TURKISH JOURNAL OF UROLOGY Turkish Journal of Urology; 39(4): 264-9 • doi:10.5152/tud.2013.064

ANDROLOGY

Review

The role of phosphodiesterase type-5 inhibitors in treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia

Benign prostat hiperplazisi ile ilişkili alt üriner sistem semptomlarının tedavisinde fosfodiesteraz tip-5 inhibitörlerinin rolü

Mehmet Umul, Tekin Ahmet Serel

ABSTRACT

Phosphodiesterase type-5 (PDE-5) inhibitors are approved as the first line of therapy for the treatment of erectile dysfunction. However, different studies have been performed to study the use of these agents in other areas of urology. There are many studies related to the use of PDE-5 inhibitors as a monotherapy or combination therapy with alpha-blockers for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). It has been shown that contractions induced by various agents or electrical field stimulation in organ bath models of prostatic tissue can be reversed by PDE-5 inhibitors. Age, body mass index and the severity of LUTS are important factors for the selection of patients suitable for this treatment. It has also been reported that the use of PDE-5 inhibitors can relieve the chronic pelvic ischemia and endothelial dysfunction associated with metabolic syndrome. Most of the side effects observed with PDE-5 inhibitors are minimal and tolerable. The use of PDE-5 inhibitors is absolutely contraindicated in patients taking nitrate preparations. A significant interaction has not been observed even when a patient is taking several antihypertensive agents concurrently. Co-administration of alpha-blockers and PDE-5 inhibitors may result in orthostatic hypotension; therefore, patients should be stable on α-blocker therapy before the initiation of the combination therapy, and the initial PDE-5 inhibitor dose should be the lowest possible. In this review, our aim was to evaluate the role of PDE-5 inhibitors in the treatment of LUTS associated with BPH by analyzing the current literature.

Key words: Benign prostatic hyperplasia; lower urinary tract symptoms; Phosphodiesterase type-5 inhibitors.

ÖZET

Fosfodiesteraz tip-5 (PDE-5) inhibitörleri erektil disfonksiyonun medikal tedavisinde ilk seçenek olarak kullanılmaktadır. Bununla birlikte ürolojinin diğer alanlarında da kullanımları farklı çalışmalar aracılığı ile gündeme getirilmiştir. Benign prostat hiperplazisi (BPH) ile ilişkili alt üriner sistem semptomlarının (AÜSS) medikal tedavisinde monoterapi yada alfa blokerlerle birlikte kombinasyon tedavisi şeklinde PDE-5 inhibitörlerinin kullanımı ile ilgili pek çok çalışma mevcuttur. Organ banyosu modellerinde prostat dokusunda çeşitli ajanlar veya elektriksel alan uyarımı ile oluşturulan kontraksiyonların PDE-5 inhibitörleri ile geri dönüştürülebildiği gösterilmiştir. Yaş, vücut kitle indeksi ve AÜSS ciddiyeti bu tedaviye uygun hasta seçiminde önemlidir. Metabolik sendrom ile ilişkili kronik pelvik iskemi ve endotelyal disfonksiyonun PDE-5 inhibitörlerinin kullanımı ile düzelebileceği yönünde yayınlar mevcuttur. PDE-5 inhibitörleri ile görülen yan etkilerin çoğu minimal ve tolere edilebilir niteliktedir. Nitrat preparatları kullanan hastalarda PDE-5 inhibitörlerinin kullanımı kesinlikle kontrendikedir. Hipertansiyon hastalarında çok sayıda antihipertansif ilaç kullanımı dışında belirgin bir etkileşim gözlenmemiştir. Alfa blokerler ile PDE-5 inhibitörlerinin kombinasyonu sonrasında ortostatik hipotansiyon görülebilmektedir. Bu nedenle, hastalar kombinasyon tedavisi öncesi alfa bloker tedavi açısından stabil olmalı ve PDE-5 inhibitörü başlangıç dozu en düşük düzeyde tutulmalıdır. Bu derleme ile BPH ile ilişkili AÜSS'nin tedavisinde PDE-5 inhibitörlerinin rolünün güncel literatür eşliğinde değerlendirilmesi amaçlandı.

Anahtar sözcükler: Alt üriner sistem semptomları; benign prostat hiperplazisi; Fosfodiesteraz tip-5 inhibitörleri.

Department of Urology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey

Submitted:
05.03.2013

Accepted:
30.04.2013

Correspondence:
Mehmet Umul
Department of Urology, Faculty of Medicine, Süleyman Demirel University, 32260 Isparta, Turkey
Phone: +90 246 211 92 63
E-mail: umul7@yahoo.com

Available online at
www.turkishjournalofurology.com

Introduction

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) are bothersome and highly prevalent in men >50 years.[1,2] The following hypotheses are under investigation to explain the relationship between LUTS

and erectile dysfunction (ED): (i) increased Rho-kinase activation[3], (ii) nitric oxide synthase (NOS)/nitric oxide (NO) level decrease or alteration[4], (iii) atherosclerosis affecting the small pelvis[5] and (iv) autonomic nervous system (ANS) hyperactivity.[6] Investigation of these mechanisms and the effect of therapeutic agents, such as PDE inhibitors, on these pathways may provide new treatment options for both ED and LUTS.

The cycle of normal micturition is a complex neuromuscular process involving the bladder, prostate and urethra and the vascular and neurogenic support of these organs. Various adrenergic, cholinergic, and nonadrenergic noncholinergic neurotransmitters released from nerve terminals and endogenous factors released from vascular endothelial sources are responsible for the smooth muscle tone in the lower urinary tract (LUT). The nitric oxide/cyclic guanosine monophosphate signaling pathway and enzymes related to that pathway, such as phosphodiesterase type-5 (PDE-5), seem to play an important role in the relaxation of the smooth muscle of the LUT. PDE inhibitors contribute to the treatment of LUTS by restricting the degradation of the second messenger cyclic GMP. The distribution and functional significance of PDE enzymes vary in different tissues of the LUT. PDE-4 and 5 dominantly appear in the prostate, PDE-1 and 4 are thought to affect the detrusor smooth muscle function, and PDE-5 may be functionally important in the urethra and vasculature.[7-10] Furthermore, Uckert et al.[7] determined the expression of PDE-1, 2, 4, 5, 7, 8, 9 and 10 in the prostate. Therefore, based on the activity of PDE-5 detected in the prostate, PDE-5 inhibitors were assessed for their therapeutic effects on BPH; beneficial effects of the PDE-5 inhibitors, such as sildenafil and tadalafil, on the symptoms and quality of life of men with LUTS, erectile dysfunction, and BPH have also been demonstrated.[11-13] The aim of this review is to present an update on the role of PDE-5 inhibitors in the treatment of LUTS associated with BPH.

Results of basic research studies

The expression of various PDE isoenzymes in prostate tissue has been documented by the agency of molecular biological methods by Uckert et al.[14] PDE isoenzymes were isolated by a reverse transcription polymerase chain reaction (RT-PCR) and anion exchange chromatography. Macroscopically normal, nontumorous prostatic tissues of patients who had undergone radical surgery for prostate carcinoma were used for a basic research study. Although, messenger RNA transcripts encoding PDE-1, 2, 4, 5, 7, 8, 9 and 10 in the various anatomical regions of the prostate were detected, only PDE-4 and 5 were found to have hydrolytic activity in the cytosolic and microsomal fractions.[14] As a result, the authors concluded that PDE-4 and 5 inhibitors may be a therapeutic option for the treatment of urinary obstructions related to BPH.

Phosphodiesterase type-4 was detected in the stromal and glandular areas of the transitional zone by means of laser fluorescence microscopy.[7] However, immunoactivities of PDE-5 and PDE-11 were detected in the glandular and subglandular areas. These findings were also presented as supportive data for the hypothesis of a justification for the use of PDE inhibitors in the treatment of BPH and LUTS.[7]

The effects of different PDE-5 inhibitors (sildenafil, vardenafil, and tadalafil) and PDE-4 inhibitors (rolipram and RP 73401) with increasing concentrations on the tension induced by norepinephrine were analyzed by using the organ bath technique.[15] The tissues were obtained from specimens of patients who underwent surgery for cancer of the prostate or bladder. After exposure of the tissue strips to norepinephrine, PDE-5 and PDE-4 inhibitors were added to the bath. The maximal reversion of tension was obtained with tadalafil.[15] The findings of this study were presented by the authors as the potential mechanism by which PDE inhibitors can impact LUTS and BPH.

The effect of specific PDE inhibitors (PDE 1, 2, 4 and 5 inhibitors) on the contraction of prostatic tissue induced by a vasoconstrictor peptide (endotethelin-1) were also analyzed by the organ bath technique. Rolipram and tadalafil appeared to be the most effective agents to reverse the tension caused by endothelin-1.[16]

The effect of vardenafil, a PDE-5 inhibitor, in a bladder outlet obstruction (BOO) model was investigated. The contractile response of bladder strips to electrical field stimulation (EFS), carbachol and potassium chloride (KCl) was determined for different experimental groups. Chronic treatment with a high dose of vardenafil was found to be protective against BOO-induced contractile dysfunction by carbachol.[17]

Beamon et al.[18] investigated whether sildenafil citrate can inhibit the functional and structural changes of the detrusor in relation to BOO in a murine model. They demonstrated the preventive effects of oral sildenafil treatment for 6 weeks on detrusor hyperactivity and the increase in detrusor muscle hypertrophy and collagen deposition associated with BOO.

Effects of PDE-5 inhibitors in LUTS/BPH

Lower urinary tract symptoms and ED are common problems in aging males. A relationship between these clinical conditions has been proposed. Basic and translational research efforts have provided new medical approaches for the treatment of LUTS associated with BPH.[19] The relationship between storage and voiding dysfunction and benign prostatic obstruction due to prostatic enlargement may develop on the basis of the bladder dysfunction associated with prostatic enlargement or hyperplastic enlargement as a biomarker for generalized LUT dysfunction.[20] The current approach for medical management

Turkish Journal of Urology 2013; 39(4): 264-9
doi:10.5152/tud.2013.064

of LUTS associated with BPH depends on the usage of alpha-1 receptor blockers, such as alfuzosin, doxazosin, silodosin, tamsulosin and terazosin or suppression of the hormonal growth of the prostate by the 5-alpha reductase inhibitors finasteride and dutasteride.[21]

The effect of sildenafil on LUTS/BPH was initially demonstrated by preliminary open-labeled reports.[22,23] These studies indicated a positive effect of sildenafil on LUTS/BPH. A larger randomized, double-blind study on the efficacy of sildenafil that included patients with LUTS, either with or without ED, further supported the data obtained from the initial studies.[24] The improvement of erectile function and LUTS by treatment with sildenafil citrate was thought to be associated with improved quality of life and treatment satisfaction. An improvement in urinary flow rates was not detected.[24] The authors concluded that there may be a new basic pathophysiologic mechanism underlying the relationship between ED and LUTS/BPH.[24] Tuncel et al.[25] compared the efficacy of sildenafil citrate (25 mg, four times per week for 8 weeks), tamsulosin (0.4 mg, once daily for 8 weeks) and the combination of both regimens in 60 men presenting with BPH/LUTS. Although an improvement in the International Prostate Symptom Score (IPSS) was detected in all groups, the improvement of IPSS in the combination and tamsulosin only groups were more prominent in comparison with the sildenafil citrate only group (40.1%, 36.2% and 28.2%, respectively). The improvement of the maximum urinary flow rate (Qmax) was found to be similar in the sildenafil citrate and tamsulosin only groups; however, a significant improvement was observed in the combination group compared with the other groups. Furthermore, the reduction of post void residual urine volume (PVR) was significantly greater in the combination and tamsulosin only groups. The authors concluded that treatment with the combination of sildenafil citrate and tamsulosin was not superior to tamsulosin only for improving voiding symptoms.[25] There is a need for additional, large-scale, randomized, placebo-controlled studies to assess the clinical effects of combination therapies. The acute administration of sildenafil was shown to have a significant effect on urinary flow rates.[26,27] Single-dose (50-100 mg) use of sildenafil citrate seems to provide a significant increase in the Qmax and average urinary flow rate as well as the mean voided volume.

The efficacy of vardenafil twice daily treatment in the management of LUTS/BPH was assessed in a randomized, placebo-controlled study.[28] A significant improvement was indicated by the IPSS, International Index of Erectile Function (IIEF) and quality of life-9 (QoL) scores. No significant change was observed for Qmax or PVR in patients with vardenafil treatment. Consequently, vardenafil treatment was presented as a promising option for LUTS/BPH.[29]

Double-blind randomized, placebo-controlled clinical studies to evaluate the effect of different doses of tadalafil on LUTS/BPH revealed a significant improvement in IPSS scores.[29-32] A significant improvement in the urinary flow rate was not reported. However, only Egerdie et al.[30] reported a significant increase of Qmax with a 2.5 mg daily dosage of tadalafil compared to placebo (1.7 mL/s vs. 1.2 mL/s, respectively).

A recent randomized, double-blind, international, placebo-controlled, parallel-group study assessed men ≥45 yr of age with LUTS/BPH, an International Prostate Symptom Score (IPSS) ≥13, and a maximum urinary flow rate (Qmax) ≥4 to ≤15 mL/s.[33] As a primary objective, the effect of the 5 mg once daily dosage of tadalafil on LUTS/BPH was compared with placebo. The secondary objective was to compare tamsulosin, an alpha blocker that is often used as a first-line treatment for LUTS/BPH, with placebo as an active control. Although, tadalafil and tamsulosin were not directly compared in this study, monotherapy with tadalafil or tamsulosin was found to have a significant effect on LUTS/BPH and Qmax versus placebo.[33]

Impairment of the blood supply of the prostate is one proposed mechanism that is under investigation to explain the relationship between BPH/LUTS and ED. Some studies have shown that the impairment of the perfusion of the transition zone of the prostate was significantly lower and the mean flow resistance index was significantly higher in men with BPH versus healthy subjects.[34-36] These findings may indicate that regular usage of PDE-5 inhibitors may improve the vascular supply of the prostate and be beneficial for the medical management of BPH/LUTS.

To our knowledge, studies examining the efficacy and the adverse effects of the combination therapy of PDE-5 inhibitors with 5-alpha reductase inhibitors have not yet been published.

The improvement of the LUTS seems to be highly associated with the scoring of the baseline IPSS: a better response to the treatment can be obtained with the PDE-5 inhibitors in cases with higher baseline scores.[37] The effectiveness of PDE-5 inhibitor treatment for BPH/LUTS also seems to depend on age and body mass index (BMI). Younger men with low BMI and more serious urinary symptoms have been presented as the best candidates for PDE-5 inhibitor treatment.[37]

Metabolic syndrome and its components, such as diabetes, hypertension and obesity, have major impacts on the quality of life of patients and have socio-economic implications.[38] Although there is no direct medical treatment for metabolic syndrome, lifestyle changes, such as diet modification and increased physical activity, have been shown to be related with an improvement in endothelial function resulting in a reduction in the vascular complications of metabolic syndrome, such as ED. Chronic

ischemia caused by pelvic atherosclerosis and the functional and morphologic changes in the bladder and prostate in relation to metabolic syndrome and its components can be restored by the use of PDE-5 inhibitors.[39,40] Additionally, autonomic nervous system hyperactivity, which is considered to be one of the factors underlying the relationship between LUTS and ED, can be modulated by the use of PDE-5 inhibitors.[41,42]

The current data do not suggest a relationship between the efficacy of PDE-5 inhibitor treatment and prostatic volume, prostate-specific antigen value, acute urinary retention or the need for surgical intervention.[37]

Treatment with PDE-5 inhibitors has not been covered yet by insurance policies for certain indications in Turkey. A retrospective study, including patients who were recommended to take PDE-5 inhibitors for ED complaints, revealed that 10.7% of patients never used the medication and 50% could not continue due to its high cost.[43] After the expansion of the scope of insurance policies, more patient compliance can be achieved in the treatment of ED and other urological disorders. Additionally, successful communication with the patient may be necessary to ensure the continuity of treatment.

Safety

Flushing, headache, dyspepsia, and back pain are the most frequently observed side-effects of PDE-5 inhibitor treatment.[24,28,29,32] The usage of PDE-5 inhibitors with organic nitrates and other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate is absolutely contraindicated.[44] The side-effects of a PDE-5 inhibitors are not worsened by antihypertensive therapy, even when patients are taking several antihypertensive agents.[44] Under some conditions, co-administration of alpha-blockers and PDE-5 inhibitors may result in orthostatic hypotension. Therefore, patients should be stable on α-blocker therapy before the combination therapy is initiated, and the initial dose of PDE-5 inhibitors should be the lowest possible.[44]

In conclusion; the usage of PDE-5 inhibitors for the management of various urogenital disorders comes into question with the growing knowledge of the mechanisms controlling the urogenital system. PDE-5 inhibition results in smooth muscle relaxation and increased pelvic blood perfusion in these tissues and likely modulates afferent nerve activity. This might represent a novel approach in addition to the first line medical treatment for BPH/LUTS. Furthermore, the combination of PDE-5 inhibitors with an alpha-adrenoceptor antagonist or antimuscarinic agent may affect multiple peripheral targets of the urogenital tract. Combination therapy with alpha-blockers may lead to orthostatic hypotension. There is a need for randomized controlled trials to analyze the efficacy and side-effects of combination therapy with PDE-5 inhibitors and 5-alpha reductase inhibitors. Age, BMI and LUTS severity seem to be important parameters in determining the most appropriate candidates for PDE-5 inhibitor treatment. Pelvic atherosclerosis associated with metabolic syndrome can be restored by PDE-5 inhibitor treatment.

Conflict of Interest
No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Author Contributions
Concept - M.U.; Design - M.U.; Supervision - T.A.S.; Funding - M.U.; Materials - M.U.; Data Collection and/or Processing - M.U.; Analysis and/or Interpretation - M.U., T.A.S.; Literature Review - M.U., Writer - M.U.; Critical Review - M.U., T.A.S.

Çıkar Çatışması
Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

Hakem değerlendirmesi: Dış bağımsız.

Yazar Katkıları
Fikir - M.U.; Tasarım - M.U.; Denetleme - T.A.S.; Kaynaklar - M.U.; Malzemeler - M.U.; Veri toplanması ve/veya işlemesi - M.U.; Analiz ve/veya yorum - M.U., T.A.S.; Literatür taraması - M.U., Yazıyı yazan - M.U.; Eleştirel İnceleme - M.U., T.A.S.

References

1. Garraway WM, Collins GN, Lee RJ. High prevalence of benign prostatic hypertrophy in the community. Lancet 1991;338:469-71. [CrossRef]
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994;151:54-61.
3. McVary KT, McKenna KE. The relationship between erectile dysfunction and lower urinary tract symptoms: epidemiological, clinical and basic science evidence. Curr Urol Rep 2004;5:251-7. [CrossRef]
4. Bloch W, Klotz T, Loch C, Schmidt G, Engelmann U, Addicks K. Distribution of nitric oxide synthase implies a regulation of circulation, smooth muscle tone, and secretory function in the human prostate by nitric oxide. Prostate 1997;33:1-8. [CrossRef]
5. Tarcan T, Azadzoi KM, Siroky MB, Goldstein I, Krane RJ. Age-related erectile and voiding dysfunction: the role of arterial insufficiency. Br J Urol 1998;82:26-33. [CrossRef]
6. Golomb E, Rosenzweig N, Eilam R, Abramovici A. Spontaneous hyperplasia of the ventral lobe of the prostate in aging genetically hypertensive rats. J Androl 2000;21:58-64.
7. Uckert S, Oelke M, Stief CG, Andersson KE, Jonas U, Hedlund P. Immunohistochemical distribution of cAMP- and cGMP-phosphodiesterase (PDE) isoenzymes in the human prostate. Eur Urol 2006;49:740-5. [CrossRef]
8. Truss MC, Uckert S, Stief CG, Kuczyk M, Jonas U. Cyclic nucleotide phosphodiesterase (PDE) isoenzymes in the human detrusor

Turkish Journal of Urology 2013; 39(4): 264-9
doi:10.5152/tud.2013.064

smooth muscle. I. Identification and characterization. Urol Res 1996;24:123-8. [CrossRef]
9. Werkström V, Svensson A, Andersson KE, Hedlund P. Phosphodiesterase 5 in the female pig and human urethra: morphological and functional aspects. BJU Int 2006;98:414-23. [CrossRef]
10. Polson JB, Strada SJ. Cyclic nucleotide phosphodiesterases and vascular smooth muscle. Annu Rev Pharmacol Toxicol 1996;36:403-27. [CrossRef]
11. McVary KT, Monnig W, Camps JL Jr, Young JM, Tseng LJ, van den Ende G. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. J Urol 2007;177:1071-7. [CrossRef]
12. Yokoyama O, Yoshida M, Kim SC, Wang CJ, Imaoka T, Morisaki Y, et al. Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men. Int J Urol 2013;20:193-201. [CrossRef]
13. Andersson KE, Wein AJ. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence. Pharmacol Rev 2004;56:581-631. [CrossRef]
14. Uckert S, Küthe A, Jonas U, Stief CG. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. J Urol 2001;166:2484-90. [CrossRef]
15. Uckert S, Sormes M, Kedia GT, Scheller F, Knapp WH, Jonas U, et al. Effects of phosphodiesterase inhibitors on tension induced by norepinephrine and accumulation of cyclic nucleotides in isolated human prostatic tissue. Urology 2008;71:526-30. [CrossRef]
16. Kedia GT, Ückert S, Kedia M, Kuczyk MA. Effects of phosphodiesterase inhibitors on contraction induced by endothelin-1 of isolated human prostatic tissue. Urology 2009;73: 1397-401. [CrossRef]
17. Matsumoto S, Hanai T, Uemura H, Levin RM. Effects of chronic treatment with vardenafil, a phosphodiesterase 5 inhibitor, on female rat bladder in a partial bladder outlet obstruction model. BJU Int 2009;103:987-90. [CrossRef]
18. Beamon CR, Mazar C, Salkini MW, Phull HS, Comiter CV. The effect of sildenafil citrate on bladder outlet obstruction: a mouse model. BJU Int 2009;104:252-6. [CrossRef]
19. Giuliano F, Ückert S, Maggi M, Birder L, Kissel J, Viktrup L. The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. Eur Urol 2013;63:506-16. [CrossRef]
20. Guess HA. Etiology, epidemiology, and natural history of benign prostatic hyperplasia. Urol Clin North Am 1995;22:247-61.
21. Dutkiewics S. Efficacy and tolerability of drugs for treatment of benign prostatic hyperplasia. Int Urol Nephrol 2001;32:423-32. [CrossRef]
22. Sairam K, Kulinskaya E, McNicholas TA, Boustead GB, Hanbury DC. Sildenafil influences lower urinary tract symptoms. BJU Int 2002;90:836-9. [CrossRef]
23. Mulhall JP, Guhring P, Parker M, Hopps C. Assessment of the impact of sildenafil citrate on lower urinary tract symptoms in men with erectile dysfunction. J Sex Med 2006;3:662-7. [CrossRef]
24. McVary KT, Monnig W, Camps JL, Young JM, Tseng LJ, van den Ende G. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. J Urol 2007;177:1071-7. [CrossRef]
25. Tuncel A, Nalcacioglu V, Ener K, Aslan Y, Aydin O, Atan A. Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. World J Urol 2010;28:17-22. [CrossRef]
26. Gülcer C, Tüzel E, Dogantekin E, Kiziltepe G. Does sildenafil affect uroflowmetry values in men with lower urinary tract symptoms suggestive of benign prostatic enlargement? Urol Int 2008;80:181-5. [CrossRef]
27. Guven EO, Balbay MD, Mete K, Serefoglu EC. Uroflowmetric assessment of acute effects of sildenafil on the voiding of men with erectile dysfunction and symptomatic benign prostatic hyperplasia. Int Urol Nephrol 2009;41:287-92. [CrossRef]
28. Stief CG, Porst H, Neuser D, Beneke M, Ulbrich E. A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol 2008;53:1236-44. [CrossRef]
29. McVary KT, Roehrborn CG, Kaminetsky JC, Auerbach SM,Wachs B, Young JM, et al. Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol 2007;177:1401-7. [CrossRef]
30. Egerdie RB, Auerbach S, Roehrborn CG, Costa P, Garza MS, Esler AL, et al. Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study. J Sex Med 2012;9:271-81. [CrossRef]
31. Porst H, Kim ED, Casabé AR, Mirone V, Secrest RJ, Xu L, et al. Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial. Eur Urol 2011;60:1105-13. [CrossRef]
32. Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. J Urol 2008;180:1228-34. [CrossRef]
33. Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. Eur Urol 2012;61:917-25. [CrossRef]
34. Berger AP, Deibl M, Leonhartsberger N, Bektic J, Horninger W, Fritsche G, et al. Vascular damage as a risk factor for benign prostatic hyperplasia and erectile dysfunction. BJU Int 2005;96:1073-8. [CrossRef]
35. Berger AP, Horninger W, Bektic J, Pelzer A, Spranger R, Bartsch G, et al. Vascular resistance in the prostate evaluated by colour Doppler ultrasonography: is benign prostatic hyperplasia a vascular disease? BJU Int 2006;98:587-90. [CrossRef]
36. Berger AP, Bartsch G, Deibl M, Alber H, Pachinger O, Fritsche G, et al. Atherosclerosis as a risk factor for benign prostatic hyperplasia. BJU Int 2006;98:1038-42. [CrossRef]
37. Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, et al. A Systematic Review and Meta-analysis on the Use of Phosphodiesterase 5 Inhibitors Alone or in Combination with a-Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. Eur Urol 2012;61:994-1003. [CrossRef]
38. Corona G, Monami M, Rastrelli G, Aversa A, Tishova Y, Saad F, et al. Testosterone and metabolic syndrome: a meta-analysis study. J Sex Med 2011;8:272-83. [CrossRef]
39. Morelli A, Sarchielli E, Comeglio P, Filippi S, Mancina R, Gacci M, et al. Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats. J Sex Med 2011;8:2746-60. [CrossRef]

40. Morelli A, Filippi S, Comeglio P, Sarchielli E, Chavalmane AK, Vignozzi L, et al. Acute vardenafil administration improves bladder oxygenation in spontaneously hypertensive rats. J Sex Med 2010;7:107-20. [CrossRef]
41. McVary KT, Rademaker A, Lloyd GL, Gann P. Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol 2005;174:1327-33. [CrossRef]
42. Behr-Roussel D, Oger S, Caisey S, Sandner P, Bernabé J, Alexandre L, et al. Vardenafil decreases bladder afferent nerve activity in unanesthetized, decerebrate, spinal cord-injured rats. Eur Urol 2011;59:272-9. [CrossRef]
43. Cimen S, Demir O, Aslan G, Esen AA. Factors associated with phosphodiesterase type 5 inhibitor treatment satisfactions: results of patient interrogation. Aging Male 2009;12:58-61. [CrossRef]
44. Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. European Association of Urology. Eur Urol 2010;57:804-14. [CrossRef]