Vardenafil and tadalafil
Options for erectile dysfunction

Two new PDE-5 inhibitors have demonstrated efficacy and tolerability in clinical trials.

Lesley M. Arnold, MD
Associate professor of psychiatry
Director, Women's Health Research Program
University of Cincinnati College of Medicine
Cincinnati, OH

Sildenafil has revolutionized management of erectile dysfunction (ED) over the past 5 years. The FDA recently approved two additional medications, vardenafil and tadalafil, for treating ED.

HOW VARDENAFIL AND TADALAFIL WORK
Like sildenafil, vardenafil and tadalafil are selective inhibitors of the phosphodiesterase (PDE) isoenzyme PDE-5, which is predominantly responsible for degrading cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum.

During sexual stimulation, nitric oxide is released from cavernous nerves and endothelial cells and activates the enzyme guanylate cyclase, resulting in increased cGMP synthesis. The cGMP triggers relaxation of smooth muscles, allowing increased blood flow into the penis and expansion of sinusoidal spaces; this prevents venous blood outflow and results in erection. The PDE-5 inhibitors can potentiate erections by enhancing and prolonging the smooth muscle-relaxant effects of the nitric oxide-cGMP cascade in the corpus cavernosum.1 PDE-5 inhibitors have no effect without sexual stimulation.

Pharmacokinetics of the PDE-5 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil 100 mg</th>
<th>Vardenafil 20 mg</th>
<th>Tadalafil 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>450 ng/mL</td>
<td>20.9 ng/mL</td>
<td>378 ng/mL</td>
</tr>
<tr>
<td>concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to</td>
<td>1.0 hour</td>
<td>0.7 hours</td>
<td>2.0 hours</td>
</tr>
<tr>
<td>maximum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>4 hours</td>
<td>3.9 hours</td>
<td>17.5 hours</td>
</tr>
</tbody>
</table>

Source: References 2 and 3

continued on page 51
Although the three PDE-5 inhibitors have similar mechanisms of action, their selectivity differs for PDE-5 compared with the PDE-6 and PDE-11 isoenzymes. Sildenafil and vardenafil have lower selectivity than tadalafil for PDE-5 over PDE-6, which plays a role in phototransduction, the process by which light impulses are converted into nerve impulses in the retina. Thus, tadalafil is less likely than the other agents to cause visual disturbances such as abnormal color vision, increased brightness of light, or mild haziness.

Tadalafil shows lower selectivity than sildenafil or vardenafil for PDE-5 over PDE-11, meaning that tadalafil inhibits PDE-11 at clinical doses. PDE-11 is found in various tissues, but its physiologic significance and consequences of its inhibition are unknown.2

PHARMACOKINETICS
Vardenafil, tadalafil, and sildenafil have different pharmacokinetic characteristics (Table 1). A lower starting dosage is required with vardenafil than with sildenafil because of the former agent’s greater in vitro and in vivo potency, but whether this results in greater clinical efficacy or tolerability is unknown.3

Vardenafil and sildenafil reach maximum plasma concentration within 30 minutes to 2 hours (median 1 hour for sildenafil and 0.7 hour for vardenafil). By contrast, tadalafil reaches maximum concentration within 30 minutes to 6 hours (median 2 hours). However, studies of time to onset of erection indicate that about one-third of patients using the maximum recommended doses of any of these agents will experience onset within 14 to 16 minutes.4–6

Absorption rates for sildenafil and vardenafil are reduced when they are taken with a high-fat meal. High-fat foods do not affect tadalafil’s absorption rate.

Table 2
Vardenafil: Fast facts

| Drug brand name: | Levitra |
| Class: | Phosphodiesterase-5 inhibitor |
| FDA-approved indication: | Erectile dysfunction |
| Approval date: | August 19, 2003 |
| Manufacturer: | Bayer Corp. (distributed by GlaxoSmithKline) |
| Dosing forms: | 2.5 mg, 5 mg, 10 mg, 20 mg |
| Dosing recommendations: | Start at 10 mg about 1 hour before sexual activity. Maximum recommended dose is 20 mg; maximum dosing frequency is once per day. Consider 5-mg starting dose for patients age 65 and older. |

Because of its 17.5-hour half-life, tadalafil has a longer period of activity than the other PDE-5 inhibitors. Most patients can complete sexual intercourse up to 36 hours after taking tadalafil, which potentially allows spontaneous sexual activity. Sildenafil and vardenafil each are effective for about 4 hours.

All three PDE-5 inhibitors are eliminated by hepatic metabolism, mainly by the CYP 3A4 hepatic enzyme. Therefore, concomitant use with CYP 3A4 inhibitors—such as ketoconazole, ritonavir, grapefruit juice, or erythromycin — results in increased plasma levels of these agents, and the use of CYP 3A4 inducers such as rifampin reduces plasma levels of the concomitant agent.
Like sildenafil, the newer PDE-5 inhibitors vardenafil and tadalafil have shown efficacy in treating erectile dysfunction in placebo-controlled trials. All three agents are generally safe and well-tolerated. Comparative data are needed to determine their relative efficacy and tolerability.

**Efficacy**

**Vardenafil** *(Table 2).* In a placebo-controlled, 12-week trial, 601 men with mildly to severely impaired erectile function received placebo or 5, 10, or 20 mg of vardenafil. Subjects receiving vardenafil at any dose saw significantly greater improvement in erectile function than did the placebo group. Percentage of successful intercourse ranged between 71% and 74% for the three vardenafil doses. For the 20-mg dose, 80% of patients experienced improved erections compared with 30% of those taking placebo.\(^7\)

In another trial of 805 men with mild to severe ED,\(^8\) vardenafil in 5-mg, 10-mg, and 20-mg doses demonstrated efficacy versus placebo. Eighty-five percent of men using vardenafil, 20 mg, reported improved erections at 26 weeks compared with 28% in the placebo group.

Vardenafil, 10 mg and 20 mg, was also an effective ED treatment in men with type 1 or type 2 diabetes mellitus\(^9\) and in men who underwent radical prostatectomy.\(^10\)

**Tadalafil** *(Table 3).* An integrated analysis\(^11\) of five randomized, placebo-controlled trials of tadalafil at 2.5, 5, 10, or 20 mg for at least 12 weeks found that the agent at all doses significantly enhanced erectile function in mild to severe ED compared with placebo. Successful intercourse was reported in 61% and 75% of sexual encounters among men treated with tadalafil, 10 and 20 mg respectively, compared with 32% in controls. Eighty-one percent of men taking tadalafil, 20 mg, reported improved erections compared with 35% of those taking placebo.

Tadalafil, 10 and 20 mg, also improved erectile function in men with type 1 or type 2 diabetes.\(^12\)

**Tolerability**

All three PDE-5 inhibitors have been shown in clinical trials to be generally safe and well-tolerated. Apart from visual disturbances, all three agents have similar side effects:

- Patients taking vardenafil most commonly reported headaches, flushing, rhinitis, and dyspepsia. These effects were generally mild to moderate, dose-related, and transient.\(^1\)

- Headache, back pain, myalgia, and dyspepsia were most commonly reported with tadalafil.\(^13\) Similarly, adverse events were mild or moderate, dose-related, and generally abated with treatment.

Treatment-related visual disturbances have been reported in 3% of patients taking sildenafil,
>0.1% to <1% of men taking vardenafil, and <0.1% of those taking tadalafil. Laboratory parameters have been unaffected by treatment with the PDE-5 inhibitors, and treatment discontinuation due to adverse events has been consistently low. All three PDE-5 inhibitors cause vasodilatory effects and are contraindicated in patients using organic nitrates. Consensus guidelines have been developed for using PDE-5 inhibitors in patients with cardiovascular conditions.14

References

---

**Have a case from which other psychiatrists can learn?**

Check your patient files for a case that offers “lessons learned” and send it to pete.kelly@dowdenhealth.com. Keep it to 2,000 words, outlining history and treatment options, with interspersed commentary to reinforce the key points.

If you have questions before writing, contact Pete Kelly. Our editorial board and case history editor will review your article—and you’ll hear from us soon.