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**Learning Objectives (Part 1):**

This activity is designed for urologists and other physicians who treat patients with erectile dysfunction (ED). At the conclusion of this activity, the participant should be able to:

- Describe the prevalence of and risk factors for ED.
- Recognize factors that promote or discourage treatment-seeking behavior for ED.
- Recognize patients' goals for treatment of ED and concerns about therapy.
- Enhance access to therapy for ED and perform appropriate follow-up and ongoing care to ensure that treatment goals are met.

**CME Information**

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This 2-part activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Wisconsin Medical School and Health Focus, Inc. The University of Wisconsin Medical School is accredited by the ACCME to provide continuing medical education for physicians.

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Length of time to complete each activity: 1 hour

**Disclosure Information**

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## Update on Erectile Dysfunction

### Part 1: Focus on the Latest from the Men's Attitudes to Life Events and Sexuality (MALES) Study

Sexual dysfunction is a common and complicated problem that is almost always multi-dimensional: interrelated biologic, psychological, and relationship issues are virtually always associated with the sexual problem. Maximizing conservative management of men with erectile dysfunction (ED) means combining biologic and psychological therapeutic modalities. In our experience, 70% of patients with ED will achieve satisfactory erectile function without second-line (intracavernosal self-injections) or third-line (penile prosthesis) treatment options after 1 year follow-up in treatment that includes some combination of: (1) sexual/psychological/cognitive-behavioral therapy, (2) pre-coital vasodilator therapy with a PDE5 inhibitor (try all 3 PDE5 inhibitors, as there are interesting differences in some patients), and/or (3) chronic sex steroid hormone therapy in men with concomitant hypogonadism.

Despite the availability of safe and effective conservative treatment options, new epidemiologic information in over 27,000 men from 8 countries indicates that the majority of men with ED are either not seeking treatment for ED or not receiving appropriate care when they do seek treatment. In Part 1 of this 2-part series, we explore the epidemiology of sexual dysfunction, focusing on new data from the Men's Attitudes to Life Events and Sexuality (MALES) study,<sup>1</sup> which elucidates prevalence and correlates of ED and explores how the attitudes and illness experience of men with ED are associated with the care they receive. I am excited to bring you these important new data, since they highlight a tremendous opportunity for physicians to educate and influence how patients think about ED and to improve patients' receptivity to contemporary sexual medicine treatments that are now available.

### International Prevalence of ED

*You've said that ED is a very common problem, but relatively few of my patients present with complaints about sexual function. How prevalent is ED in the general population?* ED is a lot more common than you probably think, but many patients hide the problem rather than seek help. The MALES study interviewed a representative sample of men (ages 20 to 75 years) from 8 countries (United States, n = 9283; Mexico, n = 2735; Brazil, n = 5091; and 5 countries in the European Union, n = 10,729) who were recruited by random digit dialing or random email invitation for a study of men's health issues. Interviews were conducted from February through April in 2001 using a standardized questionnaire. Of the 27,838 participants, 4422 (16%) had ED. However, only a little more than half of these men had sought treatment for their ED.<sup>1</sup>

*Is the prevalence of ED the same everywhere in the world? And what risk factors should prompt me to ask a patient about sexual dysfunction, so I can identify the ones who aren't seeking treatment?* In the MALES study, the prevalence of ED varied by age and country. Age-depend-

ent prevalence ranged approximately linearly, from about 8% in 20 to 29 year olds to 37% among those aged 70 to 75 years. The United States had the highest prevalence of ED across all age groups, with an overall prevalence of 22%.<sup>1</sup> The reason for the higher prevalence in the United States is not clear, though I would speculate that it's because American men are more open to discussing ED, or because they are more stressed or have higher cholesterol levels and more vascular disease. The lowest

*(Continued on page 2)*

**Part 1**

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rates of ED were among European men, with intermediate prevalence in the Latin American countries.<sup>1</sup>

A correlation was also observed between ED and comorbid illnesses, particularly those associated with endothelial dysfunction. Men with ED were significantly ( $p < .05$ ) more likely than those without ED to have comorbid illnesses, including high blood pressure, heart disease/angina, high cholesterol, diabetes, and depression. Conversely, the prevalence of ED was also higher among those with comorbid illnesses.<sup>1</sup> I like to point out that ED = ED (erectile dysfunction = endothelial dysfunction), because this disease truly has a vascular component. In addition, a subgroup analysis showed that men with diabetes were more likely to see their condition as permanent and to talk about the problem with a physician than those without diabetes, so the presence of comorbidities also affects how men perceive sexual difficulties.<sup>1</sup>

Given the high prevalence of ED and its covariation with age and comorbidity, you should ask patients—particularly older patients and those with comorbid illnesses—about sexual function. In addition, you should have a high index of suspicion for comorbid conditions among men who present with ED.

### Use of PDE5 Inhibitors

**Were any of the ED patients who were using medications for other medical conditions (diabetes, hypertension, etc) also using PDE5 inhibitors?** Some did, but an analysis of MALES study data clearly shows that most patients with ED were not using PDE5 therapy. The 4422 men who reported ED in the MALES study showed significantly lower treatment rates for ED than for other medical conditions. Antidiabetic therapies were being used by almost three quarters of those with diabetes. Of those with hypertension, 60% had been treated with antihypertensive agents. More than half of those with coronary heart disease/angina were currently treated. More than one third of those with depression/anxiety were receiving treatment. In contrast, only 21% of those with ED—about 1 in 5 men with ED—were currently using PDE5 inhibitor therapy for ED.<sup>1</sup>

Lack of treatment cannot be blamed entirely on patient reluctance to discuss ED. In a second phase of the MALES study, a subset of 2912 men, matched to the original cohort for country, age, income, employment, relationship status, comorbidity, and consultation rates, were reinterviewed. More than half (58%)

said they had discussed the problem with a physician, but about 63% of men with ED had never tried a PDE5 inhibitor, and 71% had never received a prescription for one. All told, the data showed that 84% of men with ED are not utilizing an available effective therapy to treat their sexual dysfunction. (Table 1)<sup>1</sup>

These statistics appear to reflect a negative attitude toward treatment of ED on the part of physicians as well as patients. Physicians are more likely to address and treat conditions like diabetes and hypertension, in part, because they are more comfortable managing these conditions. This may be because the consequences of those conditions are perceived as being more serious, or because physicians are embarrassed to discuss ED with their patients, or just because treatments for ED are newer and less well established and understood. These statistics also show that it is not enough for physicians to hand a patient a sample or a prescription. Physicians need to follow up to find out if the prescription is being filled and used and to assess patient concerns and degree of satisfaction with the treatment.

**What about patient attitudes toward therapy? We know PDE5 inhibitors are effective, so why are many ED patients not using them?** The second phase of the MALES study focused on factors associated with seeking treatment for ED, and several important correlates of treatment seeking were identified.<sup>2</sup> In general, it was found that men with milder ED, men who believed that ED medication was dangerous, and men who felt they had little social support for seeking treatment were unlikely to utilize PDE5 inhibitor therapy. Among men who had never used PDE5 inhibitor therapy or who had used it only once, 42% reported worry that the treatment is dangerous. This is a somewhat surprising response because there is overwhelming evidence to the contrary. Public perception that the class of PDE5 medications is dangerous dates to a few months after PDE5 inhibitor therapy for ED was first released in 1998. Initially, the media coverage was favorable; in fact, media coverage was continuous, overwhelming, and uncontrolled. The positive coverage changed, however, when a few cases of myocardial infarction (MI) occurred in persons taking PDE5 treatment. We now know that the risk of MI increases because sexual activity is a form of physical exertion (like any kind, including shoveling snow). In placebo-controlled studies, the risk of

Behavior	% Men
Spoke with a physician about ED	58.1%
Spoke with a physician about PDE5 inhibitors*	41.5%
Tried PDE5 inhibitors at least once	34.1%
Received prescription for PDE5 inhibitors	28.9%
Filled prescription for PDE5 inhibitors	25.2%
Used PDE5 inhibitors more than once	22.4%
Still using PDE5 inhibitors	15.7%
Stopped using PDE5 inhibitors	6.3%

\*Sildenafil was the only PDE5 inhibitor available at the time of the MALES study. Two other PDE5 inhibitors are now available for treatment of ED: vardenafil and tadalafil. Differences among these 3 therapies are discussed in Part 2 of this series.

Table 1. Use of PDE5 Inhibitor Therapy Among Men With ED in the MALES Study<sup>1</sup>

serious cardiovascular events is actually lower in those taking the PDE5 inhibitor drug.<sup>3</sup> Clearly, it is important for physicians to take the time to reassure patients that PDE5 therapies are not dangerous and that such therapy may, in fact, have cardiovascular benefits.<sup>4</sup> PDE5 inhibitors are, one day, expected to have indications for the safe and effective treatment of conditions such as pulmonary hypertension, congestive heart failure, and angina. By 2010, ED will probably be the least common indication for PDE5 inhibitors as their use in cardiovascular disease expands. Other reasons ED patients gave for not initiating treatment included expense (31%), the perception that ED is not important enough to treat (29%), and embarrassment (20%).<sup>2</sup>

**Why do so many patients not stay with treatment once they start it?** The MALES study also asked men who had tried PDE5 inhibitor therapy why they had discontinued its use. The main reason was lack of sufficient effectiveness, with 34% saying their erections were not hard enough, 34% saying that therapy “did not work at all,” and 22% saying it worked only occasionally. In addition, 29% said it was too expensive and 19% discontinued use due to side effects.<sup>5</sup> (Percentages add up to >100% because multiple answers were permitted.) And note, these figures relate to reasons for discontinuation among those who have tried PDE5 inhibitor therapy, while nearly 65% of men with ED have not even done so. Overall, these findings emphasize the need for patient education and follow-up to find out whether patients are satisfied with their ED therapy. If patients are not fully satisfied, there are practical strategies that can be employed: (1) review the package insert (PI) with the patient/partner, (2) try all 3 PDE5 inhibitors, as we and others have noted that some patients find better success with 1 of the 3 medications over the other 2, (3) measure sex hormone

levels, as androgens have been shown to facilitate PDE5 inhibitor function, and (4) treat comorbid conditions contributing to the ED. Please refer to the Case Vignettes and the Tips & Resources sidebar for simple strategies on how to enhance treatment outcomes with PDE5 inhibitor therapy for patients who do not initially respond as well as they would like.

## What Do Men Want?

**What do men with ED see as the goals of treatment?** Data from the MALES study show that the obvious thing that men with ED want is a reliably rigid, well-maintained erection so they can successfully engage in sexual intercourse. Thus, with regard to therapy for ED, MALES study findings indicate that treatment that works reliably every time is most frequently (47%) judged to be the most important attribute of ED therapy. Reliability was considered essential by 38% of ever-users and 28% of never-users of therapy, and rapidity of action was rated essential by 39% and 49%, respectively. Respondents also wanted therapy to be safe (40%) with few side effects (40%), and for PDE5 inhibitor therapy to be able to be taken with other medications (29%). After these efficacy and safety issues, men wanted therapy to have a reasonable price (19%) and to work as soon as needed (16%) and for a full 24 hours (13%).<sup>6</sup>

## Promoting Access to and Maintenance of Therapy

**Which patients are most likely to seek treatment and why?** The MALES study found a correlation between severity of ED and treatment-seeking behavior. Men with severe ED were the most likely to speak to physicians about the problem and about PDE5 inhibitors, and were also the most likely to have received and filled a prescription and to be still using it at the time of the survey. The odds ratio (OR) for seeking treatment was 3.5 for those with severe disease compared with

those with mild ED. Other factors that promoted treatment seeking included the recognition that ED was associated with aging (OR 1.42), feeling less confident as a result of ED (OR 1.33), and being afraid of losing a partner because of ED (OR 1.22). Factors that decreased the likelihood of treatment seeking included the perception that ED therapy is dangerous (OR 0.428), the belief that lifestyle modifications would relieve the problem (OR 0.71), and the feeling that it is impossible to discuss ED face-to-face (OR 0.79).<sup>5</sup> Physicians should educate men with ED that it is OK to talk about their condition, to treat the ED condition in most cases, and to think that their ED condition is associated, in part, with a physical, comorbid, cardiovascular/aging problem.

**What can physicians do to help promote treatment seeking among patients with ED?** One of the most surprising findings from the MALES study is that of all of the people who interface with the patient, physicians are the most influential when it comes to treatment seeking for ED (OR 29.72). The influence of physicians tremendously outranked that of partners/spouses (OR 1.54) or family members (OR 1.26). Other common sources of information about ED actually discouraged treatment seeking, including telephone help lines (OR 0.38) and Internet chat groups (OR 0.31).<sup>2</sup> Patients felt encouraged about treatment if they had a good discussion about ED with the first physician they spoke with about it or if the physician prescribed therapy. Patients were most likely to discontinue PDE5 inhibitor therapy if they were dissatisfied or extremely dissatisfied with the way the physician dealt with the problem. The key message here is that there are now new objective data, based on interviews from thousands of men from 8 countries, showing that physicians are the most critical and vital link, more than ever previously understood, to successful management of sexual dysfunction.

## References — Part 1

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## Tips & Resources

### Patient Education

Patients are most likely to start and continue PDE5 inhibitor therapy if:

- ED is severe.
- ED makes them feel older, less confident, or threatens their relationship with a partner.
- They recognize the safety of therapy.
- Treatment is reliable and has rapid onset.
- Treatment has few side effects and can be taken with other medications.
- They are satisfied with how their physician addresses the problem.

Dissatisfaction with the efficacy of treatment is the number one reason for discontinuation of use. If a PDE5 inhibitor is not working well enough:

- Review the PI with the patient, and make sure he understands and is following instructions.
- Try the other PDE5 inhibitors; each is different and patients respond differently to different formulations.
- Measure sex hormone levels and consider androgen supplementation to normalize low levels of androgens and enhance PDE5 inhibitor function.
- Treat any comorbid conditions that might be contributing to ED (eg, diabetes, high cholesterol), and discourage cigarette smoking and alcohol consumption.

### News and Notes

Free public seminars presented by Irwin Goldstein, MD, at the Holiday Inn, Newton, Mass. "Female Sexual Dysfunction: Symptoms and Solutions," May 23, 2004: For information and online registration, [www.bumc.bu.edu/sexualmedicine/fsdprogram](http://www.bumc.bu.edu/sexualmedicine/fsdprogram) or call 617-638-8576; and "Sexual Dysfunctions in Men: Symptoms and Solutions," June 6, 2004: For information and online registration, [www.bumc.bu.edu/sexualmedicine/edprogram](http://www.bumc.bu.edu/sexualmedicine/edprogram) or call 617-638-8576.

International Society for the Study of Women's Sexual Health (ISSWSH) Annual Meeting, October 28-31, 2004, Hyatt Regency, Atlanta, Ga.

The ISSWSH is a multidisciplinary, academic and scientific organization that provides opportunities for communication among scholars, researchers, and practitioners and provides the public with accurate information about women's sexuality and sexual health.



## Case Vignettes

*I prescribed a PDE5 inhibitor for a patient with ED, but at follow-up he reported that he is not using it anymore because it had not worked well enough. What should I do next?* This is a common scenario. If the PDE5 inhibitor therapy does not seem to be working, patients and physicians should not give up. The last patient I saw who reported ED received a prescription for all 3 PDE5 inhibitors. I explained to him that there are differences among the 3 agents, and that if one doesn't work well enough, another one may. (I will discuss differences in PDE5 inhibitors in more detail in Part 2 of this series). This patient returned for 2-month follow-up and reported that none of the 3 had helped sufficiently. The first thing I did was to ask him to read the PIs carefully, and I reviewed the directions for appropriate use with him. He had been expecting to get an erection merely by taking the pill, and I had to remind him that sexual stimulation is required. In addition, he had not tried increasing the dose, as the PI recommends, after starting with the initial low dose, and he was not waiting long enough for the medication to begin working before trying to have sex. Some patients also do not realize that taking PDE5 inhibitors with a high fatty food diet can affect the absorption and limit efficacy of some of the PDE5 inhibitors.

Six weeks later he returned and said that he tried all 3 again, following the instructions, and noted differences among the 3 medications in terms of speed of erection onset, hardness of the erection, and side effects. He questioned whether there was anything else medically that could be tried to help the ED treatment. Suspecting low androgen levels, I screened him using the Androgen Deficiency in the Aging Male (ADAM) questionnaire, which helped me get a more thorough history. His responses indicated that he was also falling asleep early after dinner, had less energy when playing sports with his children, and that he had been frequently feeling sad and grumpy. Subsequent laboratory evaluation indicated low total testosterone, low free testosterone, and relatively high sex-hormone binding globulin level, with normal luteinizing hormone, follicle-stimulating hormone, and prolactin levels. After a discussion of the risks and benefits of androgen therapy, he began

testosterone supplementation and continued the PDE5 inhibitor therapy. Within 3 to 6 months, he experienced improved sexual function, including not only better erections during PDE5 inhibitor use, but also improvements in libido, orgasmic function, and ejaculation. (For a more complete discussion of the role of androgens and androgen supplementation, please refer to the *Expert Insights* series, "The Link Between Sexual Dysfunction (Desire & Arousal Disorders) and Hypogonadism," available at [www.expertinsightscme.com/igoldstein.html](http://www.expertinsightscme.com/igoldstein.html).)

*A 28-year-old patient presented for consultation concerning ED management. His internist prescribed a PDE5 inhibitor without much information about how to use the medication or attention to his ED condition.*

*The medication worked on most occasions, but the patient wants to know what is causing ED. What should I do next?*

ED is an early and sensitive indicator of endothelial dysfunction. Numerous studies, such as MALES presented above, have shown that men with ED have exposure to risk factors that are disorders of endothelial cell function, such as diabetes, hypertension, high cholesterol, cigarette smoking, obesity, etc. Endothelial cell dysfunction can also occur focally in the common penile/cavernosal artery as a consequence of blunt perineal trauma. Independent of the reason for endothelial dysfunction, injury to the endothelial cells can lead to atherosclerosis. In this patient, a thorough history revealed that he went to summer camps for trick bicycle riding and had a bicycle ramp in his summer home. He described multiple episodes of falls onto the narrow bicycle saddle. A duplex Doppler ultrasound study was performed and revealed marked diminished flow in both cavernosal arteries. After the condition of cavernosal arterial insufficiency and vasculogenic ED was explained to the patient, he was more receptive to the idea of pharmacologic management. He greatly appreciated the physician attention to the ED condition. He eventually tried all 3 PDE5 inhibitors and found that different agents were useful in different situations. He described interest one day in the idea of undergoing microvascular arterial bypass surgery to correct the arterial pathology.

## Put It Into Practice

- ED is prevalent, age dependent, and associated with aging and endothelial dysfunction but is underrecognized in clinical practice.
- Because of the correlation between ED and comorbid illnesses, physicians should ask patients, particularly older patients and those with comorbid illnesses, about sexual function.
- Physicians have the most influence over treatment-seeking behavior.
- Patient attitudes that affect treatment seeking include the degree to which they are bothered by ED, fear of losing a partner, and denial of ED as a problem.
- Misperceptions about PDE5 safety are the main reason for avoidance of treatment.
- Abandonment of PDE5 therapy is strongly associated with lack of efficacy, warranting more follow-up by physicians.
- Reliability, safety, tolerability, and rapidity of onset are important characteristics of therapy for men with ED who are seeking treatment.

## Issues In This Series

**Part 1: Focus on the Latest from the Men's Attitudes to Life Events and Sexuality (MALES) Study**

Part 2: Focus on the Unique Properties and Differences Among PDE5 Inhibitors

Read both issues and receive 2.0 hours of CME credit.

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## Update on Erectile Dysfunction

## Learning Objectives (Part 2):

This activity is designed for urologists and other physicians who treat patients with erectile dysfunction (ED). At the conclusion of this activity, the participant should be able to:

- Describe the biochemical cascade responsible for penile erection and the influence of PDE5 inhibitors on this cascade.
- Educate patients about differences among PDE5 inhibitors, including molecular structure, biochemical potency, PDE enzyme selectivity, and pharmacokinetics.
- Guide patients in choosing PDE5 inhibitors based on new data from a head-to-head comparative study of patient preferences.
- Reassure patients of the safety of PDE5 inhibitors based on the latest data on cardiovascular and other risks.
- Select appropriate candidates for PDE5 inhibitors based on potential for drug interactions.

## CME Information

Please see page 1 for complete information and disclosures.

## Biochemical/Pharmacological Differences Among PDE5 Inhibitors

**Don't all PDE5 inhibitors have the same mechanism?** We now know much about the biochemical cascade responsible for penile erection. Response to sexual stimuli is mediated by the neurotransmitter nitric oxide (NO). NO activates guanylate cyclase, which stimulates formation of cyclic GMP (cGMP). By lowering calcium within the cytoplasm of smooth muscle cells, cGMP induces vasodilation of the cavernous artery and helicine arterioles and relaxation of the corporal smooth muscle. Smooth muscle relaxation results in engorgement of blood in the sinusoidal spaces of the corpora cavernosa and spongiosum, resulting in penile erection. The enzyme phosphodiesterase 5 (PDE5), in conjunction with other phosphodiesterases, reverses this process, returning the penis to a flaccid state by hydrolyzing cGMP into an inactive form, 5'-GMP. There are 2 catalytic sites and 4 potential allosteric sites on the PDE5 enzyme where binding to cGMP takes place. PDE5 inhibitors work by blocking the catalytic sites of the PDE5 enzyme (personal communication, Jackie Corbin, April 2004).

**In that case, how do the 3 PDE5 inhibitors differ—for example, in molecular structure?** Differences in molecular structure account for differences in biochemical potency, PDE enzyme selectivity, and pharmacokinetics. Both sildenafil and vardenafil have a bicyclic ring that mimics the structure of the purine ring of cGMP. The molecular structure of tadalafil is different, although it is believed to mimic the substrate cGMP.

## Part 2: Focus on the Unique Properties and Differences Among PDE5 Inhibitors

Three PDE5 inhibitors are currently available for the management of erectile dysfunction. Sildenafil has been approved by the Food and Drug Administration (FDA) for 6 years and has the longest record of safety and efficacy. Vardenafil and tadalafil have been approved more recently. Physicians should not rely on only 1 PDE5 inhibitor for all patients with ED all the time. It is important to understand their biochemical, pharmacological, and clinical differences. In sexual medicine, it is important to recall that patients are the ultimate decision makers about their treatment. This issue of *Expert Insights*, representing the second part of the 2-part series, "Update on Erectile Dysfunction," provides you with the latest information on the unique features of the PDE5 inhibitors, so that you can give more complete information and guidance about these therapies to your ED patients.

The bicyclic rings of sildenafil and vardenafil differ only in the location of a single nitrogen, which appears to account for differences in biochemical potency between these agents. The nitrogen shift on the bicyclic ring structure of vardenafil is primarily responsible for higher affinity binding to the catalytic site of PDE5. Sildenafil does not have an additional methyl group found on vardenafil, but this methyl substitution of vardenafil appears to have little effect on PDE5 binding, as evidenced by a lack of difference in the inhibition of binding to the PDE5 enzyme by vardenafil or a demethylated version of vardenafil (personal communication, Jackie Corbin, April 2004).

**How do the 3 PDE5 inhibitors differ in biochemical potency?** The combination of "onset time"—ie, the affinity of the PDE5 inhibitor to bind to the catalytic receptor sites on PDE5—and the "dwell time"—ie, the ability of the PDE5 inhibitor to remain bound to the catalytic sites on PDE5—defines biochemical potency. There are significant differences in onset and dwell time among the 3 PDE5 inhibitors. Over a given observation period, the agent with the highest biochemical potency could have the highest rate of rise of intracellular cGMP and the highest intracellular cGMP concentration. Theoretically, biochemical potency translates to improved erectile hardness/rigidity, although scientific data concerning this link is lacking. The distinct differences in biochemical potency among the 3 PDE5 inhibitors have been repeatedly demonstrated in multiple, basic-science laboratory

settings. Vardenafil is significantly more biochemically potent than either tadalafil or sildenafil.

New data further separate biochemical differences among the PDE5 inhibitors. In one recent head-to-head comparison study, biochemical potency was assessed by examining IC<sub>50</sub> values (ie, the concentration of PDE5 inhibitor needed to block 50% of PDE). A far smaller quantity (<0.2 nM) of vardenafil was needed to achieve the same inhibition of enzyme activity as larger amounts (1.4–4 nM) of sildenafil and tadalafil. Using K<sub>D</sub> analysis is a direct measure of PDE5 inhibitor potency which assessed the amount of tritiated PDE5 inhibitor that is bound to PDE5 over time. These data again showed vardenafil to be more biochemically potent with K<sub>D</sub> = 0.38 nM. The K<sub>D</sub> for tadalafil was 2.4 nM, and the K<sub>D</sub> for sildenafil was 4.8 nM (personal communication, Jackie Corbin, April 2004).

Competition assays show biochemical differences in a different light. Displacement of PDE5-bound, radiolabeled sildenafil by unlabeled sildenafil was examined. At 20 minutes, <20% of the radioactivity remained PDE5 bound. Displacement of radiolabeled tadalafil by unlabeled tadalafil was also studied, and at 30 minutes, <30% of the radioactivity was PDE5 bound. In contrast, displacement of PDE5-bound, radiolabeled vardenafil by unlabeled vardenafil revealed a significant difference from tadalafil and sildenafil. At 60 minutes, >50% of the vardenafil remained PDE5 bound. Additional competition assays show that high concentrations of cGMP (equivalent to sexual stimulation) inhibit binding



to PDE5 of sildenafil and tadalafil but not of vardenafil at 30°C. In a study examining the effect of temperature on PDE5 binding, the binding of tadalafil and sildenafil were both less at higher temperatures (30°C) compared with low temperatures (0°C). In contrast, vardenafil binding to the PDE5 enzyme increased at higher temperatures (30°C) compared with low temperatures (0°C). While there may be no clinical relevance to this temperature effect, it illustrates another biochemical difference among the PDE5 inhibitors (personal communication, Jackie Corbin, April 2004).

Further investigations have revealed that the catalytic domain of PDE5 appears not to be a single component but is comprised of a slow (high-affinity) and fast (low-affinity) component. For vardenafil, the high-affinity component predominates (85% versus 15%, respectively), whereas high- and low-affinity are approximately equal for tadalafil and sildenafil. Vardenafil equilibrated in vitro within approximately 5 minutes. Since its half-life is about 25 minutes (at 37°C), this implies a prolonged time within the cell. One possibility is that the vardenafil binds to the catalytic site, but after detaching, it should rebind to PDE5 more efficiently than does sildenafil and tadalafil. This could theoretically extend vardenafil duration of action as an inhibitor of PDE5. Preliminary results suggest that vardenafil could concentrate inside the cell. The drug level seems to be 100 nM intracellularly and 10 nM extracellularly in rat aorta cells (personal communication, Jackie Corbin, April 2004).

### **How do the 3 PDE5 inhibitors differ in selectivity for other PDE enzymes?**

Selectivity for PDE5 differs among PDE5 inhibitors. Sildenafil has the highest affinity for PDE6 in the retina, specifically for retinal rods. Both vardenafil and sildenafil have high specificities for PDE6 retinal cones. Tadalafil has virtually no affinity for PDE6, but has considerably greater affinity for PDE11. Vardenafil and sildenafil have no affinity for PDE11.<sup>1</sup>

**How do the 3 PDE5 inhibitors differ in pharmacokinetics?** Time to maximum concentration is shorter with vardenafil or sildenafil ( $\leq 1$  hour) compared with tadalafil (approximately 2 hours); however, tadalafil has a significantly longer half-life: 17.5 hours compared with 3 to 4 hours for sildenafil and 4 to 5 hours for vardenafil.

## Translating Basic Science Differences Into Clinical Differences and Patient Preferences

**What is the clinical relevance of these basic science distinctions?** Translation of the biochemical/pharmacologic differences among the 3 PDE5 inhibitors to clinically relevant differences is likely, but independent, prospective, head-to-head, placebo-controlled, multi-institution clinical trials are needed.

Pharmacokinetic differences among the PDE5 inhibitors account for differences in onset of action and duration of action. Based on the time to maximum concentration ( $\leq 1$  hour), it takes approximately 15 minutes from dosing of vardenafil or sildenafil to attainment of an erection adequate for successful completion of intercourse. The long half-life of tadalafil (17.5 hours) allowed successful intercourse over 36 hours in 62% of attempts compared with 33% of attempts on placebo. With 20 mg vardenafil or 100 mg sildenafil, the half-life (3 to 6 hours) allowed significant improvement in successful completion of intercourse over placebo for 8 to 12 hours after administration.<sup>2,3</sup>

Differences in specificity for other PDEs account for differences in the adverse events of PDE5 inhibitors. Sildenafil and, to a lesser extent, vardenafil, result in blue vision in some patients. The clinical significance of tadalafil's PDE11 inhibition is still poorly understood, but PDE11 is found in the testes, pituitary, and heart.<sup>1</sup>

### **Are there any clinical trials directly comparing PDE5 inhibitors? Which agents do patients generally prefer?**

To the best of my knowledge, there have not been any large clinical trials directly comparing PDE5 inhibitors. However, a comparative trial was presented at the European Society for Sexual Medicine 2003 meeting.<sup>4</sup> This independent study (not supported by pharmaceutical grants), was a double-blind, placebo-controlled, randomized, multicenter study. Participants were men with ED of at least 6 months' duration who were in a stable heterosexual relationship and who had never taken PDE5 inhibitors. Two separate evaluations were performed, the first using half-strength doses (50 mg sildenafil, 10 mg tadalafil, and 10 mg vardenafil), and the second using maximum doses of all 3 drugs. After randomization, 6-week treatment periods, separated by 1-week washout periods before crossover to other arms, continued until

each group had tried all of the active medications and placebo, and then repeated one of the active treatments a second time. Data presented at the meeting were an interim analysis: 47 of the 211 patients in the half-strength analysis and 86 of the 237 in the maximum-dose analysis had completed the study. Efficacy was assessed using the International Index of Erectile Function.

With half-strength doses, differences among the 3 PDE5 inhibitors were demonstrated on question 3 (0–2 where 2 = always able to attain an erection with vaginal penetration) and question 4 (0–2 where 2 = always able to maintain the erection to completion of intercourse). Half-strength vardenafil was associated with the highest values on question 3 (1.5) and question 4 (1.7); whereas, half-strength sildenafil and tadalafil were associated with lower values on question 3 (1.2, 0.9) and question 4 (1.4, 1.4), respectively. It is tempting to relate the higher efficacy to vardenafil's higher biochemical potency, but more data are required for such a conclusion. With full-strength doses, differences among PDE5 inhibitors were less apparent, but there was still a trend toward better efficacy with vardenafil.

Patients also rated their preferences for treatment. Each agent was found to have specific advantages and, therefore, might be favored under particular circumstances or by individual patients. Vardenafil was preferred for ease of getting an erection and hardness of erection, and tadalafil for duration of the erection. Sildenafil was considered to have the fewest side effects. The important message to be gleaned is that patients should try all 3 PDE5 inhibitors to see which best meets their individual needs at different times.

**The package inserts recommend starting at the half-strength dose, but is the full strength usually more effective?** The package inserts do recommend starting at half doses and increasing the dose if needed, but this may not be the best approach in the majority of patients. Data from the randomized trial reviewed above indicate that there are differences in efficacy at the half-strength doses and less so at the full-strength doses. As long as they are generally healthy and without cardiovascular disease, not using organic nitrates, <65 years old, without renal or hepatic impairment, and not using potent CYP450 3A4 inhibitors, I usually start patients at the full strength to maximize efficacy. However, I tell them that if the full strength works, they should try the half strength. If that turns out to be effec-

tive also, they can stay with it. Cutting the pills in half to get the half dose provides an economic advantage and exposes the patient to less medication.

## Addressing Patient Concerns About Safety

*Some of my patients with ED are reluctant to take PDE5 inhibitors because they are concerned about safety, particularly cardiovascular side effects. How much do we know about safety of the newer PDE5 inhibitors?* Side effects of all 3 PDE5 inhibitors are minimal, occurring in very few patients, and relatively benign. The most common side effects are headache, flushing, and rhinitis. Tadalafil tends to have a higher incidence of dyspepsia, and muscle and back pain, but a lower incidence of flushing compared with the other PDE5 inhibitors.

The FDA has focused on the ability of PDE5 inhibitors to widen QT intervals (the duration of ventricular depolarization and repolarization on ECG). QT prolongation is a poorly sensitive and specific surrogate marker for certain ventricular arrhythmias, particularly Torsades de Pointes, which is a polymorphic tachyarrhythmia that can lead to ventricular fibrillation. QT intervals with all 3 PDE5 inhibitors are considered acceptable and have not been associated with arrhythmias.

As noted in Part 1, PDE5 inhibitors do not appear to directly increase cardiovascular risk and may, in fact, provide cardiovascular benefits.<sup>5</sup> Any kind of physical exertion can increase the risk of myocardial infarction. Sexual activity is associated with less of an increased risk than many other types of normal activities, at approximately 3 METS (metabolic equivalent of oxygen consumption). This is equivalent to performing office work or strolling in a park, compared with 4 to 5 METS for walking, golfing, or gardening and 5 to 6 METS for running, fast biking, or heavy snow shoveling.<sup>6</sup> (Also, please refer to the Tips & Resources sidebar for 2 new studies confirming cardiovascular safety of PDE5 inhibitors in high-risk patients.)

### References — Part 2

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*I have a patient who is taking an alpha-blocker for treatment of lower urinary tract symptoms (LUTS). What is the contemporary view of PDE5 inhibitor use in such patients?*

All of the PDE5 inhibitors contain either warnings or contraindications in patients taking alpha-blockers; however, this may be excessively cautious. The US label for sildenafil permits concurrent use, but now includes a warning against taking sildenafil within 4 hours of alpha-blocker dosing. Tadalafil is contraindicated in the United States at all doses except 0.4 mg in patients using alpha-blockers.<sup>2</sup> Vardenafil is also contraindicated in patients taking alpha-blockers. However, this was based on a “worst-case scenario” study requested by the FDA, in which healthy volunteers showed an increased risk of hypotension and dizziness when there was a rapid titration of vardenafil and alpha-blocker doses.<sup>7</sup> Emerging data that I have seen from separate post-approval investigations of “patients on stable alpha-blocker doses for LUTS or benign prostatic hyperplasia” found only minimal increase in risk of hypotension/dizziness with use of vardenafil, suggesting that patients already taking highly selective alpha-blockers may be able to tolerate PDE5 inhibitors. In my opinion, this will be a generalized PDE5 inhibitor class effect and not a specific drug effect.

Other drug interactions with PDE5 inhibitors are of greater concern. Use of nitrates is a contraindication for all 3 PDE5 inhibitors. This drug combination decreases blood pressure and increases heart rate in a population already at risk of hypotension. In addition, most of the PDE5 inhibitors are cleared through the liver by CYP3A4 enzymes, so drugs that block these enzymes (eg, erythromycin, ketoconazole, protease inhibitors) can affect clearance of PDE5 inhibitors.

In general, most patients with ED are candidates for PDE5 inhibitors and can be reassured that these therapies are safe and effective.

## Tips & Resources

### News and Notes

#### Recent Publications

Two recent publications confirm the cardiovascular safety of sildenafil for the treatment of ED in patients with CAD or CHF:

DeBusk RF, Pepine CJ, Glasser DB, Shpilsky A, DeRiesthal H, Sweeney M. Efficacy and safety of sildenafil citrate in men with erectile dysfunction and stable coronary artery disease. *Am J Cardiol.* 2004;93:147-153.

Webster LJ, Michelakis ED, Davis T, Archer SL. Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-controlled, double-blind crossover trial. *Arch Intern Med.* 2004;164:514-520.

#### Meetings

AASECT's 36th Annual Conference  
SPEAKING OUT: Advocating for Sexual Health and Sexual Rights  
May 12-16, 2004  
Hilton Chicago  
Chicago, Illinois

The conference will have workshops, brief presentations, and live educational demonstrations on topics including sexuality and disability, sexuality and spirituality, aging and sexuality, and medical aspects and advances in sexuality. For information, [www.aasect.org](http://www.aasect.org) or call 804-644-3288.

17th World Congress of Sexology  
July 10-15, 2005  
Montreal Convention Centre  
Montreal, Canada

The conference theme, “Unity in Diversity,” highlights the diversity of approaches and disciplines in the field of sexology. For information, [www.montrealsex.com](http://www.montrealsex.com), or call 514-855-4257.



Have a question for Dr. Goldstein?  
Email him at: [goldstein@expertinsights.com](mailto:goldstein@expertinsights.com)



## Case Vignettes

### *Which PDE5 inhibitor do you start with?*

I generally give patients a prescription for all 3 and encourage them to try them all, since they may find different benefits with each. For example, I have an older patient with diabetes and erectile dysfunction. We are still awaiting the results of his androgen testing, but in the meantime, he has been experimenting with the PDE5 inhibitors and has reported that different ones work for him at different times. New data from the Patient Response with Vardenafil in Sildenafil Nonresponders (PROVEN) study further support trying all of the PDE5 inhibitors, because success may be achieved with one even if it wasn't with the first drug tried. The PROVEN study was a prospective, multicenter, double-blind, placebo-controlled trial of vardenafil in men with moderate-to-severe ED that had previously failed to respond to sildenafil. Criteria for unresponsiveness to sildenafil were fairly rigorous, including failing at least 4 of the last 6 attempts at intercourse and at least 1 failed attempt with the highest available sildenafil dose (100 mg). Participants (N = 463) took vardenafil (10 mg, titrated to 5 or 20 mg at weeks 4 and 8 based on efficacy/tolerability) or placebo for 12 weeks. Successful completion of sexual intercourse was 3 times more likely with vardenafil than with placebo (46.1% versus 11.6%, respectively) and 4 times more likely with vardenafil compared with baseline (46.1% versus 10.1%).<sup>1</sup>

***If a patient finds one PDE5 inhibitor to be effective, shouldn't he just stick with that one?*** Some of my patients use different PDE5 inhibitors at different times. For example, I have a young patient whose family life tends to be a bit hectic during the week, since he and his wife both work, and they have children to take care of as well. When they find time to have sex during the week, they usually prefer a PDE5 inhibitor with a rapid onset so that they do not have a long wait after he takes the pill before they can engage in sexual activity. On the other hand, they sometimes leave the children with his in-laws and get away for the

weekend. At those times, they prefer a PDE5 inhibitor with a long duration, so they can be more spontaneous about when they want to engage in sexual activity. So again, differences among PDE5 inhibitors offer advantages to different patients at different times.

***Why are the doses of PDE inhibitors that facilitate penile erection so minimal? In some patients, excellent penile rigidity and sustaining capability can occur with doses ranging from 5–20 mg vardenafil and tadalafil and 25–100 mg sildenafil. What is happening at the level of the PDE5 enzyme that such a low dose is needed to improve erectile function?*** According to Dr. Jackie Corbin, a positive feedback system helps explain why low doses of PDE5 inhibitor (sildenafil, vardenafil and tadalafil) are needed to facilitate penile erection. As discussed above, the substrate cGMP binds to the catalytic and allosteric sites of the PDE5 enzyme. Further, the PDE5 inhibitors only bind to the catalytic sites. The key to this new finding is that cGMP binding to the PDE5 allosteric sites stimulates/activates the PDE5 catalytic sites. This activation stimulates PDE5 inhibitor binding to the activated PDE5 catalytic sites. In combination with the "concentrating" effect discussed on page 6, this mechanism should reduce the required dose of inhibitor.

So when a patient takes a PDE5 inhibitor, there is an increase in the cGMP in the smooth muscle cell. The increased cGMP binds to the allosteric site. This allosteric binding stimulates/activates the PDE5 catalytic sites. The activated PDE5 catalytic sites encourage binding by the PDE5 inhibitors to the PDE5 enzyme.

Thus, elevation of cGMP by PDE5 inhibitor stimulates further binding of inhibitor to PDE5. What does this mean clinically? If it were not for the existence of this built-in positive feedback mechanism, perhaps 5 times the dose of PDE5 inhibitor would be needed for these PDE5 inhibitor drugs to enhance penile erection. This observation, again, emphasizes the importance of the biochemical potency of the PDE5 inhibitors.

1. Carson C, Hatzichristou D, Carrier S, et al. 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 Nonresponders (PROVEN). Presented at: 5th Annual Fall Research Meeting of the Sexual Medicine Society of North America; October 11, 2003; Denver, Colo.

## Put It Into Practice

- Vardenafil exhibits greater biochemical potency than other PDE5 inhibitors in numerous in vitro analyses.
- Sildenafil and vardenafil work more quickly but do not last as long compared with tadalafil.
- Assess the preferences of individual patients in choosing a PDE5 inhibitor. According to patients in a comparative study (interim analysis only), at low doses, vardenafil was most effective in terms of achieving and maintaining an erection, tadalafil was preferred for duration of action, and sildenafil for least side effects.
- Poor success with one PDE5 inhibitor does not necessarily mean that the others won't work—encourage patients to try them all.
- When using tadalafil, the full strength is more likely to be effective than the half dose.
- Reassure patients about cardiovascular and general safety of PDE5 inhibitors.

## Issues In This Series

**Part 1: Focus on the Latest from the Men's Attitudes to Life Events and Sexuality (MALES) Study**

**Part 2: Focus on the Unique Properties and Differences Among PDE5 Inhibitors**

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