Original Article

Electronic medical records-based retrospective, longitudinal, observational study to understand the patient management of benign prostatic hyperplasia with alpha-blockers monotherapy in Indian population

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Abstract

Objective: The present retrospective study evaluates the effectiveness and tolerability of alpha-blockers as monotherapy in patients with benign prostatic hyperplasia associated with lower urinary tract symptoms (LUTS).

Materials and Methods: A total of 335 male patients >50 years were categorized into four groups (Alfuzosin: 166, Silodosin: 67, Tamsulosin: 70, Prazosin: 32). The efficacy evaluated as a change in International Prostate Symptom Score (IPSS), peak flow rate (Qmax), residual urine volume, and relief from LUTS, and tolerability of the various alpha-blockers was assessed across the study group.

Results: At baseline, most of the patients in alfuzosin (60%), silodosin (77%), and tamsulosin (90%) groups presented with severe IPSS (20–35), whereas patients in the prazosin group (69%) presented with a moderate score. At the end of the study, the mean IPSS gradually improved to moderate (41%, 62%, 66%, and 28%) and mild (59%, 38%, 28%, and 72%) in the alfuzosin, silodosin, tamsulosin, and prazosin groups, respectively ($P = 0.004$), with improvement in mean change in residual urine volume and complete relief from LUTS symptoms with no surgical or radiological interventions. Overall, 194 adverse events (AEs) were observed in 38.8% of patients. Of the total AEs, patients in the alfuzosin, silodosin, tamsulosin, and prazosin groups experienced 21%, 22%, 39%, and 18% of AEs, respectively.

Conclusion: The nonselective alpha-adrenergic receptor antagonist, alfuzosin, emerged as noninferior in effectiveness and superior in tolerability than other selective alpha-blockers, silodosin, tamsulosin, and prazosin.

Keywords: Alpha-blockers, benign prostatic hyperplasia, international prostatic symptom score, lower urinary tract symptoms, real-world evidence

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INTRODUCTION

Benign prostatic hyperplasia (BPH), as defined by the American Urological Association, is a histologic diagnosis alluding to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.[1] The prostate continues to grow with age and about 50% of men above 60 years of age present with BPH. In older men, BPH presence is strongly associated with the co-existence and development of lower urinary tract symptoms (LUTS), characterized by several symptoms including nocturia, urgency, dysuria, frequency, weak streaming, difficulty initiating micturition, and weak or interrupted stream during micturition.[2] Although BPH does not have any fatal effects, its potential risk of complications affects the quality of life (QoL).[3]

The treatment options for BPH range from monitoring to medical and surgical interventions. Two different medical strategies are currently available for managing LUTS/BPH-the alpha-adrenergic antagonists (alpha-blockers) and the 5-alpha-reductase inhibitors, acting on the dynamic and static components of the BPH, respectively. The alpha-blockers help in the relaxation of the stromal smooth muscle and address the dynamic component of BPH, thus improving the flow. Caine *et al*.[4] were the first to report the therapeutic application of alpha-adrenergic-receptor. The significant advantage of alpha-blockers over other medications is their rapid onset of action and eluding surgery.[5]

There are several alpha-blockers in clinical use. While the FDA-approved alpha-blockers (alfuzosin, tamsulosin, and silodosin) show similar efficacy, they differ in tolerability, with reports of ejaculatory dysfunction.[6] These compounds have been analyzed on several criteria, including pharmacological selectivity, clinical selectivity, the onset of action, efficacy, safety, dosage intervals, the role of dose titration, and cost. An ideal clinically uroselective alpha-blocker, with maximum clinical efficacy on LUTS and urodynamic variables without any harmful effects, must be the first choice. Undesired effects such as orthostatic hypotension or cerebral penetration should be considered, particularly when treating elderly patients and those on antihypertensive regimens.

All four alpha-blockers have similar efficacy, but they differ in tolerability. Many studies have shown the efficacy of the various alpha-blockers studied in BPH patients. However, a real-world understanding of alpha-blockers' clinical effectiveness and tolerability is still unclear, especially in the Indian population.

This study provides a real-world evidence-based insight into the long-term effectiveness and tolerability of various alpha-blockers in BPH patients with respect to their demographic patterns.

MATERIALS AND METHODS

Subjects and methods

The present study is a real-world, retrospective, observational, multicentric study designed to evaluate the

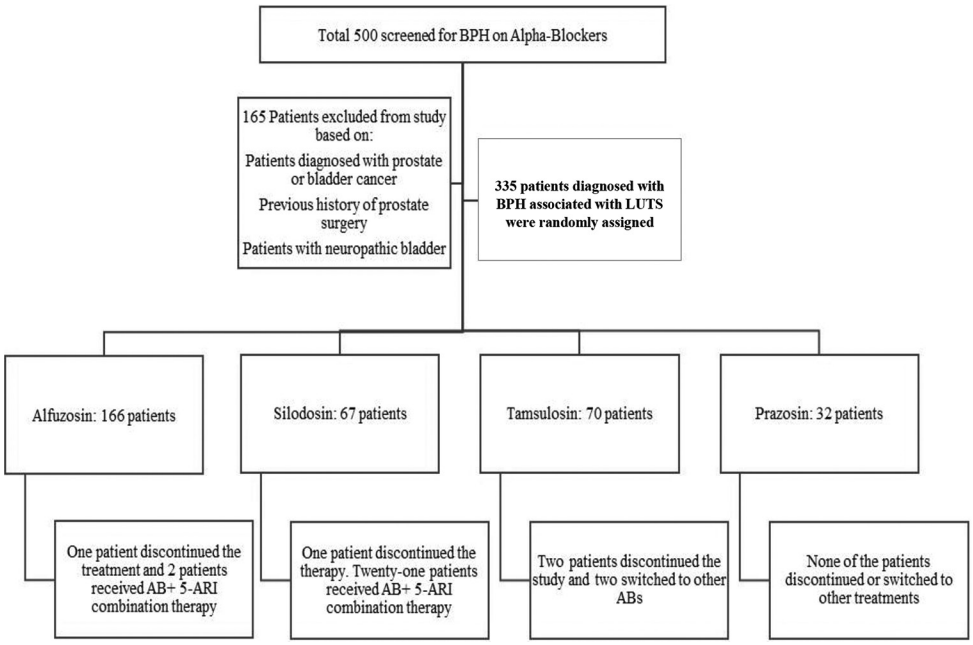

Figure 1: Flow chart for study participants diagnosed with BPH and receiving Alpha-blocker treatment

effectiveness and tolerability of four majorly prescribed alpha-blockers (alfuzosin, silodosin, tamsulosin, and prazosin) in the treatment and management of BPH associated with LUTS. The electronic medical records (EMR) data of all eligible patients as per the selection criteria were collected from February 2015 to January 2020. The Royal Pune Independent Ethical Committee (Pune, India) approved the study, and all procedures were conducted as per the World Medical Association Declaration of Helsinki.

All adult male patients >50 years of age, suffering from BPH associated with LUTS, as diagnosed by the investigator and confirmed by ultrasound report, on alpha-blocker monotherapy, and with a follow-up data for a minimum of two visits in 1 year duration were included in the study. Patients with prostate or bladder cancer, history of prostate surgery, neuropathic bladder, or concomitant application of another alpha-blocker at baseline were excluded from the study [Figure 1].

Effectiveness evaluation

The effectiveness was assessed for the prescribed alpha-blocker regimen in the management of BPH. The effectiveness outcomes included a change in daytime urine frequency, nocturia, residual urine volume, urinary peak flow improvement, relief from the most bothersome BPH symptoms, or any other related parameters (International Prostate Symptom Score [IPSS]) as available and as captured by the treating clinician.

Tolerability evaluation

The tolerability of the prescribed dose regimen was assessed as all treatment-related side-effects reported by patients, including already known side-effects as reported in the package insert and any new observations found relevant to the treatment as per the treating clinician.

Statistical analysis

All outcomes were presented using descriptive statistics. Continuous data were expressed as mean and standard deviation, while categorical data were presented as numbers and percentages. The comparison of mean differences of data was analyzed by *t*-test and categorical variables by the Chi-square test. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the R-statistical tool version 4.0.2 and Microsoft excel. Microsoft excel, Developer: Microsoft Corporation, Redmond, Washington, U.S.

RESULTS

Baseline general characteristics of benign prostatic hyperplasia patients

EMR data of a total of 335 BPH patients with LUTS were included in the study with the following representative patient number in each drug group: Alfuzosin-166; Silodosin-67; Tamsulosin-67; and Prazosin-32 patients [Figure 1]. The demographic details and other baseline characteristics are as represented in Table 1. The mean age of the patients across the group was almost similar except for the tamsulosin group with a mean age of 68.71 ± 7.14 years with a statistically significant difference of $P < 0.0001$. Similarly, patients in the tamsulosin group had a lesser mean weight than the patients in the other three groups. The patients in the prazosin group reported mean high diastolic and systolic blood pressure.

The comorbidities and lifestyle risk factors are shown in Table 1. The most observed comorbidities across all the treatment groups were diabetes, hypertension, and cardiovascular diseases. Lifestyle risk factors such as smoking, alcoholism, and sedentary lifestyles with significant risks associated with the development and progression of BPH were notable in the study population.

Benign prostatic hyperplasia patient characteristics at baseline visit

Before initiation of alpha-blocker therapy, baseline characteristics for all the patients concerning the duration of symptoms, family history of BPH, and sexual activity of the patients were retrieved. The duration of symptoms varied from one month to up to 48 months (patients having persistent symptoms) before initiating the therapy. The mean duration (in months) across the groups are as follows: Alfuzosin - 4.44 ± 6.16; silodosin - 2.88 ± 2.40; tamsulosin - 4.28 ± 6.16; and prazosin - 4.25 ± 1.43, respectively, with a statistically significant difference of $P = 0.0008$. Out of the 335 patients, 264 (78.81%) reported no family history of BPH. Furthermore, only 20.60% (69/335) of patients were sexually active at baseline, most noted in the alfuzosin treatment group.

Ultrasound examination was conducted to measure the prostate size, prostate volume, and BPH grade. Majority of the patients (260/335, 77.61%) presented with enlarged prostate size, with 92.84% of patients in the silodosin group with a statistical difference of $P < 0.0001$ between the mildly enlarged and enlarged group. The mean prostate volume (cc) across the groups is represented in Table 2, with the least prostate volume recorded in the prazosin group (30.67 ± 5.18 cc), with a $P < 0.0001$ across the groups. Most patients presented with Grade II BPH (alfuzosin-56%; silodosin-34%; tamsulosin-40%; and prazosin-38%). Grade I BPH was predominantly observed in the prazosin group (63%), and 42% of patients in the silodosin group reported Grade III BPH.

Clinical examination such as Digital Rectal Examination and laboratory examinations such as uroflowmetry, Urinary Tract Infections (UTIs), and Prostate-Specific

Antigen (PSA) were also conducted at the baseline visit. The PSA test report was available for all the 335 patients, 13 patients reported positive rectal examination, and three patients suffered from UTIs during the baseline visit.

Uroflowmetry was used to determine the mean urine flow rate (mL/sec), urine voided volume (mL), voiding time, maximum flow rate (Q_{max}), flow time (sec), and average flow rate. At the baseline visit, the minimum flow rate and voided volume were reported in the tamsulosin group at 7.48 ± 1.46 mL/s and 191.77 ± 42.82 mL, respectively. The highest mean flow time was recorded in the prazosin group (26.75 ± 6.81 s). No other significant pathological or radiological observations were observed except for nine patients, as shown in Table 2.

Alpha-blocker treatment outcome

Effectiveness outcome

The alpha-blocker treatment effectiveness outcome was assessed as relief from LUTS-associated BPH symptoms

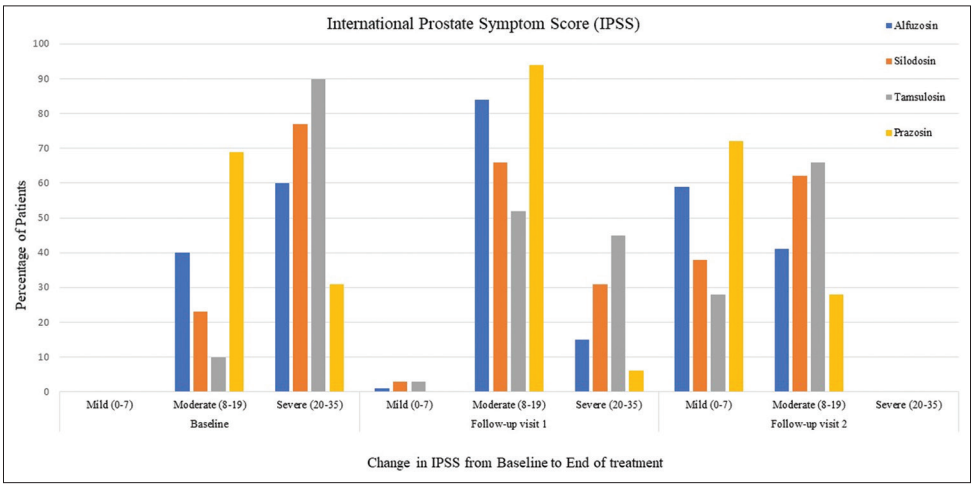

Figure 2: Effectiveness evalutions of Alpha blocker therapy across BPH patients. IPSS was used a measurement to evaluate the severity of BPH condition classified as Mild (0-7), Moderate (8-19), and Severe (20-35). At the baseline all the patients reported Moderated to Severe BPH (Baseline) but at the end of treatment (6 months period) all the patients responded well to the therapy and showed a drastic improvement in the IPSS

Table 1: Baseline patient profile (*N*=335)

Parameter name	Alfuzosin (*n*=166), *n* (%)	Silodosin (*n*=67), *n* (%)	Tamsulosin (*n*=70), *n* (%)	Prazosin (*n*=32), *n* (%)	*P*
Demographic profile (mean±SD)					
Age (years)	59.74 ± 7.47	59.95 ± 8.66	68.71 ± 7.14	62.46 ± 7.29	<0.0001
Weight (kg)	68.24 ± 5.63	68.13 ± 6.57	65.64 ± 5.24	67.75 ± 5.04	0.013
Height (cm)	169.35 ± 4.47	169.82 ± 4.19	168.45 ± 3.89	169.25 ± 3.96	0.288
General examination (mean±SD)					
Pulse (bpm)	78.36 ± 4.41	77.71 ± 5.00	78.3 ± 4.58	76.93 ± 4.25	0.353
Blood pressure (mmHg)					
SBP	127.04 ± 8.09	126.82 ± 7.99	127.31 ± 9.88	134.37 ± 7.31	0.0001
DBP	78.89 ± 5.75	79.00 ± 4.17	79.08 ± 5.20	83.25 ± 4.97	0.0003
Surgical history					
Appendix	1 (0.60)	1 (1.49)	0	0	0.928
Hernia	0	0	1 (1.43)	0	
Perforation	0	1 (1.49)	0	0	
Lipoma	1 (0.60)	0	0	0	
Comorbidities					
Diabetes mellitus	41 (24.69)	6 (8.95)	20 (28.57)	5 (15.62)	
Hypertension	23 (13.85)	10 (14.92)	12 (17.14)	12 (37.5)	
Cardiovascular disease	27 (16.26)	4 (5.97)	39 (55.71)	10 (31.25)	
Renal disease	3 (1.85)	1 (1.49)	0	0	
Hyperlipidemia	28 (16.86)	6 (8.95)	32 (45.71)	8 (25)	
Obesity	16 (9.63)	9 (13.43)	2 (2.85)	2 (6.25)	
Others	0	1 (1.49) [a]	1 (1.42) [b]	0	
Lifestyle-related risk factors					
Smokers	42 (25.30)	14 (20.89)	7 (10)	8 (25)	
Alcoholics	28 (16.86)	10 (14.92)	5 (7.14)	4 (12.5)	
Sedentary lifestyle	12 (7.22)	4 (5.97)	4 (5.71)	2 (6.25)	
Other*	1 (0.60)	0	0	0	

[a]Parkinsonism, [b]CVA, *Drug abuse. CVA: Cerebrovascular accident, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2: Baseline visit details (*N*=335)

Baseline details	Alfuzosin (*n*=166), *n* (%)	Silodosin (*n*=67), *n* (%)	Tamsulosin (*n*=70), *n* (%)	Prazosin (*n*=32), *n* (%)	*P*
BPH history					
Mean duration of BPH symptoms (months)	4.44 ± 6.16	2.88 ± 2.40	4.28 ± 6.16	4.25 ± 1.43	0.0008
Family history of BPH					
Yes	38 (23)	16 (24)	13 (19)	4 (13)	0.51*
No	128 (77)	51 (76)	57 (81)	28 (88)	
Sexually active					
Yes	48 (29)	12 (18)	5 (7)	4 (13)	0.001
No	118 (71)	55 (82)	65 (93)	28 (88)	
Age-wise distribution of sexual activity (years)					
<50	15 (31.25)	2 (16.66)	0	0	NA
50-59	28 (58.33)	10 (83.33)	3 (60)	4 (100)	
60-69	5 (10.42)	0	2 (40)	0	
Ultrasound report					
Prostate size					
Mildly enlarged	37 (22.29)	5 (7.46)	13 (18.57)	20 (62.50)	<0.0001
Enlarged	129 (77.71)	62 (92.54)	57 (81.43)	12 (37.50)	
Mean prostate volume (cc)	44.09 ± 12.53	52.69 ± 11.62	50.56 ± 13.43	30.67 ± 5.18	<0.0001
BPH grade#					
I	33 (20)	3 (4)	11 (16)	20 (63)	<0.0001
II	93 (56)	23 (34)	28 (40)	12 (38)	0.006
III	25 (15)	28 (42)	10 (14)	0	<0.0001
IV	12 (7)	13 (19)	20 (29)	0	<0.0001
DRE					
Positive	10 (6)	2 (3)	3 (4)	0	0.712
Negative	156 (94)	65 (97)	67 (96)	32 (100)	
PSA test available					
Yes	166 (100)	67 (100)	70 (100)	32 (100)	NA
No	0	0	0	0	
History of UTI					
Yes	3 (2)	0	1 (1)	0	0.935
No	163 (98)	67 (100)	69 (99)	32 (100)	
Uroflowmetry (mean±SD)					
Flow rate (mL/sec)	7.71 ± 1.61	7.81 ± 1.26	7.48 ± 1.46	8.34 ± 1.94	0.075
Voided volume (mL)	212.93 ± 57.29	209.40 ± 60.03	191.77 ± 42.82	245.93 ± 65.33	0.001
Voiding time (micturition time)	21.90 ± 5.17	20.82 ± 2.96	21.10 ± 3.79	21.93 ± 4.80	0.299
Maximum flow rate (Q_{max})	12.23 ± 3.25	12.21 ± 3.12	11.62 ± 3.43	12.09 ± 2.65	0.592
Flow time (sec)	23.95 ± 5.61	23.13 ± 5.58	22.28 ± 4.74	26.75 ± 6.81	0.002
Average flow rate (voided volume/flow time)	9.11 ± 2.25	9.33 ± 2.46	8.84 ± 2.10	9.32 ± 2.02	0.586
Other (radiological/pathological) observations I					
Yes	2 (1.20)	5 (7.46)	2 (2.86)	0	0.264
Bilateral hydroureteronephrosis	0	0	1 (1.43)	0	
Cholelithiasis	0	1 (1.49)	1 (1.43)	0	
Stricture	1 (0.60)	1 (1.49)	0	0	
Urinary bladder thickness	0	1 (1.49)	0	0	
Splenomegaly	0	1 (1.49)	0	0	
Bladder calculi	1 (0.60)	0	0	0	
Renal stone	0	1 (1.49)	0	0	
No	164 (98.80)	62 (92.54)	68 (97.14)	32 (100)	

*Kruskal-Wallis test was used to calculate the *P* value, #Foo KT. Diagnosis and treatment of benign prostate hyperplasia in Asia. Transl Androl Urol 2015;4:478-83. PSA: Prostate-specific antigen, DRE: Digital rectal examination, BPH: Benign prostatic hyperplasia, SD: Standard deviation, UTI: Urinary tract infection, NA: Not available

measured from the IPSS and related parameters from the baseline visit to the end of the follow-up visit.

The IPSS is a cumulative score evaluated based on incomplete emptying or sensation of incomplete emptying of the bladder, frequency of urination, intermittency (urination stopped and started several times), urgency (difficult to postpone urination), weak stream (weak urinary system), straining, and nocturia. Based on the presence or absence of these parameters, the IPSS was classified as mild (0–7), moderate (8–19), and severe (20–35). Most of the patients in the alfuzosin, silodosin, and tamsulosin groups were presented with severe IPSS with a mean value of 21.92 ± 4.81, 24.12 ± 4.95, and 25.81 ± 4.55, respectively, at the baseline visit.

Table 3a: The effectiveness outcomes of alpha-blocker treatment (*N*=335)

Alpha-blocker treatment outcome	Alfuzosin (*n*=156), *n* (%)	Silodosin (*n*=65), *n* (%)	Tamsulosin (*n*=67), *n* (%)	Prazosin (*n*=32), *n* (%)	*P*
Baseline report					
IPSS					
Mild (0-7)	0	0	0	0	<0.001
Moderate (8-19)	63 (40)	15 (23)	7 (10)	22 (69)	
Severe (20-35)	93 (60)	50 (77)	60 (90)	10 (31)	
Overall mean score (±SD)	21.92 ± 4.81	24.12 ± 4.95	25.81 ± 4.55	18.12 ± 4.34	<0.001
Residual urine volume (mL), mean (±SD)	94.79 ± 26.76	94.15 ± 27.87	96.59 ± 28.39	96.43 ± 20.77	0.943
Urinary peak flow (mL), mean±SD	14.04 ± 2.75	14.22 ± 2.69	13.36 ± 2.53	13.87 ± 2.85	0.264
LUTS symptoms	156 (100)	65 (100)	67 (100)	32 (100)	NA
Presence of UTI	0	0	0	0	NA
Other radiological/pathological evaluations	0	0	0	0	NA
Follow-up visit 1					
IPSS					
Mild (0-7)	2 (1)	2 (3)	2 (3)	0 (0)	<0.001
Moderate (8-19)	131 (84)	43 (66)	35 (52)	30 (94)	
Severe (20-35)	23 (15)	20 (31)	30 (45)	2 (6)	
Overall mean score (±SD)	14.79 ± 4.14	16.52 ± 4.66	17.46 ± 4.63	11.40±3.37	<0.001
Residual urine volume (mL), mean±SD	57.27 ± 19.93	56.73 ± 19.05	58.65 ± 21.37	56.56 ± 22.03	0.94
Patients with improved urinary peak flow	156 (100)	65 (100)	67 (100)	32 (100)	NA
Relief from LUTS symptoms	156 (100)	65 (100)	67 (100)	32 (100)	NA
Presence of UTI	0	0	0	0	NA
Surgical interventions	0	0	0	0	NA
Other radiological/pathological evaluations	0	0	0	0	NA
Follow-up visit 2					
IPSS					
Mild (0-7)	92 (59)	25 (38)	19 (28)	23 (72)	0.0004
Moderate (8-19)	64 (41)	40 (62)	44 (66)	9 (28)	
Severe (20-35)	0	0	0	0	
Mean score (±SD)	7.80 ± 2.12	9.43 ± 3.08	9.65 ± 3.16	7.18 ± 2.94	<0.001
Residual urine volume (mL), mean ± SD	32.14 ± 10.99	34.03 ± 12.63	35.47 ± 12.31	33.15 ± 9.31	0.237
Urinary peak flow improvement	156 (100)	65 (100)	67 (100)	32 (100)	NA
Relief from LUTS symptoms	156 (100)	65 (100)	67 (100)	32 (100)	NA
Presence of UTI	0	0	0	0	NA
Surgical interventions	0	0	0	0	NA
Other radiological/pathological evaluations	0	0	0	0	NA

SD: Standard deviation, UTI: Urinary tract infection, NA: Not available, LUTS: Lower urinary tract symptoms, IPSS: International prostate symptom score

The effectiveness during the follow-up was evaluated in terms of change in IPSS, mean residual volume (mL) as obtained from the USG reports, mean peak urinary flow (mL) from the uroflowmetry reports, and relief from LUTS symptoms as mentioned in Table 3a. There was a significant improvement in the IPSS at the end of the treatment as none of the patients reported a severe IPSS [Figure 2]. All the patients were relieved from LUTS symptoms, and none of them underwent any surgical interventions or radiological interventions during the study. The overall treatment effectiveness is as represented in Table 3b. All prescribed alpha-blockers were effective in the management of BPH associated with LUTS symptoms.

Tolerability evaluation of alpha-blockers in benign prostatic hyperplasia management

Tolerability assessments consisted of all side effects (adverse events [AE] and adverse drug reactions [ADRs]) reported across the four alpha-blockers drugs captured during the study period.

All reported AEs were ADRs, as all ADRs were assessed concerning their causal relationship to study medications, i.e., "probable" or "possible." ADRs were evaluated as related to occur in patients in all four study drugs, broken down by MedDRA coding SOC, HLT, and PT, are presented in Figure 3. A total of 194 (100.0%) ADRs were documented for 130/335 (38.81%) patients across all four study drugs. Out of which, 21.24% of ADR events

Table 3b: Overall effectiveness analysis (*N*=320)

Alpha-blocker treatment outcome	Alfuzosin (*n*=156), *n* (%)	Silodosin (*n*=65), *n* (%)	Tamsulosin (*n*=67), *n* (%)	Prazosin (*n*=32), *n* (%)	*P*
Mean change in BPH symptoms from baseline to follow-up visits					
Percentage of patients with improved IPSS - i.e., number of patients improved in score from severe to moderate/mild and moderate to mild					
Mild (0-7)	92 (59)	25 (38)	19 (28)	23 (72)	0.004
Moderate (8-19)	64 (41)	40 (62)	44 (66)	9 (28)	
Severe (20-35)	0	0	0	0	
Percentage of patients with reduced residual urine volume	156 (100)	65 (100)	67 (100)	32 (100)	NA
Percentage of patients with a change in urinary peak flow	156 (100)	65 (100)	67 (100)	32 (100)	NA
Percentage of patients with relief from LUTS symptoms	156 (100)	65 (100)	67 (100)	32 (100)	NA
Percentage of patients with presence of UTI	0	0	0	0	NA
Percentage of patients with underwent surgical interventions for BPH	0	0	0	0	NA
Patients with other pathological or radiological interventions	0	0	0	0	NA

UTI: Urinary tract infection, NA: Not available, LUTS: Lower urinary tract symptoms, IPSS: International prostate symptom score, BPH: Benign prostatic hyperplasia

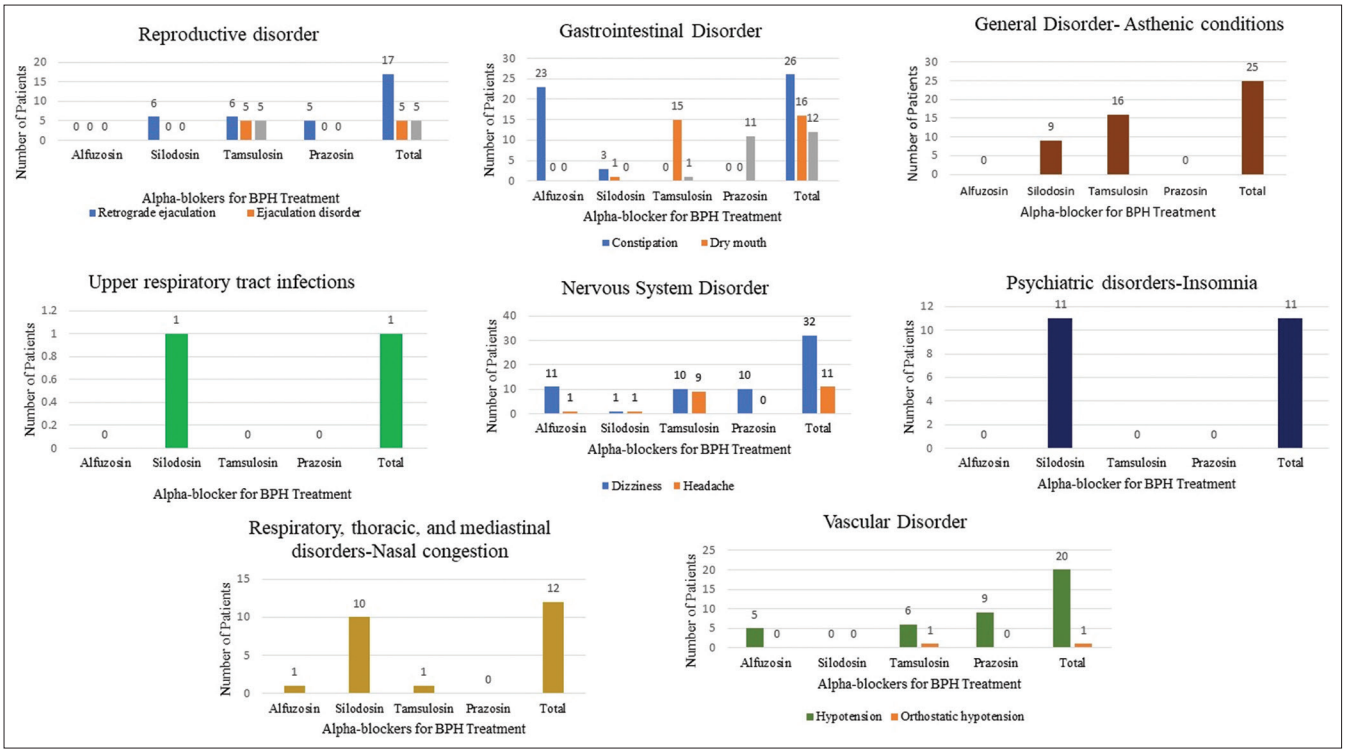

Figure 3: Sub-categorization of ADRs across the four Alpha-blockers (Alfuzosin, Silodosin, Tamsulosin, and Prazosin)

were reported by 24% of patients on alfuzosin, 22.28% of events in 48% of patients on silodosin, 38.66% of events in 56% of patients on tamsulosin, and 18.04% of events in 66% of patients on prazosin. The total incidence of ADRs was lowest with prazosin followed by alfuzosin, and higher incidences were associated with tamsulosin. On aggregate, one in every four patients in the alfuzosin group had ADR. In silodosin and tamsulosin one in two, and approximately two in three patients had reported ADR in the prazosin group. Although in each group, the patients continued treatment and completed the study.

The causality assessment of these ADRs had suggested that out of the total 194 ADRs reported, 166 ADRs had "possible" causality relation with the study alpha-blockers. The remaining 20 ADRs had "probable" causality relation with the study alpha-blockers (the causality assessment of the remaining 8 ADRs was not available).

In all four alpha-blocker therapies combined, the most frequently reported ADR among the study patients were dizziness (9.55%), followed by constipation (7.76%), asthenia (7.46%), hypotension (5.97%), retrograde

ejaculation (5.07%), dry mouth (4.77%), dyspepsia and nasal congestion (3.58%), insomnia and headache (3.28%), ejaculation disorder and libido decreased (1.49%), orthostatic hypotension and nasopharyngitis (0.29%) in at least one patient.

DISCUSSION

Alpha-adrenergic receptors, a class of transmembrane glycoproteins, are responsible for smooth muscle contractions of the prostate.[7,8] Studies have shown that alpha-blockers increase the urinary flow rate to 30% and residual urine flow by 29%, with subsequent improvement in LUTS.[9] Prazosin was the first commercially available selective alpha-blocker utilized in BPH treatment as early as 1970.[8] Alfuzosin, silodosin, and tamsulosin were third-generation alpha-blockers with better tolerability and do not require dose titration.[10]

The present real-world evidence-based study was set up in a tertiary care center in India. It evaluated the long-term efficacy and tolerability of commonly prescribed alpha-blockers such as alfuzosin (10 mg OD), silodosin (8 mg OD), tamsulosin (0.4 mg OD), and prazosin (0.5 mg BD) in the management of BPH associated with LUTS as a monotherapy. Our study's age ranged between 43 and 90 years, with LUTS and only 21.19% of patients had BPH family history. About 77.61% of patients presented with enlarged prostate size, the majority suffering from grade II BPH (alfuzosin-56%; silodosin-34%; tamsulosin-40%; and prazosin-38%). At baseline, patients in the tamsulosin group had a minimum post-void residual volume of 191.77 ± 42.82 mL and the least flow time of 22.28 ± 4.74 s with a $P = 0.002$. Like other studies, our data also showed that patients with moderate to severe BPH based on the IPSS score (moderate-36.42% and severe-63.58%) had the highest in the tamsulosin group and minimum in the prazosin group. By the end of a 90-day follow-up, there was a significant reduction in the overall mean IPSS ($P < 0001$), with 47.46% (159/335) reporting mild IPSS (0–7) and the remaining 52.53% of falling under the moderate score (8–17). More than three times reduction in the residual urine volume across all the treatment groups from baseline to the last follow-up period was noted. None of the patients enrolled in the study had to undergo any surgical interventions during the study. There was significant relief from LUTS at the end of the study duration.

Similarly, Manjunatha *et al*.,[11] in their randomized, comparative open-label study using 90 subjects with BPH and LUTS, evaluated the efficacy and safety of alfuzosin, tamsulosin, and prazosin. The study reports a progressive decrease in IPSS ($P < 0.001$) with an overall 75% improvement in QoL across all the treatment groups. Another randomized double-blinded placebo-controlled phase III study on 457 patients treated with silodosin (4 mg BID) and tamsulosin (0.2 mg OD) also reported a significant improvement in IPSS and maximum uroflow rate across both the groups.[12] Contrasting to our study report, Wang *et al*.,[13] in a 2017 study using 80 middle-aged patients (30–60 years) receiving alfuzosin (2.5 mg TID) and tamsulosin (0.2 mg OD), had a different observation. The study reported higher efficacy of tamsulosin in relieving LUTS and improving the semen quality, sexual life, and QoL in young and middle-aged patients. Similar reports were also stated by Buzelin *et al*., affirming the superiority of a once-daily dose of tamsulosin compared to short-term acting agents such as prazosin and alfuzosin.[14] Our study reports strongly suggest equivalent efficacy of all alpha-blockers (selective or nonselective androgenic antagonists), with improvement in the QoL and progressive decrease in the IPSS.

Alpha-blockers are particularly associated with three side effects. First, cardiovascular events such as asthenia, hypotension, and dizziness. Second, ejaculatory dysfunction, and third, intraoperative floppy iris syndrome.[15,16] They are also known to cause retrograde ejaculation but do not decrease libido. Literature evidence from various meta-analysis had suggested that tamsulosin and silodosin are associated with retrograde ejaculation, while alfuzosin had a far more negligible impact.[17-19] A similar trend was noticed in the present study with a high incidence of retrograde ejaculation with silodosin (8.95%) and tamsulosin (8.57%), while there was no incidence in the alfuzosin group. In numerous studies, silodosin was reported as a superior alpha-blocker in BPH treatment, particularly in improving urinary symptoms such as postvoid residual volume but was mainly associated with a high risk of retrograde ejaculation.[18-21] A very recent systemic review on 1,371 patients from six cohort studies provided positive evidence supporting alfuzosin and its role in improving ejaculatory function.[16,22,23] In another RWE-based research, alfuzosin was well tolerated from a cardiovascular and sexual standpoint, including the elderly group.[23] In a double-blind, placebo-controlled study using alfuzosin 10 mg OD, lower incidences of postural hypotension (1%) and improved cardiovascular tolerability were noted.[24]

Kuritzky *et al*., in their review article from a pooled analysis of three-phase III trials, support the efficacy of 10 mg OD dose of alfuzosin with high tolerability and low incidences

of sexual (0.6%) and vasodilatory (7%) side-effects.[25] In our study, zero incidences of sexual abnormality and 3% incidences of vasodilatory side effects were reported in the alfuzosin group. Two pivotal studies also demonstrated a lack of ejaculatory dysfunction and a lower incidence of asthenia and dizziness using 10 mg once daily dose of alfuzosin.[6] Similarly, a real-world study conducted on an Indian population had supported that a 10 mg daily dose of alfuzosin produced a low incidence of cardiovascular effects like postural hypotension (0.5%) and asthenia with a positive benefit/risk ratio.[26] A meta-analysis of data pooled from two pivotal phase III randomized trials support the assertion that a 10 mg OD dose of alfuzosin was well tolerated and induced a low incidence of vasodilatory effects, i.e., hypotension/postural hypotension (0.6%).[23]

Limitations

Like other retrospective RWE studies, our study has the limitation that patients themselves were responsible for adhering to and complying with the given prescription. As EMR contains only the prescription data, we cannot exclude the possibility of some patients missing one or multiple doses, which could have contributed to a low observed therapeutic effect. Instead of a single protocol, different methods were used to measure the outcome parameters at various centers. This may have caused a variation in the measurements. Some of the outcome parameters were represented as categorical variables, i.e., the presence or absence of relief from the BPH symptom from the baseline to the end of study duration. A more accurate effectiveness outcome could be drawn if the clinical and laboratory test values were available.

CONCLUSION

The present retrospective real-world evidence study showcases the four major alpha-blockers' efficacy and safety profile (alfuzosin, silodosin, tamsulosin, and prazosin) across various age groups. The effectiveness parameters showed a gradual improvement from baseline to follow-up visits, and similarly, the drugs were safe with variable tolerability index in all the patient groups. Overall, one in four patients in the alfuzosin group had reported ADR. In silodosin and tamsulosin, one in two and prazosin group, approximately two in three patients had reported ADR.

In the study, the nonselective alpha-adrenergic receptor antagonist, alfuzosin, has emerged as noninferior in terms of effectiveness and superior in terms of tolerability compared to other third-generation selective alpha-blockers such as silodosin, tamsulosin, and prazosin. The superiority of 10 mg once daily dose of alfuzosin could be due to its administration with no initial titration and well-tolerated with very low cardiovascular and sexual function effects in all age groups. This improved effect of alfuzosin when compared with with other third-generation selective alpha-blockers is probably related to its formulation, preferential distribution into the prostate, and pharmacokinetics. The lack of ejaculatory dysfunction is also one of the advantages of alfuzosin.

Author's contribution

The authors' responsibility was as follows-Authors from Dr. Reddy's Laboratories had contributed towards conceptualizing the study hypothesis, design of the study, data analysis and interpretation of study outcomes, and compiling the manuscript. The advisory board members had significantly contributed to revising the manuscript critically for important intellectual content and final approval and review.

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Conflicts of interest

There are no conflicts of interest.

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