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# Management of erectile dysfunction by the primary care physician

## ABSTRACT

Erectile dysfunction is common and closely associated with age and risk factors for cardiovascular disease. The oral selective inhibitors of phosphodiesterase type 5 (PDE5) have become the treatments of choice, owing to their convenience, general safety, and broad-spectrum effectiveness. For the same reasons, they have greatly simplified the workup. Thus, the general practitioner has gradually replaced the urologist for the initial management of erectile dysfunction and the proper evaluation of cardiac status before starting treatment with the PDE5 inhibitors. The following review provides a practical approach for the management of erectile dysfunction in primary care.

## KEY POINTS

The initial workup for erectile dysfunction is simple and includes assessment of cardiac risk factors and measurement of serum testosterone.

The main contraindications to PDE5 inhibitors include hypotension, concomitant use of any form of nitrates, and decompensated cardiac disease. The use of alpha-blockers other than tamsulosin (Flomax) 0.4 mg daily is contraindicated with tadalafil (Cialis), and all alpha blockers are contraindicated with vardenafil (Levitra).

To obtain an optimal response, patient should be adequately informed of the proper use, precautions, and adverse effects of PDE5 inhibitors.

ALTHOUGH EFFECTIVE THERAPY for erectile dysfunction was available before 1998, it involved intracavernous injection[1] or intraurethral application of vasodilators such as alprostadil (prostaglandin E1).[2] These invasive treatments were associated with high drop-out rates.[3] Moreover, they required evaluation and training by a urologist.

Then, in March 1998, sildenafil (Viagra) became available, followed by vardenafil (Levitra) in August 2003 and tadalafil (Cialis) in November 2003. These effective oral agents have revolutionized this area of medicine.

While the efficacy of these drugs, which inhibit phosphodiesterase type 5 (PDE5), may vary somewhat depending on the population studied, the response is generally satisfactory irrespective of the underlying condition causing erectile dysfunction, the patient's age, or the severity or duration of erectile dysfunction.[4] Therefore, the initial workup to identify the specific cause of erectile dysfunction has been significantly reduced.

In addition, one concern about therapy with PDE5 inhibitors—their safety in patients with cardiac risk factors—can be appropriately addressed by the primary care physician and medical specialist. In fact, the main conditions associated with erectile dysfunction are essentially the same as cardiac risk factors, ie, medical and not surgical causes.[5]

Hence, the management of erectile dysfunction has undergone a major shift to become the responsibility of the primary care physician, whereas the role of the urologist has become limited to cases in which oral therapy has failed or surgery is required. Now, sildenafil is more frequently prescribed by general practitioners than by urologists.[6]

**TABLE 1**

## Sexual health inventory for men

Circle the number of the response that best describes your own situation. Please select one and only one response for each question.

**Over the past 6 months:**

**1 How do you rate your confidence that you could get and keep an erection?**
Very low = 1
Low = 2
Moderate = 3
High = 4
Very high = 5

**2 When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?**
No sexual activity = 0
Almost never or never = 1
A few times (much less than half the time) = 2
Sometimes (about half the time) = 3
Most times (much more than half the time) = 4
Almost always or always = 5

**3 During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?**
Did not attempt intercourse = 0
Almost never or never = 1
A few times (much less than half the time) = 2
Sometimes (about half the time) = 3
Most times (much more than half the time) = 4
Almost always or always = 5

**4 During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?**
Did not attempt intercourse = 0
Extremely difficult = 1
Very difficult = 2
Difficult = 3
Slightly difficult = 4
Not difficult = 5

**5 When you attempted sexual intercourse, how often was it satisfactory for you?**
Did not attempt intercourse = 0
Almost never or never = 1
A few times (much less than half the time) = 2
Sometimes (about half the time) = 3
Most times (much more than half the time) = 4
Almost always or always = 5

**Add the numbers** corresponding to questions 1–5. If your score is 21 or less, you may be showing signs of erectile dysfunction and may want to speak with your doctor.

**Score:**_____

FROM ROSEN RC, CAPPELLERI JC, SMITH MD, LIPSKY J, PENA BN. DEVELOPMENT AND EVALUATION OF AN ABRIDGED 5-ITEM VERSION OF THE INTERNATIONAL INDEX OF ERECTILE DYSFUNCTION (IIEF-5) AS A DIAGNOSTIC TOOL FOR ERECTILE DYSFUNCTION. J IMPOT RES 1999; 11:319-326.

Furthermore, from 1998 through 2001, the estimated number of prescriptions for sildenafil increased by 87%, whereas those for penile injections of alprostadil decreased by 33% and those for urethral suppositories decreased by 67%.[6]

## DEFINITION AND PREVALENCE

Erectile dysfunction, as defined by a National Institutes of Health Consensus Development Conference, is the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance.[7]

Epidemiologic studies have shown that erectile dysfunction affects a substantial proportion of men, with prevalence rates increasing with aging. The Massachusetts Male Aging Study included 1,290 men 40 to 70 years old who responded to a self-administered sexual activity questionnaire; the prevalence of self-reported erectile dysfunction of all degrees was 52%. The probability of complete erectile dysfunction tripled from 5.1% to 15% between the ages of 40 and 70 years, while the probability of moderate erectile dysfunction doubled from 17% to 34%.[5]

Although erectile dysfunction is common, it is underreported, mainly due to patient embarrassment.[7] Physicians may overlook it, owing to various reasons such as lack of time, unwillingness to embarrass patients, or unfamiliarity with its management. In one telephone survey, 71% of responders said their doctors would dismiss any concerns about sexual problems they may bring up.[8]

## INITIAL EVALUATION OF ERECTILE DYSFUNCTION

Primary care physicians should take the initiative and ask patients about sexual function.

A useful tool to diagnose and evaluate the severity of erectile dysfunction is the Sexual Health Inventory for Men (TABLE 1), an abridged, five-item version of the International Index of Erectile Function.[9] Patients can respond to the questionnaire without pressure or embarrassment at home or in the waiting room.

The most common disorders associated with erectile dysfunction are hypertension,

TABLE 2

**Initial evaluation of erectile dysfunction**

**History**
- Hypertension
- Diabetes mellitus
- Hyperlipidemia
- Smoking
- Alcohol, substance abuse
- Drugs (most common: diuretics, beta-adrenergic blockers, digoxin, spironolactone, cimetidine, antidepressants)
- Depression, anxiety
- Hypogonadism
- Thyroid dysfunction
- Uremia
- Pelvic surgery or trauma
- Partner problems
- Libido
- Nocturnal erection

**Physical examination**
- Blood pressure
- Cardiac, thyroid, testicular, prostate examination
- Penile anatomical abnormalities
- Gynecomastia

**Laboratory tests**
- Fasting glucose
- Fasting lipid profile
- Blood chemistry
- Serum testosterone (preferably free or bioavailable testosterone)*
- Hemogram
- Electrocardiogram

**Exercise treadmill test** (if cardiac risk factors are present)†

*Serum prolactin and gonadotrophins are measured when free or bioavailable testosterone levels are low.
†Many physicians prefer prescribing an exercise treadmill test even in absence of known cardiac risk factors (see text).

diabetes mellitus, hyperlipidemia, and smoking.[5] Therefore, it is of utmost importance to carefully screen for these cardiac risk factors in any patient presenting with erectile dysfunction.

**The history** should address symptoms of cardiac disease, cardiovascular risk factors, pelvic surgery, medications, depression, partner problems, and other problems of sexual dysfunction such as decreased libido and premature ejaculation. Frequently, the etiology is multifactorial.

**The physical examination** should focus on the cardiovascular system, evidence of hypogonadism, and abnormalities of the thyroid, penis, and prostate (TABLE 2).

**Initial laboratory tests** are simple and routinely ordered by the primary care physician for screening or follow-up purposes.

The only additional test is serum testosterone. However, hypogonadism is not commonly associated with erectile dysfunction (being present in about 6% of cases).[10] Although the role of testosterone in erection is unclear, its positive effect on libido in hypogonadal men may help the initiation of the sexual act.

A meta-analysis showed that testosterone supplementation in hypogonadal men may be superior to placebo in improving erection (the mean response rates to testosterone and placebo were 65.4 and 16.7%, respectively).[11] In addition, a recent trial demonstrated that a 1-month treatment with transdermal testosterone improved the erectile response to sildenafil in men with low-normal testosterone levels.[12]

Free or bioavailable testosterone assays are preferred over measurement of the total testosterone level because sex hormone-binding globulin increases with age. Obtaining several morning samples or pooling of multiple samples is advisable owing to the diurnal variation of testosterone secretion.

Because hyperprolactinemia is present in fewer than 2% of men with erectile dysfunction,[10] the routine measurement of serum prolactin is not recommended. However, serum levels of prolactin and gonadotrophins should be measured if serum testosterone levels are low, to clarify the cause of hypogonadism.

## PDE5 INHIBITORS ARE THE TREATMENTS OF CHOICE

In many cases, erectile dysfunction persists or only partially improves despite treatment of the apparent cause. Therefore, other therapies are needed. Selective inhibitors of PDE5 are currently the treatments of choice, owing to their general efficacy, safety, convenience, and physiologic mechanism of action.

### PDE5 inhibitors prolong the action of the vasodilator cGMP

The PDEs comprise 11 distinct families of enzymes (PDE1–PDE11). PDE5 is present in high concentrations in the smooth muscles of the corpus cavernosum of the penis.[13]

Normally, sexual stimuli result in the release of the vasodilator nitric oxide from nonadrenergic noncholinergic nerve fibers in the penile cavernous tissue and from the endothelial cells of the penile arterioles.[14] Nitric oxide activates the enzyme guanylyl cyclase, resulting in generation of the second messenger, cyclic guanosine monophosphate (cGMP). Then, cGMP decreases calcium uptake into cavernosal and vascular smooth muscle, leading to dilation of cavernosal sinusoids and penile erection. Subsequently, degradation of cGMP by PDE5 leads to loss of arteriolar dilation and penile detumescence.[14] Thus, inhibition of PDE5 facilitates erection as result of the prolongation of cGMP action.

As expected from their mechanism of action, PDE5 inhibitors do not affect libido and do require sexual stimulation to exert their effect, a fact that should be clarified to patients prior to their use. In one study, absence of sexual stimulation was the commonest cause of sildenafil failure, reported by one third of patients who did not respond to the drug.[15]

## EFFICACY OF PDE5 INHIBITORS

Sildenafil, the first PDE5 inhibitor approved by the US Food and Drug Administration (FDA) for treatment of erectile dysfunction, has been more extensively studied than vardenafil[16] or tadalafil.[17]

In the largest study evaluating sildenafil,[4] 69% of all attempts of sexual intercourse were successful for the men receiving sildenafil compared with 22% for those receiving placebo. Moreover, efficacy was dose-related: improved erection was reported by 25% of men taking placebo, 56% of men taking sildenafil 25 mg, 77% of those taking 50 mg, and 84% of those taking 100 mg.[4]

In a meta-analysis of 27 randomized trials, mean rates of successful sexual intercourse were 57% in sildenafil recipients and 21% in placebo recipients.[18] The response rates to sildenafil may be somewhat lower in men older than 65 years, in patients with diabetes, after radical prostatectomy, and in patients with severe erectile dysfunction at baseline.[18]

Although there are no head-to-head trials to compare the three PDE5 inhibitors, available data suggest that they generally have similar efficacy.

## ADVERSE EFFECTS OF PDE5 INHIBITORS

Overall, adverse effects of PDE5 inhibitors are mild, transient, and dose-related. The most commonly reported adverse effects are:

- Headache (reported by 10% to 30% of patients)
- Flushing (10%–20%)
- Dyspepsia (3%–16%)
- Rhinitis (1%–11%)
- Changes in color perception (2%–10%)
- Myalgia and back pain (0%–10%)
- Dizziness (0%–5%)
- Priapism, ie, erection lasting more than 6 hours (rare).

The undesirable effects are mainly due to two limitations of PDE5 inhibitors.

**Available PDE5 inhibitors all have similar efficacy**

First, PDE5 is widely distributed in other tissues in addition to the penis, and inhibition of PDE5 in these tissues can lead to various systemic symptoms. For example, inhibition of PDE5 in the peripheral arterioles and veins may result in vasodilation and a drop in blood pressure, whereas inhibition of PDE5 in the esophagus may lead to dyspepsia. However, the cause of back pain and myalgia, which may be somewhat more reported with tadalafil, is less clear.

Second, the PDE5 inhibitors are not absolutely selective for PDE5; they can also inhibit other types of PDEs, albeit with much less affinity. For instance, visual changes are due to inhibition of PDE type 6 (PDE6) located in the rods and cones of the retina.[13]

## DRUG INTERACTIONS WITH PDE5 INHIBITORS

### Nitrates

The PDE5 inhibitors potentiate the hypotensive effect of nitrates. Nitrates lead to the for-

mation of nitric oxide, which interacts with and activates guanylyl cyclase. The latter increases the synthesis of cGMP in smooth muscles, resulting in vasodilation.

Since PDE5 inhibitors prolong cGMP action, concomitant use of PDE5 inhibitors and nitrates can result in excessive hypotension and even death, and this combination is absolutely contraindicated.[19–21]

### Alpha-adrenergic blockers

The coadministration of sildenafil and antihypertensive agents appears to be generally safe. Post hoc analysis of 18 randomized trials did not show a difference in adverse effects, including those potentially related to hypotension, between sildenafil-treated men receiving one or more antihypertensive medication and sildenafil-treated men not taking antihypertensive agents.[22]

However, when sildenafil in doses higher than 25 mg was taken simultaneously with doxazosin 4 mg, there were some reports of postural hypotension within 4 hours of dosing.[19] Therefore, the manufacturer recommends that doses of 50 mg or 100 mg of sildenafil not be taken within 4 hours of an alpha-blocker, but the 25-mg dose may be taken at any time.[19]

Vardenafil use is contraindicated in conjunction with alpha-blockers because the combination can produce severe hypotension.[20] Likewise, all alpha-blockers are contraindicated with tadalafil except tamsulosin 0.4 mg once daily.[21]

### Inhibitors of cytochrome P450 CYP3A4

The three PDE5 inhibitors are metabolized in the liver mainly by cytochrome P450 CYP3A4. Therefore, their concomitant use with P450 CYP3A4 inhibitors may increase their plasma levels.[19–21] Such inhibitors include:

- Protease inhibitors
- Erythromycin
- Ketoconazole
- Itraconazole
- Cimetidine.

Small doses of sildenafil (≤ 25 mg daily), vardenafil (≤ 5 mg daily), and tadalafil (≤ 10 mg every 72 hours) are recommended when used in conjunction with the above agents.[19–21] However, the highly potent protease inhibitor ritonavir increases sildenafil's area under the plasma concentration-time curve 11-fold and its maximum plasma concentration 3.9-fold.[23] Corresponding values with vardenafil are even higher, 49-fold and 13-fold, respectively.[20]

Therefore, I strongly discourage the concomitant use of sildenafil or vardenafil with ritonavir. If it is absolutely necessary, small doses (≤ 25 mg of sildenafil over 48 hours or ≤ 2.5 mg of vardenafil over 72 hours) can be used as suggested in the prescribing information.[19,20]

Tadalafil seems to have the least interaction with ritonavir, with a modest (124%) increase in tadalafil's area under the curve and no change in its maximum concentration.[21]

Maximum plasma levels of ritonavir and indinavir are decreased with the concomitant administration of vardenafil (by 20% and 40%, respectively),[20] whereas sildenafil has no effects on the pharmacokinetics of ritonavir and saquinavir. (Sildenafil's effects on the pharmacokinetics of indinavir were not reported.)[19]

### Inducers of cytochrome P450 CYP3A4

**I strongly discourage the use of sildenafil or vardenafil with ritonavir**

Drugs that induce P450 CYP3A4, such as rifampin, carbamazepine, and phenytoin, are expected to decrease plasma levels of PDE5 inhibitors and probably their effectiveness as well. Rifampin 600 mg daily reduced the area under the curve of tadalafil 10 mg by 88% and its maximum concentration by 46%.[21] There are no available data on the interactions of other PDE inhibitors with cytochrome P450 CYP3A4 inducers, but the tadalafil manufacturer does not recommend changing tadalafil dosage in this setting.[21]

### Drugs that prolong the QT interval

One study suggested that vardenafil could prolong the QT interval,[20] a condition that can potentially predispose to fatal ventricular arrhythmias (torsade de pointes). Therefore, vardenafil must be avoided in conditions associated with prolonged QT intervals, such as use of class Ia antiarrhythmic drugs (eg, quinidine, procainamide), class III drugs (eg, amiodarone, sotalol), or cases of congenital QT prolongation.[20]

**TABLE 3**

**Drug interactions with PDE5 inhibitors**

**Nitrates:** absolutely contraindicated with all PDE5 inhibitors

**Alpha-blockers:** contraindicated with tadalafil (except tamsulosin) and vardenafil

**Drugs that prolong the QT interval** (class IA and III antiarrhythmic drugs) should be avoided with vardenafil

**Drugs that increase plasma levels of PDE5 inhibitors** (cytochrome P450 CYP3A4 inhibitors)
- Protease inhibitors (particularly ritonavir)
- Ketoconazole, itraconazole
- Erythromycin
- Cimetidine

**Drugs that are expected to decrease plasma levels of PDE5 inhibitors** (cytochrome P450 CYP3A4 inducers)
- Phenytoin
- Rifampin
- Phenobarbitol
- Carbamazepine

Drug interactions with PDE5 inhibitors are summarized in TABLE 3.

**Many experts consider erectile dysfunction a marker of generalized vascular disease**

## CONDITIONS IN WHICH DOSES OF PDE5 INHIBITORS SHOULD BE DECREASED

Conditions that may result in increased plasma levels of PDE5 inhibitors include[19,20]:
- Age above 65 years
- Hepatic insufficiency
- Severe renal insufficiency (creatinine clearance < 30 mL/minute).

In these conditions, small starting doses (sildenafil 25 mg or vardenafil 5 or 10 mg) are recommended.[19,20] However, no dose adjustment is recommended when tadalafil is used in the elderly.[21] Sildenafil 25 or 50 mg was evaluated in small, non-placebo-controlled trials of patients on hemodialysis and peritoneal dialysis, with overall satisfactory efficacy and safety.[24]

## ERECTILE DYSFUNCTION AS A MARKER OF GENERALIZED VASCULAR DISEASE

Because most cases of erectile dysfunction are closely associated with cardiovascular risk factors,[5] many investigators consider it a marker of generalized vascular disease.[25]

A hypothetical link between erectile dysfunction and cardiovascular disease is endothelial dysfunction.[25] Indeed, cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and smoking are all associated with endothelial dysfunction, which could also lead to impairment of vasodilation and subsequent penile erection as a result of decreased nitric oxide production or through other unclear mechanisms.

In one study, diabetic patients with erectile dysfunction exhibited abnormal blood-pressure and platelet-aggregation responses suggestive of endothelial dysfunction compared with diabetic patients without erectile dysfunction.[26] Endothelial integrity in patients with erectile dysfunction of various etiologies deserves further investigation.

## CARDIOVASCULAR SAFETY OF PDE5 INHIBITORS

In the post-marketing period, more than 500 deaths and many cases of acute myocardial infarction were reported in relation to sildenafil.[27] However, it was not clear whether these events were caused by the drug per se, its improper use, cardiovascular risk factors that frequently coexist in patients with erectile dysfunction, the stress of sexual intercourse, or a combination of these factors.

Multiple careful but single-dose studies[28,29] showed no evidence that sildenafil caused cardiac ischemia or arrhythmias. However, it is possible that the hypotensive effects of sildenafil and other selective PDE5 inhibitors could precipitate a cardiac event in a patient with poor cardiac functional reserve or occult coronary artery disease. In fact, hemodynamic studies demonstrated a slight (< 10%) but statistically significant decrease in average blood pressure following a single dose of sildenafil, with relatively wide variation in blood pressure response.[28] Furthermore, at least one case of acute myocardial infarction was documented in a man with no known history of cardiac disease shortly after receiving a single 50-mg dose of sildenafil before starting sexual intercourse.[30]

Unfortunately, few studies have examined the safety of PDE5 inhibitors in cardiac

patients. In a 12-week crossover trial of 35 patients with New York Heart Association classes II and III congestive heart failure, Webster et al[31] reported similar adverse events after sildenafil 50 mg compared with placebo. DeBusk et al[32] studied the safety of sildenafil (in maximum doses in most patients) in men with stable coronary artery disease. Worsening of the angina score occurred in 3 of 70 patients in the sildenafil group and 2 of 72 patients in the control group.

Of note: patients with blood pressure higher than 170/110 mm Hg, myocardial infarction, stroke, or life-threatening arrhythmias within the last 6 months have been excluded from trials of PDE5 inhibitors. Thus, great caution must be exercised before prescribing PDE5 inhibitors in these situations. Likewise, PDE5 inhibitors should be prescribed very cautiously in patients with left ventricular outflow obstruction (eg, aortic stenosis, hypertrophic cardiomyopathy) because subsequent vasodilation can increase the outflow obstruction.[33]

In view of these findings, cardiac status should be thoroughly evaluated in all patients with erectile dysfunction before starting a PDE5 inhibitor.

## Cardiac risk stratification is essential before starting PDE5 inhibitors

Guidelines, based mostly on expert opinions rather than clinical evidence, categorize patients as being at low, medium, or high risk, according to the severity of cardiovascular disease.[34]

**Low-risk patients** (eg, with no symptoms of cardiac disease, with controlled hypertension, or with mild stable angina) can engage in sexual intercourse and can receive a PDE5 inhibitor in the primary care setting.

**High-risk patients** (eg, with unstable angina, severe heart failure, valvular disease, uncontrolled hypertension, or myocardial infarction within 14 days) should defer sexual activity and erectile dysfunction treatment until the cardiac condition is stabilized.

**Patients at intermediate risk** have cardiac disease whose severity lies between the previous two categories. In these patients, noninvasive cardiac evaluation such as the exercise treadmill test may be useful to reclassify them as being at high or low risk.[35] However, many physicians prefer to order an exercise treadmill test before prescribing a PDE5 inhibitor even in patients without obvious cardiac risk factors based on the assumption that erectile dysfunction per se could be a marker of an occult cardiovascular disease.

In fact, the exercise treadmill test was shown to be a good predictor of cardiac ischemia during sexual intercourse in patients with known coronary artery disease. In a study by Drory et al[36] that included 88 subjects with stable coronary artery disease, all patients who had ischemia during coitus also demonstrated ischemia during exercise treadmill testing. Conversely, none of the patients who did not exhibit ischemia at the exercise treadmill test had ischemia during intercourse.

Earlier studies[37] showed that energy expenditure during sexual intercourse is 3.5 to 5.5 METs. Accordingly, if a patient can perform 5.5 METs or more on exercise treadmill testing, it is probably safe to start the smallest dose of a PDE5 inhibitor and let him resume sexual intercourse.

Data from the Determinants of Myocardial Infarction Onset Study,[38] based on interviewing patients with recent myocardial infarction, suggest that sexual activity may approximately double the risk of myocardial infarction (relative risk 2.5). However, the absolute risk was low. For instance, it was estimated that for a man free of coronary artery disease, weekly sexual activity would increase his annual risk of myocardial infarction from 1% to only 1.01%. Interestingly, the same study showed that the risk of myocardial infarction triggered by sexual activity was not increased further by prior history of myocardial infarction (relative risk 2.9), but significantly decreased by regular exercise (relative risk 1.2).

**Exercise treadmill testing may be a good predictor of cardiac ischemia during sexual intercourse**

## When to refer to the cardiologist

Cardiology consultation will be of great value to assist the primary care physician in the following settings:

- In most high-risk patients, in order to optimize therapy and stabilize cardiac condition.
- In patients who require specialized cardiac testing when the interpretation of the exercise treadmill test is difficult, eg, in the presence of atrial fibrillation or left bundle branch block.
- When there is any doubt about the car-

TABLE 4

**Instructions to patients regarding the proper use of PDE5 inhibitors**

| |
|---|
| Take the drug about 1 hour before the anticipated sexual intercourse. |
| Fatty meals delay the onset of action of sildenafil (Viagra) by about 1 hour. Food intake does not have a major effect on the action of vardenafil (Levitra) or tadalafil (Cialis). |
| The starting dose depends on your age and other conditions, and should be determined by your doctor. |
| Do not take the drug more than once a day. |
| The drug has no effect on libido, and sexual stimulation is necessary for erection to occur. |
| The drug does not offer protection against sexually transmitted diseases. |
| Allow 6 to 8 attempts before concluding the drug has failed. |
| Inform your doctor(s) about all medications you receive to avoid drug interactions. |
| The drug should not be taken with any form of nitrates, including amyl nitrate "poppers." |
| Adverse effects are usually mild. Possible effects include flushing, headache, nasal congestion, dyspepsia (gastric upset), visual changes, and muscular and back pain. |
| Stop taking the drug and inform your physician if you experience dizziness, chest pain, shortness of breath, prolonged erection (more than 4 hours), or any serious adverse effect that may be related to the drug. |

diac condition with respect to resumption of sexual intercourse or treatment with PDE5 inhibitors.

**A low affinity of tadalafil and vardenafil for PDE6 should mean fewer or no ocular adverse effects**

## CONTRAINDICATIONS TO PDE5 INHIBITORS

The concomitant use of PDE5 inhibitors and any form of nitrate, eg, amyl nitrate or nitrite abused under the name of "poppers," is contraindicated.

In addition, the use of alpha-blockers is contraindicated with vardenafil and tadalafil. However, tamsulosin 0.4 mg once daily is not contraindicated with tadalafil.[21]

In patients with baseline hypotension (blood pressure < 90/50 mm Hg), PDE5 inhibitors can further lower blood pressure to detrimental levels, and they should never be used in this setting.

In addition, men who are not candidates for sexual intercourse due to severe underlying cardiac disease are also not candidates for PDE5 inhibitors.[34]

Patients with known hereditary disorders of the retina including retinitis pigmentosa were excluded from clinical trials, and the use of PDE5 inhibitors is not recommended in those patients until further data are available.[19–21]

## DIFFERENCES AMONG PDE5 INHIBITORS

Available data suggest that the three available PDE5 inhibitors have generally similar efficacy, precautions, and drug interactions. However, some important differences exist.

Tadalafil and vardenafil have low affinity for the retinal isoenzyme PDE6. This finding was demonstrated in vitro; if reproduced in vivo, it should translate into fewer or no ocular adverse effects. In fact, in a pooled analysis of more than 1,000 patients treated with tadalafil, only one case of visual disturbance was reported.[17] On the other hand, tadalafil has greater affinity for PDE11, a widely distributed isoenzyme with unknown functions.

Another important difference is their duration of action: sildenafil and vardenafil have terminal plasma half-lives of about 4 hours, vs 17.5 hours for tadalafil. Indeed,

**TABLE 5**

## Differences among the three PDE5 inhibitors used for erectile dysfunction

**Sildenafil** (Viagra)
Initial dose: 50 mg, titrated up to 100 mg or down to 25 mg based on efficacy and tolerability, no more than once daily
Mean terminal half-life: about 4 hours
Duration of action: up to 4 hours
Selectivity: 10-fold more potent for PDE5 than for PDE6 (present in the retina); more than 700-fold more potent for PDE5 than for PDE11
Use with alpha-blockers: 50-mg or 100-mg doses should not be taken within 4 hours of alpha-blocker administration; a 25-mg dose may be taken at any time
Use with congenital or acquired QT prolongation or with class Ia or III antiarrhythmic drugs: no special precautions
Use in renal insufficiency: dose decreased to 25 mg not more than once daily in severe renal failure (creatinine clearance < 30 mL/minute); limited experience in patients on hemodialysis
Use in age > 65 years: initial dose decreased to 25 mg
Effect of food: high-fat meals decrease maximum plasma concentration by 29% and delay time to maximum plasma concentration by 60 minutes
Effect of alcohol: sildenafil 50 mg did not potentiate the hypotensive effect of alcohol, with mean maximum blood alcohol level of 0.08%

**Vardenafil** (Levitra)
Initial dose: 10 mg titrated up to 20 mg or down to 5 mg based on efficacy and tolerability, no more than once daily
Mean terminal half-life: about 4 hours
Duration of action: up to 4 hours
Selectivity: 15-fold more potent for PDE5 than for PDE6; more than 300-fold more potent for PDE5 than for PDE11
Use with alpha-blockers: contraindicated
Use with QT prolongation or with class Ia or III antiarrhythmic drugs: should be avoided
Use in renal insufficiency: no dose adjustment recommended; not yet evaluated in patients on dialysis
Use in age > 65 years: initial dose decreased to 5 mg
Effect of food: high-fat meals decrease maximum plasma concentration by 18% to 50%; can be taken with or without food
Effect of alcohol: vardenafil 20 mg did not potentiate the hypotensive effect of alcohol when given with alcohol 0.5 g/kg (equivalent to about 40 mL of absolute alcohol in a 70-kg person); plasma levels of alcohol and vardenafil were not altered when given simultaneously

**Tadalafil** (Cialis)
Initial dose: 10 mg titrated up to 20 mg or down to 5 mg based on efficacy and tolerability, no more than once daily
Mean terminal half-life: about 17.5 hours
Duration of action: up to 36 hours
Selectivity: 700-fold more potent for PDE5 than for PDE6; 14-fold more potent for PDE5 than for PDE11A1 (in skeletal muscle)
Use with alpha-blockers: contraindicated except with tamsulosin 0.4 mg once daily
Use with QT-prolongation or with class Ia or III antiarrhythmic drugs: no special precautions recommended
Use in renal insufficiency: dose decreased to 5 mg not more than once daily in moderate or severe renal insufficiency (creatinine clearance < 30 mL/minute); no data available in patients on dialysis
Use in age > 65 years: no dose adjustment is warranted on the basis of age alone
Effect of food: rate and extent of absorption are not affected by food; may be taken without regard to food
Effect of alcohol: postural hypotension and dizziness may occur with coadministration of tadalafil 20 mg with alcohol 0.7 g/kg but not with 0.6 g/kg; plasma levels of alcohol and tadalafil were not altered when given simultaneously

tadalafil has a period of responsiveness lasting up to 36 hours,[39] allowing more flexibility in timing of intercourse.

Main differences among the three PDE5 inhibitors are shown in TABLE 5.

## PROPER USE OF PDE5 INHIBITORS

To ensure safety and obtain the best results with PDE5 inhibitors, the patient (and preferably his partner) should be adequately

informed about timing of the drug intake in relation to the anticipated sexual intercourse, as well as about efficacy, limitations, adverse effects, precautions and contraindications of PDE5 inhibitors.

In a recent study, approximately 40% of sildenafil nonresponders could be converted to responders through reeducation.[15] Furthermore, incorrect drug administration accounted for 81% of patients for whom sildenafil initially failed.[15]

In addition to physician's instructions, an information sheet (TABLE 4) or a video tape (provided by the manufacturer) regarding the proper use of the drug can be given to the patient and his partner.

## IF PDE5 INHIBITORS FAIL, ALPROSTADIL MAY SUCCEED

Occasionally, the first few attempts at sexual intercourse after starting a PDE5 inhibitor may be unsuccessful because of performance anxiety. Before declaring the experience a treatment failure, six to eight attempts at optimum doses should be allowed.

Preliminary data suggest that patients for whom sildenafil fails could respond to vardenafil.[40]

In case of failure or intolerance to PDE5 inhibitors, urology referral is appropriate to evaluate alprostadil therapy. The latter was shown to be effective in patients for whom sildenafil failed.[41]

## FUTURE DIRECTIONS

Despite the remarkable progress recently achieved in erectile dysfunction as a result of the introduction of selective PDE5 inhibitors, there are still many unresolved issues.

The long-term efficacy and safety of PDE5 inhibitors need to be addressed in randomized trials, particularly in patients with preexisting heart disease. Current studies are focusing on the development of newer, more effective, and more selective PDE5 inhibitors that lack undesirable systemic effects.

Preclinical investigations in rat models are under way using gene transfection techniques to transfer candidate genes involved in the erectile process, such as the gene for the endothelial nitric oxide synthase.[42]

The future of management of erectile dysfunction is promising and is progressively becoming less invasive and more physiological, allowing the primary care physician and medical specialist to assume a pivotal role in this area of medicine.

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