# The Efficacy and Safety of Tamsulosin for the Medical Treatment of Benign Prostate Hyperplasia

*Levent Ozdal, MD,* *Research Fellow, Department of Urology, McGill University, Montreal, QC.*

*Simon Tanguay, MD, FRCS(C),* *Associate Professor, Department of Urology, McGill University, Montreal, QC.*

Benign prostate hyperplasia (BPH) is the most common benign neoplasm in aging men. Although microscopic evidence of BPH occurs in 80% of men who are at least 80 years old, clinical enlargement of the gland only occurs in half of all men in this age group. Furthermore, symptomatic disease only develops in about half of men with clinically enlarged prostate glands.[1]

Lower urinary tract symptoms (LUTS) of BPH can be obstructive or irritative in nature. Most symptoms occur and progress slowly in aging men. The treatment of BPH is usually indicated once patients develop either moderate or severe symptoms, or in the presence of complications due to bladder obstruction. Complications of BPH due to chronic obstruction include recurrent urinary tract infection, bladder stones, incontinence, gross hematuria, urinary retention or renal failure.

The aim of BPH treatment should include improving or eradicating symptoms, reversing the complications of the disease and preventing additional sequelae. Treatment is typically based on the severity of symptoms and patient preference.[2] Although treatment options include both medical and surgical approaches, medical therapy remains the first-line treatment for most patients with LUTS suggestive of BPH. Medical treatment can be directed at either the static (related to mechanical obstruction by an enlarged prostate) or the dynamic (caused primarily by the smooth muscle tone in the prostatic urethra and bladder neck) components of BPH. Finasteride, a 5-α reductase inhibitor, reduces dihydrotestosterone (DHT) by blocking its conversion from testosterone.[3-5] This reduction in DHT provokes a slow decrease in prostate volume affecting the static component of BPH.[6] Given that its clinical efficacy is associated with a reduction in prostate size, it is not surprising that finasteride was found to be effective mainly in men with enlarged prostates (≥ 40 g).[7] Furthermore, symptomatic relief is usually noticed only months after initiation of therapy.

**The treatment of BPH is usually indicated once patients develop either moderate or severe symptoms, or in the presence of complications due to bladder obstruction.**

The dynamic component of obstruction can be treated with $\alpha_1$-adrenergic antagonists. Three types of $\alpha_1$-adrenergic receptors have been identified. The $\alpha_{1A}$ adrenoreceptors are found predominantly in the prostate, whereas the $\alpha_{1B}$ and $\alpha_{1D}$ receptor subtypes are present in higher concentrations in the smooth muscle of large arteries. The pharmacological effect of this class of medication leads to smooth muscle relaxation within the prostate gland and urethra, resulting in enhanced urinary outflow. These agents are effective in producing symptomatic relief of obstructive voiding in 60-70% of treated patients and increase peak and mean urinary flow rate by 16-25%.[2,8]

There has recently been an evolution in the availability and use of different α-blockers for the treatment of BPH. Non-selective agents such as phenoxybenzamine were initially used and subsequently replaced by a short-acting α1 blocker (prazosin), by a long-acting α1 blocker (terazosin, doxazocin) and, finally, by the availability of uroselective $\alpha_{1A}$-adrenergic antagonists such as tamsulosin or alfuzocin (not yet available in Canada).[1] The selective $\alpha_{1A}$-adrenoreceptor antagonists became more popular because of their specificity to the urinary tract, their reduced adverse effects and the simplicity of the dosing regimen.[9]

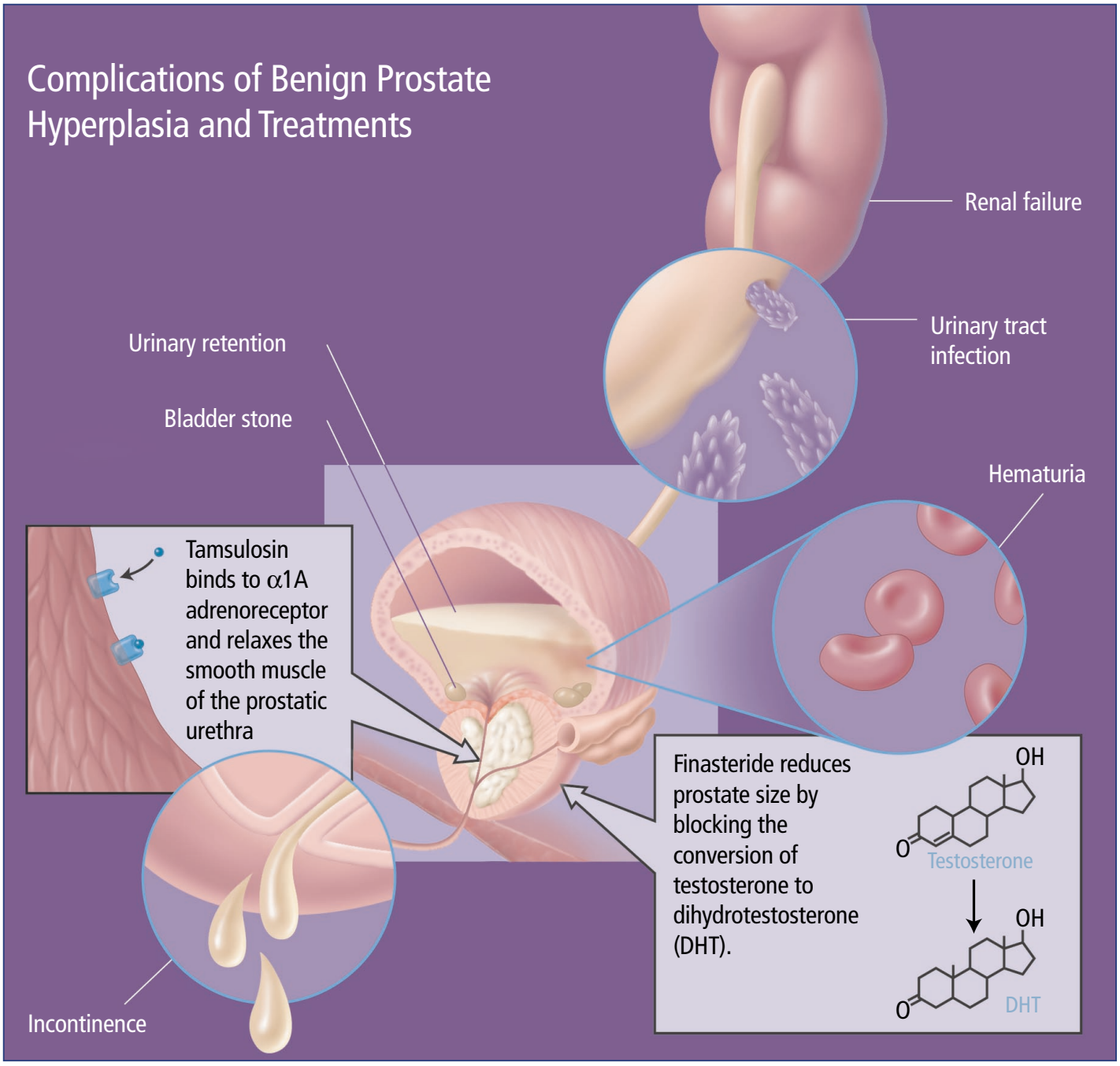
The safety and efficacy of tamsulosin were tested in a number of placebo-controlled studies. The extensive evaluation confirmed the ability of tamsulosin to significantly improve both urinary flow rates and symptom scores in the patient population tested. These two measures represent the objective assessment of the efficacy of any therapeutic approach used in patients with BPH. The benefit observed with tamsulosin was not dose-related, as no clinical benefit was observed in most patients when dosage was increased from 0.4 mg to 0.8 mg. Therefore, 0.4 mg was selected as the recommended dose.[10-14]

Tamsulosin is well tolerated by the vast majority of patients. The most common side effect observed is retrograde ejaculation. Other side effects reported were observed in less than 5% of treat-

ed patients and consist of dizziness, headache, rhinitis and tachycardia / palpitation. These adverse events were found to be dose-related and more frequent in patients treated with a higher dose (0.8 mg). Interestingly, tamsulosin was found to have no significant effect on blood pressure. Orthostatic hypotension was reported in only 0.2–0.4% of treated patients.[12-14]

In treating elderly patients, an important factor in the selection and use of an α-blocker relates to interactions with other medications. Michel *et al.* evaluated the tolerability of tamsulosin in over 19,000 patients and found that a small subset of patients may have decreased tolerability related to either comorbid disease (hypertension, cardiovacular disease) or to the use of medications such as diuretics and antihypertensives. However, despite these minor interactions, 90-95% of patients reported a good to very good tolerability and only 5% of patients had to discontinue treatment because of drug-related side effects.[15]

One of the major benefits associated with the use of tamsulosin relates to the absence of a 'first dose' effect, observed with the other α-blockers. This benefit allows the clinician to initiate therapy at the maximal dose, avoiding the need for titration that constituted an occasional source of confusion for the elderly patient.[16-22]



Although tamsulosin constitutes a good therapeutic choice, other α-blockers such as terazosin and doxazosin have proven efficacy in patients with symptomatic BPH. Both medications were found to significantly improve both urinary flow rates and symptom score when compared to placebo. However, their side effect profiles differ from the uro-selective tamsulosin. As expected from their pharmacodynamics, both terazosin and doxazosin may affect patient's blood pressure, although this effect on blood pressure was only observed in hypertensive patients. No significant change in systolic or diastolic blood pressure was observed in normotensive patients. Although usually minor, these adverse effects can lead to significant morbidity in elderly patients. Therefore, when prescribing these drugs, blood pressure must be carefully monitored with readjustment of antihypertensive medication as needed.[23-25]

The long-term efficacy of tamsulosin was extensively evaluated. The consensus resulting from different studies confirmed that the clinical improvement observed during the first four weeks of therapy is maintained for the long term. Furthermore, tamsulosin remains well tolerated. In fact, the side effect profile remains similar during either short- or long-term use with the most common adverse event being retrograde ejaculation. This adverse event is dose-related and occurs in 26% and 10% of patients treated with 0.8 mg and 0.4 mg of tamsulosin, respectively.[26-29]

In conclusion, the α-adrenoceptor antagonists are commonly used and constitute an effective treatment for symptomatic BPH. The development of a new generation of uroselective α-blockers has greatly facilitated the use of this class of medication and improved the side effect profile of these drugs. The use of tamsulosin in elderly patients with comorbid disease remains safe and rarely requires dose titration or the adjustment of antihypertensive medications. ◆

## References


1. Lee M. Tamsulosin for the treatment of benign prostate hypertrophy. Ann Pharmacother 2000; 34: 188-99.
2. US Department of Health and Human Services Public Health Service Agency for Health Care Policy and Research. Clinical practice guideline number 8. Benign Prostate Hyperplasia diagnosis and treatment. Rockville, MD: US Department of Health and Human Services, 1994: 1-215.
3. Rittmaster RS, Stoner E, Thompson DL, et al. Alpha reductase inhibitor, on serum androgens and androgen conjugates in normal men. J Androl 1989; 10: 259-62.
4. Grino P, Stoner E and the Finasteride Study Group. Finasteride for the treatment and control of benign prostatic hyperlasia: Summary of phase III controlled studies. Eur Urol 1994; 25(Suppl 1): 24-8.
5. Stoner E. Three year safety and efficacy data on the use of finasteride in the treatment of benign prostate hyperplasia. Urol 1994; 43: 284-92.
6. Boyle P, Gould A, Roehborn C. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride; meta-analysis of randomized clinical trials. Urol 1996; 48: 398-405.
7. Tammela T. Benign prostatic hyperplasia. Drugs and Aging 1997; 10: 349-66.
8. Chapple CR. Selective α1-adrenorecetor antagonists in Benign Prostatic Hyperplasia: Rationale and Clinical Experience. Eur Urol 1996: 29; 129-44.
9. Holtgrewe HL. Current trends in management of men with lower urinary tract symptoms and benign prostatic hyperplasia. Urol 1998; 51 (Suppl 4A): 1-7.
10. Chapple CR, Wyndaele JJ, Nordling J, et al. Tamsulosin, the first prostate-selective α1a-adrenoreceptor antagonist. Eur Urol 1996; 29: 155-67.
11. Abrams P, Schulman CC, Vaage S, et al. Tamsulosin, a selective α1a-adrenorecetor antagonist: A randomized, controlled trial in patients with benign prostatic "obstruction" (symptomatic BPH). Br J Urol 1995; 76: 325-36.
12. Narayan P, Tewari A and Members of United States 93-01 Study Group. A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. J Urol 1998; 160: 1701-6.
13. Lepor H for the Tamsulosin Investigator Group. Phase III placebo controlled study of tamsulosin in benign prostatic hyperplasia. Urol 1998; 51: 892-900.
14. Narayan P, Bruskewitz R. A comparison of two phase III multicenter placebo-controlled studies of tamsulosin in BPH. Adv In Ther 2000: 17; 287-300.
15. Michel MC, Mehlburger L, Bressel HU, et al. Tamsulosin treatment of 19365 patients with lower urinary tract symptoms: Does comorbidity alter tolerability? J Urol 1998; 160: 784-91.
16. Lee E, Lee C. Clinical comparison of selective and non-selective α1-adrenoreceptor antagonists in benign prostatic hyperplasia: Studies on tamsulosin in a fixed dose and terazosin in increasing doses. Br J Urol 1997; 80: 606-11.
17. Tsujii T. Comparison of prazosin, terazosin and tamsulosin in the treatment of symptomatic benign prostatic hyperplasia: A short-term open, randomized multicenter study. Int J Urol 2000; 7: 199-205.
18. Homma Y, Kawabe K, Tsukamoto T, et al. Estimate criteria for efficacy of treatment in symptomatic benign prostatic hyperplasia. Int J Urol 1996; 3: 267-73.
19. Heimbach D and Müller SC. Die behandlung der BPH mit α1 adrenozeptorantagonisten. Urologe A 1997; 36: 18-34.
20. Debruyne FMJ. Alpha blockers: Are all created equal? Urology 2000; 56(Suppl 5A): 20-2.
21. Michel MC, Flannery MT, Narayan P. Worldwide experience with alfuzosin and tamsulosin. Urol 2001; 58: 508-16.
22. Yasukawa K, Swarz H and Ito Y. Review of orthostatic tests on the safety of tamsulosin, a selective α1a-adrenergic receptor antagonist, shows lack of othostatic hypotensive effects. J Int Med Res 2001; 29: 236-51
23. Lepor H, Auerbach S, Puras-Baez A, et al. A randomized, placebo controlled multicenter study of efficacy and safety of terazosin in the treatment of benign prostate hyperplasia. J Urol 1992; 148: 1467-74.
24. Fawzy A, Braun K, George P, et al. Doxazosin in the treatment of benign prostate hyperplasia in normotensive patients: A multicenter study. J Urol 1992; 154: 105-9.
25. Wilde MI, Fitton A, McTawish D. Alfuzosin. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in benign prostate hyperplasia. Drugs 1993; 45: 410-29.
26. Schulman CC, Cortvriend J, Jonas U, et al. Tamsulosin, the first prostate selective α1a-adrenoceptor antagonist. Eur Urol 1996; 29: 145-54.
27. Lepor H for the Tamsulosin Investigator Group. Long term evaluation of tamsulosin in benign prostatic hyperplasia: Placebo controlled, double blind extension of phase III trial. Urol 1998; 51: 901-6.
28. Narayan P, Lepor H. Long term, open label, phase III multicenter study of tamsulosin in benign prostatic hyperplasia. Urol 2001; 57: 466-70.
29. Schulman CC, Tycho M, Lock MTW, et al. Long-term use of tamsulosin to treat lower urinary tract symptoms / benign prostatic hyperplasia. J Urol 2001; 166: 1358-63.