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Sildenafil (Viagra) for treating male erectile dysfunction

ABSTRACT

Sildenafil, the first oral drug for treating male erectile dysfunction, appears effective and well tolerated. However, more time and experience will be needed to establish this drug's true efficacy and safety.

KEY POINTS

The usual dosage of sildenafil is 50 mg by mouth, 1 hour before initiating sexual activity.

Sildenafil is strictly contraindicated in patients using oral or transdermal nitrates, as it dangerously potentiates the hypotensive effects of these drugs.

Patients should understand that sildenafil only potentiates penile tumescence: it is not an aphrodisiac and does not produce instant erections.

SILDENAFIL CITRATE (Viagra) was recently approved by the Food and Drug Administration for treating male erectile dysfunction. The manufacturer, Pfizer Inc, is aggressively marketing the drug directly to patients, and media coverage has bordered on sensationalism.

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Not surprisingly, early sales have been outstanding. In fact, patients are aggressively demanding the drug from physicians in a frenzy never before seen with the release of a new medication.

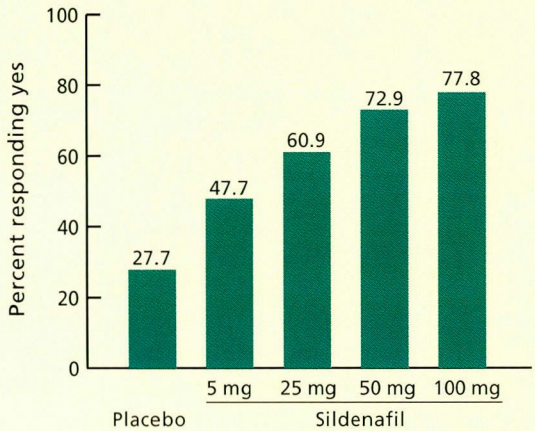
The sudden popularity of sildenafil may have taken many physicians by surprise. However, it remains incumbent upon the physician to perform a thorough history and physical examination before prescribing sildenafil, as well as to discuss realistic expectations of the drug's effectiveness with the patient.

This article reviews the pharmacology and use of sildenafil.

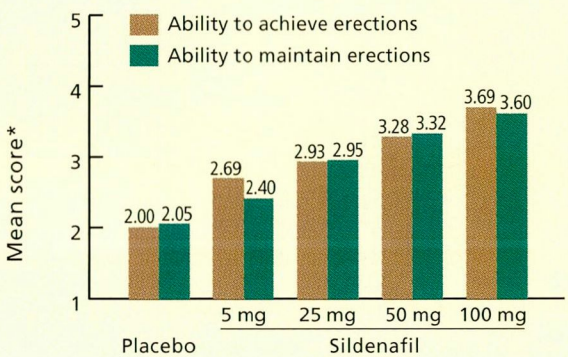
ERECTILE DYSFUNCTION IS COMMON

By one estimate, 52% of men between the ages of 40 and 70 have some impairment in erectile function.[1] Many treatments have been tried, including vacuum erection devices, prosthetic implants, and vasoactive drugs that are either injected into the corpus cavernosum or inserted into the urethra. Although these therapies can improve or restore erectile function, each of them either requires the use of mechanical devices or is invasive. Up to now, no oral medications for erectile dysfunction have been successful.

Did treatment improve your erections? Results of sildenafil in 416 men with erectile dysfunction



Did treatment improve your ability to achieve or maintain erections?



*1 = never or almost never; 5 = almost always or always

SOURCE: DATA FROM LUE ET AL, REFERENCE 4

FIGURE 1

PHYSIOLOGY OF ERECTIONS AND SILDENAFIL ACTION

In its flaccid state the penis receives minimal blood flow. Smooth muscle cells within the paired corpora cavernosa—the erectile chambers of the penis—are normally in a contracted state under sympathetic nervous system control. Sexual arousal stimulates the parasympathetic nervous system, which initiates relaxation of smooth muscle cells in the corpora cavernosa and arteries. The rapid increase in arterial blood flow to the penis fills the spongy tissue within the corpora cavernosa, leading to penile tumescence. Full rigidity occurs and is maintained when veins exiting the corpora are compressed, limiting outward blood flow.

At a molecular level, nitric oxide released by neurons is the mediator of smooth muscle relaxation.[2] Nitric oxide (NO) diffuses into smooth muscle cells, where it activates the guanylate cyclase enzyme. This increases the intracellular level of cyclic guanosine monophosphate (cGMP), and smooth muscle relaxation ensues. Thus, the neuronal NO-cGMP system is the main mechanism for corporal smooth muscle relaxation and development of an erection.

The erection subsides when phosphodiesterase (PDE) enzymes catalyze the breakdown of cGMP (SEE HOW SILFENADIL POTENTIATES ERECTIONS). One of the PDE enzymes, PDE5, is the active isoenzyme involved in the metabolism of cGMP in the penis. Sildenafil citrate is a selective inhibitor of PDE5. By inhibiting cGMP breakdown in a dose-dependent fashion in penile smooth muscle, sildenafil has been shown in vitro to potentiate the natural process leading to penile erection.[3]

CLINICAL TRIALS WITH SILDENAFIL

In trials to date, sildenafil appeared to be effective and well-tolerated and had few significant side effects or drug interactions. The true efficacy and safety of the drug, however, will not be completely known until it is on the market for 6 months to a year.

Short-term study

In a double-blind study, Lue et al[4] gave sildenafil in various doses or placebo to 416 patients with erectile dysfunction. The etiology of the dysfunction was organic in 73% of the patients, psychogenic in 9%, and mixed in 18%.

At the end of 8 weeks of treatment, patients answered a questionnaire. Asked if their erections had improved, significantly more men receiving sildenafil at any dose answered yes than did men receiving placebo ($P < .0001$). Further, response to the drug increased with dose (FIGURE 1).

The men responded similarly when asked

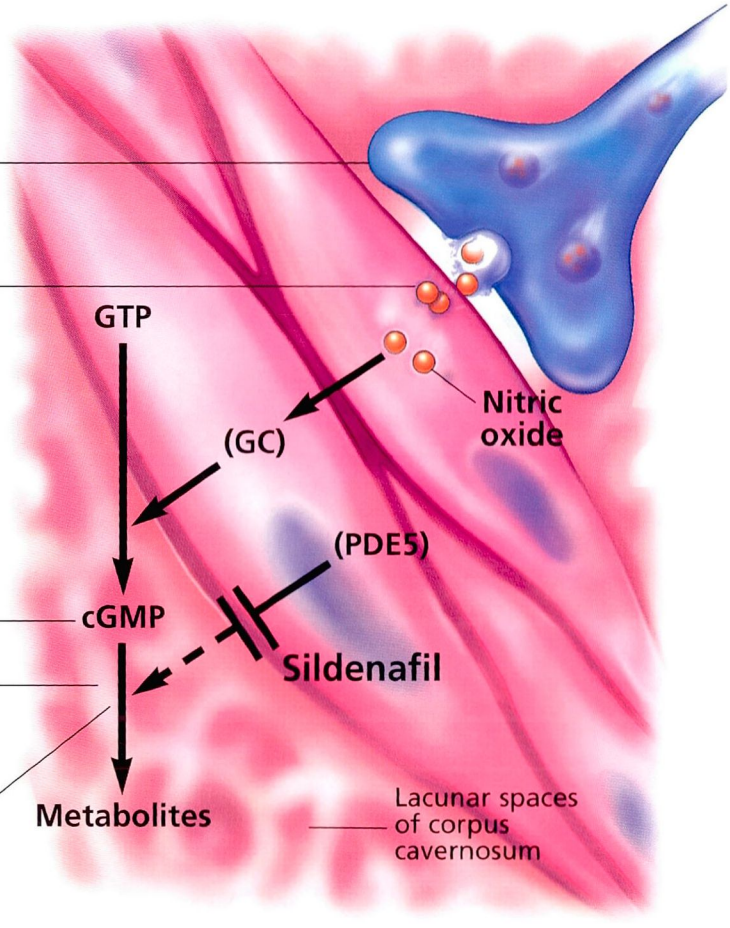
How sildenafil potentiates erections

PARASYMPATHETIC NERVE FIBERS, in response to sexual stimulation, release nitric oxide, which diffuses into smooth muscle cells in the corpus cavernosum.

NITRIC OXIDE activates the enzyme guanylate cyclase (GC), which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP).

CYCLIC GUANOSINE MONOPHOSPHATE (cGMP) causes smooth muscle fibers to relax; this relaxation allows arterial blood to flow into the corpus cavernosum.

PHOSPHODIESTERASE 5 (PDE5) breaks down cGMP into inactive products, causing smooth muscle cells to resume their usual contracted state.



SILDENAFIL blocks the action of PDE5, allowing cGMP to accumulate and potentiating and maintaining penile erections.

to grade their ability to achieve and maintain an erection on a scale of 1 to 5, in which 1 represented "never or almost never", and 5 represented "always or almost always" (FIGURE 1). Again, all differences were statistically significant from placebo ($P < .0001$).

Adverse effects were few and mild, and included:

- Headaches (reported by up to 11% of the men)
- Vasodilation (8.5%)
- Dyspepsia (8.5%)
- Diarrhea (4.9%)
- Visual disturbances (a blue tinge to vision, sensitivity to bright light, and blurred vision, all mild and transient, experienced by a few patients).

The authors concluded that sildenafil is an effective and well-tolerated treatment for erectile dysfunction of different etiologies.

Long-term study

Buvat et al[5] recently reported on the results of a 1-year open-label extension study using sildenafil in 317 patients with erectile dysfunction of no known organic cause. They found that 271 patients (87.1%) continued to benefit from taking sildenafil after 1 year.

Only 13 patients (4.2%) withdrew from the study because of lack of drug efficacy, and only 3 patients (1%) had adverse events attributable to sildenafil; these included headache, facial flushing, and indigestion.

WHO WILL BENEFIT FROM SILDENAFIL?

Given the limited data from clinical trials, few conclusions can be reached regarding the effectiveness of treatment of specific causes of erectile dysfunction. Generally, patients with psychogenic erectile dysfunction or those with mild organic causes are most likely to benefit from sildenafil. The drug may not be as effective in patients with diabetes, peripheral vascular disease, or pelvic surgery.

Patients should undergo a complete history and physical examination. A sexual history should also be obtained. Routine laboratory testing should include a serum testosterone level.

CONTRAINDICATED WITH NITRATES

Sildenafil is strictly contraindicated in patients using oral or transdermal nitrates, as it dangerously potentiates the hypotensive effect of these drugs.

Sildenafil is not an aphrodisiac

DOSAGE AND USE

To allow time for absorption, patients should take sildenafil 1 hour before initiating sexual activity. Sexual stimulation is then required for onset of action. The drug is not an aphrodisiac, nor does it initiate a rapid-onset erection as is achieved with a pharmacological injection. Sildenafil can be effective for up to 4 hours after it is ingested.

The usual dosage is 50 mg by mouth, which can be increased to a maximum of 100 mg or decreased to 25 mg depending on clinical response and adverse effects. Patients with cirrhosis or severe renal insufficiency should start at a 25 mg dose.

Sildenafil is expensive: approximately $8 to $10 per pill. Therefore, I recommend that the patient try 50 mg for three doses. If he cannot achieve an erection sufficient for intercourse at this dose, then he should try 100 mg for three doses. If the patient is still unable to achieve intercourse while being treated with sildenafil, he should explore other treatment options with his physician.

The manufacturer currently does not recommend the use of sildenafil together with any other form of pharmacological treatment for erectile dysfunction. However, as physicians learn about the efficacy of the drug and its limitations, sildenafil may eventually be used as an adjunct to improve the effects of other forms of therapy in patients whose erectile dysfunction is difficult to treat.

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