

USEFULNESS OF TRIPLE THERAPY WITH TADALAFIL, TAMSULOSIN AND DUTASTERIDE IN BENIGN PROSTATIC HYPERPLASIA (BPH)

Opinion article

AUTHORS:

Carlos Trodler¹ and Javier Sciuto²

1. Former Prof. Internal Medicine, Universidad de Buenos Aires, Argentina

2. Master in Biostatistics, Former Prof. Schools of Medicine (Uruguay and Brasil)

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SUMMARY

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) represent a prevalent condition that severely impacts the quality of life of aging men. The traditional pharmacological approach combines an alpha-1 adrenergic receptor antagonist (tamsulosin) with a 5-alpha reductase inhibitor (dutasteride), aiming for relaxation of the bladder/prostate smooth muscle and a reduction in glandular volume in the medium to long term. However, this regimen has limitations in providing rapid relief of storage symptoms and is frequently associated with sexual dysfunction (erectile dysfunction, ejaculation disorders, and decreased libido). The addition of tadalafil (a phosphodiesterase type 5 inhibitor , PDE5i) to the tamsulosin and dutasteride combination emerges as a pharmacologically synergistic triple therapy approach. This paper analyzes the pathophysiological basis, clinical efficacy profile, and tolerability balance of this combined strategy.

KEYWORDS: benign prostatic hyperplasia, tadalafil, tamsulosin, dutasteride

INTRODUCTION AND THEORETICAL FRAMEWORK

The pathogenesis of LUTS secondary to BPH involves two main components:

1. Static component: Growth of the stroma and prostatic epithelium mediated by dihydrotestosterone (DHT).

2. Dynamic component: Increased smooth muscle tone in the bladder neck, prostate and its capsule, mediated by the sympathetic nervous system through alpha-adrenergic receptors.

Additionally, factors such as chronic pelvic ischemia, oxidative stress, alteration in the nitric oxide/cyclic GMP (NO/ cGMP) pathway and detrusor overactivity contribute to the persistence of storage symptoms (nocturia, urgency and frequency).

Standard bimodal therapy (tamsulosin + dutasteride), supported by seminal trials such as the CombAT study (Combination of Avodart and Tamsulosin), has been shown to effectively reduce the risk of acute urinary retention and the need for surgery. However, dutasteride takes 3 to 6 months to reach its maximum clinical effect and can induce or worsen erectile dysfunction and loss of libido. Tamsulosin , on the other hand, frequently causes retrograde ejaculation or anejaculation .

The addition of Tadalafil 5 mg daily , approved for the simultaneous treatment of LUTS/BPH and erectile dysfunction (ED), complements a therapy capable of comprehensively addressing the urinary and sexual spheres.

MECHANISTIC BASIS OF TRIPLE THERAPY

The combination of these three drugs acts on complementary and independent pathways:

- **Tamsulosin** (0.4 mg/day): Blocks alpha-adrenergic receptors in the prostate and bladder neck, rapidly

reducing resistance to urine outflow and improving maximum urinary flow rate.

- **Dutasteride** (0.5 mg/day): Inhibits the type 1 and type 2 isoenzymes of 5- α reductase, blocking the peripheral and intraprostatic conversion of testosterone to DHT. This induces apoptosis of the glandular epithelium, achieving a sustained reduction in prostate volume (approximately 20–25% at 12

months).

- **Tadalafil** (5 mg/day): Inhibits PDE5, increasing cGMP levels in prostatic, bladder, and pelvic vascular smooth muscle. It promotes vasodilation, improves tissue perfusion, reduces chronic inflammation in the prostatic stroma, and modulates afferent activity of bladder nerves. Furthermore, it preserves and improves bladder function erectile.

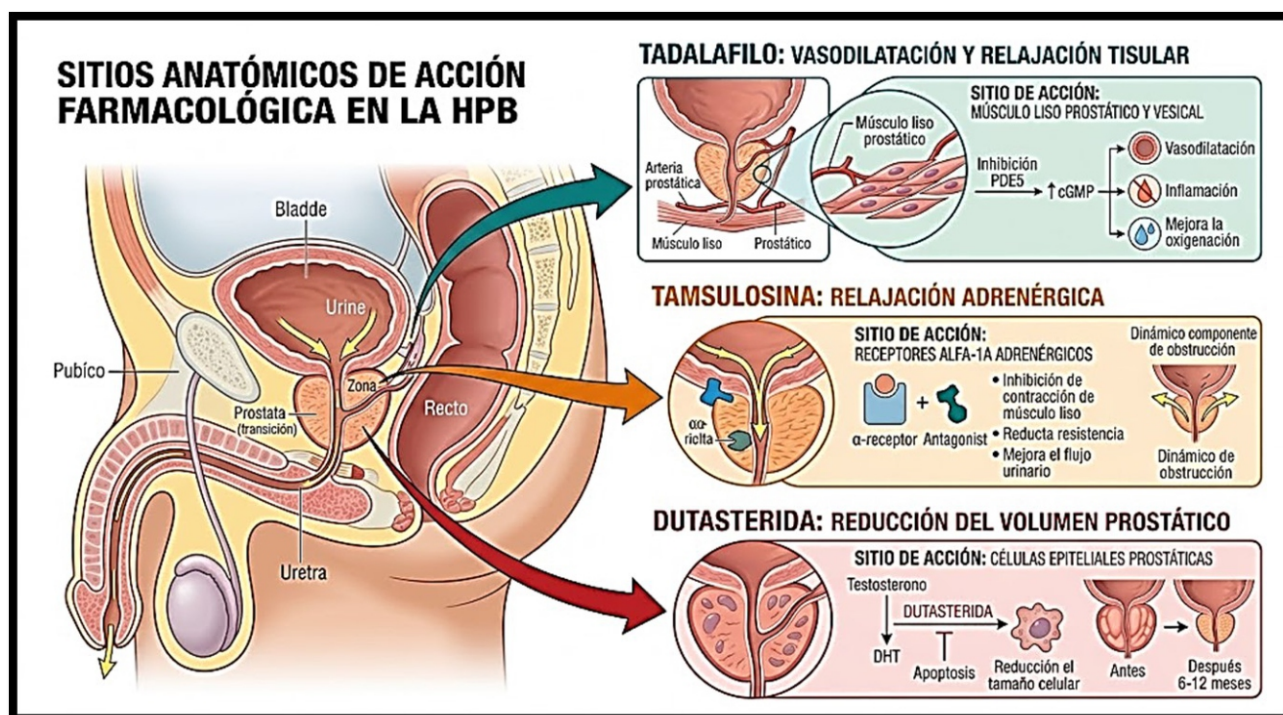


FIGURE 1: SITES OF ACTION OF EACH DRUG

CRITICAL ANALYSIS OF CLINICAL EVIDENCE

1. Urinary Symptoms

Studies evaluating the combination of PDE5i inhibitors with alpha-blockers and 5ARIs show that the addition of tadalafil achieves a significantly greater reduction in International Prostate The Intraperitoneal Symptom Score (IPSS) was compared to monotherapies or dual combinations. In particular, the irritative or storage symptom subscale (urgency, nocturia, and frequency) showed the most marked improvement when tadalafil was included, a domain where tamsulosin and dutasteride often leave a residual deficit.

2. Impact on Sexual Function

The key point in favor of including tadalafil lies in its ability to counteract the adverse sexual effects induced by dutasteride and tamsulosin:

- In randomized clinical trials (e.g., Casabé et al., Roehrborn et al.), the combination of tadalafil with a 5ARI prevented the decline of the International Index of Erectile Function (IIEF) typically observed in the first few months of treatment with dutasteride.
- While tamsulosin and dutasteride may discourage adherence to treatment due to iatrogenic erectile dysfunction, the presence of tadalafil from the initial phase maintains or increases overall patient satisfaction.

3. Considerations on Tolerability and Safety

- **Hypotension and Vasodilation:** Tamsulosin and tadalafil can cause vasodilation. However, clinical data demonstrate that the hemodynamic profile of tamsulosin (highly selective for alpha receptors) combined with 5 mg tadalafil does not result in a statistically significant increase in episodes of

orthostatic hypotension compared to tamsulosin alone.

- **Cumulative Side Effects:** The most commonly reported adverse events in combination regimens include headache, dyspepsia, lumbago and nasal congestion (associated with PDE5i), along with dizziness (associated with the alpha blocker).

CONCLUSIONS

The published scientific evidence supports the addition of tadalafil 5 mg to the combination therapy of tamsulosin and dutasteride, which enhances the therapeutic benefits in the management of BPH. This triple combination holistically addresses smooth muscle relaxation, reduces tissue hypertrophy, and preserves sexual health, with a tolerable and manageable safety profile in clinical practice.

The combination of tadalafil, tamsulosin, and dutasteride constitutes a high-value therapeutic alternative for a well-defined clinical phenotype:

1. Patients with enlarged prostates (>30–40mL) and moderate to severe LUTS who present with concomitant erectile dysfunction.
2. Men with predominantly storage symptoms who do not achieve complete relief with conventional dual therapy (tamsulosin + dutasteride).
3. Patients at high risk of discontinuing dutasteride therapy due to fear or development of induced sexual dysfunction.

From a pragmatic perspective, triple therapy can be used as a rapid induction strategy: administering all three drugs for the first 6 to 12 months to achieve immediate symptomatic relief (tamsulosin + tadalafil) while dutasteride reduces prostate volume. Subsequently, depending on clinical progress and patient preference, gradual discontinuation of tamsulosin can be reassessed, while maintaining dutasteride and tadalafil (or adjusting according to erectile function).

REFERENCES

- [1] Roehrborn, C. G., Siami, P., Barkin, J., Damião, R., Major-Walker, K., Nandy. CombAT Study Group. (2010). The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with benign prostatic hyperplasia: 4-year results from the CombAT study. *European Urology*, 57(1), 123-131.
- [2] Casabé, A., Roehrborn, C. G., Da Pozzo, L. F., Zepeda, S., Sorsaburu, S., D'Vora, (2014). Efficacy and safety of the coadministration of tadalafil 5 mg once daily and finasteride 5 mg once daily in men with lower urinary tract symptoms associated with benign prostatic hyperplasia and erectile dysfunction: a randomized, double-blind, placebo-controlled trial. *The Journal of Sexual Medicine*, 11(5), 1277-1288.
- [3] Becher, E. F., McVary, K. T., & Schulman, C. C. (2014). Tadalafil 5 mg once daily for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. *Expert Opinion on Pharmacotherapy*, 15(11), 1613-1627.
- [4] Gacci, M., Corona, G., Salvi, M., Vignozzi, L., McVary, K. T., Kaplan, S. A. (2012). A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms secondary to benign prostatic hyperplasia. *European Urology*, 61(5), 994-1003.
- [5] Chapple, C. R., Montorsi, F., Tammela, T. L., Wirth, M., Koldewijn, E., & Castro-Díaz, D. (2011). Silodosin versus tamsulosin in the treatment of benign prostatic hyperplasia in men with lower urinary tract symptoms: a randomized, double-blind, placebo-controlled trial. *European Urology*, 59(3), 342-352.
- [6] Singh, D. V., Mete, U. K., Mandal, A. K., & Singh, S. K. (2014). A comparative study of tadalafil alone and in combination with tamsulosin in patients of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Indian Journal of Urology*, 30(2), 194-198.
- [7] Gratzke, C., Bachmann, A., Descazeaud, A., Drake, M. J., Madersbacher, S., Mamoulakis, C. (2015). EAU guidelines on the assessment and non-surgical management of male non-neurogenic lower urinary tract symptoms (LUTS), including benign prostatic obstruction (BPO). *European Urology*, 67(6), 1099-1109.