Erectile dysfunction (ED) refers to the inability of a man to achieve or maintain an erection that is sufficient for his sexual needs or the needs of his partner. ED affects 150 million men worldwide, including an estimated 15 to 30 million men in the U.S. The incidence of the disorder increases with age. Chronic ED affects approximately 5% of men in their 40s and 15% to 25% of men by the age of 65. As many as 50% of men between ages 40 and 70 are affected by transient ED and inadequate erections.

The incidence of ED is projected to increase sharply over the next 25 years. It may also be a biobehavioral marker for diabetes mellitus, depression, and/or cardiovascular disorders.

Advances in protein chemistry and molecular biology, along with an increased understanding of the mechanisms involved in a penile erection, have sparked the development of medicinal approaches to the treatment of ED. The three orally active medications available for patients with ED are sildenafil citrate (Viagra®, Pfizer), vardenafil (Levitra®, Bayer/GlaxoSmithKline), and tadalafil (Cialis™, Eli Lilly). Tadalafil is the latest of the three to be approved by the Food and Drug Administration (FDA). This medication is a highly selective, potent, reversible inhibitor of phosphodiesterase type 5 (PDE5).

In the treatment of any disorder for which more than one drug in the same or a similar class is available, the patient’s preference is an important issue for physicians to consider; this is true in the case of ED because it is a subjective complaint. Tadalafil differs from the other two products in that it stays in the body for a longer time, which is an advantage for men with ED.

**ETIOLOGY**

For a penile erection to occur, a sequence of events must take place. ED can result if the order of any of these events is disrupted. These events include the transmission of nerve impulses in the brain, spinal column, and the area around the penis as well as responses in the muscles, fibrous tissues, veins, and arteries in and near the corpus cavernosum. Nerve damage and a reduced blood flow to the penis are the most common physical causes of disruption. Underlying conditions associated with ED include the following:

- **Arteriosclerosis.** Thickening of the arterial walls results in a reduced blood flow throughout the body and can lead to impotence. Arteriosclerosis is associated with aging and accounts for 50% to 60% of impotence in men above age 60. Risk factors for arteriosclerosis include hypertension, diabetes mellitus, smoking, and hyperlipidemia. Smoking is the most significant risk factor for impotence related to arteriosclerosis.
- **Diabetes.** Chronic hyperglycemia associated with diabetes mellitus damages the nerves and small blood vessels throughout the body. Some antihypertensive medications, heart medications, tranquilizers, antidepressants, and sedatives contribute to or cause ED.
- **Drug use.** Long-term use of alcohol and illicit drugs may affect the vascular and nervous systems and are associated with ED.
- **Hormonal disorders.** Testosterone deficiency can result in a loss of libido and loss of erections. Hormone imbalances can result from kidney or liver disease.
- **Neurological conditions.** Brain or spinal cord injuries such as a stroke or paraplegia can cause ED when the transfer of nerve impulses from the brain to the penis is blocked. Multiple sclerosis, Parkinson’s disease, and Alzheimer’s disease are other nerve disorders that sometimes also result in ED.
- **Surgery and radiation therapy.** Surgery or irradiation of the prostate, bladder, colon, or rectum may damage the nerves and blood vessels involved in erection.
- **Injury or trauma.** Trauma to the spinal cord or pelvic region can damage the veins and nerves needed for an erection.
- **Peyronie’s disease.** This rare inflammatory disorder causes scarring of erectile tissue. The scarring produces curvature of the penis and can cause painful erections that often interfere with sexual function. An erection cannot be maintained if the veins in the penis cannot prevent blood from leaving the penis during an erection.
- **Venous leakage.** A venous leak can result from injury, disease, or damage to the veins in the penis.
- **Psychological state.** Depression, guilt, stress, and anxiety all contribute to a loss of libido and to ED.
TREATMENT

Treatment should begin with the least invasive therapies. Any drugs that might be contributing to ED should be discontinued. In the case of antihypertensive agents, other drugs with a different mechanism of action should be considered. Next, psychotherapy and behavior modifications might be considered, followed by oral drugs; locally injected drugs; vacuum devices; and, finally, implanted devices.

PHARMACOLOGY

During sexual stimulation, an erection is caused by increased blood flow in the penile area. The increased blood flow is the result of relaxation of penile arteries and the smooth muscle of the corpus cavernosum. The release of nitric oxide (NO) arbitrates this response, which stimulates the synthesis of cyclic guanosine monophosphate (cGMP) in smooth muscle cells. cGMP causes smooth muscle relaxation and increases blood flow into the corpus cavernosum. The inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. Although tadalafil inhibits PDE5, this inhibition has no effect in the absence of sexual stimulation because sexual stimulation is required to initiate the local release of NO.2,7,8

PHARMACOKINETICS

An increased dose of tadalafil (2.5–20 mg) corresponds to a proportional elevation in serum concentrations in healthy subjects. Steady-state plasma concentrations are reached within five days of once-daily dosing. Exposure is approximately 1.6-fold higher than after a single dose. After a single oral dose, the maximum observed plasma concentration of tadalafil is achieved between 30 minutes and six hours, with an average time of two hours. Because the rate and extent of absorption of tadalafil are not influenced by food, this agent may be taken with or without food.

The mean apparent volume of distribution following oral administration is approximately 63 liters, indicating dissemination into the tissues. At therapeutic concentrations, 94% of tadalafil is bound to proteins in plasma. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects. Tadalafil is eliminated primarily by hepatic metabolism via the cytochrome P450 3A4 (CYP3A4) pathway. The average terminal half-life of tadalafil is 17.5 hours in healthy subjects. It is excreted mainly as metabolites in the feces (61% of the dose) and, to a lesser extent, in the urine (30% of the dose).7

Efficacy

The Padman-Nathan Study4 and Manufacturer’s Data7

Tadalafil was studied in the general ED population in seven randomized, multicenter, double-blind, placebo-controlled trials of 12 weeks’ duration. Two of the studies were conducted in the U.S., and five were conducted in centers outside the U.S.

The patients took tadalafil as needed, at doses ranging from 2.5 to 20 mg, up to once a day. They were free to choose the time of sexual attempts and the time interval between dosage administrations.4,7

The three outcome measures were the erectile function (EF) domain of the International Index of Erectile Function (IIEF) and two questions from the Sexual Encounter Profile (SEP).

The IIEF questionnaire was administered.

Table 1 Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two Primary U.S. Trials of Tadalafil

| Study | Placebo (No. = 49) | Tadalafil 20 mg (No. = 146) | P value | Placebo (No. = 48) | Tadalafil 20 mg (No. = 159) | P value |
|-------|-------------------|-----------------------------|---------|-------------------|-----------------------------|---------|
| Erectile Function Domain Score | | | | | | |
| Endpoint | 13.5 | 19.5 | | 13.6 | 22.5 | |
| Change from baseline | -0.2 | 6.9 | <.001 | 0.3 | 9.3 | <.001 |

Insertion of Penis (SEP 2)

| Study | Placebo (No. = 48) | Tadalafil 20 mg (No. = 159) | P value |
|-------|-------------------|-----------------------------|---------|
| Endpoint | | | |
| 39% | 62% | 43% | 77% |
| Change from baseline | | | |
| 2% | 26% | <.001 | 2% | 32% | <.001 |

Maintenance of Erection (SEP 3)

| Study | Placebo (No. = 49) | Tadalafil 20 mg (No. = 146) | P value | Placebo (No. = 48) | Tadalafil 20 mg (No. = 159) | P value |
|-------|-------------------|-----------------------------|---------|-------------------|-----------------------------|---------|
| Endpoint | | | | | | |
| 25% | 50% | 23% | 64% |
| Change from baseline | | | |
| 5% | 34% | <.001 | 4% | 44% | <.001 |

Data from Cialis™ prescribing information, Eli Lilly, November 2003.7 SEP = Sexual Encounter Profile.
The etiologic mechanisms were similar to those of the other group, and these patients also had various comorbid conditions. In the five trials, 5-, 10-, and 20-mg doses of tadalafil brought about statistically significant improvements (Tables 2 to 4).7 The Govier Study3

Govier et al. conducted a multicenter, randomized, double-blind, crossover study to compare patients’ preferences for tadalafil 20 mg or sildenafil 50 mg during the initial treatment of ED; 190 patients completed the study. The men were between 18 and 65 years of age. None of them had ever received tadalafil or sildenafil for ED or had undergone an inadequate trial of tadalafil at a maximum dose of 50 mg.3 After a treatment-free screening period of one week, patients were randomly assigned to the first week treatment period with tadalafil 20 mg or sildenafil 50 mg. After a one-week washout period following the first treatment, they were switched to the alternative treatment for the second four-week period.

After completing the second treat-

| Table 2 | Mean Endpoint and Change from Baseline for the Erectile Function Domain of the IIEF Questionnaire in the General Erectile Dysfunction Population in Five Primary Trials Outside the U.S. |
|---------|---------------------------------|
|         | Placebo | Tadalafil 5 mg | Tadalafil 10 mg | Tadalafil 20 mg |
| Study C | Endpoint (change from baseline) | 15.0 (0.7) | 17.9 (4.0) | 20 (5.6) |
|         |        |                |                |                |
|         |         |                |                |                |
| Study D | Endpoint (change from baseline) | 14.4 (1.1) | 17.5 (5.1) | 20.6 (6.0) |
|         |        |                |                |                |
| Study E | Endpoint (change from baseline) | 18.1 (2.6) | 22.6 (8.1) | 25 (8.0) |
|         |        |                |                |                |
| Study F* | Endpoint (change from baseline) | 12.7 (–1.6) | 22.8 (6.8) | 23.3 (8.0) |
|         |        |                |                |                |
| Study G | Endpoint (change from baseline) | 14.5 (–0.9) | 21.2 (6.6) | 23.3 (8.0) |
|         |        |                |                |                |

* Treatment duration in Study F was six months.
IIEF = International Index of Erectile Function.
Data from Cialis™ prescribing information, Eli Lilly, November 2003.7

| Table 3 | Mean Post-Baseline Success Rate and Change from Baseline for Sexual Encounter Profile Question 2* in the General Erectile Dysfunction Population in Five Trials Outside the U.S. |
|---------|---------------------------------|
|         | Placebo | Tadalafil 5 mg | Tadalafil 10 mg | Tadalafil 20 mg |
| Study C | Endpoint (change from baseline) | 49% (6%) | 57% (15%) | 73% (29%) |
|         |        |                |                |                |
| Study D | Endpoint (change from baseline) | 46% (2%) | 56% (18%) | 68% (15%) |
|         |        |                |                |                |
| Study E | Endpoint (change from baseline) | 55% (10%) | 77% (35%) | 85% (35%) |
|         |        |                |                |                |
| Study F† | Endpoint (change from baseline) | 42% (–8%) | 81% (27%) |                |
|         |        |                |                |                |
| Study G | Endpoint (change from baseline) | 45% (–6%) | 73% (21%) | 76% (21%) |
|         |        |                |                |                |

* The question was: “Were you able to insert your penis into your partner’s vagina?”
† The treatment duration in Study F was six months.
Data from Cialis™ prescribing information, Eli Lilly, November 2003.7
ment, the patients were asked: “Which treatment did you prefer?” Of the 190 patients, 66.3% preferred tadalafil 20 mg and 33.7% preferred sildenafil 50 mg.3

The Porst Study10

Porst and colleagues conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 348 men (average age, 57 years) in Europe and the U.S. to examine the therapeutic effects of tadalafil on ED at 24 and 36 hours after dosing.10 The participants were randomly assigned to two four-week treatment intervals, during which they were asked to attempt sexual intercourse approximately 24 and 36 hours after taking tadalafil 20 mg or placebo.

The main outcome measure was the number of successful sexual intercourse attempts (completed to ejaculation) according to the patients’ self-report using the SEP diary. At 24 hours, for the tadalafil group, 52.9% of intercourse attempts were successful; for the placebo group, 29.1% of attempts succeeded. At approximately 36 hours after treatment, the proportion of successful intercourse attempts for the tadalafil patients was 59.2%; it was 28.3% for the placebo patients.

The results indicate that tadalafil 20 mg is effective for ED, with a period of responsiveness of up to 36 hours (Table 5).10

ADVERSE DRUG REACTIONS

Tadalafil causes a variety of adverse reactions (Table 6). Nearly all patients in the clinical trials experienced one or more adverse events. The most commonly reported adverse reactions were headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and painful limbs.4,7,10

CONTRAINDICATIONS AND PRECAUTIONS

Coadministration of Nitrates and Alpha Blockers

Concomitant administration of tadalafil and organic nitrates, either regularly or intermittently, is contraindicated. Tadalafil exacerbates the hypotensive effect of nitrates in clinical studies, presumably as a result of the combined effects of both agents on the NO/cGMP pathway.7,9

Simultaneous administration of tadalafil and the alpha-adrenergic antagonists, except for 0.4 mg once-daily tamsulosin (Flomax®, Boehringer Ingelheim), is contraindicated. In a study of drug–drug interactions, 20 mg of tadalafil was administered to healthy subjects taking 8 mg of doxazosin mesylate (Cardura®, Pfizer) daily. A significant increase in the blood pressure–lowering effect of doxazosin was observed.7

Extended-Duration Erections and Priapism

In rare instances, PDE5 inhibitors have been associated with erections lasting longer than four hours and with priapism, a persistent abnormal penile erection, accompanied by pain and tenderness. If priapism is not treated in a timely manner, irreversible damage to the erectile tissue can occur. If an erection lasts more than four hours, whether

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**Table 4** Mean Post-Baseline Success Rate and Change from Baseline for Sexual Encounter Profile Question 3* in the General Erectile Dysfunction Population in Five Trials Outside the U.S.

| Placebo | Tadalafil 5 mg | Tadalafil 10 mg | Tadalafil 20 mg |
|---------|----------------|----------------|----------------|
| Study C | Endpoint (change from baseline) | 26% (4%) | 38% (19%) | 58% (32%) |
|         | P = .040       | P < .001      |                |
| Study D | Endpoint (change from baseline) | 28% (4%) | 42% (24%) | 51% (26%) |
|         | P = .001       | P < .001      |                |
| Study E | Endpoint (change from baseline) | 43% (15%) | 70% (48%) | 78% (50%) |
|         | P < .001       | P < .001      |                |
| Study F† | Endpoint (change from baseline) | 27% (1%) | 74% (40%) |                |
|         | P < .001       |                |                |
| Study G | Endpoint (change from baseline) | 32% (5%) | 57% (33%) | 62% (29%) |
|         | P < .001       | P < .001      |                |

* The question was: “Did your erection last long enough for you to have successful intercourse?”
† The treatment duration in Study F was six months.

Data from Cialis™ prescribing information, Eli Lilly, November 2003.7

**Table 5** Effects of Tadalafil on Successful Sexual Intercourse Completed at 24 and 36 Hours

| Placebo (n = 173) | Tadalafil (n = 175) |
|------------------|---------------------|
| **Time Point**   | **No. of Intercourse Attempts** | **No. of Successful Intercourse Attempts** | **No. of Patients Reporting Successful Intercourse** | **No. of Intercourse Attempts** | **No. of Successful Intercourse Attempts** | **No. of Patients Reporting Successful Intercourse** |
| 24 hours         | 247 | 72 (29.1) | 36.8% | 227 | 120 (52.9) | 60.9 |
| 36 hours         | 212 | 60 (28.3) | 35.2% | 223 | 132 (59.2) | 64.1 |

**Table 4** Mean Post-Baseline Success Rate and Change from Baseline for Sexual Encounter Profile Question 3* in the General Erectile Dysfunction Population in Five Trials Outside the U.S.

**Table 5** Effects of Tadalafil on Successful Sexual Intercourse Completed at 24 and 36 Hours
or not it is painful, the patient should seek emergency medical attention.7

Renal and Hepatic Disorders

Before prescribing tadalafil, health care providers should note any history or presence of renal insufficiency or hepatic impairment. For men with mild or moderate renal insufficiency, their tadalafil concentrations doubled. Following a single dose of 10 or 20 mg, men with end-stage renal disease who were undergoing hemodialysis experienced a 2.7-fold to 4.1-fold increase in area-under-the curve (AUC) concentration and a two-fold increase in maximum concentration. Several precautions apply:

- For patients with severe renal insufficiency or end-stage renal disease, the tadalafil dose should be limited to 5 mg no more than once daily.
- For patients with moderate renal insufficiency, a starting dose of 5 mg, taken not more than once daily, is recommended. The maximum dose should be 10 mg, to be taken not more than once in 48 hours.
- For patients with mild renal insufficiency, no dosage adjustment is required.7

For patients with severe hepatic impairment, tadalafil is not recommended because the data are insufficient.7

CONCLUSION

Tadalafil is the newest agent to be approved by the FDA for the treatment of ED. The recommended starting dose for most patients is 10 mg, to be taken before anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, depending on the agent’s efficacy and the patient’s tolerability. For most patients, the maximum dosing frequency is once a day.

Unlike other available treatments, tadalafil may enable a patient to take a pill on a Friday evening and have intercourse with his partner on a Saturday night or a Sunday morning. This extended period of responsiveness afforded by tadalafil may lead to a new treatment paradigm for men with ED.7,10

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Table 6  Frequency of Adverse Drug Events Reported by 2% or More of Patients Taking Tadalafil 5, 10, or 20 mg

| Adverse Event       | Placebo (No. = 476) | Tadalafil 5 mg (No. = 151) | Tadalafil 10 mg (No. = 394) | Tadalafil 20 mg (No. = 635) |
|---------------------|---------------------|-----------------------------|-----------------------------|-----------------------------|
| Headache            | 5%                  | 11%                         | 11%                         | 15%                         |
| Dyspepsia           | 1%                  | 4%                          | 8%                          | 10%                         |
| Back pain           | 3%                  | 3%                          | 5%                          | 6%                          |
| Myalgia             | 1%                  | 1%                          | 4%                          | 3%                          |
| Nasal congestion    | 1%                  | 2%                          | 3%                          | 3%                          |
| Flushing            | 1%                  | 2%                          | 3%                          | 3%                          |
| Pain in limb        | 1%                  | 1%                          | 3%                          | 3%                          |

Data from Cialis™ prescribing information, Eli Lilly, November 2003.7