

## Advances in the Treatment of Patients with Erectile Dysfunction

a report by

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The problem of erectile dysfunction (ED) affects millions of men in the US and throughout the world. ED, defined as a persistent inability to obtain and maintain an erection satisfactory for sexual activity, has been poorly understood. In the latter half of the 20th century the issue of ED changed from a little-discussed area of primarily psychological discussion to an active field of medical, psychological, and pharmacological research and development. The pejorative term 'impotence' was replaced in the 1990s with 'erectile dysfunction' and 'erectile difficulties'. During the past two decades, the physiology and molecular biology of erection and erectile dysfunction have been studied carefully and translational research has led not only to the elucidation of the physiology of erection, but also to significant progress in the diagnosis and treatment of men with ED.

Basic scientific investigation over the past two decades has clarified the anatomy, physiology, and pharmacology of the *corpus cavernosum* as well as the neurophysiology and vascular physiology of erectile function. Neurotransmitters that activate this mechanism have been clearly elucidated and, indeed, the identification of nitric oxide as the principle neurotransmitter responsible for activating relaxation of the *corpus cavernosum* smooth muscle resulted in the Nobel Prize for Louis Ignarro, PhD. This identification of nitric oxide as the principal neurotransmitter and its effect on cyclic GMP (cGMP), producing relaxation of the *corpus cavernosum* smooth muscle, has permitted the development of new pharmacological agents for the treatment of ED that are effective, safe, and tolerable for more than 70% of patients.

ED is highly prevalent. The Massachusetts Male Aging Study has documented a prevalence that reaches as high as 52% of men over the age of 40. Other epidemiological studies throughout the world have confirmed this high prevalence in men over 40 and have documented ED in men of all ages and ethnicities. Risk factors for ED are principally those of vascular dysfunction, including smoking, hypercholesterolemia, hypertension, and *diabetes mellitus*. Non-vascular risk factors include depression, neurologic abnormalities such as multiple sclerosis, spinal cord injury, and

hormonal dysfunction such as androgen deficiency in the aging male, resulting in low testosterone.

Many of the medications used to treat these conditions likewise produce erectile dysfunction. Many antihypertensive medications, especially thiazide diuretics, may be responsible for the dysfunction of smooth muscle relaxation in the *corpus cavernosum*. More erection-hospitable antihypertensives, such as calcium channel blockers, ACE inhibitors, angiotensin-2 blockers, and selective alpha-blockers, are effective in treating hypertension while helping to preserve erectile function.

Medications used to treat depression, such as selective serotonin reuptake inhibitors, not only diminish ejaculatory function but may also be responsible for erectile dysfunction. Common treatment modalities for pelvic malignancies are also responsible for many cases of erectile dysfunction. Radical surgery for carcinoma of the prostate, rectum, and bladder and radiation therapy for these malignancies may lead to erectile dysfunction in many men.

The use of nerve-sparing radical prostatectomy has decreased this prevalence of erectile dysfunction in men following prostate cancer surgery. Similar nerve-sparing surgical procedures for rectal carcinoma have not yet become widely accepted. Radiation therapy, while initially less likely to be associated with erectile dysfunction, shows an increasing incidence of erectile dysfunction between one and two years after treatment. Medications that reduce testosterone levels for patients with progressive prostatic carcinoma, such as luteinising hormone-releasing hormone agonists and antagonists, will also reduce erectile function by decreasing androgen activity in the *corpora cavernosa*.

The evaluation of patients with ED has progressed significantly in the last two decades. While little other than psychological evaluation was available in the 1970s, the 21st century has seen a more efficient, less invasive evaluation of patients with erectile dysfunction, as a result of newer treatment modalities. Prior to the introduction of effective oral agents, there was an emphasis on a 'goal-directed' approach to male



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sexual dysfunction that included a careful identification of the etiology of erectile dysfunction. The goal of this approach was to identify a specific etiology and it led frequently to more invasive, costly, uncomfortable treatment modalities being applied, based on the patient's treatment goals. Examples of such treatments, performed in many patients, included nocturnal penile tumescence monitoring, pharmacotherapeutic injection with Doppler blood flow evaluation, and dynamic infusion cavernosography and cavernosometry.

While these studies continue to be useful in highly selected patients, most patients can be evaluated more directly by primary care physicians, urologists, and others interested in treating patients with ED. Current evaluation consists of a full and careful sexual history and a focused physical examination. The history should include not only the onset and duration of erectile dysfunction but also symptoms of depression, surgery, and medications. Laboratory studies to evaluate patients for ED risk factors are also important. These laboratory studies should include fasting blood glucose, lipid profile, and screening morning testosterone. These laboratory studies are important as many patients will suffer ED as the first symptom of diabetes or hypercholesterolemia. Similarly, patients treated with oral medication will respond best if eugonadal.

Treatment of ED has seen the most dramatic improvement over the past five years. The introduction of the first effective, well-tolerated oral agent for erectile dysfunction began in 1998 with the introduction of sildenafil for the treatment of ED. Sildenafil, a phosphodiesterase type-5 (PDE5) inhibitor, blocks the enzyme PDE5 in the *corpus cavernosum* smooth muscle. This permits the secondary neurotransmitter, cGMP, to persist longer and be present in higher concentrations, facilitating relaxation of the *corpus cavernosum* smooth muscle and hence the erectile function. This and other PDE5 agents facilitate erections and produce successful improvement in erectile function in more than 70% of men treated for erectile dysfunction.

Since its introduction into the worldwide market, 13,000 men exposed to Viagra have completed clinical trials, with more than 130 completed and on-going clinical trials and a database of more than 13,000 patient years of exposure in 8,000 men. These patients, from diverse geographic locations, etiologies, and durations of erections, have demonstrated excellent efficacy and tolerability. Sildenafil is currently available in 119 countries and more than 133 million prescriptions have been written worldwide. Indeed, more than 6,000 physicians have prescribed sildenafil and eight tablets of sildenafil are sold every second throughout the world.

The distribution of those physicians who prescribe in the US is as follows: 65.7% family practice, 12.1% urologists, 2.5% cardiologists, and 2.5% psychiatrists.

Sildenafil has been demonstrated to be effective across all the different etiologies of ED. Indeed, patients with diabetes, whether Type 1, Type 2, complicated or uncomplicated, have significant responses to sildenafil, compared with placebo. Patients who have undergone radical prostatectomy, especially nerve-sparing procedures, ischemic heart disease, treated and untreated hypertension, peripheral vascular disease, and depression, all respond well to sildenafil.

Difficult-to-treat patients have likewise responded well to sildenafil. In a measurement of the patient's ability to penetrate his partner's vagina, 71.7% of men with bilateral nerve-sparing, 50% with unilateral nerve-sparing, and 15.4% with non-nerve-sparing radical prostatectomy reported success. These numbers were reflected and supported by spousal satisfaction percentages of 66%, 41.6%, and 15.4%, respectively. Indeed, patients who have undergone nerve-sparing radical prostatectomy will see improved results with time from surgery, demonstrating higher success two years after radical prostatectomy than immediately following radical prostatectomy.

A single study recently reported by Padma-Nathan and colleagues demonstrated the usefulness of daily sildenafil dosing in patients who have undergone nerve-sparing radical prostatectomy as a prophylaxis for the improvement of erectile function. Similarly, diabetics respond well to sildenafil. Their responses, while less robust than those of patients without diabetes, are demonstrated in Type 1 diabetes, Type 2 diabetes, and patients with complications of diabetes.

Improvement of diabetes control will ameliorate a diabetic's response to sildenafil. Sildenafil has been demonstrated to be effective in all ethnic populations. While we know that erectile dysfunction occurs equivalently in American white, African American, and Hispanic men, sildenafil appears to respond equally well in each of these ethnic groups.

Long-term data has confirmed the effectiveness of sildenafil over time. In patients whose treatment was initiated with sildenafil more than four years earlier, satisfaction with erections at one year, two years, three years, and four years were 98.1%, 96.6%, 94.8%, and 96.3%, respectively. This demonstrates the continued effectiveness of PDE5 inhibitor medication and documents the lack of tachyphylaxis in humans taking this on-demand medication. While it is recognized that the duration of sildenafil effectiveness corresponds approximately to its half-life ( $T_{1/2}$ ) of four hours, new

data has demonstrated that onset of action of sildenafil may be more rapid than the maximum concentration ( $T_{max}$ ) of one hour. Padma-Nathan and colleagues demonstrated that more than one-third of patients experienced the onset of action at less than 14 minutes and more than half of patients did at less than 20 minutes following dosage administration.

Sildenafil appears to be safe as well as effective. The side effects are usually transient and the most common include headache, flushing, dyspepsia, and blue haloed vision; however, pivotal studies have demonstrated that these adverse events and side effects decrease rapidly with experience and PDE5 inhibitors have virtually resolved 16 weeks after initiation of treatment. Indeed, fewer than 2% of patients discontinued sildenafil as a result of adverse events – a number equivalent to those discontinuing while taking placebo.

It is therefore clear that in its five years of clinical experience, sildenafil has accrued a body of evidence supporting its efficacy and safety. Sildenafil is broadly effective across etiologies of erectile dysfunction in patients of all ages, ED severities, and ethnic backgrounds. There is strong evidence for long-term efficacy and little evidence of tachyphylaxis. Its onset of action is rapid, its time of effectiveness greater than four hours, and it can be used in patients with vascular disease who are not taking nitrates for cardiovascular disease (CVD). Sildenafil can also be taken by patients using alpha-blocking medications with reduced initial dose.

The field of erectile dysfunction treatment and the market for PDE5 have recently been expanded by two unique new compounds – vardenafil and tadalafil. These two agents, whose profiles are different from sildenafil, are now approved in the US, Europe, Canada, and most countries throughout the world. Vardenafil, a unique agent similar in its chemical structure to sildenafil, is a highly potent PDE5 inhibitor with a rapid onset and excellent efficacy and tolerability.

Worldwide phase III clinical trials of vardenafil have been completed in large numbers of men with a variety of severities and etiologies of erectile dysfunction, across multiple age groups. These studies have demonstrated the high effectiveness of between 10mg and 20mg of vardenafil, compared with the baseline and placebo. Indeed, the efficacy of vardenafil appears to be comparable to that of sildenafil, and adverse events are similar with both agents. The only exception is that abnormal vision was reported in few patients with vardenafil, with rare reports of blue tinted vision.

While patients with vardenafil, like all patients on PDE5 inhibitors, may not be treated with nitrate

medications because of concern for significant hypotension, vardenafil appears to produce few cardiac events and in studies performed, patients on placebo and patients with age-expected myocardial infarction rates are equivalent to, or greater than, those treated with vardenafil. The pharmacokinetics of vardenafil demonstrates a higher biochemical potency than that of sildenafil but similar time to  $T_{max}$  in the serum as well as  $T^{1/2}$ . Onset of action has been demonstrated in some patients as early as 16 minutes after administration. At its highest dose, 20mg, vardenafil has sustained long-term efficacy in up to 92% of patients with improved erections – a high rate of satisfaction with durations of treatment of more than two years in clinical studies.

A recent study demonstrated the effectiveness of vardenafil in patients who are not responsive to sildenafil. In a randomized, placebo-controlled dose escalation study, vardenafil was demonstrated to produce satisfactory erectile function in more than 60% of these non-responders. In this group of non-responders, more than 30% of patients on 20mg of vardenafil had recorded improvements in erectile function to the normal category using standardized international questionnaires.

Vardenafil is available throughout the world in 5mg, 10mg, and 20mg doses, has adverse events similar to those of sildenafil, including headache, flushing, and dyspepsia with reduced abnormal vision, and in studies it has discontinuation rates similar to those of placebo with somewhat less food interaction. Vardenafil appears to be a highly effective, well tolerated, biochemically potent PDE5 inhibitor for the treatment of erectile dysfunction.

Tadalafil, a PDE5 inhibitor of unique chemical structure and clinical profile, has been approved for clinical use in Europe, North America, and most other countries throughout the world. While sildenafil, vardenafil, and tadalafil have similar mechanisms of action in inhibiting PDE5 in the *corpus cavernosum*, tadalafil has a unique pharmacological profile. The time to reach serum  $T_{max}$  is two hours for tadalafil, compared with one hour for sildenafil and vardenafil; however, the difference in serum  $T^{1/2}$  is most significant. Tadalafil has a  $T^{1/2}$  of 17½ hours, compared with four hours for sildenafil and vardenafil. This difference in  $T^{1/2}$  translates clinically into a longer duration of action and a longer opportunity for patients taking tadalafil to have erectile function.

While all three agents are metabolized predominantly by the liver through the cytochrome P450 3A4 pathway, tadalafil maintains its presence for four times longer than the other two agents. Tadalafil appears to take the least impact from food and alcohol of the three

PDE5 agents, yet its clinical outcomes are similar. In reviewing the efficacy of tadalafil using standard questionnaire outcome measures, erectile function outcomes appear to be similar for all three agents. These efficacy results persist with tadalafil for up to 36 hours following administration. Tadalafil appears to be effective at 5mg, 10mg, and 20mg doses in patients with mild, moderate, and severe erectile dysfunction of all etiologies.

A major difference occurs in other PDE isoenzymes inhibited. While sildenafil and vardenafil appear to have some inhibitory activity against PDE6, accounting for some of the visual changes, tadalafil has little activity against PDE6. Unlike sildenafil and vardenafil, however, tadalafil does appear to have more inhibitory activity toward the isoenzyme PDE11. The clinical impact of this inhibition remains as yet unclear. PDE11 appears to occur in skeletal muscle, seminiferous tubules, and anterior pituitary and other tissues.

Similar to vardenafil and sildenafil, tadalafil appears to be safe as well as effective. Adverse events are similar to those of the other PDE5 inhibitors, with headache, dyspepsia, and rhinitis being common; however, unlike the other PDE5 inhibitors, back pain following administration of tadalafil may occur in as many as 10% of patients treated with high-dose tadalafil.

The safety profile for the cardiovascular (CV) system is similar to other PDE5 agents, with no observed increase in cardiac or vascular events in patients treated with tadalafil, in contrast to those treated as placebo, or age-matched patients in a general population. While the additive vasodilatory effect of tadalafil can produce hypotension in selected patients on alpha-blocking medications, tadalafil appears to be safe when used in combination with highly selective alpha-blocking agents such as tamsulosin.

The relative activity, tolerability, and preference of the three PDE5 inhibitors has not, as yet, been established. Indeed, wide experience in the world market by patients of many agents, severities, and etiologies of erectile function will be necessary to demonstrate the advantages of each of these agents. To date, no effective, well

designed, head-to-head comparative or switch study has been carried out, presented, and published in a peer-review publication. The field of erectile dysfunction, indeed, has room for more than one agent. As in many other areas where multiple pharmacologic agents are available, individual patients may prefer a specific agent over another because of lifestyle, effectiveness, adverse events, price, or other distinguishing properties of individual agents. International physicians and patients await widespread experience with these agents to further elucidate the qualities of each.

With the US Food and Drug Administration's (FDA) non-approval of apomorphine – the only currently well-studied central nervous system (CNS) acting agent for erectile dysfunction – unique and novel approaches to the treatment of erectile dysfunction continue to be elusive. Newer CNS-acting agents in phase I and phase II trials may provide other ways of treating patients, alone or in combination with PDE5 agents.

PT-141, a melanocortin-stimulating hormone analog, is currently undergoing clinical phase II and phase III studies. This agent, available from Palatin Pharmaceuticals, is an active metabolite of melanotan-iii and has been demonstrated to have potent activity as an erectogenic agent. Introduced intranasally, PT-141 was demonstrated to have effectiveness and tolerability in both healthy males and ED patients. While phase III studies have yet to be completed and data to be submitted for drug approval, this agent holds promise in expanding the options available to our patients with erectile dysfunction.

The field of erectile dysfunction has been revolutionized over the past decade by active basic science investigation, which has resulted in the elucidation of the physiology and pathophysiology of erectile function. The development of new pharmacologic agents and their widespread use internationally in a variety of patient groups have demonstrated the effectiveness of treating patients with erectile dysfunction. The introduction of newer agents with unique pharmacological profiles may further our advances in the treatment of patients with erectile dysfunction. ■