

# The $\alpha_1$ Adrenoceptor Antagonist Tamsulosin for the Treatment of Voiding Symptoms Improves Nocturia and Sleep Quality in Women

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Received February 2013  
Accepted March 2014

**Purpose:** Nocturia is the main cause of disturbance of sleep maintenance and negatively impacts quality of life (QoL). We assessed the effects of the  $\alpha_1$ -adrenoceptor antagonist, tamsulosin, on nocturia and quality of sleep, for the treatment of lower urinary tract symptoms (LUTS) in women with a maximal flow rate (Qmax) less than 15 mL/sec.

**Materials and Methods:** From January 2008 to December 2009, women with LUTS [Qmax  $\leq$  15 mL/s, International Prostate Symptom Score (IPSS)  $\geq$  8] and nocturia (void/night  $\geq$  1) were selected for this study. Two hundred ninety six patients completed voiding diary, a questionnaire on the Medical Outcomes Study (MOS) sleep scale and underwent follow-up evaluation after 4 weeks of treatment (tamsulosin, 0.2 mg, once daily). Effectiveness was assessed by analysis of the IPSS, the bother score, the Qmax, and postvoid residual urine (PVR).

**Results:** The mean number of voids per night was  $2.66 \pm 1.3$ , and the total IPSS and bother scores were  $15.2 \pm 8.9$  and  $3.4 \pm 1.2$ , respectively. Clinical parameters, including the IPSS, the bother score, the Qmax and the PVR, improved significantly from baseline after treatment ( $P < .05$ ). The change in nocturia was  $-1.12$  ( $P < .05$ ). Concerning sleep quality, the sleep problem index showed a significant decrease. Among the items on the sleep subscale, sleep disturbance, somnolence, and sleep adequacy were significantly changed ( $P < .05$ ).

**Conclusion:** The  $\alpha_1$ -adrenoceptor antagonist tamsulosin significantly improved nocturia and sleep quality as well as LUTS in women with low Qmax.

**Keywords:** adrenergic alpha-1 receptor antagonists; therapeutic use; lower urinary tract symptoms; drug therapy; urination disorders; female; quality of life; treatment outcome.

## INTRODUCTION

Nocturia is a common symptom in adult women and has a pronounced impact on sleep, quality of life (QoL) and general health.<sup>(1)</sup> According to the definition of the International Continence Society, “nocturia” is the complaint that an individual wakes one or more times during the night to void urine.<sup>(2)</sup> Due to the presumed correlation between nocturia and bladder outlet obstruction (BOO), most published studies have tended to focus on nocturia in men<sup>(3)</sup> even though nocturia is also common in women.<sup>(4)</sup> A large number of studies have demonstrated that a high proportion of patients with nocturia, estimated from 63% to 75%, complain of nocturia as a troublesome symptom.<sup>(4,5)</sup> The fragmented and disturbed sleep patterns observed in patients with nocturia can result in daytime sleepiness and can lead to serious health risks.<sup>(6)</sup>

BOO is known to cause irritative and obstructive symptoms. Although BOO in women has traditionally been considered uncommon, recent studies have shown that it is an underdiagnosed cause of female lower urinary tract symptoms (LUTS).<sup>(7)</sup> BOO may induce secondary changes in the bladder, such as bladder overactivity, that can result in decreased bladder capacity and storage symptoms, including nocturia. Some reports have shown that the real incidence of voiding difficulty in women is between 6.5% and 24%.<sup>(8)</sup> Use of  $\alpha$ -blockers has been reported in women with obstructed urine flow.<sup>(9-11)</sup> Athanasopoulos and colleagues reported that alfuzosin significantly improved urodynamic parameters and alleviated bothersome symptoms in women with BOO.<sup>(11)</sup>

Interest has focused on the  $\alpha_{1D}$ -adrenoceptor subtype in the bladder as an important target in the treatment of LUTS.<sup>(12)</sup> Tamsulosin is a potent, specific and selective  $\alpha_1$ -adrenoceptor antagonist that is known to have greater specificity for  $\alpha_{1A}$  and  $\alpha_{1D}$  receptors than for  $\alpha_{1B}$ <sup>(13)</sup> and that thus might have a role in the management of both voiding symptoms and storage symptoms in women. However, little research has been conducted on the efficacy of  $\alpha$ -blockers in female patients with a low maximal flow rate (Qmax) who are suspected of having functional BOO and nocturia. In the present study, therefore, we aimed to determine the effect of tamsulosin on LUTS and nocturia in women with low Qmax. We also attempted to evaluate the related impact of nocturia on sleep quality.

## MATERIALS AND METHODS

### *Participants and Study Design*

In this prospective observational study conducted from January 2008 to December 2009, 324 women aged > 20 years who had moderate to severe LUTS [International Prostate Symptom Score (IPSS)  $\geq$  8, Qmax  $\leq$  15 mL/s at voided volume over 150 mL] and nocturia of at least once per night (IPSS nocturia score of question 7) were included. All patients underwent urological evaluation before treatment, including a medical history, physical and neurologic examinations, urine analysis, urine culture and urethrocytoscopy. Participants completed three day voiding diary and a questionnaire on the Medical Outcomes Study (MOS) sleep scale. The effectiveness of tamsulosin (0.2 mg/day) was assessed by analysis of the IPSS, the bother score, the Qmax, and postvoid residual urine (PVR). Data for these parameters were acquired at baseline and after 4 weeks of treatment. All participants provided written informed consent with data collection and the study received approval from the local ethics committee and the institutional review board. The study procedures complied with the guidelines provided by the Declaration of Helsinki.

### *Exclusion Criteria*

Subjects with confused or depressed mental status; taking medications such as sedatives or tranquilizers that may alter or control bladder symptoms; with a history of previous surgery for LUTS; any implication of detrusor dysfunction, detrusor sphincter dyssynergia or neurogenic bladder; with symptomatic urinary tract infection; with uropathologic conditions, such as urinary stones and urogenital cancer; with pelvic organ prolapse of higher than stage 2; or with a history of insomnia or a sleep disorder were excluded. We also excluded any patients with iatrogenic, anatomic, or neurogenic causes of BOO. Patients with nocturnal polyuria from the voiding diary, severe symptoms of stress urinary incontinence of Stamey grade 3, patients with restricted mobility, and patients who worked at night were also excluded from this analysis. Patients who had received an  $\alpha$ -blocker during the 3 months before enrollment and patients with contraindications to the use of  $\alpha$ -adrenergic receptor antagonists were also excluded.

### *Medical Outcome Study Sleep Scale*

The MOS sleep measure yields a sleep problems index and six scale scores: sleep disturbance (have trouble falling

**Table 1.** Changes in IPSS and uroflowmetry parameters after treatment with tamsulosin.

Voiding	Baseline	4 Weeks after Treatment	P
IPSS			
Total	15.2 ± 8.9	13.6 ± 3.4	.003
Voiding symptoms	9.0 ± 6.2	7.7 ± 3.1	.001
Storage symptoms	6.7 ± 3.9	5.8 ± 0.9	.005
Bother symptom	3.4 ± 1.2	2.9 ± 1.6	.001
Uroflowmetric parameters			
Maximal flow rate (mL/s)	13.3 ± 7.8	20.4 ± 8.2	.001
Residual urine (mL)	75.3 ± 23.7	54.8 ± 27.5	.001

**Key:** IPSS, International Prostate Symptom Score.

asleep, how long to fall asleep, sleep was not quiet, awaken during sleep time, and have trouble falling asleep again), sleep adequacy (get enough sleep to feel rested upon waking in the morning, get the amount of sleep needed), daytime somnolence (drowsy during the day, have trouble staying awake during the day, take naps), snoring, awaken short of breath or with headache, and quantity of sleep<sup>(14)</sup> Quantity of sleep is scored as the average number of hours slept per night. The other scales and problems index are scored on a possible range of 0-100, with higher scores indicating more of the concept being measured.

#### Statistical Analysis

The statistical package for the social science (SPSS Inc, Chicago, Illinois, USA) version 17.0 was used for statistical analyses. Data were analyzed by Student's *t* test. *P* values < .05 were deemed statistically significant.

## RESULTS

The women's mean age was 58.3 ± 11.2 years (range, 41-68 years) and the mean nocturnal frequency during the night was 2.66 ± 1.3. The mean duration of symptoms was 20.3 ± 36.6 months. The incidence of hypertension, diabetes mellitus, and cardiovascular disease was 27.0%, 18.9%, and 5.4%, respectively. Among the subject 28 women discontinued because of lost to follow-up for personal reason<sup>(18)</sup> and lack of efficacy<sup>(10)</sup>, the remainder 296 women who completed data were selected as subjects for final analysis. After treatment, there was no reported significant treatment related complications. However, 7 reported mild dizziness or fatigue and 3 reported incontinence without discontinuation of  $\alpha$ -blocker therapy. Concerning uroflowmetric parameters, the baseline

Qmax and PVR were 13.3 ± 7.8 mL/s and 75.3 ± 23.7 mL, respectively.

At 4 weeks after tamsulosin treatment, the IPSS total (*P* = .03), voiding symptoms (*P* = .01), storage symptoms (*P* = .05), the bother score (*P* = .01), Qmax (*P* = .001) and PVR (*P* = .001) showed significant improvement from baseline (Table 1). The overall mean change in nocturnal frequency after tamsulosin treatment was -1.12 times per night (*P* = .001).

Concerning sleep quality, the sleep problem index (*P* = .012) showed a significant decrease. On the MOS sleep scale, the subcategories of sleep disturbance (*P* = .004), somnolence (*P* = .001), and sleep adequacy (from *P* = .001) changed significantly after treatment (Table 2). The subcategories of hours of sleep, shortness of breath, and snoring, however, were not significantly changed after treatment.

## DISCUSSION

LUTS resulting from BOO are commonly associated with detrusor overactivity and storage symptoms. The efficacy of  $\alpha$ -blockers for relief of the symptoms of BOO has been well demonstrated; however, less information is available on how this treatment affects the increased nocturia and sleep quality. In the present study, we found that treatment with tamsulosin resulted in significant improvement of both voiding symptoms and storage symptoms in female patients with low Qmax and significant improvement of Qmax and PVR. Furthermore, nocturia was significantly reduced after tamsulosin treatment. Thereby, sleep quality was also improved. Tamsulosin treatment appears to be effective in female patients with a low Qmax with respect to reducing both storage symptoms including nocturia and voiding symptoms. Therefore,

**Table 2.** Changes in nocturia and medical outcome study sleep scale after tamsulosin treatment.

Voiding	Baseline	4 Week after Treatment	P
No. of nocturia	2.66 ± 1.2	1.54 ± 1.1	.001
Sleep problem index I	40.3 ± 16.7	35.9 ± 15.7	.012
Hours of sleep	6.1 ± 1.8	6.2 ± 1.5	.58
Sleep disturbance	39.7 ± 23.0	34.9 ± 21.5	.004
Somnolence	33.2 ± 25.7	28.7 ± 25.9	.001
Shortness of breath	28.4 ± 57.5	27.3 ± 30.6	.68
Sleep adequacy	46.1 ± 22.1	40.7 ± 23.4	.001
Snoring	40.3 ± 16.7	38.3 ± 18.8	.167

therapy could be an initial treatment option for the patients with LUTS associated with low Qmax who do not have other distinct factors causing BOO.

The adrenergic receptors found at the bladder neck are  $\alpha_1$ -adrenergic receptors, and three subtypes have been identified:  $\alpha_{1A}$ ,  $\alpha_{1B}$ , and  $\alpha_{1D}$ .<sup>(15)</sup> The  $\alpha_1$ -adrenergic blocking agents with subselectivity for  $\alpha_{1A}$  and  $\alpha_{1D}$  might be the most useful in the management of lower urinary tract dysfunction. Accordingly, it was speculated that the  $\alpha_{1D}$  receptor might mediate overactive symptoms and LUTS, whereas the  $\alpha_{1A}$  receptor subtype would mediate obstructive symptoms.<sup>(16)</sup> Tamsulosin is a potent, specific, and selective  $\alpha_1$ -adrenoceptor antagonist that is known to have greater specificity for  $\alpha_{1A}$  and  $\alpha_{1D}$  receptors than for  $\alpha_{1B}$ .<sup>(13)</sup> and that thus might have a role in the management of LUTS in women.

Currently, there is little objective evidence to support the efficacy of tamsulosin for the treatment of storage symptoms. Alpha-blocker therapy is an established treatment for BOO related to benign prostatic enlargement in men. The use of  $\alpha$ -blockers in women with obstructed urine flow has also been reported.<sup>(9-11)</sup> Kessler and colleagues examined the effect of terazosin on functional BOO in women and concluded that terazosin had significant symptomatic and urodynamic effects in two-thirds of patients.<sup>(10)</sup> Athanasopoulos and colleagues reported that alfuzosin induced significant improvement of urodynamic parameters and alleviated the bothersome symptoms of patients with BOO.<sup>(11)</sup> In the present study, we also observed a significant improvement in uroflowmetric parameters and subjective symptom scores after tamsulosin treatment in patients with a low urine flow rate.

Nocturia is common in women and its prevalence increases

with age.<sup>(17)</sup> Although nocturia is not a life-threatening symptom, it is known to have a significant effect on QoL, including sleep quality. Fragmented and disturbed sleep patterns are observed in patients with nocturia and can result in daytime sleepiness and lead to serious health risks.<sup>(4)</sup> Middelkoop and colleagues suggested that nocturia is a main factor of disturbance of sleep maintenance in adults aged 50 years or older.<sup>(5)</sup> Su and colleagues reported that nocturia increases the risk of insomnia by 20.6-fold.<sup>(6)</sup> In our previous study, we already found that nocturia appeared to be associated with further negative effects on sleep quality, health-related QoL and symptom bother in men.<sup>(18)</sup> For this reason, it is important to determine the impact of nocturia on sleep quality and related QoL and how they are correlated. In the present study, we found consistent result with the above-mentioned report showing clear correlation between nocturia and sleep quality. Even though men and women share a common micturition character, the definitions used to describe BOO in men do not apply to women. Diagnosis of BOO in women is still controversial; however, obstruction is characterized by a decreased flow rate and a high detrusor pressure, both of which are due to increased bladder outlet resistance. Urodynamic study currently remains the gold standard for assessing the presence of BOO by measurement of Qmax and detrusor pressure at Qmax.<sup>(7)</sup> During urodynamic study, an obstruction is highly suspected when the study results show a low urine flow rate despite a detrusor contraction of adequate power.<sup>(19,20)</sup> Blavivas and Groutz suggested the usefulness of the free flow rate, and they reported that BOO can be diagnosed if the free flow Qmax is  $\leq 12$  mL/s with normal detrusor power.<sup>(21)</sup> However, abnormal uroflowmetry has been used as a surrogate

marker for voiding dysfunction.<sup>(22)</sup> Some authors have suggested that an abnormal flow rate of  $15 \leq \text{mL/s}$  can be used for reliable prediction of patients who are more likely to have voiding disturbance.<sup>(23)</sup> In the present study, considering the invasiveness of urodynamic study and on the basis of a clinical diagnosis of suspected BOO, we included patients with a low Qmax of less than 15 mL/s on free uroflowmetry and a complaint of voiding symptoms on the IPSS.

In the present study, we clearly found an effect of tamsulosin on both voiding symptoms and storage symptoms for the patients with female LUTS associated with low Qmax. Therefore, it would be logical to expect that  $\alpha$ -blocker therapy in patients with a low maximal flow rate and mixed urinary tract symptoms of voiding and storage symptoms. We suggest that clinicians consider  $\alpha$ -blocker treatment as an initial medical treatment of choice for these patients. Clinicians should expect improvement of nocturia and related quality of sleep with  $\alpha$ -blocker treatment.

This study has a few limitations. This small scale study does not have placebo control group. We could not fully evaluate the exact reason of follow-up loss with personal issues from the study. Thus, considering the low number of female patients with low Qmax, a multicenter, double-blind, placebo-controlled trial would be ideal for further determination of the efficacy and safety of  $\alpha$ -blocker treatment in these patients. Nocturia is associated with various conditions and circumstances. The major causes of nocturia fall into three categories: diurnal polyuria, nocturnal polyuria, and low nocturnal bladder capacity. Nocturia may represent nocturnal frequency from the symptoms of frequent voiding of small volumes, possibly secondary to bladder overactivity and decreased nocturnal bladder capacity, or nocturnal polyuria due to large amounts of urine production during the night that may suggest pathology other than from the lower urinary tract.<sup>(24)</sup> Another limitation of this study was that we could not evaluate the individual cause of nocturia, neither could we consider the effect of treatment with tamsulosin by the exact cause of nocturia.

## CONCLUSION

The  $\alpha_1$ -adrenoceptor antagonist tamsulosin significantly improved nocturia and sleep quality as well as voiding symptoms in women with a Qmax of less than 15 mL/s. These

improvements were confirmed by measurement of clinical parameters and administration of a sleep-related questionnaire in this study, warranting further study well designed and large sampled.

## CONFLICT OF INTEREST

None declared.

## REFERENCES

1. Lose G, Alling-Moller L, Jennum P. Nocturia in women. *Am J Obstet Gynecol.* 2001;185:514-21.
2. Van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardization of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn.* 2002;21:179-83.
3. Asplund R, Aberg H. Health of the elderly with regard to sleep and nocturnal micturition. *Scand. J Prim Health Care.* 1992;10:98-104.
4. Weiss JP, Blaivas JG. Nocturia. *J Urol.* 2000;163:5-12.
5. Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA, Springer CP. Subjective sleep characteristics of 1,485 males and females aged 50-93: Effects of sex and age, and factors related to self-evaluated quality of sleep. *J Gerontol A Biol Sci Med Sci.* 1996;51:M108-15.
6. Su TP, Huang SR, Chou P. Prevalence and risk factors of insomnia in community-dwelling Chinese elderly: A Taiwanese urban area survey. *Aust N Z J Psychiatry.* 2004;38:706-13.
7. Nitti VW, Tu LM, Gitlin J. Diagnosing bladder outlet obstruction in women. *J Urol.* 1999;161:1535-40.
8. Stanton SL, Ozsoy C, Hilton P. Voiding difficulties in the female: prevalence, clinical and urodynamic review. *Obstet Gynecol.* 1983;61:144-7.
9. Pischedda A, Pirozzi Farina F, Madonia M, Cimino S, Morqia G. Use of alpha1-blockers in female functional bladder neck obstruction. *Urol Int.* 2005;74:256-61.
10. Kessler TM, Studer UE, Burkhard FC. The effect of terazosin on functional bladder outlet obstruction in women: a pilot study. *J Urol.* 2006;176:1487-92.
11. Athanasopoulos A, Gyftopoulos K, Giannitsas K, Perimenis P. Effect of alfuzosin on female primary bladder neck obstruction. *Int Urogynecol J Pelvic Floor Dysfunct.* 2009;20:217-22.
12. Dreikorn K. The role of phytotherapy in treating lower urinary tract symptoms and benign prostatic hyperplasia. *World J Urol.* 2002;19:426-35.
13. Chapple CR.  $\alpha_1$ -Adrenergic blocking drugs in bladder outflow obstruction: What potential has  $\alpha_1$ -adrenoceptor selectivity? *Br J Urol.* 1995;76 (Suppl. 1):47-55.
14. Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE, eds. *Measuring Functioning and Well-Being: The Medical Outcomes Study Approach.* Durham, NC: Duke University Press; 1992. p. 235-59.

15. Malloy BJ, Price DT, Price RR, et al. Alpha1-adrenergic receptor subtypes in human detrusor. *J Urol*. 1998;160:937-43.
16. Schwinn DA. Novel role for alpha 1-adrenergic receptor sub-types in lower urinary tract symptoms. *BJU Int*. 2000;86(Suppl. 2):11-20.
17. Robinson D. Nocturia in women. *Int J Clin Pract Suppl*. 2007;155:23-31.
18. Kim SO, Choi HS, Kim YJ, et al. Impact of Nocturia on Health-Related Quality of Life and Medical Outcomes Study Sleep Score in Men. *Int Neurourol J*. 2011;15:82-6.
19. Farrar DJ, Osborne JL, Stephenson TP, et al. A urodynamic view of bladder outflow obstruction in the female: factors influencing the results of treatment. *Br J Urol*. 1975;47:815-22.
20. Diokno AC, Hollander JB, Bennett CJ. Bladder neck obstruction in women: a real entity. *J Urol*. 1984;132:294-8.
21. Blaivas JG, Groutz A. Bladder outlet obstruction nomogram for women with lower urinary tract symptomatology. *Neurourol Urodyn*. 2000;19:553-64.
22. Dietz HP, Haylen BT. Symptoms of voiding dysfunction: what do they really mean? *Int Urogynecol J Pelvic Floor Dysfunct*. 2005;16:52-5.
23. Costantini E, Mearini E, Pajoncini C, Biscotto S, Bini V, Porena M. Uroflowmetry in female voiding disturbances. *Neurourol Urodyn*. 2003;22:569-73.
24. Matthiesen TB, Rittig S, Nørgaard JP, Pedersen EB, Djurhuus JC. Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. *J Urol*. 1996;156:1292-9.