

MEDICAL THERAPY FOR ASYMPTOMATIC MEN WITH BENIGN PROSTATIC HYPERPLASIA: PRIMUM NON NOCERE

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Medical therapy for benign prostatic hyperplasia (BPH) has become the most widely accepted first-line therapy for symptomatic men with BPH. Alpha-blockade and 5-alpha-reductase inhibitors are safe and effective and have long-term durability. During the past 5 years, an increasing body of evidence has emerged that suggests that medical therapy may also impact on the progression of BPH. Specifically, the Proscar Long-Term Efficacy and Safety (PLESS) and Medical Therapy of Prostate Symptoms (MTOPS) studies have clearly demonstrated that medical therapy can halt various progression parameters, including worsening of symptoms, incidence of urinary retention, and the need for invasive surgery.^{1,2} On the basis of these exciting results, some have suggested that even earlier intervention with medical therapy for men at risk of BPH should be considered and, at times, instituted. These suggestions do not seem scientifically, economically, or logistically reasonable.

The incidence of BPH is increasing, along with an increasing average life expectancy. Data have suggested that the incidence of histologic BPH is 50% in men who are 60 years old, and as great as 88% in men up to 80 years of age.³ Clinical BPH, defined as a prostate weight greater than 20 g (as measured by transrectal ultrasonography) in association with symptomatic urinary dysfunction and/or a urinary flow rate less than 15 mL/s, without associated malignancy, has been identified in 1 in 5 men between the ages of 40 and 64 and 2 in 5 men older than 65 years of age.⁴ Clearly, BPH impacts significantly on the aging male population. However, it should be emphasized that these estimates are in men with lower urinary tract symptoms.

Most of the superb longitudinal data analyzing community-dwelling men with BPH such as the Olmsted County studies have consistently identified men at risk of progression of disease. These include men older than 60 years of age, those who have lower flow rates at baseline (ie, less than 12 mL/s), and have larger prostate volumes (ie, greater than 30 cm³).⁵ However, the seminal baseline parameter in distinguishing men at risk of progression is identifiable lower urinary tract symptoms. Asymptomatic men have not been found to be at increased risk.

In a more recent analysis of this population, Sarma *et al.*⁶ demonstrated that longitudinal changes in men with lower urinary tract symptoms is highly variable, with an average of 0.3 points per year on the International Prostate Symptom Score questionnaire. This may not be associated with concomitant changes in bother. Does this warrant intervention in patients who are asymptomatic? In fact, in these population studies, men with an International Prostate Symptom Score of 0 to 7 are assigned a relative risk of 1 (ie, a control).

Perhaps symptoms are not a good proxy for identifying men at risk of disease progression. Are there asymptomatic men who may be highly obstructed and theoretically at risk of progression? Walker *et al.*⁷ performed an elegant study examining pressure flow data in asymptomatic men 45 years old or older. In this group of men, 13% had unequivocal obstruction, 29% were equivocally obstructed, and 58% were unobstructed. The investigators concluded that obstruction might not be important in the development of symptoms.

In a review by Tubaro *et al.*,⁸ the tenuous association among urodynamic findings, symptoms, and ultrastructural changes within the bladder were examined. Detrusor hypertrophy, defined as smooth muscle proliferation, fibroblast hyperplasia, and reorganization of the extracellular matrix, occurs as a patient ages. These aforementioned changes affect detrusor contractility, function, and presumably lower urinary tract symptoms. The association between these ultrastructural changes and bladder outlet obstruction is more defined

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than their relationship to the presence or absence of lower urinary tract symptoms.

Ultimately, does early intervention alter or reverse the changes within the bladder? Heretofore, the methods used to answer these questions used proxies for "progression events" (ie, urinary retention and the need for surgery such as in the PLESS trial).¹ In addition, preliminary data from the MTOPS study suggest that monotherapy with an alpha-blocker or a 5-alpha-reductase inhibitor or combination therapy with both of these agents significantly reduces symptom progression.² However, in both of these studies, patients randomized into the study had moderate or severe symptoms. One cannot extrapolate these findings to an asymptomatic group of men. These findings underscore that until definitive proxies for disease progression in this population are better defined, medical therapy seems imprudent.

Practical considerations also exist. Compliance with medication is, at best, tenuous. Even when medication is provided without cost and patients are followed up on a regular basis, the drop-off rate with medications approaches anywhere from 10% to 20% annually. Kaplan *et al.*⁹ found that 35% of patients stopped medications after 2 years. Moreover, these findings were in men who were symptomatic. What is the motivation for a patient to take daily medications, either as monotherapy or in combination, who has no symptoms, is not bothered by his condition, and with no data to document that his therapy is halting disease progression?

Finally, the economic considerations involved in treating asymptomatic men with BPH are substantial. Some urologists have criticized the results of the PLESS and MTOPS trials because the absolute number of patients who enjoyed these benefits was small. One could argue that these results have increasing clinical significance as the duration of therapy and follow-up increases. However, given the low likelihood of finding significant benefit in asymptomatic men, even fewer physicians would

prescribe these medications, and, certainly, less insurance reimbursement would be expected.

Our primary goal in treating BPH is not to increase the number of prescriptions written. Moreover, we should not be in the business of expanding indications for treating quality-of-life disorders. It is incumbent on us to continue to develop recognizable and widely accepted baseline proxies that help us to identify which patients should be treated and who would benefit most. The concept of, "first, no harm to our patients" has never been more evident than in unnecessarily and imprudently treating asymptomatic men with BPH.

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