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VIEWPOINT

Based on the following articles:
***BJU Int* 15 Oct 2010;Epub ahead of print, *J Sex Med* 2010;7(11):3725-35.**

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CANADIAN DATA ON MILD ERECTILE DYSFUNCTION: OFTEN AN EARLY SIGN OF VASCULAR DISEASE

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INTRODUCTION

Erectile dysfunction (ED) is both a common source of diminished quality of life (QoL) and a signal for potential serious underlying pathologies. Of these, impairment in blood flow secondary to progressive vascular disease is one of the most common. This association has been well demonstrated in moderate-to-severe ED, but may be at least as important in milder forms, where ED symptoms may provide the first clinical evidence of an advancing occult vascular pathology. Two related and recently published studies underline the importance of screening patients for mild ED. One of these studies establishes that a phosphodiesterase type 5 inhibitor can provide improvements in QoL in mild ED similar to those previously observed in more severe forms. The other confirms mild ED as a marker of increased risk for vascular disease. Both studies encourage greater attention to identification and treatment of mild ED.

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Erectile dysfunction (ED) is common. In a Canadian cross-sectional study of males older than 40 years (mean age 57 years) visiting their primary care physician, 49.4% met diagnostic criteria for ED (Grover et al. *Arch Intern Med* 2006;166:213-9). This prevalence, which includes all grades of ED, is consistent with data generated by similar studies in the US and Europe (Feldman et al. *J Urol* 1994;151:54-61, Koskimaki et al. *J Urol* 2000;164:367-70). Of those with ED, approximately 10% in the Canadian cross-sectional study had mild involvement on the basis of the self-administered International Index of Erectile Function (IIEF), one of the most frequently employed methods for scoring relative ED severity (Miller TA. *Am Fam Physician* 2000;61:95-104). While mild ED is defined by only intermittent sexual dysfunction, it is not necessarily benign. Data evaluated in this review will suggest that even modest impairment in sexual function can be a source of distress, undermining a sense of well-being, decreasing self-esteem and adversely affecting quality of life (QoL).

ED AND VASCULAR DISEASE

Of the long list of potential etiologies for ED, vascular disease alone or in association with other conditions, such as anxiety or depression, is associated with approximately 70% to 80% of cases of ED (Chiurlia et al. *J Am Coll Cardiol* 2005;46:1503-6). While many individuals who report ED already have a diagnosis of coronary heart disease (Feldman et al. *J Urol* 1994;151:54-61), ED is sometimes the first sign of vascular disease (Kaiser et al. *J Am Coll Cardiol* 2004;43:179-84). The close association of ED and vascular disease is reinforced by shared risk factors such as hypertension, smoking and diabetes (Cheitlen MD. *J Am Coll Cardiol* 2004;43:185-86). Moreover, the severity of ED and severity of cardiovascular (CV) disease are correlated (Greenstein et al. *Int J Impot Res* 1997;9:123-6). Perhaps most importantly, the presence of ED has been shown to be a predictor of CV events (Schouten et al. *Int J Impot Res* 2008;20:92-9).

The efficacy of phosphodiesterase type 5 (PDE-5) inhibitors in the treatment of moderate-to-severe ED has been well established with multiple large trials and many agents in this drug class. In a pivotal phase III study with sildenafil, the first and most widely used PDE-5 inhibitor, the number of successful intercourse attempts were 2 to 3 times greater than that observed on placebo and highly statistically significant ($P<0.001$) (Goldstein et al. *N Engl J Med* 1998;338:1397-404). These results and those of subsequent trials were instrumental in drawing attention to the problem of ED and have been credited with increasing the proportion of individuals who volunteer this complaint to their physician.

Most clinical studies in ED have concentrated on individuals with moderate-to-severe symptoms, where need for treatment and the opportunity to show a treatment effect are presumably greater. However, ED occurs on a continuum of severity, whether measured objectively by ability to achieve an erection of sufficient quality to achieve penetration or by the frequency with which attempts are successful; or by patient satisfaction with their sexual performance.

There are a number of reasons to hypothesize that mild ED, likes its more severe forms, also represents a significant clinical problem. Even if symptoms of ED are intermittent, the anxiety produced by undependable sexual function might reasonably be predicted to produce significant levels of distress. Moreover, the same etiologies, if less severe, are likely to be relevant to mild ED, suggesting that this complaint may provide an early signal of the same vascular diseases linked to more severe ED.

The significance of mild ED as a clinical issue in regard to patient well-being and as a signal of underlying disease has been recently evaluated in 2 related studies published separately. One evaluated the impact of the PDE-5 inhibitor sildenafil in patients with mild ED. The other compared the incidence of comorbidities in patients with mild ED to those with more severe ED who had participated in previous clinical studies. Together, both studies support the premise that mild ED is an important clinical entity for which active screening programs have the potential to both increase QoL and identify patient groups with underlying vascular disease who can benefit from therapies for their comorbidities.

STUDY FINDINGS IN MILD ED

The trial by Bénard et al. (*J Sex Med* 2010;7(11):3725-35) is the first double-blind randomized study of ED that limited entry to patients with mild impairment as defined by a validated scoring system. This entry criterion was an IIEF-EF score of 22 to 25. Most of the 176 patients who entered the trial had an organic cause of ED, i.e. a vascular, neural or hormonal etiology, although a proportion had a mixed etiology, suggesting organic disease with a psychogenic component. The randomization was either to 50 mg sildenafil with the option to lower the dose to 25 mg, or increase the dose to 100 mg or to placebo. The 8-week double-blind portion of the study was followed by a 6-week open-label phase.

Much like the pivotal studies that established the efficacy of PDE-5 inhibitors in moderate-to-severe

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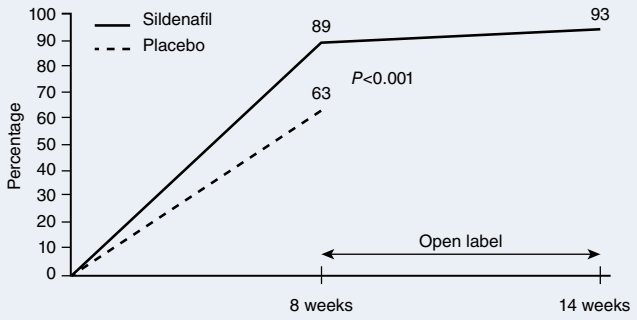
ED, sildenafil was associated with improvements in both objective and subjective measures relative to those randomized to placebo. Specifically, on the primary end point of the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) index score, the mean 18.2 point difference (80.3 vs. 62.1) was highly statistically significant ($P<0.0001$). Overall, treatment satisfaction was achieved in 89% of those randomized to active treatment vs. 63% ($P=0.0001$) of those randomized to placebo (Figure 1). The proportion of patients with normal erectile function on IIEF-EF (score >25) at the end of the study was 58% of those receiving sildenafil vs. 39% of those receiving placebo ($P<0.05$).

Figure 1. **Treatment Satisfaction Results**



Adapted from Bénard et al. *J Sex Med* 2010;7(11):3725-35.

The advantage of the PDE-5 inhibitor over placebo was also observed on a variety of other secondary end points, such as the Quality of Erection Questionnaire (QEQ) and the Erection Hardness Score (EHS). On EHS, the proportion reaching the highest score of 4 was 47.2% on sildenafil vs. 25.2% on placebo ($P<0.0001$). Overall, the odds of successful intercourse were >4.9-fold in the active treatment group when compared to the group randomized to placebo. In the open-label extension, all outcomes on the PDE-5 inhibitor improved. For example, those returning to a normal erectile function on the IIEF-EF scale rose to 77% during the extension, while treatment satisfaction rose to 93%.

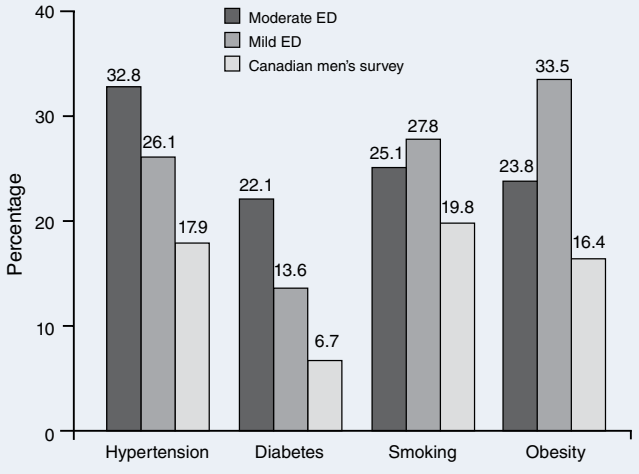
The substantial relative advantages of PDE-5 inhibition over placebo in mild ED confirm an important treatment effect. Equally important, the large degree of improvement in a variety of clinical measures suggests that untreated ED is an important source of patient dissatisfaction. Mild to moderate adverse events, such as headache, nasal congestion and flushing, were reported in a minority of patients and were consistent with the previous clinical trials evaluating these agents. The overall benefits of therapy demonstrate an important opportunity for the identification and relief of mild ED to improve patient well-being.

MILD ED: AN EARLY SIGN OF VASCULAR DISEASE

A separate but related study by Lee et al. (*BJU Int* 15 Oct 2010;Epub ahead of print) supports mild ED as an important early signal of vascular disease, which provides an additional but perhaps equally important reason to actively identify patients with this condition. In this study, the demographics and comorbidities of the 176 participants were compared to those with more severe forms of ED who had participated in previous double-blind ED trials with sildenafil. This comparative group included 14,537 patients who had participated in one of 67 studies. While the prevalence of many comorbidities were lower in the mild ED group when compared to those with more severe disease, the data are consistent with the conclusion that mild ED may simply provide an opportunity to diagnose comorbidities earlier.

Specifically, when compared to individuals with more advanced ED, patients with mild ED had lower rates of hyperlipidemia (7.1% vs. 11.3%), hypertension (26.1% vs. 32.8%) and diabetes mellitus (13.6% vs. 22.1%) (Figure 2). Yet those with mild ED were younger (mean age 50 years vs. 55 years), suggesting that they may just be at an earlier point in the same trajectory in regard to comorbid diseases. Indeed, the body mass index (BMI) (29 vs. 28 kg/m^2) was almost the same, while the rate of dyslipidemias was actually higher in the mild ED group (5.1% vs. 0.4%). Other comorbidities, such as depression (6.3% vs. 5.6%) and benign prostatic hyperplasia (9.7% vs. 9.9%), were similar.

Figure 2. **Comorbidity and CV Risk Factor Rates**



Adapted from Lee et al. *BJU Int* 15 Oct 2010;Epub ahead of print.

The study further confirmed mild ED as a signal of important comorbidities and CV risk factors by comparing the mild ED population with a nationwide

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survey of Canadian men. Findings were consistent with the premise that identification of mild ED can help physicians increase their level of suspicion in regard to comorbidities and CV risk factors. The mild ED patients had a higher prevalence of hypertension (26.1% vs. 17.9%) and smoking (27.8% vs. 19.8%). The prevalence of diabetes (13.6% vs. 6.7%) and obesity (33.5% vs. 16.4%) were both approximately twice as high in the mild ED population when compared to an unselected population of men.

IMPLICATIONS FOR CLINICAL PRACTICE

The data from these studies indicate that mild ED is an important clinical entity that should be identified and treated. As implied from these data, the opportunity for benefit is twofold. A large proportion of patients with mild ED can achieve improvement or relief of symptoms with a PDE-5 inhibitor. Secondly, the presence of mild ED may signal individuals with CV risk factors who will benefit from treatments directed at these comorbidities. Formal strategies for identifying these patients are appropriate.

Due to the close correlation between the presence of mild ED and CV risk factors, these should be considered reciprocal signals for evaluation. Specifically, middle-aged male patients with elevated blood pressure and blood lipids, diabetes mellitus, metabolic syndrome or other signs of CV risk should be screened for mild ED. In smokers, the risk of ED is an excellent incentive to initiate a smoking cessation plan in addition to lowering CV risk. Conversely, a thorough examination of CV risk factors is appropriate in those who present with a history of ED, including mild ED.

The evaluation of sexual function should not be reserved for those who volunteer this complaint. Rather, questions of sexual function are appropriate in routine history-taking because of the relationship between sexual function and life satisfaction as well as the relationship of sexual function with underlying pathologies, including those involving urological, psychological or CV systems. Formal methodology for evaluating sexual function, such as the IIEF self-report, is appropriately reserved for detailed clinical investigation in those who have already reported impaired sexual function, but questions that provide the patient with the opportunity to report even mild symptoms of ED are needed.

The first well-controlled trial to evaluate a PDE-5 inhibitor in mild ED by Bénard et al. validates the benefits of treatment, but also provides a basis for encouraging clinicians to recognize the link between ED and vascular disease. While not all patients with vascular disease have ED and vice-versa, mild ED, like ED of greater severity, does signal an increased likelihood of the presence of treatable CV risk factors. It is important to routinely pursue both diagnoses when either one is present.

SUMMARY

The recently published study of sildenafil in the treatment of mild ED demonstrates that even modest ED symptoms represent a threat to patient well-being. Data generated by this study have also provided the basis for concluding that mild ED, like the more severe forms, may represent a signal of underlying vascular disease. Indeed, the term "mild ED" appears to be misleading. While the term "mild" may be appropriate as a relative descriptive term for the degree of dysfunction, the implication that this condition does not deserve the degree of attention provided to more severe forms of ED is challenged by these new data. Instead, mild ED appears to be at least as responsive to therapy, to provide large improvements in patient satisfaction and to provide a similar signal of vascular disease when compared to more severe forms of ED. □

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