

Optimizing Response To Phosphodiesterase Therapy: Impact of Risk-Factor Management

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The key to successful treatment of any condition is to understand and treat its causes. The same is true for erectile dysfunction (ED). In the past several decades, the causes of ED have been elucidated and are constantly being redefined. In the 1950s and 1960s, the etiology was thought to be psychological in the majority of cases. Continued research in this area now shows that organic or medical causes predominate in the majority of cases. The NIH consensus conference in 1992 solidified this focus and began to highlight specific medical conditions (NIH Consensus Development Panel on Impotence, 1993). Many men have both organic and psychological causes of ED and sometimes relationship issues as well, so one has to include the partner in the evaluation (AAACE, 1998).

An important point to keep in mind is the specialty that controls the sexual function clinic. Although the same complete evaluation can be done by any interested specialty, the focus for referrals might be different. A clinic in a urology department might have a higher percentage of men with penile fibrosis or ED after radical prostatectomy. A clinic that is a secondary referral center will generally see a more severely affected population. A sexual clinic managed by someone in internal medicine or a clinic receiving referrals primarily from internists or primary care physicians will see a different mix of patients (Slag et al, 1983; Guay et al, 1999). In this instance, the majority of cases will have medical disease etiologies. In any clinic, there are a large number of patients who will have both medical and psychological aspects to their ED problem. In our evaluation of 990 consecutive consultations, the percentage of men with mixed ED was 28.2% (Guay et al, 1999).

The following discussion will highlight the causes of the ED and how a practitioner might be able to optimize therapy by paying attention to the various etiologies. It is also recognized that men prefer oral therapy for ED, when possible. Because sildenafil has been recognized as the definitive first-line drug, some emphasis will be given to

methods of optimizing treatment with this drug. The same will undoubtedly hold true for other phosphodiesterase inhibitors that will follow.

Progression of Ideas in ED

During the 1950s and 1960s, ED (or impotence, as it was referred to then) was separated into psychogenic and organic causes, with vague relationships to specific etiologies. As more research developed in the 1970s, the organic or medical components began to be outlined a little more specifically (Carrier et al, 1994). It was recognized that medications played a part in the problem. Also, neurological, hormonal, and vascular causes were recognized. Vascular flow in the penis was investigated, and a difference between arteriogenic and venogenic causes was appreciated (Lue and Donatucci, 1994; Sharlip, 1994). Hormonal factors were being noticed as early as the early 1980s (Spark et al, 1980, 1984). In the late 1980s and into the 1990s, penile physiology and erectile pathophysiology moved into the biochemical sphere as endothelial function and neurotransmitters were being identified and studied, especially nitric oxide (Rajfer et al, 1992; Pickard et al, 1995). All these factors have to be considered in outlining the oftentimes multiplicity of causes of ED in order to better plan a treatment regimen.

Psychogenic Factors

The most commonly seen emotional problems associated with ED are anxiety and depression. Anxiety has many causes: performance anxiety (fear of failure); stressors, such as job and financial worries; and family problems (aging parents or adolescent problems in children). Although anxiety may be related to fear of failure, separate relationship problems may be at issue. Partner disinterest may be present, especially prevalent at the time of menopause where many bodily changes are occurring. Depression can certainly cause or aggravate ED and is a leading cause of decreased libido.

The sex therapist should be an integral part of the management team in a sexual function clinic. Very commonly, the therapist deals with performance anxiety and relationship problems. Sometimes, even though physicians have provided a successful treatment, the couple will need some help combating the avoidance that often accompanies ED. The therapist sometimes needs to rule out a more serious anxiety or depression disorder, which may need to be addressed by a psychiatrist.

On the other hand, there is evidence that medically

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treating the ED has an ameliorative effect on relationships and primary emotional disorders. It can also reverse adverse sexual side effects from the medications themselves. Nurnberg et al (2003) found that sildenafil improved erectile function, arousal, ejaculation, orgasm, and overall satisfaction in men who had dysfunction related to selective serotonin reuptake inhibitor antidepressants. Even in men who have organic or mixed ED, Paige et al (2001) reported that sildenafil not only improved overall sexual satisfaction and increased intercourse satisfaction, but also improved the quality of life in 38% of the men and improved partner relationship in 29% of the men.

ED Is Vascular

It has become apparent that the most common cause of ED is vascular. The majority of medical conditions that we commonly see as causes of ED affect the endothelial cell, which is a key component of the corpora cavernosum in causing vasodilatation and increased blood flow. These conditions are thought to cause an imbalance between penile vasoconstrictors and vasodilators (Taub et al, 1993; Seftel, 2002). Also, an imbalance between trabecular smooth muscle and connective tissue is thought to be important, especially if one is to factor in aging changes in the penis (Moreland, 2000).

Even early on, the NIH consensus conference noted that ED occurred more commonly with diabetes mellitus, hypertension, vascular disease, hypogonadism, and elevated cholesterol (NIH Consensus Development Panel on Impotence, 1993). The ongoing Massachusetts Male Aging Study has been following men over time, and apart from the known increase in ED with age, a correlation was found with diabetes mellitus, coronary artery disease, and hypertension (Feldman et al, 1994). In addition to coronary artery disease, smoking and even passive smoke exposure was correlated with ED (Feldman et al, 2000).

The Penile Stress Test

Dr Pritzker, a cardiologist from Minneapolis, Min, brought notice to the relationship of ED and cardiovascular disease when he studied 50 men who had ED but no history or symptoms of heart disease (Pritzker, 1999). Forty of the 50 men had multiple risk factors for heart disease. Cardiac stress tests were done. None of the men had symptoms, but 28 of the 50 (56%) had a positive test, consistent with silent ischemia. Twenty of these 28 men submitted to coronary angiography, and all had significant 1-, 2-, or 3-vessel disease. Dr Pritzker believed that ED might be an early warning sign of impending symptomatic coronary disease. The rationale proposed is that symptoms occur first in the penis because the arteries are smaller.

Similar Risks in ED and Cardiovascular Disease

In clinical practice, the results are the same. In 62 general medical practices, Chew et al (2000) found that a predominance of conditions that affect the vascular system are correlated with ED. These included hypertension, ischemic heart disease, peripheral vascular disease, and diabetes mellitus. In our previous study evaluating the causes of ED in 990 consecutive consultations, we found hypertension in 35.8%, diabetes mellitus in 23.1%, atherosclerotic cardiovascular disease in 19.9%, tobacco abuse in 14.1%, and peripheral vascular disease in 5.6% (Guay et al, 1999). In a more recent and more focused study of 154 consultations, we found hypertension in 44%, abnormal glucose metabolism (diabetes mellitus and glucose intolerance) in 34%, tobacco abuse in 16%, and coronary artery disease in 9% (Walczak et al, 2002). The surprising findings were that 74% of the men had elevated low-density lipoprotein (LDL) cholesterol (defined as LDL > 120 mg/dL) and that 79% were overweight (defined as body mass index >26). Obesity has recently been proven to be a specific and separate primary risk factor for coronary artery disease (Suwaidi et al, 2001).

All the above conditions affect the intracorporeal biochemistry, and most will cause endothelial dysfunction with a resultant decrease in nitric oxide metabolism. Other mechanisms at work are the accumulation in the penis of angiotensin II, a powerful vasoconstrictor in hypertension, and decreased neuronal nitric oxide production in diabetes mellitus caused by clinical or subclinical neuropathy. Even the HbA1C molecule itself will affect the endothelial cell in diabetes.

Risk-Factor Modification

Sildenafil has been successful because it will increase the nitric oxide activity of the penis by retarding the breakdown of its product, cyclic guanosine monophosphate. In conditions where the neuronal production of nitric oxide is curtailed, the results with sildenafil have been decreased, such as nerve damage from radical prostatectomy or neuropathy in persons with diabetes.

Modification of the medical conditions that affect endothelial function and nitric oxide production will lead to enhanced treatment success, either as the sole treatment or as an adjunct to other treatments. Our group found a greater success (82%) with sildenafil than what was found in the literature when risk-factor management was undertaken (Guay et al, 2001). We also showed that control of diabetes made a difference in the response to sildenafil, such that men with diabetes with an HbA1C less than 9.0% had a 63% success rate with sildenafil, whereas those with an HbA1C greater than 9.0% had a decreased success rate of 44%. We also showed that as the testosterone level fell, the response to sildenafil decreased and

*Important points in the management of ED (adapted from McCullough et al, 2002)**

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- A. Importance of identifying ED
Many of the risks of ED are shared with cardiovascular disease (diabetes mellitus, hypertension, hyperlipidemia, tobacco abuse, obesity)
- B. Identification of ED if desired by patients
Primary care physicians are less likely to:
Screen their patients for sexual dysfunction symptoms
Refer treatment failures for specialty evaluation
Primary care physicians must introduce the subject
Primary care physicians must use screening tools to be efficient
The SHIM is a valuable tool
Five questions; easy scoring (21 or less consistent with ED)
- C. Proper use of sildenafil needs to be taught
Need for foreplay
Need to take several hours after eating (or 1 h before)
Need to try a particular dose 5 to 8 times before claiming failure
Need to titrate up to maximum dose of 100 mg if needed
Need to recognize negative effects of alcohol, tobacco, or fatigue
- D. Follow-up of both partners important
Was treatment used properly?
Were risk factors evaluated if success of treatment declines?
Was partner encouraged to return to rule out relationship issues?
Is referral of either partner to a specialty clinic warranted?
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* ED indicates erectile dysfunction; SHIM, Sex Health Inventory for Men.

eventually became ineffective. Derby et al (2000) warn, however, that modification works better at an earlier age because older men may not be able to reverse the effects of smoking, obesity, and alcohol abuse. Increasing age adds another burden to whatever medical factors are present.

An interesting report in 9 men showed objectively that lowering cholesterol increased penile erectile activity after atorvastatin therapy (Guay and Jacobson, 2002). These men, after careful evaluation, had only elevated cholesterol as a risk factor for organic ED, proven by abnormal baseline nocturnal testing with the RigiScan portable home monitor. Improved erections and sexual activity occurred after only several months of therapy, as reflected by improvement in the Sex Health Inventory for Men (SHIM) scores and in nocturnal erection parameters. Several of the men who were using sildenafil no longer needed it.

Optimization of Treatment of ED: General

Thus, the first order of business should be to modify the risk factors whenever possible. This would include bringing blood sugar or blood pressure under control. It might involve changing offensive medications whenever possible. Substance abuse should be stopped and hypogonadism, when present, should be treated. Obesity should be

corrected and more aggressive therapy for hyperlipidemia is necessary.

Optimization of Treatment of ED: Sildenafil

Because sildenafil is the recognized first-line therapy for ED, it is important to consider what steps should be taken to ensure its maximum effectiveness. As previously mentioned, we obtained an 82% success rate in 521 men by modifying the medical risk factors (Guay et al, 2001).

Most prescriptions for sildenafil, however, are not written by specialists in the field but by primary care physicians. More education of primary care physicians is needed. Fawzy (2000) has shown that fewer than half of these physicians routinely questioned their patients about ED symptoms. Time is very limited in a primary care physician's office, and means have to be found to effectively but practically evaluate this situation. Perhaps the abridged form of the International Index of Erectile Function questionnaire could be filled out by the patient in the waiting room (Rosen et al, 1999); its 5 questions are easy to answer and score, which makes it an adequate screening tool. Primary care physicians also have to be trained in sexual dysfunction, as this subject is just starting to be discussed in more depth in medical school.

A frequent scenario is the patient returning to the office claiming failure with sildenafil. Barada (2001) has shown that over half of these men may be salvaged with reeducation. There are identifiable common mistakes. The first is that the patient did not titrate his dose to the maximum of 100 mg. Another common mistake is that men often do not try to use the drug enough times. McCullough et al (2002) have shown that the cumulative probability of success increases with the number of attempts. Men should try each dose 5 or 6 times, up to 8 in some cases, before claiming failure. Another common error is the ingestion of sildenafil too soon after eating, especially a fatty meal. It should be taken several hours after a meal, followed by the 30 to 60 minutes required for activity. Most men are aware that foreplay is needed for sildenafil to have an effect. Many men have to be reminded that maximum effectiveness will be blunted by tobacco usage, excess alcohol, or fatigue.

Treatment satisfaction by both patient and partner is quite important for long-term success of therapy with sildenafil. The need for follow-up is very important, and having the partner present with the patient at some point is equally important in bringing up issues that may have been missed. The Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire was developed specifically to evaluate satisfaction of treatment (Althof et al, 1999), but the IIEF-5 abbreviated questionnaire, also called the SHIM, is also accurate for follow-up evaluation. Satisfaction, both for men previously treated with other methods of ED correction and for those using sil-

denafil as their first treatment, was shown to be equally positive (above 80%) (Althof, 1999). Partner satisfaction was shown to be quite positive as well (Lewis et al, 2001).

Summary of Important Points

The Table highlights some of the important factors in the evaluation and treatment of men with ED. Better education of both patients and physicians caring for them is the common denominator. Initiatives for medical school education of sexual function and dysfunction have begun and are gaining momentum. Until these effects are felt in the practice community, educating physicians in this field will remain a priority.

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