



# The Adverse Effects of Tamsulosin in Men with Benign Prostatic Hyperplasia, a Review of the Literature

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**Abstract:** In the United States, tamsulosin is the most prescribed drug for benign prostatic hyperplasia (BPH) treatment. However, less is known about the adverse effects and mechanism of action of the drug in the organism. So, the aim of this review is to evaluate the benefits and harms of tamsulosin therapy in patients with BPH. A literature analysis was realized using the database of the National Center for Biotechnology Information (NCBI) MEDLINE®. The data collection was carried out in a retrospective of 10 years from 2008. Thus, we considered some measurements parameters used in different studies for a reliable comparison of the works. Tamsulosin has been characterized as an effective treatment for BPH. However, some studies demonstrate that the epithelial elements remain proliferative even after the administration of the drug and may be involved in the continuous growth of the gland. Also, tamsulosin can directly impact on the ejaculation process, cognitive functions and mental health of men. BPH affects approximately 50% of men between 50 and 60 years old. Beyond that, 90% of men in their eighth decade of life will present anatomical evidence of BPH. Therefore, the treatment with tamsulosin, an  $\alpha 1$ -adrenergic antagonist that promotes the relaxation of the prostate smooth muscle, is essential to diminish the gland size and restore the urinary flow. However, its administration must be assessed for a better response and lower risk of adverse effects in those patients.

**Keywords:** Tamsulosin, Benign Prostatic Hyperplasia, Lower Urinary Tract Symptoms, Adverse Effects, Alpha Antagonist, Prostate

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## 1. Introduction

Benign Prostatic Hyperplasia (BPH) affects 50% of men between 50 and 60 years of age and approximately 90% of men in the eighth decade of life will present anatomical evidence of BPH [1-4]. This pathology is characterized by the proliferation of both smooth muscle cells of the stroma and prostatic epithelial cells, which gradually modify the structure of the organ and cause its increase [5, 6].

Prostate development occurs in three distinct phases throughout a man's life. In the fetal stage, occurs the primary development which is resumed during puberty. In the second phase occurs the differentiation and transition to the adult-like gland. In adulthood, the prostate enlarges over time in only one of its anatomic areas (anterior lobe, middle lobe, posterior lobe, left lateral lobe and right lateral lobe), which

at one time may manifest classic obstructive symptoms of BPH [5, 7].

Some studies indicate that the proliferation of the stromatic and epithelial elements could be correlated to the imbalance between growth factors and steroid hormones that are found inside the gland. Physiologically, the interaction between these molecules would coordinate the rate of proliferation and cell death [5, 8].

In this way, the exacerbated and abnormal proliferation of prostate cells causes glandular growth and compression of adjacent structures, resulting in obstruction of the urinary flow. This dynamic affects directly the patients' quality of life [8-10]. The Lower Urinary Tract Symptoms (LUTS) are classified in obstructive symptoms (reduced urinary flow and incomplete voiding of the bladder) and bothering symptoms (increased frequency of urination, nocturia, urinary urgency

and burning when urinating) [11-13].

The main pharmacological treatment line indicated by the American Urology Association and the European Association of Urology for BPH are the inhibitors of the 5- $\alpha$ -reductase (5-ARI) [14-18]. However, these drugs generate many adverse effects, including the alteration of the corpus cavernosum morphology and the reduction of nitric oxide synthesis in the vascular endothelium [19, 20].

To diminish these adverse effects, some lines of pharmacological treatments and protocols have been reviewed, in which the tamsulosin therapy is highlighted. Tamsulosin was the 45<sup>th</sup> most prescribed drug in the United States in 2017 [21] and it is part of the class of selective  $\alpha$ -blockers for subtype 1A [13, 22, 23].

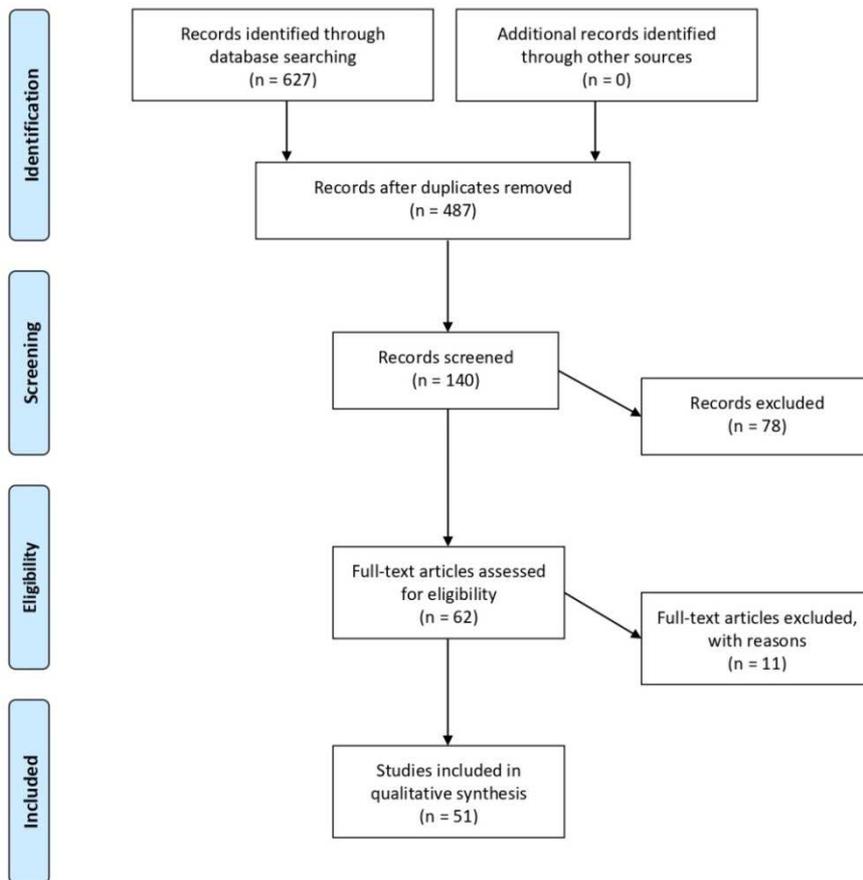
The majority of adrenergic receptors found in the prostate gland are part of the subtype  $\alpha$ 1A that are correlated with the contraction of the stromal smooth muscle. The  $\alpha$ 1B receptors

are predominant in the smooth muscle of the tunica media, in the arteries and veins. There,  $\alpha$ 1B receptors guarantee the vascular tone and regulate the vasoconstriction process.

Thus, tamsulosin, as an  $\alpha$ -blocker 1A, has a therapeutic advantage over non-specific  $\alpha$ -blockers, since they interact with both  $\alpha$ 1A and  $\alpha$ 1B receptors. Blockade of  $\alpha$ 1B receptors causes vascular smooth muscle relaxation, that can result in severe hypotension as the main adverse effect. Tamsulosin, however, proves to be safer in this regard because of its selectivity [12, 23, 24].

While some tamsulosin effects are well known, many others are not a consensus in the scientific community. Therefore, the present literature review seeks to determinate the updates of BPH treatment with tamsulosin in order to expose and analyze the benefits and harms related to its administration.

## 2. Methods



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Figure 1. Flowchart of articles assessed during the study.

A literature analysis was realized using the database of the National Center for Biotechnology Information (NCBI) MEDLINE®, from the PubMed tool. The Medical Subject Heading (MeSH) and key-words used for identification of relevant studies were “tamsulosin”, “benign prostatic hyperplasia”, “lower urinary tract symptoms”, “BPH” and “LUTS”. The data collection was carried out in a retrospective of 10 years from 2008. Thus, we considered some measurements parameters used in different studies for a reliable comparison of the works.

For this, the following parameters were validated: International Prostate Symptom Score (IPSS), which consist in seven questions about the symptoms and one question about the quality of life, classifying the patients according to the severity of the symptoms in mild, moderate and severe; Prostate Volume (PV), which evaluates the size of the gland by transurethral ultrasound; Maximum Flow Rate (Qmax) that determines the maximum urinary flow through uroflowmetry; and IPSS-QoL (Quality of Life) that consists of subjective questions about the patient coexistence with BPH. Other parameters of evaluation were used in some articles, as The International Index of Erectile Function (IIEF-5), important in the correlation between LUTS treatment with tamsulosin and erectile dysfunction.

In the data identification period, 627 articles were found. Among them, divergent articles were excluded from the subject matter. Economic analysis, pharmacodynamic approaches, drug interactions, dose adjustments, combined therapies, and clinical trials were excluded. In the end, 140 articles were evaluated within the established parameters. Thus,

62 articles followed for eligibility and among them, 11 were excluded due to failures or inconsistencies. Therefore, 51 articles were included in the analysis of this review [figure 1].

### 3. Results

Data from the articles included in this study showed aspects concerning the effects of tamsulosin. According to Wein et al., Aslan et al. and Rosen et al. the presence of LUTS associated with BPH is a major factor for the development of sexual dysfunction. Therefore, the therapy with tamsulosin could act as a predisposing factor for even higher risk of sexual dysfunction. However, some studies demonstrated that the drug does not alter this function, as shown by Matsushita et al., Kim et al., Seo et al. and Traish et al. For Shelbaia et al., the tamsulosin treatment showed improvement in erectile function and sexual desire. Choi et al. found that patients receiving tamsulosin had a better profile of premature ejaculation. Overall, the majority of placebo-controlled studies showed that tamsulosin could have some impact on those sexual functions and cause abnormalities.

The quality of life in patients with LUTS/BPH appears to increase when treated with tamsulosin. Yoshida et al. and Kim et al. showed the impact that symptoms regression could do on men mental health. Other effects correlated with this treatment is a higher risk of hypotension, as demonstrated by the study of Bird et al. and a higher risk of developing dementia found by the researcher Duan et al. The findings are summarized in Table 1.

*Table 1. Effects of Tamsulosin and 5-ARIs in different studies.*

Reference	Type of Article	Year	Country	Sample	Dose	Conclusion
Wein et al. <sup>13</sup>	Original	2009	USA	11834 men	-	LUTS are associated with common sexual dysfunctions in men.
Da Silva et al. <sup>19</sup>	Original	2018	Brazil	30 SHR; 30 Wistar-Kyoto	Dutasteride 0.5 mg.kg <sup>-1</sup> OD and Finasteride 5.0 mg.kg <sup>-1</sup> OD	Both 5-ARI promoted penile morphological modifications in control and BPH rat models.
Pinsky et al. <sup>20</sup>	Original	2011	USA	20 Sprague-Dawley	Dutasteride 0.5mg.kg <sup>-1</sup> OD	DHT reduction by 5-ARIs would impair the nitric oxide relaxant pathway that facilitates erection.
Bird et al. <sup>24</sup>	Original	2013	USA, Canada	383567 men	-	The incidence for hypotension was higher for tamsulosin than for 5-ARIs.
Kim et al. <sup>30</sup>	Original	2014	Korea	220 men	Tamsulosin 0.2 mg OD and Tamsulosin 0.4 mg OD	Tamsulosin 0.4 mg is safe for treatment of LUTS secondary to BPH in patients who do not respond to 0.2 mg treatment.
Matsushita et al. <sup>33</sup>	Original	2010	Japan	75 men	Tamsulosin 0.2 mg OD	Significant improvement of LUTS in men with BPH, however it was not noticed changes of erectile functions.
Yoshida et al. <sup>35</sup>	Original	2010	Japan	160 men	Tamsulosin 0.2 mg OD	The Tamsulosin treatment improved the quality of life of patients with BPH by reducing the nocturnal frequency.
Kim et al. <sup>36</sup>	Original	2015	Korea	93 men	Tamsulosin 0.2 mg OD	Treatment with tamsulosin improved LUTS and decreased depressive symptoms in men with BPH.
Duan et al. <sup>40</sup>	Original	2016	USA	253136 men	Tamsulosin 0.2 mg OD and Tamsulosin 0.4 mg OD	Tamsulosin may increase the risk of dementia in older men with BPH.
Choi et al. <sup>42</sup>	Original	2014	Korea	29 men	Tamsulosin 0.4 mg OD	Patients with BPH that received Tamsulosin showed an improvement in LUTS and better profile of premature ejaculation.
Kim et al. <sup>43</sup>	Original	2013	Korea	138 men	Tamsulosin 0.2 mg OD	Tamsulosin improved the symptoms of men with BPH. However, it did not exhibit impact on sexual function or ejaculatory function.

Reference	Type of Article	Year	Country	Sample	Dose	Conclusion
Yu et al. <sup>45</sup>	Original	2011	Taiwan	209 men	Tamsulosin 0.2 mg OD and Silodosin 4.0 mg twice a day	The trial shows the non-inferiority of Silodosin to Tamsulosin in patients with symptoms of BPH. The combination therapy with Tamsulosin and Solifenacin was effective for LUTS, but not to erectile function.
Seo et al. <sup>46</sup>	Original	2010	Korea	57 men	Tamsulosin 0.2 mg OD and Solifenacin 5.0 mg OD	Tamsulosin showed an improvement on the erectile function and sexual desire.
Shelbaia et al. <sup>47</sup>	Original	2011	Egypt	60 men	Tamsulosin 0.2 mg OD	Silodosin is comparable to Tamsulosin in the treatment of BPH. However, retrograde ejaculation can be caused as an adverse effect.
Pande et al. <sup>48</sup>	Original	2014	India	53 men	Tamsulosin 0.4 mg OD and Silodosin 8.0 mg OD	Long-term Finasteride therapy results in worsening of ED, effect that is not noticed in Tamsulosin therapy.
Traish et al. <sup>49</sup>	Original	2015	USA	470 men	Tamsulosin 0.4 mg OD and Finasteride 5.0 mg OD	Sildenafil combined with Tamsulosin improved LUTS, erectile function, and quality of life more than Tamsulosin monotherapy.
Fawzi et al. <sup>51</sup>	Original	2016	Egypt	150 men	Tamsulosin 0.4 mg OD and Sildenafil 25.0 mg OD	Watchful waiting is an appropriate for those with minimal symptoms, as ejaculatory disorders were seen in 18% of patients using $\alpha$ -blockers.
Herberts et al. <sup>10</sup>	Review	2016	USA	-	-	Treatment may include lifestyle interventions and behavioral modifications as well as medication and surgery. Only treatments with clinical effectiveness should be used.
Abrams et al. <sup>11</sup>	Review	2009	USA	-	-	The data showed that tamsulosin offers advantages over other $\alpha$ 1-antagonists in patients with LUTS.
Dunn et al. <sup>22</sup>	Review	2002	New Zealand	-	-	Tamsulosin showed improvement in symptoms related to BPH. The adverse events of Tamsulosin were not different to the placebo group.
Ren et al. <sup>32</sup>	Review	2005	China	2455 men	-	The LUTS was significantly associated as a risk factor for erectile dysfunction.
Aslan et al. <sup>34</sup>	Review	2009	Turkey	69 men	-	The research firmly established that ED is highly prevalent in men with LUTS associated to BPH.
Rosen et al. <sup>44</sup>	Review	2005	USA, France	-	-	Combination treatment with Dutasteride and Tamsulosin is significantly superior to monotherapies in terms of symptom improvement.
Dimitropoulos et al. <sup>50</sup>	Review	2015	Greece	-	-	

Legend: LUTS = Lower Urinary Tract Symptoms; SHR = Spontaneously Hypertensive Rats; 5-ARI = 5-alpha reductase; BPH = Benign Prostatic Hyperplasia; DHT = Dihydrotestosterone; ED = Erectile Dysfunction.

## 4. Discussion

The progression of BPH would be related to sex hormones, which act together after binding on their receptors. Thus, the conversion of 5- $\alpha$ -androstenedione in dihydrotestosterone (DHT) by the 17 $\beta$ -hydroxysteroid dehydrogenase, is directly related to the proliferation of the epithelial elements of the prostate [2]. In addition, androstenedione is converted by aromatase into estrogen (E1) which is later converted to estradiol (E2). This hormone will bind to estrogen-alpha receptors that regulate cell proliferation in the prostatic stroma of patients with BPH [2, 25-27].

The glandular growth, then, is directly related to the intra-prostatic concentration of DHT and E2 throughout the life of a man. Although there is a basal rate of apoptosis, the constant activation of those receptors by sexual hormones propitiates cellular proliferation that causes an unbalance in the prostatic tissue homeostasis [28].

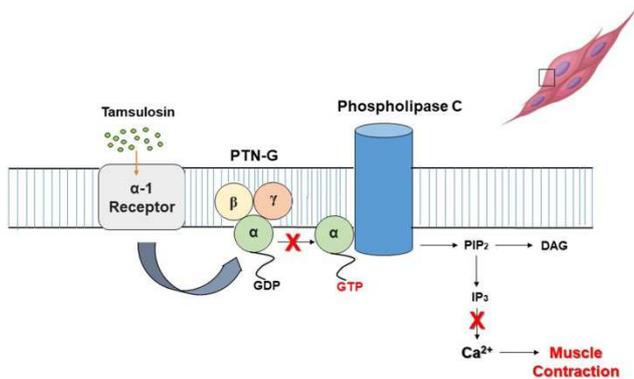
Regarding pharmacokinetics, Tamsulosin has a half-life of 9 to 13 hours in healthy people and 14 to 15 hours in the elderly. The drug is administrated by the oral route, which the

time needed to reach the maximum concentration is 4 hours fasting and 6 hours after a meal. The bioavailability of tamsulosin is complete (100%) and the drug has a 99% binding rate to plasma proteins, being metabolized in the liver by cytochrome P450 (CYP3A4 and CYP2D6). Elimination occurs from urine (76%) and feces (21%) [22].

Androgenic receptors are located in large proportions in the prostate, representing about 90% of all receptors for sex hormones present in the gland [2]; the most prevalent  $\alpha$  receptor subtype is the 1A [26]. On average, prostate stromal proliferation accounts for 80% of the volume of hyperplasia, while epithelial proliferation accounts for 20% of that volume. Muscle cells, in turn, correspond to 50% of the stromal volume of the gland [23, 29], where tamsulosin has its effect. In this context, the drug allows the relaxation of the smooth muscle promoting relief of the obstruction in the urethra, decompression of adjacent tissues and improvement of urination [24, 30].

Once the tamsulosin molecule binds to the  $\alpha$ 1-adrenergic receptor, there is an interruption of signal transduction via G protein (PTN-G). In this mechanism, the  $\alpha$ 1A subunit of

PTN-G becomes unable to form the guanosine triphosphate (GTP), which is essential for the activation of phospholipase C. Thus, muscle contraction is inhibited by the absence of calcium ( $\text{Ca}^{2+}$ ) release by the sarcoplasmic reticulum and calcium entry into the cell through the ion channels [figure 2] [31], causing the relaxation of the prostatic stroma and, as a consequence, less troubled voiding profile.



**Figure 2.** Schematic drawing of the inhibitory action of tamsulosin in calcium release.

Legend:  $\alpha$  = Alpha;  $\beta$  = Beta;  $\gamma$  = Gama; PTN-G = Protein G; GTP = Guanosine triphosphate; GDP = Guanosine Diphosphate; PIP2 = Phosphatidylinositol phosphate; IP3 = Inositol triphosphate; DAG = Diacylglycerol;  $\text{Ca}^{+}$  = Calcium.

Wherefore, drug therapy with  $\alpha$ -blockers aims to decrease urinary resistance so the retrograde pressure on the lower urinary system decreases. This relief prevents the progression of the obstruction caused by BPH to acute urinary retention. Hence, there is a reversal of the reduced flow and the incomplete emptying of the bladder symptoms.  $\alpha$ -Blockers are also shown to be effective in reducing spasms of the smooth muscle of the prostate and bladder neck, promoting relief and improvement of patients' quality of life [32].

Although tamsulosin is effective for short-term smooth muscle regression, the drug is not able to prevent the conversion of E1 to E2 by the enzyme aromatase, which allows the continued proliferation of the stromal elements. So, the effects of tamsulosin on this route, both during and after discontinuation of the drug, are still uncertain.

Matsushita et al. hypothesized that tamsulosin may still have a beneficial effect in patients with associated erectile dysfunction since  $\alpha$ -blockers 1A also act to relax the cavernous body and allow the necessary blood flow to the erection [33]. Although this study did not identify a significant improvement of erectile function in patients who used tamsulosin, Aslan et al. identified an improvement of erectile dysfunction in patients taking tamsulosin in his study [34].

The evaluation of nocturia in patients with BPH is contained in the IPSS. Therefore, Yoshida et al. have observed that the administration of tamsulosin guarantees an improvement in this symptom, and hence in the patient's quality of life. It was hypothesized, then, that the lower urinary resistance promoted by the  $\alpha$ -blocker has an

inhibitory effect on the sensitive branch of the urethral nerve, which allows greater complacency of the bladder and greater filling. Thus, increased storage decreases the nocturnal urinary frequency and, in the long term, allows the adjustment of the circadian cycle of regulating hormones, such as vasopressin and atrial natriuretic peptide. The latter promotes fluid reabsorption in the nephron and guarantee less formation of urinary volume [35].

The effect of nocturia on the quality of life of patients with BPH is reflected in the work of Kim et al. which evaluated the incidence of depression in those patients. Thus, the researcher established that the presence of nocturia is one of the symptoms with the greatest impact on mental health. Such a phenomenon can be triggered by the fragmented sleep and incomplete rest of these patients. Treatment with tamsulosin, however, reverses the symptoms of depression in some patients by improving the nocturia profile and other obstructive symptoms of BPH, making it possible to readjust sleep and improve quality of life [36].

Among the  $\alpha$ -blockers available for the treatment of BPH (terazosin, doxazosin, alfuzosin, silodosin, and tamsulosin), tamsulosin has reached higher popularity due to its 10 to 12-fold selectivity for subtype 1A receptors over subtype 1B receptors. When compared to the 5-ARI, tamsulosin presents an advantage in relation to the speed of action in the improvement of the urinary flow profile, which can occur in days, while the 5-ARI take months to present its effects [23, 37, 38].

Some studies, however, suggest that the class of alpha-blockers may be detrimental to various organs that present  $\alpha$ -receptors [24, 39], since the relative specificity of tamsulosin may unbalance the  $\alpha$ -adrenergic ratio in these tissues. That way, it is corroborated that this may be one of the mechanisms behind some adverse effects, such as the findings relating BPH to the cognitive deficit, in which higher rates of dementia were found in patients that have taken tamsulosin for a long period of time [40, 41].

Concurrently, there is a correlation between patients with ejaculatory disorders after the use of  $\alpha$ -blockers, whose explanation is that blockade of  $\alpha$ -adrenergic receptors in the urinary tract causes relaxation of the smooth muscle of the epididymis, seminal ducts, and vas deferens, which can lose the power of contraction and, therefore, of semen ejection. The ejaculatory disorder resulting from tamsulosin is characterized as retrograde ejaculation [33, 42-51].

In order to recognize tamsulosin as an effective treatment for rapid regression and improvement of the prognosis of patients with BPH (especially those at risk of developing acute urinary retention), the possible adverse effects suggested by different studies must be evaluated. Therefore, it is recommended to the physician always to consider the desired effects and possible adverse effects, in order to guarantee the best treatment to the patient.

## 5. Conclusion

Studies on the efficacy and adverse effects of tamsulosin

demonstrated that the drug acts directly on the smooth muscle of the prostatic stroma in order to accomplish a good pharmacological treatment for patients with symptomatic BPH. The epithelial elements, however, do not regress with the administration of tamsulosin and may be involved in the growth of the gland even in patients with regular use of  $\alpha$ -blockers. Although effective, tamsulosin causes adverse effects of ejaculatory and cognitive origin, which should be carefully assessed. So, it's important to compare the side effects that involve  $\alpha$ -blockers and 5-ARI, in order to adjust the treatment according to the patient's perspective. Therefore, further studies are needed to determine whether tamsulosin therapy is more effective than 5-ARI therapy.

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