Clinical evidence in men with erectile dysfunction (ED) shows that the phosphodiesterase type 5 (PDE5) inhibitors sildenafil citrate, tadalafil, and vardenafil hydrochloride have favorable safety and efficacy profiles. However, as mild vasodilators, the PDE5 inhibitors are also associated with hemodynamic effects that may be clinically significant, especially when treating men with ED who have comorbid cardiovascular disease. Hemodynamic studies have shown that therapeutic dosages of the PDE5 inhibitors produce only mild and transient changes in mean systolic and diastolic blood pressure and heart rate in healthy men as well as those with ischemic heart disease or chronic stable angina. Overall, PDE5 inhibitors are safe and effective in most patient populations, including men with ischemic cardiovascular disease or those receiving antihypertensive agents, and men with diabetes or those who have undergone nerve-sparing retropubic radical prostatectomy. With the entry of three novel PDE5 inhibitors into the therapeutic armamentarium for ED, differentiating properties of the new agents may confer clinical benefits that physicians as well as patients and their partners should consider when selecting a PDE5 inhibitor.

According to the Massachusetts Male Aging Study (MMAS), the estimated prevalence of erectile dysfunction (ED) of any degree in men 40 to 70 years of age is 52%, with 25% having moderate dysfunction and the rest of this age group unable to achieve erections at all. Data from a wide range of clinical trials demonstrate that the oral phosphodiesterase type 5 (PDE5) inhibitors offer efficacy in the treatment of this disorder. Further, as each of these agents—shorter-acting sildenafil citrate and vardenafil hydrochloride, and longer-acting tadalafil—was developed, it proved to confer benefits over placebo in healthy men, in men with comorbidities such as diabetes and cardiovascular disease (CVD), and in men with surgically induced ED. All the PDE5 inhibitors are generally safe and well tolerated, a finding that greatly enhances any and all efficacy benefits. Sildenafil, the first of these agents, offered early onset of action, a favorable side effect profile, efficacy in men with diabetes, and the return, in some men, of spontaneous erections after nerve-sparing retropubic radical prostatectomy (NSRP); the development of vardenafil brought these features plus efficacy in men previously nonresponsive to sildenafil. Tadalafil, with its extended duration of activity, then built on the established foundation of benefits by expanding the window of time in which couples could attempt and complete successful intercourse.

Onset and Duration of Action and Overall Efficacy

- **Sildenafil**—In healthy men with ED, onset of activity with sildenafil may be seen as early as 11 minutes postdose. In one study, within 14 and 20 minutes of dosing, 35% and 51% of patients treated with sildenafil, respectively, versus 22% and 30% of patients receiving placebo, respectively, had one or more erections leading to successful intercourse ($p<0.05$). The median time after sildenafil dosing that led to erection resulting in successful intercourse was 36 minutes (versus 141 minutes for placebo).

- **Vardenafil**—In a large (n=471) at-home study of vardenafil, onset of action leading to intercourse completion was reported as early as 16 minutes after ingestion.

In the first of its at-home trials (N=601), vardenafil treatment resulted in a high efficacy rate in a population of patients with ED of mixed etiologies. When comparing the study drug with placebo and using the 15-question International Index of Erectile Function (IIEF) Erectile Function (EF) domain as well as global assessment questions (GAQ) as metrics to measure patient responses, the percentage of successful intercourse attempts reported was between 71% and 75% for the three available vardenafil hydrochloride doses (5 mg, 10 mg, and 20 mg). Moreover, vardenafil has produced statistically and clinically significant improvements in key efficacy measures in men with severe ED and a documented history of nonresponse to sildenafil, including a fourfold increase in successful intercourse completion rates over baseline. It has also brought mean erectile function in one group into the mild-to-moderate range.

- **Tadalafil**—The onset of action of tadalafil has been demonstrated at 16 to 30 minutes postdose.

In a study by Carson et al., men with ED reported significant improvement in each severity category after taking tadalafil, 10 mg or 20 mg, versus placebo. Mean IIEF EF domain scores improved by least one category. More than 70% of men with mild dysfunction and 40% with severe dysfunction returned to a normal EF domain score.
at study end point with tadalafl, 20 mg.11
The feature that most distinguished
tadalafl from its predecessors was its
duration of action: with its mean terminal
half-life of 17.5 hours, tadalafl has
allowed couples to engage in successful
intercourse up to 36 hours postdose.
However, just because couples could try
intercourse 36 hours after taking a med-
cation did not necessarily mean they
would try.

Therefore, the next question to inves-
tigate became: When do couples try, if
not constrained by the effectiveness
of their medication? An analysis of 1414
tadalafl-treated patients drawn from 11
randomized, double-blind, 12-week effi-
cacy studies at multiple institutions
revealed that couples took advantage of
the drug’s pharmacokinetic profile. Of a
total of 33,472 attempts at intercourse
that took place after taking tadalafl, 82%
of men attempted, at least once, to have
intercourse 4 to 36 hours later and more
than 59% attempted to have intercourse
12 to 36 hours after taking the drug
(Table 1).12

PDE5 Inhibitors in the
Treatment of Patients
With Surgically Induced
Erectile Dysfunction

More than a third of men who undergo
nerve-sparing retroperitoneal radical prostatectomy (NSRKP) may have ED.13 In
this category of patients, all three PDE5
inhibitors offer benefits.

■ Sildenafil—Nightly administration
of sildenafil for 9 months after NSRKP
has been shown to increase the return of
spontaneous erections in 20% of patients
when compared with placebo; the drug
was also well tolerated.14 A possible
explanation for this result is that this
gagent may improve oxygenation at the
time of nocturnal erections or neuronal
regeneration (or both).

■ Vardenafil—Vardenafil has also con-
firmed benefits on patients after pro-
stectomy, but results have been seen in a
shorter time. After 12 weeks, 65.2% of
patients receiving 20 mg and 59.4% of
patients receiving 10 mg of vardenafil
hydrochloride and only 12.5% taking
placebo reported improved erections,
determined by use of the EF domains of
the IIEF as well as the GAQ (P<.0001).

The average success rate of intercourse
was 74% in patients with mild to mod-
erate ED and 28% in men with severe
dysfunction versus 49% and 4%, respec-
tively, with placebo.13

In a separate trial, vardenafil demonstra-
ted positive results as well, as mea-
sured by two items in the Sexual
Encounter Profile (SEP) diary:
□ Item 2 (SEP-Q2), which asks whether
erection was sufficient for penetration, and
□ Item 3 (SEP-Q3), which asks whether
penetration was sufficient for the com-
pletion of intercourse.

In this study, vardenafil significantly
improved the overall per-patient rate of
achieving an erection sufficient for pen-
etration (SEP-Q2): 61% of men taking the
10-mg dose and 64% taking the 20-mg
dose versus 36% receiving placebo
reported this improvement (P<.0001).15
Also, vardenafil demonstrated a clini-
cally meaningful and statistically signif-
ificant increase in the overall per-patient
rate of maintenance of erection to suc-
cessful intercourse (SEP-Q3): improve-
ment was reported by 49% of men taking
the 10-mg dose and 54% of men taking
the 20-mg dose versus 23% taking
placebo (P<.0001).15 The inverse rela-
tionship between the percentage
reporting improvement in SEP-Q3 and
the respective drug doses has not been
explained.

■ Tadalafil—Similarly, tadalafil has
proved to be efficacious and well toler-
ated among men who are post-NSRKP.
For all randomly assigned patients in a
study of 303 men, a GAQ revealed that
62% receiving 20 mg of tadalafil versus
23% receiving placebo reported
improved erections. The IIEF EF domain
score in patients receiving tadalafil
improved by 5 points (a rating of 18)
versus a 1-point increase to a score of 13
in patients receiving placebo.16 In patients
who had some tanscience in greater
than or equal to 50% of sexual attempts
before treatment, 71% taking tadalafil
reported improved erections as com-
pared with 24% receiving placebo. Also,
55% of patients taking tadalafil versus
28% of patient receiving placebo reported
successful sexual attempts (P<.001 for
both).17

Table 1
Distribution of Attempts at Intercourse Over Time
With Tadalafil Versus Placebo (N=2102)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Intercourse Attempted Postdose or After Taking Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 0 to &lt; 1</td>
</tr>
<tr>
<td>Men receiving 10 mg or 20 mg of tadalafil, %</td>
<td>70.5</td>
</tr>
<tr>
<td>Men receiving placebo, %</td>
<td>73.0</td>
</tr>
</tbody>
</table>

Source: Shabsigh R, et al. Abstract presented at the 5th Annual Fall Research Meeting of the
Sexual Medicine Society of North America; October 10 to 12, 2003; Denver, Colo.

Treating Patients With Diabetes:
Efficacy and Tolerability

In more than 50% of men with dia-
betes, ED develops within 10 years of the
diagnosis of diabetes, and the prevalence
of ED among his group increases greatly
with age.18 In the MMAS sample, men
who reported being treated for diabetes
had three times the age-adjusted proba-
bility of complete dysfunction (28% vs
9.6%) as the total population.2 These men
tend to be less responsive to treatment,
perhaps because the pathogenesis of dia-
betes-related ED is multifactorial.
Response to the PDE5 inhibitors, how-
ever, has demonstrated efficacy and rel-
ative safety, though the results vary
between the three agents.18

■ Sildenafil—A 12-week sildenafil
study in patients with diabetes used
questions 3 and 4 of the IIEF. These ques-

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Susman • Phosphodiesterase Type 5 Inhibitors
tions assess the ability to achieve erection for sexual intercourse and the ability to maintain erection after penetration, respectively. They specifically address the key aspects of ED as defined by the National Institutes of Health. The study also used the Global Efficacy Question, “Did the treatment improve your erections?” Seventy-four (56%) of the 131 men in the group treated with sildenafil reported improved erections compared with 13 (10%) of the 127 men in the group receiving placebo ($P<0.001$).

Among the patients taking sildenafil versus those taking placebo, 11% versus 2%, respectively, reported headache; 9% versus 0%, respectively, reported dyspepsia; and 6% versus 2%, respectively, reported respiratory tract disorder. A few patients in the sildenafil-treated group had flushing, rhinitis, or abnormal vision (3% vs 0% with placebo in separate worldwide trials). Abnormal vision may be attributable to sildenafil’s relative selectivity to the PDE6 isoenzyme, a feature not shared with other PDE5 inhibitors.\(^1\,\!^{19}\)

Adverse events related to treatment, though transient and mild to moderate, were reported for 16% of patients taking sildenafil versus 1% of patients taking placebo.\(^1\)

**Vardenafil**—Vardenafil is more selective than sildenafil for PDE5, and in vitro and in vivo studies have shown vardenafil to be more biochemically potent.\(^18\) In a prospective, fixed-dose study of 439 patients in the group receiving 10 mg of tadalafil versus 25% of 71 patients who had taken placebo reported positive responses to a GAQ regarding improved erections. This therapy, particularly at 20 mg, significantly enhanced erectile function across all three coprimary efficacy variables: IIEF EF domain, SEP-Q2, and SEP-Q3.\(^20\,\!^{21}\) Men who received tadalafil were also more likely to have an increase of more than 5 points in the IIEF EF domain score than patients in the control group. Approximately 44% of the men taking 10 mg, 56% taking 20 mg, and 13% taking placebo reported this change. An increase of this magnitude, which is consistent, for example, with an improvement from severe to moderate ED (a score of 18), is clinically noteworthy when considered in a population of men who are likely to have longstanding and fairly advanced diabetes.\(^21\)

The 10-mg dose and the 20-mg dose of tadalafil are equally well tolerated, and both have an adverse event profile that is superior to that of the other PDE5 inhibitors. Among those receiving the 10-mg dose of tadalafil, 20-mg dose of tadalafil, and those receiving placebo, 9.6%, 8.3%, and 2.8%, respectively, reported headache; 2.7%, 4.2%, and 0%, respectively, reported flushing; 1.4%, 5.6%, and 1.4%, respectively, reported back pain; 11.0%, 11.1%, and 0%, respectively, reported dyspepsia.\(^21\)

### PDE5 Inhibitors and Cardiovascular Health and Safety

Men with CVD are more likely to have ED than the general male population because both conditions share risk factors (eg, age, hypertension, diabetes mellitus, obesity, smoking, hyperlipidemia, physical inactivity) and because some drugs used to treat CVD may induce ED.\(^22\,\!^{23}\) which may be a marker for CVD.\(^23\) One of the positive side effects of this drug class is that PDE5 inhibition has been shown to dilate epicardial coronary arteries, improve endothelial dysfunction, and inhibit platelet activation in patients with coronary artery disease. This activity also has an intermediate effect on myocardial ischemia compared with isosorbide dinitrate and placebo.\(^24\)

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**Table 2**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Men With Positive Responses to GAQ, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group (placebo)</strong></td>
<td>13</td>
</tr>
<tr>
<td><strong>Treatment group</strong></td>
<td></td>
</tr>
<tr>
<td>Vardenafil hydrochloride, 10 mg</td>
<td>57†</td>
</tr>
<tr>
<td>Vardenafil hydrochloride, 20 mg</td>
<td>72†</td>
</tr>
</tbody>
</table>


* GAQ indicates global assessment of quality; question, “Has the treatment you have been taking improved your erections?”

† $P<0.0001$ versus placebo.
Another positive side effect of PDE5 inhibition can be seen in the brachial artery flow-mediated dilation that results from short-term and prolonged PDE5 inhibitor therapy. This activity is of particular benefit to men with diabetes who have the endothelial abnormalities that contribute to ED and vascular disease.23

Overall, PDE5 inhibitors are safe in most male patient populations, including men with ischemic CVD or those receiving antihypertensive agents. They are not associated with increases in myocardial infarction (MI) or death rates in controlled clinical trials. In treating patients with concomitant ED and CVD, it is important to first remember that sexual activity, with or without the use of a PDE5 inhibitor, may carry a potential cardiac risk for patients with CVD.15,17

As part of patient assessment, use of the Princeton Consensus Panel’s classification system23 is helpful in determining the level of cardiac risk in patients with cardiovascular risk factors or established disease. Based on these guidelines, risk is stratified as follows:

- High risk factors:
  - Unstable angina;
  - Uncontrolled hypertension;
  - Left ventricular dysfunction/congestive heart failure (New York Heart Association [NYHA] class III, IV);
  - Recent (within 14 days) MI or cardiovascular accident;
  - High-risk arrhythmias;
  - Hypertrophic obstructive and other cardiomyopathies; and
  - Moderate to severe valvular disease.
- Indeterminate risk factors:
  - Three or more major risk factors for coronary artery disease (CAD);
  - Moderate, stable angina;
  - Recent MI (>2 weeks to <6 weeks);
  - Left ventricular dysfunction/congestive heart failure (NYHA class II); and
  - Noncardiac sequelae of atherosclerotic disease (eg, cardiovascular accident, peripheral vascular disease).
- Low risk factors:
  - Asymptomatic, fewer than three major risk factors for CAD;
  - Controlled hypertension;
  - Mild, stable angina;
  - Post-successful coronary revascularization;
  - Uncomplicated past MI (>6 to 8 weeks); and
  - Mild valvular disease/congestive heart failure (NYHA class I).

Treatment for ED—including but not limited to prescription of a PDE5 inhibitor—should be delayed until the cardiac condition stabilizes and the patient’s cardiovascular specialist approves of the initiation of treatment.22,23

Patients at indeterminate risk should undergo specialized testing and be reclassified. Most men, after reclassification, fall into the low-risk category and can safely resume sexual activity and receive therapy with PDE5 inhibitors if needed.

In patients at low or indeterminate risk, prescription of a PDE5 inhibitor must always be viewed in the context of any other medications the patient is taking. It is with regard to potential drug-drug interactions that the PDE5 inhibitors exhibit more similarities than dramatic differences.

- Contraindication With Nitrates—Nitrates have a hypotensive effect. The combined effects of nitrates and PDE5 inhibitors on the nitric oxide/cyclic guanosine monophosphate pathway may augment this effect. As such, even though controlled clinical trials coadministering PDE5 inhibitors and nitrates have not been associated with increased rates of MI or death, both sildenafil and vardenafil are contraindicated in patients receiving nitrates. It is important to note that sildenafil has hemodynamic effects resembling those of modest nitrates (it has modest effects on blood pressure in healthy subjects—a decrease of approximately 10 mm Hg after a single 100-mg dose).

Vardenafil, which is associated with slight decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) (although it is associated also with a minor compensatory increase in heart rate),27,29 is contraindicated in patients receiving organic nitrates. The prescribing information for tadalafil states that its use in patients taking any form of nitrates is contraindicated. In a patient who has taken tadalafil, and in whom nitrate administration is deemed necessary in a life-threatening situation, a minimum of 48 hours should pass between dosing with tadalafil and administration of nitrates, and then be commenced only under close medical supervision and with appropriate hemodynamic monitoring.15,17

- Patients Taking Antihypertensives—Hypertension is also an important risk factor for ED, and the drugs used to treat hypertension may further exacerbate the condition.20,31 Because of the systemic vasodilatory effects of PDE5 inhibitors, coadministration of some of these drugs and some antihypertensive medications, specifically α-blockers, may cause additive but not necessarily potentiating decreases in blood pressure. Vardenafil use has resulted in transient decreases in SBP in healthy volunteers (mean maximum decrease of 7 mm Hg SBP and 8 mm Hg DBP). Tadalafil at a 10-mg dose is associated with mean decreases in SBP of 4.5 mm Hg and DBP of 2.5 mm Hg (measured with the subject standing).15,17

An early placebo-controlled, double-blind, crossover study (N = 16) that assessed the potential for interaction of sildenafil and the antihypertensive amloidipine. The study found a significant decrease 4 hours postdose in the mean maximum blood pressure with subjects in the supine and standing positions (8 mm Hg and 7 mm Hg, respectively), when compared with subjects receiving the amloidipine-placebo combination.32 Although prescribing information for sildenafil does not recommend a waiting period after ingestion of all antihypertensives, it does state that patients should wait to take sildenafil for at least 4 hours after taking an α-blocker.22 Similarly, although concomitant use of vardenafil and most antihypertensives (eg, the calcium channel blocker nifedipine) have not been found to lead to serious hemodynamic events, use of vardenafil is contraindicated in patients taking α-blockers.15,33

With regard to tadalafil, its use is contraindicated with α-blockers, except tamsulosin, 0.4 mg once daily. A study of the potential for a hemodynamic interaction between tadalafil and doxazosin showed that tadalafil at a dose of 20 mg produced mean maximal postbaseline reductions in SBP and DBP measured with the subject supine and standing significantly greater than those with placebo...
during treatment with doxazosin mesylate, 8 mg.17

In a clinical pharmacology study, a single dose of tadalafil, 20 mg, administered to healthy subjects taking the α1A-adrenergic receptor blocker tamsulosin, 0.4 mg once daily, resulted in no significant decreases in blood pressure.17

The difference between the hypotensive effects observed after concomitant administration of tadalafil and doxazosin compared with that of tadalafil and tamsulosin are notable. One explanation may be the greater selectivity of tamsulosin. The α1A-adrenergic receptors inhibited by tamsulosin are located mainly in nonvascular smooth muscle, such as the prostate.

**Comment**

Based on their efficacy profile, the novel PDE5 inhibitors tadalafil and vardenafil are a bit more highly selective than sildenafil. Tadalafil, with its 36-hour duration, offers increased dosing flexibility over sildenafil and vardenafil, both of which last for about 4 hours. The results of noncomparative studies suggest that tadalafil and vardenafil improve erections in the general population as well as in men with diabetes and men with hypertension. Adverse events are mild to moderate and transient, and they generally dissipate as treatment continues.

In the evolution of PDE5 inhibitors, as in most scientific and historic endeavors, the past is prologue. Clearly, the development of this drug class has followed a logical progression of continued discovery and improvement. The result is that patients with ED can now select from among several agents in the class of PDE5 inhibitors for ease of administration and optimal outcomes.

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