential elements of human sexuality are many years behind the understanding of erections. As the scientific, diagnostic, and therapeutic tools become available, the understanding of the essential elements of CNS involvement in sexual function will improve.

Overall Organization

There are many primary sources of information from which to piece together the central contributions of the NVGA. Most of the knowledge is derived from animal modeling, which increases the details of the analysis and the interpretation, but lacks direct applicability to the human situation. The complexity of the human sexual response places some severe limitations on the relevance of animal studies. A few excellent detailed reviews of the neural substrates of female *(1)* and male *(2)* sexual function are available.

Various models can be constructed to explain the relationship between the CNS and sex, although the more discrete the required resolution, the greater the required complexity and uncertainty. The neural control of sexual function, including penile erection and female genital arousal, may on a practical basis be divided into three main areas: local neural pathways, midbrain and spinal cord pathways, and higher brain centers. Local neural pathways incorporate genital and pelvic nerves and plexi. These function as cables—hard-wiring that connects the genital structures with central organization and control. Within these pathways, there is relatively limited self-regulation of the signal (for instance, by feedback loops). At many points, there is ample opportunity to modulate the signaling in local neural pathways through pharmacological, hormonal, or traumatic or surgical means. In the midbrain and spinal cord, there are many complex pathways with extensive interconnections and many possibilities for signal modulation or conditioning. Although reflexive erections can take place with the involvement of only processes within and below the spinal cord, coordination of genital, hemodynamic, erectile, and ejaculatory responses depends on the midbrain and spinal cord. Higher brain centers are critical in generating signals essential to the human sexual response that indicate or provoke reward, awareness, visualization, sensory responses, and motor function, as well as imagination and memory.

Higher Brain Centers

The four major categories of sexual stimulation are tactile sensation, visual input, imagination, and olfactory input *(3)*. Imagination, particularly in healthy middle-aged and older married individuals, has been shown to be an important determinant of sexual activity, although the partner's desire must always be considered a factor *(4)*. In men with ED of no evident organic cause, enhancing imaginative stimuli has been shown to be more efficacious than placebo medication in improving erectile response *(5)*. Studies in rats involving lesioning of particular brain regions or injection of drugs directly into the brain have shown that the amygdala has an important role in determining the putative imaginative components of recognition of sexual partner, acquisition, and the corresponding sexual arousal *(6)*. Simple peptide neurotransmitters, such as vasopressin and oxytocin, have been thought to be involved in these mechanisms.

Brief Overview of Neuroanatomy

The neurons of the supraspinal control systems involved in generating erectile responses in men, and most probably arousal in women, are mainly located in the limbic system (olfactory nuclei, medial preoptic area [MPOA], nucleus accumbens, amygdala, hippocampus) and in the hypothalamus (paraventricular and ventromedial nuclei).

Neural information travels via the brainstem, spinal cord, and autonomic nervous system to the genitalia (*see* Fig. 2). The prosexual function neurotransmitters involved include dopamine (DA), oxytocin, nitric oxide (NO), adrenocorticotropic hormone–melanocyte-stimulating hormone peptides, and glutamic acid, whereas serotonin, γ-aminobutyric acid (GABA), and the opioid peptides are recognized to be inhibitory.

Functional magnetic resonance imaging and derivative techniques, as well as PET, have been used used to identify areas of the brain relevant to sexual function. Although the images are useful in documenting overall changes in activity, the interpretation of the images is limited because of inadequate spatial resolution and differences in the imaging protocols themselves. Despite the progress in medical imaging, most of the understanding of what links the active or inactive regions to each other and to the periphery is still based on traditional neuroanatomical dissection.

A number of issues need to be controlled to achieve greater consensus regarding the approach to imaging studies to be taken by various investigators. In addition, in these studies, there should be an appropriate categorization of the sexual function status of the men and women studied, as well as some standardization of the sexual stimuli (usually neutral and erotic film clips), for comparing active drug to placebo. The sophistication of the studies would benefit further if there were controls of nonspecific behav-

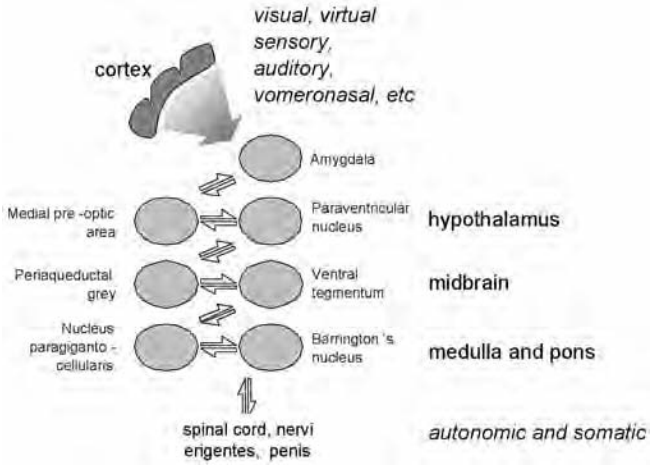

Fig. 2. A diagram of the multiple levels of central signal processing involved in the generation of erectile signals for the periphery. The interconnectivity suggested is not intended to be literal or exclusive in that multiple further connections exist and may be important.

ioral excitation and movement and brain activities that are not sexual in content.

Based on current approaches, imaging-based measurements are still indirect and for the most part correspond to increased local brain perfusion. In general, findings detail changes by anatomical brain region, although the exact degree of change and the precise neurons or nuclei involved are not commonly provided. The findings in nine recent reports are summarized in Table 1.

Of interest is that the overall pattern of activation corresponds to the current concepts linking cortical areas, cingulate gyrus, and basal nuclei and the predominant patterns of cholinergic, serotonergic, and dopaminergic neurons. More advanced techniques will illuminate the active pathways, probably in the next 5 yr.

The sensory, sexual receptivity, and reward aspects of the CNS response to sexual activity are of particular interest and importance. It is only via signals in these areas that we appreciate or are conscious of the gratification associated with sexual activity. Greater understanding of this aspect of the role of the brain in sexual health will open major new therapeutic possibilities. For example, the pleasant aspects of sexual imagery are primarily associated with activation in the dominant (or left moreso than right) brain hemisphere *(16)*.

Table 1
Alphabetical Listing of Relevant Brain Areas

Technique	*BOLD MRI*	*BOLD MRI*	*BOLD MRI*	*fMRI*	*fMRI*	*PET*	*PET*	*PET*	*PET*
Subjects	*NM*	*NM*	*NF*	*NM*	*NM and ED*	*NM*	*NM*	*ED*	*NM*
Stimulus	*VSS*	*VSS*	*VSS*	*VSS*	*VSS*	*VSS*	*VSS*	*VSS*	*Manual*
Drug (if used)						*PCBO or APO*			*PCBO or APO*
(Ref. no.)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
Amygdala, anterior temporal limbic	+				+				—
Anterior cingulate, cingulate gyrus	+	+	+	Bilateral			+	+	
Caudate nucleus, nucleus accumbens, ventral striatum	+	+	+	Left	+ APO in ED		+		
Cerebellum									+
Claustrum, insula gyrus, insular	+	+	+				+		+
Corpus callosum		+	+						
Frontal basal					—				
Globus pallidus		+	+						
Hypothalamus	men only			Right	+ APO in ED				
Inferior frontal								+	
Inferolateral prefrontal cortex						Right			
Medial prefrontal	+								
Midbrain						+			

(Continued on next page)

Table 1 *(Continued)*
Alphabetical Listing of Relevant Brain Areas

Technique	*BOLD MRI*	*BOLD MRI*	*BOLD MRI*	*fMRI*	*fMRI*	*PET*	*PET*	*PET*	*PET*
Subjects	*NM*	*NM*	*NF*	*NM*	*NM and ED*	*NM*	*NM*	*ED*	*NM*
Stimulus	*VSS*	*VSS*	*VSS*	*VSS*	*VSS*	*VSS*	*VSS*	*VSS*	*Manual*
Drug (if used)						*PCBO or APO*			*PCBO or APO*
(Ref. no.)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
Midbrain lateral central tegmental field, zona incerta, subparafascicular nucleus									+
Middle temporal gyri				+					
Motor and premotor				Right	+				
MPOA									No change
Occipital cortex		+	+	Right-middle					
Occipitotemporal	+	+	+		+				
Orbitofrontal	+	+	+				+		
Putamen				+			+		+
PVN							+		No change
Superior prefrontal								Right (APO)	
Temporal limbic cortex					—		—	—	
Thalamus	+	+			+				+
Ventral tegmental area (reward)									+

A blank in the table indicates that no record of response was made specific to this anatomical site. APO, apomorphine; ED, men with erectile dysfunction; MPOA, medial preoptic area; NF, normal female subjects; NM, normal male subjects; PCBO, placebo; PVN, paraventricular nucleus; VSS, visual sexual stimulation with neutral and sexual content manual—female partner manual simulation.

The ongoing development and improvement of new technologies that enable the mapping of human sexual response in the brain will assist in the visualization of abnormal responses, the classification of the CNS states that contribute to sexual dysfunction, and the documentation of the impact of therapies.

Midbrain and Spinal Cord

The first level of reflex organization for signals supporting sexual function is in the lumbar spinal cord. Nerve tracing studies using neurotropic viruses show that pelvic and sexual reflexes depend on the central gray region for coordination and generation of sexual responses, including erection, arousal, and orgasm *(17)*.

Spinal reflexes may be activated by sensory changes at the level of the penile or clitoral skin, with the bulbocavernosus reflex being an obvious exam-ple. Stimulation of the glans penis evokes a contraction in the bulbocavernosus muscles; the equivalent stimulus in the female manifests as contraction of elements of the pelvic floor *(18)*. Stimulation of the clitoris and vagina inhibits bladder activity, a response appropriate to sexual activity *(19)*.

These spinal reflexes can be vitally regulated by descending signals from the midbrain and higher centers and by hormonal milieu. Spinal reflexes rest in an inhibited state. The efferent side is tonically directed to nonsexual function (penile flaccidity, lack of engorgement, baseline lubrication). Local sensory input and descending spinal signals can change the balance and activate a prosexual cascade of parasympathetic activity, reduced sympathetic activity, and somatic muscular support. The stimulus-selective use of particular spinal pathways that target the peripheral nervous system in a stimulus response-specific manner has not been fully worked out. There is a suggestion that GABA plays a critical role as an inhibitory neurotransmitter *(20)*. For instance, experimentally it can be shown that reflexive erections can be modulated by learning and opportunity (here correctly labeled psychogenic) and that this modulation does not depend on the hypogastric nerves, showing that this is a CNS-driven change *(21)*.

A critical recent addition to the understanding of the importance of spinal events in sexual function comes from a study showing that a population of lumbar spinothalamic cells is essential in the generation of ejaculatory behavior *(22)*. These cells, found to express neurokinin-1, relay ejaculation-related signals from reproductive organs to the brain. Importantly, if this population of cells is destroyed, the only aspect of sexual behavior that is altered is ejaculation. Further work is needed to establish the human implications of this concept and how the central and peripheral efferent and sensory signals integrate with the experience of ejaculation.

Sensory information is conveyed cephalad through spinothalamic (fast fibers serving the penis and clitoris), spinoreticular (slower fibers), and vagal (extraspinal fibers) pathways. Electrophysiological studies have revealed that the thalamus has significant input from the male genitalia relevant to various aspects of penile sensation associated with sexual response *(23)*.

The nucleus paragigantocellularis (nPG) receives ascending sensory input *(24)* and also has neurons that innervate the penis *(25)*. The nPG appears to have a role in orgasm but is not vital to erection. The most common neurotransmitter that has been identified in the nPG is serotonin. The nPG, as with other central sites of sexual function, is not exclusively employed in regulating sexual response. In fact, the major output from the midbrain that affects sexual response is autonomic. Furthermore, it is completely appropriate that points of control that autonomically regulate circulatory and respiratory homeostasis, as well as other pelvic functions, are found in the same regions. One such common region is the periaqueductal gray; this area has a large number of connections with hypothalamic sites involved in sexual response *(26)*.

The paraventricular nucleus (PVN) has a major role in controlling genital responses. PVN neurons send direct projections via the nPG onto neurons that innervate the penis *(27)*. The PVN has direct projections to pelvic and autonomic efferents and is reciprocally connected to the MPOA. Experiments indicate that penile erections, associated with the largely dopaminergic and oxytocinergic receptor population of the PVN, are eliminated by lesioning *(28)*. PVN activation has also been shown to be critical in models of female response *(29)*.

In addition to its role in blood pressure and respiratory control, the MPOA has been shown in many studies to have a vital role in controlling sexual behavior. Not surprisingly, it is well connected through reciprocal links with the nPG and periaqueductal gray. Much of this pathway has been shown to be under sex hormone modulation *(30)*—a characteristic that should eventually be proven to be more widespread than is currently the case. It makes sense that the pathways actively involved in reproduction and possibly gender-specific function should depend on sex hormones *(31)*. Of interest is that neurons lying within the MPOA have been shown to regulate timing aspects of female rat copulatory behavior *(32)*, as well as potentially playing a role in copulatory ability *(33)*.

Local Neural Pathways

Clitoral and vaginal responses and erections occur via activation of efferent fibers that originate in the sacral parasympathetic center and pass through the pelvic nerve bundles (preganglionic neurons from the interme-

diolateral cell column through S2, S3, and S4). These neurons, together with fibers from the inferior hypogastric (sympathetic) nerves, form the pelvic plexus. This major pelvic ganglion, also called the paracervical ganglion or the uterine cervical ganglion, innervates the pelvic organs, including the clitoris, penis, vagina, urethra, and bladder. The cavernous nerves are postganglionic, mixed parasympathetic, and sympathetic types and they supply the erectile tissue. A simple demonstration of the efferent circuit in females is the increase in vaginal blood flow that follows pelvic plexus nerve stimulation *(34)*.

There is a more generalized nerve distribution to the pelvic viscera from the pelvic plexus that may account for the regulation of pelvic prepenile, prevaginal, and preclitoral resistance vessels, and possibly the crosstalk between genitals and bladder, and between prostate function and dysfunction. This wider distribution is also important because there are multiple pathways by which vasodilator fibers reach the penis in the rat; this suggests that if a similar situation exists in humans, the telephone-cable model of penile vasodilator innervation involving two cavernous nerves may be an oversimplification *(35)*. The pudendal nerve innervates the striated muscles of the pelvis, as well as sphincters, in a very similar pattern in males and females. The lumbar spinal cord provides the origin for these nerves, and the number of motoneurons is roughly proportional to the muscle bulk.

In the male, the afferent neural pathway consists of sensory receptors in penile skin connecting through the dorsal nerve of the penis to the pudendal nerve and then the sacral cord. The female afferent equivalent involves sensations detected in clitoral skin, perineum, and urethra, which are then connected via fibers tracking through the pudendal nerve. In addition, there are pelvic and hypogastric nerve sensory fibers from the internal pelvic organs (in the female, vagina and uterus; in the male, prostate). Within the spinal cord, the pudendal afferents are medial, whereas the other afferents terminate in the dorsal horn and dorsal gray commissure. Evidence from spinal cord-injured women in particular suggests that vagus nerves can convey genital sensory input directly to the brain in women *(36)*. This concept is supported by animal studies and suggests the presence of at least four distinct pathways for the communication of genital signals in women: clitoral, perineal, and inner thigh via the pudendal nerves; cervix and proximal three-fifths of the uterus via the hypogastric nerves; vagina, cervix, and perineal skin via the pelvic nerves; and cervix and deep pelvic sensations via vagal fibers.

Intuitively, both hormones and age should be expected to significantly affect the peripheral innervation of genital structures, as well as other components of the NVGA. Sex hormones have potent effects on the struc-

ture of many pelvic ganglion cells. There may be complex interactions between steroids, notably testosterone and nerve growth factors, in maintaining neuronal structure and function in vivo *(37)*. Age has been experimentally shown to induce degenerative changes in the pelvic nerves. The sympathetic and parasympathetic preganglionic neuronal populations change in aged rats differentially *(38)*. These changes should be expected to play a role in dysfunction of both genital and urinary structures (i.e., ED and lower urinary tract symptoms).

Because of the way in which the CNS circuitry detail is arranged in any given species, it is not surprising that the inhibitory side of the equation at almost any level dominates *(39)*. Conceptually, it seems almost universally accurate to portray control of sexual function within the NVGA as a balance between erectogenic and erectolytic influences. This balance is common in simpler autonomic systems and permits subtle changes in set point, equilibration at high or low levels of activation, and time-dependent variations in balance. Interestingly, this negative balance is not just seen in the brain because there is a preponderance of inhibitory influence in the spinal cord as well. It appears that humans have the greatest constitutive presence of central inhibitory control—an overriding factor that we have failed to address up to this point in the development of therapies for sexual dysfunction. Therefore, it is not surprising that in men, enhancing the central proerectile signal by enhancing imagination or by pharmacological means will reasonably be expected to enhance the erection. A stronger neural signal at the level of the peripheral vasculature causes better erection, as seen in postprostatectomy patients (in whom two *nervi erigentes* are better than one or none) *(40)*, reversible nerve-lesioning experiments, and with graded stimulation (imagination is less effective than visual stimulation studies, which is in turn less effective than vibratory stimulation) *(41)*.

Essential Neurotransmitters

In any discussion of neurotransmitters relevant to the NVGA, it is necessary to recall that general measurements, such as the concentration of a particular molecule in cerebrospinal fluid or brain tissue homogenate, reveal little about the actual activity of that molecule at synapses in select brain areas. One of the most critical elements of the NVGA in erection is a group of oxytocinergic neurons in the PVN of the hypothalamus that project to functionally important and related brain areas (spinal cord, hippocampus, and medulla oblongata) *(42)*. Activation of these neural pathways by DA and DA agonists, oxytocin, excitatory amino acids (*N*-methyl-D-aspartic acid), or electrical stimulation, results in penile erection. The activation of oxytocinergic neurons in the PVN at least in part, appears

to be dependent on the production of NO via NO synthase. Oxytocin, which is also associated with reproductive pathways, has been shown to be capable of inducing erection when introduced into the hippocampus, whereas intracavernous oxytocin is not effective *(43)*. The potential for oxytocinergic compounds that cross the blood–brain barrier and can be delivered readily has yet to be fully explored.

Many studies have detailed the role of DA in the MPOA in promoting erections. Increased levels of DA in the MPOA have been shown to increase reflexive and noncontact erections in rodents *(44)*. The MPOA and the PVN have been considered to be prime sites—as well as some spinal centers—for the action of DA agonists, such as apomorphine in facilitating erections. Apomorphine is a nonselective dopaminergic receptor agonist (binding affinity [Kd] of D_1:101; D_2:32; D_3:26; D_4:2.6; and D_5:10 n*M*) that can induce erections more effectively after subcutaneous or intracerebroventricular injection than after intrathecal administration *(45)*. For the most part, human evidence of the effects of activation of DA receptors in the erectile pathway is derived from clinical trial responses to sublingual (SL) apomorphine *(46)*. Although apomorphine-induced D_2 receptor activation is normally a recognized target, it is interesting that in one study the erectogenic effect was thought to be particularly associated with the D_4 receptor, whereas others have found a role for D_1 receptor activation *(47)*.

DA is an important neurotransmitter that has a positive impact on the perception of reward *(48)*, although the implications of this in the context of sexual pleasure or reward in humans have not been fully investigated. The data from women are limited, but there are indications that dopaminergic treatment (apomorphine) has a positive impact on general measures of sexual function in certain women.

Neurons of the MPOA have high densities of α_2-adrenergic receptors, as well as DA receptors. Some studies have suggested that the effects of DA in the MPOA, at least in part, include the activation of α_2 (inhibition) and α_1 (excitation) adrenoceptors *(49)*. α_2-Adrenoceptor antagonists, by blocking this inhibitory influence, may have a stimulatory effect on ejaculatory function, although the dose range for this has been shown to be narrow *(50)*.

The melanocortins have effects in similar anatomical regions, and the melanocortin-4 receptor (MC4R) appears to be most responsible for the stimulation of penile erection (and appetite control) *(51)*. PT-141 is a synthetic peptide analogue of α-melanocyte-stimulating hormone (MSH) and is an agonist at melanocortin receptors, including the MC3R and MC4R. The positive effect on erections is considered to be via actions in the hypothalamus, as documented by the selective increase in c-Fos immu-

noreactivity in this brain region *(52,53)*, although oxytocinergic pathways are also believed to be involved *(54)*. Administration of PT-141 to rats and nonhuman primates results in penile erections.

Certain peptide analogues of hexarelin, a growth hormone-releasing peptide, have also been found to induce penile erection. Similar to DA and MC4R agonists, these substances are thought to act in the PVN and influence oxytocinergic neurons *(55)*. This erectogenic action of some elastic peptides has been compared with that of apomorphine. Certain of these elastic peptides actually prevent penile erection, an action that has been associated with preventing the increase in NO production that occurs with proerectile stimulation *(56)*.

There is growing evidence of the importance of NO in central signaling related to erectile function. For example, experimental inhibition of NO activity in the CNS negatively affected erectile response *(57)*. Manipulation of NO or cyclic guanosine monophosphate levels specifically alter MPOA-triggered intracavernous pressure responses via a CNS mechanism. The expression of inducible NO synthase increases with age in the PVN and MPOA and in regions known to control the synthesis and release of gonadotropin-releasing hormone and oxytocin, although whether this is a compensatory or primary increase is not known. In fact, many, if not all, of the pathways necessary for normal function of the NVGA are NO-dependent.

Activation of GABA type A receptors in the PVN can reduce both pharmacologically (apomorphine) and physiologically induced erections. Thus, it appears that increased GABAergic activity in the PVN provides a mechanism to balance (inhibit) proerectile signaling *(58)*. Other candidates for inhibitory control are serotonin (5-HT) and thyrotropin-releasing hormone (TRH). Both 5-HT and TRH (intrathecal) exhibit inhibitory effects on penile erection through common or parallel sets of neurons *(59)*. Therapeutic modulation of 5-HT and TRH activity may have potential benefit for erectile function if suitable compounds and routes of delivery can be found.

Apomorphine

Apomorphine was developed to facilitate erections in humans based on the understanding of dopaminergic effects in the CNS. Apomorphine hydrochloride was formulated as a tablet for SL administration to gain the benefit of rapid but controlled absorption without gastric effect. The pharmacokinetic characteristics were manipulated to enhance the predominance of the proerectile effects and blunt other potential dopaminergic effects *(60)*. The dose and subsequent serum concentrations contemplated were so small that significant peripheral activity was not a concern.

The clinical program began in the late 1990s, and the results from the pivotal and supportive clinical trials have been published. Apomorphine was approved for clinical use in more than 50 countries, but in its SL form it is not currently available or in trials in the United States or Canada.

The role of a potential agent that has a CNS proerectile effect has changed radically since the introduction of PDE inhibitors. Periodic use of apomorphine has an effect in terms of improving penile rigidity less than that of sildenafil in most men and is active in a smaller percentage of men. In a context where the expectations of success are measured in terms of penile rigidity with administration somewhat in advance of the time of need, the subtle differences and the potential advantages of a CNS agent in select groups of men (and women?) has not been realized. There are no published, well-designed and conducted clinical trials comparing PDE inhibitors and SL apomorphine in terms of erectile effect, but, arguably, none are needed to determine that PDE inhibitors are more effective.

Temporarily lost in the rush to treat the majority are some interesting minorities, as well as the larger issue of exploring the human benefits of CNS strategies for the remediation of sexual dysfunction. There have been no good clinical trials (looking for sexually relevant end points) of suitable dopaminergics in women, in people with CNS disease (e.g., depression), in men with disturbed androgen milieu, or in men and women with disturbances of desire or orgasm or in instances when the treatment has been based on chronic or semiacute rather than situational administration.

A particular minority that has been studied but not targeted for SL apomorphine (or the same drug administered by any other route) are men taking short- and long-acting nitrates, for whom PDE inhibitor-administration is contraindicated. Apomorphine, unlike PDE inhibitors, does not have a mechanism of action that would lead to clinically relevant hemodynamic problems when given to a patient taking a nitrate *(61)*. In fact, in a subgroup analysis, these patients were shown to be responsive to SL apomorphine and not suffer any increase in the rate of side effects.

The clinical trials of SL apomorphine were designed before the advent of the International Index of Erectile Function (IIEF) at a time when regulatory experts favored the use of objective criteria, such as RigiScan measurements, for inclusion in the studies. The primary outcome variable was therefore different from the current trend, the IIEF (based on 4-wk recall) and custom scales and questions relating to general improvement in erection. Instead, patients recorded their day-by-day success in diaries, and the investigators' review of these data generated the percentage of attempts resulting in erections firm enough for intercourse. This different assessment methodology has added to the difficulty of comparing trials and

different drugs in different trials. More than 5000 treatment-naïve patients were enrolled in phase II and III clinical trials, and doses from 2 to 6 mg were assessed *(62)*.

Early analysis of clinical data identified that 3 mg was an optimal point for risk vs benefit. One pivotal study measured the efficacy and safety of a fixed 3-mg dose of SL apomorphine compared with placebo and compared it with a fixed 4-mg dose of SL apomorphine in patients with typical ED *(63)*. A total of 296 men were studied in this randomized, double-blind, crossover study. The reported outcomes were the percentage of attempts resulting in erections firm enough for intercourse, the percentage of attempts resulting in actual intercourse, the time to erection, and partner assessment. It was found that 3 mg of SL apomorphine was significantly more effective than placebo ($p < 0.001$) in the percentage of attempts resulting in erections firm enough for intercourse (apomorphine 48%, placebo 32%) and resulting in intercourse (apomorphine 49%, placebo 32%). The assessment by partners yielded similar numbers. The median time to erection was confirmed at 18.8 min. The most frequent adverse event was nausea, reported by 3.3% of patients on 3 mg vs 14.1% by those on 4 mg of SL apomorphine.

Altwein and Keuler summarized the key clinical data in the pivotal trials, and determined that the overall proportion of attempts resulting in erections firm enough for intercourse was 49.4% for 3 mg of SL apomorphine, compared with a baseline value of 24.3% *(64)*. The overall proportion of erections was significantly increased over patient baseline and over the results with placebo. The studies revealed that vasovagal syncope was seen in less than 0.2% of men, and, whenever seen, it was preceded by clear prodromal symptoms. Nausea was again the most frequently observed side effect. As is typical for dopaminergics, the impact of nausea decreased quickly with repeated use (within eight doses).

A multicenter, open-label, uncontrolled, phase III, dose-optimization study of SL apomorphine was conducted in 849 men with ED *(65)*. The enrollment included the usual preponderance of men with severe dysfunctional ED (mild in 11.5%, moderate in 23.8%, and severe in 48.1%), possibly reflecting the difficulty of recruiting treatment-naive patients when sildenafil was available for prescription. As could be expected, the overall percentage of attempts resulting in erections firm enough for intercourse decreased to 39.4%, although baseline frequency was only 13.1%.

A total of 507 patients were enrolled at 34 European sites for a forced dose-escalation study (2 to 3 to 4 mg) of SL apomorphine in men with ED *(66)*. The patients had a representative spectrum of comorbidities (24% had hypertension, 11% had coronary artery disease, 10% had diabetes, and

5.5% had benign prostatic hypertrophy), and 62.6% of treated patients were taking medications for these problems. Adverse events included nausea (9.8%), dizziness (7.1%), and headache (6.7%). (These effects had a frequency of 0.4, 2.4, and 4.0%, respectively.) The proportion of successful attempts resulting in sexual intercourse followed the expected pattern, with statistically significant enhancement over placebo with drug use.

Analysis of the available data suggested that the probability of success increased over the first six to eight doses *(67)*. The overall picture was established of a drug that clearly worked to ameliorate erectile function, was better than placebo, and had an acceptable safety profile and good tolerability. It met current criteria for clinically meaningful improvement and was usable in difficult-to-treat patients (e.g., those taking nitrates). Like the PDE inhibitors, SL apomorphine requires the simultaneous presence of a sexual stimulus for the erectile effect. The therapeutic potential of this medication has not been realized, in part because it does not give patients the same sensations, signs, and symptoms as a PDE inhibitor. There is no persuasive flushing, cardioacceleration, headache, or age-defying erection. SL apomorphine is a drug that can be used well in select men who pay attention to the global CNS sensations, who want a prompt effect, who usually have mild to moderate ED, and who have an awareness of the softer issues (relationship, partnership, and so forth) involved in reviving their sex life.

SL apomorphine may be the choice of a minority of men, some of whom cannot use PDE inhibitors and some of whom simply chose apomorphine. With ED, the patient's choice is the determining factor in the therapeutic strategy selected. The basis for choosing one therapy over another is strongly influenced in most cases by the quest for a rigid erection. However, apomorphine is currently the proof that diversity exists in oral therapeutics for sexual dysfunction, although PDE inhibitors are currently the better way to treat erectile problems.

SL apomorphine is the first approach to the oral therapy of sexual dysfunction that pharmacologically targets the CNS, but it will certainly not be the last.

Alternative routes for delivering apomorphine have received some attention. The bioavailability of conventional gastric absorption is poor, but it may be possible to achieve a suitable pharmacokinetic profile from this. Intranasal forms of apomorphine have been reported, but there are currently no data beyond phase II trials. The critical question regarding these other routes of administration is whether there is a true ceiling effect for the action of apomorphine, or whether the ceiling results from determination of a risk–benefit ratio that has not been fully optimized with use of the SL form. If lower rates of adverse events can be achieved with apomor-

phine delivered via other routes, then higher doses (and, hence, serum concentrations) can be used for potentially better therapeutic effects.

One further aspect of apomorphine use that remains unanswered is the potential for combination therapy. Treating a dysfunctional NVGA at two or more points simultaneously can potentially further enhance the final result of an improved erection. Whether one can combine apomorphine with a PDE inhibitor and thereby both activate the CNS cascade and boost the responsiveness of the penile vasculature has yet to be properly addressed. The pharmacokinetic, pharmacodynamic, and economic issues of the combination are not insignificant, but the concept has occurred to many observers. There would appear to be an obvious basis for predicting that this is a combination that will offer advantages. It is one that may well be revisited as other new, probably selective, dopaminergic agonists advance through the drug development process.

Melanocortins

Early human studies with the melanocortin Melanotan II have been published *(68)*. Melanotan II is a nonselective MCR agonist that was selected for human trial based on its effects in dogs. In early phase II studies, men with ED were documented to experience erections when injected with Melanotan II subcutaneously. Sometimes, changes in desire and nausea were also seen.

PT-141, a synthetic peptide analogue of α-MSH chosen for potential human use, has undergone early clinical trials in humans as an intranasal preparation *(52)*. Significant erectile effects were observed in normal men, using objective measures, starting approx 30 min after administration. In these conditions, doses ranging from 4 to 20 mg were seen to induce responses without the need for sexual stimulation. When patients with mild to moderate ED were studied using a dosage of 20 mg of PT-141 and visual stimulation studies, increases in erection duration and rigidity were seen. Further studies of its efficacy and tolerability in phase III clinical trial settings are anticipated.

CONCLUSIONS

The CNS harbors all the mechanisms that make human sexuality so vital. The brain and spinal cord are much more than just control mechanisms for penile erection, although they do, in concert with the cardiovascular system, fulfill that role. The CNS provides the basis for all the aspects of human sexuality outside genital and hormonal function. The contribution of the CNS to sexual dysfunction in age and disease is only just now being assessed. The exquisite complexity of the neural substrates

of sexuality is slowly being revealed in new animal and human studies, through new imaging techniques in humans, and in the results of therapeutic advances in humans. The rapid progress in imaging technology will undoubtedly yield a dramatic new understanding of the CNS's role in human sexual function and dysfunction. The parallel advances in genomics and proteomics should provide further clues to disease mechanisms and reveal new therapeutic targets for untreated aspects of sexual dysfunction in men and women.

REFERENCES

1. McKenna KE. (2002) The neurophysiology of female sexual function. World J Urol 20:93–100.
2. McKenna KE. (2000) Some proposals regarding the organization of the central nervous system control of penile erection. Neurosci Biobehav Rev 24:535–540.
3. Andersson KE. (2003) Erectile physiological and pathophysiological pathways involved in erectile dysfunction. J Urol 170(2 Pt 2):S6–S13.
4. Mazur A, Mueller U, Krause W, Booth A. (2002) Causes of sexual decline in aging married men: Germany and America. Int J Impot Res 14:101–106.
5. Sommer F, Obenaus K, Engelmann U. (2001) Creative-dynamic image synthesis: a useful addition to the treatment options for impotence. Int J Impot Res 13:268–274.
6. Smock T, Albeck D, Stark P. (1998) A peptidergic basis for sexual behavior in mammals. Prog Brain Res 119:467–481.
7. Karama S, Lecours AR, Leroux JM, et al. (2002) Areas of brain activation in males and females during viewing of erotic film excerpts. Hum Brain Mapp 16:1–13.
8. Park K, Seo JJ, Kang HK, et al. (2001) A new potential of blood oxygenation level dependent (BOLD) functional MRI for evaluating cerebral centers of penile erection. Int J Impot Res 13:73–81.
9. Park K, Kang HK, Seo JJ, et al. (2001) Blood-oxygenation-level-dependent functional magnetic resonance imaging for evaluating cerebral regions of female sexual arousal response. Urology 57:1189–1194.
10. Arnow BA, Desmond JE, Banner LL, et al. (2002) Brain activation and sexual arousal in healthy, heterosexual males. Brain 125(Pt 5):1014–1023.
11. Montorsi F, Perani D, Anchisi D, et al. (2003) Brain activation patterns during video sexual stimulation following the administration of apomorphine: results of a placebo-controlled study. Eur Urol 43:405–411.
12. Bocher M, Chisin R, Parag Y, et al. (2001)Cerebral activation associated with sexual arousal in response to a pornographic clip: a 15O-H2O PET study in heterosexual men. Neuroimage 14(1 Pt 1):105–117.
13. Redoute J, Stoleru S, Gregoire MC, et al. (2000) Brain processing of visual sexual stimuli in human males. Hum Brain Mapp 11:162–177.
14. Hagemann JH, Berding G, Bergh S, et al. (2003) Effects of visual sexual stimuli and apomorphine SL on cerebral activity in men with erectile dysfunction. Eur Urol 43:412–420.
15. Holstege G, Georgiadis JR, Paans AM, Meiners LC, van der Graaf FH, Reinders AA. (2003) Brain activation during human male ejaculation. J Neurosci 23: 9185–9193.
16. Henkin RI, Levy LM. (2002) Functional MRI of congenital hyposmia: brain activation to odors and imagination of odors and tastes. J Comput Assist Tomogr 26: 39–61.

17. Marson L, Platt KB, McKenna KE. (1993) Central nervous system innervation of the penis as revealed by the transneuronal transport of pseudorabies virus. Neuroscience 55:263–280.
18. Vodusek DB. (1990) Pudendal SEP and bulbocavernosus reflex in women. Electroencephalogr Clin Neurophysiol 77:134–136.
19. Lindstrom S, Fall M, Carlsson CA, Erlandson BE. (1983) The neurophysiological basis of bladder inhibition in response to intravaginal electrical stimulation. J Urol 129:405–410.
20. Bitran D, Miller SA, McQuade DB, Leipheimer RE, Sachs BD. (1988) Inhibition of sexual reflexes by lumbosacral injection of a GABA B agonist in the male rat. Pharmacol Biochem Behav 31:657–666.
21. Sachs BD, Liu YC. (1998) Mounting and brief noncontact exposure of males to receptive females facilitate reflexive erection in rats, even after hypogastric nerve section. Physiol Behav 65:413–421.
22. Truitt WA, Coolen LM. (2002) Identification of a potential ejaculation generator in the spinal cord. Science 297:1460–1461.
23. Hubscher CH, Johnson RD. (2003) Responses of thalamic neurons to input from the male genitalia. J Neurophysiol 89:2–11.
24. Hubscher CH, Johnson RD. (1996) Responses of medullary reticular formation neurons to input from the male genitalia. J Neurophysiol 76:2474–2482.
25. Marson L. (1995) Central nervous system neurons identified after injection of pseudorabies virus into the rat clitoris. Neurosci Lett 190:41–44.
26. Behbehani MM. (1995) Functional characteristics of the midbrain periaqueductal gray. Prog Neurobiol 46:575–605.
27. Bancila M, Giuliano F, Rampin O, et al. (2002) Evidence for a direct projection from the paraventricular nucleus of the hypothalamus to putative serotoninergic neurons of the nucleus paragigantocellularis involved in the control of erection in rats. Eur J Neurosci 16:1240–1248.
28. Argiolas A, Melis MR, Mauri A, Gessa GL. (1987) Paraventricular nucleus lesion prevents yawning and penile erection induced by apomorphine and oxytocin but not by ACTH in rats. Brain Res 421:349–352.
29. Flanagan-Cato LM, McEwen BS. (1995) Pattern of Fos and Jun expression in the female rat forebrain after sexual behavior. Brain Res 673:53–60.
30. Murphy AZ, Hoffman GE. (2001) Distribution of gonadal steroid receptor-containing neurons in the preoptic-periaqueductal gray-brainstem pathway: a potential circuit for the initiation of male sexual behavior. J Comp Neurol 438:191–212.
31. Putnam SK, Sato S, Hull EM. (2003) Effects of testosterone metabolites on copulation and medial preoptic dopamine release in castrated male rats. Horm Behav 44:419–426.
32. Yang LY, Clements LG. (2000) MPOA lesions affect female pacing of copulation in rats. Behav Neurosci 114:1191–1202.
33. Dominguez J, Riolo JV, Xu Z, Hull EM. (2001) Regulation by the medial amygdala of copulation and medial preoptic dopamine release. J Neurosci 21:349–355.
34. Vachon P, Simmerman N, Zahran AR, Carrier S. (2000) Increases in clitoral and vaginal blood flow following clitoral and pelvic plexus nerve stimulations in the female rat. Int J Impot Res 12:53–57.
35. Dail WG, Harji F, Gonzales J, Galindo R. (1999) Multiple vasodilator pathways from the pelvic plexus to the penis of the rat. Int J Impot Res 11:277–285.
36. Whipple B, Komisaruk BR. (2002) Brain (PET) responses to vaginal-cervical self-stimulation in women with complete spinal cord injury: preliminary findings. J Sex Marital Ther 28:79–86.

37. Meusburger SM, Keast JR. (2001) Testosterone and nerve growth factor have distinct but interacting effects on structure and neurotransmitter expression of adult pelvic ganglion cells in vitro. Neuroscience 108:331–340.
38. Santer RM, Dering MA, Ranson RN, Waboso HN, Watson AH. (2002) Differential susceptibility to aging of rat preganglionic neurones projecting to the major pelvic ganglion and of their afferent inputs. Auton Neurosci 96:73–81.
39. Bancroft J. (1999) Central inhibition of sexual response in the male: a theoretical perspective. Neurosci Biobehav Rev 23:763–784.
40. Rabbani F, Stapleton AM, Kattan MW, Wheeler TM, Scardino PT. (2000) Factors predicting recovery of erections after radical prostatectomy. J Urol 164:1929–1934.
41. Chun SS, Fenemore J, Heaton JP, Johnston B, Morales A. (1996) Enhancement of erectile responses to vasoactive drugs by a variable amplitude oscillation device. Int J Impot Res 8:221–225.
42. Melis MR, Argiolas A. (2003) Central oxytocinergic neurotransmission: a drug target for the therapy of psychogenic erectile dysfunction. Curr Drug Targets 4: 55–66.
43. Chen K, Chang LS. (2001) Oxytocinergic neurotransmission at the hippocampus in the central neural regulation of penile erection in the rat. Urology 58:107–112.
44. Adachi H, Sato Y, Kato R, et al. (2003) Direct evidence of facilitative actions of dopamine in the medial preoptic area on reflexive and noncontact erections in male rats. J Urol 169:386–389.
45. Hsieh GC, Hollingsworth PR, Martino B**,** et al. (2004) Central mechanisms regulating penile erection in conscious rats: the dopaminergic systems related to the proerectile effect of apomorphine [Epub]. J Pharmacol Exp Ther 308:330–308.
46. Altwein JE, Keuler FU. (2001) Oral treatment of erectile dysfunction with apomorphine SL. Urol Int 67:257–263.
47. D'Aquila PS, Panin F, Cossu M, et al. (2003) Dopamine D_1 receptor agonists induce penile erections in rats. Eur J Pharmacol 460:71–74.
48. Lopez HH, Ettenberg A. (2002) Sexually conditioned incentives: attenuation of motivational impact during dopamine receptor antagonism. Pharmacol Biochem Behav 72:65–72.
49. Cornil CA, Balthazart J, Motte P, et al. (2002) Dopamine activates noradrenergic receptors in the preoptic area. J Neurosci 22:9320–9330.
50. Yonezawa A, Ando R, Watanabe C, et al. (2001) Alpha$_2$-adrenoceptor antagonists: effects on ejaculation, penile erection and pelvic thrusting behavior in dogs. Pharmacol Biochem Behav 70:141–147.
51. Sebhat IK, Martin WJ, Ye Z, et al. (2002) Design and pharmacology of N-[(3R)-1,2,3,4-tetrahydroisoquinolinium- 3-ylcarbonyl]-(1R)-1-(4-chlorobenzyl)- 2-[4-cyclohexyl-4-(1H-1,2,4-triazol- 1-ylmethyl)piperidin-1-yl]-2-oxoethylamine (1), a potent, selective, melanocortin subtype-4 receptor agonist. J Med Chem 45: 4589–4593.
52. Molinoff PB, Shadiack AM, Earle D, Diamond LE, Quon CY. (2003) PT-141: a melanocortin agonist for the treatment of sexual dysfunction. Ann NY Acad Sci 994:96–102.
53. Wessells H, Hruby VJ, Hackett J, et al. (2003) MT-II induces penile erection via brain and spinal mechanisms. Ann NY Acad Sci 994:90–95.
54. Martin WJ, McGowan E, Cashen DE, et al. (2002) Activation of melanocortin MC(4) receptors increases erectile activity in rats ex copula. Eur J Pharmacol 454: 71–79.

55. Melis MR, Spano MS, Succu S, et al. (2000) EP 60761- and EP 50885-induced penile erection: structure-activity studies and comparison with apomorphine, oxytocin and N-methyl-D-aspartic acid. Int J Impot Res 12:255–262.
56. Melis MR, Succu S, Spano MS, Deghenghi R, Argiolas A. (2001) EP 91073 prevents EP 80661-induced penile erection: new evidence for the existence of specific EP peptide receptors mediating penile erection. Neuropharmacology 41: 254–262.
57. Sato Y, Zhao W, Christ GJ. (2001) Central modulation of the NO/cGMP pathway affects the MPOA-induced intracavernous pressure response. Am J Physiol Regul Integr Comp Physiol 281:R269–R278.
58. Melis MR, Succu S, Mascia MS, Argiolas A. (2001) The activation of gamma aminobutyric acid(A) receptors in the paraventricular nucleus of the hypothalamus reduces non-contact penile erections in male rats. Neurosci Lett 314:123–126.
59. Holmes GM, Bresnahan JC, Beattie MS. (2001) Inhibition of pudendal reflexes in spinal rats. Reassessing the role of serotonin. Physiol Behav 74:57–64.
60. Heaton JP, Morales A, Adams MA, Johnston B, el-Rashidy R. (1995) Recovery of erectile function by the oral administration of apomorphine. Urology 45:200–206.
61. Fagan TC, Buttler S, Marbury T, Taylor A, Edmonds A, SL APO Study Group. (2001) Cardiovascular safety of sublingual apomorphine in patients on stable doses of oral antihypertensive agents and nitrates. Am J Cardiol 88:760–766.
62. Altwein JE, Keuler FU. (2001) Oral treatment of erectile dysfunction with apomorphine SL. Urol Int 67:257–263.
63.Dula E, Bukofzer S, Perdok R, George M, Apomorphine SL Study Group. (2001) Double-blind, crossover comparison of 3 mg apomorphine SL with placebo and with 4 mg apomorphine SL in male erectile dysfunction. Eur Urol 39: 558–563.
64. Altwein JE, Keuler FU. (2001) Oral treatment of erectile dysfunction with apomorphine SL. Urol Int 67:257–263.
65. Mulhall JP, Bukofzer S, Edmonds AL, George M, Apomorphine SL Study Group. (2001) An open-label, uncontrolled dose-optimization study of sublingual apomorphine in erectile dysfunction. Clin Ther 23:1260–1271.
66. Von Keitz AT, Stroberg P, Bukofzer S, Mallard N, Hibberd M. (2002) A European multicentre study to evaluate the tolerability of apomorphine sublingual administered in a forced dose-escalation regimen in patients with erectile dysfunction. BJU Int 89:409–415.
67. Heaton JP, Dean J, Sleep DJ. (2002) Sequential administration enhances the effect of apomorphine SL in men with erectile dysfunction. Int J Impot Res 14:61–64.
68. Wessells H, Levine N, Hadley ME, et al. (2000) Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. Int J Impot Res 12(Suppl 4):S74–S79.

15 Sustaining the Cure

Oral Pharmacotherapy Failure Salvage With Vacuum Devices and Penile Implants

Ronald W. Lewis, MD

CONTENTS

INTRODUCTION

Oral pharmacotherapy fails to provide an adequate erection in approx 30 to 35% of all patients tried on this initial therapy, and at higher rates in those patients who have diabetes mellitus and those who have had radical pelvic cancer surgery. In those patients with initial success from oral pharmacotherapy, there have been few reports of complete tachyphylaxis, although many who are started on lower doses initially feel that they obtain better results from the oral therapy by increasing to the higher dose recommended for use. Dropout rates owing to intolerable side effects are rare with all of the phosphodiesterase inhibitors. Occasionally, some users of oral therapy cannot afford to continue the use of the oral agents and prefer a more economical treatment for their erectile dysfunction (ED). Vacuum therapy provides such a solution. Certainly, penile prostheses are less economical for such patients. If there is a progression of disease—such as Peyronie's disease of a severe nature, or more fibrosis of sinus smooth muscle, such as that associated with diabetes mellitus—then

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a penile prosthesis may become the next step in therapy for the patient with ED.

The patient and his partner who move away from oral therapy as the solution for ED should already be aware of the choice of vacuum therapy. This should have been presented to the patient in the beginning of the process—when the different therapies for ED were discussed—as one of the primary choices for the management of ED. Many, if not most couples, when hearing about the two primary choices of oral therapy or vacuum therapy, naturally prefer oral therapy. The mechanical nature of the vacuum therapy is a perceived drawback for most men with ED, although some couples that hear about the two types of primary therapy do select vacuum therapy as their first choice. These are usually the older couples that have a very stable marriage and a very adaptable sexual satisfaction level. Moving to vacuum therapy can be a smooth transition for the patient who has failed oral pharmacotherapy, particularly because it is noninvasive and safe compared to the more invasive secondary therapeutic choices, such as injection therapy, or urethral suppositories, such as the Medical Transurethral System for Erection (MUSE).

EXTERNAL VACUUM THERAPY

The use of external vacuum therapy for the treatment of ED has been extensively reviewed in the past *(1,2)*. Vacuum devices can now be purchased over-the-counter, but the author still prefers the prescription-only products because they offer more physiological tension bands as regards to shape and ease of removal.

Some vacuum cylinders have pop-off valves to limit the amount of negative pressure applied to the penis during the erection phase, and some have more secure adaptable cylinder inserts for more efficient vacuum seal at the start of the vacuum phase. Many of the prescription devices also have different cylinder sizes provided with the initial purchase, which allows for better individualization for penile size variation, and accommodation for minimal Peyronie's disease curvatures. Finally, some of the prescription vacuum devices offer a technical support staff available for users who might be having some problems using the vacuum device to reach by telephone, greatly aiding in success for the couple who may need minor adjustments in their use of this ED solution.

Satisfaction rates for the vacuum devices vary in reports, reaching as high as 94%, and as low as 26.7%. Dropout rates have been reported from 20 to 30% *(1,2)*. The reasons for dropouts include the following:

1. Inability to achieve and maintain a full erection.
2. Pain and discomfort from use of the device.
3. Poor health.

4. Marital problems or the loss of a spouse.
5. Unnatural interruption of the act of love-making.
6. The return of natural erections.
7. Too much trouble to use.
8. Nonacceptance by partner.
9. Desire to switch to another type of therapy.
10. Inability to use because of worsening of Peyronie's curvature.
11. Cool penile temperature obtained by the patient with the use of the device *(1,2)*.

Complications from the vacuum devices are rare. They include the following:

1. Occasional mild numbness and numbness of the penis as a problem.
2. Decreased or increased time to orgasm.
3. Pivoting of the base of the penis.
4. Bruising of the penis.
5. Penile petechiae.
6. Pain or swelling of the penis after use of the device.
7. Pain with orgasm because of the tension rings.
8. Rarely, penile skin necrosis.
9. Fournier's gangrene.
10. Urethral bleeding
11. Herniation of the scrotal tunica vaginalis into the penile shaft *(1,2)*.

Even patients who have experienced failure or the removal of a penile prosthesis have been successful in subsequent use of the vacuum device to solve their erectile dysfunction problem *(3,4)*. The first authors reported successful salvage in four of five patients with an explanted penile prosthesis, and an enhanced erection in four patients who had a semirigid penile prosthesis *(3)*. In the second study of 14 explanted men, which included six men who had the implant removed because of infection, 10 (71%) engaged in regular intercourse using the vacuum device (5 of the 6 who had infected associated removed devices). Of the 11 who tried the vacuum device at home, six reported that the device was a better solution for their ED than the previous implant *(4)*. However, patients who have severe penile scarring of the corpora cavernosa, such as that seen with priapism, or those who have had extensive penile scarring because of cavernosal infection in association with a penile prosthesis, may not obtain full engorgement with the vacuum device *(5)*. Patients on well-controlled anticoagulant therapy have been shown to be at no added risk by using vacuum therapy as a solution for their ED *(6)*.

Composition of the Vacuum System

There are three components of the vacuum system: the cylinder, the pump, and the tension rings *(1)* (Fig. 1).

Fig. 1. An example of a vacuum device with an attached battery-powered pump on one end of the cylinder, and the cylinder with the insert ring in place (photograph provided by Augusta Medical Systems, Augusta, GA).

The cylinders are generally constructed of clear plastic, some of them tapering out distally, with a nipple-like extension for the attachment of plastic tubing to a hand-held vacuum pump. Some cylinders are open-ended at the distal end to allow for direct attachment of the pump, comprising a one-piece unit with a pump handle, or with an outer pumping cylinder over an inner cylinder. Several companies also produce a battery-driven pump particularly designed for patients who lack the mechanical facility or strength to produce hand-motion pumping. Some companies provide different cylinder choices with each unit to allow for variance in penile size, whereas others use various optional inserts to modify the internal diameter of the cylinder. Larger cylinders are available for the rare patient who obtains significantly greater penile circumference with application of the vacuum device. Larger cylinders may also be necessary for patients with severe penile angulation secondary to Peyronie's disease who have difficulty removing the cylinder once engorgement has been obtained.

Fig. 2. An example of a tension band that has been designed for temporary use and easy removal by a tear apart system (SureRelease™. Figure provided by Augusta Medical Systems, Augusta, GA).

As a safety feature built into the pump, most devices have a vacuum valve that activates after a certain negative pressure has been reached (300–350 mmHg). To produce adequate rigidity of the penis, the vacuum pressure must exceed 90 mmHg. All devices have a release mechanism built into the pump for the release of the negative pressure when adequate penile engorgement has occurred and tension rings have been placed around the base of the penis.

Tension prostheses can be wide-width rubber bands, rings of varying size and tension, or plastic discs with a central opening. Some companies produce round tension bands of varying width, whereas another company produces rings molded to include a urethra-sparing notch on the inside curve of the ventral position of the ring. Tension rings must have tabs or strings to ease their removal after use. Recently, one company has created disposable tear off tension bands (Fig. 2; SureRelease, Augusta Medical Systems, Augusta, GA).

After use, all parts of the vacuum devices, except for the pump itself, can be submerged in soapy water for cleaning.

The patient assembles the device by placing the tension apparatus (sometimes using more than one tension ring) on the proximal end of the cylinder and connecting the pump to the cylinder on the distal end. He then lubricates the proximal open end of the cylinder with a water-soluble lubricant to obtain a better seal to the skin surrounding the base of the penis. If excessive pubic hair prevents a tight seal at the abdomen, the patient may have to shave or cut some of this hair. With one hand around the cylinder, the patient presses the device against the skin surrounding the base of the penis and begins to pump by hand or by activating the pump switch on the battery-powered model. If the cylinder design allows it, some users press the distal end of the cylinder against a table or counter to free one hand. Once adequate penile rigidity has been obtained, the preloaded tension rings are eased off of the proximal end of the cylinder and onto the base of the penis. The vacuum is released by a valve or button on the pump, the cylinder is removed, and the patient is ready for intercourse. It is recommended that the tension rings be left in place for no longer than 30 min.

THE VACUUM-ASSISTED ERECTION

The assisted erection obtained with a vacuum device is slightly different from an erection obtained normally in that there is no initial relaxation of the sinus smooth muscle within the corpora cavernosa. Instead, all tissue of the penis becomes engorged with trapped blood, which has been drawn into the penis by the action of negative pressure. In some cases, the actual penile size (especially the glans) achieved by vacuum-assisted erection is larger than that obtained with a natural erection. Because the buried portion of the corpora cavernosa proximal to the tension ring does not usually become tumescent, there is some lack of fixation of the penis, and the resulting hinged effect is bothersome to some patients. The penis may become slightly cool or numb, and may become slightly bluish in color owing to cyanosis. Some partners are unhappy with the coldness of the penis and the need to use lubricating jelly.

Pain with penile engorgement and the application of the vacuum device is rare, mostly of a mild nature, and usually not a concern for the patient. Pain with ejaculation related to trapping of the ejaculatory fluid is extremely rare. With orgasm and ejaculation, there may not be expulsion of fluid from the penis because of the tension apparatus around the shaft of the penis. This is not always the case (present in 30–40% of cases), but is commonplace and does not present a problem, especially if the patient has been forewarned. When the rings have been removed after intercourse and ejaculation, the seminal fluid will usually run or drip from the penile meatus.

Table 1
Currently Available Penile Implants

Type	*Prosthesis*	*Vendor*
Semirigid		
• Malleable	Acu-form™	Mentor [a]
	Malleable™650	AMS [b]
	Malleable™ 600M	AMS
• Mechanical	Dura II Malleable	AMS
Inflatable		
• Two-piece	Ambicor®	AMS
	Excel™ (investigational use only)	Mentor
• Three-piece	Titan™	Mentor
	Titan Narrow Base™	Mentor
	Lock-out valve reservoir	Mentor
	700 CX™	AMS
	700 CX™ Preconnected	AMS
	700 CXR™	AMS
	700 Ultrex®	AMS
	700 Ultrex® Preconnected	AMS
	(Last five come with or without Inhibizone™ antibiotic surface treatment).	

[a] Mentor Corporation, Santa Barbara, California.
[b] American Medical Systems, Minnetonka, Minnesota.

PENILE PROSTHESES

Penile prostheses are very successful and provide a high satisfaction rate for the patient with ED. They are, of course, one of the most invasive solutions for the treatment of ED *(7)*. They are not usually the next choice for those who have failed oral pharmacotherapy, but, as mentioned previously, there are certain penile cavernous disease states where penile prostheses are certainly a reasonable choice. Fibrosis of the corpora cavernosal tissue, especially if severe, and severe curvature as a result of Peyronie's disease, often preclude the patient's ability to use vacuum therapy or other more invasive therapy such as intracavernous injection or urethral suppositories in place of failed oral therapy. The use of a vacuum device preoperatively has been reported to improve penile length and assist in softening corporeal fibrosis *(8)*. The two major choices for prostheses include malleable devices and the hydraulic devices (*see* Table 1; Figs. 3–5). The hydraulic devices include so-called two- and three-piece devices.

A more physiological duplication of a normal erection and normal flaccidity is offered by the hydraulic devices, particularly the three-piece

Fig. 3. Two malleable devices marketed by AMS (American Medical Systems, Minnetonka, Minnesota). **(A)** Two malleable cylinders (malleable 600). **(B)** A single Dura II device in the straight position (Dura II). **(C)** Shows the flexibility (180°) and memory obtainable by the Dura II device. (These photos are provided by American Medical Systems, Minnetonka, MN).

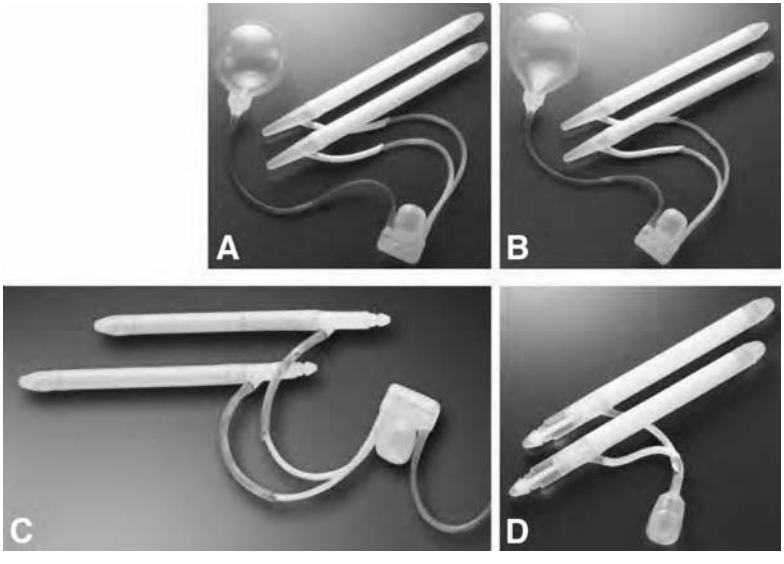

Fig. 4. Shown are the examples of inflatable devices produced by American Medical Systems. **(A)** Three-piece 700 CX penile prosthesis. **(B)** Three-piece inflatable prosthesis that has a capacity to increase in girth and length called the Ultrex. **(C)** Example of an antibiotic-coated three-piece inflatable CXR system. Note that the rear tip extenders are snap-on rear tip extenders for this particular device. **(D)** Two-piece inflatable device called the Ambicor. (These photos are provided by American Medical Systems, Minnetonka, MN).

devices, but the choice of a particular device should be the decision of the patient with information provided by the implanting surgeon, who will also have some preferences regarding the best device for a particular patient. Cost may play a role in the type of prosthesis chosen because the

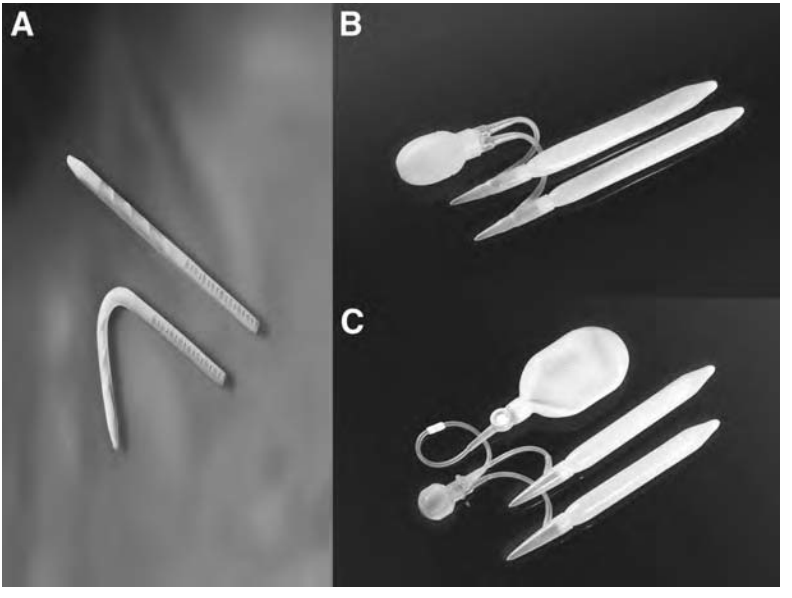

Fig. 5. This figure shows examples of the three penile prostheses produced by the Mentor Corporation. **(A)** Two malleable cylinders called the Acu-Form.**(B)** Two-piece investigational device that is called the Excel device. **(C)** Three-piece Titan.Shown with this model is the lock-out reservoir (this prosthesis has a hydrophilic coat that has the ability of the device cylinders to retain more of the antibiotic on soaking the device before placement).
(Photographs supplied by Mentor Corporation, Santa Barbara, CA).

semirigid devices, for the most part, are less expensive than the hydraulic devices. The reader is referred to other publications for a more detailed discussion of current indications for the different types of penile prostheses *(7,9,10)*.

The patient who is considering a penile prosthesis needs to know the following information:

1. Are there any other possible conservative therapeutic options for management of his ED?
2. What will the prosthesis do for him and what changes in body status will result?
3. In layman's terms, where will the components of the selected device be placed?
4. What are the expected functional and cosmetic results afforded by the selected prosthesis?

5. What are the possible complications, including increased risks from other disease states, such as diabetes mellitus, and the possible need for revision surgery (particularly the complication of infection)?
6. What is the longevity of the selected prosthesis?

Whenever possible, the patient's partner should be involved in this informed consent, and certainly when the partner may be involved with mechanical inflation or deflation of the device. The patient and partner, when included, should be encouraged to ask questions about the prosthesis and the planned surgery. A most important message to deliver to the patient is that no penile prosthesis will restore the full length previously achieved by the patient with his natural erection. A large part of the preparation of the patient is ensuring that he and his partner have realistic expectations for the device and an understanding that any present residual erectile activity may be lost, particularly if the device has to be removed, and that future revision surgery may be necessary.

PENILE PROSTHESIS PLACEMENT

The technique of penile prosthesis placement for primary and more complicated secondary procedures has been presented in other publications by this author *(7,11)*. Basically, the patient is placed in a supine position on the operating room table, and an extended antibiotic scrub and painting is performed for 15 min. Usually the hair in the suprapubic and scrotal region is removed by an electric razor just before this preparation. Some surgeons prefer 2- or 3-d phisohex showers to be performed by the patient at home in the days just before the surgery. All infection, including urinary tract infection, should have been eliminated prior to the placement of a prosthesis. A urinary catheter is placed in the bladder, especially if a reservoir is to be placed in the suprapubic area with a three-piece device, to lessen the possibility of bladder perforation when making the space for the reservoir. Most surgeons prefer some type of broad-spectrum prophylactic parenteral antibiotic therapy started at the time of the prep of the patient. A plastic adhesive barrier drape placed over the exposed operative skin helps to control skin contact with the device components during the rest of the case. The incision can be a circumcising incision for placement of the semirigid devices, necessitating a circumcision in those who are uncircumcised (usually recommended at an earlier time if phimosis or paraphimosis or history of balanoposthititis is present) or a penile–scrotal incision. For the placement of two-piece devices, a penile–scrotal incision is usually the preferred incision, although a few surgeons still prefer an infrapubic incision for even this type of prosthesis. For three-piece inflatable devices, the choice of incision is penile–scrotal or infrapubic.

The potential advantages and disadvantages of each of these approaches is discussed in more detail elsewhere (*see* ref. *7*).

The corpora cavernosa tunica albuginea is exposed on the lateral ventral aspect of the penis, depending on the type of incision. A longitudinal incision of about 2 cm is made into the tunica albuginea to expose the underlying corporeal spongy tissue. This author prefers these to be as close to the crural end of the corpora as possible for the inflatable cylinders to decrease the amount of rear tip extenders needed so that the tubing attached to the cylinder exits from the corpora in as direct a manner as possible. This also allows for the selection of the maximum cylinder length possible. A space is made in the corpora with dilators of the surgeon's preference large enough to accept the chosen cylinders. Usually, particularly in inflatable device surgery, closing sutures are placed on either side of the corporotomy incisions prior to the placement of the cylinder, so that risk of injury to the cylinders is minimal. However, with semirigid devices, the corporotomy can be closed after placement of the cylinders in a running fashion, preferably burying the knots inside the corpora. Long-lasting absorbable suture is preferred for use with inflatable cylinders so that knots tied on the outside eventually dissolve and are no longer palpable to the patient or partner. A subcutaneous or subdartos scrotal pouch is made on the side of the handedness of the patient for placement of the pump or resipump in two-piece devices. Most modern inflatable devices have eliminated the need for connectors between cylinder tubing and pump tubing by providing preconnected devices.

A space for the reservoir is made behind the rectus muscle in the midline in infrapubic approaches, and through the external ring and the floor of the inguinal canal in penile–scrotal approaches. The reservoir is placed and filled with appropriate amounts of sterile injectable saline or, more rarely today, prescribed mixtures of radiographic agent and saline defined by the prosthetic companies. Usually, spaces created for the placement of the cylinders, pump, and reservoir are irrigated with antibiotic solution. Devices are presoaked in antibiotic solution, except those precoated with antibiotic coatings. Usually, a single connection is made between the tubing of the pump and the tubing of the reservoir. Some surgeons prefer to separate the tubings from the various components in different planes with tissue suture. Some also like to fix the pump into the scrotum with tissue suture above the pump to minimize upward migration of the pump. Surgical wounds are closed in two or three layers to provide deeper placement of the device's tubing. Usually, subcutaneous absorbable skin suture is used for the final closure. Some surgeons prefer surgical drains to minimize hematoma formation, whereas others feel that they increase the possibility of wound infection and thus do not provide an acceptable risk benefit to be used.

Most surgeons continue parenteral prophylactic antibiotics during the first 24 h after the placement of the device. Others use oral antibiotics for several d or wk after placement of the device. Certainly, continued several-week broad-spectrum oral antibiotic coverage may be helpful in the patient with diabetes mellitus. With the use of the antibiotic-coated devices from one of the makers of inflatable devices, antibiotic coverage beyond the initial parenteral tissue coverage at the time of initiation of the anesthesia may not be indicated.

PENILE PROSTHESIS COMPLICATIONS

Complications from penile prosthesis consist of the intraoperative technical problems, infection, and other postoperative surgical problems; and mechanical failures. One intraoperative problem is crural perforation of the corpora which can be repaired with perineal exposure of the crura for intraoperative closure, placement of a wind sock with artificial material, or using one of the rear tip extenders via the corporotomy incision sutured to the inside wall of the tunica albuginea. In the case of inflatable cylinders, fixing corpora sutures on either side of the exiting cylinder tubing migration unlikely in the 5 or 6 wk that the cylinders are in a deflated state, during which time the crural tear usually scars closed. Usually, distal corporeal perforation is rare unless the urethra can be closed via a distal penile circumcision incision and the device still placed. However, if a tear is made into the urethra, the cylinder should not be placed, and the placement should be abandoned and rescheduled at a later date. This is particularly recommended if a tear occurs during the dilation of the first corpora. If it is elected to place cylinders in these cases, urinary diversion is recommended by suprapubic catheter placement or perineal catheter placement, and the tear into the urethra can be repaired by exposing the tear via a more distal circumcising incision. However, this is recommended only for the experienced prosthetic surgeon. No one will criticize abandonment of the procedure and a return at another time after the perforation has healed. Infection is the most dreaded and potentially severe complication of any prosthetic device, including the penile prosthesis. It occurs in less than 1% of patients without other known medical risk factors at the time of placement of primary devices. For secondary and tertiary placement of devices, the risk of infection is much higher. Most infections occur within the first 3 mo of surgery. The best control of infection is preventive and is spelled out in Table 2. Salvage procedures are discussed in detail in refs. *7* and *11*.

Other surgical complications include problems with position, pain, encapsulation, and pressure erosion. The three most common position problems are inadequate cylinder length, producing what has become

Table 2
Prosthetic Infection Prevention

- Short hospital stay preoperatively and postoperatively.
- Elimination of other sites of infection preoperatively.
- Discontinuation of chronic indwelling urethral catheters 2 wk before surgery and diversion of urine drainage.
- Antiseptic soap shower three nights before and the morning of surgery.
- Prophylactic perioperative antibiotics.
- Shaving immediately before surgery with an electric razor in the operating room immediately before the skin preparation.
- 15-min skin preparation with antibiotic scrub and paint.
- Strict intraoperative sterile technique (curtail operating room traffic).
- Intraoperative antibiotic wound irrigation and prosthesis soaking (except for antibiotic-coated products).

known as *SST deformity of the glans*; high-riding pump or reservoir/pump for the two-piece devices; and a kinked reservoir neck.

The SST deformity can be corrected by the Ball procedure *(12)*. Gradual decreasing pain may be present in patients receiving penile prosthesis for 4 to 6 wk after surgery, but by the end of this time it should dissolve. It may be inexplicably more severe in patients with diabetes mellitus. Pain associated with elevated white blood cell count and fever should suggest infection. Oversized cylinder placement may also cause pain. Another complication of cylinder length is the S-shaped deformity of the Ultrex cylinders when not downsizing with original placement by 1 cm in length. This type of device is not recommended in patients with Peyronie's disease, nor as a replacement device for previously removed semirigid or self-contained hydraulic devices. Encapsulation of a reservoir or the pump reservoir of the two-piece device may preclude full deflation of the device and may require operative hydrodilation of the entrapped component. The annoying self-inflation of the three-piece device with any increase in intra-abdominal pressure has been greatly eliminated for the Mentor three-piece inflatable device with the lockout valve at the base of the reservoir. Pressure erosion does not necessarily mean infection, although it can be associated with infection. Salvage procedures without frank purulent material may be indicated. Mechanical complications from breakdown of the devices are more likely to occur with the more complicated three-piece hydraulic devices, but changes in the design, such as kink-proof tubing, wear-resistant coating and reinforcement of wear sites, elimination of certain connector sites, and improving cylinder design for strength

and use of more wear-resistant material for these cylinders, eliminated some of the more likely mechanical problems. Today, these devices will only have mechanical breakdown in approx 5% of these devices within 5 to 10 yr of placement *(7)*.

PATIENT SATISFACTION

In general, patient and partner satisfaction with penile prostheses range from 60 to 80% *(7)*. One paper published in 2003 compared satisfaction rates and erectile function in patients treated with sildenafil, intracavernous prostaglandin E1, and penile implant surgery for ED *(13)*. One hundred six patients were followed by using two tools for evaluation. The first, the Erectile Dysfunction Inventory for Treatment Satisfaction (EDITS), was a measure of satisfaction of treatment; and the second, erectile function domain (EFD) of the International Index of Erectile Dysfunction (IIEF), evaluated erectile status while in treatment. Of the 106 patients, 74 (70.59%) used multiple forms of therapy and changed from one therapy to another before continuing with the final form of therapy. In the end, 31 were using sil-denafil therapy, 22 were using intracavernous injection therapy (ICI), and 32 had penile prosthesis and were using the implant for sexual activity. Average follow-up was similar in the three treatment groups, 20.16 mo for those on oral therapy; 19.59 mo for those on ICI therapy; and 18.91 mo for those who underwent penile implant therapy. Twenty-one patients were undergoing no form of treatment for erectile function and thus were incapable of sexual intercourse. In those patients who had penile implants, mean EDITS score, mean EDITS index, and mean EFD scores were significantly higher than the other two treatment groups. This difference persisted when patients who had undergone radical prostate surgery were eliminated because these patients had a natural bias against oral therapy. There was no significant difference in these three measurements between those on oral therapy and those on intracavernous injection therapy.

REFERENCES

1. Lewis RW,Witherington R. (1997) External vacuum therapy for erectile dysfunction: use and results. World J Urol 15:78–82.
2. Levine LA,Dimitriou RJ. (2001) Vacuum constriction and external erection devices in erectile dysfunction. Urol Clinics NA 28:335–341.
3. Korenman SG, Viosca SSP. (1992) Use of vacuum tumescence device in the management of impotence in men with a history of penile implant or severe pelvic disease. JAGS 40:61–64.
4. Moul MW, McLeod DG. (1989) Negative pressure devices in the explanted penile prosthesis population. J Urol 142:729–731.

5. Meinhardt W, Lycklama A, Nijeholt AAB, Kripman RF, Zwartendijk J. (1993) The negative pressure device for erectile disorders: when does it fail? J Urol 149: 1285–1287.
6. Limoge J, Olin E, Kreder K, Donatucci CF. (1994) External vacuum therapy versus intracavernous autoinjection of vasoactive drugs in anticoagulated patients with erectile dysfunction: a study of safety. J Urol 151:478A.
7. Lewis RW, Jordan GH. (2002) Surgery for Erectile Dysfunction. In: Walsh PC, Retnik AB, Vaughan ED Jr., et al., eds., Campbell's Urology, 8th Ed., Philadelphia, PA: Saunders, pp. 1673–1709.
8. Soderdahl DW, Betroski RA, Mode D, Schwartz BF, Thrasher JB. (1997) The use of an external vacuum device to augment a penile prosthesis. Tech Urol 3:100–102.
9. Mulcahy JJ. (1997) Overview of penile implants. In: Mulcahy JJ, ed., Topics in Clinical Urology: Diagnosis and Management of Male Sexual Dysfunction. New York, NY: Igaku-Shoin, pp. 218–230.
10. Wang R, Lewis RW. (2000) Penile Implants—types and current indications. In: Mulcahy JJ, ed., Current Urology Series on Male Sexual Dysfunction: A Guide to Clinical Management. Totowa, NJ: Humana Press, pp. 263–277.
11. Wang R, Lewis RW. (2002) Reoperation for penile prosthesis implantation. In: Carson CC, ed., Urologic Prostheses. Totowa, NJ: Humana Press, pp. 231–247.
12. Ball TP. (1980) Surgical repair of the "SST" deformity. Urol 15:603—604.
13. Rajpurkar A,Dhabuwala B. (2003) Comparison of satisfaction rates and erectile function in patients treated with sildenafil, intracavernous prostaglandin E1 and penile implant surgery for erectile dysfunction in urology practice. J Urol 170: 159–163.

16 Prevention and Treatment of Erectile Dysfunction Utilizing Lifestyle Changes and Dietary Supplements

What Works and What Is Worthless?

Mark A. Moyad

CONTENTS

INTRODUCTION

Lifestyle Changes: Heart Health Equals Erectile Health

No conversation on dietary supplements, prescription drugs, or any conventional intervention for erectile dysfunction (ED) should ever begin without discussing lifestyle changes that may favorably impact the risk of ED A basic analogy to this situation exists for cholesterol reduction, where diet or lifestyle changes are generally the initial interventions utilized and drug therapy follows if lifestyle changes do not have a dramatic impact

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(1,2). Even if drug therapy is initiated, lifestyle changes should continue to be emphasized because of potential synergistic effects, and the general goal of patients should be a better quality and quantity of life and not just to treat their ED. Lifestyle changes may assist the patient in reaching these goals when initiated early and emphasized often.

Sexual function in general tends to decline in healthy aging men *(3).* The latent time period between sexual stimulation and erection increases, erectile turgidity is reduced, ejaculation is not as forceful, the volume of the ejaculate declines, and the interval between erections becomes greater. A decrease in testosterone and an increase in cavernous muscle tone occur, and the penile sensitivity to stimulation also declines.

Approximately 50% of men with chronic diabetes have ED *(3).* Chronic renal failure has also been associated with reduced erectile function and libido. Men with coronary artery disease (CAD) or heart disease, peripheral vascular disease, and stroke also have an increased risk of ED *(4–6).* Other factors associated with ED include: smoking, hypertension, obesity, hypercholesterolemia, minimal physical activity, stress, and chronic alcoholism or drug abuse *(7,8).*

A specific ongoing concern is the lack of understanding that surrounds basic cholesterol values and management. Despite cardiovascular disease being the number cause of death in men and women, surveys continue to demonstrate the need for the general public to understand basic cardiovascular health markers *(9).* How can clinicians educate patients on basic cardiovascular risks and lifestyle interventions when such a large proportion of adults have a deficient understanding of this condition overall? In other words, it would seem difficult to teach prevention in an ED clinic when a majority of individuals do not have a good knowledge of basic cardiovascular risk factors. However, if the connection between heart health and ED health is stressed to men, the potential of a greater adherence to moderate lifestyle changes may be within reach. Patients need to understand that starting from an early age, cardiovascular health is basically equivalent to health and longevity in other areas of life *(10,11),* including living longer and better, and possibly reducing the incidence of numerous health conditions, which would include ED itself.

Past and recent large epidemiology studies continue to suggest that emphasizing heart-healthy lifestyle changes may reduce the overall risk of ED. For example, one of the largest, most cited, past epidemiological studies is the Massachusetts Male Aging Study that found a fairly consistent association between cardiovascular disease and ED *(12).* Follow-up to this same investigation has continued to demonstrate this correlation *(13).* Most recently, results of the Health Professionals Follow-up Study (HPFS) were published in regards to lifestyle risk factors for ED *(14).* This is one

of the largest ongoing prospective epidemiological investigations in medicine. A total of 31,742 US male health professionals were included in this 14-yr follow-up study. Physical activity correlated with a 30% reduced risk of ED, whereas obesity correlated with a 30% higher risk of ED. Smoking, alcohol intake, and television viewing time were also associated with an increased risk of ED. Males with the lowest risk of ED were those without chronic medical conditions and who regularly participated in healthy activities. Other smaller clinical studies also suggest a correlation between cardiovascular and erectile health. For example, a recent cross-sectional study from the UK of 132 men with angiographic CAD demonstrated that objective ED existed in 65% of this study population *(15).* Erectile function scores were significantly ($p < 0.001$) associated with cardiovascular risk factors and with the overall atherosclerotic disease burden ($p < 0.001$), even after allowing for drug treatments associated with ED. In fact, what may be even more alarming are the recent reports and surveys from around the world that have found some association between cardiovascular and erectile health. Investigations from the US *(16),* Thailand *(17),* Korea *(18),* Saudi Arabia *(19),* Turkey *(20),* Spain *(21),* Norway *(22),* Belgium *(23),* the Netherlands *(24),* Brazil *(25),* and many other countries *(26),* recently demonstrated this apparent worrying association between cardiovascular risk factors and ED risk overall in young and older men. Indeed, this issue has become a global concern.

Research continues to suggest that healthy lifestyle modifications initiated early in life may have a profound impact on reducing the risk of ED. Whether or not lifestyle changes initiated later in life have any effect on reducing ED itself remains to be determined from future investigations. Regardless, it has become apparent that implementing healthy changes at any age can affect the quality and quantity of an individual's life. This needs to be emphasized by clinicians attempting to encourage patients to adopt overall healthy behaviors. Cardiovascular health continues to mirror erectile health *(27).*

IMPACT AND REGULATIONS FOR DIETARY SUPPLEMENTS: DOES ANYONE ADHERE TO THE CURRENT RULES?

Complementary or alternative medicine (CAM) continues to enjoy tremendous attention around the world *(28–30).* One of the most rapidly increasing areas of CAM utilization is dietary supplements, which includes herbs, vitamins, minerals, and other compounds *(31).* Sales of dietary supplements have increased dramatically, from approx $9 billion in 1994 to almost $16 billion in 2000. This may be partially the result of the US 1994 Dietary Supplement Health and Education Act (DSHEA), which was

easily approved by both Houses of Congress and also approved at by the President *(32).* This act permitted virtually almost any substance to be promoted as a dietary supplement as long as no specific health claims or benefits are made on the label of the supplement container. No specific claims are permitted that say a supplement can treat, cure, mitigate, or diagnose any disease or condition. Only general claims are permitted, such as "promotes sexual health" or "promotes cardiovascular function." The Food and Drug Administration (FDA) reserves the right to remove any supplement that is in violation of this 1994 act. However, even when specific health claims are advertised without any medical research, the actual burden of proof falls on the US federal government to prove that a claim is actually false, misleading, inaccurate, or irresponsible. Therefore, this act reduces the authority of the FDA to strictly regulate or control manufacturers of dietary supplements. The supplement industry is not held to the same standards as the pharmaceutical industry, which needs to demonstrate to the FDA that their product is safe, effective, and has good or adequate quality control.

Which manufacturers actually follow the guidelines set forth by Congress and DSHEA? Interestingly, one of the largest Internet investigations was recently published *(33),* and the results of this study need to be discussed with patients *(34),* Researchers attempted to access Internet information for the top eight selling supplements in the US *(33).* A total of 443 websites met the inclusion criteria for the study. A total of 81% of the retail websites made one or more health claims, and 55% actually claimed to treat, prevent, diagnose, or cure specific diseases. More than 50% of the websites with a health claim omitted the standard federal disclaimer. The researchers of this unique investigation essentially concluded that a large number of manufacturers are not adhering to the federal guidelines.

Large-scale surveys suggest that the American public does not believe that physicians have adequate knowledge about dietary supplements and are probably biased against them *(31).* However, the majority of the individuals surveyed were also in favor of more government regulations of supplements in general to determine whether claims about the overall benefits of dietary supplements are indeed valid. Participants also generally stated that the FDA should have more authority to evaluate the safety of new dietary supplements before they are marketed. Some dietary interventions and supplements may gain FDA approval if adequate clinical evidence suggests a potential health benefit may exist. Manufacturers need to submit a specific claim along with clinical evidence for potential approval. A commonly cited example is soy protein. Several years ago, the FDA approved a specific health claim for the use of soy protein to reduce the risk of heart

disease because past investigations demonstrated cholesterol reduction from, for example, a specific published meta-analysis of clinical trials *(35).* The FDA only approved soy protein and not the "plant estrogens," or isoflavones, in soy for cholesterol reduction. This finding occurred mostly in individuals with hypercholesterolemia who reduced saturated fat and increased consumption of soy protein. Thus, companies can now advertise that 25 g/d of soy protein may reduce the risk of heart disease. In the near future, manufacturers of other dietary interventions or supplements will probably continue to seek FDA approval for the treatment of a variety of conditions or ailments. For example, the use of fish oil supplements to reduce the risk of heart disease. Whether or not FDA approval will be granted for a claim depends on the sum total of the evidence.

QUALITY CONTROL

Dietary supplements sold in the US are not required to follow specific standards or to ensure quality control *(34,36).* Other parts of the world (including many European countries) demonstrate an entirely different scenario. One prime urological example that highlights this discrepancy includes the use of saw palmetto in France for benign prostatic hyperplasia. Manufacturers in this country have to demonstrate some quality control, but many of these so-called "supplements" sold in the US are actually prescription drugs in these other countries. In the US, a supplement label may report a specific dosage of a substance, but in reality the actual pills or capsules may contain higher, lower, or no specific amounts of this supplement. Therefore, without any proper independent and universal randomized quality control studies, it is a formidable task to evaluate the actual quality and quantity of any of the thousands of dietary supplements sold in the US. Another prime urological example involves a recent study of ginseng supplements (discussed for ED later in this chapter). Researchers found that out of 25 preparations analyzed, a concentration variability of 15 to 200-fold in the main active ingredients existed between products *(37).* Another investigation of 16 different dehydroepiandrosterone (DHEA) dietary supplements (also discussed later in this chapter) found the actual dosage range of contents to be 0 to 150% of what was actually promoted on the label *(38).* Additionally, a journalist from the Newark, New Jersey *Star-Ledger* purchased 10 over-the-counter (OTC) products that advertised enhancement of sexual function *(39,40).* The newspaper submitted these products to an independent laboratory for chemical analysis and found that nine out of the 10 products contained at least one or more compounds that could not be identified or were detected in minimal concentrations compared to what was advertised on the bottle label. The tenth product had less than 50% of the

promoted amount of its only compound, yohimbine. Again, without any enforced standards or regulations, the consumer must be constantly reminded by the clinician that the adage "anything goes" applies, or simply not to be surprised to expect the unexpected when purchasing some dietary supplement products.

DRUG–SUPPLEMENT AND DRUG–PROCEDURE INTERACTIONS: A GROWING PROBLEM

Drug–supplement interactions are also a constant source of difficulty because very little clinical research has been obtained in this specific discipline. A recent study highlights this ongoing serious problem. One of the biggest selling herbal supplements for depression, St. John's wort, is specifically metabolized by the cytochrome P450 3A4 pathway in the liver, and this may cause over 50% of the available prescription drugs in the US to be rendered less efficacious when combined with this specific and commonly used herbal supplement *(41).* Clinicians need to tell patients that when a prescription drug is combined with any dietary supplement the potential for increased or decreased metabolism of the prescription agent could theoretically occur unless some specific past investigation has been conducted that suggests otherwise. It is also for this reason and other concerns that this author suggests that most supplements should not be taken before any surgical procedure or, initially, with any other prescription medications because numerous supplements have already demonstrated the ability to interact with either an anesthetic or a parameter of coagulation *(42).* For example, initial evidence demonstrated that some of the dietary supplements that should be discontinued before surgery include: echinacea, ephedra, garlic, ginkgo, ginseng, kava, St. John's wort, and valerian. The only time a prescription agent should be combined with a supplement is after proper clinical drug–supplement interactions have been researched. In other words, it is imperative to tell patients that it is better to be safe than sorry.

This does not mean that no supplements are useful during or immediately after a surgical procedure or in association with a prescription agent (discussed later in the chapter). For example, initial evidence has found that use of vitamin C during and after cardiac bypass graft surgery may reduce the risk of postoperative atrial fibrillation *(43,44).* A current, large, randomized trial is attempting to determine if this should become standard medical surgical practice.

PLACEBO EFFECTS AND ED SUPPLEMENT UTILIZATION

Randomized, controlled clinical trials are generally considered the gold standard for determining causality *(45).* Some investigations tend to utilize a placebo group when it is deemed appropriate. Other investigations may

utilize the standard treatment as the comparison group. The first article on the overall placebo effect was published in 1945 *(46),* and 10 yr later, another publication suggested that, in general, about one-third of patients in clinical studies experience this response *(47).*

Later publications demonstrated its effects when investigating some conditions *(48),* but currently, this one-third response may be an oversimplification. Another perspective of a wide range of medical conditions found that objective studies, such as serum and imaging tests, demonstrate little, if any, placebo response, whereas subjective improvements or self-evaluations and symptoms tend to have larger placebo response rates *(49).* Two prime examples are the HMG-CoA reductase inhibitors, or statin drugs *(50–53),* and FDA-approved osteoporosis drugs *(54)* because both agents have demonstrated minimal to no response in the placebo group. The situation becomes remarkably different when utilizing subjective or patient-evaluated endpoints. Pain is one example of a symptom that is subjectively evaluated by the patient in clinical studies. Clinical studies have demonstrated a 25 to 40% overall placebo response when investigating medications for pain control *(49).* Other subjective outcomes, such as hair growth or a decrease in hair loss for men or women, have also been quite sensitive to rather notable placebo response rates in clinical trials designed to determine a drug's effectiveness for this specific condition *(55,56).*

ED is usually defined as the persistent inability to achieve or maintain an erection necessary for sexual performance *(57).* It has a wide variety of etiologies and is estimated to affect approx 30 million men in the US alone *(58).* Aging and numerous other factors are correlated with this condition. Currently, numerous treatments exist; however, ED studies that usually include some subjective self-evaluations are also prone to some rather large placebo responses *(3).*

The first effective oral agent for ED, sildenafil (Viagra®), was approved by FDA in the 1990s. An evaluation of past clinical trials also illustrates that the placebo response demonstrated in these trials was modest but fairly consistent. A 24-wk dose-response investigation of 532 men demonstrated improved erections 56, 77, and 84% of men taking 25, 50, and 100 mg of sildenafil, respectively *(59).*

These response rates were significantly larger than placebo, but the placebo response was a modest and consistent value of 25%. Other clinical studies have found similar results. A 26-wk investigation of 315 men from five countries was completed *(60),* and ED was the result of a wide variety of causes, such as hypertension, history of pelvic surgery, diabetes, and heart disease. Approximately 79 to 82% of men taking sildenafil self-reported improved erectile function, compared with 23 to 24% of men taking placebo after 12 and 26 wk of intervention. An earlier but similar 12-wk, randomized

trial of 514 men was completed *(61)*. The etiology of ED was organic in 32% of men, psychogenic in 25%, and mixed in 43%. Again, a variety of dosages were tested and erectile function improved in 67 to 86% of men receiving sildenafil compared with 24% receiving placebo. Partner responses even mirrored the patient reports in this study. Minimal attention regarding this consistent and moderate placebo effect from ED clinical trials can be found in past medical literature. Newer oral agents that have already been approved in other countries and may soon gain FDA approval for ED, observed placebo responses of 25 to 41% *(62)*. Interestingly, many of the best selling and most popular dietary supplements are for conditions that have observed dramatic placebo response rates (benign prostatic hyperplasia, depression, ED, hair loss, pain, etc.) from clinical studies *(63,65)*. Two new oral prescribed agents for ED, vardenafil and tadalafil, were approved by the FDA during the time of this manuscript's preparation *(8)*, and this fact alone may spark a dramatic increase in the advertising and promotion of numerous novel and untested ED dietary supplement compounds.

Clinical trials of female sexual dysfunction (FSD) are not immune to these apparent placebo effects. A trial of transdermal testosterone therapy for sexual dysfunction in women postoophorectomy found a placebo response that was approximately as large or even larger with some sexual function dimensions vs the lower received dosage of testosterone *(66)*. An editorial published in the New England Journal of Medicine mentioned that the utilization of a placebo in this clinical study was important because without it, the apparent benefit of the lower-dose testosterone patch would have been significant *(67)*. Therefore, determining the precise placebo response rates in ED or another related or unrelated condition seems to be of primary importance in evaluating the precise effective dosage of a prescription product.

Surveys or studies attempting to establish the prevalence of ED dietary supplement use in the US and other countries have not been completed. A daily rapid search and review of the Internet, magazines, and national newspapers reveals numerous potential sources whereby the public is able to purchase a wide variety of ED supplements. It is not possible to analyze the benefits and detriments of the thousands of supplements that do exist, but several procedures or compounds seem to be more commonly recommended or found in most of these dietary supplements, and many of these are listed in this chapter for clinician and patient guidance.

ALTERNATIVE PROCEDURE/THERAPY FOR ED

Acupuncture

Acupuncture has been advocated for a variety of medical conditions *(68–70)*. China has used some form of this procedure for over 2500 yr, and

it is currently a component of their health care system. The general theory behind acupuncture in traditional Chinese medicine supports the thought that there are circuits of energy flow (Qi) throughout the human body that are vital for maintaining adequate health. Any potential disruption of this flow is believed to be responsible for illness or disease. A trained or licensed acupuncturist can apparently fix inadequate Qi at various locations close to the skin with the insertion of fine needles or by applying heat or electrical stimulation at a number of acupuncture points. Auricular acupuncture may also be used during a specific session, because the ear in traditional Chinese medicine has a series of sites that represent various anatomic locations throughout the human body.

Science-based findings that may interpret acupuncture's effectiveness is that placing a needle(s) at a specific site(s) may stimulate the nervous system or physiological pathways to produce and secrete a variety of endogenous compounds—opioids, for example—in the muscles, spinal cord, and brain *(70).* These compounds may either alter the perception of symptoms, or stimulate the production and release of other compounds and hormones that affect the body's internal regulating system. The natural healing potential of the body may also be apparently upregulated with the use of this procedure. It is also possible that some of the results with acupuncture may demonstrate symptomatic relief by eliciting nothing more than a placebo response.

The National Institutes of Health (NIH) published a consensus document on acupuncture in November 1997, after a 2 1/2 d conference organized by the NIH Office of Alternative Medicine and the NIH Office of Medical Applications of Research *(71,72).* This unique alternative medicine session gathered numerous experts in the fields of acupuncture, drug abuse, epidemiology, biostatistics, health policy, pain, physical medicine, physiology, primary care, and psychiatry. This NIH report basically stated that the overall effectiveness of acupuncture could be appropriately considered because of the variety of clinical studies that have already been completed in this discipline. However, this consensus report also stated that quality research of acupuncture vs placebo is severely limited and more randomized trials are needed. The majority of published data are on traditional needle insertion acupuncture and have not adequately involved additional forms of apparent synergistic acupuncture stimuli techniques, such as electrostimulation (electroacupuncture), laser (laser acupuncture), external pressure (acupressure), or heat (moxibustion). The majority of the research on acupuncture has focused on its use for acute and chronic pain relief or the management of pain. The consensus statement also stated that the evidence does support needle acupuncture's effectiveness for relief from two distinct conditions: postoperative pain and chemotherapy-

induced nausea. There are virtually no large randomized studies to date that have been published which demonstrate the potentail role of this treatment in patients experiencing side effects, such as ED from cancer treatment, or that experience ED from other etiologies.

Adverse effects from this procedure itself have been minimal in the hands of a well-trained or licensed practitioner. A larger investigation demonstrated that forgotten needles and transient hypotension were some of the more common side effects *(73)*. Moderate to severe side effects are a possibility with an acupuncturist who has received little or improper training. Pneumothorax and infection from an aseptic procedure is possible in the hands of the less trained practitioners *(74–76)*. Also, before this treatment is initiated many patients generally have to self-evaluate whether or not proper education and training was completed by the specific practitioner(s) in question. Some states do not require or demand additional training in acupuncture to perform this procedure. An MD or DO degree is the only basic requirement, regardless of the clinical background of the practitioner.

A preliminary and pilot study of the effect of acupuncture in the treatment of psychogenic ED was completed and presented, but not yet published, in a peer review journal *(77)*. Ten patients (median age 41.8 yr) were included in this crossover study. Group 1 ($n = 7$) received a total of 10 wk of acupuncture (2 sessions/wk) that specifically addressed ED, whereas group 2 (placebo group, $n = 3$) was treated for 4 wk with general acupuncture that did not specifically address ED The patients in group 2 were crossed over into group 1 in the case of placebo nonresponses. It should be noted that prior to acupuncture treatment, all of these patients responded to 0.01 mg of Alprostadil with a full and rigid erection. Overall, seven patients self-reported "good results" with improvements noted in their sexual performance, and six patients did not require additional treatment and were self-defined as successfully cured. In three cases, acupuncture was not helpful and these patients were successfully treated with 50 mg of oral sildenafil. This small preliminary study obviously requires a larger randomized trial to validate these results, but it seemed worthy of mentioning. Currently, it is not realistic to determine the true effectiveness of acupuncture for any type of ED. However, these initial results were interesting, and perhaps it is possible that acupuncture may have additional benefits beyond a placebo response, but the possibility of a large placebo response with this procedure needs to be addressed. For example, acupuncture has garnered some attention for the relief of hot flashes from prostate cancer treatment, but this study did not utilize a placebo group *(78)*. Other supplements and alternative procedures that have reported a dramatic benefit for hot flash reduction from initial nonplacebo studies have been a major disappointment when large placebo-

controlled trials were completed *(79)*. For example, a study of soy pills found that 36% of patients receiving placebo and only 24% receiving soy pills reported a hot flash reduction frequency of 50% *(80)*. More patients actually preferred the placebo at the end of the study compared to the soy pill for hot flash reduction. Results with vitamin E for hot flashes demonstrated a somewhat similar story and conclusion *(81),* as did a recent, large, randomized trial of red clover ("plant estrogen") pills *(82)*. A recent small and preliminary randomized trial of acupuncture for lower urinary tract symptoms and prostate-specific antigen (PSA) reduction observed that it was not superior to watchful waiting or sham acupuncture over the 12-wk study time *(83)*. The symptom scores were actually reduced to a greater degree in the sham acupuncture group vs the acupuncture group. Therefore, clinicians need to be extremely careful before recommending acupuncture for ED until some type of randomized study is published. Perhaps one could argue that patients with psychogenical ED having nothing to lose when attempting acupuncture in the hands of a well-trained practitioner, but of course this is would still be quite controversial until more data is published. Regardless, if a clinician wants to establish an objective discussion with a patient inquiring about acupuncture, a summary of its potential uses and limitations for a variety of medical conditions are provided in Table 1 *(68,70,71,77,83)*.

L-Arginine: An Amino Acid Supplement and a Potential Precursor to Nitric Oxide

The primary neurotransmitter that mediates penile erection is most likely the compound nitric oxide (NO) *(3,84,85)* It is released during non-adrenergic, noncholinergic neurotransmission from the endothelium. Within the muscle itself, NO activates a guanylyl cyclase, which increases the production of intracellular levels of cyclic guanosine monophosphate. Cyclic guanosine monophosphate is an intracellular second messenger that mediates smooth muscle relaxation, activates specific protein kinases that phosphorylate specific proteins to cause an opening of potassium channels, and a closing of calcium channels and an overall sequestration of intracellular calcium. The decrease in intracellular calcium results in smooth muscle relaxation, and an increase in the flow of penile blood. L-arginine, an amino acid, is a precursor to NO. It does seem plausible that an adequate amount of this precursor via a concentrated pill has the potential to improve ED in some men. Large sources of dietary nonconcentrated L-arginine do exist in the food supply. Whether or not these sources improve ED is unknown, but they may improve cardiovascular function *(86),* which in turn could theoretically promote healthy erectile or sexual function. For example, legumes, whole grains, and a variety of nuts may be a source of several grams or more of L-arginine daily when consumed in moderate to large amounts *(87)*.

Table 1
A Partial Summary of the Current Apparent Potential Benefits and Limitations of Acupuncture for Diverse Medical Conditions

Good evidence	*Undetermined evidence*	*Weak/minimal evidence*
Back pain	Addictions	Lower urinary tract symptoms (BPH) and PSA reduction
Dental pain	Asthma	Smoking cessation
Migraine	Chronic pain (general)	Weight loss
Nausea/vomiting	Erectile dysfunction (ED): psychogenic	
Xerostomia or dry-mouth (refractory) from radiation treatment for head and neck cancer	Experimentally generated pain Headache (common) Hot flashes from cancer treatment Menopausal symptoms, i.e., hot flashes, etc. Neck pain Osteoarthritis Rheumatoid arthritis Stroke recovery and rehabilitation Temporomandibular joint syndrome (TMJ) Tinnitus	

BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen.

Three noteworthy, small, pilot clinical studies of L-arginine vs placebo have been completed to date. The first study was a placebo-controlled clinical trial that used 2800 mg/d of L-arginine for only 2 wk, and found that 40% of patients had improvement in their erections *(88)*. Actual responders were younger and had better overall vascular function by hemodynamic investigation vs the nonresponders. The second pilot trial included 1500 mg/d of L-arginine vs placebo for 2 wk for men with mixed type ED. L-arginine at this specific dosage did not demonstrate a benefit compared to placebo *(89)*. In the third small trial, 50 patients were given a high dosage (5 g/d) of L-arginine or placebo for 6 wk for organic EDs that were mostly the result of diabetic or arteriogenic etiologies *(90)*. Approximately 31% of the men in the L-arginine group self-reported an improvement compared with 12% in the placebo arm. The difference was statistically significant. Additionally, men who improved were found to have low concentrations of NO in the urine. The primary side effect was a reduction of systolic and/or diastolic blood pressure of approx 10% in the L-arginine group. It seems plausible that men secreting low levels of NO who are willing to take fairly large daily dosages of L-arginine may observe a benefit. Larger randomized clinical trials are needed in this area, but currently L-arginine seems to be one of several possible exceptions to the observation that dietary supplements currently provide little to no benefit for men with ED. Recent cardiovascular studies utilizing very large oral dosages (12 g/d) of oral L-arginine vs placebo for short time periods (3 wk) in hypercolesterolemic men with normal blood pressures have demonstrated reductions in blood pressure and homocysteine levels *(91)*. The ability of this supplement to improve certain types of ED seems plausible given its effects on vascular endothelial function, but whether or not ingesting rather expensive mega-doses of L-arginine for a long period of time for the prevention or treatment of ED is another issue entirely that eventually needs to be addressed in the medical literature.

Anabolic Steroid Supplements Androstenedione and DHEA: Why Are They for Sale OTC, Do They Work for ED, and Why Not Just Use Testosterone?

Why are anabolic steroid supplements even available for OTC purchase in the US by individuals of any age? This is the initial question that should be addressed before discussing the benefits and limitations in detail. The brief answer to this question is a result of two federal laws and rulings approved by Congress in the past 15 yr *(32)*. The DSHEA was mentioned earlier and was easily approved by Congress in 1994. This act allows virtually any substance to become a dietary supplement as long as the manufacturer does not make any specific health claims on the label of the supplement container. More specific to these anabolic supplements is

the approval of the 1990 Anabolic Steroid Control Act. This act requires four different criteria be fulfilled before for the removal of any anabolic-type dietary supplement can occur. These criteria include: (1) Molecular structure related to testosterone; (2) pharmacology related to testosterone; (3) cannot be an estrogen, progestin, or orticosteroid; and (4) the substance cannot promote muscle growth.

Androstenedione (andro) and/or DHEA has a molecular structure and pharmacology quite similar to testosterone, and it is not an estrogen, progestin, or corticosteroid. The reason that these supplements are still available for purchase OTC is because they have not yet clearly demonstrated muscle enhancement or growth in past clinical trials utilizing smaller dosages. It seems possible that they promote muscle growth when higher dosages are used, but these trials either have not been completed or the initial current findings have not been consistent *(92)*. Therefore, under current federal law, manufacturers are still allowed to sell these types of supplements.

Other androgenic–anabolic steroids have demonstrated some positive effects on muscle size and strength with certain types of resistance training *(93,94)*. Normally, andro is produced by the gonads and adrenal glands and can be converted to testosterone *(95)*. This steroid can also be produced by some plants and has been touted as a "natural" alternative to anabolic steroid utilization, and as a potential supplement for ED. Several randomized trials of short duration have been completed with this supplement to determine its effects on a variety of body functions.

For example, one trial was conducted in 1998 *(96)*. A total of 30 healthy young men, ages 19 to 29 with normal testosterone levels were randomly assigned 300 mg of andro or placebo over an 8-wk period. Significant increases in testosterone levels did not occur and supplementation had no effect on muscle size and strength. Individuals in the andro group did experience an increase in serum levels of estrone and estradiol. These findings suggested that more aromatization occurred with this supplement and/or from increasing testosterone levels. The ingestion of this dietary supplement was also associated with reduced serum levels of high-density lipoproteins (HDL), or "good cholesterol," of approx 10%.

Other clinical studies have found similar and other unique effects of andro dietary supplements *(97–102)*. For example, 42 healthy men, ages 20 to 40, received 100 or 300 mg of andro daily for 7 d vs a similar group not receiving any supplements *(99)*. The men receiving no supplements or 100 mg of andro demonstrated no significant mean increases in testosterone. The group receiving 300 mg experienced a mean increase in testosterone of 34%. Estradiol levels increased significantly by 42 and 128% for the 100 mg and 300 mg groups, respectively.

A short clinical trial of 55 healthy men (30–56-yr-old) utilized either a 100 mg of andro or placebo three times daily for 28 d *(101)*. Total serum testosterone and PSA levels were not affected by supplementation. Although, increases in free testosterone (FT), estradiol, and dihydrotestosterone (DHT) were observed. Decreases in serum HDL cholesterol also occurred with the supplemented group. No difference in the perception of mood, health, or libido occurred between treatment and placebo groups. This has also been documented in other studies with this and other related supplements *(102)*.

In summary, several randomized trials of andro demonstrated a good correlation between dosage and estradiol levels and an inverse relationship with HDL levels. Other proposed or potential benefits, such as an increase in muscle mass or improved sexual function, have not been found vs placebo. This should be a concern for any individual hoping to utilize these supplements at any age regardless of their condition, especially because these supplements may even demonstrate an opposite effect to what has been touted by some manufacturers. Estrogen has been associated with some favorable cardiovascular benefits *(103)*, but in men these increases may also increase the risk of cardiovascular disease *(104)*, gynecomastia *(105)*, pancreatic cancer, and other abnormal medical conditions *(106)*. Reductions in HDL also contribute negatively to cardiovascular protection *(107)*. It is plausible that with greater andro intake or in men with baseline-low levels of testosterone, an increase in testosterone can be observed with these supplements *(99,101)*. However, the combined negative effects associated with these supplements do not make them a valid option for most individuals. The results of past short-term clinical trials should encourage individuals (men and women) to inquire about testosterone replacement instead of attempting to consume a supplement that only provides a precursor to this and other hormones. For example, a small pilot study (n = 30) of postmenopausal women randomly assigned to a single oral dose of 0, 50, or 100 mg of andro was published *(108)*. Large increases in serum testosterone and estrone levels were observed only with the 50 or 100-mg dose of andro. This was not surprising given that these women already had lower levels of these two hormones. Again, these supplements tend to produce higher quantities of hormones that are initially low, and have a smaller effect on hormones that are already in the normal to high range. This demonstrates that testosterone replacement may be attractive option for some women or men, but more research is needed *(66,67,109)*.

DHEA Equals Andro?

DHEA supplements belong in the same category and discussion as andro supplements. These supplements, derived from such plants as the wild

yam, carry an added potential limiting factor of the requirement to be converted in a laboratory to produce an actual DHEA-like structure *(110).* Many OTC DHEA supplements have not undergone this conversion, and thus contain minimal to no actual DHEA-specific activity. In postmenopausal women, orally active DHEA increases serum testosterone levels *(111–115).* Studies with DHEA also demonstrate increases in estradiol levels in postmenopausal women and women with panhypopituitarism *(111,112,116).* Other potentially potent DHEA supplements contain the same estrogen producing qualities from past clinical trials with men *(117).* Hypogonadal men, or those receiving androgen suppression or luteinizing-hormone releasing hormone (LHRH) agonist treatment for prostate cancer may experience a subsequent testosterone increase (flare) or transient symptomatic benefit with DHEA, but other associated negative effects do not currently make these supplements an attractive option *(118,119).* Receiving a precursor to testosterone does not seem to make clinical sense when just testosterone by itself (if a patient qualifies) seems like the most sensible and practical approach at this time. An analogy to this situation would be choosing a precursor to salicylic acid vs aspirin for cardiovascular prophylaxis. One does not necessarily substitute one for the other, and the precursor may not be nearly as effective for the condition.

An exception to testosterone replacement lies in men with normal levels of testosterone, but with potentially low levels of serum DHEA. A small, randomized trial of men ($n = 40$) fitting this unique and specific category was published in 1999 *(120.)* Men with DHEA sulfate levels below 1.5 μmol/L and normal serum levels of testosterone, dihydro-testosterone (DHT), prolactin, and PSA, were recruited to ingest 50 mg DHEA/d vs placebo for 6 mo. All of the men in this study had initially achieved a full erection with 10 μg of prostaglandin E_1, and patients with obvious or well-known causes of organic ED were also excluded from the study. DHEA treatment was correlated with higher mean scores for all five domains of the International Index of Erectile Function (IIEF), despite no increases in most hormone serum levels or other parameters, except a significant increase in serum DHEA that began at 8 wk and remained throughout the treatment's duration compared to placebo.

An initial significant increase in testosterone also occurred and remained in the DHEA group, compared to placebo (at 8 wk), but estrogen levels or lipid markers were not measured in this study. Some men with early organic or psychogenic ED may benefit from small doses of DHEA. However, larger randomized trials of greater duration are required. A follow-up to this study that included more men and more definable etiologies for ED demonstrated that oral DHEA could potentially benefit men with ED because of hypertension or without an organic etiology *(121).*

Men with diabetes or neurological conditions did not benefit from DHEA. It is noteworthy that from the Massachusetts Male Aging Study, the only hormone measured that demonstrated an inverse correlation with ED was DHEA *(122)*. Overall, these studies are interesting and further studies should be noteworthy, such as studies that address whether or not replacement or pharmacological doses of DHEA have any impact on ED *(92)*.

Ginkgo Biloba—A Circulation Enhancement Supplement: Good for Demetia and Erectile Function?

Using Ginkgo biloba for ED seems to have garnered some interest in alternative medicine circles for a number of reasons, including the apparent benefits of this herbal product in other areas of medicine. There is some clinical evidence that demonstrates Ginkgo extracts can improve vascular perfusion; however, most of these trials have focused primarily on its use in dementia, where a specific extract is utilized rather than a variety of compounds from the plant itself *(123–125)*.

It has been approved in Germany for demetia, and it has some limited clinical data that it may improve chronic cerebrovascular insufficiency. No studies to date have been published on the use of Ginkgo for ED following localized or advanced prostate cancer treatment, but there have been other relevant studies.

One study included 60 patients who did not respond to papaverine injections (50 mg or less) and were treated with 60 mg of an extract of Ginkgo biloba for 12 to 18 mo, but no placebo group was included *(126)*. Ultrasound techniques detected an improved blood perfusion after 6 to 8 wk in some men, and after 6 mo, 50% of these patients regained erectile function. In a smaller number, papaverine injections were later successful. The authors concluded the study by mentioning that a randomized controlled trial was going to be initiated, and the results of their follow-up study were presented in 1998 *(127)*. The follow-up study was a placebo-controlled, double-blind, randomized study utilizing 240 mg daily of an extract of Ginkgo for 24 wk vs placebo for vasculogenic ED. No significant difference was found between the two groups, which highlights the ongoing need for quality randomized studies before recommendations can be proffered. Although Ginkgo still needs to be tested alone or in combination with other drugs for patients who experience ED from a variety of etiologies before a definitive conclusion can be made, it is important to emphasize that there is no current data to support its use for patients with any type of ED. Perhaps the most disconcerting issue is that several studies have suggested that Ginkgo may increase bleeding time, increase the risk of hemorrhages, and further enhance the action of anti-

coagulants *(42,128–130).* Further studies need to be completed to confirm this finding because of its widespread overall use in the population compared with the limited number of observed adverse effects published *(131),* but again, for patients it seems that it is better to be safe than sorry.

A clinical study of sexual dysfunction apparently caused by the use of antidepressants (SSRIs) reported a 91% "relative success" rate in women ($n = 33$) and 76% in men ($n = 30$) when 209 mg/d of Ginkgo extract was taken daily for approx 1 mo *(132).* Ginkgo was credited for improving sexual functions that included enhanced desire, excitement, orgasm, and resolution. A closer analysis of this study revealed numerous problems *(133).* No placebo group was utilized and the apparent overall success rate was either misinterpreted or miscalculated. The study reported a success rate of 84%, but when all of these numbers are added, this rate was approx 68%. The authors also did not document other important details. There was no report of the treatment success or benefits with the antidepressant for depression itself. Other current medications that these patients were taking for other comorbidites were also not listed or obtained for the publication. The authors concluded that the sexual side effects "appeared" to be a result of the use of the SSRIs, but no pretreatment evaluation was described or reported, so how the authors arrived at this conclusion is unknown. Finally, the authors mentioned "no adverse side effects were reported" with the use of Ginkgo. Again, a closer evaluation of the data described some adverse effects (headaches, for example) after ingesting Ginkgo, so again how the authors arrived at this conclusion is unknown. A similar or adequate comparative clinical investigation found no improvement in similar patients with Ginkgo compared to a placebo arm *(134).* Other recent Ginkgo studies utilizing a placebo for some other non-ED type conditions have also failed to observe significant or even noteworthy benefits *(135).* Thus, any previous data advocating Ginkgo supplements for sexual function improvement or ED is suspect at this time until larger randomized trials are completed. In addition, the best possible approach for a future clinical study of ED would be for researchers to utilize the exact same Ginkgo extract that has been already utilized in clinical trials that demonstrated some past success for patients with dementia compared to placebo *(125).*

Korean Red Ginseng: Another Potential NO Producer With Initial Promising Studies

Another recent potential exception to the observation that many dietary supplements do not have initial promising data comes from the supplement Korean red ginseng (panax ginseng). It is one of the most commonly used

ginseng products in the US, and many brands are marketed under the name Panax *(136).* It has been preliminarily investigated against human immunodeficiency virus *(137),* and as a potential agent for reducing severe climacteric symptoms or improving mood in postmenopausal women with some limited positive results compared to placebo *(138,139).* Other studies with this herbal product have found that it may contain numerous active compounds *(140),* some with antiplatelet and blood thinning potential *(141).* It may also improve vascular endothelial abnormalities in hypertensive patients by increasing the concentration of NO *(142).* A laboratory investigation of this form of ginseng on rabbit corpus cavernosal smooth muscle found that it can cause dose-dependent relaxation by increasing the release of NO from corporal sinusoids, and may increase intracellular sequestration of calcium *(143).* A recent laboratory study has confirmed this previous finding and also found that this product may enhance peripheral neurophysiological mechanisms *(144).* Two small clinical trials of Korean red ginseng have provided some encouraging results *(145,146).* The older trial was published in 1995 and utilized 90 patients with ED that were divided into three groups of 30 and were given Korean red ginseng, placebo, or trazodone *(145).* No significant changes in the frequency of intercourse, premature ejaculation, and morning erections occurred post-treatment in any arm. The group taking Korean red ginseng experienced significant positive changes in a number of other erectile parameters, such as penile rigidity, penile girth, libido, and patient satisfaction vs the other groups. Approximately 60% of the patients taking ginseng experienced a therapeutic benefit vs 30% for the placebo and drug groups. Only responses of partial ED remission were recorded. Penile hemodynamic changes did not occur after the administration of this specific form of ginseng. Thus, it is difficult to currently conclude whether or not ginseng had a noticeable objective effect without further investigations. Other trials are needed, but its apparent ability to increase NO levels or reduce fatigue, insomnia, and/or depression demonstrates that specific compound(s) from this herb may have some activity for some types of ED or sexual dysfunction *(138,144).* Another preliminary trial of Korean red ginseng was recently published *(146).* A total of 45 patients with ED without previous treatment were recruited from a urology clinic in Korea and enrolled in this double-blind, placebo-controlled, crossover study that consisted of 8 wk of treatment, a 2-wk washout period, and another 8 wk of treatment. The dose of oral ginseng was 900 mg three times daily. The mean patient age was 54 yr, 70% of the men had moderate or severe ED as measured by a Korean version of the IIEF, and organic comorbidities (hypertension, diabetes, dylipidemia) were found in over 50% of the men. Exclusion criteria included men with a history of radical prostatectomy, neurological problems, hormonal and

chemotherapy treatment, Peyronie's disease, substance abuse. and drugs that interfere with sexual function. All patients had baseline evaluations including IIEF self-assessment, measurement of rigidity and tumescence experienced during audiovisual sexual stimulation, penile duplex ultrasound, and response to an intrapenile injection of papaverine, phentolamine, and prostaglandin E_1. Patients were assessed every 4 wk during the two 8-wk treatment intervals. Improvement was measured by self-report on the IIEF and its subscales, and by objective assessments of penile blood flow, size, and rigidity. Follow-up was complete at 16 wk of treatment. The study was underpowered to find statistically significant improvement in some clinical outcomes, such as improvement in orgasmic function or overall satisfaction for men and their partners. Regardless, the mean IIEF scores were significantly higher (baseline, 28.0 ± 16.7 to a score of 38.1 ± 16.6 with ginseng) in the ginseng-treated patients compared with placebo (baseline, 28.0 ± 16.7 to a score of 30.9 ± 15.7), as well as the parameters of penetration and maintenance. When analyzed individually, scores for erectile function, sexual desire, and intercourse satisfaction were significantly improved with ginseng. Approximately 60% of treated patients experienced an improvement in erection compared with 20% with placebo. This places the number needed to treat at 2.5, but caution should be urged because this is a small study, and no data were reported for partner satisfaction. Penile tip rigidity (RigiScan) also demonstrated significant improvement for ginseng compared with placebo. However, another noteworthy but cautionary finding was the absence of significant difference recorded for orgasmic function and overall satisfaction between the two treatments. The authors also commented that the mechanism of action for ginseng was probably not related to testosterone increases that did not change significantly during the study. Although it was noted that serum testosterone normalized in four of the seven patients with a decreased baseline level after ginseng was received, so more research is needed to resolve this issue. Other potential mechanisms of action, such as an inhibitory effect on the uptake of γ-aminobutyric acid, glutamate, dopamine, and other neurotransmitters along with increased production of NO were proffered as potential mechanisms of action from animal data *(147,148).* This small trial offered some support for ginseng for some subjective symptoms of ED and an enhanced penile tip rigidity, but this supplement still needs a larger placebo trial to determine its overall role for ED treatment. Regardless, this small trial has already generated some positive attention in primary care medicine, and part of the attention, as explained by some authors, might be a result of the cost of Korean red ginseng, which is approx ¢6 for one 500-mg capsule compared with the profoundly higher price of conventional FDA-approved prescribed oral agents *(149).*

During the time of the submission of this chapter, another small but interesting trial of Korean red ginseng was presented. Researchers from Brazil included 60 men (mild to moderate ED) with a mean age of 53.4 yr (range 26–74 yr) in a double-blind trial of 3 g/d of Korean red ginseng compared with placebo for 3 mo *(150)*. Compared with the placebo group, the group taking Korean red ginseng experienced a significant improvement in the erectile domain score of the IIEF, and to all the questions of this domain individually, with a maintenance of response during the 3 mo of follow-up. The percentage of men that felt the treatment with ginseng improved their erections and sexual intercourse was significantly higher (66.6%) compared with placebo (18.5%; $p < 0.001$). Interestingly, the basal- and 3-mo glucose, cholesterol (total cholesterol and triglycerides), and hormone levels (testosterone and prolactin) were approx similar for both agents. The side effects observed in the treatment arm (3.7%) were headache, insomnia, drowsiness, and spontaneous regression during the first month. A total of two patients (7.4%) noted delayed ejaculations during the second and third mo of treatment. Again, this small trial may be an indication that Korean red ginseng may benefit some men with ED. However, the presentation did not mention the etiology of ED in these men.

Yohimbine: an Apparent Drug Copycat That Is Difficult to Find in Most Dietary Supplements

Yohimbine is an indole alkaloid extracted from the bark of West African yohim trees *(151)*. It is a prescription drug that obtained previous FDA approval for pupillary dilation. It appeared to produce blood vessel dilation and increase perfusion, therefore, some researchers began to test its ability to improve erectile function. It contains some compounds similar to an α-2 adrenoreceptor antagonist with some central and peripheral effects. Apparently it functions primarily at receptors in brain centers associated with libido and erections. A meta-analysis of seven randomized trials of over 400 men with ED from a variety of etiologies found that yohimbine (15–43 mg/d) was better vs placebo for all forms of ED combined, but its most apparent improvement occurred with nonorganic ED *(152)*. The most common adverse effects are palpitations, fine tremor, elevation of diastolic blood pressure, anxiety, and nausea. Yohimbine should not be recommended for individuals with organic ED because of novel and more effective ED agents, and its overall effect seems minimal *(3)*.

Yohimbine is also available as an OTC supplement, but it is questionable whether or not they have any value or contain any of the active ingredients found in the drug yohimbine itself *(39,40,153)*. In 1995, the FDA found little or no yohimbine in the majority (11 of 18) of yohimbine supplements brands that were tested *(153)*.

Table 2
Current Government Guidelines for Daily Recommended Dietary Allowance and Appropriate Intake Levels of Daily Zinc and Copper

Age	*Zinc (mg)*	*Copper (mcg)*
0–6 mo	2	200
7–12 mo	3	220
1–3 yr	3	340
4–8 yr	5	440
9–13 yr	8	700
14–18 yr	11 (male); 9 (female)	890
19 yr or older	11 (male); 8 (female)	900

None of the other seven brands contained amounts of yohimbine that were similar to what has been utilized in past clinical trials. Thus there seems no current justification for purchasing any dietary supplement that claims to contain yohimbine. If an individual patient expresses interest in this compound or combining this drug with other ED treatments, the potential for using the prescription drug should be the focus of this conversation.

Zinc: Hype, Hope, Minimal Medical Evidence, and a Major Potential Health Concern for Many Individuals?

Dietary supplements with the mineral zinc are used by approx 15% of the US population *(154)*. This should be a concern because the actual current recommended government dietary intake of zinc is low and may be a surprise to some individuals. The current recommended intake levels are listed in Table 2 along with dietary levels of copper because large doses of zinc can decrease the concentration of copper in the body, so a proper balance or intake between the two makes the most sense *(155)*.

The recommended daily allowance (RDA) of zinc is only 11 mg/d for men, but it seems that some individuals ingest far greater daily quantities than the RDA *(156)*. The reasons for this discrepancy are not currently understood, but may include some highly publicized alternative medicine magazines/books that advocate the use of zinc supplements for everything from the common cold to ED to cancer. Other potential reasons for greater zinc intake are the observations from several laboratory studies that zinc may inhibit the growth and progression of prostate cancer *(157–161)*.

The concentration of zinc in the prostate gland is greater than that in any other human tissue in the body *(162)*. Zinc levels in prostate cancer are substantially reduced vs normal prostate tissue, which may lead some

individuals to suggest that prostate cancer is actually a state of zinc deficiency that may be corrected or prevented by larger intakes of zinc.

Other laboratory and clinical studies suggest that larger intraprostatic or serum zinc concentrations may increase the risk or progression of prostate cancer. For example, zinc promotes the activity of the enzyme telomerase, which is thought to have a role in the ongoing proliferation of cancer cells and whose overall activity is increased in prostate cancer tissue *(163,164).* Zinc has also demonstrated the ability to abolish the inhibitory activity of bisphosphonate drugs on prostate cancer cell invasion, which is a serious potential concern *(165,166),* because these drugs have demonstrated some ability to impact a variety of cancers *(167,168).* Human studies also suggest that higher zinc intakes are positively correlated to circulating levels of insulin-like growth factor-I *(169)*, and testosterone *(170)*. Both of these compounds may be related to an increased risk of prostate cancer.

In summary, several studies have now demonstrated the potential for zinc to increase prostate carcinoma risk, but perhaps one of the most prominent epidemiological investigations to implicate greater intake of zinc supplements as one apparent etiology of prostate cancer was recently published. This finding was taken from the Health Professionals Follow-Up Study *(156).* A total of approx 47,000 US men were included in this prospective investigation. During 14 yr of follow-up, a total of 2901 new cases of prostate cancer were found and 434 of these cases were diagnosed as advanced prostate cancer. Researchers found zinc supplement doses equal to or less than 100 mg/d were not correlated to a risk of prostate cancer. However, compared with nonusers of these dietary supplements, men that ingested more than 100 mg/d of zinc supplements had a significantly higher risk of being diagnosed with advanced prostate cancer (RR = 2.29). Men that consumed zinc supplements for 10 yr or more also had a significantly higher risk of being diagnosed with advanced prostate cancer (RR = 2.37). In this cohort, approx 32% of the total zinc intake was from dietary supplements, which represented the largest source of zinc intake. Other sources, which were much lower, were from beef (11%) and breakfast cereals (5%). However, zinc from food sources was not correlated with prostate cancer risk. Men consuming zinc supplements also consumed more supplemental calcium, multivitamins, vitamin E supplements, lycopene, iron, copper, folate, and fish, but consumed less red meat and were less likely to have had a history of PSA screening compared to nonusers of zinc supplements. Researchers also attempted to identify any other confounding factors in this investigation. One analysis restricted the study population to men reporting lower levels of calcium supplement intake, and adjusting for intakes of iron, copper, folate, BPH, and other factors, but this had no

impact on the final results of the study. Therefore, zinc supplements themselves were still the most likely etiology from this investigation.

Increased zinc ingestion may also increase the risk of BPH. The impact of dietary zinc intake on subsequent intraprostatic zinc levels is not currently known. However, a case-control study from Greece of diet and BPH observed that greater intakes of dietary zinc had the most significant correlation with the overall risk of BPH (OR = 1.89) *(171)*. Zinc (mostly from meat and some seed sources) was more closely correlated with BPH risk than any other evaluated dietary nutrient, and zinc also strongly confounded the relationship of saturated fat with the risk of BPH. Therefore, the suggestion that meat consumption increases the risk of prostatic disease may be too simplistic. Other factors in meat, such as zinc, may have a more profound impact. Interestingly, zinc concentration increases in BPH tissue *(162,172–178)*. Testosterone appears to be involved in the development of BPH and prostate cancer, and it significantly increases the concentration of cellular and mitochondrial zinc. Laboratory investigations have also observed that androgen uptake by the prostate was significantly increased by the addition of zinc *(175)*. Zinc also appears to impact the enzyme 5-α-reductase in the prostate *(179)*. Whether or not this is a favorable or unfavorable affect has yet to be researched.

Zinc supplements may be beneficial for a variety of medical conditions including the common cold *(180)*, acne *(181)*, acute diarrhea *(182)*, progressive myoclonic epilepsy *(183)*, and Wilson's disease (abnormal accumulations of copper resulting from an autosomal recessive genetic mutation) *(184,185)*. However, the negative effects of zinc supplements may outweigh the potential benefits in many or most individuals, and the current benefits of zinc supplements for more benign conditions, such as the common cold, have been challenged by other investigations *(186)*. Zinc supplements also seem to be associated with other negative affects. For example, excess zinc intake must be included in the overall differential diagnosis of sideroblastic anemia *(187)*. The diagnosis of zinc-promoted copper deficiency can be established from reduced serum copper and ceruloplasmin levels along with an increased zinc serum level. Therefore, a reversible cause of anemia and neutropenia in some individuals may occur via a reduction or cessation of zinc supplementation.

A small, older clinical study suggested a concern with the ingestion of larger doses of zinc supplements. Ingestion of 150 mg of elemental zinc twice a day (300 mg/d total) for only 6 wk in 11 healthy adult men demonstrated general immune dysfunction that began to reverse with the cessation of the zinc supplements *(188)*. Levels of serum high-density lipoproteins ("good cholesterol") were also significantly decreased, and levels of low-density lipoproteins ("bad cholesterol") were increased in

these men. These negative effects on cholesterol may have contributed to the lymphocyte and polymorphonuclear leukocyte abnormalities in this small investigation. Zinc supplements in large doses may also decrease antioxidant defense pathways that may be vital to cancer or other disease prevention *(189)*. Animal studies have also found that zinc may inhibit the cancer-protective ability related to selenium ingestion *(190)*.

There is minimal evidence that zinc supplements can impact ED. Several previous studies have tested zinc supplements on sexual function, but these mostly included men on kidney dialysis. Some studies demonstrated a benefit, while in the other studies no benefits were found *(191,192)*. Patients on dialysis may have a zinc deficiency with hyperprolactinemia and consuming supplemental zinc may correct this deficiency and produce greater levels of male hormone *(175,193)*. However, these investigations cannot provide a proper assessment of what role, if any, zinc has in general ED treatment. Clinicians should explain to patients that the evidence is not available and taking zinc supplements can result in numerous adverse effects.

It is disconcerting that many of the popular alternative medicine books seem to promote the use of zinc supplements for "prostate health" or "sexual health" with very little data to support or refute this thought. Recent and past research not only challenges this thought, but it seriously questions larger intake of zinc supplements and perhaps dietary zinc. More research is required in this area. Currently, health professionals should express to patients concerned with prostate disease, ED, and other conditions that with few exceptions, the potential for zinc supplements to promote a serious adverse consequence is plausible. Zinc in many multivitamins seems to be adequate, especially when the RDA level is generally contained in the supplement, but larger intakes of individual zinc supplements ($\geq$100 mg/d, for example) should be absolutely discouraged until adequate research resolves this controversial issue.

Other OTC Dietary Supplements: Looking Into the Present and Future

Numerous dietary supplements have limited clinical data, so it is currently difficult to evaluate their effect on any form of ED. For example, *Avena sativa* is another name for wild oats, oat bran, or oatstraw. It has the ability to reduce cholesterol and possibly blood pressure *(194–197)*. Several dietary supplements for ED tend to contain some concentrations of Avena sativa, perhaps with the thought that reducing cholesterol levels/blood pressure or altering the male hormone milieu may impact ED favorably. No specific trials of Avena sativa and ED have been published to date. Outside of a potential cardiovascular benefit, no comment can be made

with regard to its efficacy. Numerous other OTC soluble fiber products *(198–200)*, also with some limited cholesterol-lowering ability, such as psyllium, pectin, guar gum, and locust bean gum, may make up a portion of some ED supplements, again with the thought that cholesterol reduction could lead to enhanced erectile function. However, no clinical trials have used these specific compounds for ED. Other potential cholesterol-lowering products or supplements, such as soy, may be found in some supplements, but the minimal-to-moderate ability, along with other OTC products mentioned above, to decrease cholesterol remains controversial *(201–203)*. It seems that any product that can impact cholesterol (or weight) has the potential to become a part of some herbal blend for ED in the future, and the limitations of this marketing decision without appropriate clinical trials should always be discussed with patients inquiring about these agents.

Tribulus terrestris is a plant that grows in numerous countries around the world. It contains many unique compounds that have steroid-like or steroid saponin activity *(204–206)*. A compound called *protodioscin* can be extracted from some of these plants under the appropriate conditions and can apparently be transformed into the compound DHEA *(207)*. Some initial laboratory investigations have found some activity with this compound for potentially improving erectile function *(208,209)*, but this plant supplement has failed, at least in initial studies, to change body composition, enhance exercise, or impact testosterone levels in young men, but it has demonstrated an ability to increase levels of andro and/or estradiol at least when combined with other DHEA-like products *(98,210)*. It seems plausible that somewhat similar results could be expected as have been observed with andro/DHEA in the past, but specific and adequate clinical trials addressing their individual impact or other unique effects on hormonal levels in hypogonadal men and/or those with ED have not been published to date.

Other ED supplements, such as damiana (*Turnera diffusa*) combined with numerous other herbals, vitamins, and minerals, or other plants and their extracts, have demonstrated some initial promising results in women and men *(211,212)*, but larger randomized trials are required to confirm this efficacy and to determine its safety profile and any potential mechanisms of action.

COMBINING PRESCRIPTION DRUGS AND SUPPLEMENTS THROUGH ADEQUATE CLINICAL RESEARCH—THE NEW FRONTIER?

Perhaps one of the most fascinating and exciting potential uses of dietary supplements for ED may be the potential for some agents to

enhance some of the available prescription agents for ED In other words, the potential for a synergistic affect exists from some early preliminary research. Recent animal studies have suggested that diabetic rats given a combination of sildenafil and vitamin demonstrated lower activities of phosphodiesterase-5 activity compared with those rats given sildenafil alone *(213)*. Thus, the potential for an antioxidant to enhance the response of sidenafil in diabetic men seems at least plausible, but clinical studies are needed. In addition, a recent small study of men with ED as a result of etiologies not mentioned that did not respond to sildenafil, were instructed to take 800 International Units and 5 mg of folic acid daily along with 50 to 100 mg of sildenafil when necessary *(214)*. The response to this therapy was evaluated at a 6 to 12 wk interval. A total of 124 sildenafil nonresponders were included in this study. The mean age of the participants was 57.2 yr. Researchers found that 59 (89.4%) of these men chose this combined regimen and three chose sildenafil only. Interestingly, a total of 36 (61%) men had a partial or complete response to this regimen, with 32 men (88.9%) reporting excellent/satisfactory results. A total of 17 men (28.8%) reported a poor response, four men (6.8%) reported a moderate response, and six men (10.2%) did not use the dietary supplement regimen or sildenafil. Among men that did not respond to the supplement regimen with sildenafil, a total of eight men responded to further treatments, such as intracaversonal injection (six men), testosterone (one man), and a penile implant (one man). An impressive 84.7% of the original nonresponders were actually salvaged using the dietary supplement and/or salvage treatments. No side effects were found or reported in the vitamin E and folic acid group. A placebo-controlled trial is needed, but the potential for these dietary supplements to enhance the response to a conventional drug does seem intriguing. In fact, a recent cardiovascular study of patients postangioplasty found that individuals taking a supplement that included 1 mg/d of folic acid, 400 mcg/d of B12, and 10 mg/d of B6 compared to placebo had a lower risk of another procedure, fewer deaths, and nonfatal myocardial infarctions after 1 yr of study *(215)*. Thus, the potential for antioxidants to improve vessel patency exists, which can be indirectly translated to studies of men with ED that have at least a vasculogenic etiology. Other potential combinations of supplements and drugs, such as L-arginine and yohimbine, also demonstrated some efficacy for ED patients in a smaller trial *(216)*, but more studies utilizing these supplements and many others are needed because other unique combinations of supplements alone have not necessarily provided a benefit in some trials *(217)*. Regardless, minimal research has been completed in this area and more definite answers will only be achieved through adequate research.

CONCLUSIONS

It seems naïve to steadfastly believe that some plants/herbs do not contain specific compounds that could benefit ED. However, many supplements have not been investigated in a laboratory or clinical research setting prior to commercial sale, and this will generally set up a large and potentially complex situation. If efficacy is demonstrated or not demonstrated through adequate research, then this benefit or lack of benefit cannot be advertised or mentioned on the label. Also, the public and clinicians cannot be made acutely aware of which compounds or supplements are indeed effective if no general standards for sale currently exist under the present guidelines. Dietary supplements have received and enjoyed a tremendous amount of publicity. The large and growing market that exists for ED treatment seems to have been the partial impetus for numerous supplements to advertise and promote apparent benefits with their product(s). Whether or not many of these dietary supplements have merit is currently questionable. Some supplements may actually provide the opposite result of what is touted in advertising. Other supplements may be enjoying the overall benefits of the placebo effect. Because a general placebo response of 25 to 50% has been recorded in past clinical trials with effective agents, it is not difficult to understand why some supplements continue to enjoy tremendous financial success despite the limited research espousing their actual use. In other words, if 1 to 2 out of four individuals or one of every three individuals who try a dietary supplement actually derive some benefit for their ED, the market for these supplements will still remain extraordinary. On a larger scale this means that of 100,000 men who try a supplement, approx 25,000 to 50,000 will claim some success with any particular agent in question. The challenge for clinicians is to properly discuss the placebo response and the need for good research before any intervention, especially when supplements can be advocated for general public use. Table 3 provides a summary of some of the more popular ED supplements and some general conclusions that can be derived from past clinical investigations.

There seems to be little doubt that at least some dietary supplements may, in the near future, have some active ingredient or impact those with certain types of ED in a favorable manner. Another novel and exciting future area of dietary supplement research is the ability of certain agents to have a synergistic effect with prescription agents for ED, thereby improving the response rates in men that have initially failed approved ED therapy, especially with oral agents. Regardless, randomized clinical trials are still the most direct route of determining which specific dietary supplements will or will not become a part of conventional medicine. Therefore, more randomized trials for dietary supplements are desperately needed,

Table 3
A Summary of Alternative Therapies and Commercially Available ED Supplements (From A–Z)

ED alternative/supplement	*Overall evidence*
Acupuncture	Psychogenic ED. Needs a randomized trial.
Androstenedione/DHEA	Increases estradiol and possibly testosterone in men with normal testosterone levels, and lowers HDL by an average of 10%. May increase testosterone dramatically in hypogonadal men. May provide a benefit for nonorganic ED and others in men with suboptimal levels of these precursors only.
Ginkgo biloba	May have a blood thinning effect (be careful). Lacks any benefit thus far in a small number of studies with men with ED.
Korean red ginseng (Panax ginseng)	Three preliminary trials suggest a potential benefit for men with ED. However, quality control is a serious issue with this supplement and more randomized trials are needed.
L-Arginine	A precursor to nitric oxide (NO). High doses may benefit a minority of men that secrete low levels of NO. May lower blood pressure. Needs more randomized trials.
Yohimbine	Supplements probably contain little to no yohimbine. Prescription form is best and may benefit some with psychogenic ED. Can cause serious side effects.
Zinc	May benefit only those with a severe zinc deficiency. Otherwise there is a lack of data, and high dosages can be dangerous and immunosuppresive.
Other Supplements	Avena sativa and other potential cholesterol and blood pressure reducers, and *Tribulus terrestris* (precursor to DHEA?) needs clinical trials. A recent study of a Chinese herbal combination demonstrated no impact on sexual function vs placebo.
Antioxidants in combination with orally approved FDA medications	Folic acid + vitamin E may enhance the response to sildenafil in men that failed to initially respond to sildenafil. Other oral drugs + a variety of other supplements, e.g., yohimbine and arginine, may enhance erectile response. Large placebo-controlled trials are needed in this area to support or refute these recent observations.

DHEA, dehydroepiandrosterone; ED, erectile dysfunction; FDA, Food and Drug Administratiomn; HDL, high-density lipoprotein.

which means that more money or funding needs to be made available for ED studies that are testing alternative agents so that they may at least have the opportunity to become a part of the mainstream milieu. Indeed, the next few years of research should bring enormous excitement and objectivity to this area of medicine.

REFERENCES

1. Anderson JW. (2003) Diet first, then medication for hypercholesterolemia. JAMA 290:531–533.
2. Ernst ND, Cleeman JI. (2002) National cholesterol education program keeps a priority on lifestyle modification to decrease cardiovascular disease risk. Curr Opin Lipidol 13:69–73.
3. Lue TF. (2000) Erectile dysfunction. N Engl J Med 342:1802–1813.
4. Feldman HA, Johannes CB, Derby CA, et al. (2000) Erectile dysfunction and cardiovascular risk: prospective results from the Massachusetts Male Aging Study. Prev Med 30:328–338.
5. Michal V. (1982) Arterial disease as a cause of impotence. Clin Endocrinol Metab 11:725–748.
6. Agarwal A, Jain DC. (1989) Male sexual dysfunction after stroke. J Assoc Physicians India 37:505–507.
7. Derby CA, Mohr BA, Goldstein I, et al. (2000) Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 56:302–306.
8. Levine SB. (2003) Erectile dysfunction: why drug therapy isn't always enough. Cleve Clin J 70:241–246.
9. Nash IS, Mosca L, Blumenthal RS, et al. (2003) Contemporary awareness and understanding of cholesterol as a risk factor. Results of an American Heart Association National Survey. Arch Intern Med 163:1597–1600.
10. Navas-Nacher EL, Colangelo L, Beam C, Greenland P. (2001) Risk factors for coronary heart disease in men 18 to 39 years of age. Ann Intern Med 134:433–439.
11. Stamler J, Daviglus ML, Garside DB, et al. (2000) Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. JAMA 284:311–318.
12. Feldman HA, Goldstein I, Hatzichristou DG, et al. (1994) Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 151:54–61.
13. Johannes CB, Araujo AB, Feldman HA, et al. (2000) Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study. J Urol 163:460–463.
14. Bacon CG, Mittleman MA, Kawachi I, et al. (2003) Sexual function in men older than 50 years of age: results from the Health Professionals Follow-up Study. Ann Intern Med 139:161–168.
15. Solomon H, Man JW, Wierzbicki AS, Jackson G. (2003) Relation of erectile dysfunction to angiographic coronary artery disease. Am J Cardiol 91:230–231.
16. Walczak MK, Lokhandwala N, Hodge MB, Guay AT. (2002) Prevalence of cardiovascular risk factors in erectile dysfunction. J Gend Specif Med 5:19–24.
17. Kongkanand A. (2003) Prevalence of erectile dysfunction in Thailand. Thai Erectile Dysfunction Epidemiological Study Group. Int J Androl 23(Suppl 2):77–80.
18. Chung WS, Sohn JH, Park YY. (1999) Is obesity an underlying factor in erectile dysfunction? Eur Urol 36:68–70.

19. Al Helali NS, Abolfotouh MA, Ghanem HM. (2001) Pattern of erectile dysfunction in Jeddah city. Saudi Med J 22:34–38.
20. Aydin S, Unal D, Erol H, et al. (2001) Multicentral clinical evaluation of the aetiology of erectile dysfunction: a survey report. Int Urol Nephrol 32:699–703.
21. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, Rodriguez-Vela L, Jimenez-Cruz JF, Burgos-Rodriguez R. (2001) Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfunction Erectil Masculina Study. J Urol 166:569–574.
22. Vaaler S, Lovkvist H, Svendsen KO, Furuseth K. (2001) Erectile dysfunction among Norwegian men over 40 years of age. Tidsskr Nor Laegeforen 121:28–32.
23. Mak R., De Backer G, Kornitzer M, De Meyer JM. (2002) Prevalence and correlates of erectile dysfunction in a population-based study in Belgium. Eur Urol 41:132–138.
24. Blanker MH, Bohnen AM, Groeneveld FP, et al. (2001) Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. J Am Geriatr Soc 49:436–442.
25. Moreira ED Jr., Bestane WJ, Bartolo EB, Fittipaldi JA. (2002) Prevalence and determinants of erectile dysfunction in Santos, southeastern Brazil. Sao Paulo Med J 120:49–54.
26. Nicolosi A, Moreira ED Jr., Shirai M, Bin Mohd Tambi MI, Glasser DB. (2003) Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology 61:201–206.
27. Kolodny L. (2003) Erectile function and vascular disease: What is the connection? Postgrad Med 114:30–40.
28. Eisenberg DM, Davis RB, Ettner SL, et al. (1998) Trends in alternative medicine use in the United States, 1990-1997. JAMA 280:1569–1575.
29. Crocetti E, Crotti N, Feltrin A, et al. (1998) The use of complementary therapies by breast cancer patients attending conventional treatment. Eur J Cancer 34:324–328.
30. MacLennan AH, Wilson DH, Taylor AW. (1996) Prevalence and cost of alternative medicine in Australia. Lancet 347:569–573.
31. Blendon RJ, DesRoches CM, Benson JM, et al. (2001) Americans' views on the use and regulation of dietary supplements. Arch Int Med 161:805–810.
32. Yesalis CE. (1999) Medical, legal, and societal implications of androstenedione use. JAMA 281:2043–2044.
33. Morris CA, Avorn J. (2003) Internet marketing of herbal products. JAMA 290:1505–1509.
34. DeAngelis CD, Fontanarosa PB. (2003) Drugs alias dietary supplements. JAMA 290:1519–1520.
35. Anderson JW, Johnstone BM, Cook-Newell ME. (1995) Meta-analysis of the effects of soy protein intake on serum lipids. New Engl J Med 333:276–282.
36. Moyad MA. (2002) Rules to follow before advising patients on dietary supplements/alternative medicine: part I. Urol Nurs 22:99–110.
37. Harkey MR, Henderson GL, Gershwin ME, et al. (2001) Variability in commercial ginseng products: an analysis of 25 preparations. Am J Clin Nutr 73:1101–1106.
38. Parasrampuria J, Schwartz K, Petesch R. (1998) Quality control of dehydroepiandrosterone dietary supplement products. JAMA 280:1565.
39. Silverman E. (2000) Herbal sex pills thrive on fantasy more than fact. Newark, NJ: *The Star-Ledger*, January 30.
40. Sharlip I. (2001) Report on "herbal sex pills thrive on fantasy more than fact." International Society for Sexual and Impotence Research Newsbulletin, Summer:17.

41. Markowitz JS, Donovan JL, DeVane CL, et al. (2003) Effect of St. John's Wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA 290:1500–1504.
42. Ang-Lee MK, Moss J, Yuan C-S. (2001) Herbal medicines and perioperative care. JAMA 286:208–216.
43. Carnes CA, Chung MK, Nakayama T, et al. (2001) Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. Circ Res 89:E32–E38.
44. Korantzopoulos P, Kolettis T, Siogas K, Goudevenos J. (2003) Atrial fibrillation and electrical remodeling: the potential role of inflammation and oxidative stress. Med Sci Monit 9:RA225–RA229.
45. Byers T. (1999) What can randomized controlled trials tell us about nutrition and cancer prevention? CA Cancer J Clin 49:353–361.
46. Pepper OHP. (1945) A note on placebo. Ann J Pharm 117:409–412.
47. Beecher HK. (1955) The powerful placebo. JAMA 159:1602–1606.
48. Turner JA, Deyo RA, Loeser JD, et al. (1994) The importance of placebo effects in pain treatment and research. JAMA 271:1609–1614.
49. Hrobjartsson A, Gotzsche PC. (2001) Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 344:1594–1602.
50. Knopp RH. (1999) Drug treatment of lipid disorders. N Engl J Med 341:498–511.
51. Shepherd J, Cobbe SM, Ford I, et al. (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 333:1301–1307.
52. Schrott H, Fereshetian AG, Knopp RH, et al. (1998) A multicenter, placebo-controlled, dose-ranging study of atorvastatin. J Cardiovasc Pharmacol Ther 3: 119–124.
53. Gentile S, Turco S, Guarino G, et al. (2000) Comparative efficacy study of atorvastatin vs. simvastatin, pravastatin, lovastatin and placebo in type 2 diabetic patients with hypercholesterolaemia. Diabetes Obes Metab 2:355–362.
54. Ravin P, Bidstrup M, Wasnich RD, et al. (1999) Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study. A randomized, controlled trial. Ann Int Med 131:935–942.
55. McClellan KJ, Markham A. (1999) Finasteride: a review of its use in male pattern hair loss. Drugs 57:111–126.
56. Whiting DA, Jacobsen C. (1992) Treatment of female androgenetic alopecia with minoxidil 2%. Int J Derm 31:800–804.
57. NIH Consensus Development Panel on Impotence. (1993) NIH Consensus Conference: impotence. JAMA 270:83–90.
58. Benet AE, Melman A. (1995) The epidemiology of erectile dysfunction. Urol Clin N Am 22:699–709.
59. Goldstein I, Lue TF, Padma-Nathan H, et al. (1998) Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 338:1397–1404.
60. Meuleman E, Cuzin B, Opsomer RJ, et al. (2001) A dose-escalation study to assess the efficacy and safety of sildenafil citrate in men with erectile dysfunction. BJU Intl 87:75–81.
61. Montorsi F, McDermott TE, Morgan R, et al. Efficacy and safety of fixed-dose oral sildenafil in the treatment of erectile dysfunction of various etiologies. Urology 1999;53:1011–1018.
62. Dula E, Buttler S, Perdok R, Agre K. (2000) Efficacy and safety of apomorphine SL vs placebo for erectile dysfunction in patients with coronary artery disease. J Urol 163:200 (abstract no. 889).

63. Moyad MA. (2002) The placebo effect and randomized trials: analysis of conventional medicine. Urol Clin N Amer 29:125–133, ix–x, Review.
64. Moyad MA. (2002) The placebo effect and randomized trials: analysis of alternative medicine. Urol Clin N Amer 29:135–155, x, Review.
65. Moyad MA. (2003) The ABCs of nutrition and supplements for prostate cancer. Ann Arbor, MI: JW Edwards Publishing.
66. Shifren JL, Braunstein GD, Simon JA, et al. (2000) Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 343:682–688.
67. Guzick DS, Hoeger K. (2000) Sex, hormones, and hysterectomies. N Engl J Med 343:730–731.
68. Ernst E. (2001) A primer of complementary and alternative medicine commonly used by cancer patients. Med J Australia 174:88–92.
69. Avants SK, Margolin A, Holford TR, Kosten TR. (2000) A randomized controlled trial of auricular acupuncture for cocaine dependence. Arch Intern Med 160:2305–2312.
70. Moyad MA, Hathaway S, Ni H-S. (1999) Traditional Chinese Medicine, acupuncture, and other alternative medicines for prostate cancer: an introduction and the need for more research. Semin Urol Oncol 17:103–110.
71. NIH Consensus Development Panel on Acupuncture. (1998) Acupuncture. JAMA 280:1518–1524.
72. Morey SS. (1998) NIH issues consensus statement on acupuncture. Am Fam Phys 57:2545–2546.
73. Yamashita H, Tsukayama H, Tanno Y, et al. (1998) Adverse effects related to acupuncture. JAMA 280:1563–1564.
74. Norheim AJ, Fonnebo V. (1995) Adverse effects of acupuncture. Lancet 345:1576.
75. Rosted P. (1998) The use of acupuncture in dentistry: a review of the scientific validity of published papers. Oral Dis 4:100–104.
76. Peacher WG. (1975) Adverse reactions, contraindications, and complications of acupuncture and moxibustion. Am J Chin Med 3:35–46.
77. Engelhardt PF, Daha K, Zils T, Pfluger H. (2000) Acupuncture in the treatment of erectile dysfunction: first results of a placebo controlled prospective study. J Urol 163:203 (abstract no. 902).
78. Hammar M, Frisk J, Grimas O, et al. (1999) Acupuncture treatment of vasomotor symptoms in men with prostatic carcinoma: a pilot study. J Urol 161:853–856.
79. Kronenberg F, Fugh-Berman A. (2002) Complementary and alternative medicine for menopausal symptoms: a review of randomized controlled trials. Ann Intern Med 137:805–813.
80. Quella SK, Loprinzi CL, Barton DL, et al. (2000) Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: a North Central Cancer Treatment Group Trial. J Clin Oncol 18:1068–1074.
81. Barton DL, Loprinzi CL, Quella SK, et al. (1998) Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. J Clin Oncol 16:495–500.
82. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. (2003) Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study. A randomized controlled trial. JAMA 290:207–214.
83. Johnstone PAS, Bloom TL, Niemtzow RC, et al. (2003) A prospective, randomized pilot trial of acupuncture of the kidney-bladder distinct meridian for lower urinary tract symptoms. J Urol 169:1037–1039.

84. Saenz de Tejada I, Goldstein I, Azadzoi K, et al. (1989) Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med 320:1025–1030.
85. Ignarro LJ, Bush PA, Buga GM, et al. (1990) Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem Biophys Res Commun 170:843–850.
86. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. (2002) Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA 288:2554–2560.
87. Oomen CM, van Erk MJ, Feskens EJ, et al. (2000) Arginine intake and risk of coronary heart disease mortality in elderly men. Arterioscler Thromb Vasc Biol 20:2134–2139.
88. Zorgniotti AW, Lizza AF. (1994) Effect of large doses of nitric oxide precursor L-arginine, on erectile dysfunction. Int J Impot Res 6:33–35.
89. Klotz T, Mathers MJ, Braun M, et al. (1999) Effectiveness of oral L-arginine in the first-line treatment of erectile dysfunction in a controlled crossover study. Urol Int 63:220–223.
90. Chen J, Wollman Y, Chernichovsky T, et al. (1999) Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study. BJU Int 83: 269–273.
91. Likos A, Mariotti F, Brown PH, West, SG. (2003) Oral l-arginine reduces blood pressure, cardiac output, and homocysteine levels in men with high cholesterol. Circulation 108:iv–784 (abstract no. 3538).
92. Dhatariya KK, Nair KS. (2003) Dehydroepiandrosterone: is there a role for replacement? Mayo Clin Proc 78:1257–1273.
93. Kuipers H, Wijnen JAG, Hartgens F, Willems SMM. (1991) Influence of anabolic steroids on body composition, blood pressure, lipid profile and liver functions in body builders. Int J Sports Med 12:413–418.
94. Bhasin S, Storer TW, Berman N, et al. (1996) The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 335:1–7.
95. Horton R, Tait JF. (1966) Androstenedione production and interconversion rates measured in peripheral blood and studies on the possible site of its conversion to testosterone. J Clin Invest 45:301–313.
96. King DS, Sharp RL, Vukovich MD, et al. (1999) Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men. A randomized controlled trial. JAMA 281:2020–2028.
97. Ballantyne CS, Phillips SM, MacDonald JR, et al. (2000) The acute effects of androstenedione supplementation in healthy young males. Can J Appl Physiol 25: 68–78.
98. Brown GA, Vukovich MD, Reifenrath TA, et al. (2000) Effects of anabolic precursors on serum testosterone concentrations and adaptations to resistance training in young men. Int J Sport Nutr Exerc Metab 10:340–359.
99. Leder BZ, Longcope C, Catlin DH, et al. (2000) Oral androstenedione administration and serum testosterone concentrations in young men. JAMA 283:779–782.
100. Rasmussen BB, Volpi E, Gore DC, Wolfe RR. (2000) Androstenedione does not stimulate muscle protein anabolism in young healthy men. J Clin Endocrinol Metab 85:55–59.
101. Brown GA, Vukovich MD, Martini ER, et al. (2000) Endocrine responses to chronic androstenedione intake in 30- to 56-year-old men. J Clin Endocrinol Metab 85: 4074–4080.

102. Wallace MB, Lim J, Cutler A, Bucci L. (1999) Effects of dehydroepiandrosterone vs androstenedione supplementation in men. Med Sci Sports Exerc 31:1788–1792.
103. Stevenson JC. (1996) Mechanisms whereby oestrogens influence arterial health. Eur J Obstet Gynecol Reprod Biol 65:39–42.
104. Phillips GB, Pinkernell BH, Jing TY. (1996) The association of hyperestrogenemia with coronary thrombosis in men. Arterioscler Thromb Vasc Biol 16: 1383–1387.
105. Berkovitz GD, Guerami A, Brown TR, et al. (1985) Familial gynecomastia with increased extraglandular aromatization of plasma carbon 19-steroids. J Clin Invest 75:1763–1769.
106. Fyssas I, Syrigos KN, Konstandoulakis MM, et al. (1997) Sex hormone levels in the serum of patients with pancreatic adenocarcinoma. Horm Metab Res 29:115–118.
107. Gordon DJ, Probstfield JL, Garrison RJ, et al. (1989) High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. Circulation 79:8–15.
108. Leder BZ, Leblanc KM, Longcope C, et al. (2002) Effects of oral androstenedione administration on serum testosterone and estradiol levels in postmenopausal women. J Clin Endocrinol Metab 87:5449–5454.
109. Gruenewald DA, Matsumoto AM. (2003) Testosterone supplementation therapy for older men: potential benefits and risks. J Am Geriatr Soc 51:101–115.
110. Araghiniknam M, Chung S, Nelson-White T, et al. (1996) Antioxidant activity of dioscorea and dehydroepiandrosterone (DHEA) in older humans. Life Sci 59:147–157.
111. Genazzani AD, Stomati M, Strucchi C, et al. (2001) Oral dehydroepiandrosterone supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women. Fertil Steril 76:241–248.
112. Stomati M, Monteleone P, Casarosa E, et al. (2000) Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. Gynecol Endocrinol 14:342–363.
113. Morales AJ, Haubrich RH, Hwang JY, et al. (1998) The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. Clin Endocrinol 49:421–432.
114. Morales AJ, Nolan JJ, Nelson JC, Yen SSC. (1994) Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab 78:1360–1367.
115. Mortola JF, Yen SSC. (1990) The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. J Clin Endocrinol Metab 71:696–704.
116. Young J, Couzinet B, Nahoul K, et al. (1997) Panhypopituitarism as a model to study the metabolism of dehydroepiandrosterone (DHEA) in humans. J Clin Endocrinol Metab 82:2578–2585.
117. Arlt W, Haas J, Callies F, et al. (1999) Biotransformation of oral dehydroepiandrosterone in elderly men: significant increase in circulating estrogens. J Clin Endocrinol Metab 84:2170–2176.
118. Jones JA, Nguyen A, Straub M, et al. (1997) Use of DHEA in a patient with advanced prostate cancer: a case report and review. Urology 50:784–788.
119. Goldberg M. (1998) Dehydroepiandrosterone, insulin-like growth factor-I, and prostate cancer. Ann Intern Med 129:587–588.

120. Reiter WJ, Pycha A, Schatzi G, et al. (1999) Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study. Urology 53:590–595.
121. Reiter WJ, Schatzl G, Mark I, et al. (2001) Dehydroepiandrosterone in the treatment of erectile dysfunction in patients with different organic etiologies. Urol Res 29: 278–281.
122. Feldman HA, Goldstein I, Hatzichristou DG, et al. (1994) Impotence and its medical and psychological correlates: results of the Massachusetts Male Aging Study. J Urol 151:54–61.
123. Kleijnen J, Knipschild P. (1992) Ginkgo biloba. Lancet 340:1136–1139.
124. Mashour NH, Lin GI, Frishman WH. (1998) Herbal medicine for the treatment of cardiovascular disease: clinical considerations. Arch Intern Med 158:2225–2234.
125. Le Bars PL, Katz MM, Berman N, et al. (1997) A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. JAMA 278:1327–1332.
126. Sikora R, Sohn MH, Deutz F-J, et al. (1989) Ginkgo biloba extract in the therapy of erectile dysfunction. J Urol 141:188A (abstract no. 73).
127. Sikora R, Sohn MH, Engelke B, et al. (1998) Randomized placebo-controlled study on the effects of oral treatment with Ginkgo biloba extract in patients with erectile dysfunction. J Urol 159:240A(abstract no. 917).
128. Rowin J, Lewis SL.(1996) Spontaneous bilateral subdural hematoma associated with chronic Ginkgo biloba ingestion. Neurology 46:1775–1776.
129. Rosenblatt M, Mindel J. (1997) Spontaneous hyphema associated with ingestion of Ginkgo biloba extract. N Engl J Med 336:1108.
130. Fong KC, Kinnear PE. (2003) Retrobulbar haemorrhage associated with chronic Ginkgo biloba ingestion. Postgrad Med J 79:531–532.
131. Wong AH, Smith M, Boon HS. (1998) Herbal remedies in psychiatric practice. Arch Gen Psychiatry 55:1033–1044.
132. Cohen AJ, Bartlik B. (1998) Ginkgo biloba for antidepressant-induced sexual dysfunction. J Sex Marital Ther 24:139–143.
133. Balon R. (1999) Ginkgo biloba for antidepressant-induced sexual dysfunction? J Sex Marital Ther 25:1–2.
134. Kang BJ, Lee SJ, Kim MD, Cho MJ. (2002) A placebo-controlled, double-blind trial of Ginkgo biloba for antidepressant-induced sexual dysfunction. Hum Psychopharmacol 17:279–284.
135. Solomon PR, Adams F, Silver A, et al. (2002) Ginkgo for memory enhancement: a randomized controlled trial. JAMA 288:835–840.
136. Coon JT, Ernst E. (2002) Panax ginseng: a systematic review of adverse effects and drug interactions. Drug Safety 25:323–344.
137. Cho YK, Sung H, Lee HJ, et al. (2001) Long-term intake of Korean red ginseng in HIV-1-infected patients: development of resistance mutation to zidovudine is delayed. Int Immunopharmacol 1:1295–1305.
138. Tode T, Kikuchi Y, Hirata J, et al. (1999) Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int J Gynaecol Obstet 67:169–174.
139. Wiklund IK, Mattson LA, Lindgren R, Limoni C. (1999) Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group. Int J Clin Pharmacol Res 19:89–99.
140. Park JD, Lee YH, Kim SI. (1998) Ginsenoside Rf2, a new dammarane glycoside from Korean red ginseng (Panax ginseng). Arch Pharm Res 21:615–617.

141. Yun Y, Do J, Ko S, et al. (2001) Effects of Korean red ginseng and its mixed prescription on the high molecular weight dextran-induced blood stasis in rats and human platelet aggregation. J Ethnopharmacol 77:259–264.
142. Sung J, Han KH, Zo JH, et al. (2000) Effects of red ginseng upon vascular endothelial function in patients with essential hypertension. Am J Chin Med 28:205–216.
143. Choi YD, Xin ZC, Choi HK. (1998) Effect of Korean red ginseng on the rabbit corpus cavernosal smooth muscle. Int J Impot Res 10:37–43.
144. Choi YD, Rha KH, Choi HK. (1999) In vitro and in vivo experimental effect of Korean red ginseng on erection. J Urol 162:1508–1511.
145. Choi HK, Seong DH, Rha KH. (1995) Clinical efficacy of Korean red ginseng for erectile dysfunction. Int J Impot Res 7:181–186.
146. Hong B, JI YH, Hong JH, et al. (2002) A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report. J Urol 168:2070–2073.
147. Chen X, Lee TJ. (1995) Ginsenosides-induced nitric oxide-mediated relaxation of the rabbit corpus cavernosum. Br J Pharmacol 115:15–18.
148. Tsang D, Yeung HW, Tso WW, Peck H. (1985) Ginseng saponins: influence on neurotransmitter uptake in rat brain synaptosomes. Planta Med 3:221–224.
149. Price A, Gazewood J. (2003) Korean red ginseng effective for treatment of erectile dysfunction. J Fam Practice 52:20–21.
150. Andrade EM, Messina LE, Alarcon G, et al. (2003) Korean red ginseng in the treatment of erectile dysfunction: a prospective controlled double-blind clinical trial. J Urol 169(Suppl 4):380 (abstract no. 1419).
151. Goldberg MR, Robertson D. (1983) Yohimbine, a pharmacological probe for the study of the alpha2-adrenoreceptor. Pharmacol Rev 35:143–180.
152. Ernst E, Pittler MH. (1998) Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. J Urol 159:433–436.
153. Foster S, Tyler VE. (2000) Tyler's Honest Herbal, 4th Ed., New York, NY: The Haworth Herbal Press, pp. 393–395.
154. Briefel RR, Bialostosky K, Kennedy-Stephenson J, McDowell MA, Ervin RB, Wright JD. (2000) Zinc intake of the U.S. population: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Nutr 130 (5Suppl):1367S–1373S.
155. Food and Nutrition Board, National Academy of Sciences. (2001) Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington DC: National Academy Press, pp. 177–204, 351–398.
156. Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. (2003) Zinc supplement use and risk of prostate cancer. J Natl Cancer Inst 95: 1004–1007.
157. Ishii K, Usui S, Sugimura Y, Yamamoto H, Yoshikawa K, Hirano, K. (2001) Inhibition of aminopeptidase N (AP-N) and urokinase-type plasminogen activator (uPA) by zinc suppresses the invasion activity in human urological cancer cells. Biol Pharmacol Bull 24:226–230.
158. Ishii K, Usui S, Sugimura Y, et al. (2001) Aminopeptidase N regulated by zinc in human prostate participates in tumor cell invasion. Int J Cancer 92:49–64.
159. Iguchi K, Hamatake M, Ishida R, et al. (1998) Induction of necrosis by zinc in prostate carcinoma cells and identification of proteins increased in association with this induction. Eur J Biochem 253:766–770.
160. Feng P, Liang JY, Li TL, et al. (2000) Zinc induces mitochondria apoptogenesis in prostate cells. Mol Urol 4:31–36.

161. Liang JY, Liu YY, Zou J, Franklin RB, Costello LC, Feng P. (1999) Inhibitory effect of zinc on human prostatic carcinoma cell growth. Prostate 40:200–207.
162. Zaichick V, Sviridova TV, Zaichick SV. (1997) Zinc in the human prostate gland: normal, hyperplastic and cancerous. Int Urol Nephrol 29:565–574.
163. Nemoto K, Kondo Y, Himeno S, et al. (2000) Modulation of telomerase activity by zinc in human prostatic and renal cancer cells. Biochem Pharmacol 59:401–405.
164. Sommerfeld HJ, Meeker AK, Piatyszek MA, Bova GS, Shay JW, Coffey DS. (1996) Telomerase activity: a prevalent marker of maliginant human prostate tissue. Cancer Res 56:218–222.
165. Boissier S, Ferreras M, Peyruchaud O, et al. (2000) Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. Cancer Res 60:2949–2954.
166. Hidalgo M, Eckhardt SG. (2001) Development of matrix metalloproteinase inhibitors in cancer therapy. J Natl Cancer Inst 93:178–193.
167. Dearnaley DP, Sydes MR, Mason MD, et al. (2003) A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). J Natl Cancer Inst 95:1300–1311.
168. Saad F, Gleason DM, Murray R, et al. (2002) For the Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 94:1458–1468.
169. Holmes MD, Pollak MN, Willett WC, Hankinson SE. (2002) Dietary correlates of plasma insulin-like growth factor-1 and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomark Prevent 11:852–861.
170. Prasad AS, Mantzoros CS, Beck FW, Hess JW, Brewer GJ. (1996) Zinc status and serum testosterone levels of healthy adults. Nutrition 12:344–348.
171. Lagiou P, Wuu J, Trichopoulou A, Hsieh C-C, Adami H-O, Trichopoulos D. (1999) Diet and benign prostatic hyperplasia: a study in Greece. Urology 54:284–290.
172. Dunzendorfer U, Drahovsky D. (1980) C-peptide, testosterone, estrogen, cortisol and zinc in patients with benign prostatic hyperplasia of the prostate. Urol Int 35:369–374.
173. Wilden EG, Robinson MR. (1975) Plasma zinc levels in prostatic disease. Brit J Urol 47:295–299.
174. Tisell LE, Fjelkegard B, Liessner KH. (1982) Zinc concentration and content of the dorsal, lateral and medial prostatic lobes and of periurethral adenomas in man. J Urol 128:403–405.
175. Leake A, Chrisholm GD, Busuttil A, et al. (1984) Subcellular distribution of zinc in the benign and malignant human prostate: evidence for a direct zinc androgen interaction. Acta Endocrinology (Copenh) 105:281–288.
176. Feustel A, Wenrich R. (1984) Zinc and cadmium in cell fractions of prostatic cancer tissues of different histological grading in comparison to BPH and normal prostate. Urol Res 12:147–150.
177. Lahtonen R. (1985) Zinc and cadmium concentrations in whole tissue and in separated epithelium and stroma from human bengin hypertrophic glands. Prostate 6:177–183.
178. Brys M, Nawrocka AD, Miekos E, et al. (1997) Zinc and cadmium analysis in human prostate neoplasms. Biol Trace Elem Res 59:145–152.
179. Leake A, Chrisholm GD, Habib FK. (1984) The effect of zinc on the 5 alpha-reduction of testosterone by the hyperplastic human prostate gland. J Steroid Biochem 20:651–655.
180. Prasad AS, Fitzgerald JT, Bao B, Beck FW, Chandrasekar PH. (2000) Duration of symptoms and plasma cytokine levels in patients with the common cold treated with

zinc acetate. A randomized, double-blind, placebo-controlled trial. Ann Int Med 133:245–252.
181. Verma KC, Saini AS, Dhamija SK. (1980) Oral zinc sulphate therapy in acne vulgaris: a double-blind trial. Acta Derm Venereol 60:337–340.
182. Sazawai S, Black RE, Bhan MK, Jalla S, Sinha A, Bhandari N. (1997) Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea—a community-based, double-blind, controlled trial. Am J Clin Nutr 66:413–418.
183. Hurd, RW, Wilder BJ, Helveston WR, Uthman BM. (1996) Treatment of four siblings with progressive myoclonus epilepsy of the Unverricht-Lundborg type with N-acetylcysteine. Neurology 47:1264–1268.
184. Brewer GJ, Hill GM, Dick RD, Prasad AS, Cossack ZT. (1985) Interactions of trace elements: clinical significance. J Am Coll Nutr 4:33–38.
185. El-Youssaef M. (2003) Wilson disease. Mayo Clin Proc 78:1126–1136.
186. Macknin ML, Piedmonte M, Calendine C, Janosky J, Wald E. (1998) Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. JAMA 279:1962–1967.
187. Irving JA, Mattman A, Lockitch G, Farrell K, Wadsworth LD. (2003) Element of caution: a case of reversible cytopenias associated with excessive zinc supplementation. CMAJ 169:129–131.
188. Chandra RK. (1984) Excessive intake of zinc impairs immune responses. JAMA 252:1443–1446.
189. Samman S, Roberts DC. (1988) The effect of zinc supplements on lipoproteins and copper status. Atherosclerosis 70:247–252.
190. Schrauzer GN, White DA, Schneider CJ. (1976) Inhibition of the genesis of spontaneous mammary tumors in C3H mice: effects of selenium and of selenium-antagonistic elements and their possible role in human breast cancer. Bioinorg Chem 6:265–270.
191. Mahajan SK, Abbasi AA, Prasad AS, et al. (1982) Effect of oral zinc therapy on gonadal function in hemodialysis patients. A double-blind study. Ann Intern Med 97:357–361.
192. Brook AC, Johnston DG, Ward MK, et al. (1980) Absence of a therapeutic effect of zinc in the sexual dysfunction of haemodialysed patients. Lancet 2(Pt. 1):618–620.
193. Mahajan SK. (1989) Zinc in kidney disease. J Am Coll Nutr 8:296–304.
194. Bell S, Goldman VM, Bistrian BR, et al. (1999) Effect of beta-glucan from oats and yeast on serum lipids. Crit Rev Food Sci Nutr 39:189–202.
195. Onning G, Wallmark A, Persson M, et al. (1999) Consumption of oat milk for 5 weeks lowers serum cholesterol and LDL cholesterol in free-living men with moderate hypercholesterolemia. Ann Nutr Metab 43:301–309.
196. Saltzman E, Das SK, Lichtenstein AH, et al. (2001) An oat-containing hypocaloric diet reduces systolic blood pressure and improves lipid profile beyond effects of weight loss in men and women. J Nutr 131:1465–1470.
197. Zava DT, Dollbaum CM, Blen M. (1998) Estrogen and progestin bioactivity of food, herbs, and spices. Proc Soc Exp Biol Med 217:369–378.
198. Jensen CD, Haskell W, Whittam JH (1997) Long-term effects of water-soluble dietary fiber in the management of hypercholesterolemia in healthy men and women. Am J Cardiol 79:34–37.
199. Brown L, Rosner B, Willett WW, Sacks FM. (1999) Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr 69:30–42.
200. Anderson JW, Allgood LD, Lawrence A, et al. (2000) Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. Am J Clin Nutr 71:472–479.

201. Moyad MA. (1999) Soy, disease prevention, and prostate cancer. Semin Urol Oncol 17:97–102.
202. Dent SB, Peterson CT, Brace LD, et al. (2001) Soy protein intake by perimenopausal women does not affect circulating lipids and lipoproteins or coagulation and fibrinolytic factors. J Nutr 131:2280–2287.
203. Gerhardt AL, Gallo NB. (1998) Full-fat rice bran and oat bran similarly reduce hypercholesterolemia in humans. J Nutr 128:865–869.
204. Yan W, Ohtani K, Kasai R, Yamasaki K. (1996) Steroidal saponins from fruits of Tribulus terrestris. Phytochemistry 42:1417–1422.
205. Bedir E, Khan IA. (2000) New steroidal glycosides from the fruits of Tribulus terrestris. J Nat Prod 63:1699–1701.
206. Cai L, Wu Y, Zhang J, et al. (2001) Steroidal saponins from Tribulus terrestris. Planta Med 67:196–198.
207. Adimoelja A. (2000) Phytochemicals and the breakthrough of traditional herbs in the management of sexual dysfunctions. Int J Androl 23(Suppl 2):82–84.
208. Acrasoy HB, Erenmemisoglu A, Tekol Y, Kurucu S, Kartal M. (1998) Effect of Tribulus terrestris L. saponin mixture on some smooth muscle preparations: a preliminary study. Boll Chim Farm 137:473–475.
209. Adaikan PG, Gauthaman K, Prasad RN, Ng SC. (2000) Proerectile pharmacological effects of Tribulus terrestris extract on the rabbit corpus cavernosum. Ann Acad Med Singapore 29:22–26.
210. Antonio J, Uelmen J, Rodriguez R, Earnest C. (2000) The effects of Tribulus terrestris on body composition and exercise performance in resistance-trained males. Int J Sport Nutr Exerc Metab 10:208–215.
211. Ito TY, Trant AS, Polan ML. (2001) A double-blind placebo-controlled study of ArginMax, a nutritional supplement for enhancement of female sexual function. J Sex Marital Ther 27:541–549.
212. Sperling H, Lorenz A, Krege S, Michel MC. (2001) An extract from the bark of the tree Aspidosperma Quebracho Blanco inhibits human penile alpha-adrenoceptors. J Urol 165:227 (abstract no. 938).
213. De Young L, Yu D, Freeman D, Brock GB. (2003) Effect of PDE5 inhibition combined with free oxygen radical scavenger therapy on erectile function in a diabetic animal model. Int J Impot Res 15:347–354.
214. Kuan JK, Brock GB. (2003) Oral vitamin E and folic acid supplementation during sildenafil therapy for erectile dysfunction improves salvage in non-responders. J Urol 169:379 (abstract no. 1417).
215. Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. (2002) Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention. The Swiss Heart Study: a randomized controlled trial. JAMA 288:973–979.
216. Lebret T, Herve JM, Gorny P, Worcel M, Botto H. (2002) Efficacy and safety of a novel combination of L-arginine glutamate and yohimbine hydrochloride: a new oral therapy for erectile dysfunction. Eur Urol 41:608–613.
217. Bent S, Xu L, Li-Yung L, et al. (2003) A randomized controlled trial of a Chinese herbal remedy to increase energy, memory, sexual function, and quality of life in elderly adults in Beijing, China. Am J Med 115:441–447.

17 Pharmacological Strategies in the Management of Rapid Ejaculation

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CONTENTS

INTRODUCTION

Rapid ejaculation is one of the most common male sexual disorders and has been estimated to occur in 4 to 39% of men in the general community *(1–5)*. The Diagnostic and Statistical Manual of Psychiatry (DSM-IV) defines it as "persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it ..." which is associated with "...marked distress or interpersonal difficulty..." *(6)*. Most of the community-based epidemiological studies employ inconsistent and poorly validated definitions of rapid ejaculation and true normative data is lacking. The true prevalence of rapid ejaculation cannot be determined without conducting a large community-based, age-ranging study involving stopwatch timing of the intravaginal ejaculation latency time (IELT), and regarding rapid ejaculation as ejaculation within 1 min of intromission.

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Table 1
The Three Mechanisms of Normal Antegrade Ejaculation

Emission
• Sympathetic spinal cord reflux (T10–L2).
• Genital and or cerebral erotic stimuli with considerable voluntary control.
• Peristaltic contraction of epididymis and vas deferens.
• Contraction of seminal vesicles and prostate.
• Expulsion of spermatozoa/seminal/prostatic fluid into posterior urethra.
• Ejaculatory inevitability sensation resulting from distension of posterior urethra.
Ejection
• Paraympathetic spinal cord reflex (S2–S4).
• Limited voluntary control.
• Rhythmic contractions of bulbocavernous/pelvic floor muscles.
• Bladder neck closure.
• Relaxation of external urinary sphincter
Orgasm
• Build-up and release of pressure in posterior urethra.
• Smooth muscle contraction of accessory sexual organs and urethral bulb.
• Sensation owing to cerebral processing of pudendal nerve sensory stimuli.

PHYSIOLOGY OF EJACULATION

There are three basic mechanisms involved in normal antegrade ejaculation—emission, ejection, and orgasm (Table 1) *(7)*.

Ejaculatory dysfunction can result from disruption at any point in this cascade of events. Emission is the result of a sympathetic spinal cord reflex initiated by genital and/or cerebral erotic stimuli (Fig. 1).

Emission involves the sequential contraction of accessory sexual organs and the sensation of emission is a result of distension of the posterior urethra. There is considerable voluntary control of emission *(7)*. As the sensation of ejaculatory inevitability increases, voluntary control progressively decreases until a point at which ejaculation cannot be stopped is reached. Ejection also involves a sympathetic spinal cord reflex over which there is limited voluntary control. Ejection involves bladder neck closure to prevent retrograde flow, rhythmic contractions of bulbocavernous, bulbospongiosus and other pelvic floor muscles, and relaxation of the external urinary sphincter. Intermittent contraction of the urethral sphincter prevents retrograde flow into the proximal urethra *(8)*. Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising

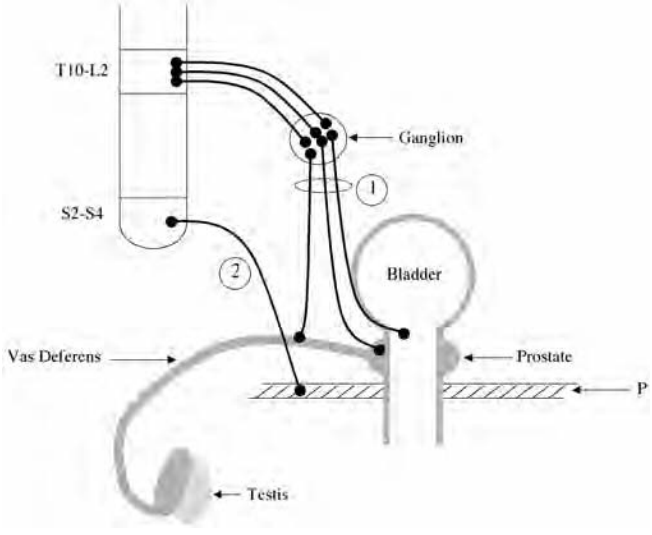

Fig. 1. 1. Nerves involved with emission and ejection. Sympathetic nerves from T10-L2 innervate the vas deferens, prostate, and bladder neck. Contraction results in emission and bladder neck closure. 2. Somatic nerve fibers in the pudendal nerve arise fom S2–S4 and innervate the pelvic floor musculature, the contraction of which causes forceful ejection.

from the veramontanum, and contraction of the urethral bulb and accessory sexual organs.

DEFINING RAPID EJACULATION

The first report of rapid ejaculation in the medical literature appeared in 1887 *(9)*. In 1901, Von Krafft-Ebing described a case of abnormally rapid ejaculation *(10)*. The first use of the term *ejaculatio praecox* was attributed to Abrahams in 1917 *(11)*. The current classification of rapid ejaculation into primary (lifelong) and secondary (acquired) forms evolved from the initial suggestion by Schapiro in 1943 that rapid ejaculation was a psychosomatic disturbance *(12)*. He proposed that rapid ejaculation was the result of a combination of a psychologically overanxious personality and "an inferior ejaculatory apparatus as a point of least resistance for emotional pressure." The behavioristic view that chronic rapid ejaculation was the result of performance anxiety related to a disturbing initial episode of rapid ejaculation was first proposed by Masters and Johnson *(13)*. Most of the behavioral treatments currently used are based on this premise.

Over the past 15 yr, an increasing number of publications have reported the pharmacological treatment of rapid ejaculation with a variety of different medications which act either centrally or locally to retard the psychoneurological control of ejaculation and subsequent orgasm. It is well-established that major tranquillizers, such as the phenothiazine, Melleril, and the selective serotonin reuptake inhibitor drugs (SSRIs), retard ejaculation significantly and will, in a small percentage of men, result in anejaculation *(14–16)*. The efficacy of these drugs in delaying ejaculation combined with the low-side effect profile made them first choice agents for rapid ejaculation on a daily, as well as an on-demand, basis *(17,18)*. At the same time, animal and sexual psychopharmacological human studies attributed a serotonergic genesis and possible genetic etiology to the neurobiological view of rapid ejaculation *(19–22)*.

Medical literature contains several one-dimensional and multidimensional operational definitions of rapid ejaculation. The lack of agreement as to what constitutes rapid ejaculation has hampered basic and clinical research into the etiology and management of this condition. Quantitative measures of intercourse, such as the IELT, the number of thrusts between penetration and ejaculation, the extent of partner sexual satisfaction, and the patient's assessment of his voluntary control over ejaculation have been described. All definitions of rapid ejaculation assume heterosexual intercourse initiated by the male partner and are limited to actual sexual intercourse, ignoring other forms of noncoital sexual expression.

Number of Thrusts

Operationalization of rapid ejaculation using the quantifiable and objective number of intravaginal thrusts between penetration and ejaculation has been reported by several authors *(23,25–28)*. Segraves et al. proposed ejaculation prior to eight thrusts as a standard definition of rapid ejaculation, whereas Fanciullacci et al. suggested 15 thrusts as a more appropriate defining limit *(24,28)*.

These definitions were subjective, had neither a rational nor empirical basis, and no normative data was presented.

IELT

Operationalization of rapid ejaculation using the length of time between penetration and ejaculation, the IELT forms the basis of most current clinical studies on rapid ejaculation. There is considerable variance of the latencies used to identify men with rapid ejaculation with IELTs ranging from 1 to 7 min, and none of the definitions offer any supportive rationale for their proposed cut-off time or normative data *(29–37)*. Waldinger et al.

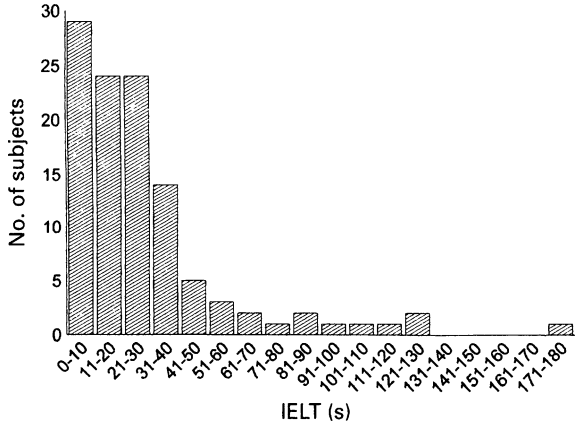

Fig. 2. Intravaginal ejaculation latency time measure with a stopwatch in 110 men with lifelong premature ejaculation, of whom 90% ejaculated within 1 min of vaginal penetration, 80% of whom ejaculated within 30 s *(67)*. IELT, intravaginal ejaculation latency time.

reported IELTs of less than 30 s and less than 60 s in 77 and 90% of 110 men with premature ejaculation (PE), respectively *(38)*. (Fig. 2).

McMahon et al. reported similar results in 1346 consecutive men with rapid ejaculation and mean IELT of 43.4 ± 40.8 seconds *(39)*. Ejaculation *ante portas* (during foreplay) occurred on the majority of occasions in 5.6% of men. Lifelong rapid ejaculation was present in 736 men (74.4%), and acquired rapid ejaculation was present in 253 men (25.6%).

Partner Satisfaction

The inability to control and defer ejaculation until the female partner was sexually satisfied on at least 50% of intercourse attempts was proposed as a definition of rapid ejaculation by Masters and Johnson *(13)*. Although the sexual pleasure of both partners must be considered when assessing the extent of sexual dysfunction, an inherent problem exists in defining a man as dysfunctional based on the sexual responsivity of his partner. What constituted sexual satisfaction was not defined and no rationale is offered for the 50% cutoff figure. This definition implies that any male whose female partner has difficulty in reaching orgasm should be labelled as a rapid ejaculator. Furthermore, it suggests that female partners should achieve orgasm in 50% of intercourse episodes, which is at odds with the report that only 30% of women achieve orgasm during sexual intercourse regardless of the extent of their partner's ejaculatory control and latency.

Voluntary Control

Kaplan and other authors have suggested that an inability to voluntarily defer ejaculation defines rapid ejaculation *(25,40–42)*. This definition has yet to be adequately operationalized to allow comparison across subjects or across studies. Grenier and Byers failed to demonstrate a strong correlation between ejaculatory latency and subjective ejaculatory control *(5,43)*. They reported that some men with a brief ejaculatory latency time reported adequate ejaculatory control and vice versa, and concluded that the dimensions of ejaculatory control and latency are distinct concepts. Contrary to this, Waldinger et al. reported a moderate correlation between the IELT and the feeling of ejaculatory control *(44)*.

The use of a combination of the control and latency dimensions was first reported by Strassberg et al. *(31)* in 1990, and forms the basis of the DSM-IV definition of rapid ejaculation.

Although this approach is somewhat of an improvement over previous definitions in that it acknowledges that rapid ejaculation may have aspects of both control and latency, the lack of operationalization of the control dimension, and the lack of guidelines offering a rationale for the use of age, novelty, situation, or frequency of sexual activity diagnosing rapid ejaculation. limits its application.

The lack of a reliable operational definition for rapid ejaculation severely limits clinical research into the understanding of rapid ejaculation. Studies that fail to define rapid ejaculation offer meaningless or difficult-to-interpret results. The lack of a universally accepted, operationalized definition makes comparison of different studies difficult or impossible, as experimental group subjects in one study may very well have been placed in the control group of a second study. The ability to compare study results and generalize study results requires the development of a uniform, operationalized, multivariate definition of rapid ejaculation including the dimensions of latency and control. Both dimensions should be defined, measuredm and analyzed as continuous variables without arbitrary cutoff values. The development of a nomogram of age-specific latency and degree of ejaculatory control is an integral part of the development of clinical research in ejaculatory dysfunction.

THE ETIOLOGY OF RAPID EJACULATION

Historically, attempts to explain the etiology of rapid ejaculation has included a diverse range of biogenic and psychological theories (Figs. 3 and 4).

Most of these proposed etiologies are speculative and not evidence-based. Psychological theories include the effect of early experience and

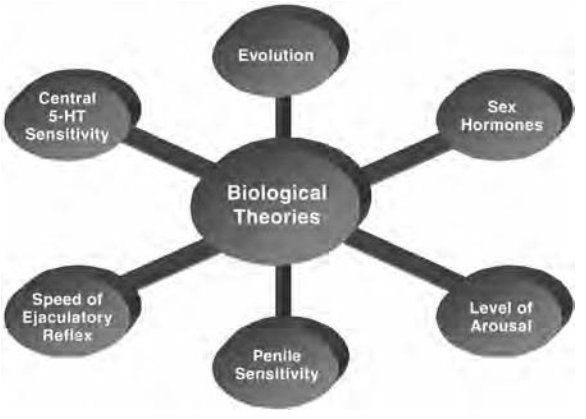

Fig. 3. Proposed biogenic etiologies of premature ejaculation.

Fig. 4. Proposed psychosocial etiologies of premature ejaculation.

sexual conditioning, anxiety, sexual technique, the frequency of sexual activity, and psychodynamic explanations. Biogenic explanations include evolutionary theories, penile sensitivity, central neurotransmitter levels and receptor sensitivity, degree of arousability, the speed of the ejaculatory reflex, and the level of sex hormones. The lack of an operationalized definition for rapid ejaculation, and the presence of methodological problems related to the inadequate definitions used are common flaws in the majority of these studies.

Anxiety

Anxiety has been reported as a cause of rapid ejaculation by multiple authors and is entrenched in the folklore of sexual medicine as the most likely cause of rapid ejaculation despite scant empirical research evidence to support any causal role *(25,26,42,45,46)*. Several authors have suggested that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation *(25,45)*. Strassberg et al. failed to demonstrate any difference in sexual anxiety between a control group of men with normal ejaculatory control and men with rapid ejaculation *(31)*.

The possibility that high levels of anxiety and excessive and controlling concerns about sexual performance and potential sexual failure might distract a man from monitoring his level of arousal and recognizing the prodromal sensations that precede ejaculatory inevitability has been suggested as a possible cause of rapid ejaculation by several authors *(25,42, 46,47)*. The causal link between anxiety and rapid ejaculation is speculative, is not supported by any empirical evidence, and is, in fact, contrary to empirical evidence from other researchers.

Early Sexual Experience

Masters and Johnson were the first of several researchers to suggest that early sexual experiences characterized by anxiety and rush might condition men to develop a subsequent pattern of rapid ejaculation *(13,48)*. However, no empirical evidence was offered to support this hypothesis, and no distinction was made between men with lifelong rapid ejaculation and men with acquired rapid ejaculation.

Frequency of Sexual Intercourse

The evidence to support a link between ejaculatory control and frequency of sexual activity is conflicting. Speiss reported that the frequency of sexual activity in men with rapid ejaculation is lower than age-matched controls with normal ejaculatory control, whereas Strassberg failed to demonstrate any relationship *(30,32)*. The observation that men with rapid ejaculation may develop a pattern of sexual avoidance may also explain this observed reduced frequency of sexual intercourse, indicating that the polarity of the relationship between rapid ejaculation and frequency of sexual activity remains undetermined *(49)*.

Ejaculatory Control Techniques

Zilbergeld suggested that some men with ejaculatory control might consciously learn a variety of effective sexual techniques for deferring ejaculation during their early sexual experiences and unconsciously use

those techniques later *(42)*. Data to support this hypothesis are weak and studies to evaluate the use and effectiveness of control techniques in men with rapid ejaculation is lacking.

Evolutionary

Hong suggested that rapid ejaculation was the result of evolutionary natural selection, arguing that rapid copulation allowed copulation with more females with transmission of a possible genetic basis for rapid ejaculation to more offspring *(50)*. The observation that primate courtship and sexual contact are often extended is inconsistent with this hypothesis *(51)*.

Psychodynamic Theories

Abraham was the first to suggest a psychodynamic basis of rapid ejaculation. He theorized that rapid ejaculation was the adult manifestation of unresolved and excessive narcissism during infancy that resulted in exaggerated importance being placed on the penis and the associated pleasure of urination *(52)*.

He offered no empirical basis for this theory, and subsequent studies by other authors have failed to demonstrate any evidence for his narcissism hypothesis *(12)*.

Penile Hypersensitivity

Multiple authors have proposed that men with rapid ejaculation have hypersensitive penises, and either reach ejaculatory threshold more rapidly, or have a lower ejaculatory threshold than men with normal ejaculatory control *(12,31,52,53)*. A limitation of the universal applicability of this theory is its inability to explain acquired rapid ejaculation. Xin et al. demonstrated that men with rapid ejaculation have lower biothesiometric vibration perception thresholds and significantly shorter mean somatosensory-evoked potential latency times of the glans and penile shaft than controls *(54,55)*. However, Paick et al. and Rowland were unable to reproduce these findings, reporting no significant statistical differences between normal controls and patients with primary rapid ejaculation *(56,57)*.

Hyperexcitable Ejaculatory Reflex

Several authors have suggested that rapid ejaculation is the result of a defective and rapid ejaculatory reflex with either a faster emission or expulsion phase *(23,28,58,59)*. Several authors have reported a link between rapid ejaculation and a malfunctioning bulbocavernosal reflex. The bulbocavernosus muscle surrounds the urethral bulb and is one of several muscles responsible for the expulsive phase. This hypothesis lacks a firm physiological basis, as the emission phase of the ejaculatory process has already started by the time the bulbocavernosus muscle contracts.

Arousability

Laboratory studies using solitary stimulation during audiovisual stimulation have failed to demonstrate greater, more frequent, or more rapid arousal in men with rapid ejaculation compared with a control group of sexually nondysfunctional men *(30)*.

Endocrinopathy

Although there are several reports of a possible link between rapid ejaculation and levels of sexual hormones, a careful review of the published literature fails to confirm any causal link *(60,61,62)*.

Genetic Predisposition

Schapiro first reported a familial predisposition to rapid ejaculation in 1943 *(12)*. Waldinger reported that 10 of 14 first-degree male relatives of men with lifelong rapid ejaculation also suffered from rapid ejaculation with an IELT of less than 1 min *(22)*. Based on this small study, the odds ratio of a familial occurrence of rapid ejaculation far exceeds the incidence in the general community and supports Schapiro's contention that rapid ejaculation may have a genetic basis.

Serotonin (5-HT) Receptor Sensitivity

The current understanding of the functional neuroanatomy and the role of central serotonin and dopamine neurotransmission in ejaculation are based on male rat studies. The hypothalamic medial preoptic area (MPOA) and the medullary nucleus paragigantocellularis (nPGI) in the ventral medulla have pivotal roles in the central control of ejaculation (Fig. 5) *(63,64)*.

Electrical stimulation of or microinjection of dopamine agonists into the MPOA promotes ejaculation *(65)*. It has been suggested that descending serotonergic pathways from the nPGI to the lumbosacral motor nuclei tonically inhibit ejaculation, and that disinhibition of the nPGI results in ejaculation *(66)*.

Five types of dopaminergic receptors have been identified and 16 types of human 5-HT receptors have been identified. Studies using highly selective 5-HT receptor agonists and antagonists identified a pivotal role of 5-HT2C and 5-HT1A receptors in the central control of ejaculation.

Stimulation of the 5-HT2C receptors in male rats with nonselective 5-HT2C agonists, such as D-lysergic acid diethylamide, delays ejaculation *(67)*. Contrary to this, activation of postsynaptic 5-HT1A receptors by the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-*n*-propylamino-tetralin) in male rats facilitates ejaculation *(67)*.

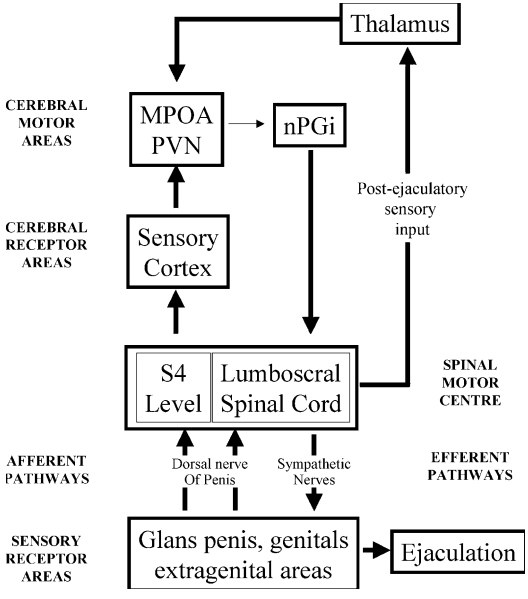

Fig. 5. The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centers, spinal motor centers, and efferent pathways. MPOA, medical preoptic area; PVN, paraventricular nucleus; nPGi, nucleus paragigantocellularis. (Adapted from ref. *67.*)

Waldinger et al. hypothesized that lifelong rapid ejaculation in humans may be explained by either hyposensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptor *(68)*. Therefore, men with low 5-HT neurotransmission and probable 5-HT2C receptor hyposensitivity may have their ejaculatory threshold genetically "set" at a lower point and ejaculate quickly with minimal stimulation, often prior to reaching their erectile threshold. Men with a genetically determined higher set point can sustain longer and higher levels of sexual stimulation and can exert more control over ejaculation. Finally, men with a very high set point may experience delayed or absent ejaculation despite prolonged sexual stimulation and achieving a full erection *(69)*. Treatment with an SSRI-class drug will activate the 5-HT2C receptor, adjust the ejaculatory threshold set point, and delay ejaculation. The extent of ejaculatory delay may vary widely in different men according to the dosage and frequency of administration of SSRI, and the genetically determined ejaculatory threshold set point. Cessation of treatment results in re-establishment of the previous set point within 5 to 7 d in men with lifelong rapid ejaculation.

TREATMENT

Psychosexual Counselling

In many marriages, rapid ejaculation causes few, if any, problems. In others, the couple may reach an accommodation of the problem through various strategies—young men with a short refractory period may often experience a second and more controlled ejaculation during an episode of lovemaking, whereas many other men with rapid ejaculation learn to help their spouse reach an orgasm manually or orally. Frequently, however, rapid ejaculation eventually leads to significant problems in the relationship: the spouse comes to feel the sexual relationship is completely one sided, regards their husband as selfish, and develops a pattern of avoiding intercourse.

The cornerstone of treatment is the Seman's "stop-start" maneuver *(59)*. The Seman's maneuver was designed to teach men with rapid ejaculation to monitor the sensations immediately premonitory to orgasm, and reduce or slow their thrusting sufficiently in order to allow the sensations to subside. The Seman's maneuver was modified by Masters and Johnson, who encourage the woman to give the penis a hard squeeze for 3 or 4 s at the level of the frenulum and the coronal ridge when the man signals awareness of sensations premonitory to orgasm *(26)*. As most men with rapid ejaculation are aware of their anxiety and the sources of that anxiety tend to be relatively superficial, treatment success with the Seman's maneuver or Master's and Johnson's squeeze technique is relatively good in the short term. However, convincing long-term treatment outcome data are lacking *(70,71)*.

Many men decline psychosexual counselling for a variety of reasons. Men may regard attending a psychiatrist or psychologist as stigmatized, may be unable to devote the time required to attend several counselling sessions, or may demand a quicker response than psychosexual counselling is reported to offer. Optimal results are highly dependent on the participation of the sexual partner in the counselling sessions—many men do not have a current partner or may have a noncompliant sexual partner. Clearly, a significant treatment "hiatus" exists in the management of rapid ejaculation that may be filled by alternate noncounselling treatment methods.

Pharmacological Treatment

Rapid ejaculation may be treated pharmacologically with a variety of different medications which act either centrally or locally to retard the psychoneurological control of ejaculation and subsequent orgasm. It is well-established that major tranquillizers, such as the phenothiazine *(72)*,

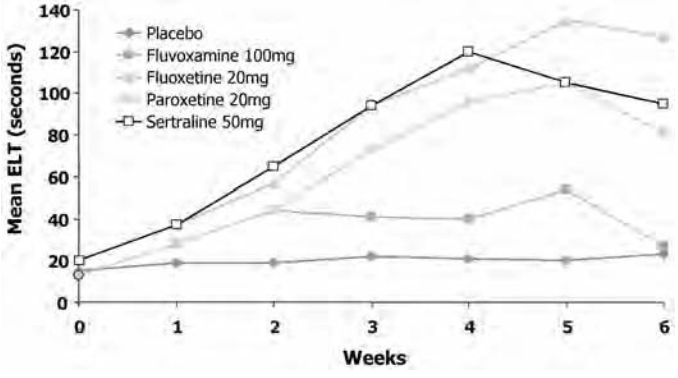

Fig. 6. Effect on pareoxetine, sertraline, fluoxetine, and clomipramine on the intravaginal ejaculatory latency time in men with premature ejaculation. IELT, intravaginal ejaculatory latency time. (Adapted from ref. *72.*)

Melleril, and antidepressants, particularly members of the SSRI class, will retard ejaculation significantly and, in a small percentage of men, result in anejaculation *(14–16)*. Deveaugh-Geiss et al. reported a complete failure of ejaculation in 42% of 520 depressed patients treated with clomipramine *(15)*. Monteiro et al. reported a similar incidence with clomipramine (33%), whereas Patterson reported a 75% incidence of anejaculation in fluoxetine-treated depressed men *(16,73)*. These reports identify a high incidence of SSRI-associated sexual adverse effects, and underscore the under-reported nature of antidepressant-associated sexual dysfunction in the drug manufacturer's prescribing information, which is owing, in part, to the hypoactive sexual desire of depressed patients, but also to less than ideal initial clinical trial design.

SSRIs have revolutionized the approach to and the treatment of rapid ejaculation. SSRIs encompass five compounds—citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline—with a similar pharmacological mechanism of action. There is some evidence that citalopram and fluvoxamine have less effect in delaying ejaculation than paroxetine, sertraline, and fluoxetine (Fig. 6) *(72,74,75)*.

Although the methodology of the initial drug treatment studies was inadequate, subsequent placebo-controlled studies provide a high level of evidence supporting the role of daily and/or "on-demand" serotonergic antidepressants, and topical local anesthetics in the treatment of rapid ejaculation *(76,77)*.

Clomipramine

In 1979, Ahlenius et al. reported that the serotonergic tricyclic antidepressant clomipramine prolonged ejaculatory latency in rats by inhibition of central 5-HT uptake *(78)*. Several anecdotal and controlled human studies have reported that clomipramine is efficacious in the treatment of rapid ejaculation. Its efficacy is limited by a reported 5 to 15% incidence of adverse reactions, which include drowsiness, and less commonly, dry mouth, blurred vision, and other cholinergic side effects.

In 1980, Goodman reported improved ejaculatory control in nine of 16 men with rapid ejaculation following treatment with clomipramine *(79)*. Girgis et al. reported similar results but qualified his reported 51% response rate as complicated by dose-related anticholinergic adverse effects, reduced sexual desire, and genital anesthesia *(80)*. Segraves et al. reported a dose-dependent increase in IELT, which was superior to placebo *(28)*.

Althof et al. had similar findings reporting 250 and 500% increases in IELT with doses of 25 and 50 mg, respectively; and statistically significant improvements in male and female sexual satisfaction scores in a double-blind placebo-controlled trial of 15 couples *(81)*. Montorsi et al. reported that 10 of 33 responders had maintained improved ejaculatory control following withdrawal of the drug *(82)*. Haensel et al. first reported that on-demand clomipramine taken 12 to 24 h before anticipated sexual activity is more effective than placebo in men with primary rapid ejaculation, but is ineffective in men with both rapid ejaculation and ejaculatory dysfunction *(83)*. Strassberg et al. subsequently reported that clomipramine at doses as low of 25 mg taken on demand 3 to 4 h prior to coitus was more effective than placebo in delaying ejaculation in a laboratory setting using vibrotactile stimulation *(84)*.

SSRIs

The SSRIs enhance 5-HT neurotransmission and activate 5-HT receptors by blocking presynaptic and somatodendritic 5-HT reuptake transporter receptors. Their action is assumed to be central but Hseih et al. demonstrated that serotonin, fluoxetine, and clomipramine can reduce the pressure response of the seminal vesicle to electrical nerve stimulation of the lesser splanchnic nerve, suggesting an additional peripheral action *(85)*.

Berendson and Broekkamp observed that the responses to SSRIs in rats resembled 5-HT1C receptor activation and suggested that SSRI-induced inhibition of male ejaculatory dysfunction results from 5-HT1C receptor stimulation *(86)*. Contrary to this, Hillegaart and Ahlenius suggested that SSRI-induced inhibition of male ejaculatory dysfunction is because of 5-HT1B receptor stimulation *(87)*. However, SSRIs may have

different effects on the various subpopulations of serotonin receptors; e.g. fluvoxamine, in contrast to other SSRIs, has little effect on ejaculatory latency. Olivier et al. took a more balanced approach and suggested that fluvoxamine actions are primarily mediated via 5-HT1A receptors, whereas those of fluoxetine and paroxetine are primarily mediated via 5-HT2C receptors *(20)*. After chronic administration of an SSRI, Waldinger et al. suggested that a number of adaptive processes, possibly including presynaptic 5-HT1A and 5-HT1B/1D receptor desensitization may play a role in achieving the observed greatly enhanced 5-HT neurotransmission *(68)*.

Fluoxetine

Fluoxetine achieves peak plasma concentrations within 6 to 8 h of administration and is metabolized in the liver predominantly by demethylation to an active metabolite, norfluoxetine, which has equivalent potency and selectivity as a SRI to its parent molecule. Both fluoxetine and norfluoxetine are slowly eliminated, the former having nonlinear pharmacokinetics, ensuring significant accumulation of both species with chronic dosing and persistence of active drug for several weeks after drug withdrawal *(88)*.

Crenshaw first reported the efficacy of fluoxetine treatment of rapid ejaculation describing a dose-related improvement in ejaculatory control in 46 men, with some men maintaining improvement after withdrawal of fluoxetine after 3 to 6 mo of treatment *(89)*. Several other authors have suggested a potential role for fluoxetine in the treatment of rapid ejaculation *(90–94)*.

Kara et al. in a double-blind, placebo-controlled study of fluoxetine demonstrated a sevenfold increase in the ejaculatory interval which was noted as early as 1 wk after initiation of treatment *(94)*. Ejaculatory delay is clearly an acute adverse effect of fluoxetine consistent with rapid achievement of peak plasma concentrations and prompt augmentation of 5-HT synaptic neurotransmission. Haensel et al., in a prospective, double-blind, placebo-controlled, crossover study of 40 men with either rapid ejaculation, combined rapid ejaculation/ejaculatory dysfunction, ejaculatory dysfunction alone, or a control group of normal men, reported a significant increase in IELT in the rapid ejaculation group; and, contrary to their earlier findings with clomipramine, they found a subjective, but not objective, improvement in erectile function, and no major adverse effects in the rapid ejaculation/ejaculatory dysfunction group following treatment with fluoxetine *(95)*.

Fluoxetine is generally well tolerated by most patients, with adverse effects including drowsiness, insomnia, anxiety, and nausea and, less com-

monly, reduced sexual desire, and ejaculatory dysfunction. Anejaculation is a dose-dependent adverse effect and may persist for several wk after drug withdrawal because of the slow elimination of fluoxetine and its first active metabolite. There have been infrequent anecdotal reports of fluoxetine-related prolonged erection and priapism and spontaneous involuntary orgasm *(96,97)*.

Sertraline

Sertraline has a relatively long half-life of 26 h, allowing once-daily dosing. It promptly achieves peak plasma levels within 4 to 6 h and undergoes extensive first-pass metabolism to less active desmethylsertraline. In addition to its selective 5-HT inhibitory actions, sertraline also appears to inhibit excitatory responses through blocking dopamine receptors and effecting amino acid σ-receptors, and by downregulating central adrenergic receptors *(98)*. The most common side effects are sexual and gastrointestinal, but a very occasional patient will experience the agitation and tremor seen with fluoxetine.

In 1994, Swartz first reported that sertraline at doses of 25 to 50 mg daily improved the mean IELT to 20 min in a case series of 10 men with rapid ejaculation *(99)*. Balbay et al. reported improved ejaculatory control in 11 of 16 men after 1 wk and in a further three at the end of a second treatment week *(100)*. McMahon also reported the occurrence of improved ejaculatory control and improved sexual satisfaction, as evidenced by subsequent increased frequency of intercourse within 1 to 2 wk, and a direct dose-related increase in IELT which may be associated with anejaculation with doses of 50 mg or higher *(101)*. Similar case-series findings have been reported by Kaplan and Wise *(102,103)*.

Mendels et al., McMahon, and Biri et al. confirmed superiority to placebo in the treatment of rapid ejaculation in separate controlled studies *(104–106)*. McMahon also demonstrated a dose-dependent superiority to placebo and reported that staged drug withdrawal allowed 20 of the 29 patients (67%) to discontinue treatment after a mean treatment interval of 7.3 mo yet maintain improved ejaculatory control *(105)*.

Paroxetine

Paroxetine has a relatively long half-life of 24 h also allowing once-daily dosing. It achieved peak plasma levels within 2 to 8 h with steady-state systemic levels occurring after 7 to 14 d *(107)*. Paroxetine selectively uptakes 5-HT in brain neurons, but unlike sertraline, has little affinity for dopamine receptors and central adrenergic receptors. Its adverse effect profile parallels that of sertraline, and drug interactions with warfarin, tryptophan, and dilantin have been reported.

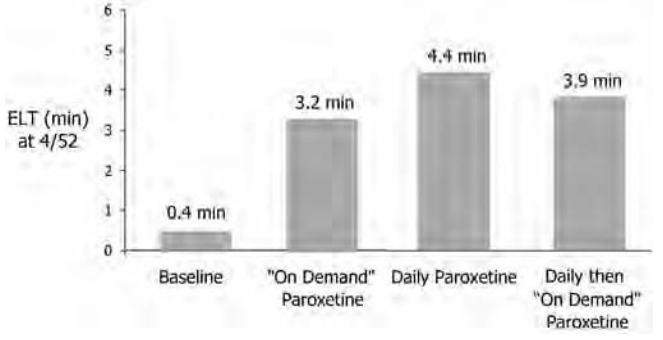

Fig. 7. Effect on "on-demand" paroxetine, daily paroxetine, and initial daily followed by "on-demand" paroxetine, on the intravaginal ejaculation latency time in men with premature ejaculation. ELT, ejaculation latency time. Adapted from ref. *18.*

Waldinger et al. first reported a significant improvement in ejaculatory control with paroxetine compared to placebo in a double-blind study of 17 men with rapid ejaculation *(17)*. In a subsequent study, Waldinger et al. demonstrated that improved ejaculatory control achieved with paroxetine was dose-related *(108)*.In an uncontrolled study of 32 men with rapid ejaculation treated with 20 mg paroxetine for 2 mo, Ludovico et al. reported improved ejaculatory control in all subjects with recurrence of symptoms in 28 men within 3 wk of drug withdrawal *(109)*. Reported adverse effects included sleepiness (61%) and mild sensory confusion (68%). Giammusso et al., McMahon and Touma, and Isaksen have reported similar efficacy in uncontrolled case series but less adverse effects because of the lower dose of paroxetine employed (10 mg) *(110–112)*.

The use of "on-demand" paroxetine administered 3 to 4 h before planned coitus was first reported by McMahon and Touma in an uncontrolled case series of 94 men, and later in a crossover placebo-controlled study of 42 men *(18,111)*. They reported an eightfold increase in the IELT with "on-demand" paroxetine, which improved significantly if patients were initially treated with daily paroxetine for 3 wk (Fig. 7).

This "ejaculatory recruitment" is related to the greater 5-HT neurotransmission seen with chronic administration and to the nonlinear pharmacokinetics of paroxetine. Paroxetine is a potent inhibitor of the P450 2D6 enzyme, which is responsible for its first-pass metabolism, resulting in prolonged drug clearance as the paroxetine concentration increases with multiple dosing, and disproportionately greater increases in its concentration with every dose *(113–115)*.

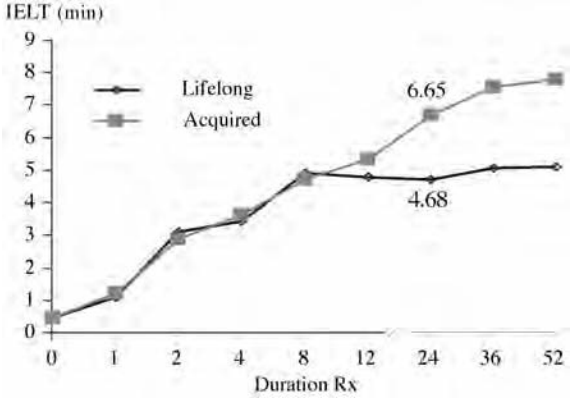

Fig. 8. Intravaginal ejaculation latency time (IELT) during long-term treatment with paroxetine for men with lifelong and acquired premature ejaculation where IELT-acquired PE > IELT, lifelong IELT > 24/52 ($p < 0.05$). IELT, intravaginal ejaculation latency time; PE, premature ejaculation.

SSRIs are an effective treatment for 80 to 85% of men with rapid ejaculation. Most men will notice an increase in their IELT within 2 to 3 d, and this rate will increase by six- to eightfold and plateau after 3 to 4 wk treatment. Paroxetine, fluoxetine, Sertraline, and clomipramine appear to have similar efficacy in several short term and longitudinal studies *(74,116,117)*. SSRIs are generally well-tolerated. Adverse effects are usually minimal and include minor drowsiness and gastrointestinal upset. Side effects usually attenuate and disappear after 3 to 4 wk treatment. The occasional patient who experiences anejaculation with inappropriate high-starting doses or too rapid dose titration, will respond to drug withdrawal and rechallenge at a lower dose after a brief washout period. Minor hyperactivity and anxiety are occasionally seen as transient acute adverse effects, SSRIs are best avoided in patients with current or controlled bipolar affective disorders, as frank mania may occur.

McMahon reported that men with lifelong rapid ejaculation respond differently to SSRI drugs than do men with acquired rapid ejaculation. Treatment with SSRI drugs was associated with a significantly lower IELT in men with lifelong rapid ejaculation compared with acquired rapid ejaculation after 24 wk of treatment (Fig. 8) *(39)*. Restoration of ejaculatory control after drug withdrawal occurred in 68.2% of men with acquired rapid ejaculation within 12 mo following treatment with combined paroxetine and ejaculatory control "re-education" using Seman's stop-start technique. The average duration of treatment was 4.7 mo, and the prospect of restoration was directly related to the frequency of inter-

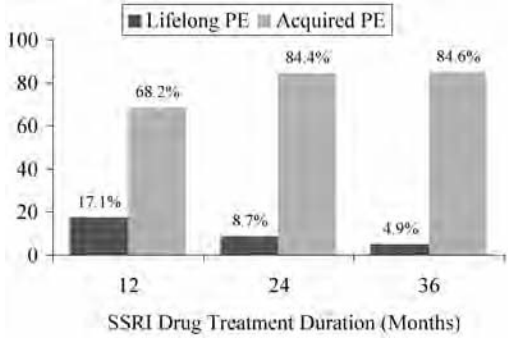

Fig. 9. Restoration of ejaculatory control in men with lifelong and acquired premature ejaculation following withdrawal of selective serotonin reuptake inhibitor drug treatment. PE, premature ejaculation; SSRI, selective serotonin reuptake inhibitor.

course and inversely related to age. Only 17.1% of men with lifelong rapid ejaculation achieved restoration of ejaculatory control within 12 mo and rapid ejaculation recurred in 50% of this group over the following 12 mo (Fig. 9).

This variance in response to treatment suggests that lifelong rapid ejaculation has a different etiology than acquired rapid ejaculation, consistent with Waldinger's hypothesis that lifelong rapid ejaculation is a biological variance of ejaculatory function with a lower ejaculatory threshold "set-point" possibly owing to 5-HT receptor malfunction *(69)*.

Phosphodiesterase Inhibitors

Nitric oxide (NO) is recognized as one of the important intracellular messengers in the brain *(118,119)*. Several authors have reported that NO might be involved in the regulation of emotional and sexual behavior *(120–122)*. Microinjection of the NO precursor, L-arginine, into the rat MPOA, induced significant elevations of extracellular NO and an increased male copulatory behavior with a significant increase in mount rates *(123)*. Microinjection of the NO synthase inhibitor *N*-monomethyl-L-arginine significantly reduced NO levels, inhibited copulatory behavior, and decreased the latency to the first seminal emission *(123,124)*. There is a possibility that NO facilitates male copulatory behavior through acceleration of dopamine release. Lorrain and Hull reported that microinjection of the NO precursor, L-arginine, into the MPOA, increased the extracellular dopamine level *(125)*. Consistent with these studies, Kreigsfeld reported that mice homozygous for endothelial NO synthase gene deletion have striking reduction in ejaculatory latency *(126)*. The results indicate that not

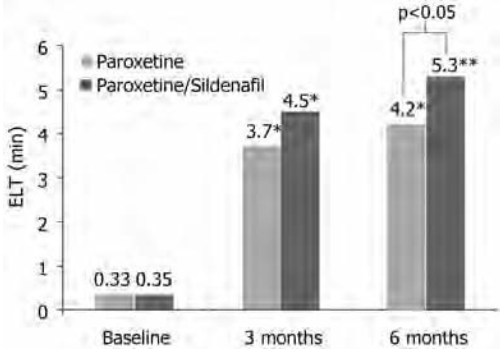

Fig. 10. Effect of paroxetine on the intravaginal ejaculatory latency time in men with premature ejaculation, using initial chronic and then "on-demand" dosing; and a combination of paroxetine and sildenafil, using the same dosing regimen for paroxetine and sildenafil, administered 1 h prior to intercourse (* $p < 0.01$, ** $p < 0.001$). ELT, ejaculation latency time. Adapted from ref. *167.*

only does NO promote erection in intact male rats, but it may also inhibit seminal emission, probably by decreasing sympathetic nervous system activity.

Several authors have reported their experience with sildenafil citrate as a treatment for rapid ejaculation *(127–129)*. Abdel-Hamid et al. compared the efficacy and safety of the "on-demand" clomipramine, sertraline, paroxetine, sildenafil, and the pause/squeeze technique in the treatment of lifelong rapid ejaculation in a prospective noncontrolled study of 31 potent men *(5,127)*. Treatment with sildenafil was associated with a significantly higher IELT (15 min) and sexual satisfaction score than all other treatments and sexual satisfaction scores positively correlated with the IELT for each treatment.

In an open-label study of 80 potent men, Salonia et al. compared treatment with paroxetine alone using initial chronic and then "on-demand" dosing, with a combination paroxetine and sildenafil, using the same dosing regime for paroxetine and sildenafil administered 1 h prior to intercourse (Fig. 10) *(128)*.

Both treatments significantly improved the IELT and intercourse satisfaction domain of the International Index of Erectile Function.

The combination of paroxetine and sildenafil produced superior results in both endpoints at 6 mo treatment, and the authors suggested a possible role of sildenafil in the treatment of rapid ejaculation.

The proposed mechanisms for the effect of sildenafil on ejaculatory latencies include a central effect involving increased NO and reduced

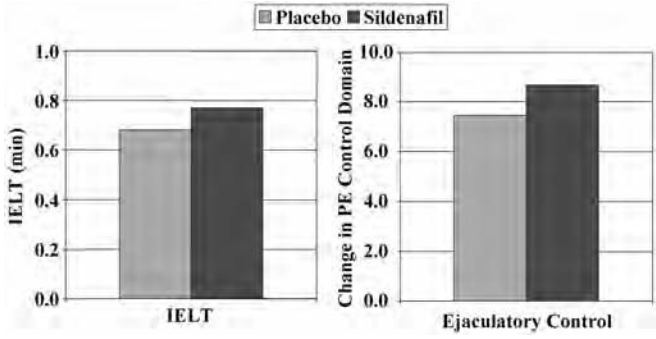

Fig. 11. Effect of sildenafil (100 mg) and placebo on intravaginal ejaculatory latency time and ejaculatory control domain score in 147 men with lifelong premature ejaculation *(130)*. IELT, intravaginal ejaculation latency time; PE, premature ejaculation.

sympathetic tone, smooth muscle dilatation of the vas deferens and seminal vesicles which may oppose sympathetic vasoconstriction and delay ejaculation, reduced performance anxiety owing to better erections, and downregulation of the erectile threshold to a lower level of arousal so that higher levels of arousal are required to reach the ejaculation threshold.

None of these studies are placebo-controlled and most have several methodological flaws, resulting in confusing and difficult to interpret results. It is unlikely that phosphodiesterase inhibitors have a significant role in the treatment of rapid ejaculation, with the exception of men with acquired rapid ejaculation secondary to comorbid ED. Consistent with this, McMahon et al. *(130)* reported the results of the only double-blind, placebo-controlled, multicenter study which demonstrated no significant difference in the IELT of sildenafil compared to placebo, but did demonstrate significant improvements in the ejaculatory control domain and the ejaculatory function global efficacy question (Fig. 11). The latter is possibly consistent with the erectile response of sildenafil.

Topical Treatment

Application of the topical anesthetics to the penis virtually abolishes the display of penile reflexes in rats *(131)*. Sachs and Liu demonstrated that division of the sensory branches of the pudendal nerves severely impaired the ability of male rats to achieve intromission, and hence ejaculation *(132)*. Weidner reported that ejaculatory response to penile vibrotactile stimulation in spinal cord-injured men requires the presence of intact dorsal penile nerves *(133)*.

The use of topical local anesthetics, such as lignocaine and/or prilocaine as a cream, gel, or spray, is well established, and they appear moderately effective in retarding ejaculation, but do so at the price of possibly causing significant penile hypoanesthesia, and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used *(134–137)*. Atan et al. reported the combined use of fluoxetine and topical lidocaine in 43 men with rapid ejaculation. Seventy two percent of the fluoxetine-treated group improved, as opposed to 83.3% of the fluoxetine/lidocaine group *(138)*.

Xin et al. reported significantly improved ejaculatory control in 89.2% of patients treated with SS-cream *(139,140)*. SS-cream is made with extracts from nine natural herbs, some of which have local anesthetic properties; it is applied to glans penis 1 h before and washed off immediately prior to coitus. Adverse effects were noted in 5.9% of patients, which included mild local irritation and delayed ejaculation. Both the latency and amplitude of somatosensory-evoked potentials measured at the glans penis were increased over baseline after the application of SS-cream *(141)*.

THE OFFICE MANAGEMENT OF RAPID EJACULATION

Men with ejaculatory dysfunction should be evaluated with a detailed medical and sexual history, a physical examination, appropriate investigations to establish the true presenting complaint, identify obvious biological causes, such as medication or recent pelvic surgery, and uncover sufficient detail to establish the optimal treatment plan (Fig. 12).

Relevant information to obtain from the patient includes:

1. A basic medical history, including the use of prescribed and recreational medications.
2. The cultural context and developmental history of the disorder, including whether the rapid ejaculation is global or situational, lifelong or recent in its development.
3. Measures of the quality of each of the three phases of the sexual response cycle: desire, arousal, and ejaculation, because the desire and arousal phases may impact the ejaculatory response.
4. Details about the ejaculatory response, including the patient's subjective assessment of his IELT and sense of ejaculatory control, the level of sexual dissatisfaction and distress, the frequency of sexual activity, etc.
5. The partner's assessment of the situation, including whether the partner suffers from female sexual dysfunction.
6. Assessment of the sexual and overall relationship.

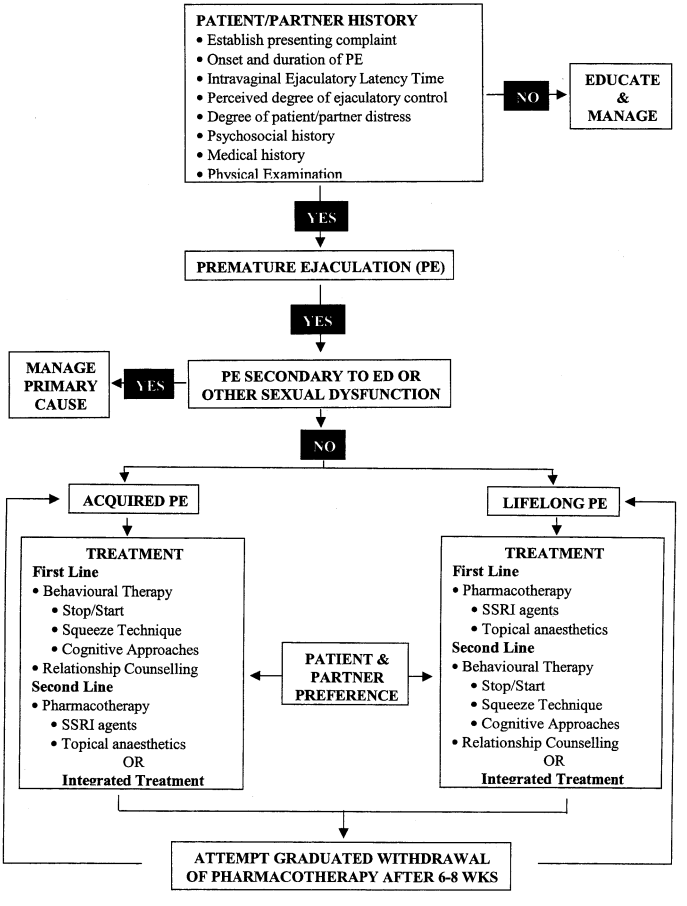

Fig. 12. Management of algorithm for premature ejaculation. PE, premature ejaculation; SSRI, selective serotonin reuptake inhibitor.

Psychophysiological and/or electrophysiological evaluation is time-consuming, labor-intensive, and has not been demonstrated to reliably discriminate between individual patients. These evaluations typically have no current role in the initial clinical evaluation of men with rapid ejaculation.

Men with rapid ejaculation secondary to erectile dysfunction, other sexual dysfunction or genitourinary infection should receive appropriate etiology-specific treatment. Men with lifelong rapid ejaculation should be managed with pharmacotherapy. Men with significant contributing psychogenic or relationship factors may benefit from concomitant behavioral therapy. Recurrence of rapid ejaculation is highly likely to occur following

withdrawal of treatment. Men with acquired rapid ejaculation can be treated with pharmacotherapy and/or behavioral therapy according to patient/partner preference. Restoration of ejaculatory control in men with acquired rapid ejaculation is likely to occur following completion of treatment, but is the exception in men with lifelong rapid ejaculation. Behavioral therapy may augment pharmacotherapy to enhance relapse prevention.

CONCLUSION

The psychosexual model of treatment has previously been regarded as the cornerstone of treatment of rapid ejaculation. Pharmacological modulation of ejaculatory threshold represents a novel and refreshing approach to the treatment of rapid ejaculation. It appears to fill a treatment "hiatus" produced by both the limitations and nonacceptance of psychosexual counselling by some sufferers, and by the lack of convincing longitudinal clinical efficacy data. Pharmacological treatment offers patients a high likelihood of achieving improved ejaculatory control within a few days of initiating treatment, consequential improvements in sexual desire and other sexual domains, and a favorable adverse effect profile. It fails to directly address causal psychological or relationship factors, and is perhaps best employed in combination with behavioral treatment approaches as part of an integrated approach to treatment.

REFERENCES

1. Reading AE, Wiest WM. (1984) An analysis of self-reported sexual behavior in a sample of normal males. Arch Sex Behav 13:69–83.
2. Nathan SG. (1986) The epidemiology of the DSM-III psychosexual dysfunctions. J Sex Marital Ther 12:267–281.
3. Spector KR, Boyle M. (1986) The prevalence and perceived aetiology of male sexual problems in a non-clinical sample. Br J Med Psychol 59:351–358.
4. Spector IP, Carey MP. (1990) Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. Arch Sex Behav 19:389–408.
5. Grenier G, Byers ES. (1997) The relationships among ejaculatory control, ejaculatory latency, and attempts to prolong heterosexual intercourse. Arch Sex Behav 26: 27–47.
6. American Psychiatry Association. (1994) Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, 4th Ed. Washington, DC: American Psychiatric Association, pp. 509.
7. Lipshultz LI, McConnell J, Benson GS. (1981) Current concepts of the mechanisms of ejaculation. Normal and abnormal states. J Reprod Med 26:499–507.
8. Yeates W. (1987) Ejaculatory disturbances. In: Pryor JP, Lipschultz L, eds., Andrology. London, UK: Butterworths, pp. 183–216.
9. Gross S. (1887) Practical Treatise on Impotence and Sterility. Edinburgh, Scotland: YJ Pentland.
10. von Krafft-Ebing RF. (1901) Psychopathia Sexualis, 11th Ed., Stuttgart, Germany: Publishing Hause Enke.

11. Abraham K. (1917) Ueber Ejaculatio Praecox, Zeitschr Aerztl Psychoanal 4:171.
12. Schapiro B. (1943) Rapid ejaculation: a review of 1130 cases. J Urol 50:374–376.
13. Masters W, Johnson V. (1966) Human Sexual Response. Boston, MA: Little, Brown.
14. Kotin J, Wilbert DE, Verburg D, et al. (1976) Thioridazine and sexual dysfunction. Am J Psychiatry 133:82–.
15. Deveaugh-Geiss J, Landau P, Katz R. (1989) Preliminary results from a multicentre trial of clomipramine in obsessive compulsive disorder. Psychopharmacol Bull 25:36–40.
16. Monteiro WO, Noshirvani HF, Marks IM, Elliott PT. (1987) Anorgasmia from clomipramine in obsessive-compulsive disorder: a controlled trial. Br J Psychiatry 151:107–112.
17. Waldinger MD, Hengeveld MW, Zwinderman AH. (1994) Paroxetine treatment of rapid ejaculation: a double-blind, randomized, placebo-controlled study. Am J Psychiatry 151:1377–1379.
18. McMahon CG, Touma K. (1999) Treatment of rapid ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. J Urol 161:1826–1830.
19. Waldinger MD, Hengeveld MW. (2000) Neuroseksuologie en seksuele psychofarmacologie. Tijdschr Psychiatr 8.
20. Olivier B, van Oorschot R, Waldinger MD. (1998) Serotonin, serotonergic receptors, selective serotonin reuptake inhibitors and sexual behaviour. Int Clin Psychopharmacol 13(Suppl 6):S9.
21. Waldinger MD, Olivier B. (2001) Hersenonderzoek en farmacologie: serotonine, seks en agressie. In: Wolters-Schweitzer MHJ, Beuger CL, eds., Het Brein Belicht: Opstellen over Niet-Aangeboren Hersenletsel. Utrecht: Uitgeverij Lemma, pp. 55–63.
22. Waldinger MD, Rietschel M, Nothen MM, et al. (1998) Familial occurrence of primary rapid ejaculation. Psychiatr Genet 8:37–40.
23. Colpi GM, Fanciullacci F, Beretta G, et al. (1986) Evoked sacral potentials in subjects with true rapid ejaculation. Andrologia 18:583–586.
24. Segraves RT, Saran A, Segraves K, et al. (1993) Clomipramine versus placebo in the treatment of rapid ejaculation: a pilot study. J Sex Marital Ther 19:198–200.
25. Kaplan HS, Kohl RN, Pomeroy WB, et al. (1974) Group treatment of rapid ejaculation. Arch Sex Behav 3:443–452.
26. Masters W, Johnson V. (1970) Human Sexual Inadequacy. Boston, MA: Little, Brown.
27. Segraves RT, Saran A, Segraves K, Maguire E. (1992) Clomipramine vs placebo in the treatment of rapid ejaculation. Paper presented at the meeting of the International Academy of Sex Research, Prague, Czechoslovakia.
28. Fanciullacci F, Colpi GM, Beretta G, et al. (1988) Cortical evoked potentials in subjects with true rapid ejaculation. Andrologia 20:326–330.
29. Cooper AJ, Magnus RV. (1984) A clinical trial of the beta blocker propranolol in rapid ejaculation. J Psychosom Res 28:331–336.
30. Spiess WF, Geer JH, O'Donohue WT. (1984) Rapid ejaculation: investigation of factors in ejaculatory latency. J Abnorm Psychol 93:242–245.
31. Strassberg DS, Mahoney JM, Schaugaard M, et al. (1990) The role of anxiety in rapid ejaculation: a psychophysiological model. Arch Sex Behav 19:251–257.
32. Strassberg DS, Kelly MP, Carroll C, et al. (1987) The psychophysiological nature of rapid ejaculation. Arch Sex Behav 16:327–336.
33. LoPiccolo J. (1978) Direct treatment of sexual dysfunction in the couple. In: Money J, Mesaph H, eds., Handbook of Sexology: Selected Syndromes and Therapy, Vol. 5. New York, NY: Elsevier, pp. 1227–1246.

34. Kilmann PR, Auerbach R. (1979) Treatments of rapid ejaculation and psychogenic impotence: a critical review of the literature. Arch Sex Behav 8:81–100.
35. Trudel G, Proulx S. (1987) Treatment of rapid ejaculation by bibliotherapy: an experimental study. Sex Marital Ther 2:163–169.
36. Zeiss RA, Christensen A, Levine AG. (1978) Treatment for rapid ejaculation through male-only groups. J Sex Marital Ther 4:139–143.
37. Schover LR, Friedman JM, Weiler SJ, Heiman JR, LoPiccolo J. (1982) Multiaxial problem-oriented system for sexual dysfunctions. Arch Gen Psychiatry 39:614–619.
38. Waldinger M, Hengeveld M, Zwinderman A, et al. (1998) An empirical operationalization of DSM-IV diagnostic criteria for rapid ejaculation. Int J Psychiatry Clin Pract 2:287–294.
39. McMahon CG. (2002) Long term results of treatment of rapid ejaculation with selective serotonin re-uptake inhibitors. Int J Imp Res 14:S19.
40. McCarthy B. (1988) Cognitive-behavioural strategies and techniques in the treatment of early ejaculation. In: Leiblum S, Rosen R, eds., Principles and Practices of Sex Therapy: Update for the 1990's, New York, NY: Guilford Press, pp. 141–167.
41. Vandereycken W. (1986) Towards a better delineation of ejaculatory disorders. Acta Psychiatry Belg 86:57–63.
42. Zilbergeld B. (1978) Male Sexuality. Toronto, Ontario: Bantam Books.
43. Grenier G, Byers ES. (1993) Controlling ejaculation: reality or pipe dream. In: Byers ES (Chair), Testing Common Assumptions About Human Sexuality. Symposium presented at the meeting of the Canadian Psychological Association, Montreal, Canada, May.
44. Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. (1998) An empirical operationalization study of DSM-IV diagnostic criteria for rapid ejaculation. Int J Psych Clin Pract 2:287.
45. Williams W. (1984) Secondary rapid ejaculation. Aust NZ J Psychiatry 18:333–340.
46. Zilbergeld B. (1992) The New Male Sexuality, Toronto, Ontario: Bantam Books
47. Kaplan HS. (1989) PE: How to Overcome Rapid Ejaculation, New York, NY: Brunner/Mazel.
48. Crooks R, Baur K. (1990) Our Sexuality. Don Mills, Ontario: Benjamin/Cummings.
49. Kockott G, Feil W, Revenstorf D, et al. (1980) Symptomatology and psychological aspects of male sexual inadequacy: results of an experimental study. Arch Sex Behav 9:457–475.
50. Hong LK. (1984) Survival of the fastest: on the origin of rapid ejaculation. J Sex Res 20:109–122.
51. Bixler RH. (1986) Of apes and men (including female!). J Sex Res 22:255–267.
52. Ellis H. (1936) Studies in the Psychology of Sex. New York, NY: Random House.
53. Rowland DL, Greenleaf W, Mas M, Myers L, Davidson JM. (1989) Penile and finger sensory thresholds in young, aging, and diabetic males. Arch Sex Behav 18:1–12.
54. Xin ZC, Chung WS, Choi YD, et al. (1996) Penile sensitivity in patients with primary rapid ejaculation. J Urol 156:979–981.
55. Xin ZC, Choi YD, Rha KH, et al. (1997) Somatosensory evoked potentials in patients with primary rapid ejaculation. J Urol 158:451–455.
56. Paick JS, Jeong H, Park MS. (1998) Penile sensitivity in men with rapid ejaculation. Int J Impot Res 10:247–250.
57. Rowland DL, Haensel SM, Blom JH, et al. (1993) Penile sensitivity in men with rapid ejaculation and erectile dysfunction. J Sex Marital Ther 19:189–197.
58. Gospodinoff M. (1989) Rapid ejaculation: clinical subgroups and etiology. J Sex Marital Ther 15:130–134.

59. Semans JH. (1956) Rapid ejaculation: new approach. South Med J 49:353–358.
60. Pirke KM, Kockott G, Aldenhoff J, et al. (1979) Pituitary gonadal system function in patients with erectile impotence and rapid ejaculation. Arch Sex Behav 8:41–48.
61. Cohen PG. (1997) The association of rapid ejaculation and hypogonadotropic hypogonadism. J Sex Marital Ther 23:208–211.
62. Cohen PG, Holbrook JM. (1999) Effects of fenfluramine on ejaculatory function, luteinizing hormone and testosterone levels in men with hypogonadotropic hypogonadism and rapid ejaculation. Int Clin Psychopharmacol 14:91–95.
63. Marson L, McKenna KE. (1990) The identification of a brainstem site controlling spinal sexual reflexes in male rats. Brain Res 515:303–308.
64. Yells DP, Prendergast MA, Hendricks SE, et al. (1994) Fluoxetine-induced inhibition of male rat copulatory behavior: modification by lesions of the nucleus paragigantocellularis. Pharmacol Biochem Behav 49:121–127.
65. MacLean PD. (1975) Brain mechanisms of primal sexual functions and related behavior. In: Sandler M, Gessa GL, eds., Sexual Behavior: Pharmacology and Biochemistry. New York, NY: Raven Press.
66. Yells DP, Hendricks SE, Prendergast MA. (1992) Lesions of the nucleus paragigantocellularis: effects on mating behavior in male rats. Brain Res 596:73–79.
67. Ahlenius S, Larsson K, Svensson L, et al. (1981) Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. Pharmacol Biochem Behav 15: 785–792.
68. Waldinger MD, Berendsen HH, Blok BF, et al. (1998) Rapid ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. Behav Brain Res 92:111–118.
69. Waldinger MD. (2002) The neurobiological approach to rapid ejaculation. J Urol 168:2359–2367.
70. De Amicis LA, Goldberg DC, LoPiccolo J, et al. (1985) Clinical follow-up of couples treated for sexual dysfunction. Arch Sex Behav 14:467–489.
71. Hawton K, Catalan J, Martin P, et al. (1986) Long-term outcome of sex therapy. Behav Res Ther 24:665–675.
72. Kery S, Kozma A. (1995) Ejaculatio praecox citalopram kezelese. Magyar Urologia (Hungarian) 7:359–365.
73. Patterson WM. (1993) Fluoxetine-induced sexual dysfunction. J Clin Psychiatry 54:71.
74. Waldinger MD, Hengeveld MW, Zwinderman AH, et al. (1998) Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. J Clin Psychopharmacol 18:274–281.
75. Waldinger MD, Zwinderman AH, Olivier B. (2001) SSRIs and ejaculation: a double-blind, randomized, fixed-dose study with paroxetine and citalopram. J Clin Psychopharmacol 21:556–560.
76. Atmaca M, Kuloglu M, Tezcan E, et al. (2002) The efficacy of citalopram in the treatment of rapid ejaculation: a placebo-controlled study. Int J Impot Res 14: 502–505.
77. Waldinger MD. (2003) Towards evidenced based drug treatment research on rapidejaculation: a critical evaluation of methodology. J Impot Res 15:309–313.
78. Ahlenius S, Heimann M, Larsson K. (1979) Prolongation of the ejaculation latency in the male rat by thioridazine and chlorimipramine. Psychopharmacol (Berl) 65:137–140.
79. Goodman RE. (1980) An assessment of clomipramine (Anafranil) in the treatment of rapid ejaculation. J Int Med Res 8:53–59.

80. Girgis SM, El-Haggar S, El-Hermouzy S. (1982) A double-blind trial of clomipramine in rapid ejaculation. Andrologia 14:364–368.
81. Althof SE, Levine SB, Corty EW, et al. (1995) A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. J Clin Psychiatry 56:402–407.
82. Montorsi F, Guazzoni L, Barbieri L, Rigatti P. (1994) Clomipramine for rapid ejaculation: a randomized, double blind placebo controlled study. Proceedings, VI World Meeting on Impotence, Singapore (abstract no. D74).
83. Haensel SM, Rowland DL, Kallan KT. (1996) Clomipramine and sexual function in men with rapid ejaculation and controls. J Urol 156:1310–1315.
84. Strassberg DS, de Gouveia Brazao CA, Rowland DL, et al. (1999) Clomipramine in the treatment of rapid (rapid) ejaculation. J Sex Marital Ther 25:89–101.
85. Hsieh JT, Chang HC, Law HS, et al. (1998) In vivo evaluation of serotonergic agents and alpha-adrenergic blockers on rapid ejaculation by inhibiting the seminal vesicle pressure response to electrical nerve stimulation. Br J Urol 82: 237–240.
86. Berendsen H, Broekkamp CL. (1990) Behavioural evidence for functional interactions between 5-HT receptor sub-types in rats and mice. Br J Pharmacol 101: 667–673.
87. Hillegaart V, Ahlenius S. (1998) Facilitation and inhibition of male rat ejaculatory behaviour by the respective 5-HT1A and 5-HT1B receptor agonists 8-OH-DPAT and anpirtoline, as evidenced by use of the corresponding new and selective receptor antagonists NAD-299 and NAS-181. Br J Pharmacol 125:1733–1743.
88. Bergstrom RF Lemberger L, Farid NA Wolen RL. (1998) Clinical pharmacology and pharmacokinetics of fluoxetine: a review. Br J Psychiatry Suppl Sep:47–50.
89. Crenshaw RT. (1992) Treatment of rapid ejaculation with fluoxetine. In: Proceedings of American Psychiatric Association Meeting, May.
90. Power-Smith P. (1994) Beneficial sexual side-effects from fluoxetine. Br J Psychiatry 164:249–250.
91. Forster P, King J. (1994) Fluoxetine for rapid ejaculation. Am J Psychiatry 151:1523.
92. Lee H S, Song DH, Kim CH, et al. (1996) An open clinical trial of fluoxetine in the treatment of rapid ejaculation. J Clin Psychopharmacol 16:379–382.
93. Grazziotin A. (1995) Prozac in the treatment of rapid ejaculation. J Urol 153: 474A.
94. Kara H, Aydin S, Yucel M, et al. (1996) The efficacy of fluoxetine in the treatment of rapid ejaculation: a double-blind placebo controlled study. J Urol 156: 1631–1632.
95. Haensel SM, Klem TM, Hop WC, Slob AK. (1998) Fluoxetine and rapid ejaculation: a double-blind, crossover, placebo-controlled study. J Clin Psychopharmacol 18:72–77.
96. Murray MJ, Hooberman D. (1993) Fluoxetine and prolonged erection. Am J Psychiatry 150:167–168.
97. Benazzi F. (1995) Involuntary sperm emission with fluoxetine. Can J Psychiatry 40:431.
98. Koe BK, Lebel A, Burkhart CA, Schmidt AW (1989) Sertraline: a potent inhibitor of (+) [3H]3-PPP binding to brain sigma (o-) receptors. 19th meeting, Society for Neuroscience Abstracts, 15(pt. 2):1235.
99. Swartz DA. (1994) Sertraline hydrochloride for rapid ejaculation. J Urol 151:3454.
100. Balbay MD, Yildiz M, Salvarci A, et al. (1998) Treatment of rapid ejaculation with sertralin. Int Urol Nephrol 30:81–83.
101. McMahon CG. (1998) Treatment of rapid ejaculation with sertraline hydrochloride. Int J Impot Res 10:181–184.

102. Kaplan PM. (1994) The use of serotonergic uptake inhibitors in the treatment of rapid ejaculation. J Sex Marital Ther 20:321–324.
103. Wise TN. (1994) Sertraline as a treatment for rapid ejaculation. J Clin Psychiatry 55:417.
104. Mendels J, Camera A, Sikes C. (1995) Sertraline treatment for rapid ejaculation. J Clin Psychopharmacol 15:341–346.
105. McMahon CG. (1998) Treatment of rapid ejaculation with sertraline hydrochloride: a single-blind placebo controlled crossover study. J Urol 159:1935–1938.
106. Biri H, Isen K, Sinik Z, et al. (1998) Sertraline in the treatment of rapid ejaculation: a double-blind placebo controlled study. Int Urol Nephrol 30:611–615.
107. Kaye CM, Haddock RE, Langley PF, et al. (1991) A review of the metabolism and pharmacokinetics of paroxetine in man. Acta Psychiatry Scand 80:60–75.
108. Waldinger MD, Hengeveld MW, Zwinderman AH. (1997) Ejaculation-retarding properties of paroxetine in patients with primary rapid ejaculation: a double-blind, randomized, dose-response study. Br J Urol 79:592–595.
109. Ludovico GM, Corvasce A, Pagliarulo G, et al. (1996) Paroxetine in the treatment of rapid ejaculation. Br J Urol 77:881–882.
110. Giammusso B, Morgia G, Spampinato A, et al. (1997) Paroxetine in the treatment of rapid ejaculation. Arch Ital Urol Androl 69:11–16.
111. McMahon CG, Touma K. (1999) Treatment of rapid ejaculation with paroxetine hydrochloride. Int J Impot Res 11:241–245.
112. Isaksen PM. [The effect of an antidepressive agent on rapid ejaculation. Tidsskr Nor Laegeforen 115:1616–1617.
113. Hiemke C. (1994) Paroxetine: pharmacokinetics and pharmacodynamics. (Article in German.) Fortschritte der Neurologie-Psychiatrie 62:2–8.
114. Bloomer JC, Woods FR, Haddock RE, Lennard MS, Tucker GT. (1992) The role of cytochrome P450 2D6 in the metabolism of paroxetine by human liver microsomes. Br J Clin Pharmacol 33:521–523.
115. Preskorn S. (1993) Pharmacokinetics of anti-depressants: why and how they are relevant to treatment. J Clin Psychiatry 54:14–34.
116. McMahon CG. (2002) High dose sildenafil citrate as a salvage therapy for severe erectile dysfunction. Int J Impot Res 14:533–538.
117. Murat Basar M, Atan A, Yildiz M, et al. (1999) Comparison of sertraline to fluoxetine with regard to their efficacy and side effects in the treatment of rapid ejaculation. Arch Esp Urol 52:1008–1011.
118. Dawson T, Snyder SH. (1994) Gases as biological messengers: nitric oxide carbon monoxide in the brain. J Neurosci 14:5147–5159.
119. Garthwaite J, Charles, SL, Chess-Williams, R. (1988) Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. Nature 336:385–388.
120. Bredt DS, Glatt CE, Hwang PM, Fotuhi M, Dawson TM, Snyder SH. (1991) Nitric oxide synthase protein and mRNA are discretely localized in neuronal populations of mammalian CNS together with NADPH diaphorase. Neuron 7:615–624.
121. Nelson RJ, Demas GE, Huang PL, et al. (1995) Behavioral abnormalities in male mice lacking neuronal nitric oxide synthase. Nature 378:383–386.
122. Vincent SR, Kimura H. (1992) Histochemical mapping of nitric oxide synthase in the rat brain. Neuroscience 46:755–784.
123. Sato Y, Horita H, Kurohata T, et al. (1998) Effect of the nitric oxide level in the medial preoptic area on male copulatory behavior in rats. Am J Physiol 274:R243–R247.
124. Hull EM, Lumley LA, Matuszewich L, et al. (1994) The roles of nitric oxide in sexual function of male rats. Neuropharmacology 33:1499–1504.

125. Lorrain DS, Hull EM. (1993) Nitric oxide increases dopamine and serotonin release in the medial preoptic area. Neuroreport 5:87–89.
126. Kriegsfeld LJ, Demas GE, Huang PL. et al. (1999) Ejaculatory abnormalities in mice lacking the gene for endothelial nitric oxide synthase (eNOS–/–). Physiol Behav 67:561–566.
127. Abdel-Hamid IA, El Naggar EA, El Gilany AH. (2001) Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in rapid ejaculation. Int J Impot Res 13:41–45.
128. Salonia A, Maga T, Colombo R, et al. (2002) A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with rapid ejaculation. J Urol 168:2486–2489.
129. Chen J, Mabjeesh NJ, Matzkin H, et al. (2003) Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating rapid ejaculation. Urology 61:197–200.
130. McMahon CG, Anderson M, Boolell M, et al. (2003) Efficacy of Viagra® (sildenafil citrate) in men with premature ejaculation. Int J Impot Res 15(Suppl 6):S23.
131 Stefanick ML, Smith ER, Davidson JM. (1983) Penile reflexes in intact rats following anesthetization of the penis and ejaculation. Physiol Behav 31:63–65.
132. Sachs BD, Liu YC. (1991) Maintenance of erection of penile glans, but not penile body, after transection of rat cavernous nerves. J Urol 146:900–905.
133. Wieder JA, Brackett NL, Lynne CM, et al. (2000) Anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation in men with spinal cord injuries. Urology 55:915–917.
134. Aycock L. (1949) The medical management of rapid ejaculation. J Urol 62:361–365.
135. Damru F. (1963) Rapid ejaculation: use of ethyl aminibenzoate to prolong coitus. J Urol 89:936–939.
136. Berkovitch M, Keresteci AG, Koren G. (1995) Efficacy of prilocaine-lidocaine cream in the treatment of rapid ejaculation. J Urol 154:1360–1361.
137. Sahin H, Bircan MK. (1996) Re: efficacy of prilocaine-lidocaine cream in the treatment of rapid ejaculation. J Urol 156:1783–1784.
138. Atan A, Basar MM, Aydoganli L. (2000) Comparison of the efficacy of fluoxetine alone vs. fluoxetine plus local lidocaine ointment in the treatment of rapid ejaculation. Arch Esp Urol 53:856–858.
139. Xin ZC, Choi YD, Choi HK. (1996) The effects of SS-cream and its individual components on rabbit corpus cavernosal muscles. Yonsei Med J 37:312–318.
140. Xin ZC, Choi YD, Lee SH, et al. (1997) Efficacy of a topical agent SS-cream in the treatment of rapid ejaculation: preliminary clinical studies. Yonsei Med J 38:91–95.
141. Xin ZC, Choi YD, Seong DH, Choi HK. (1995) Sensory evoked potential and effect of SS-cream in rapid ejaculation. Yonsei Med J 36:397–401.

18 Sexual Dysfunction After Radical Prostatectomy and the Use of PDE-5 Inhibitors

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CONTENTS

INTRODUCTION

Prostate cancer and its treatment invoke the fear of "castration" and death in many men. Every man has heard of notable men with prostate cancer (Table 1).

Fear of the condition can lead to avoidance of physicians and screening. In an American Urological Association survey in 2000 by Roper Starch Worldwide of over 1000 men, 74% of men over the age of 50 felt that the fear of the side effects of treatment prevented men from being screened. Twenty percent of men who were not being screened annually acknowledged that their avoidance was a result of fear, both of the side effects of treatment and/or of learning that they had cancer. Their wives felt the number was closer to 33%. To worsen matters, prostate cancer affects men during a period of their life of waning hormonal, sexual, and erectile function. Over 50% of the men diagnosed with prostate cancer will be at risk for erectile dysfunction (ED), hypogonadism, or both (Table 2).

In a study at The Cleveland Clinic, as many as 36% of the men had ED at the time of diagnosis *(1)*. In a community practice where the average age

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Table 1
Famous Men With Prostate Cancer

Name	*Profession*	*Name*	*Profession*
Louis Farrakhan	Evangelist, Activist	Richard Petty	NASCAR champion driver
Norman Schwartzkopf	General, Desert Storm	Len Dawson	NFL Hall-of-Famer
Francois Mitterand	President of France	Jim Calhoun	College basketball coach
Nelson Mandela	President of South Africa	Fred Bilentnikoff	NFL player and coach
Rudy Giuliani	Former Mayor of New York City	Stan Musial	Baseball Hall-of-Famer
John Kerry	Presidential candidate	Marv Levy	NFL coach, Buffalo Bills
Bob Dole	Presidential candidate	Jim Colbert	PGA Champion
Linus Pauling, PhD	Nobel Prize-winner	Joe Torre	Manager, New York Yankees
Andy Grove	CEO of INTEL Corporation	Frank Gifford	NFL Hall-of-Famer/TV sports announcer
Pat Robertson	TV evangelist	Bill Bixby	Actor
Desmund Tutu	Nobel Peace Prize-winner	Roger Moore	Actor
Rupert Murdoch	Media magnate	Frank Zappa	Singer/Composer/Performer
Richard Riordan	Former Mayor of Los Angeles	Henry Belafonte	Actor/Musician
Robert Mueller	FBI Director	Charlton Heston	Actor
Herb Kelleher	Airline President and CEO	Herbie Mann	Musician
Wayne Calloway	PEPSICO Chairman	Barry Bostwick	Actor
Ben Campbell	US Senator	Robert Novak	TV Journalist
Arnold Palmer	PGA champion	Robert Goulet	Musician/Actor
Bob Hayes	Olympic Gold-medalist	Louis Gossett, Jr.	Academy Award®-winning actor
Bobby Riggs	Tennis Champion	Telly Savalas	Actor
Don Nelson	NBA coach	Robert De Niro	Academy Award®-winning actor
Dusty Baker	Manager, San Francisco Giants	Hume Cronyn	Actor
Eddie Arcaro	Master jockey	Sean Connery	Academy Award®-winning actor

Table 2
Prevalence of Prostate Cancer,[a] ED *(29)*, and Hypogonadism *(30)* vs Age

	35–44	*45–54*	*55–64*	*65–74*	*75–84*	*85+*
Prostate cancer prevalence (%)	.4	7.1	24.6	39.3	23.6	4.9
ED prevalence (%)	4	26	40	60	60+	—
Hypogonadism incidence (%)	2	10	30	45	70	—

[a] SEER Cancer Review 1975–2000. ED, erectile dysfunction.

at the time of diagnosis is higher, one can anticipate an even higher rate of sexual dysfunction. These fears, as well as the fears of death and incontinence, all surface with the words "Mr. Smith your PSA is elevated. I think we need to do a prostate biopsy."

The incorporation of the prostate-specific antigen (PSA) and the transrectal ultrasound (TRUS) biopsy probe into the standard urological practice had a dramatic impact on the incidence of prostate cancer in the US, and a downward stage migration at presentation. No longer were men presenting with late-stage disease or undergoing painful perineal biopsies. The biopsy no longer required an anesthetic or a hospitalization. Within a 6-yr (1986–1992) period, the annual number of cases diagnosed doubled. Most patients are now detected by PSA elevation, not palpable disease.

Though generally well-tolerated under a local anesthetic, the TRUS biopsy in not without side effects or complications. In a prospective study of 211 men undergoing prostate biopsies, intraoperative pain was considered severe in 20% of the biopsy events. Preoperative anxiety was reported in 64% of biopsy events and predictive of intraoperative pain. Anxiety continued post biopsy and peaked before result disclosure. ED attributed to anxiety in anticipation of biopsy was reported in 7% of cases. The rate of ED doubled to 15% at 7 and 30 d after the biopsy, well after the anxiety of the biopsy resolved *(2)*. Although it might be natural to attribute the increase in ED to the psychological stress and trauma of the biopsy, the location of the posterolateral location of the delicate cavernous nerves make them subject to injury during extensive transrectal biopsies. The trend for an increasing number of biopsy samples and the increasingly liberal recommendation for prostate biopsies theoretically increases the risk of cavernous nerve injury. Experiencing hematospermia for 6 wk after the biopsy can increase anxiety around sexual activity.

Men who receive news of a positive biopsy will usually go on to treatment that will invariably worsen their function. Men with negative biopsies are so relieved, that they may attribute their decreased function to the stress of the process. More prospective studies should be undertaken to objectively evaluate the risk of ED after prostate biopsy, as it may have some bearing on subsequent posttreatment function.

Table 3
Results of "Google" Search

Search word	*Number of sites*
Prostate cancer	1,550,000
Prostate cancer surgery	785,000
Prostate cancer radiation	354,000
Prostate cancer alternative approach	260,000
Prostate cancer observation	58,800
Radical prostatectomy	46,400
Prostate cancer cryosurgery	12,200

THE PATIENT'S UNDERSTANDING OF DIAGNOSIS

Patients receiving the diagnosis of prostate cancer are devastated. The diagnosis of cancer is accompanied with a high incidence of anxiety, depression, self-image insult, sexual dysfunction, social isolation, and dysfunction *(3)*. The patient's understanding of what is discussed is frequently different from the physicians' perception. Under favorable circumstances, we are lucky if patients remember 50% of what is communicated. In a prospective study of orthopedic patients repeatedly educated preoperatively about the risks and benefits of joint replacement until they could answer all questions correctly, postoperatively, only 25% remembered the risk of infection, 22% recalled the potential benefits for relief of pain, improved function or improved motion, and 2% remembered the risk of damage to a nerve or artery *(4)*. It is a small wonder that a patient and his partner will fail to understand that nerve sparing does not necessarily mean preservation of potency or that, even if he has postoperative potency, it will not be comparable to his preoperative state and may require erectogenic aids. His concern about a cancer cure and survival far outweigh trying to sort out the fine details of semantics.

After leaving the physician's office, patients, their partners, or their families will turn to most the readily accessible information source—the Internet. Although only 19% of patients in 2000 sought information on the Internet, that number has undoubtedly increased. A "Google" search in February 2004 revealed more sites than can be investigated in a lifetime (Table 3). Patients are flooded with information and misinformation. Unfortunately, many sites are nothing more than commercial sites. There is no peer review or oversight of the Internet. By the time the patient comes to treatment, his understanding of the treatment and its risks and benefits are a combination of the physicians' advice (including possibly conflicting second opinions), Internet information, and anecdotal information from family and friends.

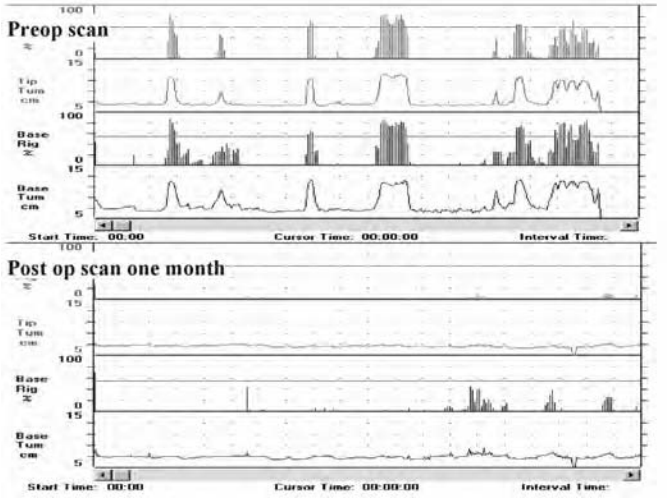

Fig. 1. Nocturnal penile tumescence scan pre- and postsurgery.

RADICAL SURGERY

The treatment of prostate cancer invariably results in changes in sexual and erectile function. The degree to which the patient will be distressed will depend on his level of pretreatment function and drive, the degree functional impairment, and his sexual partner. Assuming that the man does not choose observation, his choices of treatment are radical surgery, external beam or interstitial radiation therapy with or without adjuvant hormonal therapy, and cryosurgery. For the purposes of this chapter, we will focus on the treatment of sexual dysfunction after radical prostatectomy.

The advantages of surgery include definitive staging, possible cure if the tumor is pathologically confined, treatment of concomitant benign prostatic hyperplasia (BPH), reliable PSA suppression to nonrecordable levels, easy monitoring for recurrent disease, and arguably decreased patient anxiety during follow-up. The disadvantages are that it is a major operation with low but definite mortality (<0.3%) and definite morbidity—impotence (>50%), ejaculatory dysfunction (100%), orgasmic dysfunction (50%), incontinence (<5–30%), pulmonary embolism (<1%), rectal injury (<1%), urethral stricture (<5%), and transfusion (20%).

The sexual dysfunction begins immediately after the surgery, with virtually all men experiencing ED. Nocturnal, morning, and psychogenic erections disappear instantly. Though an occasional man will report erections with the catheter indwelling, this occurrence is clearly the exception. The profound loss of nocturnal erections had been reported in both retrospective and prospective series *(5–7)* (Fig. 1).

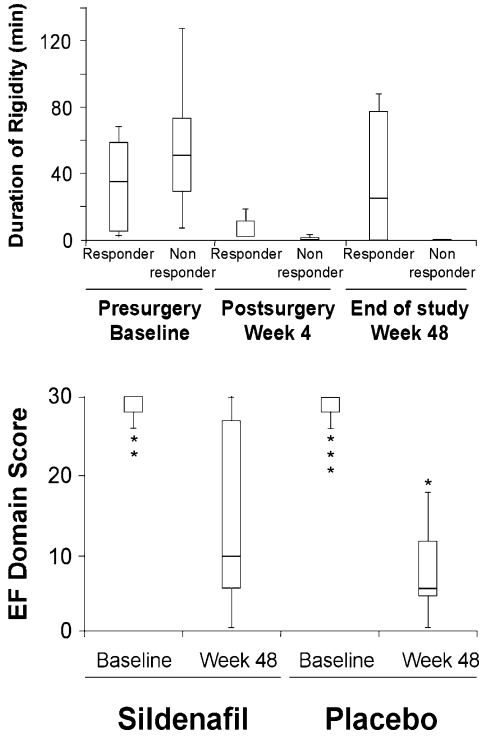

Fig. 2. Nocturnal erection rigidity and erectile function domains in men preoperatively and postoperatively *(5)*. EF, erectile function.

The etiology of the immediate loss of nocturnal activity, although debated by experts in the past, appears to be the result of intraoperative neuropraxia. There is little evidence of arterial injury on such a large scale after radical prostatectomy *(8)*. Over time, there does appear to be recovery of the nocturnal activity that corresponds with an increase in natural erectile function *(5)* (Fig. 2).

The recovery of erectile function is agonizingly slow, requiring as many as 18 to 24 mo, consistent with a slowly resolving neuropraxia *(9)*. As the neuropraxia resolves, the penis becomes increasingly responsive to sildenafil as one might expect, because the mechanism of sildenafil and the other phosphodiesterase (PDE)-5 inhibitors is dependent of the production of nitric oxide from the nerve endings. Success with sildenafil in the first 6 mo can be expected to be very low *(10)*.

With increasingly accurate predictors of localized disease, most patients will know with some degree of certainty whether of not they will have a bilateral, unilateral, or nonsparing surgery before the surgery itself *(11,12)*.

They again assume that bilateral nerve sparing is synonymous with preservation of potency, not realizing that few men are as good postoperatively as they were preoperatively, and the term *potent* is increasingly defined as "with the aid of the PDE-5 inhibitors"*(9)*.

The initial euphoria of having survived the operation is replaced by the reality of incontinence, which resolves for the most part in the first 3 mo. Concern over survival and continence then gets replaced with concern about potency. Patents do not understand why they have not yet regained their erectile function if their nerves were preserved, their PSA is 0, and the continence is near perfect. To make matters worse, it appears that their penises are shrinking. Most of the reduction in circumference and length occurs in the first 3 mo *(13)*. These observations are supported by animal models of penile denervation *(14,15)*. Age of 65 and preoperative sildenafil predict a poor postoperative response rate *(16,17)*. Many patients and their physicians become discouraged with early unsuccessful attempts with PDE-5 inhibitors not realizing that a rechallenge at 18 to 24 mo postoperatively might result in a successful outcome *(10)*. Experiencing repeated failure, many lose interest in attempting sexual activity and withdraw from sexual intimacy, despite normal preoperative drive. In a longitudinally followed consecutive cohort of 130 men with intact preoperative erectile function and normal sexual desire at New York University, only 48% and 58% maintained their sexual desire at 3 and 24 mo, respectively (unpublished data). Their partner, not wanting to pressure them or make them feel badly, withdrew sexually as well.

Ultimately, the response to the three PDE-5 inhibitors—sildenafil, varedenafil, and tadalafil—appears to be similar, although no direct comparator trials exist for the radical prostatectomy patients.

The efficacy of sildenafil was evaluated in the initial pivotal trials as patients after prostatectomy were included in the general trials. No stratification was made as to age or nerve-sparing status. An overall response rate of 43% was seen in improvement of erection quality with a placebo rate of 14%. In a nonrandomized, nonconsecutive, highly selected population of 91 men taking sildenafil after radical retropubic prostatectomy, Zippe reported a 72% rate of "erections satisfactory for vaginal penetration" in patients with bilateral nerve-sparing vs 50% in men with unilateral nerve-sparing *(18)*. At 3 yr, 31 (71%) of the 43 patients who had returned the surveys were still responding to sildenafil. Of these 31 respondents, 10 (31%) had augmented their dose from 50 to 100 mg. The dropout rate was 27%; six of 12 had discontinued use because of the return of natural erections, five because of a loss of efficacy, and one because his spouse had died *(19)*.

In a double-blind, placebo-controlled study, vardenafil was studied in 440 men after unilateral and bilateral nerve-sparing starting 6 mo after

surgery. Seventy percent had severe ED. Among men with bilateral neurovascular bundle-sparing, improved erections were reported by 71.1% and 59.7% of patients on 20 and 10 mg of vardenafil, respectively, vs 11.5% of those on placebo. The average intercourse success rate per patient receiving 20 mg vardenafil was 74% in men with mild to moderate ED, and 28% in men with severe ED, compared with 49 and 4% for placebo, respectively. Sildenafil nonresponders were excluded from the studies, and over 50% of men were at least partial responders to sildenafil prior to entry. The inclusion of such a high proportion of sildenafil responders is reflected in the high placebo response rate in the placebo group of men with mild to moderate ED. The exclusion of sildenafil failures and enrichment with sildenafil responders must be taken into consideration when counseling patients on this medication *(20)*.

Tadalafil was similarly studied in a group of 303 men (mean age 60 yr) with preoperative normal erectile function who had undergone a bilateral nerve-sparing RRP 12 to 48 mo prestudy, randomized (2:1) to tadalafil (n = 201) or placebo (n = 102). The three coprimary endpoints were changes from baseline in the International Index of Erectile Function (IIEF) erectile function domain score, and the percentage of positive responses to Sexual Encounter Profile questions two (successful penetration) and three (successful intercourse). The Global Assessment Question and the Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire were secondary endpoints. A subgroup of patients (n = 201) was *a priori*-identified, reporting evidence of postoperative tumescence, defined as greater than or equal to 50% "yes" responses to Sexual Encounter Profile question one (ability to achieve at least some erection) during baseline intercourse attempts and stratified randomization based on this criterion. During treatment for all randomized patients receiving tadalafil, the mean percentage of successful penetration attempts was 54% and the mean percentage of successful intercourse attempts was 41%. For the subgroup with evidence of postoperative tumescence, these values were 69% and 52%, respectively. Sixty-two percent of all patients randomized to tadalafil and 71% of the subgroup patients randomized to tadalafil reported improved erections *(21)*. Eighty percent of the men were previous sildenafil users, although failure to respond to sildenafil was not exclusionary, unlike the vardenafil study.

With overall success rates hovering around 50%, McMahon researched using high doses of sildenafil in sildenafil failures in 54 patients with chronic erectile failure who had previously failed to respond to a home trial of sildenafil (100 mg) and with erections suitable for sexual intercourse were studied. Each man was treated at home with sildenafil at escalating doses of up to 200 mg until either maximal response or intolerable adverse

effects occurred. Erectile function was quantified using the erectile function domain of the IIEF before treatment, with 100 mg sildenafil, a maximal dose of sildenafil, and a global efficacy question after 4 wk of treatment.

The mean age of the study group was 59.6 with 11 of 54 (20%) showing post-RRP ED. Thirteen of 54 (24.1%) responded to sildenafil at a median maximal dose of 200 mg, four of 13 required 150 mg, and nine of 13 required 200 mg. Forty-one of 54 (76%) failed to respond to sildenafil. Mean IIEF question three and four scores were 1.5 and 1.4 at baseline, 2.2 and 1.9 with 100 mg of sildenafil, 2.8 and 2.5 with 150 mg of sildenafil, and 3.0 and 2.9 with 200 mg of sildenafil, respectively. After 4 wk, treatment was regarded as having improved their erections by 37, 46.3, and 68% of patients with 100, 150, and 200 mg of sildenafil, respectively. Thirty-four of 54 (63%) reported adverse effects with a maximal dose of sildenafil comprising headache (19), facial flushing (32), dyspepsia (14), nasal congestion (11), dizziness (5), and visual disturbances (5). Four of 13 (31%) responders refused to continue treatment because of adverse effects. It was concluded that sildenafil at doses of up to 200 mg was an effective salvage therapy for 24.1% of previous sildenafil nonresponders, but was limited by a significantly higher incidence of adverse effects and a 31% treatment discontinuation rate. High dose studies have not been carried out for vardenafil or tadalafil. Currently the maximum doses approved by the FDA are 100, 20, and 20 mg for sildenafil, vardenafil, and tadalafil, respectively *(22)*.

The options for nonresponders include injection therapy, intraurethral prostaglandin, vacuum erection devices, or penile implant. The concomitant use of the PDE-5 inhibitors is discouraged in the regulatory document for all three PDE-5 inhibitors. Nonetheless, there exists a rationale for combination therapy. Corpus cavernosum smooth muscle relaxation and, hence penile erection, are regulated in part by increases in smooth muscle synthesis of the second messengers cyclic adenosine monophosphate and cyclic guanosine monophosphate. Intraurethral or intracorporal prostaglandin E1 increase both second messengers. Therefore, in men failing PDE-5 inhibition or prostaglandin therapy, perhaps a synergistic effect might occur with combination therapy. Nehra studied 28 patients using sildenafil and medicated uretheral system for erection (MUSE) (mean age of 59), 17 who had undergone radical prostatectomy, and 11 who had a diagnosis of organic erectile dysfunction for 30 mo.

Treatment with either 100 mg of sildenafil citrate and/or 1000 μg of MUSE had failed in these patients. Combination therapy was initiated using 100 mg of sildenafil citrate orally 60 min before intercourse, and 500 μg of MUSE intraurethrally immediately before intercourse. At 30 mo, all 28 patients reported erections sufficient for vaginal penetration, with

3.6 intercourse episodes per month. None of the patients crossed over to intracavernosal therapy or penile prosthesis. It was concluded that combination therapy, incorporating both pathways cyclic adenosine monophosphate and cyclic guanosine monophosphate, might succeed when single therapies fail *(23)*. Along those lines in my practice, I also combine sildenafil with intracorporal injections after radical prostatectomy in men who are failing intracorporal injection therapy. The combined use of sildenafil with injection therapy, though logistically cumbersome, had allowed some patients to avoid implant therapy *(24)*.

We reported sildenafil usage longitudinally in 200 men with preoperative normal sexual function and bilateral nerve-sparing surgery at the American Urological Association in 2003 *(25)*. At 3 mo 52% were utilizing sildenafil, although less than 10% were able to achieve and maintain erections satisfactory for intercourse vs 35% in subsequent follow-up at 24 mo. At 24 mo, 50% of men were still on sildenafil, 27% were using injection therapy, and 22% were using nothing. Erectile function after surgery can still be improved.

Might there be a benefit for earlier exposure to PDE-5 inhibitors with respect to subsequent return of function? There is some evidence that early postoperative intervention with intracavernosal injection of vasoactive drugs may improve the rate-of-return of spontaneous erections *(26)*. Additionally, it has been demonstrated that sildenafil taken prior to sleep may improve nocturnal erections in men with general ED *(27)*.

Padma Nathan reported the results of a randomized, placebo-controlled study, examining the benefits of nightly administration of sildenafil during the postoperative period for the return of natural function at 48 wk after surgery following a bilateral nerve-sparing RRP. This study included 125 men with normal preoperative erectile function (a combined score of $\geq$8 for questions three and four from the IIEF indicating that they were able to achieve and maintain an erection on the majority of occasions). Four weeks postsurgery, patients were randomized to either sildenafil (50 mg, $n = 23$; 100 mg, $n = 28$) or placebo ($n = 25$) and entered a 36-wk, double-blind, randomized, parallel-phase, placebo-controlled, fixed-dose treatment period with drug administration nightly, prior to bedtime; the postoperative assessment occurred 8 wk after discontinuation of drug treatment. The return of normal erectile function was assessed at wk 48 by asking the question, "Over the past 4 wk, have your erections been good enough for satisfactory sexual activity?" and by administration of the IIEF and nocturnal RigiScan assessment. A positive responder to the study was one who responded "yes" to the above question and who also scored greater than or equal to eight on the sum of questions three and four of the IIEF. Of 76 patients analyzed for efficacy postbilateral nerve-spar-

ing RRP, 15 of 76 patients (19.7%) were categorized as responders with the return of normal spontaneous erectile function; six of 23 (26%) and eight of 28 patients (29%) were responders in the 50- and 100 mg sildenafil group, respectively, compared with one of 25 (4%) in the placebo group ($p = 0.037$). Nightly administration of sildenafil post-RRP resulted in an approximately sevenfold increase in return of spontaneous erections with placebo *(5)*. The results, though impressive, need further validation before this innovative approach is generally recommended.

Would the longer-acting PDE-5 inhibitor tadalafil provide additional benefit? Currently, long-term studies on the daily use of tadalafil have only been performed for 6 mo in the assessment of sperm toxicity, not erectile function. No studies have been carried out on the effect of long-term daily use in erectile function. With a long half-life, there exists the theoretic possibility of PDE-5 upregulation and tachyphylaxis *(28)*. Currently, the daily use of a PDE-5 inhibitor for the prevention of ED is considered "off-label" use for any of the PDE-5 inhibitors.

CONCLUSION

The PDE-5 inhibitors are the first line of therapy for ED. The response rate after radical prostatectomy is the lowest of any treatment group and reflects intraoperative nerve damage and probable secondary smooth muscle damage. Age at the time of surgery, time from surgery, preoperative ED, and type of surgery clearly affect eventual response rates. All PDE-5 inhibitors have comparable response rates. Combination therapy may be useful in salvaging failures. The early use of sildenafil after surgery may improve the eventual return of function.

REFERENCES

1. Schover LR, Fouladi RT, Warneke CL, et al. (2002) Defining sexual outcomes after treatment for localized prostate carcinoma. Cancer 95:1773–1785.
2. Zisman A, Leibovici D, Kleinmann J, et al. (2001) The impact of prostate biopsy on patient well-being: a prospective study of pain, anxiety and erectile dysfunction. J Urol 165:445–454.
3. Turns D. (2001) Psychosocial issues: pelvic exenterative surgery. J Surg Oncol 76: 224–236.
4. Hutson MM, Blaha JD. (1991) Patients' recall of preoperative instruction for informed consent for an operation. J Bone Joint Surg Am 73:160–162.
5. Padman-Nathan H, McCullough A,Guiliano F,Toler S,Wohlhuter C, Shlipsky A. (2003) Postoperative nightly administration of sildenafil citrate significantly improves normal spontaneous erectile function after bilateral nerve-sparing radical prostatectomy. JUrol 169:375.
6. Fraiman M, Lepor H, McCullough A. (1991) Nocturnal penile tumescence activity in 81 patients presenting with erectile dysfunction after nerve sparing radical prostatectomy. J Urol 161:179.

7. McCullough A, Levine L, Padma-Nathan H. (2002) A prospective study of preoperative and postoperative nocturnal penile tumescence (npt) in men undergoing bilateral nerve sparing radical prostatectomy (BNSRRP). J Androl March/Apri:59.
8. McCullough A, Woo K, Telegrafi S, Lepor H. (2002) Is sildenafil failure in men after radical retropubic prostatectomy (RRP) due to arterial disease? Penile duplex doppler findings in 174 men after RRP. Int J Impot Res 14:462–465.
9. Walsh PC. (2000) Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. J Urol 164:242.
10. Hong EK, Lepor H, McCullough AR. (1999) Time dependent patient satisfaction with sildenafil for erectile dysfunction (ED) after nerve-sparing radical retropubic prostatectomy (RRP). Int J Impot Res 11(Suppl 1):S15–S22.
11. Partin AW, Kattan MW, Subong EN, et al. (1997) Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA 277:1445–1451.
12. Blute ML, Bergstralh EJ, Partin AW et al. (2000) Validation of Partin tables for predicting pathological stage of clinically localized prostate cancer. J Urol 164:1591–1595.
13. Fraiman MC, Lepor H, McCullough AR. (1999) Changes in penile morphometrics in men with erectile dysfunction after nerve-sparing radical retropubic prostatectomy. Mol Urol 3:109–115.
14. Klein LT, Miller MI, Buttyan R, et al. (1997) Apoptosis in the rat penis after penile denervation. J Urol 158:626–630.
15. User HM, Hairston JH, Zelner DJ, et al. (2003) Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. J Urol 169:1175–1179.
16. McCullough A, Ip C, Lepor H. (2001) The effect of preoperative potency on return of erectile function and viagra response after radical retropubic prostatectomy RRP. Andrew McCullough, Christopher Ip, Herbert Lepor, Sexual Medicine Society North America (podium) Charleston, NC. December 2001. Int J Impot Res 13:S68.
17. McCullough A, Ip C, Lepor H. (2001) The effect of age at the time of surgery on potency after nerve sparing radical prostatectomy. Int J Impot Res 13:S68.
18. Zippe CD, Jhaveri FM, Klein EA, et al. (2000) Role of Viagra after radical prostatectomy. Urology 55:241–245.
19. Raina R, Lakin MM, Agarwal A, et al. (2003) Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. Urology 62: 110–115.
20. Brock G, Nehra A, Lipshultz LI, et al. (2003) Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. J Urol 170:1278–1283.
21. Montorsi F, Padma Nathan H, McCullough A, et al. (2003) Tadalafil in the treatment of erectile dysfunction following bilateral nerve-sparing radical retropubic prostatectomy: a randomized, double-blind, placebo-controlled study. Int J Impot Res 15:190.
22. McMahon CG. (2002) High dose sildenafil citrate as a salvage therapy for severe erectile dysfunction. Int J Impot Res 14:533–538.
23. Nehra A, Blute ML, Barrett DM, et al.(2002) Rationale for combination therapy of intraurethral prostaglandin E(1) and sildenafil in the salvage of erectile dysfunction patients desiring noninvasive therapy. Int J Impot Res 14:S38–S42.
24. Mydlo JH, Volpe MA, Macchia RJ. (2000) Initial results utilizing combination therapy for patients with a suboptimal response to either alprostadil or sildenafil monotherapy. Eur Urol 38:30–34.

25. McCullough A, Kau E, Kaci L, Lepor H. (2003) A 12 month longitudinal study of treatment seeking behavior in 200 men after radical retropubic prostatectomy. J Urol 169:379.
26. Montorsi F, Guazzoni G, Strambi LF, et al. (1997) Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol 158:1408–1410.
27. Montorsi F, Maga T, Strambi LF, et al. (2000) Sildenafil taken at bedtime significantly increases nocturnal erections: results of a placebo-controlled study. Urology 56:906–911.
28. El-Galley R, Rutland H, Talic R, et al. (2001) Long-term efficacy of sildenafil and tachyphylaxis effect. J Urol 166:927–931.
29. Bacon CG, Mittleman MA, Kawachi I, et al. (2003) Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann Intern Med 139:161–168.
30. Morley JE, Kaiser FE, Perry HM, 3rd, et al. (1997) Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism 46:410–413.

19 Female Sexual Dysfunction

Is There a Magic Pill?

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CONTENTS

INTRODUCTION

Female sexual dysfunction (FSD) is a complex set of conditions associated with multiple anatomical, physiological, biological, medical, and psychological factors. It can be age-related and appears to be highly prevalent, affecting 20 to 50% of women *(1)*. Data from the National Health and Social Life Survey (NHSLS), a large representative sample of US women, reported that one-third of women experienced loss of sexual interest, and nearly one-fourth reported lack of orgasm during the past year *(2)*. Sexual dysfunctions are associated with problems of mood, self-esteem, quality of life, emotional distress, and relationship difficulties *(1)*.

The etiologies of FSD include anatomical, vasculogenic, neurogenic, hormonal, endocrine, psychogenic, medical, and pharmacological factors, and some cases are multifactorial *(3)*. Further subclassfication may include

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FSD as lifelong or acquired, generalized or situational, according to a recently recommended diagnostic classification system, which also considers personal distress as a criterion for most diagnostic categories *(1)*.

CLASSIFICATION SYSTEMS

Most FSD classification systems are based on both the Masters and Johnson, and Kaplan *(4,5)* model ofthe sexual response cycle. Masters and Johnson characterized the female sexual response as consisting of the four successive phases: excitement, plateau, orgasm, and resolution *(5)*. Kaplan proposed the aspect of "desire" and a three-phase model, consisting of desire, arousal, and orgasm *(4)*. The phase of *sexual desire* consists of the motivational or appetitive aspects of sexual response, and includes sexual urges, fantasies, and wishes. The phase of *sexual excitement* refers to a subjective feeling of arousal or sexual pleasure and accompanying physiological changes, includes vaginal lubrication and genital swelling. The *orgasm* is defined as the peak of sexual pleasure, with the rhythmic contractions of the genital musculature. In the final phase, *resolution*, a general sense of relaxation and well-being is experienced *(6)*.

This four-phase model forms the basis for classification of FSD in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) *(7)*. In the DSM-IV, sexual dysfunctions are defined as "disturbances in sexual desire and in the psychophysiological changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty." FSD includes hypoactive sexual desire disorder (HSDD, 302.71), sexual aversion disorder (302.79), female sexual arousal disorder (FSAD, 302.72), female orgasmic disorder (302.73), and sexual pain disorders, including dyspareunia (302.76), and vaginismus (306.51).

According to the World Health Organization International Classifications of Diseases-10 (ICD-10), the definition of sexual dysfunction includes "the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish" *(8)*. Specific categories in the nomenclature include a lack or loss of sexual desire (F52.0), sexual aversion disorder (F52.1), failure of genital response (F52.2), orgasmic dysfunction (F52.3), nonorganic vaginismus (F52.5), nonorganic dyspareunia (F52.6), and excessive sexual drive (F52.7).

Both classification systems are based on the sexual response cycle, and both include subjective distress as a criterion in their definitions. Neither classification system for FSD distinguishes between psychogenical and organically based disorders. Basson *(1)* has presented a model that may more accurately depict the responsive component of desire and the underlying motivational forces that trigger it. The interdependency of arousal and orgasm was also acknowledged. In 1998, an international multidisci-

Table 1
Classification and Definintions of Female Sexual Dysfunctions According to the 1999 Consensus Classification System [a]

I. Sexual desire disorders
A. Hypoactive sexual desire disorder
"The persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity, which causes personal distress."
B. Sexual aversion disorder
"The persistent or recurrent phobic aversion to and avoidance of sexual contact with a sexual partner, which causes personal distress."
II. Sexual arousal disorder
"The persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress, which may be expressed as a lack of subjective excitement, or genital (lubrication/swelling) or other somatic responses."
III. Orgasmic disorder
" The persistent or recurrent difficulty, delay in or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress."
IV. Sexual pain disorders:
A. Dyspareunia
"The recurrent or persistent genital pain associated with sexual intercourse."
B. Vaginismus
"The recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress."
C. Other sexual pain disorders
"Noncoital sexual pain disorder is recurrent or persistent genital pain induced by noncoital sexual stimulation."

[a] From ref. *1*.

plinary consensus development conference on FSD convened to begin to address the shortcomings and problems associated with the above-mentioned previous classifications *(1)*. The objective of the panel was to evaluate and revise existing definitions and classifications of female sexual dysfunction (results presented in Table 1).

The four major categories of dysfunction described in the DSM-IV and ICD-10 were preserved in order to maintain continuity in research and clinical practice. However, the definitions of several disorders have been altered to reflect current clinical and research practice, and a new category of sexual pain disorder, including noncoital sexual pain, has been added *(1)*.

PATHOPHYSIOLOGICAL CONSIDERATIONS

Vasculogenic

Vasculogenic etiologies for FSD may include hypertension, hyperlipidemia, tobacco abuse, diabetes, and cardiovascular conditions *(10)*. Clitoral and vaginal vascular insufficiency syndromes can be related to diminished genital blood flow secondary to atherosclerosis of the iliohypogastric/pudendal arterial bed *(11)*. Vascular insufficiency can be an important cause of, and should be considered in evaluating women with, sexual arousal disorder. Diminished pelvic blood flow as a result of aortoiliac disease can lead to vaginal wall- and clitoral smooth muscle fibrosis owing to increased collagen deposition, resulting in symptoms of vaginal dryness and dyspareunia *(11,12)*. In addition, traumatic injury to the iliohypogastric/pudendal arterial bed from pelvic fractures, blunt trauma, or surgical disruption can result in diminished vaginal and clitoral blood flow and sexual dysfunction *(10)*.

Neurogenic

Neurogenic disorders that cause FSD include spinal cord injury , diseases of the central or peripheral nervous system, and diabetic neuropathy *(10)*. Women with incomplete injuries retain capacity for psychogenic arousal and vaginal lubrication *(13)*. Women with spinal cord injuries have significantly more difficulty in achieving orgasm than normal controls. The effects of specific spinal cord injuries on female sexual response, as well as the role for vasoactive pharmacotherapy in this population, are being investigated.

Musculogenic

The pelvic floor muscles, levator ani and perineal membrane, participate in female sexual function and responsiveness. The perineal membrane, consisting of the bulbocavernosus and ischiocavernosus muscles, when voluntarily contracted, can contribute to and intensify sexual arousal and orgasm *(3)*. In addition, the bulbospongiosus and ischiocavernosus muscles are responsible for the involuntary rhythmic contractions during orgasm. A hypertonic levator ani muscle can contribute to the development of vaginismus, causing dyspareunia and other sexual pain disorders. When the levator ani is hypotonic, vaginal hypoanesthesia, coital anorgasmia,

and urinary incontinence during sexual intercourse or orgasm can develop *(3)*. Levator subluxation and sagging may lead to levator dysfunction, which may ultimately result in pelvic pain, dyspareunia, decreased vaginal sensation, and decreased intensity of orgasm *(14)*.

Hormonal

Hormonal etiological factors for FSD include dysfunction of the hypothalamic–pituitary–genital axis, surgical or medical castration, and menopause *(3)*.

Estrogen, Menopause, and Sexual Function

At puberty, the ovaries produce adult quantities of estrogen, which is responsible for the maturation, maintenance, and functioning of the female genitalia *(15)*. Other likely effects include the influence of estrogen on the action of local mediators. In an animal model, neuronal nitric oxide (NO) synthase expression is dependent on the presence of estrogen in the rat vagina *(16)*. In women, clinical research suggests that sufficient estrogen levels preserve the vascular function of female genital tract structures *(17)*. Animal studies also indicate that estrogen affects genital sensory function. Estradiol administration results in expanded touch receptor zones along the distribution of the pudendal nerve in the rat model *(18)*. Atrophic genital changes occur when estrogen decreases after menopause, defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular function *(19)*. Symptoms of menopause may include hot flashes, urinary incontinence, urinary tract infection, vaginal atrophy, reduced sexual function, and depression *(19)*. A decline in serum estrogen levels results in the thinning of vaginal mucosal epithelium, atrophy of vaginal wall smooth muscle, and a reduced acidic environment in the vagina *(3)*. Common sexual complaints of women who experience changes in sexual function include loss of desire, decreased frequency of sexual activity, painful intercourse, diminished sexual responsiveness, difficulty achieving orgasm, and decreased genital sensation *(3)*. When women enter natural menopause, there is a gradual decline of estrogen and a slight increase in serum testosterone secondary to ovarian stromal hyperplasia. This increase is time-limited, and as the levels decrease by the fourth or fifth menopausal year, this may contribute to decreased libido *(15)*. In contrast, women who have undergone surgical menopause experience an abrupt loss of these hormones, which may be associated with more dramatic declines in libido *(20)*.

In order to determine whether changes in women's sexual functioning during midlife are the result of aging or menopause, Dennerstein et al. conducted a prospective, observational questionnaire study on 438 women aged 45 to 55 yr, and still menstruating at baseline. A group of 197 women

was studied for the effects of natural menopausal transition and were compared to two control groups, which remained either premenopausal or early perimenopausal for 7 yr, or remained postmenopausal for over 5 yr. By late menopause, a significant decline in sexual responsivity and an increase in the partner's problems were observed. By the postmenopausal phase, there was a further decline in sexual responsivity, frequency of sexual activities, and libido, and a significant increase in dyspareunia and partner's problems. Dennerstein concluded that sexual responsivity declines significantly with both time and the menopausal transition. Other parameters of sexual functioning, e.g., libido, frequency of sexual activities, dyspareunia, and partner problems, became more pronounced as women became postmenopausal *(21)*.

Physiological Testosterone Production in Females

The ovaries are the primary site of synthesis of the most potent androgen in women, testosterone (T), which is further hydroxylated to dihydrotestosterone or aromatized to estradiol in target organs and peripheral tissues *(20)*. The precursor hormones androstenedione (A) and dehydroepiandrosterone (DHEA) are produced by the ovaries and the adrenals and have weaker androgenic activity. The adrenals are also the main source of DHEA sulfate (DHEAS) *(22)*. Plasma A and T increase in the middle third of the menstrual cycle, as well in the luteal phase, and there is a diurnal variation in T, which peaks in the morning *(23)*. Only 1 to 2% of total T circulates unbound, the rest is bound by sex hormone-binding globulin (SHBG) or albumin, with SHBG binding 66% of total circulating T *(22)*. The non-SHBG-bound fraction of T is assumed to be biologically active. With increasing age, the mean circulating level of T declines gradually. As a result, T levels in women aged 40 are approx half those of women in their early 20s *(20)*. The levels of DHEA and DHEAS also fall linearly with age, resulting in a further decline of T *(20)*. Other iatrogenic causes besides surgical (bilateral) oophorectomy, which immediately reduces A and T levels by about 50%, include the use of gonadotropin-releasing hormone (GnRH) analogs, chemotherapy, or radiotherapy *(20)*. Exogenous oral estrogens lower circulating T levels by increasing SHBG and suppressing pituitary luteinizing hormone secretion *(24)*.

Pathophysiology of Pain Conditions

Dyspareunia

This describes pain on vaginal penetration, but dyspareunia can also occur during sexual stimulation. Superficial pain may be a result of vulvitis, vulvovaginitis, vulvovestibulitis, genital herpes, urethritis, atrophic vulvitis, irritants (e.g., spermicides and latex), gynecological and obstetric interventions (episiotomies), local radiotherapy, and sexual traumas *(3)*.

Deep dyspareunia, resulting from pelvic thrusting during sexual intercourse, may be caused by pelvic inflammatory disease, fibromyalgia, gynecological, pelvic or abdominal surgery, postoperative adhesions, endometriosis, genital or pelvic tumors (including fibroids), urinary tract infections, and ovarian cysts.

Vaginismus

This is a conditioned response that results from associating sexual activity with pain and fear. The immediate pathomechanism of vaginismus is the involuntary muscle spasm. It may be caused by physical or sexual abuse, medical procedures experienced during childhood, painful first sexual intercourse, and fear of pregnancy. Other suggested factors include religious issues, or fear of intimacy or aggression *(3)*.

Psychogenic

Emotional and relational issues can significantly affect sexual function. Self-esteem, body image, and the quality of the relationship with their partner can affect a woman's ability to respond sexually. Depression and other mood disorders are often associated with FSD. Medications commonly used to treat depression can significantly affect the female sexual response, especially serotonin reuptake inhibitors (SSRIs) *(25)*. Decreased desire, arousal, genital sensation, and difficulty achieving orgasm are commonly reported side effects, which can lead to patients' dissatisfaction and noncompliance with treatment *(26)*. It is crucial for the physician to carry out an extensive assessment of the sexual complaints and the context in which they are experienced. Some medications are more frequently associated with sexual dysfunction, and therefore a change of the medication for the treatment of depression should be considered in patients concerned about sexual functioning

DEFINITIONS (TABLE 1) AND EPIDEMIOLOGY

Sexual Desire Disorders

Hypoactive Sexual Desire Disorder

In addition to the 1998 consensus definition, Basson suggests the following expanded definition, which expands the concept of receptivity: "HSDD is the persistent or recurrent deficiency (or absence) of sexual fantasies, thoughts, desire for sexual activity (alone or with partner), and inability to respond to sexual cues that would expect to trigger responsive sexual desire. These symptoms need to be causing personal distress." *(9)*.

HSDD may be secondary to other sexual dysfunctions, such as anorgasmia. It may also result from a variety of medical and psychiatric conditions, as well as partner conflicts and loss of attraction.

Low desire is a highly prevalent sexual problem in both men and women *(6)*. In the population-based NHSLS, 33.4% of women between the ages of 18 and 59 experienced low sexual desire for at least a few months of the last year. Low desire was more common in women with the lowest education levels (42%) and in African-American women (44%) *(2)*. HSDD may be age-related, and is increasingly prevalent above the age of 60 in both sexes *(27)*. Low desire is more common in those with comorbid medical and psychiatric disorders, particularly chronic illnesses and depression. Loss of libido is a frequent complaint of patients taking antihypertensive or antidepressant medications, particularly SSRIs *(25,28)*. However, whether these medications cause low libido has yet to be determined in prospective studies.

Women are more commonly affected by HSDD than men: the female-to-male ratio is about 2:1 or 3:1; in some reports, it is even higher *(6)*. Female patients with arousal or orgasmic disorder may also have a secondary diagnosis of HSDD. Relationship conflict is often cited as an important causal factor for HSDD in women, specifically lack of trust and intimacy, conflicts over power and control, and loss of physical attraction to the partner *(27)*. In one study, women with HSDD reported increased frequency of premarital sex, poorer marital adjustment, and diminished feelings of emotional closeness with their partners *(27)*.

Sexual Aversion Disorder

The prevalence of sexual aversion disorder is currently unknown because it is considered a subcategory of HSDD and therefore, separate prevalence data for this disorder are not available. A history of sexual trauma or abuse is associated frequently with this disorder in the clinical literature *(6,29)*.

Sexual Arousal Disorders

The consensus definition accepts the interplay of psychological and biological factors and allows the woman who may be lubricated but who lacks mental excitement, to be diagnosed with female sexual arousal disorder (FSAD) *(1)*. Disorders of arousal can include decreased labial and clitoral sensation and engorgement, and the lack of vaginal smooth muscle relaxation. FSAD is associated with age, psychological factors or underlying medical conditions, which lead to diminished vaginal or clitoral blood flow. Prior pelvic surgery, trauma, or medications can be etiologically responsible *(11)*. Women with FSAD may experience pain with intercourse because of inadequate lubrication and vaginal irritation.

According to the NHSLS, approx 20% of women aged 18 to 59 reported difficulty in becoming lubricated during sexual stimulation *(2)*. Similar results were reported in a large British study, where "problems with

arousal" and "vaginal dryness" were reported as a current problem by 17 and 28% of all female respondents, respectively *(30)*. Forty-nine percent of the women with vaginal dryness reported this as a lifelong problem. In another study of 329 women attending an outpatient gynecology clinic, 13.6% of women experienced a lack of lubrication during most or all sexual activity, and 23.3% reported having this problem on occasion *(31)*. Among the postmenopausal women in this study, the incidence of lubrication problems increased to 44.2%. It should be noted that, depending on the definition of the disorder and the type of sample studied, the prevalence of FSAD can vary greatly.

Orgasmic Disorders

Orgasmic disorders may be primary or secondary: Primary orgasmic dysfunction or, anorgasmia, describes a condition in which the individual has never achieved orgasm through any means of stimulation. In contrast, individuals who are orgasmic with masturbation but not with a partner are referred to as secondary or situational orgasmic dysfunction *(5)*.

Female orgasmic dysfunction is a highly prevalent female sexual problem: The rate of anorgasmia in women among sex therapy clinic samples has been reported to range between 24 and 37% *(6)*. These rates are comparable to population-based survey studies *(25,28)*. According to the NHSLS, the prevalence of anorgasmia is significantly higher in single women, compared with married women *(2)*. The NHSLS found no relationship between anorgasmia and race, socioeconomic status, and educational or religious background *(2,32)*. In the previously mentioned study of 329 women attending an outpatient gynecology clinic, 15.4% of the premenopausal women and 34.7% of postmenopausal women reported having difficulty in achieving orgasm during sexual stimulation *(31)*.

Orgasmic dysfunction has been associated with relationship and psychological distress factors, decreased satisfaction with marital relationships, concurrent psychiatric disorders, and other relationship conflicts in several studies *(30,32)*.

A delay or absence of orgasm is a common complaint in women receiving antidepressant medications, particularly SSRIs *(25)*. This side effect has been reported to occur in up to 50% of some samples, depending on both the type of drug and the dosage. The mechanism is unknown. Possible mediators include: Drug accumulation, elevated prolactin levels, anticholinergic effects, and inhibition of NO synthetase *(25)*.

Sexual Pain Disorders

Dyspareunia

Dyspareunia is a common sexual problem. According to the NHSLS, 14.4% of women have experienced pain during sexual activity during the

past year. In this study, dyspareunia was found to be inversely related to age and minority status *(2)*. According to the previously mentioned British survey, 18% of the women reported dyspareunia as a current sexual problem and 45% reported it as a lifelong sexual problem *(30)*.

In a study from North Carolina, the prevalence of dyspareunia and pelvic pain was assessed using a questionnaire in a clinical population of 701 consecutive women aged 18 to 45 yr in obstetrics and gynecology, and family medicine practices. Dyspareunia and pelvic pain were reported by 46 and 39%, respectively. Low income was found to be a risk factor for dyspareunia, and the African-American race was found to be a risk factor for pelvic pain. Dyspareunia and pelvic pain were not associated with age, parity, marital status, income, or education *(33)*. In contrast, a study of 300 healthy women, ages 16 to 53 who sought services at family planning centers in Tehran, Iran, demonstrated a prevalence of dyspareunia of only 10%. All participants were married, and 38% of the women had at least one sexual dysfunction, including inhibited desire (15%), inhibited orgasm (26%), lack of lubrication (15%), and vaginismus (8%) *(34)*.

Two European studies addressed the prevalence of dyspareunia in postmenopausal women. One cross-sectional, nationwide survey studied 2157 noninstitutionalized Dutch women, aged 50 to 75 yr. The survey sample was representative of the female population aged 50 to 75 yr with respect to age, marital status, level of education, and menopausal age. The response rate was 81.6% (n = 1761). The prevalence of vaginal dryness, soreness, and dyspareunia was 27% *(35)*. Another study from Sweden showed a prevalence rate of 41% in 630 women in the age group of 61 to 81 yr *(36)*.

Thus far, dyspareunia is the only female sexual dysfunction in which organic factors have been shown to play a major role, and there is a need for integration of medical and psychological formulations.

Vaginismus

This disorder is frequently encountered in sex therapy clinics, occurring in approx 15 to 17% of women presenting for treatment *(37)*. The distinction between dyspareunia and vaginismus can be problematic, because pain itself can prevent penetration and cause muscular contractions. The DSM-IV distinguishes *generalized* vaginismus from *situational* vaginismus. General vaginismus refers to involuntary vaginal spasms in all situations, whereas in situational vaginismus, some penetration is possible. The cause is unknown. Vaginismus has been reported to occur in numerous medical conditions or may be related to psychological or interpersonal factors *(37)*.

Other Sexual Pain Disorders

This includes anatomic and inflammatory conditions, including infections, vestibulitis, prior genital mutilation or trauma, and endometriosis *(3)*.

THERAPY

Psychotherapy

The goal of sex therapy is to create or restore mutual sexual comfort, satisfaction, and pleasure. Specific treatment components are included in order to assist the woman and her partner in developing a "pleasure-focused" approach to sex *(29)*.

As with any form of treatment, a comprehensive diagnostic assessment must precede intervention. Subsequent treatment decisions and approaches are guided by the unique constellation of contributing etiological factors. An assessment of FSD includes: (1) an evaluation of current sexual functioning, including feelings and thoughts of desire and receptivity to sexual activity; (2) an accurate elucidation of the presenting problem and any comorbid problems; (3) the formulation of "working hypotheses" of the most relevant etiological and maintaining factors; (4) identification of treatment goals and a treatment plan; and, finally, (5) clear, constructive feedback to the woman and her partner *(38)*.

Most cases of female sexual complaints are multiply determined and, therefore, the assessment must cover a variety of different topics and may take several visits. The following areas are important topics to include in an assessment: Descriptive information, elucidation of the problem, psychosexual history, history of sexual abuse or trauma, medical history, psychological and medical functioning, current environmental stressors, relationship distress, and secrets *(38)*.

Nondemand or sensual touching exercises, conditions that facilitate sexual activity, replacing myths and misinformation with accurate information, better couple communication, bibliotherapy, and sex education, as well as systemic and psychodynamic interventions form the cornerstones of sex therapy *(38)*. Successful treatment outcome depends on successful resolution of the emotional and interpersonal issues that accompany the sexual complaint. The clinician's ability to be nonjudgmental, sensitive to gender and cultural nuances, and validating are crucial. Whether the format of treatment is individual or couple's therapy, the sexual relationship is "the client" being treated *(38)*. Most basic interventions in sex therapy include nondemand or sensual touching exercises, setting the stage for sexual activity, cognitive restructuring, communication training, education, trauma therapy, as well as psychodynamic and insight-oriented therapy.

Pharmacotherapy

Genital Arousal Disorder

Ideally, medications for genital arousal disorder would enhance the action of endogenous neurotransmitters of arousal, including nitric oxide NO and vasoactive intestinal polypeptide. NO is believed to be a major neurotransmitter involved in vulval congestion *(39)*, whereas vasoactive intestinal polypeptide is thought to be a major neurotransmitter in vaginal congestion *(40)*. Recently, a double-blind, placebo-controlled study evaluated sildenafil (25–100 mg) in women with arousal disorder *(41)*. Women were either postmenopausal or posthysterectomy. Significantly more women reported improved sensation and increased satisfaction with sildenafil compared with placebo in this report. These improvements were more pronounced in the subgroup of women without HSDD. Most adverse events were mild-to-moderate in severity. Postmenopausal women with impaired orgasmic and arousal disorder under estrogen replacement, however, showed only a limited response to sildenafil regarding arousal, although sildenafil reduced latency to orgasm. *(41)*. Increased vaginal pulse amplitude and subjective arousal just reaching statistical significance was shown in a small subgroup of women with spinal cord injury *(42)*. Similarly, Caruso *(43)* reports a study of 51 premenopausal women with genital FSAD showing benefit in subjective arousal over placebo. Despite the apparent efficacy in improving arousal and orgasm in these women, only 70% elected to continue using the medication. Several studies also documented improvements in SSRI-induced sexual dysfunction in women after administration of sildenafil *(44)*.

Topical vasodilators, such as prostaglandin E_1, may have a role in genital FSAD where there is total disruption of the autonomic nerves involved in the vulval congestive mechanism, e.g., conus lesion or after radical pelvic surgery. α-Blocking drugs, topically or even systemically if side effects are tolerable, remain another possibility. Scientific studies of directly acting vasoactive agents and subjective arousal are needed.

Hormonal Therapy

Androgen Measurements

Research in the role of testosterone in women has been limited by the insensitivity of assays for total and free T within the normal female range. In addition, many older studies did not take into account diurnal or cyclical T variation in women *(20)*.

Because of variability in measurements, physiological (cyclical/diurnal) variation, and the plethora of assays, it is often difficult to determine if androgens are normal, increased, or decreased. This is especially true for T. Methods used vary, and even use of standardized methods, such as radioim-

munoassay, are variable depending on whether serum is extracted and/or undergoes chromatography before radioimmunoassay. Upper normal ranges vary from 50 to 100 ng/dL *(45)*. T levels are considered low if they are less than 20 ng/dL, and after oophorectomy values are usually less than10 ng/dL *(45)*. The most sensitive measurement of T bioavailability is unbound or free T, although the commercial assays for "free" T can be inconsistent or invalid *(45)*. Therefore, many investigators prefer to use the free T index, which is a calculated value, usually the ratio of T-to-SHBG *(45)*.

Androgens and Their Influence on Mood, Well-Being, and Libido

Although sexuality and libido are determined by multiple factors, androgens seem to play a major role in sexual motivation behaviors and sexual desire, and low T levels have been associated with low libido *(46)*. Because androgens decrease steadily with age unrelated to menopause, decreasing levels may contribute to low libido in pre- and postmenopausal women. In younger women, bilateral oophorectomy causes a 50% decrease in A and T levels, resulting in significant deterioration in sexual desire *(20)*. Several studies in postmenopausal women on T therapy could document an improvement in multiple parameters of general health, sexuality, and well-being compared with estrogen therapy alone *(46)*. It should be pointed out, however, that the accuracy of T assays in women has been found to be lacking, and that "normal" androgen ranges in women of different age ranges are unknown *(46)*.

Although there is an increasing usage of T treatment, data on efficacy from controlled clinical trials are few, and treatment guidelines are based on limited experience on the effect of T on sexual function. Data on younger menstruating women are even more limited. Improvement of libido with androgen therapy in premenopausal women could be demonstrated only in small numbers without placebo control *(47)*. An important study published recently demonstrated decreased T, free T, and DHEAS levels in 70% of 105 women with decreased libido, including 37 premenopausal women *(48)*. Because the latter group of women were menstruating normally, indicating a normal ovarian function, the authors concluded that decreased libido in premenopausal women was because of possible defects in regulatory mechanisms of adrenal steroidogenesis.

Several studies in postmenopausal women on T therapy could document an improvement in multiple parameters of general health, sexuality, and well-being compared to estrogen therapy alone. Shifren et al. reported on a multicenter, randomized, T-replacement trial with 75 surgically menopausal women. Subjects received T patches that delivered the equivalent of either 150 or 300 µg/d, twice a week. There was a statistically significant improvement in their Brief Index of Sexual Functioning for Women score, and a

significant improvement in the depression component of the psychological general well-being questionnaire. In addition, they reported more interest in sexual activity, greater frequency of intercourse, and greater frequency and quality of orgasms when they were using the patch vs the placebo. The women did not report any incidence of acne or hirsutism. Notably, women under 47 yr of age experienced a high placebo response *(49)*.

Tuiten et al. administered sublingual 5 mg tundecanoate or placebo in a double-blind, crossover design to eight healthy premenopausal women (mean age of 28 yr). The intervention was followed by visual–sexual stimulation every 1.5 h, during which plasma hormone levels and self-report questionnaires were collected. T was associated with subjective experiences of "genital sensations" and "sexual lust" which peaked 4.5 h after T administration *(50)*. Finally, in a double blind, placebo-controlled trial, oral DHEA replacement enhanced sexual desire and improved well-being in women with adrenal insufficiency *(51)*.

Determination of Androgen Deficiency and Indications for Androgen Replacement

In the setting of bilateral oophorectomy, androgen deficiency is clear. Many other indications for androgen replacement remain controversial. Possible clinical indications for T replacement include T deficiency following natural or surgical menopause, chemotherapy or irradiation, premature ovarian failure, and premenopausal loss of libido with diminished serum-free T *(20)*. Other medical indications for T replacement include management of premenstrual syndrome, pituitary adrenal insufficiency, corticosteroid therapy, induced bone loss, management of chronic wasting syndromes secondary to chronic illnesses, malignancy, or human immunodeficiency virus infection, and premenopausal iatrogenic androgen deficiency states, including treatment of endometriosis *(20,45)*.

Currently Available Preparations for Androgen Replacement

Various androgen preparations can be used in women. However, only an estrogen–testosterone combination as an oral preparation is FDA-approved[1] for use in women. None of the substances are FDA-approved for the use in female sexual dusfunction. Regardless of the mode of administration, the initial postadministration peak is usually supraphysiological. Available preparations have been reviewed recently by Lobo and Davis and Tran *(20,45)*, and are summarized in Table 2.

In general, T injections are not recommended because of the risk of accumulation and the inconstant serum levels. Methyltestosterone is not available in some countries because of reported liver damage after long-

[1] FDA-approved for "vasomotor symptoms associated with menopause."

Table 2
Current and Future Androgen Preparations

Route of administration/compound		*Dose range*	*Frequency*
Oral	Methyltestosterone	1.25–2.5 mg	Daily
	Testosterone undecanoate [a,b]	40–80 mg	Daily
	DHEA	25–50 mg	Daily
Transdermal	T-patch [c]	150–300 mg	Twice weekly
	T-gel [b]	1 mg	1 mg/d
	1% T-cream [b]	5–10 mg	Daily
Subcutaneous	T-implant [b]	50–100 mg	3–6 mo
IM injection	Nandrolone undecanoate [b]	25–50 mg	6–12 wk
	Mixed T esters [b]	50–100 mg	4–6 wk
	Testosterone enanthate [b]	25–50 mg	4–6 wk
	Testosterone cypionate [b]	25–50 mg	4–6 wk

[a] Not available in the United States.
[b] Not approved for women.
[c] In development.
DHEA, dehydroepiandrosterone; IM, intramuscular.

term, high-dose therapy. T cream is currently undergoing clinical trials, therefore pharmacological data are required to establish efficacy and therapeutic guidelines. Other approaches include the administration of T via the vaginal, buccal, or sublingual route. Regardless of the preparation, patients have to be monitored very carefully for their serum levels and for clinical side effects.

Potential Adverse Effects and Risks of Androgen Replacement

Masculinizing side effects of androgen replacement therapy include acne, hirsutism, temporal alopecia, voice deepening, and clitoromegaly *(20)*. These side effects can be irreversible. With T injections at 2 to 4-wk intervals, there is a risk of accumulation, and elevated T levels after iatrogenically induced hirsutism (T injections or implants) may require up to 6 mo to normalize *(45)*. Judicious dosing and careful monitoring of the patients is therefore important to keep the risk of adverse events as minimal as possible. Davis and Tran suggest that postmenopausal T replacement should only be prescribed with concurrent estrogen therapy, as there are no large studies providing data regarding the use of T alone *(20)*. Undesirable effects on body composition (fluid retention, increase in lean body mass) have been described to be rare *(31)*. Effects on lipids include a decrease of high-density lipoprotein cholesterol and triglycerides. However, low-density lipoprotein is lowered to a similar extent as estrogen and lipoprotein (a) *(45)*. Regarding vascular function, a dilation and preservation of favorable effects of estrogen on coronary artery flow have been described *(20)*.

Thus, there are no known adverse cardiovascular effects of T replacement using the regimens and doses considered. Finally, there are no data suggesting a change in the risk status for developing breast cancer with the addition of androgens *(20,45)*. Similarly, there is no risk of endometrial hyperplasia when comparing estrogen to an estrogen–androgen combination *(45)*.

Mechanical Devices

Two categories of mechanical devices currently exist: mechanical vibrators and a clitoral vacuum engorgement device. Both devices rely on the finding that vascular engorgement of the clitoris is important and may be used to treat arousal and orgasm disorders *(53)*. However, the mechanism of action for mechanical vibrators and the clitoral vacuum device is believed to be different.

Mechanical vibrators have been used to treat primary and secondary anorgasmia with some success, especially when combined with psychological counseling *(54)*. The clitoral vacuum engorgement device uses a gentle vacuum to engorge the clitoris even in the presence of blood vessels affected by vascular disease. This ability to engorge the clitoris even if the genital blood flow is diminished may have important implications for treatment efficacy.

The clitoral vacuum device (EROS Therapy Device, UroMetrics, Inc., St. Paul, MN) was approved by the FDA in April 2000 and has been investigated in clinical trials designed to measure its effectiveness in treating symptoms of FSD, especially female sexual arousal disorders. A study performed by Billups et al. in 20 women with FSD (nine premenopausal and 11 postmenopausal) showed improvement in genital sensation, vaginal lubrication, orgasm, and sexual satisfaction *(53)*. During a 3-mo period of Eros Therapy-device use, a substantial majority of women with symptoms of FSD ($p < 0.001$) reported improvement in sensation (90%), vaginal lubrication (80%), orgasm (55%), and sexual satisfaction (80%). No adverse clinical events were reported and no women reported decreased function in any of the four categories. A follow-up study by Wilson et al. *(55)* showed similar ($p < 0.05$) results in 10 women with FSD with improvements in sensation (80%), vaginal lubrication (70%), orgasm (60%), and sexual satisfaction (90%). The device can be used as a monotherapy or in combination with vasoactive substances or hormonal therapy.

SUMMARY

FSD disorders are highly prevalent and often undertreated. The etiology involves multiple factors. Evaluation, diagnosis, and treatment of FSD disorders have become major areas of interest and research in the medical community (Table 3).

Table 3
Available and In-Development Therapies for FSD

Drug/product	*Manufacturer*	*Key ingredient*	*Use/potential use*	*Status*
Androsorb (cream)	Novavax	Testosterone	HSDD and possibly other FSDs.	Phase II clinical trials.
Alista	Vivus	Prostaglandin E1	Vasodilator. Increased blood flow to genitalia.	Phase II clinical trials.
EROS-CTD	Urometrics	CTD	Increases sensation and blood flow to clitoris by suction.	Available with doctor's prescription.
Estrace cream	Warner Chilcott	Estrogen	HRT. Vaginal dryness and discomfort.	Available with doctor's prescription.
Estratest (pill)	Solvay Pharmaceuticals	Estrogen–testosterone combination	HRT to treat hot flashes. Increases desire in some women.	Available with doctor's prescription.
Evista	Eli Lilly	SERM	Osteoporosis HRT, may thicken vaginal walls.	Available with doctor's prescription.
Femprox (cream)	NexMed, Inc.	Prostaglandine E1	Vasodilator. Improves blood flow to genitals.	Phase II clinical trials.
Intrinsa (patch)	Proctor & Gamble Watson Laboratories	Testosterone	HSDD and possibly other FSDs.	Completed phase III clinical trials.
Livial (pill)	Organon	SERM	Osteoporosis, desire and arousal, treatment and prevention of osteoporosis.	Phase III clinical trials.
NM1-870 (pill)	NitroMed	African tree bark fortified with nitric oxide	Increases vaginal blood flow in postmenopausal women.	Phase II clinical trials.

(Continued on next page)

Table 3 *(Continued)*
Available and In-Development Therapies for FSD

Drug/product	*Manufacturer*	*Key ingredient*	*Use/potential use*	*Status*
Premarin (pill, cream or injection) Prempro (pill) Premphase (pill)	Wyeth	Estrogen	Osteoporosis, menopause symptoms. Vaginal dryness and discomfort associated with menopause.	Available with doctor's prescription.
Steryl-Norleucine VIP (cream)	Senetek PLC	Synthetic version of verve chemical	Vaginal dryness and discomfort associated with menopause.	In clinical trials.
Testosterone creams	Off-label prescriptions from compounding pharmacies	Testosterone	Male HRT.	Not FDA-approved for use in women.
Tostrelle (gel)	Cellegy	Testosterone	Controlled delivery system for testosterone.	Advanced phase II/III clinical trials.
Vasofem (tablet)	Zonagen	Blood vessel dilator	Increases blood flow to clitoris.	Phase II clinical trials.
Viagra	Pfizer	Sildenafil	Vasodilator. Male erectile dysfunction.	Off-label prescription available. Development ment for registration discontinued by Pfizer.

CTD, clitoral therapy device; FSDS, female sexual dysfunctions; HRT, hormone replacement therapy; HSDD, hypoactive sexual desire disorder; SERM, selective estrogen receptor modulator.

Aside from psychotherapeutic approaches, which continue to be of major importance, a number of modalities to treating FSD are evolving, including vasoactive substances, hormonal therapy, and mechanical devices. The definitive role of each respective treatment has yet to be resolved. Interdisciplinary cooperation and team approach, as well as education of both the health care provider and the patient, are of paramount importance in improving quality of care in women with FSD.

REFERENCES

1. Basson R, Berman J, Burnett A, et al. (2000) Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. J Urol 163:888–893.
2. Laumann EO, Paik A, Rosen RC. (1999) Sexual dysfunction in the United States: prevalence and predictors. JAMA 281:537–544.
3. Berman JR, Goldstein I. (2001) Female sexual dysfunction. Urol Clin North Am 28:405–416.
4. Kaplan HS. (1974) The New Sex Therapy. New York, NY: Brunner Mazel.
5. Masters WH, Johnson VE. (1970) Human Sexual Inadequacy. Boston, MA: Little Brown, pp. 214–315.
6. Rosen RC. (2000) Prevalence and risk factors of sexual dysfunction in men and women. Curr Psychiatry Rep 2:189–195.
7. American Psychiatric Association. (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Washington, DC: American Psychiatric Press, pp. 543, 544,547–549,554–565.
8. World Health Organization. (1992) International Statistical Classification of Diseases and Related Health Problems, 10th Ed., Geneva, Switerland: World Health Organization, pp. 355–356.
9. Basson R. (2000) The female sexual response: a different model. J Sex Marital Ther 26:51–65.
10. Berman JR, Bassuk J. (2002) Physiology and pathophysiology of female sexual function and dysfunction. World J Urol 20:111–118.
11. Goldstein I, Berman JR. (1998) Vasculogenic female sexual dysfunction: vaginal engorgement and clitoral erectile insufficiency syndromes. Int J Impot Res 10 (Suppl 2):S84–S90; discussion S98–S101.
12. Berman JR, Berman L, Goldstein I. (1999) Female sexual dysfunction: incidence, pathophysiology, evaluation, and treatment options. Urology 54:385–391.
13. Sipski ML, Rosen RC, Alexander CJ, et al. (2000) Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. Urology 55:812–815.
14. Shafik A. (2000) The role of the levator ani muscle in evacuation, sexual performance and pelvic floor disorders. Int Urogynecol J Pelvic Floor Dysfunct 11:361–376.
15. Weber AA. (1999) Effects of estrogens and androgens on the libido of women following surgical and natural menopause. Menopausal Med 7:5–8.
16. Berman JR, McCarthy MM, Kyprianou N. (1998) Effect of estrogen withdrawal on nitric oxide synthase expression and apoptosis in the rat vagina. Urology 51:650–656.
17. Laan E, van Lunsen RH. (1997) Hormones and sexuality in postmenopausal women: a psychophysiological study. J Psychosom Obstet Gynaecol 18:126–133.
18. Kow LM, Pfaff DW. (1973) Effects of estrogen treatment on the size of receptive field and response threshold of pudendal nerve in the female rat. Neuroendrocrinology 13:299–313.

19. Greendale GA, Lee NP, Arriola ER. (1999) The menopause. Lancet 353:571–580.
20. Davis SR, Tran J. (2001) Testosterone influences libido and well being in women.Trends Endocrinol Metab 12:33–37.
21. Dennerstein L, Dudley E, Burger H. (2001) Are changes in sexual functioning during midlife due to aging or menopause? Fertil Steril 76:456–460.
22. Traish AM, Kim N, Min K, et al. (2002) Androgens in female genital sexual arousal function: a biochemical perspective. J Sex Marital Ther 28(Suppl 1):233–244.
23. Vierhapper H, Nowotny P, Waldhausl W. (1997) Determination of testosterone production rates in men and women using stable isotope/dilution and mass spectrometry. J Clin Endocrinol Metab 82:1492–1496.
24. Mathur RS, Landgrebe SC, Moody LO, et al. (1985) The effect of estrogen treatment on plasma concentrations of steroid hormones, gonadotropins, prolactin and sex hormone-binding globulin in post-menopausal women. Maturitas 7: 129–133.
25. Rosen RC, Lane RM, Menza M. (1999) Effects of SSRI's on sexual function: a critical review. J Clin Psychopharmacol 19:67–85.
26. Coleman CC, King BR, Bolden-Watson C, et al. (2001) A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther 23:1040–1058.
27. Rosen RC, Leiblum SR. (1995) Treatment of sexual disorders in the 1990s: an integrated approach. J Consult Clin Psychol 63:877–890.
28. Burchardt M, Burchardt T, Anastasiadis AG, et al. (2002) Sexual dysfunction is common and overlooked in female patients with hypertension. J Sex Marital Ther 28:17–26.
29. Stuart FM, Hammond DC, Pett MA. (1987) Inhibited sexual desire in women. Arch Sex Behav 16:91–106.
30. Dunn KM, Croft PR, Hackett GI. (1998) Sexual problems: a study of the prevalence and need for health care in the general population. Fam Pract 15:519–524.
31. Rosen RC, Taylor JF, Leiblum SR, et al. (1993) Prevalence of sexual dysfunction in women: results of a survey study of 329 women in an outpatient gynecological clinic. J Sex Marital Ther 19:171–188.
32. Heimann JR, Grafton-Becker V. (1989) Orgasmic disorders in women. New York, NY: Guidford Press.
33. Jamieson DJ, Steege JF. (1996) The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. Obstet Gynecol 87:55–58.
34. Shokrollahi P, Mirmohamadi M, Mehrabi F, et al. (1999) Prevalence of sexual dysfunction in women seeking services at family planning centers in Tehran. J Sex Marital Ther 25:211–215.
35. Van Geelen JM, van de Weijer PH, Arnolds H. (1996) Urogenital symptoms and their resulting discomfort in non-institutionalized 50-to-75-year-old Dutch women. Ned Tijdschr Geneeskd 140:713–716.
36. Stenberg A, Heimer G, Ulmsten U. (1995) The prevalence of urogenital symptoms in postmenopausal women. Maturitas 22(Suppl):S17–S20.
37. Spector IP, Carey MP. (1990) Incidence and prevalence of the sexual dysfunctions: a critical review. Arch Sex Behav 19:389–409.
38. Leiblum SR, Wiegel M. (2002) Psychotherapeutic interventions for treating female sexual dysfunction. World J Urol 20:127–136.
39. Burnett AL, Calvin DC, Silver RI, et al. (1997) Immunohistochemical description of nitric oxide synthase isoforms in human clitoris. J Urol 158:75–78.

40. Palle C, Bredjkaer HE, Ottesen B, et al. (1990) Vasoactive intestinal polypeptide and human vaginal blood flow: comparison between transvaginal and intravenous administration. Clin Exp Pharmacol Physiol 17:61–68.
41. Berman JR, Berman LA, Toler SM, et al. (2004) Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal dysfunction: a double blind placebo controlled study. J Urol 170(6 pt 1):2333–2338.
42. Sipski M, Rosen RC, Alexander CJ, et al. (2000) Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. Urology 55:812–815.
43. Caruso S, Intelisano G, Lupo L, et al. (2001) Premenopausal women affected by sexual arousal disorder treated with Sildenafil: A double blind, crossover, placebo-controlled study. Brit J Obstet Gynaecol 108:623–628.
44. Shen WW, Urosevich Z, Clayton DO. (1999) Sildenafil in the treatment of female sexual dysfunction induced by selective serotonin reuptake inhibitors. J Reprod Med 44:535–542.
45. Lobo RA. (2001) Androgens in postmenopausal women: production, possible role, and replacement options. Obstet Gynecol Surv 56:361–376
46. Guay A, Davis SR. (2002) Testosterone insufficiency in women: fact of fiction? World J Urol 20:106–110.
47. Guay AT. (2001) Decreased testosterone in regularly menstruating women with decreased libido: a clinical observation. J Sex Marital Ther 27:513–519.
48. Guay AT, Jacobson J. (2002) Decreased free testosterone and dehydroepiandrosterone-sulfate (DHEA-S) levels in women with decreased libido. J Sex Marital Ther 28(Suppl 1):129–142.
49. Shifren JL, Baunstein GD, Simon JA, et al. (2000) Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 343:682–688.
50. Tuiten A, Van Honk J, Koppeschaar H, et al. (2000) Time course and effects of testosterone administration on sexual arousal in women. Arch Gen Psychiatry 57: 149–153.
51. Arlt W, Callies F, Van Vlijmen JC, et al. (1999) Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 341:1013–1020.
52. Davis SR, Walker KZ, Strauss BJ. (2000) Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. Menopause 7:395–401.
53. Billups KL. (2002) the role of mechanical devices in treating female sexual dysfunction and enhancing the female sexual response. World J Urol 20:137–141.
54. Hurlbert DF. (1995) The coital alignment technique and directed masturbation: a comparative study on female orgasm. J Sex Marital Ther 21:21–29.
55. Wilson SK, Delk II JR, Billups KL. (2001) Treating symptoms of female sexual arousal disorder with the eros clitoral therapy device. J Gend Specif Med 4:54–58.
56. Shabsigh R, Kimoto Y, Amar E, et al. (2004) Economical aspects of sexual dysfunction. In: Jardin A, Wagner G, Khouri S, Giuliano F, Lue TF, Rosen R, eds., Erectile and Sexual Dysfunction, 2nd International Consultation on Erectile and Sexual Dysfunction co-sponsored by the World Health Organization (WHO), International Society of Sexual and Impotence Research (ISSIR) and Societe Internationale d'Urologie (SIU), Health Publications Ltd., pp. 53–64.

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