



Effect of Anti-Cholinergics with Tamsulosin for Treating Benign Prostate Hyperplasia Patients with an Overactive Bladder: A Clinico-Comparative Study

Prabhu Deva T, Mounika P, Sai Charan K, Shabnam S and Dhivya K*

Department of Pharmacy Practice and Pharm-D, Sri Venkateswara College of Pharmacy, Chittoor, India

*Corresponding e-mail: divyapharmd@gmail.com

ABSTRACT

Objective: Overactive bladder (OAB) symptoms are due to detrusor over activity (DOA) which is characterized by involuntary detrusor contractions during bladder filling. It may co-exist with BOO due to benign prostate hyperplasia (BPH) in men. Hence, the study was designed to assess and compare the clinical efficacy of combination therapy of anti-muscarinics with α -blockers versus α -blockers monotherapy in BPH patients with OAB. **Methods:** This study was carried out in the urology department of a tertiary care hospital for a period of 4 months. Clinical and biochemistry reports of 90 patients were collected in designed case report forms. All statistical analyses were performed using IBM Statistical Package for Social Sciences 17 and Graph Pad Prism 7.0. **Results:** The perceived change from baseline values was comparatively better in patients who received combination of tamsulosin with tolterodine than other two groups. All the three groups were effective in reducing the symptoms. **Conclusion:** Tamsulosin with tolterodine at a recommended dosage has shown to be clinically more effective than oxybutynin after 12 weeks of treatment for men with OAB in BPH. Patients with increased urinary retention risk should be carefully monitored during the course of treatment

Keywords: Overactive bladder, bladder obstruction, tamsulosin, oxybutynin, tolterodine

INTRODUCTION

Benign prostate hyperplasia (BPH) is a condition characterized by the non-malignant overgrowth of prostatic tissue surrounding the urethra which eventually results in constricting the urethral opening and brings about associated lower urinary tract symptoms (LUTS) [1]. Storage symptoms give rise to bladder outlet obstruction (BOO). Overactive bladder (OAB) symptoms are imputed to detrusor over activity (DOA) which is characterized by involuntary detrusor contractions during bladder filling. It may coexist with BOO due to BPH in men [2,3]. The international continence society (ICS) has defined OAB as a symptom syndrome defined as the presence of urinary urgency, with or without urge incontinence, usually with frequency and nocturia [4]. The incidence of BPH-LUTS and OAB in men increases with age. BPH is commonly seen among elderly men. Around 50% in men with above 65 years of age and more than 80% among 72 to 79 years of age, suffering with BPH [5,6]. BPH can be assessed by using international prostate symptom score (IPSS), IPSS quality of life (QOL) and the instability in detrusor activity is measured by overactive bladder symptom score (OABSS) [7]. The international prostate symptom score (IPSS) questionnaire has been used for decades to evaluate the severity of LUTS/BPH and also has been applied to conditions other than BPH that cause LUTS. A lower urinary tract symptom (LUTS) is a non-sex-specific and non-organ specific symptom syndrome that includes storage, voiding and post micturition symptoms. The IPSS consists of a total of seven questions that deal with voiding symptoms (incomplete empty, intermittency, weak stream and straining to void) and storage symptoms (frequency, urgency and nocturia) [8]. The OABSS is a symptom assessment tool designed to quantify OAB symptoms in a single score. The OABSS consists of four questions based on symptoms which include daytime frequency, night time frequency, urgency and urgency incontinence. The total score range from 0 to 15. A total score of 5 or less is defined as mild, a score of 6-11 as moderate, and 12 or more as severe [9]. The co-morbidity with potential prostatic disease adds complexity to the management of male LUTS. Anti-muscarinic agents play a significant role

in treating BPH patients who are associated with OAB symptoms and act by blocking the muscarinic receptors in the bladder wall. Anti-cholinergics, also known as anti-muscarinics involved in treating BPH are tolterodine, oxybutynin, darifenacin, solifenacin, trospium, fesoterodine [10,11]. Combination treatment with an alpha blocker plus anti cholinergics improves QOL in patients with BOO and concomitant detrusor instability [12]. Tamsulosin, tolterodine and oxybutynin are selected for the study among various alpha blockers and anti-cholinergic agents. Tamsulosin is a selective antagonist at alpha-1A and alpha-1B-adrenoceptors in the prostate, prostatic capsule, prostatic urethra and bladder neck. Approximately 70% of the alpha1-receptors in human prostate are of the alpha-1A subtype. Blockage of these receptors causes relaxation of smooth muscles in the bladder neck and prostate, and thus decreases urinary outflow resistance in men [13]. Tolterodine and its active metabolite 5-hydroxymethyltolterodine act as competitive antagonists at muscarinic receptors. This results in inhibition of bladder contraction, decrease in detrusor pressure and an incomplete emptying of the bladder [14]. Oxybutynin exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects). By inhibiting particularly the M1 and M2 receptors of the bladder, detrusor activity is markedly decreased [15]. Hence, this study is designed to assess and compare the clinical efficacy of combination therapy of anti-muscarinics with α -blockers versus α -blockers monotherapy in BPH patients with OAB.

MATERIALS AND METHODS

The study entitled “Effect of anti-cholinergics with tamsulosin for treating benign prostate hyperplasia patients with an overactive bladder-a clinico-comparative study” was conducted as a prospective observational study in the Urology department of Tertiary Care Hospital for a period of 4 months (November 2016 to February 2017). The study protocol was approved by the institutional ethical committee.

Consent from hospital authority

The protocol of the proposed study was submitted as printed copies to the medical superintendent and urologists for review and approval. Guidance of the senior urologist available was extended on request from the scholar. Consent from the hospital authorities and urologists were obtained before accessing the data from the patients. Patients who fulfilled the inclusion criterion were documented from the case sheets and recorded in a separately designed case report form. Written informed consents were obtained after explaining the study protocol to each individual patient.

Study design and sample size

A total of 90 BPH patients associated with BPH were enrolled in the study. The OABSS and IPSS scores were recorded separately. Male patients of age ≥ 45 years, IPSS ≥ 13 , PFR ≥ 4 ml/sec, PVR ≤ 200 ml, diagnosis of overactive bladder was included in the study. History of urinary retention, symptomatic urinary tract infection, bladder/prostate cancer, serious medical co-morbidities, people who are allergic to tamsulosin/tolterodine/oxybutynin and absolute indication for prostatectomy were excluded from the study. Patients were received either tamsulosin or tamsulosin with anti-muscarinics (tolterodine or oxybutynin). Treatment responses were assessed and reviewed at R0 (baseline-before drug therapy), R1 (4 weeks), R2 (8 weeks) and R3 (12 weeks) using OABSS and IPSS scores.

The study comprised of three groups and each group included 30 patients as follows:

- 1) Group I: 30 patients treated with Tamsulosin alone (0.4 mg OD) for 12 weeks.
- 2) Group II: 30 patients treated with Tamsulosin (0.4 mg OD) + Tolterodine (4 mg BD) for 12 weeks.
- 3) Group III: 30 patients treated with Tamsulosin (0.4 mg OD) + Oxybutynin (10 mg OD) for 12 weeks.

Statistical analysis

Comparison between three groups was analyzed by means of one way analysis of variance (ANOVA) to determine the presence or absence of statistically significant difference. Wherever computed, the value of $p < 0.05$ was considered statistically significant, since the confidence interval was maintained at 95%. Bivariate analysis were carried out by Pearson's correlation. Chi-square test was carried out to assess the incidence of reduction in OABSS. All statistical analyses were performed using IBM statistical package for social sciences 17 and graph pad prism 7.0.

RESULTS

A total of 90 patients who fulfilled the inclusion criteria were enrolled in the study. The demographic and clinical characteristics of the patients included in the study are shown in Tables 1 and 2. Patients with different BPH grades are shown in Figure 1.

Table 1 Age wise distribution

| Age range | No. of Patients (%) N=90 | Mean \pm SD | Age Quartile |
|-----------|--------------------------|------------------|--------------|
| 41-50 | 3 (3.3) | 48.33 \pm 1.52 | 47-50 |
| 51-60 | 23 (25.6) | 57.6 \pm 2.4 | 53-60 |
| 61-70 | 42 (46.7) | 66.23 \pm 2.66 | 62-70 |
| 71-80 | 20 (22.2) | 75.42 \pm 3.17 | 71-80 |
| 81-90 | 2 (2.2) | 86 \pm 5.65 | 82-90 |

The mean (SD) age of the studied population was found to be 65.86 (7.99) years with a median age of 65 years.

Table 2 Demographic and urodynamic characteristics of studied population

| Parameter | GROUP | | | P value |
|--------------------------------|----------------|------------------|----------------|---------|
| | I | II | III | |
| Age (years) | 65 (47-80) | 64 (48-82) | 68 (50-90) | 0.1642 |
| Married (%) | 25(83) | 23 (77) | 26 (87) | 0.326 |
| BMI (kg/m ²) | 22 (18.6-24.5) | 20.9 (18.5-24.9) | 22 (18.5-24.6) | 0.2725 |
| Smoker (%) | 11 (37) | 13 (43) | 19 (63) | 0.1004 |
| Alcoholic (%) | 7 (23) | 8 (27) | 12 (40) | 0.337 |
| Coexisting disease (%) | 19 (63) | 17 (57) | 20 (67) | 0.7254 |
| Post void residual volume (ml) | 98.5 (70-150) | 102.5 (78-110) | 99.5 (73-125) | 0.8023 |
| Peak flow rate (ml/sec) | 9.4 (5.4-14.2) | 12.15 (5.6-13.8) | 10 (5.4-14) | 0.2336 |
| Questionnaires | | | | |
| IPSS | 31 (24-34) | 27 (23-34) | 31 (24-34) | 0.1529 |
| QOL | 5 (4-6) | 5 (4-6) | 5 (4-6) | 0.8682 |
| OABSS | 13 (8-15) | 12 (8-15) | 13 (10-15) | 0.0546 |

Statistically significant difference in the above parameters was not found between the groups (one way ANOVA).

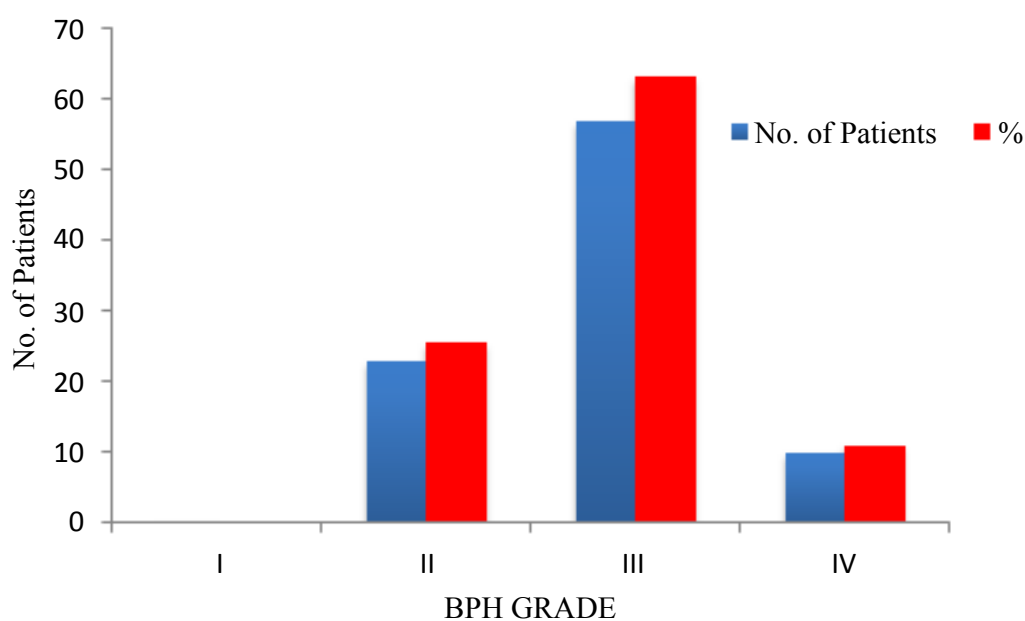


Figure 1 BPH grading

Effect of anti-muscarinic agents on symptom assessment scores

Both inter and intra group comparison was done through one way ANOVA. Presence of statistically significant difference in OABSS and IPSS scores was observed between baseline and 12 weeks. A mean decrease in scores was observed during the twelfth week. Inter group comparison showed tamsulosin with tolterodine is more effective when compared to the other two groups as shown in Tables 3-5.

Table 3 Comparison of baseline and post-treatment OABSS

| Group | OABSS | | | | P value |
|---------|--------------|--------------|-------------|-------------|---------|
| | Baseline | 4 weeks | 8 weeks | 12 weeks | |
| I | 12.46 ± 1.65 | 10.13 ± 1.92 | 7.53 ± 1.40 | 6.2 ± 1.34 | <0.0001 |
| II | 11.9 ± 1.68 | 7.03 ± 2.18 | 3.86 ± 1.45 | 2.06 ± 0.98 | <0.0001 |
| III | 12.96 ± 1.71 | 9.6 ± 1.90 | 6.1 ± 1.51 | 4.53 ± 1.30 | <0.0001 |
| P value | 0.0546 | <0.0001 | <0.0001 | <0.0001 | - |

Table 4 Comparison of baseline and post-treatment IPSS

| Group | IPSS | | | | P value |
|---------|-------------|-------------|--------------|-------------|---------|
| | Baseline | 4 weeks | 8 weeks | 12 weeks | |
| I | 29.7 ± 3.26 | 22.8 ± 3.24 | 19.4 ± 2.72 | 17.4 ± 2.94 | <0.0001 |
| II | 28.4 ± 3.50 | 15.9 ± 2.49 | 8.9 ± 1.82 | 4.7 ± 1.64 | <0.0001 |
| III | 29.9 ± 2.93 | 19.9 ± 2.77 | 13.53 ± 3.23 | 9.13 ± 2.38 | <0.0001 |
| P value | 0.1529 | <0.0001 | <0.0001 | <0.0001 | - |

Table 5 Comparison of baseline and post-treatment QOL score

| Group | QOL | | | | P value |
|---------|-------------|-------------|-------------|-------------|---------|
| | Baseline | 4 weeks | 8 weeks | 12 weeks | |
| I | 5.03 ± 0.66 | 4.3 ± 0.87 | 4.03 ± 0.99 | 3.53 ± 0.97 | <0.0001 |
| II | 5.06 ± 0.73 | 3.33 ± 0.84 | 2.23 ± 0.56 | 1.36 ± 0.49 | <0.0001 |
| III | 4.96 ± 0.80 | 3.96 ± 0.96 | 2.83 ± 0.98 | 2.33 ± 0.99 | <0.0001 |
| P value | 0.8682 | 0.0003 | <0.0001 | <0.0001 | - |

Bivariate analysis was performed to determine the relationship between IPSS and OABSS. OABSS positively correlated with IPSS in ($r^2=0.547$, $P<0.0001$) suggesting that IPSS score and OABSS score are interlinked. Pearson correlation plot of OABSS versus IPSS is shown in Figure 2.

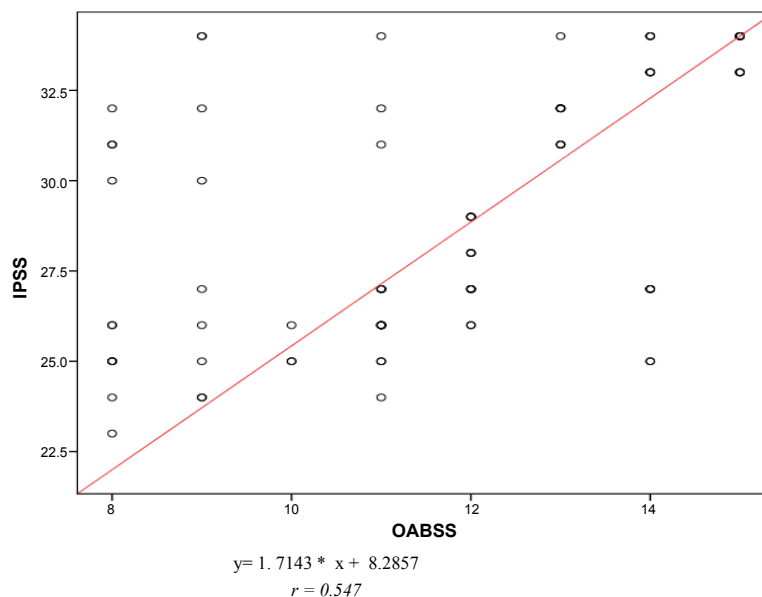


Figure 2 Correlation of OABSS with IPSS in BPH patients

Incidence of OABSS score in BPH patients with OAB before and after treatment was determined through chi-square test which is shown in Figures 3 and 4). Statistically significant difference was found in the incidence of reduction in OABSS after treatment is shown in Figure 4.

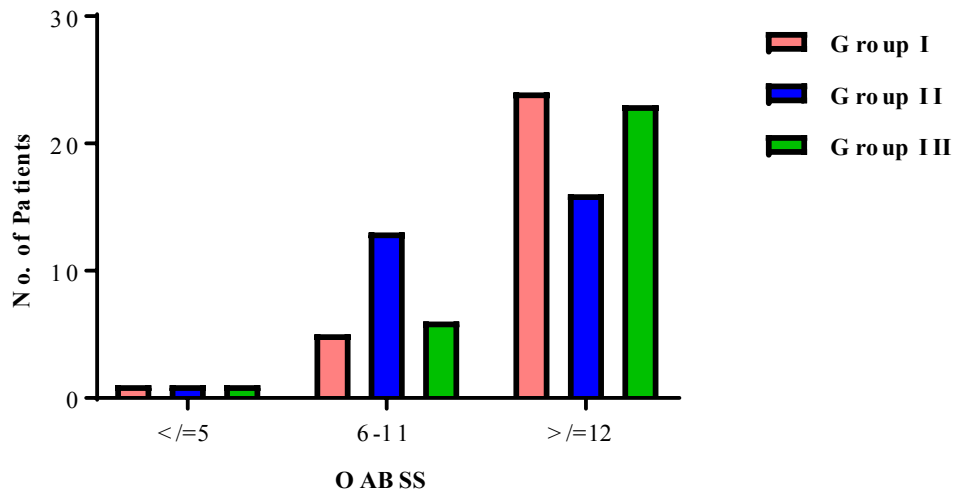


Figure 3 Incidence of OABSS before treatment in BPH patients (P=0.1611)

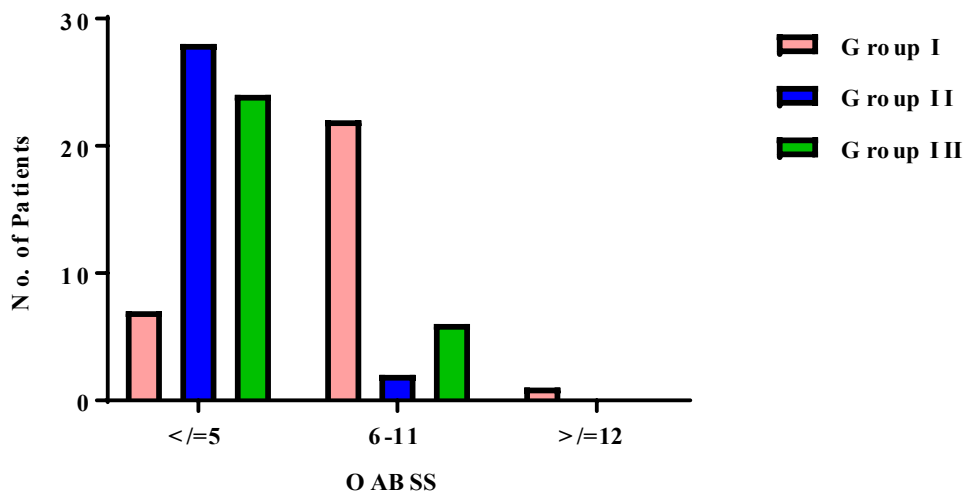


Figure 4 Effect of anticholinergic on OABSS in BPH patients (P<0.0001)

Statistically significant difference was not observed in inter-group comparison of two parameters (PVR and PFR) except in the inter-group comparison after 12 weeks of treatment. Significant difference was found only in intra-group comparison. The results of the statistical analyses are shown in Tables 6 and 7. Both inter and intra group comparison was done through one way ANOVA.

Table 6 Comparison of baseline and post-treatment PVR

| Group | PVR | | | | P value |
|---------|--------------|--------------|--------------|--------------|---------|
| | Baseline | 4 weeks | 8 weeks | 12 weeks | |
| I | 85.8 ± 16.33 | 82.4 ± 15.80 | 78.6 ± 14.92 | 72.3 ± 14.13 | 0.0034 |
| II | 83.4 ± 12.30 | 85.6 ± 12.95 | 90.5 ± 13.34 | 97.8 ± 14.11 | <0.0001 |
| III | 80.11 ± 7.84 | 87.8 ± 8.52 | 93.4 ± 9.13 | 102.6 ± 9.84 | <0.0001 |
| P value | 0.7623 | 0.0745 | 0.0432 | <0.0001 | - |

Table 7 Comparison of baseline and post-treatment PFR

| Group | PFR | | | | |
|---------|--------------|--------------|--------------|--------------|---------|
| | Baseline | 4 weeks | 8 weeks | 12 weeks | P value |
| I | 9.84 ± 2.70 | 10.68 ± 2.54 | 11.83 ± 2.51 | 13.17 ± 2.41 | <0.0001 |
| II | 10.94 ± 2.65 | 11.78 ± 2.57 | 12.92 ± 2.51 | 14.15 ± 2.40 | <0.0001 |
| III | 10.06 ± 2.51 | 10.84 ± 2.49 | 11.93 ± 2.24 | 13.33 ± 2.24 | <0.0001 |
| P value | 0.2336 | 0.2018 | 0.1652 | 0.232 | - |

DISCUSSION

LUTS is interchangeable with OAB. Generally, OAB symptoms in men are associated with bladder outlet obstruction (BOO) due to BPH [16]. The overall prevalence of OAB was 11.8% and rates were similar in men and women, increasing with age for both sexes [17]. In the current study, demographic data showed that the majority of our patients were of advanced age (mean age=65 years). The major risk factor associated with OAB is age [18]. As per American Urological Association (AUA), OAB can be managed with behavioral therapies and education, anticholinergic agents, beta-3 adrenoceptor agonists when anticholinergic agents have failed or contraindicated and sacral neuromodulation or peripheral tibial nerve stimulation (PTNS) in patients with severe refractory OAB or patients who are contraindicated to anti-muscarinics [19,20]. The combination of an alpha blocker with an anti-muscarinic agent is a deserved option for treating OAB in BPH, especially for male patients with voiding and storage symptoms. Tolterodine 2 mg twice daily is as effective as oxybutynin 5 mg three times daily [21,22]. Studies have shown that tolterodine is considered to be safe and effective in treating OAB when compare to oxybutynin because people who are taking oxybutynin are more likely to quit the drug on account of adverse effects. The incidence of side-effects is lower with tolterodine than with oxybutynin [23,24]. In our current study, patients who received combination of tamsulosin with tolterodine for a period of three months produced statistically significant reduction in OABSS, IPSS and QOL scores that are shown in Tables 3-5, which is similar to previous results [14]. Both OAB and BPH causes problem with urinating. Urinary urgency is the key symptom that generates or affects all other symptoms. Both OABSS and IPSS questionnaire have the questions related to urination frequency and urinary urgency. Therefore, the score of OABSS and IPSS is interlinked [25]. Our study showed that the OABSS is positively correlated with IPSS which is shown in Figure 2. The incidence of reduction in OABSS was found to be high in group II patients as shown in Figure 4. Anticholinergic agents can contribute to urinary retention through interference with cholinergic innervation of detrusor muscle of the bladder, decreasing the force of bladder detrusor contractions and the bladder distends until maximum bladder capacity is reached. This blocking activity occurs mainly during the storage phase of the bladder. Several studies have shown a significant increase in the bladder capacity after anticholinergic medication [26,27]. This agrees with the result of our study which showed that the escalation of PVR volume in group II and III after treatment with tolterodine and oxybutynin. Contrarily, there is reduction in PVR volume in group I patients who received tamsulosin alone as shown in Table 6. PFR increased significantly in all the three groups but significant difference was not observed in the inter-group comparison.

CONCLUSION

This study suggests that both oxybutynin and tolterodine are effective in ameliorating the severity of the symptoms of detrusor instability. But tamsulosin with tolterodine at a recommended dosage has shown to be clinically more effective than oxybutynin after 12 weeks of treatment for men with OAB in BPH. Addition of anti-muscarinic agents to the drug regimen is considered necessary for patients with LUTS attributed to BPH. The main limitation of this study is the small size of study samples. Patients with increased urinary retention risk should be carefully monitored during the course of treatment.

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CONFLICT OF INTEREST

The authors do not have any conflict of interest.

REFERENCES

- [1] Dhingra, Neelima, and Deepak Bhagwat. "Benign prostatic hyperplasia: An overview of existing treatment." *Indian journal of pharmacology* 43.1 (2011): 6.
- [2] Roehrborn, Claus G. "Benign prostatic hyperplasia: An overview." *Reviews in urology* 7. Suppl 9 (2005): S3.
- [3] Dmochowski, Roger R. "Bladder outlet obstruction: Etiology and evaluation." *Reviews in urology* 7. Suppl 6 (2005): S3.
- [4] DeMaagd, George A., and Timothy C. Davenport. "Management of urinary incontinence." *Pharmacy and Therapeutics* 37.6 (2012): 345.
- [5] Knutson, Tomas, et al. "BPH with coexisting overactive bladder dysfunction: An everyday urological dilemma." *Neurourology and urodynamics* 20.3 (2001): 237-247.
- [6] Dmochowski, Roger R., and Alex Gomelsky. "Overactive bladder in males." *Therapeutic advances in urology* 1.4 (2009): 209.
- [7] Chou, Eric Chieh-Lung, et al. "The translation and validation of Chinese overactive bladder symptom score for assessing overactive bladder syndrome and response to Solifenacin treatment." *Journal of the Formosan Medical Association* 113.8 (2014): 506-512.
- [8] Jindal, Tarun, et al. "Misinterpretation of the international prostate symptom score questionnaire by Indian patients." *Indian Journal of Urology* 30.3 (2014): 252.
- [9] Homma, Yukio, et al. "Symptom assessment tool for overactive bladder syndrome: Overactive bladder symptom score." *Urology* 68.2 (2006): 318-323.
- [10] Hesch, Kristen. "Agents for treatment of overactive bladder: A therapeutic class review." *Baylor University Medical Center. Proceedings*. Vol. 20. No. 3. Baylor University Medical Center, 2007.
- [11] MacDiarmid, Scott. "Antimuscarinic therapy for the treatment of mixed incontinence." *Reviews in urology* 5.Suppl 8 (2003): S18.
- [12] Filson, Christopher P., et al. "The efficacy and safety of combined therapy with α -blockers and anticholinergics for men with benign prostatic hyperplasia: A meta-analysis." *The Journal of urology* 190.6 (2013): 2153-2160.
- [13] Lepor, Herbert. "Alpha blockers for the treatment of benign prostatic hyperplasia." *Reviews in urology* 9.4 (2007): 181.
- [14] Gacci, Mauro, et al. "Tolterodine extended release in the treatment of male OAB/storage luts: A systematic review." *BMC urology* 14.1 (2014): 84.
- [15] Jin, Myeong Heon, and Du Geon Moon. "Practical management of nocturia in urology." *Indian Journal of Urology* 24.3 (2008): 289.
- [16] Suarez, Oscar, et al. "Mirabegron for male lower urinary tract symptoms." *Current urology reports* 14.6 (2013): 580-584.
- [17] Cheung, Wellman W., et al. "Prevalence, evaluation and management of overactive bladder in primary care." *BMC family practice* 10.1 (2009): 8.
- [18] Wen, Jian G., et al. "The prevalence and risk factors of OAB in middle-aged and old people in China." *Neurourology and urodynamics* 33.4 (2014): 387-391.
- [19] Lightner, Deborah J., Deepak Agarwal, and Ann Gormley E. "The overactive bladder and the AUA guidelines: A proposed clinical pathway for evaluation and effective management in a contemporary urology practice." *Urology Practice* 3.5 (2016): 399-405.
- [20] Srikrishna, Sushma, et al. "Management of overactive bladder syndrome." *Postgraduate medical journal* 83.981 (2007): 481-486.
- [21] Chapple, Christopher. "Systematic review of therapy for men with overactive bladder." *Canadian Urological Association Journal* 5.5 Suppl 2 (2011): S143-S143.
- [22] Appell, Rodney A. "Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: A pooled analysis." *Urology* 50.6 (1997): 90-96.
- [23] Harvey, Marie-Andrée, Kevin Baker, and George A. Wells. "Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: A meta-analysis." *American journal of obstetrics and gynecology* 185.1 (2001): 56-61.
- [24] Lai, H. Henry, Timothy B. Boone, and Rodney A. Appell. "Selecting a medical therapy for overactive bladder." *Reviews in urology* 4. Suppl 4 (2002): S28.
- [25] Kubota, Yasue, et al. "Correlation between improvements in overactive bladder symptom score and health-related quality of life questionnaires in overactive bladder patients treated with an antimuscarinic drug." *Neurourology and urodynamics* 30.7 (2011): 1309-1314.
- [26] Jamal, Arshad, et al. "Comparison of the effect of tamsulosin versus combination of tamsulosin and Oxybutynin in the medical management of patients with benign prostatic hyperplasia: A randomised double blind placebo controlled study." *International Journal of Contemporary Medical Research* 3.6 (2016):1552-1556.
- [27] Hajebrahimi, Sakineh, et al. "Effect of tamsulosin versus prazosin on clinical and urodynamic parameters in women with voiding difficulty: A randomized clinical trial." *International journal of general medicine* 4 (2011): 35.