

## Efficacy and safety of various drugs used for the treatment of nonneurogenic lower urinary tract symptoms in tertiary care hospital

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### ABSTRACT

**Background:** Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) are common in elder men. Previously surgical treatment was mainstay of treatment of BPH. But now number of drugs alone or combined are clinically used for this disorder. Primary aim was to study the prescribing pattern of different drug therapies and their role in treating LUTS/BPH by evaluating their efficacy and safety in tertiary health care centre.

**Methods:** An observational study including 78 male patients  $\geq 45$  years, newly diagnosed with LUTS from April 2014 to May 2015. Patients were followed up every 4 weeks for 3 months after the drug has been prescribed. Efficacy assessment was done on basis of change in IPSS score over 12 weeks. Data was expressed in percentage and Mean  $\pm$ SD.

**Results:** Mean age of Patients was 64.94 years. Alpha blockers are mainstay prescribed drug either as monotherapy (48.7%) or with 5 alpha reductase inhibitor-dutasteride (38.4%) and with antimuscarinic –Tolterodene (12.8%). Among alpha blockers Tamsulosin (58.97%) was most commonly prescribed, followed by Silodosin (20.5%) and Alfuzosin (20.5%). All drug treatment results in significant improvement with dizziness being the most common adverse event. A subgroup analysis in symptoms was done comparing alpha blockers. All alpha blockers have near about similar efficacy with no significant difference.

**Conclusions:** Alpha blockers are main drugs prescribed in management of LUTS/BPH with near about similar efficacy of all alpha blockers.

**Keywords:** LUTS, Prescribing pattern, Alpha blockers, Efficacy

### INTRODUCTION

Lower urinary tract symptoms (LUTS) in males occur due to structural and functional abnormalities in one or more parts of the lower urinary tract which comprises of bladder, bladder neck, prostate, distal sphincter and urethra, as a whole unit.<sup>1</sup> LUTS usually presents with voiding and/or storage disturbances in aging men. Voiding abnormalities present as slow stream, straining, intermittency, sense of incomplete emptying, hesitancy, and painful voiding, while the storage abnormalities manifest as increased frequency, nocturia, urgency and urge incontinence.<sup>2</sup>

Patients with LUTS portray a variety of urological problems depending on age, sex and associated comorbidities. LUTS are a bit complicated in men due to physiological changes in prostate as age advances. Nearly 50% of men above the age of 40 have enlarged prostate with a histological diagnosis of BPH (Benign Prostatic Hyperplasia). Of these patients, about half will develop LUTS.<sup>3</sup> Non-neurogenic LUTS in ageing male patients is mostly attributed to Benign Prostatic Hyperplasia with a significant morbidity. BPH per se is a progressive condition, with the prostate continuing to grow as men age. Progression can be associated with the worsening of

LUTS, the development of acute urinary retention, or the requirement for BPH related surgery.

With advent of a variety of newer and safer drugs in the armamentarium, surgical indications for treatment of LUTS have gone down significantly in the recent past. The preferred drug treatment for most men with BPH is with alpha blockers, (i.e Prazosin, Terazosin, Alfuzosin, Doxazosin, Tamsulosin and Silodosin) which work by relaxing smooth muscle at the bladder neck and within the prostate. Symptoms improve within days, but the full effects are seen after few weeks. Other class of drugs which help in voiding symptoms of BPH are 5  $\alpha$  reductase inhibitors i.e Finasteride and Dutasteride. Treatment with these drugs causes prostate volume reduction of approximately 25% and a reduction in prostate specific antigen levels of approximately 50% after 6-12 months.<sup>4</sup> They are usually prescribed in combination with alpha blockers due to late onset of action.

Storage function disorder mainly requires urospecific anticholinergic drugs i.e. Oxybutynin, Tolterodine, Solifenacin, Darifenacin, Trospium and Fesoterodine. The anticholinergics are relatively contraindicated in BPH when used alone, because of possibility of urinary retention. So it is a difficult proposition for clinicians to treat storage dysfunction in patients of BPH. Due to this, such patients were ignored in the past or advised to undergo surgery. But recent studies have shown that additions of anticholinergics to  $\alpha$  adrenergic antagonist for treatment of OAB symptoms in BPH patients are quite safe and tolerable. With the new insight in pathophysiology of LUTS many more drugs are emerging such as phosphodiesterase 5 inhibitors-sildenafil and Tadalafil.

Availability of a variety of drugs, other alternative drug options and lack of appropriate principle and guidelines to follow, thus applying haphazard approach particularly in Indian situation. This study aimed in assessing treatment of LUTS in Indian population and comparing it with international guidelines. With the comparative knowledge of efficacy and safety profile of various drugs, we can refine medical therapy to treat patients in more focused manner by categorizing drug treatment according to patient age, symptoms, co-morbidity and disease progression.

## **METHODS**

The study was conducted in the Departments of Pharmacology and Urology over a period of twelve months at Himalayan Institute of Medical Sciences, Dehradun. Prior to the initiation of the study, written informed consent was obtained from all the patients after full explanation of elements contained in the study protocol.

## **Study design**

This was a Prospective Observational study done in patients having non neurogenic lower urinary tract symptoms.

## **Sample size**

A total number of 78 newly diagnosed non neurogenic LUTS patients were enrolled for the study, fulfilling the inclusion and exclusion criteria, attending Urology OPD on Mondays and Fridays from January 2014 to May 2015.

## **Inclusion criteria**

Patients age >45years newly diagnosed with non-neurogenic lower urinary tract symptoms.

## **Exclusion criteria**

Patients with incomplete demographic or prescription details, patients with Prostatic cancer and other malignancies, patients requiring immediate intervention or surgery or had undergone such surgery in the past, patient with neurogenic bladder, with pelvic trauma or urethral strictures, and patient with history of drug abuse, cognitive and psychiatric disorders were excluded from the study.

## **Study tool**

Evaluation of efficacy was done with International Prostate Symptoms Score (IPSS) (Annexure I) and Qmax & Qavg values of uroflowmetry test.<sup>5</sup> The IPSS score is a single disease-specific quality of life question and these are the most widely used diagnostic tools in urology and these are widely available, validated, and translated in many languages. A score of 7 or less is considered mildly symptomatic, 8 to 19 as moderate, and a score of 20 to 35 as severely symptomatic, while Uroflowmetry test is a non-invasive test to calculate the flow rate of urine over time.

## **Study protocol**

IPSS form was to be filled by every patient at each follow up i.e. in every 4 weeks. The score was taken at the time of study enrolment, at 4<sup>th</sup>, 8<sup>th</sup> and at the end of 12<sup>th</sup> week of study period. Efficacy assessment was done by change in mean IPSS from 0 week to 12<sup>th</sup> week. Quality of life was assessed on the basis of change in QOL from 0 to 12<sup>th</sup> week as per the last question in IPSS questionnaire form. Uroflowmetry test was recorded at the time of study enrolment and at the end of 12<sup>th</sup> week (emphasis on Qmax and Qavg). The adverse drug reaction was recorded through-out the study period.

## **Statistical analysis**

Descriptive statistics was used to present the data in the form of percentage. Values were expressed in Mean  $\pm$  Standard Deviation. Intragroup analysis was done with

Paired student t-test comparing initial and final values of IPSS, Qmax, Qavg and QOL. Intergroup comparison in between groups was done with ANOVA.

**RESULTS**

The total numbers of patients enrolled for the study were 84. However, 6 patients lost to follow-up. So these patients were excluded from the analysis. The remaining 78 patients were assessed on their regular visit, by interviewing them, and a compliance rate more than 80% was ensured at each follow up with appropriate advice. As a result, a total of 78 patients completed the study.

The mean age of the patients was 64.94 years ± 6.88 ranging from 45–86 years. Majority of the patients 85.8% (n=67) were aged between 56 to 75 years with a peak in 66-75 year age group. The patients at the baseline were estimated for symptomatology of LUTS by IPSS score, Qmax, Qavg as well as by quality of life score mentioned in Table 1. Beside above 28 (35.8%) patients had significant post void residual urine volume (PVR) of more than 50ml at baseline in ultrasonic evaluation.

**Table 1: Baseline values of selected parameters of LUTS in 78 patients.**

S.no.	Variables	Mean ±S.D
1.	IPSS	21.46± 5.35
2.	Qmax	11.61 ± 5.84 ml/sec
3.	Qavg	5.45 ±2.31 ml/sec
4.	QOL	4.42±0.54

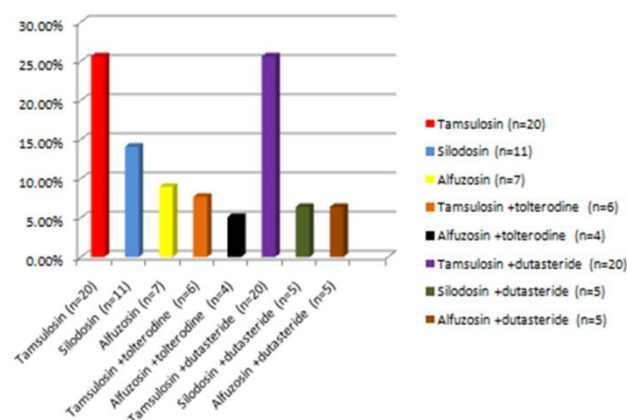
**Table 2: Distribution of patients according to class of drugs prescribed in the treatment of non-neurogenic LUTS.**

S.no.	Drugs	% patients prescribed
1.	Alpha blockers	100%
2.	5-alpha reductase inhibitors	38.4%
3.	Antimuscarinic	13%
4.	Miscellaneous	
4.a	Antibiotics (levofloxacin, cefixime, ofloxacin)	23%
4.b.	Urinary analgesic (phenazopyridium)	25.6%
4.c.	Urinary alkalizer (Na/Mg citrate)	12.8%
4.d	NSAID (Combiflame)	5.1%
4.e	Sedative (Alprazolam)	6.4%
4.f	PPI (Pantaprazole)	9%

Out of 78 patients with LUTS, 74 patients had LUTS presumably secondary to benign prostatic hyperplasia while remaining 4 patients had LUTS due to prostatitis. All patients were prescribed alpha blockers either alone or in combination with other drugs. Few patients were also prescribed antibiotics, analgesics, antacid, pyridium (phenazopyridine) and urinary alkalizer syrup. Among

the antibiotics levofloxacin was prescribed to 10 patients, cefixime to 6 patients, ofloxacin to 2 patients as per the urine microscopy routine examination. Other drugs are mentioned in Table 2.

Among the alpha blockers, the most common drug prescribed for LUTS was Tamsulosin P.O, 0.4mg once daily at bed time (n= 46). It was prescribed alone (n=20), with Dutasteride 0.5mg (n=20) & with Tolterodine in 2-4mg (n=6). Newly launched alpha blocker Silodosin 8mg, P.O once daily at bed time, was prescribed to 16 patients either alone (n=11) or in combination with Dutasteride (n=5). Another alpha blocker prescribed was Alfuzosin 10mg P.O, which was prescribed alone to 7 patients, with Dutasteride (n=5) & with toltoredine (n=4) once daily at bed time. Alfuzosin was preferably prescribed to younger age group patients due presumably lesser incidence of retrograde ejaculation. All the patients who were prescribed alfuzosin were in age group 45-55 years. All the drugs prescribed for LUTS/BPH were in near optimal doses, with appropriate route, frequency and duration as per EAU guidelines (Figure 1).



**Figure 1: no of patients prescribed specific drugs for LUTS either alone or in combination. (n = 78).**

**Table 3: Change in IPSS, Qmax, Qavg & Quality of life over a period of 12 weeks of treatment (n=78).**

	0 wk (Mean±SD)	12 wk (Mean±SD)	Change in IPSS (Mean±SD)	% improvement <sup>#</sup>
IPSS	21.46±5.35	10.35±4.90*	11.11±5.5	51.7%
Qmax	11.61±5.84	15.32±5.11*	3.71±4.47	24.2%
Qavg	5.45±2.31	8.09±2.51*	2.64±1.73	32.6%
QOL	4.42±0.54	2.59±0.76*	1.83±1.05	41.4%

\* p value<0.001 versus corresponding 0 week values; # The percent drop/increase in score was calculated ([Score [pre] - Score [post]] × 100/Score [pre] = percent improvement in score).

**Efficacy assessment of drugs**

The overall outcome of drug treatment on LUTS was recorded in the form of change in IPSS, Qmax, Qavg and

quality of life. The mean change in IPSS was -11.11(51.7%), mean change in Qmax was +3.71±4.47 (24.2%), mean change in Qavg was +2.64±1.73 (32.6%) and Change in QOL was -1.83±1.05 (41.4%). All these parameters show significant improvement, indicating that medical treatment of patients with LUTS carries substantial benefit (Table 3).

In between assessment of IPSS score was also done at 4 weeks interval. The trend of improvement of IPSS score over 12 weeks of treatment shows that initial improvement over 4 weeks was quite remarkable compared to late improvement over next 8 weeks. The drug shows early onset peak effect and then the effect is sustainable over next three weeks with slight improvement overtime as depicted in Figure 2. The quality of life showed significant improvement (p<0.05) over a period of 12 weeks but the improvement was lagging behind the improvement in IPSS score when compared in terms of % improvement. This depicts that though there was good subjective improvement but does not ensure the same magnitude of improvement in quality of life. Pearson correlation, r = -0.51. Initially at baseline 28 patients had significant PVR which reduced to only 4 patients over 12 weeks of treatment i.e. 87% improvement in PVR.

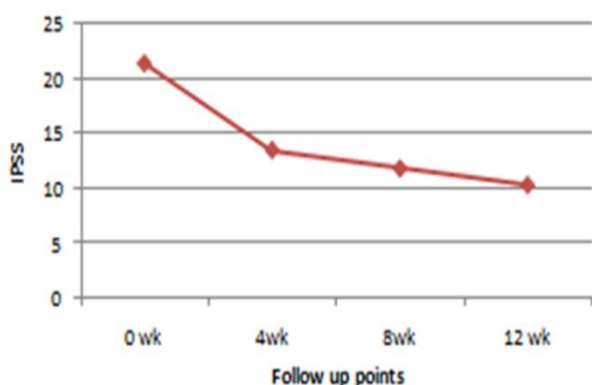


Figure 2: Change in IPSS over 12 weeks of treatment (n=78).

**Safety profile of drugs**

Total six adverse events were recorded during study. None of the adverse events was serious in nature. Two patients had dizziness, mostly during morning hours. In this one patient was on tamsulosin and another was on silodosin. Another patient on silodosin had developed retrograde ejaculation. Two patients developed feeling of incomplete voiding while taking Tolterodine which was self-resolving when drug was stopped. One patient reported dry mouth after starting Tamsulosin and dutasteride.

**Comparison between different alpha-blockers on basis of change in IPSS**

There were 3 alpha blockers used in this study namely Tamsulosin, Silodosin and Alfuzosin. Intragroup analysis of all the alpha blockers showed significant improvement (p<0.001) over a period of 12 weeks of treatment.

Inference from Intergroup analysis of alpha blockers on the basis of change in IPSS over 12 weeks of treatment was not significant (p=0.561) although the trend in present study showed insignificantly better improvement in silodosin group (Table 4).

Table 4: Comparison of different alpha blockers on the basis of IPSS score over a period of 12 weeks.

	0 week	12 week	Mean change	% improvement
Tamsulosin (n=46)	20.42± 4.19	11.23± 4.22*	-9.19± 3.44	45%
Silodosin (n=16)	18.33± 6.9	8.0± 4.2*	-11.33± 5.75	61%
Alfuzosin (n=16)	18.42± 3.45	9.28± 2.05*	-9.14± 4.4	49.6%

\* (p<0.001) versus corresponding 0 week IPSS values.

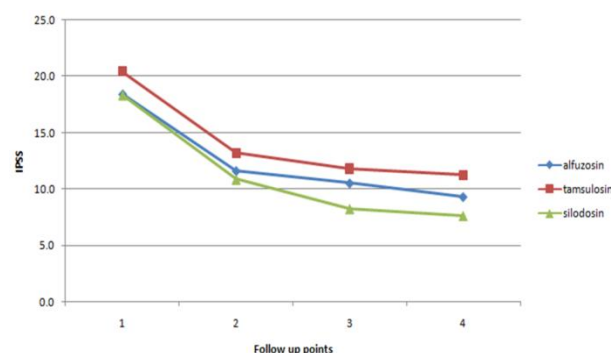


Figure 3: Change in IPSS over 12 week's periods in different alpha blocker group.

**DISCUSSION**

Since there was no clear guideline about the use of different alpha receptor antagonists for treatment of LUTS, so we assessed the pattern of prescription of different alpha receptor antagonists, their efficacy and their side effects as per EAU guidelines. The class of drugs specific for non-neurogenic LUTS in male patients used in present study were: Alpha blockers and their combination with either 5α reductase inhibitor or antimuscarinic. In present study among alpha blockers Tamsulosin (58.9%), was most commonly prescribed in comparison with Alfuzosin (20.5%) and Silodosin (20.5%). Dutasteride (38.4%) and Tolterodine (12.8%) were prescribed in combination with alpha blocker. A similar large observational study was done to evaluate treatment patterns in UK primary care for LUTS, with a



median age of 66.0 (59.0-74.0) years were identified. Most patients (90.3%) received a  $\alpha_1$ -blocker, and (24.9%) received antimuscarinic therapy. The most commonly prescribed  $\alpha_1$ -blocker was tamsulosin (81.8%); and most frequent antimuscarinics was Tolterodine (41.0%).<sup>6</sup>

The efficacies of all drugs were assessed on the basis of mean change difference in IPSS score, Qmax, and Qavg. In the present study we found that all three  $\alpha$ -blockers have near about similar efficacy with slightly better trend in Silodosin group though in between group difference of alpha blockers was nonsignificant. Indirect comparisons between  $\alpha_1$ -blockers and limited direct comparisons demonstrate that all  $\alpha_1$  blockers have a similar efficacy in appropriate doses.<sup>7</sup> All drug treatments showed significant improvement in IPSS, Qmax, Qavg for most patients over the study period. Alpha-1a blockers have a similar efficacy, expressed as a percentage improvement in International Prostate Symptom Score (IPSS) in patients with mild, moderate, or severe LUTS.<sup>8</sup> Controlled studies have shown that  $\alpha_1$ -blockers typically reduce IPSS, after a placebo run-in period, by approximately 30-40% and increase the maximum flow rate (Qmax) by approximately 20-25%. In present study we found that alpha1 blocker reduce IPSS by 47% over a period of 12 weeks and Qmax by 24.1%. A randomized, double-blind, parallel-design trial compared the efficacy and safety of tamsulosin and alfuzosin in 76 men with symptomatic benign prostatic hyperplasia. Patients were randomized to receive tamsulosin once daily orally (n = 40) or alfuzosin once daily orally (n = 36), and changes in IPSS and, maximal urinary flow rate (Qmax) was observed. There was a mean overall decrease in the IPSS and Qmax, with no significant difference between the treatment groups.<sup>9</sup>

Since Silodosin has been introduced into the Indian market recently and is reported to be highly selective for the  $\alpha_{1A}$ -adrenoceptor blocker, we sought to ascertain whether this offers any clinical advantage compared to the older drug Tamsulosin and Alfuzosin. In the present study Silodosin gives better improvement in IPSS than other alpha receptor antagonists although nonsignificant. Published studies from other countries report that silodosin is comparable to tamsulosin in the management of BPH. In a multicentric RCT it was found that the change from baseline in the IPSS total score with both silodosin and tamsulosin was significantly superior to that with placebo.<sup>10</sup> Another non-inferiority trial found that 86.2% in the silodosin group versus 81.9% in the tamsulosin group achieved a  $\geq 25\%$  decrease in IPSS.<sup>11</sup> Another study showed the non-inferiority of silodosin 4 mg twice daily to tamsulosin 0.2 mg once daily in patients with symptomatic BPH, although patients receiving silodosin had significant higher incidence of abnormal ejaculation and patient receiving Tamsulosin had significant reduction of systolic Blood Pressure.<sup>12</sup> In present study one event of retrograde ejaculation and one of dizziness associated with patient receiving silodosin (n=16), while one event of dizziness and dry mouth with

tamsulosin (n=46). In a study with 0.4 mg tamsulosin, the standard starting dose used by urologists in India, found similar results. The final IPSS scores at 12-week were significantly less than baseline for both tamsulosin and silodosin. However, scores remained comparable between the two study groups throughout the 12-week duration of the study. These results suggest that Silodosin effectiveness is similar to Tamsulosin in the short-term treatment of BPH in Indian men. The QoL component was also comparable between groups at 12-week.<sup>13</sup> The American Urological Association (AUA) guidelines committee believes that all  $\alpha$ -blockers, regardless of their selectivity for  $\alpha_1$ -receptor subtypes, including  $\alpha_{1A}$ -,  $\alpha_{1B}$ - and  $\alpha_{1D}$ -receptors, are equally effective, causing on average a 4- to 6-point improvement in the AUA symptom score, which most patients perceive as a meaningful change.<sup>14</sup>

An observational study of this nature has clear limitations for the evaluation of the efficacy. As patients were not randomized to treatments, confounding by indications cannot be excluded, and the numbers of patients receiving medications were too small to permit robust statistical analysis. The relatively short 12 weeks follow-up period was also a limitation.

## CONCLUSION

Non-neurogenic male lower urinary tract symptoms (LUTS) may have multifactorial aetiology but dominated by enlarging prostate. Treatment ranges from watchful waiting to medical therapy to surgical treatment. The choice of treatment depends cause, severity of symptoms; treatment preferences of the individual patient; and expectations to be met in terms of speed of onset, efficacy, side effects, quality of life, and disease progression. These symptom-oriented guidelines are based on the best available evidence and provide practical guidance for the management of men experiencing LUTS. It is important for clinicians to determine which patients are at increased risk of disease progression in order to optimise therapy and offer a treatment approach that correlates with patient preferences.

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