

Erectile Dysfunction: An Old Question with New Answers



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Over the years, erectile dysfunction (ED) has been defined as the inability to achieve an erection adequate for sexual intercourse. But, is this the proper definition? Practically speaking, any patient whose erections “are not what they used to be” has ED. Intercourse failure is not a prerequisite to be considered for treatment.

As of late, oral phosphodiesterase Type 5 (PDE5) inhibitors, as first-line therapy, have been said to have revolutionized the treatment of ED (Figure 1). Prior to the release of sildenafil in 1998, the only options that were available were the present second- and third-line choices which are obviously not as attractive to patients as simply “taking a pill.” Figure 2 depicts how these medications work.

Even though population and demographic studies suggest that ED is present in at least 30% to 40% of the population (and the incidence is increasing with age), it appears that < 20% of the “target population” is being treated, in spite of extensive CHE and direct-to-consumer advertising over the last eight years. More than 80% of patients state that they would discuss their sexual concerns, if asked, but only a minority of physicians actually address this issue directly.

Yves's case

Yves, 40, presents for a complete physical. He complains that over the last 6 to 12 months, he has experienced increasing difficulty in maintaining his erections, which has restricted his ability to have satisfactory sexual intercourse. His erections last only a few seconds. When Yves masturbates, his erection lasts a little longer, between 2 and 3 minutes, but he generally loses his erection before orgasm. Also, his morning erections are slowly disappearing.

Currently, Yves' sex drive is stable. His partner is understanding about the problem.

History

Yves' medical history is unremarkable, except that he occasionally takes acetaminophen. He:

- is an office worker,
- lives a sedentary lifestyle,
- smokes 1 pack of cigarettes per day (and has done so for the past 20 years),
- consumes 2 glasses of wine per week and
- does not use recreational drugs.

Questions

1. What is the most likely etiology of Yves' erectile dysfunction (ED)?
2. Would you prescribe an oral phosphodiesterase Type 5 inhibitor (PDE5) on this first visit?
3. Do you give 1 brand, 2 or all 3 that are available?
4. If you only prescribe 1 brand, what is your first choice and why?

Turn to page 94 for more on Yves.

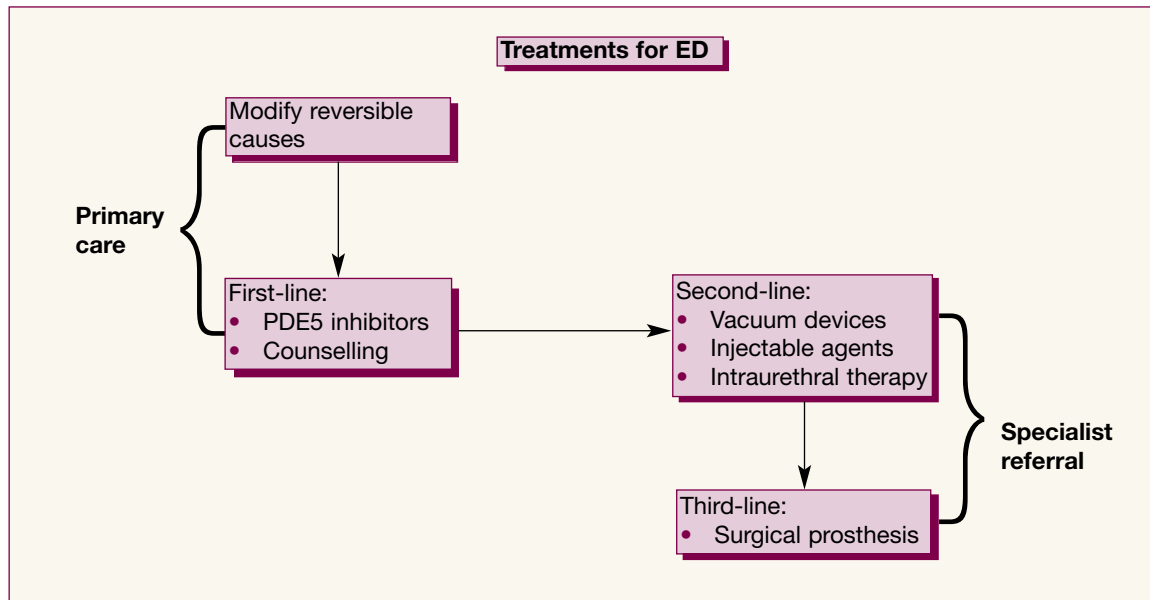


Figure 1. PDE5 inhibitors are a first-line treatment for ED.

Q *Why is there such misunderstanding?*

Why do patients who suffer from ED not know more about their treatment options? This could be due to the fact that patients:

- are not given proper instructions regarding the use of available medications to treat ED,
- are not being followed-up and
- are not having their treatment options explained to them.

Studies would imply that FPs are not overestimating the bother of sexual dysfunction. We

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need to find ways to show that ED is a disease and not just a social disorder.

Q *Is ED a precursor for CVD?*

This concept has been acknowledged since the mid-1990s when it was discovered in the original Massachusetts Male Aging Study (MMAS) population that many men who had ED in 1987 developed one or more comorbidities (i.e., hypertension, diabetes, high cholesterol, etc.) seven years later.¹ There are now many studies supporting this fact. When otherwise healthy patients ask why they have developed ED, we can simply say, in most cases, that “your penis is showing you that your blood vessels are aging.” Table 1 explains why ED occurs before actual CVD. Table 2 demonstrates how vascular ED is a possible early manifestation of CVD and Table 3 depicts the link between ED and CVD.

Q & A *What is the current share in the PDE5 market?*

The top PDE5 inhibitors currently on the market are:

- Sildenafil (55%)
- Tadalafil (30%)
- Vardenafil (15%)

Statistics show that only 50% to 60% of all prescriptions for ED are renewed. Multiple comparative studies on the effectiveness of available PDE5 inhibitors have been done, but most are of poor quality (*i.e.*, industry-sponsored, not randomized, not placebo-controlled, *etc.*). Results have implied that perhaps patients deserve a trial on all three drugs.

Patient preference

The two main factors affecting patient drug preference are hardness of erection and the duration of action. Other factors include:

- side-effects,
- safety and restrictions,
- onset and duration of action,
- food and alcohol restrictions and
- resistant patients/non-response.

Maximizing success of PDE5 inhibitors

Certain strategies can be employed to maximize the success of oral PDE5 inhibitors. These factors should be explained to patients whenever these medications are dispensed. Reasons for apparent treatment failure with oral therapy include:

- inadequate dose,
- inadequate arousal or stimulation,
- inadequate timing between taking the pill and initiating intercourse,
- lack of trials (reliability),

Table 1

Why erectile dysfunction (ED) occurs sooner than CVD²

Artery	Diameter	Critical events
Penile	1 mm-2 mm	ED
Coronary	3 mm-4 mm	Angina or MI
Carotid	5 mm-7 mm	Transient ischemic attack or stroke

Table 2

Vascular ED as a possible early manifestation of CVD³

Design

- Study of 300 men with angiographically documented coronary artery disease (CAD)

Results

- Prevalence of ED among patients was 49% (147/300)
- Among the 147 patients with coexisting ED and CAD, the onset of ED preceded CAD symptoms in 67% of patients (99/147)

Table 3

Link between ED and CVD: Clinical study⁴

Design

- Study of ED prevalence in 133 diabetic men with angiographically-verified silent CAD vs. 127 diabetic men without myocardial ischemia at exercise or 48 hour ambulatory ECG and stress ECHO

Results

- Strong and independent association of ED with angiographically-verified silent CAD in men with uncomplicated Type 2 diabetes and a relatively low CAD risk
- ED affected one-third of patients with silent CAD and 5% without

Conclusion

- ED could be a potential silent CAD predictor

- electrolyte factors outweighing the effects of oral therapy (e.g., stress, fatigue, alcohol),
- low testosterone supplementation and
- wrong diagnosis (the most common is premature ejaculation).

More than 80% of patients state that they would discuss their sexual concerns, if asked, but only a minority of physicians actually address this issue directly.

Yves's case cont'd...

- Answers**
1. Yves' ED is almost certainly on a vascular basis (endothelial dysfunction)
 2. After discussing with Yves, you prescribe a PDE5 inhibitor because it is considered first-line treatment for ED. Unless there are contraindications, it is the general practice to give a trial of these medications at the time of initial consultation
 3. Patients should be given the option of trying all 3 oral PDE5 inhibitors
 4. If you prescribe only one brand, you are likely not achieving the maximal success rate with your patients. Your first choice is likely based on your familiarity with a product, specific patient request and/or sample availability. Samples of all 3 drugs can often be given with proper explanation to the patient

Most patients can be safely started on the maximal dose of ED medications:

- 100 mg of sildenafil,
- 20 mg of tadalafil and
- 20 mg of vardenafil.

All manufacturers push the “30 minute onset of action” concept. Patients should be told to wait one hour the first few times they try one of the inhibitors; if success is achieved by waiting one hour, a shorter interval can then be attempted.

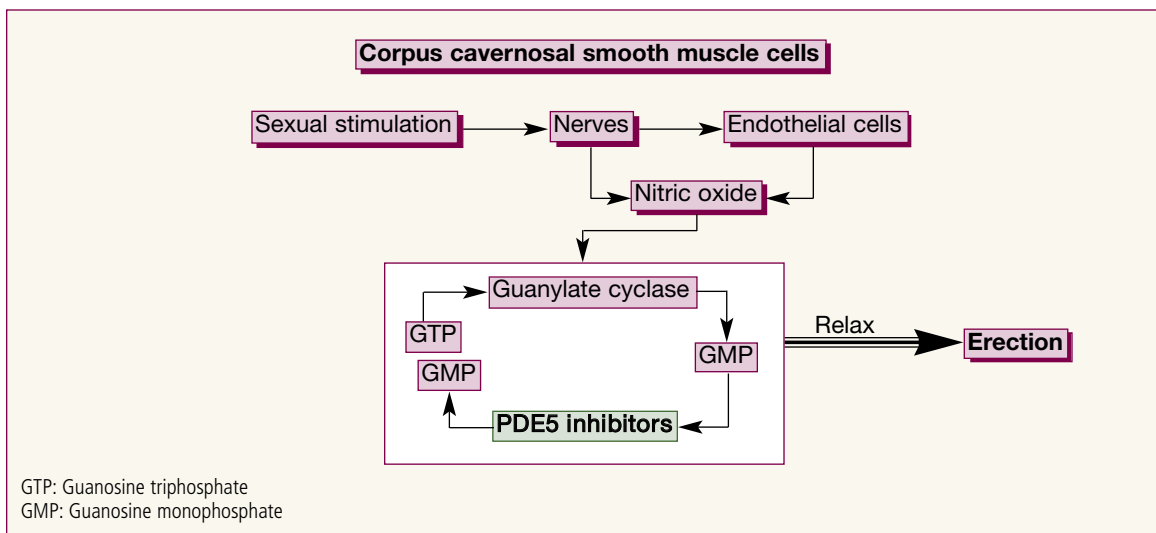


Figure 2. PDE5 inhibitor mechanism of action.

Take-home message


- ED is a precursor for CVD
- ED is often the sentinel sign of endothelial dysfunction in younger patients. A full work-up for conditions associated with ED needs to be performed at initial presentation and on an ongoing basis
- A sexual history should become part of daily practice. Ask your patients the question
- Patients deserve a trial on all 3 oral PDE5 inhibitors
- Don't just "throw pills" at your ED patients. Give proper instructions, follow-up and discuss other treatment options if oral therapy fails
- Realize that ED is a disease, just like diabetes, hypertension and lipid disorders
- Be aware of the significance of testosterone in the erectile process and its role in enhancing the efficacy of oral ED medications
- If you do not have the time, knowledge or confidence to treat ED comprehensively, please refer your patients to your local ED expert
- Successful management of ED can be one of the most gratifying aspects of your practice

Each pill should be tried four times before a switch is made. Partner issues must also be taken into consideration.

What is the role of testosterone?

The two most important chemical mediators in achieving smooth muscle relaxation and therefore, an erection, are nitric oxide and cyclic guanosine monophosphate.⁵

It has been shown that the production of nitric oxide is testosterone dependent.⁶ Many patients with ED have low testosterone and will not respond to oral PDE5 therapy unless their testosterone level is raised, as nitric oxide is necessary for the function of PDE5 inhibitors (testosterone may be a "down regulator" of PDE5 inhibitors). There are now a number of studies that show significant success rates in combining testosterone and oral PDE5 therapy.⁷⁻¹⁰ Testosterone assessment should be part of the ED work-up, especially in those considered to be PDE5 therapy failures.

In hypogonadal men, testosterone should be tried for six to eight weeks, at least, before a rechallenging with oral PDE5 inhibitors is considered. 

References

1. Feldman HA, Goldstein I, Hatzichristou DG, et al: Impotence and its Medical and Psychosocial Correlates: Results of the Massachusetts Male Aging Study. *J Urol* 1994; 151(1):54-61.
2. Montorsi P, Ravagnani PM, Galli S, et al: The Artery Size Hypothesis: A Macrovascular Link Between Erectile Dysfunction and Coronary Artery Disease. *Am J Cardiol* 2005; 96(12B):19M-23M.
3. Montorsi F, Briganti A, Salonia A, et al: Erectile Dysfunction Prevalence, Time of Onset and Association with Risk Factors in 300 Consecutive Patients with Acute Chest Pain and Angiographically Documented Coronary Artery Disease. *Eur Urol* 2003; 44(3):360-65.
4. Gazzaruso C, Giordanetti S, De Amici E, et al: Relationship Between Erectile Dysfunction and Silent Myocardial Ischemia in Apparently Uncomplicated Type 2 Diabetic Patients. *Circulation* 2004; 110(1):22-6.
5. Boolell M, Gepi-Attee S, Gingell JC, et al: Sildenafil, A Novel Effective Oral Therapy for Male Erectile Dysfunction. *Br J Urol* 1996; 78(2):257-61.
6. Morelli A, Filippi S, Mancina R, et al: Androgens Regulate Phosphodiesterase Type 5 Expression and Functional Activity in Corpora Cavernosa. *Endocrinology* 2004; 145(5):2253-63.
7. Shabsigh R, Kaufman JM, Steidle C, et al: Randomized Study of Testosterone Gel as Adjunctive Therapy to Sildenafil in Hypogonadal Men with Erectile Dysfunction Who Do Not Respond to Sildenafil Alone. *J Urol* 2004; 172(2):658-63.
8. Yassin AA, Saad F, Diede HE: Combination Therapy with Testosterone and Tadalafil in Hypogonadal Patients With Erectile Dysfunction Who Do Not Respond to Tadalafil as Monotherapy. *Blickpunkt Der Mann* 2003; 2(14):37-9. (German)
9. Kalinchenko SY, Kozlov GI, Gontcharov NP, et al: Oral Testosterone Undecanoate Reverses Erectile Dysfunction Associated with Diabetes Mellitus in Patients Failing on Sildenafil Citrate Therapy Alone. *Aging Male* 2003; 6(2):94-9.
10. Shamloul R, Ghanem H, Fahmy I, et al: Testosterone Therapy Can Enhance Erectile Function Response to Sildenafil in Patients With PADAM: A Pilot Study. *J Sex Med* 2005; 2(4):559-64.