Internal Medicine Grand Rounds
The University of Texas Southwestern Medical Center
December 1, 2006

PHOSPHODIESTERASE 5 INHIBITORS FOR TREATMENT OF ERECTILE IMPOTENCE

Jean D. Wilson, M.D.
Professor of Internal Medicine
Charles Cameron Sprague Distinguished Chair in Biomedical Research
UT Southwestern Medical Center

Dr. Wilson has no financial arrangements or affiliations with companies whose products or equipment are described in this presentation. He will discuss some "off label" uses of drugs.

OUTLINE

Introduction

The male sexual response
- Sexual arousal
- Penile erection
- Emission, ejaculation, and orgasm
- Detumescence
- Refractory period
- Neurophysiology of the sexual response
- Hormonal control
- Sex drive

Erectile Impotence
- Definition and Assessment
- Causes
- Diagnostic Evaluation

Therapy
- Phosphodiesterase 5 Inhibitors
  - Pharmacology
  - Clinical Effectiveness
  - Recreational Use
  - Use in Women
  - Drug Interactions
  - Side Effects
- Options when Phosphodiesterase 5 Inhibitors Fail
  - Intracorporeal Therapies
  - Vacuum Tumescence Devices
  - Concomitant Therapies
  - Penile Implants

Summary

INTRODUCTION

In December of 1998, I gave internal medicine grand rounds on "The Medical Management of Erectile Impotence." By that time the treatment of erectile impotence had shifted from a surgical to a medical issue. The first phosphodiesterase 5 inhibitor sildenafil had just been released for commercial use, and there were seven published papers on the drug. The initial reports were promising, but no one understood what a revolutionary impact this class of drugs would have on society or medicine. Today, a routine literature search pulls up 3500 references, amounting to 450 papers or more per year on the subject for the ensuing eight years. At the same time there has been a radical shift from an era in which reluctant and somewhat embarrassed patients confronted equally reluctant and embarrassed physicians about impotence; now patients demand and physicians prescribe the agents with abandon.

In biological terms sexuality consists of those physiological, anatomical, and behavioral functions that support or elicit the union of male and female gametes and thus ensure continuation of the species, but in human physiology the pleasurable aspects of the sex act are of equal importance in promoting a sense of well being. For this reason impotence is rarely treated to improve reproductive capacity but rather for well being, mental health, marital discord, or the underlying pathology that causes the disorder.

The aim of today's rounds is to review the mechanism of action, pharmacology, effectiveness, and complications of this interesting class of drugs and to consider the therapeutic options when they do not work. To set the stage I will review briefly the male sexual response and the mechanism of penile erection.

THE MALE SEXUAL RESPONSE

Investigation of the physiology of human sexual function lagged behind other areas of applied physiology, and our understanding of the male sexual response is almost entirely the work of Tom Lu in the Department of Urology at the UC San Francisco who applied techniques for measurement of regional blood flow and the methods of modern molecular pharmacology to this problem (1,2). [Although little is known about the female sexual response, it is assumed to be similar.] For didactic purposes the male sexual response can be divided into phases.

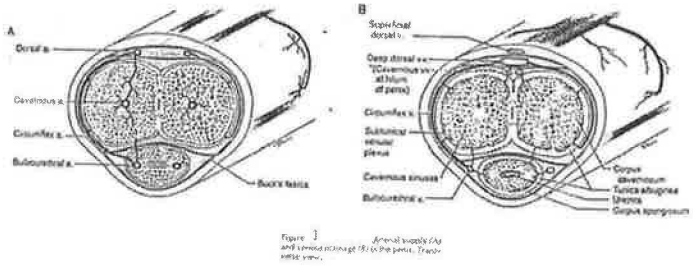
Sexual Arousal

Two types of stimuli cause sexual arousal. *Central stimuli* include auditory, visual, olfactory, gustatory, and psychogenic stimuli such as fantasy. Some of these effects are conditioned, but the control of nocturnal erections by central stimulate (see below) is responsible for the earliest and most persistent form of penile erection. In contrast *reflex stimuli* such as stroking the genitalia causes erection via spinal cord reflexes. Reflex erection is mediated by parasympathetic efferents whereas the effectors of central erections are primarily sympathetic.

Penile Erection

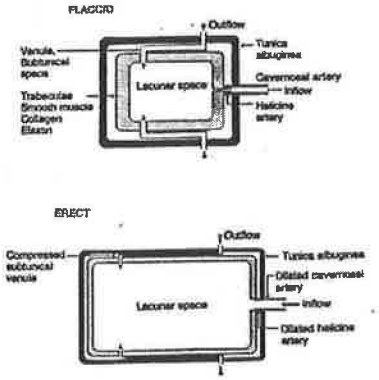
The erectile tissue of the penis is composed of two functional compartments—the corpora cavernosa and the corpus spongiosum (1,3). (Figure 1) The corpora cavernosa consist of two cylinders separated by a septum that is perforated by vessels that allow free passage of blood from one to the other, thus causing the two bodies to function as a single unit. The corpora spongiosum is a single cylinder that encompasses the urethra and enlarges distally to form the bulk of the glans penis. The erectile compartments are surrounded by a dense fascial sheath, the tunica albuginea, which at the proximal end anchors the penis to the symphysis pubis. The penile artery has three branches, the dorsal artery, the bulbourethral artery, and the cavernosal artery, all of which are connected by collateral branches. The venous drainage originates in small venules from the peripheral sinusoids beneath the tunica albuginea. These venules anastomose to form the subtunical venular plexus before exiting as the emissary veins into the deep dorsal and circumflex veins.

Figure 1. Arterial Supply (A) and Venous Draomage (B) of the Penis



The smooth muscles of the cavernous sinus and of the arterial and arteriolar walls are the key to erection.

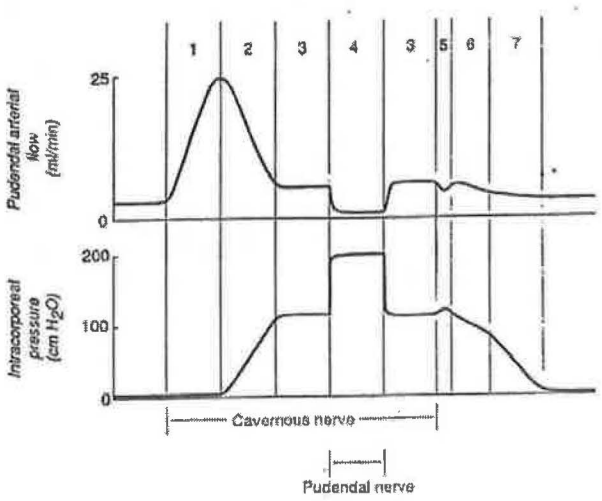
Figure 2. Schematic Diagram of Penile Erection



In the flaccid state intrinsic smooth muscle tone and sympathetic discharge provide high resistance to incoming blood. The flaccid penis is in a partial state of smooth muscle contraction, further contracting with exposure to cold and enlarging during a hot bath. For erection to occur inflow of blood must temporarily exceed outflow. The critical event is relaxation of smooth muscles of the penile arterioles under the control of neurotransmitters (Figure 2). This relaxation triggers:
1.) Dilatation of the arterioles and arteries by increased blood flow during both diastole and systole;
2.) Trapping of the incoming blood by the expanding sinusoids;
3.) Compression of the subtunical venular plexuses between the tunica albuginea and the peripheral sinusoids, reducing venous outflow (this compression is essential because erection cannot occur solely as a result of increased blood flow);
4. Stretching of the tunica to its capacity compresses the emissary veins between the inner circular and outer longitudinal layers, further decreasing the venous outflow to a minimum;
5.) Intracavernosal pressure increases to around 100 mm Hg, which transforms the penis to the fully erect state;
6.) A further pressure increase to several hundred millimeters Hg occurs when the bulbocavernosus reflex is triggered, causing profound contraction of penile smooth muscle (rigid erection phase).
7.) At this point blood flow to the penis ceases.

In brief, erection involves sinusoidal relaxation, arterial dilation, venous compression, and bulbocavernosus reflex-triggered contraction of penile smooth muscle..

Figure 3. Blood Flow and Cavernosa Pressure During Penile Erection and Detumescence



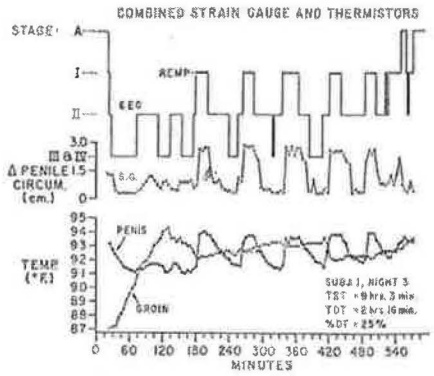
During this process, the volume of blood in the penis increases from and average of 8 ml in the flaccid state to about 62 ml, and blood flow increases from an average of 2 ml/hundred g/min to a maximal of about 50 ml/hundred g/min and then decreases to about 12 ml/hundred g/min prior to triggering the bulbocavernosus reflex. These changes are unaccompanied by changes in cardiac output or in blood flow to the pubic region.

Maximal blood flow decreases with age, and no pharmacological therapy can be effective unless blood flow is adequate.

The hemodynamics of erection of the corpus spongiosum and glans penis are somewhat different. During erection, the arterial flow in the corpus spongiosum increases in a similar manner, but the pressure in the glans and corpora spongiosum are only a fraction of that in the corpora cavernosa because the tunical covering is incomplete and allows miminal venous occlusion.

Nocturnal erections occur approximately every 80-120 minutes from puberty throughout adult life (4).

Figure 4. Nocturnal Erections in a Normal Man as Measured by Strain Gauge



Emission, Ejaculation, and Orgasm

Contraction of the ampulla of the vas deferens, the seminal vesicles, and the prostate causes *emission* of the semen into the posterior urethra, a process controlled by a spinal cord reflex. *Ejaculation*—the expulsion of the semen from the urethra—results from the rhythmical contraction of the bulbocavernosus muscles at 0.8 second intervals accompanied by simultaneous contraction of the muscles of the pelvic floor and the distal sphincter of the bladder. Ejaculation is a reflex reaction to the collection of semen in the bulbous urethra. *Orgasm*, the pleasurable sensation associated with perception of the contraction of the pelvic musculature, is associated with hyperventilation. Whatever the mechanism, orgasm can on occasion be generated centrally without input from the genitalia, as in rare cases of temporal lobe epilepsy.

Detumescence

Detumescence consists of three phases:
1.) a transient pressure increase as arterioles start to contract and bring arterial flow back to the low levels of the flaccid state;
2.) a slow decline in intracavernous pressure as the venous channels reopen;

3.) a fast decline in pressure and size as venous outflow is fully restored.

Refractory Period

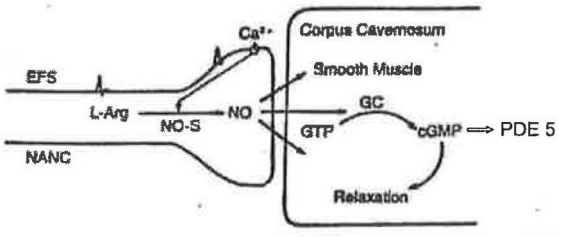
Detumescence is followed by a refractory period of variable duration, during which it is not possible to achieve an erection. The process is poorly understood, but the length of the refractory period increases with age and is influenced by many variables, including the general state of health, the degree of sexual arousal, and the vigor with which erection is attempted during the period..

Neurophysiology of the Sexual Response

Three types of nerve fibers innervate the penis. Somatic innervation is derived from S2-S4 and involves almost all components of the penis, including the sensory innervation of the skin and the motor fibers in the bulbocavernosus and ischiocavernosus muscles. Sympathetic innervation from T11-S2 and parasympathetic fibers from S2-S4 intermingle to form the prostatic plexus and cavernosus plexus of nerves.

The predominant type of nerve ending in the penis itself is adrenergic, but there are a variety of nerve endings in the penis and hence potential mediators, including acetyl choline (both muscarinic and nicotinic fibers), vasoactive intestinal peptide, prostaglandin, calcitonin gene related peptide, neuropeptide Y, endothelin, and nitrous oxide (1). It is generally believed that NO release during neurotransmission and from the endothelium is the principal mediator of penile erection. NO increases the production of cGMP, which in turn relaxes smooth muscle. The relaxation process may involve vasoactive intestinal polypeptide (VIP) but ultimately appears to result from a decrease in cytosol free Ca^{2+} levels (reviewed in Ref. 1). A simplistic view of erection is shown below:

Figure 5. NO Controls Smooth Muscle Relaxation by Initiating Hydrolysis of GTP to cGMP



Many neurotransmitters have been identified in the corporal bodies, including norepinephrine which is believed to interact with α-receptors to maintain the flaccid state. It follows that the way to enhance erection would be to either increase NO generation and hence increase cGMP generation or decrease the rate of degradation of cGMP by phosphodiesterase 5.

Detumescence is less well understood but is believed to be initiated by the release of endothelin from endothelial cells. Alternative theories of detumescence include cessation of NO release or sympathetic discharge during ejaculation. Other vasoconstrictors such as thromboxane A_2, prostaglandin F2α, leukotrienes, and angiotensin II may also play roles in vasoconstriction (1).

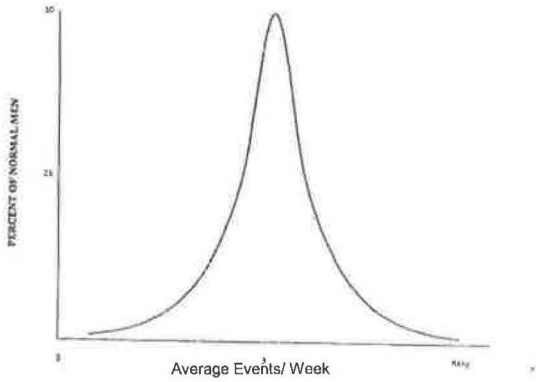
Hormonal Control

Androgens are responsible for development of the male genitalia and for maturation of the male genitalia and male sexual behavior at puberty (5). In the human prepubertal castration prevents the maturation of normal male behavior, and orchidectomy causes cessation of erectile capacity, with only occasional castrated men retaining the ability to get an erection over a period of years (6). Androgen replacement to hypogonadal men causes a rapid and reliable restoration of male sexual activity, and the principle site of this effect in the human is believed to be at the level of the central nervous system (7,8).

Sex Drive

No aspect of male function is less well understood than sex drive or potentia. The permissive role of androgen in controlling male sexual drive is well established, but among healthy, sexually active young men with similar androgen levels and available sex partners there is a striking variability in sex drive and in the frequency with which intercourse is initiated (9). The cause of this variability is obscure, but recognizing the variability is of importance when considering the causes of impotence. For example, beta adrenergic blockers cause impotence in many but not in all men.

Figure 6. Idealized curve of weekly intercourse in normal couples, age 20-30



Masters WH, Johnson VE, Kolodny RC. Human Sexuality. Boston: Little Brown & Co., 1982, p.298-300.

It is possible that drugs (and other factors) associated with impotence simply shift one's position on the Gaussian distribution curve to the left so that if one starts on the right hand portion of the curve, the likelihood of developing impotence from any cause is less than if one starts out on the left hand portion of the curve. Sexual activity in men normally declines with age. It is common that erotic stimuli must be of greater intensity to produce a response, and spontaneous erections decrease in frequency. The duration of the refractory period increases, penile filling slows, and occlusion of the venous outflow is less complete and/or the bulbocavernosus reflex is less complete, resulting in less rigid maximal erections (10).

IMPOTENCE

Men with sexual dysfunction present with several complaints, singly or in combination: loss of libido, ejaculatory failure, premature ejaculation, inability to achieve orgasm, priapism, or, most frequently, erectile dysfunction.

Loss of Libido.

A decrease in sexual desire can be due to androgen deficiency (either from pituitary or testicular disease), psychological disturbance, or to drugs. Hypogonadism can also cause absence of emission because of decreased formation of ejaculate by the prostate and seminal vesicles. Androgen status can be assessed by measurement of plasma testosterone and gonadotropin levels..

Premature Ejaculation.

This disorder seldom has an organic cause but is usually due to anxiety in the sexual situation, unreasonable expectations about sexual performance, or emotional problems. Behavioral therapy is usually successful in its management.

Insufficient Ejaculate

Absence of ejaculate can be due to retrograde ejaculation into the bladder, sympathetic denervation, androgen deficiency, or drugs. Retrograde ejaculation is common after surgery on the bladder neck and in men with diabetic autonomic neuropathy. Demonstration of sperm in a post-coital urine specimen establishes the diagnosis. Following sympathectomy or after extensive retroperitoneal surgery, the autonomic innervation of the prostate and seminal vesicles may be destroyed, causing diminution of the smooth muscle contractions at the time of ejaculation. Androgen deficiency causes diminution in the secretions of the prostate and seminal vesicles; benign prostatic hyperplasia can have the same effect. Drugs that inhibit ejaculation include guanethidine, phenoxybenzamine, phentolamine, and sertraline.

Absence of Orgasm

If libido, erection, and ejaculation are normal, absence of orgasm is usually due to a psychiatric disorder.

Priapism

Failure of Detumescence is a persistent, painful erection, usually defined as lasting several hours or more. It is often unrelated to sexual activity (it can occur with nocturnal erections) and can be secondary to clotting of blood within the sinusoidal spaces of the penis. The disorder is usually distinguished by the absence of tumescence of the glans penis because it rarely involves the corpus spongiosum. Priapism can be idiopathic or associated with sickle cell disease, chronic granulocytic leukemia, spinal cord injury, or injection of vasodilator agents into the penis (see below). Failure to treat priapism promptly can result in fibrosis and subsequent loss of erectile capacity (2).

ERECTILE IMPOTENCE

Incidence

The Massachusetts Male Aging Study discerned three levels of impotence—mild, moderate, and severe based upon several criteria, such as frequency of full erections, sexual activity, and frequency of erections upon awakening in the morning (11). In that particular study of healthy men 40 to 70 years of age, 48% were potent and 17, 25, and 10% had minimal, moderate, or complete erectile dysfunction. A longitudinal extension of the MMAS published in 2000 indicated that the risk of impotence between ages 40 to70 is about 26 cases per 1000 men per year and increases with age, lower level of education, diabetes mellitus, heart disease and hypertension (12).

Table 1. Mechanisms of Erectile Impotence

Process	Disorder
Vascular	
Obstruction of the aorto-iliac system	Aorto-occlusive disease
Obstruction of the hypogastric-penile arteries	Atherosclerosis
Arterial dysplasia	Primary impotence in young men
Veno-occlusive incompetence	Age, diabetes, Peyronie disease
Neurogenic	
Loss of CNS and/or spinal neurons	CVA, multiple sclerosis, epilepsy
Loss of autonomic neurons	Shy-Drager. Diabetes
Disordered signal transmission	Drugs
Inhibition of the erotic response	Depression, androgen deficiency
Endocrine	
Deficiency of androgen/androgen action	
Testicular failure	Castration, chemotherapy
Hypothalamic/pituitary disease	Age, pituitary adenoma
Prolactin excess	Prolactinoma, uremia, drugs
Estrogen excess	Alcoholism, cirrhosis, drugs
Inhibition of androgen receptors	Spironolactone, flutamide
Local	
Peyronie disease	
Intersinusoidal fibrosis	Diabetes mellitus
Penile trauma	Rodeo riders
Pudendal nerve trauma	Long distance bicycle riders
Penile cancer	

Causes of Impotence

A variety of etiologies and classifications have been used for erectile dysfunction (Table 1) (1, 13-15) Lue has emphasized the point that in most instances multiple factors interact; for example most cases have a psychogenic component of varying degree, and systemic diseases and pharmacologic effects can be concomitant (1). From my standpoint it is useful to classify impotence in relation to the mechanisms believed to be involved. Several of these categories deserve special comment.

Vascular disease Congenital defects in the penile vasculature are rare, but men with vascular disease may present with total erectile impotence, decreased penile rigidity, or loss of erections during intercourse. Vascular disease can be due to aortic occlusion or to distal disease, on occasion localized to the hypogastric/pudendal/cavernosa arteries. Impotence following pelvic radiation is probably due to vascular causes, but surgical correction of major artery obstruction may not necessarily alleviate erectile dysfunction.

Hypogonadism As stated above, hypogonadism impairs libido, erectile function, and ejaculate volume, and androgen replacement in such men is almost uniformly effective in restoring normal sexual function. The question as to whether lesser degrees of androgen deficiency contribute to erectile dysfunction is more complicated. Plasma levels of total and bioavailable testosterone decrease with age (16) but are no different in potent and impotent men (17). Furthermore, when testosterone levels are lowered by pharmacological means in normal men to values near the lower range of normal there is no effect on any parameter of sexual function (18). One study of endocrine screening in men presenting with impotence recommended endocrine profiling in men presenting below age 50 only in those with loss of libido but routine endocrine profiling in men above age 50 with the rationale that many men with hypogonadism as the cause of erectile impotence would otherwise be missed in that age group (19).

Diabetes mellitus In many series, the prevalence of erectile dysfunction is very common in unselected men with diabetes mellitus and increases with age (20), usually associated with decline in nocturnal penile tumescence (21). The onset of impotence is inversely related to the age at the diagnosis of diabetes (22). Both neurogenic and vascular factors are involved (23-25).

Hypertension Although hypertension is generally thought to be associated with an increased incidence of impotence, the age specific incidence of erectile dysfunction in hypertensive men probably does not differ from that in the general population of men receiving medical care (26). The onset of erectile dysfunction is often associated with initiation of antihypertensive therapy of diverse types (27). None of the published studies relate the degree of blood pressure control to sexual dysfunction, but the reduction of systemic blood pressure may accentuate reduction in flow caused by obstructive lesions (28).

Uremia About half of uremic men are impotent (29). Contributing factors may include elevated prolactin, elevated estradiol and low testosterone levels, secondary

hyperparathyroidism, zinc depletion, and autonomic neuropathy. Bromocriptine, clomiphene, and androgens are not effective in treating the erectile dysfunction, but erythropoietin has been reported to improve sexual function (30).

Neurological disease Temporal lobe epilepsy can cause erectile dysfunction, probably due to the impairment of arousal and can be worsened by antiepileptic medications (31).

Pelvic neoplasia In patients with pelvic tumors, erectile dysfunction occurs in about a fifth prior to surgery and in most after surgery. Pelvic irradiation and pelvic surgery impair erectile function by interrupting the autonomic fibers of the nervi erigentes that control the erectile process and/or by impairing penile blood flow (32-34).

Drug-related causes Drug therapy can impair libido, erectile function, and ejaculation. The principle culprits are neurotransmitter agonists or antagonists used for hypertension and angina and for treatment of psychiatric disorders; mechanisms may include inhibition of the parasympathetic erectile mechanism, stimulation of α-adrenergic constriction, impairment of central erotic responsiveness, or enhancement of prolactin secretion. Agents that reduce androgen availability and/or effectiveness or act directly as estrogens include digitalis, cimetidine, ranitidine, spironolactone, ketoconazole, progestogens, LHRH agonists/antagonists, and estrogens themselves.

Alcohol consumption per se does not affect erectile function (35). However, chronic alcoholism with liver disease is associated with a high incidence of impotence (36), and sexual function may not return to normal after long-term rehabilitation (37). Heavy cigarette smoking is associated with erectile dysfunction as a result of constriction of corporeal blood flow (38).

Diagnostic Evaluation

In the past the evaluation of impotence involved a history and workup including endocrine evaluation followed by assessment of nocturnal penile tumescence, psychological assessment when appropriate, and in some instances assessment of blood flow in the penis. These various techniques are discussed in detail in ref 2; a complete workup is expensive, involves some discomfort, and is frequently not informative. Consequently, it is now standard practice not to attempt to separate vascular from neurogenic causes but to exclude hypogonadism as a cause, treat any co-morbidities that may be contributing to the problem, and move directly to a therapeutic trial of phosphodiesterase 5 inhibitor. When such therapy is not successful, alternative therapies are tried.

THERAPEUTIC OPTIONS

Phosphodiesterase 5 Inhibitors

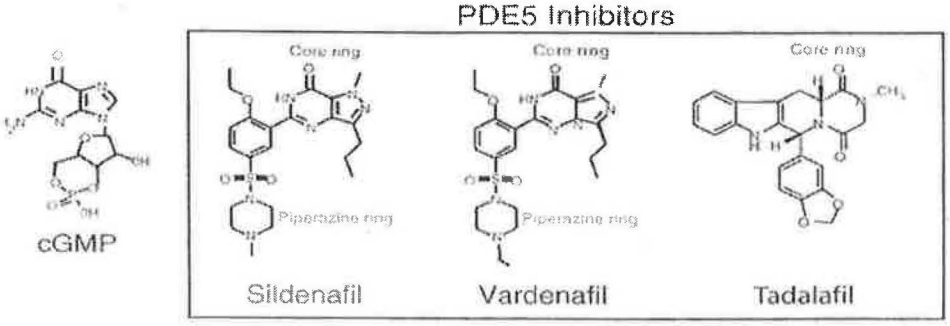
Pharmacology There are 11 phosphodiesterase (PDE) isoenzymes, each encoded by a separate gene and six of which cleave cGMP. Because phosphodiesterase 5 is the

predominant isoenzyme in the penis (39) selective inhibition of PDE 5 increases intracellular cGMP levels in vascular and corporeal smooth muscle and thus potentiates the NO-mediated vasorelaxation in response to sexual arousal. PDE 5 is widely distributed in vascular, pulmonary and visceral smooth muscle, kidney, platelets and cerebellum.

[Agents that inhibit PDE 5 have been used in a variety of medical conditions, including pulmonary arterial hypertension (40-43) and high-altitude pulmonary edema (44). Inhibitors of other PDE isoenzymes have also been widely studied. These various uses are beyond the scope of this review.]

The first PDE inhibitor for treating ED was the opium poppy alkaloid papaverine, a relatively unselective PDE inhibitor (39), but the first orally active PDE 5 inhibitor was sildenafil citrate. The structures of the three agents approved for the treatment of erectile impotence and of the substrate for the enzyme cGMP are shown in Figure 7. All three share a heterocyclic nitrogen-containing double-ring system that mimics the purine base of cGMP and interacts with the PDE5 catalytic site.

Figure 7. Structures of the PDE 5 Substrate cGMP and the PDE 5 Inhibitors



The promoter region of the PDE 5 gene is inducible by cGMP so that increased cGMP levels lead to increased PDE 5 gene expression in a positive feedback loop. There are three PDE 5 splice variants; PDE5A3 is limited to the penis, bladder, urethra, prostate, and aorta, whereas the other splice variants are widely distributed. PDE5 is a homodimeric enzyme of the cytosol consisting of two identical subunits, each of which contains a catalytic domain and an amino-terminal regulatory domain. Each of the PDE 5 inhibitors binds exclusively to the catalytic domain. The pharmacological properties of the PDE 5 inhibitors are summarized in Table 2.

The reason that vardenafil is more potent than the other two drugs is that it binds with extraordinary affinity to one specific tyrosine (tyrosine-612) in PDE 5 (45). Sildenafil response is almost twice as great in men who carry a rare polymorphism (C825T) in the G protein Gβ3, a mediator of signal transduction (46). The half life of tadalafil is longer than that of the other two drugs, a feature that is consistent with its broad window of

clinical effectiveness. The fact that the half life is longer complicates the management of drug interactions.

Table 2. Comparison of the PDE 5 Inhibitors

	Sildenafil	Vardenafil	Tadalafil
IC50, nmol/l	3.7	0.09	1.8
▪ Potency	1	41	2
▪ Tmax, h	1	1	2
▪ VD, l	105	208	63
▪ T½, h	4-5	4-5	18

Clinical Effectiveness Some of the problems involved in interpreting the literature on the effectiveness of these agents are summarized in Table 3.

Table 3. Caveats About PDE 5 Inhibitors

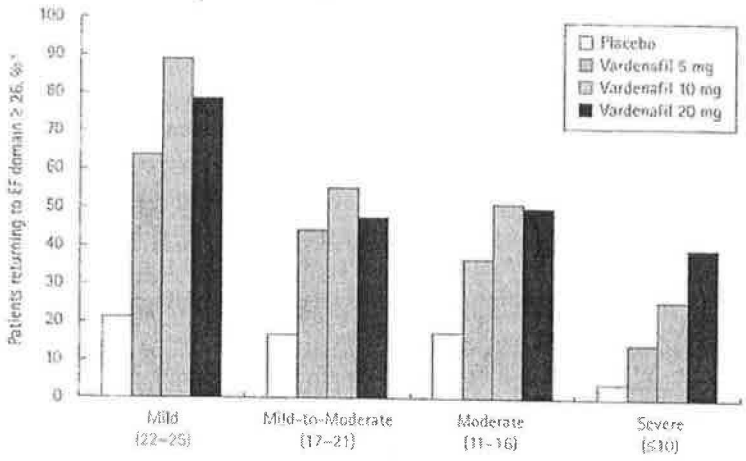
- Virtually all published studies are industry sponsored.
- No direct comparative study of different inhibitors has been done.
- Many studies include a large fraction of men with psychogenic impotence.
- Studies of effectiveness in erectile dysfunction of specific etiology are weighted toward individuals with mild to moderate degrees of impotence.
- The questionnaires used to assess response are limited in scope.
- Dropout rate in subjects who respond to the drugs is surprisingly high over time.

Since all published studies are industry sponsored it is not surprising that no blinded comparative studies of the effectiveness of the three agents have been performed. Instead, preference studies have been conducted by the pharmaceutical industry are difficult to interpret because in some maximal doses of one agent were compared with half maximal doses of another (47). Furthermore, in one study 40% of impotent men who were deemed

sildenafil failures initially were converted to responders through patient re-education (48).

The compounding problem of mixing psychogenic and organic erectile dysfunction is illustrated by the study summarized in Figure 8.

Figure 8. Percent of Vardenafil Patients Returning to Normal Stratified by Baseline Severity of Erectile Dysfunction.



Hellstrom WJ, et al. J Androl 23:763-763-771, 2002

In this highly cited paper 805 men (average age 57) with erectile dysfunction for 3 years were treated with placebo or two doses of vardenafil. As in all studies the response was greatest in the men with mild impotence; the problem in interpreting the data is that 46% of the men in each group carried the diagnosis of psychogenic impotence, a group widely believed to respond better to PDE 5 inhibitors than do men with neurogenic causes for impotence (49). Consequently, there is no way to know whether any men with severe organic impotence responded in this study.

This issue is compounded in studies of men with erectile impotence associated with a specific diagnosis, such as diabetes mellitus, in which the response to therapy was less than in a group of non-diabetic men with impotence (56 % versus 84%) because here the groups contain many or most with mild to moderate erectile dysfunction so that it is again not possible to know how many diabetic men with severe impotence respond (49, 50). Furthermore, a larger percentage of diabetics who respond initially to PDE 5 inhibitor later lose the response than occurs in non diabetics (51).

The instruments—actually questionnaires—used to assess response to therapy have their problems. As therapeutic agents became available for treatment of the disorder, it became necessary to develop means of quantifying the degree of impotence. Consequently, an international index of erectile dysfunction (IIEF) was developed (and validated for 10 languages); this questionnaire addressed 15 different components of sexual function from the level and frequency of desire to the satisfaction of the partner (52). The maximum

score on this test is 75. It is reliable, easy to administer, and highly reproducible in the same individuals. However, for unclear reasons this means of quantifying erectile dysfunction is rarely used.

Instead, a subset of these questions has commonly been widely utilized to focus on the erectile function domain of the IIEF (53). This abbreviated questionnaire has been widely utilized to define and classify impotence in most of the pharmacological studies described to date. The maximal score is 30, and 5 categories are defined: no erectile dysfunction (EF score 26-30); mild ED (EF score 22-25); mild to moderate ED (EF score 17-21); moderate ED (EF score 11-16); severe ED (EF score 1-10).

However, it has been pointed out that this system does not assess sexual function in that one can have a full erection but still have unsatisfactory intercourse because of lack of sufficient rigidity. A third type of questionnaire was consequently developed and validated to include independent assessments of subject and partner satisfaction (54), and an international consensus panel recommended that treatment response and treatment satisfaction be assessed separately and combined into an 'effectiveness scale' (55). To the extent that partner satisfaction has been studied, it is said to correlate with patient satisfaction (56). The argument has also been made that partners should be involved in decision making about the use of the agents (57).

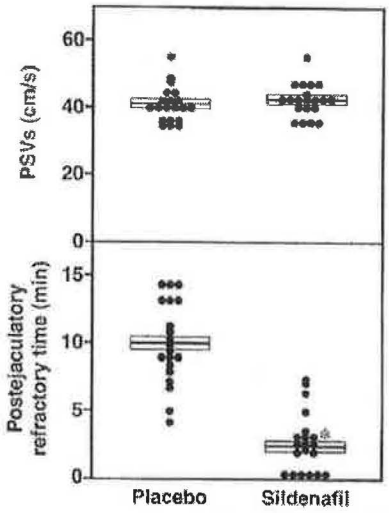
Although the compliance rate of men in most study groups is high (participants in clinical trials tend to be highly motivated), the dropout rate by men who respond to the therapy in various surveys ranges from 14 to 47% (58). The causes are multiple and simply reflect the fact that drug adherence is a complex issue.

My interpretation of this problem is that the PDE 5 inhibitors do work in men with erectile impotence of various causes but that the published numbers as to effectiveness are meaningless.

Recreational Use in Men Considering the way that these agents are advertised and promoted, it is a reasonable assumption that the sales of the drugs in large part are to potent men who wish to become supermen. If this is the case it is astonishing how few studies have been done in potent men, but the available studies are interesting. Namely, in two double-blind studies of sildenafil versus placebo in young virile men with regular sex partners, there was no effect on erection or penile blood flow, no difference in ejaculate volume, and no difference in sperm in the ejaculate (59-60). In one study of nocturnal penile erections sildenafil increased the frequency, duration, and rigidity of penile erections in 36 men with organic impotence of various types but had no effect in the 5 normal control men (61). In a non-randomized control study of 22 potent medical students and urology residents, sildenafil was said to increase the frequency and rigidity of nocturnal erections but not the duration (62) whereas in a placebo controlled study of 6 normal men sildenafil had no effect on the mean number, rigidity, or duration of nocturnal erections (63).

However, in two carefully designed studies (59, 60) sildenafil does decrease the postejaculatory refractory period as illustrated in Figure 9:

Figure 9. Effect of Sildenafil on Penile Blood Flow (Top Panel) and Post-ejaculatory Refractory Time (Lower Panel) in Normal Men



Aversa A, et al. Human Reproduction 15:131-134, 2000.

The fact that the mean refractory period declined 4-5 fold is less impressive to me than the fact that the mean refractory period in the placebo arm was only 10 minutes in these men (average age 32). This is almost certainly due to the experimental design employed. Recreational users of these drugs can draw their own conclusions from these data.

Potent men not infrequently have difficulty in producing semen samples in the hospital setting (so called temporary erectile dysfunction), and in one study the use of sildenafil prior to the collection period prevented this problem in men who had previously experienced such a difficulty (64).

Use in Women Phosphodiesterase 5 is expressed in clitoris and vagina and sildenafil enhances genital blood flow and vaginal and clitoral engorgement in women with female sexual arousal disorder (FASD) (65). In a carefully designed double-blind, placebo-controlled study sildenafil was administered to 202 postmenopausal women with FASD (66). It caused significant improvements in 5 of 6 categories of the female intervention efficacy index but only in women with normal sexual desire (66). All of these women had normal testosterone levels or were receiving testosterone, whereas in previous studies without such a stipulation the findings were less impressive (67). In all such studies in women the placebo effect is equal to or greater than that in men.

Drug Interactions Because phosphodiesterase inhibitors poteniate the vasodilator/hypotensive effects of NO donors, treatment with any of the agents is contraindicated in patients taking any form of NO donor, including organic nitrates.

Because of differences in turnover, it is generally recommended that nitrates should not be given until 24 h after ingestion of sildenafil or vardenafil and until 48 h after ingestion of tadalafil (68). The interaction of these agents with α-blockers is more complex; all α-blockers are contraindicated in patients taking vardenafil whereas all except low dose tamsulosin are contraindicated with tadalafil. Sildenafil should not be administered within 4h of an α-blocker (68). The inhibitors are safe to administer in patients taking antihypertensive medications other than α-blockers. Vardenafil should not be administered to patients taking class IA or III antiarrhythmic drugs or to patients with congenital QT prolongation (68)

Data from controlled clinical trials suggest that the risk of myocardial infarction or death is not changed with PDE5 inhibitors, but extensive studies have not been performed in men with baseline severe or unstable cardiac conditions (68).

Side Effects All three agents cause a mild lowering of blood pressure. Most adverse effects are assumed to be due to inhibition of PDE 5 in tissues other than the penis and include headache, dyspepsia, flushing, myalgia/back pain, rhinitis, and a low incidence of ophthalmologic complications (39).

Options When Phosphodiesterase 5 Inhibitors Fail

This subject is reviewed in References 2 and 69. Unfortunately, the options are the same as before introduction of PDE 5 inhibitors except for the combination therapy.

Intracorporeal Therapies With the introduction of PDE 5 inhibitors, most (but not all) men who self-administered intracorporeal therapies were successfully switched to the oral drugs (70, 71). At present these therapies are used for men who do not have an

Figure 10. Administration of Drugs into the Corpora Cavernosa

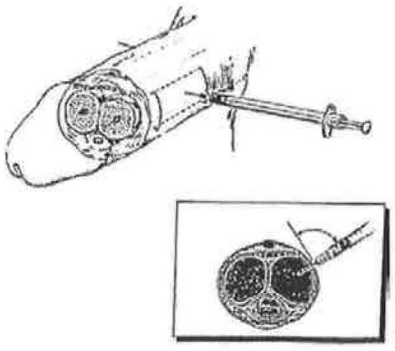
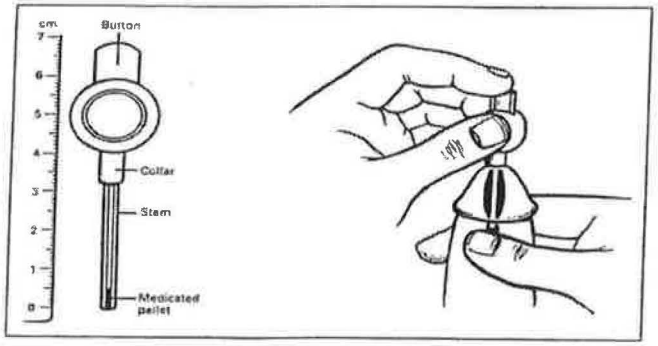


Table 4. Meta-analysis of Response in 6535 Men to Intra-corporeal Self-Injection

AGENT	RESPONDERS (DROPOUT)	PRIAPISM >6h	NODULES/ FIBROSIS	PAIN
Papaverine (1,527)	61% (47%)	7.1%	5.7%	4%
Papaverine/Phentolamine (2,263)	68% (45%)	7.8%	12.4%	11.6%
Alprostadil (2,745)	72% (37%)	0.4%	0.8%	7.2%

Porst H. J Urology 155:802-815, 1996

Figure 11. Applicator for Transurethral Administration of Alprostadil



adequate response and in men with some contraindication to PDE 5 inhibitors, such as use of organic nitrates. There are two types of such therapies—self-injection into the corpora cavernosa or administration via a pellet into the urethra (the Muse System). In general injection is more effective.

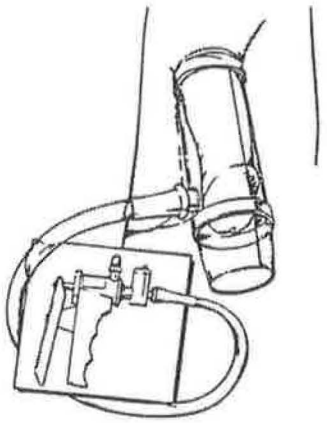
Contraindications to injection therapy include bleeding diatheses, Payronie's disease, and previous episodes of priapism (69). Initiation of these therapies consists of dose titration to identify the lowest dose required for achieving an appropriate erectile response and careful training about what the handling of complications and should only be undertaken by physicians knowledgeable about the therapies and prepared to deal with complications. The dread complication of injection therapy is priapism, but the incidence of priapism is low with alprostadil (72). Nevertheless, alprostadil can cause burning and discomfort in some men. In view of the fact that only 73 % of men respond to this therapy initially and that the dropout rate is around 37 % in those who initially respond, the therapy is effective long term in only half of men. The management of priapism when it occurs is discussed in references 2, 69, and 72.

The Muse device for the intraurethral administration of alprostadil requires administration of a larger average dose, the systemic side effects, mainly dizziness, are worse, and at best only about half of users achieve an erection sufficient to complete intercourse (73). In a study done at UT Southwestern the results were less good with a 30% response rate and a dropout of more than 80% (74).

Several combinations of three injectable drugs have been devised with the rationale that combinations of subtherapeutic doses of alprostadil, papaverine, and phentolamine (so – called trimix) would be more effective and have a lower complication rate (75). However, when these agents were compared in a randomized fashion with alprostadil, even at the lowest effective dose of trimix ingredients there are no differences in rigidity, pain, or self-satisfaction. However, trimix was associated with a significant incidence of priapism (76).

External Vacuum Tumescence Devices A variety of external vacuum devices are marketed, the common feature being a plastic cylinder enclosing the penis, a vacuum device, and a band that fits around the base of the penis (77). Application of the device causes blood to pool in the penis, and when a sufficient erection is obtained an obstructing rubber band is applied to be base of the penis to retain the accumulated blood in the penis. After the subject and partner become adept in its use, the devices are usually satisfactory to both. A normal coital pattern is usually restored with 2-10 uses per month. Erections last an average of 16 minutes, and the tissues are not damaged although the

Figure 12. Vacuum Tumescence



penis is cyanotic as long as the band is in place. The principal problems with the devices are discomfort from the band, a cold sensation in the erect penis, and either failure to ejaculate or retrograde ejaculation if the band is too tight. Despite the fact that surveys suggest both patient and partner satisfaction, there is a high dropout rate. Chen and colleagues did a very interesting patient preference study in a group of men who had been treated effectively with a vacuum erection device and were then switched to sildenafil (78). In 36 of 54 patients, the efficacy of sildenafil was similar to that of the device as assessed by the IIEF scores (62 and 62 respectively in the two groups); interestingly, 12 of the 36 elected to return to the vacuum device, whereas the remaining 24 continued.

The adverse side effects of sildenafil were the main reason for choosing the vacuum device, and the main reasons for preferring sildenafil included fewer ejaculatory difficulties, comfort, and ease of use. The authors concluded that the vacuum tumescence device is a legitimate treatment option for some patients.

Concomitant Therapies A variety of concomitant therapies have been tried in men who did not respond adequately to each alone, including sildenafil and vacuum tumescence devices (79), sildenafil and alprostadil injections (80), and testosterone and sildenafil (81).Whether any of these combinations will prove to be significant awaits further study

Penile Implants. Surgical implantation of penile prostheses confers rigidity to the penis, either continuously with semi-rigid varieties or on demand with inflatable prostheses. This therapy is now second-line, and the frequency of penile implants declined markedly with the introduction of drug therapies. Disadvantages include cost, a high complication rate, poor quality erections, and mechanical failure. None of the devices cause erection of the glans penis, which is subject to trauma during intercourse. Implantation and other surgical approaches are reviewed in ref. 13.

SUMMARY

The availability of orally active phosphodiesterase 5 inhibitors has changed the way that erectile impotence is worked up and managed. Namely, when men present with impotence of all causes, the practice is to perform a limited workup and administer PDE 5 inhibitors as a trial therapy. Because of limitations in the design of the drug trials, it is not clear how effective they are in quantitative terms, but the agents are not very effective in men with severe impotence of organic etiology. For men with contraindications to their use or treatment failure with PDE5 inhibitors, Alternative include including intracorporeal alprostadil, vacuum tumescence devices, and combination therapies. As recreational drugs in virile men the only documented effect of PDE 5 inhibitors is to shorten the refractory period after ejaculation. At present the drugs appear to have only limited use in women with sexual arousal disorder.

REFERENCES

1. Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. In, Campbell's Urology, 8th ed., Walsh PC, et al., eds., Philadelphia: Saunders. p. 1591-1618, 2002.
2. Broderick GA, Lue TF. Evaluation and nonsurgical management of erectile dysfunction and priapism. In Campbell's Urology, 8th ed., Walsh, PC, et al., eds., Philadelphia: Saunders. p.1619-1671, 2002.
3. Andersson KE, Warner G. Physiology of penile erection. Physiol Rev 75:191-222, 1996.
4. Fisher C, Groff J, Zuch J. Cycle of penile erection synchronous with dreaming (REM) sleep. Arch Gen Psychiatry 12:29-45, 1965.
5. Wilson JD. Gonadal hormones and sexual behavior. In Clinical Neuroendocrinology II, Besser GM, Martini L, eds. New York: Academic Press, p. 1-29, 1982.
6. Bremer J. Asexualization: A follow-up study of 244 cases. Oslo: Oslo University

Press, 1958.
7. Davidson JM, Kwan, M, Greenleaf WJ. Hormonal replacement and sexuality in men. Clinics Endocrinol Metab 11:599-623, 1982.
8. Kwan M, Greenleaf WJ, Man J, Crapo L, Davidson JM. The nature of androgen action on male sexuality: A combined laboratory-self-report study on hypogonadal men. J Clin Endocrinol Metab 57:557-562, 1983.
9. Masters WH, Johnson VE, Kolodny RC. Human sexuality. Boston: Little Brown & Co., p 298-300, 1982.
10. McKinlay JB, Feldman HA. Sexuality across the life course, Chicago: University of Chicago Press, p. 261-285, 1994.
11. Feldman HA, Goldstein I, Hatzichriston DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. J Urol 151:54-61, 1994.
12. Johannes CB, Araujo AB, Feldman, HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: Longitudinal results from the Massachusetts male aging study. J Urol 163: 460-463, 2000.
13. Montague DK, Jarrow JP, Broderick GA, et al. The management of erectile dysfunction: an AUA update. J Urology 174:230-239, 2005.
14. Laumann RO, Palk A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 281:537-544, 1999.
15. Melman A, Christ GJ. The hemodynamics of erection and the pharmacotherapies of erectile dysfunction. Heart Disease 4:252-264, 2002.
16. Tenover JS, Matsumoto AM, Plymate SR. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. J Clin Endocrinol Metab 65:1118-1126, 1987.
17. Korenman SG, Morley JE, Morradian AD. Secondary hypogonadism in older men: its relation to impotence. J Clin Endocrinol Metab 71:963-969, 1990.
18. Buena F, Peterson MA, Swerdloff RS, Pandian MR, Steiner BS, Galmarini M, Lutchmansingh P, Bhasin S. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal range. Fertil Steril 59:1118-1123, 1993.
19. Buvat J, Lemaire A. Endocrine screening in 1022 men with erectile dysfunction: Clinical significance and cost-effective strategy. J Urol 158:1764-1767, 1997.
20. Jensen SB Diabetic sexual dysfunction: a comparative study of 160 insulin-treated diabetic men and women and an age-matched control group. Arch Sex Behav 10:493-504, 1981.
21 Schiavi RC, Fisher C, Quadland M. Nocturnal penile tumescent evaluation of erectile function in insulin-dependent diabetic men. Diabetologia 28:90-94, 1985.
23. Bemelmans FLH, Meuleman EJH, Doesburg WH. Erectile dysfunction in diabetic men: the neurological factor revisited. J Urol 151:884-889, 1994.
24. Jevitch MJ, Edson M, Jarmon WD. Vascular factor in erectile failure among diabetics. Urology 19:163-168, 1994,
25. Benvenuti F, Boncinelli L, Vignoli GC. Male sexual impotence in diabetes mellitus: vasculogenic versus neurogenic factors. Urodynamics 12:145-152, 1985.
26. Newman HF, Marcus H. Erectile dysfunction in diabetes and hypertension. Urology 26:135-137, 1885.

27. Moss HB, Procci WR. Sexual dysfunction associated with oral antihypertensive medications: a critical survey of the literature. Gen Hosp Psychiatry 4:121-129, 1982.
28. Lue TF, Hricak H, Marich KW. Vasculogenic impotence evaluated by high resolution ultrasonography and pulsed Doppler spectrum analysis. Radiology 155:778-782, 1985.
29. Foulks CJ, Cushner HM. Sexual dysfunction in the male dialysis patient: pathogenesis, evaluation, and therapy. Am J Kidney Dis 8:211-222, 1986.
30. Schaefer F, van Kaick B, Veldhuis JD. Changes in the kinetics and biopotency of luteinizing hormone in hemodialyzed men during treatment with recombinant human erythropoietin. J Am Soc Nephrol 5:1208-1215, 1994.
31. Morrell MJ, Sperling MR, Stecker M. Sexual dysfunction in partial epilepsy: a deficit in physiologic sexual arousal. Neurology 44:243-247, 1994.
32. Pontes JE, Huben R, Wolf R. Sexual function after radical prostatectomy. Prostate 8:123-126, 1986.
33. Melman A. Iatrogenic causes of impotence. Urol Clin North Am 25:33-39, 1988.
34. Goldstein I, Feldman MI, Deckers PJ. Radiation-associated impotence: a clinical study of its mechanism. JAMA 251:903-910, 1984.
35. Schiavi RC, Stimmel BB, Mandell J. Chronic alcoholism and male sexual function. Am J Psychiatry 152:1045-1051, 1995.
36. Fahrner EM. Sexual dysfunction in male alcohol addicts: prevalence and treatment. Arch Sex Behav 16:247-257, 1987.
37. Jensen SB. Sexual function and dysfunction in younger married alcoholics. Acta Psychiatr Scand 69:543-549, 1984.
38. Juenemann K, Lue TF, Luo J. The effect of cigarette smoking on penile erection. J Urol. 138:438-441,1987.
39. Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU International 96:257-280, 2005.
40. Travadi JN, Patole SK. Phosphodiesterase inhibitors for persistent pulmonary hypertension of the newborn: A review. Pediatric Pulmonology 36:529-535, 2003.
41. Hemmes AR, Champion HC. Sildenafil, a PDE5 inhibitor, in the treatment of pulmonary hypertension. Expert Rev Cardiovasc Ther 4:293-300, 2006.
42. Karatza AA, Bush A, Magee AG. Safety and efficacy of sildenafil therapy in children with pulmonary hypertension. Int J Cardiology 100:267-273, 2005.
43. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. NEJM 353:2148-2157, 2005.
44. Maggiorini M, Brunneer-La Rocca H-P, Peth S, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema. Ann Int Med 145:497-507, 2005.
45. Gorbin, J, Francis S, Zoraghi R. Tyrosine-612 in PDE5 contributes to higher affinity for vardenafil over sildenafil. Int J Impotence Res 18:251-257, 2006.
46. Sperling H, Eisenhardt A, Virchow S, et al. Sildenafil response is influenced by the G protein β3 subunit GNB3 C825T polymorphism: A pilot study. J Urol 169:1048-1051, 2003.
47. Mulhall JP. Understanding erectile dysfunction medication preference studies. Current Opinion in Urology 14:367-373, 2004.
48. Atiemo HO, Szostak MJ, Sklar GN. Salvage of sildenafil failures referred from primary care physicians. J Urol 170:2356-2358, 2003.

49. Jarrow JP, Burnett AL, Geringer AM. Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment. J Urol 162:722-725, 1999.
50. Vickers MA, Satyanarayana R. Phosphoesterase type 5 inhibitors for the treatment of erectile dysfunction in patients with diabetes mellitus. Int J Impotence Res 14:466-471, 2002.
51. Penson DF, Wallace KI, Latini DM, et al. Do impotent men with diabetes have more severe erectile dysfunction and worse quality of life than the general population of impotent patients? Diabetes Care 26:1093-1099, 2003.
52. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick, J, Mishra A. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology 49:822-830, 1997.
53. Cappelleri JC, Rosen RC, Smith MD, Mishr A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the international index of erectile function. Urology 54: 345-351, 1999.
54. Althof SE, Corty EW, Levine SB, Levine F, Burnett AI, McVary K, Stecher V, Stefel AD. Edits: Development of questionnaires for evaluating satisfaction with treatments for erectile dysfunction. Urology 53 793-799, 1999.
55. Carson C, Giuliano F, Goldstein, et al. The 'effectiveness' scale—therapeutic outcome of pharmacological therapies for ED: an international consensus panel report. Int J Impotence Res 16:207-213, 2004.
56. Montorsi F, Althof SE. Partner responses to sildenafil citrate (Viagra) treatment of erectile dysfunction. Urology 63:62-67, 2004
57. Boisaubin EV, McCullough LB. Prescribing Viagra in an ethically responsible fashion. Journal of Medicine and Philosophy 29:739-749, 2004.
58. Seftel AD. Challenges in oral therapy for erectile dysfunction. J Androl 23:729-736, 2002.
59 Aversa A, Mazzzilli F, Rossi T, et al. Effects of sildenafil (Viagra™) on seminal parameters and post-ejaculatory refractory time in normal males. Human Reproduction 15:131-134, 2000.
60. Mondaini N, Ronchietti R, Muir GH, et al. Sildenafil does not improve sexual function in men without erectile dysfunction but does reduce the post orgasmic refractory time. Int J Impotence Res 15:225-228, 2003.
61. Terradas C, Levalle O, Nagelberg A, Mormandi E. Sildenafil improves nocturnal penile erections in organic impotence. Int J Impotence Res 13:125-129, 2001.
62. Yaman O, Tokath Z, Inal T, Anafarta K. Effect of sildenafil on nocturnal erections of potent men. Int J Impotence Res 15:117-121, 2003.
63. Salonia A, Italy L, Barbieri, Deho F, Scapaticci F, Montorsi F. Bed-time apomorphine and sildenafil: results of a placebo-controlled study in healthy potent volunteers. Int J Impotence Res 14:S4 P-083, 2002.
64. Tur-Kaspa I, Segal S, Moffa F, Massobrio M, Meltzer S. Viagra for temporary erectile dysfunction during treatments with assisted reproductive technologies. Human Reproduction 14:11783-1784, 1999.
65. Berman JR, Berman LA, Lin H, et al. Effect of sildenafil on subjective and physiologtic parameters of the female sexual response in women with sexual arousal disorder. J Sex Marital Ther 27:411-416, 2001
66. Berman JR, Verma LA, Toler SM, Gill J, Haughies S. Safety and efficacy of

sildenafil citrate for the treatment of female sexual arousal disorder: a double-blind, placebo controlled study. J Urology170:2333-2338, 2003.
67. Bassen R, McINnes R, Smith MD, Hodgson G, Koppiker N. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. J Womens Health Gend Based Med 11:367-372, 2002.
68. Kloner RA. Cardiovascular effects of the 3 phosphodiesterase-5 inhibitors approved for the treatment of erectile dysfunction. Circulation 110:3149-3155, 2004.
69. Montorsi F, Salonia A, Deho F, Cestari G, Rigatti P, Stief C. Pharmacological management of erectile dysfunction. BJU International 91:446-454, 2003.
70. Giuliano F, Montorsi F, Mirone V, et al. Switching from intracavernous prostaglandin E1 injections to oral sildenafil citrate in patients with erectile dysfunction: results of a multicenter European study. J Urology 164:708-711, 2000.
71. Hatzichristou DG, Apostolides A, Tzortzis V, et al. Sildenafil versus intracavernous injection therapy: efficacy and preference in patients on intracavernous injection for more than 1 year. J Urology 164:1197-1200, 2000.
72. Porst H. The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. J Urology 155:802-815, 1996.
73. Padema-Nathan H, Hellerstrom WJG, Kaiser FE, et al. Treatment of men with erectile dysfunction with transurethral alprostadil. N Engl J Med 336:1-7, 1997.
74. Fulgham PF, Cochran JS, Denman J, et al. Disappointing initial results with transurethral alprostadil for erectile dysfunction in a urology practice setting. J Urology 160:2041-2046.
75. Casabe A, Bechara GC, Romanmo S, Rey H, Fredotovich N. Drop-out reasons and complications in self-injection therapy with a triple vasoactive drug mixture in sexual erectile dysfunction. Int J Impotence Res 10:5-9, 1998.
76. Seyam R, Mohamed K, Akhras AA, Rashwan H. A prospective randomized study to optimize the dosage of trimix ingredients and compare its efficacy and safety with prostaglandin E_1. Int J Impotence Res 17:346-353, 2005.
77. Korenman SG, Viosca SP, Kaiser FE, et al. Use of a vacuum detumescence device in the management of impotence. J Am Geriatr Soc 38:217-220, 1990.
78. Chen J, Mabjeesh NJ, Greenstein A. Sildenafil versus the vacuum erection device: patient preference. J Urology 166:1779-1781, 2001.
79. Chen J, Sofer M, Kaver I, Matzkin H, Greenstein A. Concomitant use of sildenafil and a vacuum entrapment device for the treatment of erectile dysfunction. J Urology 171:292-295, 2004.
80. Nandipata K, Raina R, Agarwal A, Zippe CD. Early combination therapy: intracavernosal injections and sildenafil following radical prostatectomy increases sexual activity and the return of natural erections. Int J Impotence Res 18:446-451, 2006.
81. Shabsingh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as an adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urology 172:658-663, 2004.