



Erectile dysfunction: Why drug therapy isn't always enough

STEPHEN B. LEVINE, MD

Clinical Professor of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, Ohio; Co-Director, Center for Marital and Sexual Health, and President, Center for Sexual Health Research, Beachwood, Ohio

■ ABSTRACT

We increasingly recognize that erectile dysfunction (ED) usually arises from a mix of organic and psychogenic causes, yet management of this condition too often neglects the complexity of most cases of ED. While therapy with sildenafil and similar investigational drugs can play an important role in many cases of ED, physicians should recognize and try to address the psychological and interpersonal context in which ED exists in their patients.

AWARENESS of erectile dysfunction (ED) among the public and physicians has exploded in the nearly 5 years since sildenafil (Viagra) hit the market. While this attention to a once-neglected and stigmatized condition is welcome, it has come with an unfortunate tendency to oversimplify ED as solely organic and easily treated.

Sildenafil has helped many men and their partners overcome ED, and two experimental drugs from the same class as sildenafil promise to offer further oral treatment options. Still, if our treatment strategies for ED are to be broadly successful, we cannot neglect the cen-

tral role of the mind in sexual physiology and, therefore, in many cases of ED.

This article reviews ED from a psychiatric perspective and concludes by assessing current and emerging drug treatments and how they fit into a treatment approach that recognizes the importance of psychological, interpersonal, and cultural factors in this condition.

■ PREVALENCE IS HIGH, LINKED TO AGE AND CHRONIC DISEASE

Erectile dysfunction is the consistent or recurrent inability to attain or maintain a penile erection sufficient for sexual performance.¹ Defined as such, it is estimated to affect from 20 to 30 million men in the United States.^{2,3}

The prevalence of ED increases with age, particularly after age 60. The condition affects about half of men over 60 and perhaps two thirds of men by age 70.³

Advanced age is the factor most closely associated with ED, but other major risk factors include:

- Chronic disease, particularly heart disease, hypertension, diabetes, and depression
- Use of certain medications, including thiazide diuretics, beta-blockers, and selective serotonin reuptake inhibitors
- Stress from impending marital or vocational failure
- Alcohol or drug abuse
- Smoking.

The association with chronic diseases is noteworthy, since ED can sometimes be the first symptom that brings a man to medical attention and leads to a diagnosis of cardiovascular disease or diabetes.

**Half of men
over 60 have ED**

The author has indicated that he has received grant or research support from Pfizer corporation, is a consultant for Lilly-ICOS, and is on the speakers' bureaus of the Consortium for Improvement in Erectile Function and Pfizer. The presentation on which this article is based was supported by an unrestricted educational grant from Lilly-ICOS LLC. This article discusses therapies that are not approved by the US Food and Drug Administration.

Medical Grand Rounds articles are based on edited transcripts from Division of Medicine Grand Rounds presentations at The Cleveland Clinic. They are approved by the author but are not peer-reviewed.

■ ERECTILE DYSFUNCTION: BOTH MIND AND BODY HAVE A ROLE

For a long time ED was classified into two types: organic and psychogenic. Today there is broad recognition that while a minority of ED cases are purely psychogenic and some are purely organic, the most common type seen in clinics is “mixed” ED, representing a combination of biologic, psychological, interpersonal, and cultural factors.

Mixed cases tend to be most commonly diagnosed in mid-life, with psychogenic cases perceived more often among younger men and organic cases far more often among older men.

Organic causes of ED

Potential biologic contributors to ED are numerous. They include vascular, neurogenic, and hormonal causes, as well as sequelae from surgery (eg, prostatectomy) or from radiation therapy. Of course, penile injury or disease (eg, Peyronie disease) is sometimes implicated, as are certain medications, as mentioned above.

Psychogenic causes of ED

Generally, what we view as the psychogenic causes of ED have performance anxiety as their final common pathway. This anxiety may be present in just about any man who has once or twice been unable to sustain an erection. He starts thinking about performance whenever he gets into any kind of difficulty during sex, whether it's because he has an arterial diminishment in the flow to his cavernous artery or because he may feel guilty about something.

The performance anxiety is typically triggered by one of the following:

- **Anger and alienation from the sexual partner.** Anger is a major cause of inadequate erections because it leads to alienation between sexual partners, regardless of which one is angry with the other. In these cases, the couple tries to use sex to patch up their differences when they should use conversation instead, although they may lack the will or the skills to do so.
- **Separation/divorce.** Both performance anxiety and stress are likely to be issues when a relationship is failing or winding down. They also come into play after a breakup, when the

man is restructuring his life and dating someone new. Physicians will find a huge pool of men in these circumstances asking for help with ED.

- **Guilt** figures as a cause of erectile problems most commonly among men who are having or contemplating affairs or whose partners recently died. Unfortunately, men tend to be reluctant to talk to their doctor about an affair and its complications unless the doctor seems very tuned in to it.
- **Illness in self or partner.** Even if an illness does not impair sexual function through organic means, it still can psychologically disrupt the sexual balance between a couple, particularly if it is a serious illness.
- **Job failure or grave disappointment with self.** This is a very common source of performance anxiety, especially because of the man's traditional role as breadwinner.

■ SEXUAL DESIRE: BIOLOGY, PSYCHOLOGY, AND CULTURE

The recognition that most ED is mixed ED is really a recognition that ED is complex, which stems from a broader recognition that all sexual behavior simultaneously involves biology, individual psychology, interpersonal relationships, and culture. In short, sex is not simple.

What's more, sexual desire always involves interactions between three disparate components:

- **Drive**, or the biologic component
- **Motivation**, or the psychological component
- **Wish**, or the cultural component.

The biologic component

Sex drive diminishes over the life cycle. Young and middle-aged men typically recognize that they have sexual drive manifestations, whereas men over 60 often recognize that they want to be sexually active but are not as frequently and intensely driven to sexual behavior.

For this reason, sexual behavior among elderly and some middle-aged men often involves motivation that is not necessarily strongly biologically supported. The social and psychological conditions for sex must be fairly good if these older men are to have ideal sexual function.

Performance anxiety is a final common pathway for psychogenic causes of ED



The psychological component

Sexual motivation varies less with age and more with psychological and interpersonal contexts. These involve mental states, such as joy or sorrow, and relational issues between sexual partners, such as mutual affection, disagreement, or disrespect.

Sexual motivation also is related to social contexts, such as the duration of the relationship or the presence of infidelity. The power of these contexts over motivation can be enormous but hard to describe. In the case of relationship duration, for instance, a 70-year-old man who has been married for 49 years is likely to have less sexual motivation than a 70-year-old man who has been married for just a year or two.

Moreover, it's no secret that drive and motive are not always in sync. A man may have drive and he may have motive, but they are not necessarily directed toward the same person—at least not all the time. This is a paradox almost everyone has to struggle with.

The cultural component

Wishes derive ultimately from culture and thus may vary with ethnicity, religion, and family background. Values are key to this component, and values have big implications for how one conducts one's sexual life and for the internal dynamics of sexual desire. For instance, whereas some people would never think of infidelity, largely because of their values, other people are always thinking of infidelity.

Desire is a spectrum

At any given time, a person's sexual desire is being shaped by each of the above three components. Even in men with healthy sexual function, the everyday changes and interactions among these components result in very natural fluctuations in desire. The normal, ordinary state of sexual desire varies over a spectrum, with aversion and indifference at one end and interest, then need, and then passion at the other end. It's normal for all people to move back and forth across the full range of this spectrum, occasionally within the course of a single day.

Don't neglect the broader context

This complexity is why "sexual desire" is such a slippery concept, and one that we cannot

measure effectively. This also is why physicians must begin to better distinguish between the diagnosis of ED and the psychodynamics that usually surround the condition. The diagnosis of ED tends to trigger a treatment, such as drug therapy, at the risk of ignoring the complexity of the full context in which ED exists.

Take the case of a 50-year-old ED patient who is suffering guilt and remorse over a destructive affair he began in response to an increasingly remote marriage. The marriage has come to lack intimacy and he feels lonely in his wife's presence, yet they can't talk about their problem. While ED is part of this man's difficulty, as well as the presenting symptom for his larger psychodynamic issues, the first thing one thinks of is not Viagra, even though Viagra may prove very helpful for him temporarily.

This case illustrates why physicians need to look for and focus on something more complex than a diagnosis when we encounter ED, even in the face of pharmaceutical marketing focused on the diagnostic aspects of the condition.

■ HOW DRUG THERAPY CAN SUCCEED —AND FAIL

That's not to say that drug therapy for ED is not often effective. Many men have been successfully treated with sildenafil (Viagra), the one oral drug available to treat ED at present. Again, however, "success" is relative and certainly not one-dimensional.

Categories of treatment success

At my treatment center, we have observed four categories of success with sildenafil therapy in a sample of 58 men⁴:

- **Cure** (approximately 6%), in which the drug enables the man to have good erections and good intercourse, so much so that he feels he can stop taking the drug and then continues to have a good sexual life.
- **Drug-dependent success** (approximately 45%). This is the most common outcome, in which the drug enables the man to have intercourse and to regain satisfaction with his sexual life, but only as long as he uses the drug.

Look for more than just a diagnosis

- **Drug-dependent success with a new symptom.** A few men (approximately 3%) have good erections after using the drug but then develop new problems as soon as they can have intercourse again. The problem may be the inability to ejaculate, premature ejaculation, sudden lack of sexual desire (eg, hypoactive sexual desire disorder), lack of desire on the partner's part, or discord between the couple. In these cases, the drug is successful but the man's sexual life is not any better as a result.
- **Improvement but no intercourse.** Some men (approximately 6%) can get a good erection with the drug during foreplay, but then they lose the erection as soon as they attempt intercourse. So these men are doing better than they were before using the drug, but the outcome isn't adequate.

The last two categories underscore the complexity of ED and its treatment: while a drug can create erections in the penis, the penis is still attached to a mind. That mind is part of a larger body with its own complications, and it is intricately involved in an interpersonal relationship with a partner whose own body and personal issues also play a role.

Categories of treatment failure

Similarly, we have identified three categories of sildenafil treatment failure:

- **Transient unsustainable improvement.** Some men (approximately 5%) may have one or two successes after using the drug, but then the drug fails to work for them anymore.
- **Resistance failure.** Other men (approximately 12%) just can't bring themselves to swallow the drug. They are too afraid of their perceived risk of heart attack or other adverse effects, even after their physicians reassure them with safety data.
- **Pharmacologic failure.** Sildenafil simply doesn't seem to work in about 12% of men with ED who take it correctly, which is consistent with data from the drug's clinical trials.

In summary, of 58 men given sildenafil, 5 refused to return for follow-up, 32 had intercourse within the month, 4 had improvement but no intercourse, and the drug failed in 17. Ideal outcomes were seen in 52% of patients at the first follow-up visit.

■ PDE-5 INHIBITORS

What makes sildenafil work when it does prove effective? The drug is the first in a class of compounds called phosphodiesterase type 5 (PDE-5) inhibitors. Phosphodiesterase is an enzyme that catabolizes cyclic GMP, the vasodilating messenger that causes the smooth muscle cells of the corpora cavernosa to relax, allowing blood to fill the penis. By blocking this enzyme, PDE-5 inhibitors allow cyclic GMP to have a longer action, facilitating an erection.

Two investigational oral PDE-5 inhibitors, tadalafil (Cialis) and vardenafil (Levitra), are currently under US Food and Drug Administration review and are likely to soon join sildenafil on the market for the treatment of ED.

How do the drugs compare?

Evidence to date indicates that both new PDE-5 inhibitors are very similar to sildenafil, with a few exceptions:

- **Duration of action.** Sildenafil has a duration of action of about 4 hours.⁵ Vardenafil's duration of action is similar,⁶ but tadalafil's is substantially longer, approaching 36 hours.⁷ For this reason, tadalafil is likely to be marketed as a 24-hour ED drug that may offer greater sexual spontaneity.
- **Bioavailability after eating.** Patients are told not to eat fatty foods before taking sildenafil since these foods delay absorption of the drug.⁵ However, no change in the serum concentration of tadalafil has been observed after consumption of fatty foods,⁸ while no data on this score have yet been reported for vardenafil.
- **Efficacy in diabetes.** The most exciting difference between sildenafil and the new PDE-5 inhibitors is in efficacy among men with diabetes. In clinical trials of sildenafil, only about 43% of ED patients who also had diabetes achieved improvement in their erections.⁹ Much higher percentages of ED patients with diabetes have achieved improvement in their erections after using the newer agents—52% to 76% with tadalafil¹⁰ and 57% to 72% with vardenafil,¹¹ depending on the doses used.

The side-effect profiles of tadalafil and vardenafil so far appear to be similar to that of

About half of ED patients report ideal outcomes in the first month of drug therapy



TABLE 1

Princeton Consensus Panel categories of cardiovascular risk in patients with erectile dysfunction

Low risk

- Asymptomatic; < 3 coronary artery disease risk factors, excluding gender
- Controlled hypertension
- Mild, stable angina
- Has had successful coronary revascularization
- Uncomplicated past myocardial infarction (> 6–8 weeks)
- Mild valvular disease
- Left ventricular dysfunction/congestive heart failure (NYHA class I)

Intermediate risk

- ≥ 3 major coronary artery disease risk factors, excluding gender
- Moderate, stable angina
- Recent myocardial infarction (> 2 but < 6 weeks)
- Left ventricular dysfunction/congestive heart failure (NYHA class II)
- Noncardiac sequelae of atherosclerotic diseases such as stroke or peripheral vascular disease

High risk

- Unstable or refractory angina
- Uncontrolled hypertension
- Moderate, stable angina
- Left ventricular dysfunction/congestive heart failure (NYHA class III or IV)
- Recent myocardial infarction (< 2 weeks), stroke
- High-risk arrhythmias
- Hypertrophic obstructive and other cardiomyopathies
- Moderate or severe valvular disease

ADAPTED FROM DEBUSK R, DRORY Y, GOLDSTEIN I, ET AL. MANAGEMENT OF SEXUAL DYSFUNCTION IN PATIENTS WITH CARDIOVASCULAR DISEASE: RECOMMENDATIONS OF THE PRINCETON CONSENSUS PANEL. AM J CARDIOL 2000; 86:175–181.

sildenafil, with headache, flushing, and dyspepsia among the most common effects.

Can patients with heart disease use these drugs?

To avoid the risk of dramatic hypotensive effects, none of the PDE-5 inhibitors should be used in patients receiving organic nitrates.

Beyond that, the safety of their use depends largely on the patient's cardiovascular risk factors. In 2000, the Princeton Consensus Panel published recommendations for the management of sexual dysfunction in patients with cardiovascular disease¹²; the panel's cardiovascular risk categories are outlined in **TABLE 1**.

Generally, it is safe to use PDE-5 inhibitors in patients in the low-risk and intermediate-risk categories. This includes even patients who had a myocardial infarction several weeks ago, as long as nitrates are not being used. A great deal of caution, including cardiology consult, is needed before prescribing a PDE-5 inhibitor to a high-risk

patient, simply because of the physical exertion involved in sex.

■ A MODEL FOR PATIENT MANAGEMENT

Break the ice with a questionnaire

A big part of addressing ED with a patient is simply getting at the issue of sexual function and the related psychodynamics in the first place. The key is to unobtrusively let the patient know you are interested in hearing about sexual function if it is a problem.

Many busy medical practices are starting to take sexual histories by giving patients short questionnaires, such as the Sexual Health Inventory for Men (**TABLE 2**).¹³ These can make it easier for the patient to signal that he wants you to ask about sexual function.

Assess the range of possible causes

Once sexual function is established as a problem, assess the patient's interpersonal and

Speak with the sexual partner to get another perspective



TABLE 2

Questions from the Sexual Health Inventory for Men

How do you rate your confidence that you could get and keep an erection?

When you had erections with sexual stimulation, how often were your erections hard enough for penetration?

During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

When you attempted sexual intercourse, how often was it satisfactory for you?

social circumstances to determine how large a role psychodynamics may be playing. Here it is very helpful to speak with the sexual partner, in order to get another perspective on the relationship as well as on the duration and severity of the sexual dysfunction.

If the ED seems to have an organic component, screen for associated diseases (eg, diabetes, hypertension, heart disease, depression) and identify and consider modifying any drugs the patient is taking that might be contributing to the problem.

Consider drug therapy—or more

At this point the management approach depends greatly on the psychodynamics of the patient's situation and his physical find-

ings. In many cases, however, a trial of PDE-5 inhibitor therapy is appropriate. Make sure the patient understands that these drugs do not cause sexual arousal: he must do something that is arousing to set the stage for the drug to work. Make sure he also knows what should be avoided when taking the drug (alcohol and fatty foods in the case of sildenafil) and how long the drug takes to work (45 minutes).

If several trials of PDE-5 inhibitor therapy fail to improve the patient's erections, or if his situation has psychodynamic aspects that require more than drug therapy for ED, consider referral to a specialist. The patient may prefer a urologist, but strongly consider a psychotherapist as well.

Make sure patients know the drugs don't cause sexual arousal

REFERENCES

1. Recommendations of the 1st International Consultation on Erectile Dysfunction. In: Jardin A, Wagner G, et al, eds. *Erectile Dysfunction*. Plymouth, UK: Health Publications, 2000:711–726.
2. Benet AE, Melman A. The epidemiology of erectile dysfunction. *Urol Clin North Am* 1995; 22:699–709.
3. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; 151:54–61.
4. Pallas J, Levine SB, Althof SE, Risen CB. A study using Viagra in a mental health practice. *J Sex Marital Ther* 2000; 26:41–50.
5. Viagra (sildenafil citrate) package insert. New York, NY: Pfizer Inc; 2002.
6. Sorbera LA, et al. Vardenafil. *Drugs Future* 2001; 26:141–144.
7. Porst H, Rosen RC, Padma-Nathan H, et al. Tadalafil allows men with erectile dysfunction to have successful intercourse up to 36 hours postdose. *J Urol* 2002; 167(4 suppl):177. Abstract 709.
8. Patterson B, et al. Poster presented at: 4th Congress of the European Society for Sexual and Impotence Research; September 30, 2001; Rome.
9. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998; 338:1397–1404.
10. Data on file, Lilly ICOS LLC.
11. Goldstein I, et al. *Int J Impot Res* 2001; 13(suppl 5):S65. Abstract 24.
12. DeBusk R, Drory Y, Goldstein I, et al. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of The Princeton Consensus Panel. *Am J Cardiol* 2000; 86:175–181.
13. Day D, Ambegaonkar A, Harriot K, McDaniel A. A new tool for predicting erectile dysfunction. *Adv Ther* 2001; 18:131–139.

ADDRESS: Stephen B. Levine, MD, Center for Marital and Sexual Health, 3 Commerce Park Square, Suite 350, Beachwood, OH 44122-5402.