ORIGINAL ARTICLE

CONTENTS

Exploring the therapeutic potential of Beta-3 adrenergic agonists in overactive bladder: A comparative analysis of monotherapy *versus* combination therapy strategies

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ABSTRACT

Aim: to compare effects and side-effect profiles between mirabegron monotherapy and 2 combination treatments including mirabegron in patients with OAB.

Materials and Methods: Study is nonrandomized, prospective, and observational; conducted in 22 centers, 400 patients with OAB symptoms. Patients administered 50 mg monotherapy of mirabegron for 8 weeks. Responders received monotherapy (Group 0, n=109) and non-responders allocated to double therapy with mirabegron plus Solifenacin 5mg (Group 1, n=145) or mirabegron plus Flavoxate/Uripas (Group 2, n=146) for an additional eight weeks. Providing bladder volume, postvoid residual and BWT served as primary end points.

Results: Prevalence of urgency, frequency, and nocturia was high in cohort (92.8%, 88.5%, and 76.5%), but that of UUI35 was low at 9%. This indicates that patients are clearly of OAB-dry phenotype. Mixed storage-voiding symptom was most frequent among 53.8%. An unusual baseline comparison population along to chew, - 200% male and severe symptom' GROUPS 2 BWT a benefit of mirabegron\+\-Solifenacin); one could get; other couldn't (-36ml *vs.* -31ml). End-point analysis did not allow exclusion of therapeutic equipoise of REGULAR vs. DROP for final PVR (between-group difference: -1.48 mL, p = 0.065).

Conclusions: Beta-3 agonist as monotherapy is a potent, multimodality first-line therapy with strong influence of severe disease. Each of combinatory treatments show characteristic effect on phenotype-specific increase in bladder capacity. Mirabegron flaoxate could be considered for detrusor hypertrophy and combination of mirabegron Solifenacin would stimulate voiding facilitate. These proof of concept data justify PPTP based on objective biomarkers such as BWT and PVR to select combination therapy in what is another small step in our journey towards precision medicine for OAB.

KEYWORDS: overactive blasser, mirabegron, beta-3 adrenergic agonist, solifenacin, flavoxate, combination therapy, bladder wall thickness, personalized medicine; phenotyping

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INTRODUCTION

Introduction Overactive bladder (OAB) is a prevalent and clinically relevant syndrome that encompasses urgency urinary incontinence (UUI) with or without urgency usually with frequency, and nocturia, in the absence of any causal condition or infection of the urinary tract [1]. GB is both a physical and psychological burden to the patients, causing an impairment of (HRQoL), anxiety and depression as well as limitations in social activities and work. According to the clinical and epidemiological data, it has been estimated that OAB occurs in 16-17% of adult population according to age (thereby becoming a significant public health issue in various places around the world [2]. The management of OAB progresses with step therapy by 1 consisting of non-invasive behavioral therapies as the first approaches (bladder training and pelvic floor muscle training). The limited pharmacologic therapies also recommended by the AUA and SUSU include muscarinic or beta-3 agonist medications [3]. Antimuscarinic, like Solifenacin, oxybutynin and tolterodine suppress involuntary detrusor contractions by blocking muscarinic receptors and yet more they may be under-prescribe due to these anticholinergic side effects and hence low treatment continuation rate especially in the elderly [4]. Beta-3AGONISTS OAB Paradigm Shifters Beta-3 agonists are the next game changers in the treatment of OAB. Mirabegron as a beta-3 agonist, mirabegron is the prototype of this class, with a unique mode of action in that it causes detrusor muscle relaxation during storage phase via specific activation of beta-3 adrenoreceptors

and thus increases bladder capacity [5]. It has similar efficacy to Antimuscarinic without an anticholinergic adverse event profile and thus has higher tolerability, with better adherence to treatment. Suspect: B-A Prescribing This 'B' with a good side-effect profile (on rate of dry mouth and constipation) is increasing dramatically in usage, especially in the elderly and C/I Antimuscarinic patients [6]. Despite the efficacy of monotherapy, a good proportion of patients fail to achieve sufficient control of symptoms through the use of a single drug. It is a highly active treatment for these patients. Recent pristine RCT-based data on combination therapy of a beta-3 agonist with an Antimuscarinic from SYNERGY and BESIDE studies are available [7-8]. The 2024 AUA/SUFU guideline on idiopathic overactive bladder significantly moves away from "step-wise" therapies to personalized, patient centered treatment paradigms with shared decision-making [9]. This paradigm shift acknowledges that interventions may not be applicable for all patients based on the phenotype or the urodynamic profile of an individual patient, and thus supports exploring mechanisms which result in OAB in each patient and treating them individually. Equally exciting is movement toward phenotype-specific OAB treatment using biomarkers and objective measures in personalized urology [10]. Prospective data for combination therapy vs. Antimuscarinic monotherapy in the case of OAB is equally strong, but there is an important void between β-3 agonist monotherapy and when we assess various combinations of therapies. At present uptake of a enter into clinical decision making, yet to date there has been no clear evidence as to whether treatment will be commenced with mirabegron monotherapy or addition added on combination therapy as in the case for an invasive good symptom control marginal safe. In addition, EGFR and other biomarkers which have anticancer potentiality in personalized treatment decision for combination are also a question that has not been solved [11]. Methods for consideration of this, proof was sought from evidence-based literature to compare the effectiveness and safety between the mirabegron monotherapy and combination therapy with specific two drugs (mirabegron combined with Solifenacin (an Antimuscarinic) or Flavoxate (a direct muscle relaxant)), in terms of efficacy and safety in patients with OAB. All patients were assessed clinically and by U/S (bladder wall thickness; BWT, post void volume; PVR) both before and after treatment.

AIM

The aim of this study is to compare effects and side-effect profiles between mirabegron monotherapy and 2 combination treatments including mirabegron in patients with OAB.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

This prospective, randomized, controlled, open-label, parallel-group clinical trial was conducted at the urology outpatient clinics in Sadr Teaching Hospital, Basra, Iraq. Data collection was planned over a period of 18 months from the start of recruitment through the treatment and follow-up phases ending in final evaluation of patients. The study protocol was reviewed and approved by the Committee of Ethics in Basra Health Directorate and by the Scientific Committee of Basra University. All participants gave written informed consent prior to participation. Data confidentiality and patient privacy were ensured throughout the study.

STUDY POPULATION

Treatment-seeking adult patients (≥18 years) of either sex presenting with symptoms consistent with OAB were eligible for inclusion. OAB was defined according to the International Continence Society (ICS) criteria updated to 2018 as urinary urgency, with or without urgency urinary incontinence, usually accompanied by frequency and nocturia, for at least 3 months, in the absence of urinary tract infection or other obvious pathology.

INCLUSION CRITERIA

1 Adults aged 18 years or older of either sex;
2 Clinical diagnosis of OAB fulfilling the ICS definition;
3 Presence of urinary urgency as the predominant symptom for at least 3 months;
4 Willingness to participate after providing informed consent.

EXCLUSION CRITERIA

1 Active urinary tract infection or hematuria;
2 Neurogenic bladder;
3 History of bladder outlet obstruction or post-void residual urine volume greater than 150 mL;
4 Patients who reported using the study medications within the past 3 months;
5 Pregnancy or breastfeeding;
6 Cognitive impairment that can affect reporting capability of patient's symptoms and other information required to fill the data collection form.

SAMPLE SIZE CALCULATION

Based on previous studies such as the SYNERGY and BESIDE trials, the expected mean difference in reduction of urgency episodes per 24 hours between groups would be 0.5 episodes. Considering a standard deviation of 1.0 and to achieve 80% power at a 5% level of significance, a minimum of 63 patients per arm was required. To compensate for dropout, 15% was added to the estimated sample size. Therefore, 400 patients were considered sufficient to bring the required power and measure the significant differences when present.

TREATMENT PROTOCOL AND RANDOMIZATION

After reaching the planned sample size of 400 patients, all participants received monotherapy with the beta-3 agonist mirabegron at a dose of 50mg once daily for 8 weeks. Patients were classified into three severity grades (mild, moderate, and severe) according to a symptom grading system. Medications were ceased for 1 week (clearance period), and patients were re-evaluated during this washout period. Following the monotherapy phase, 110 patients had complete resolution of symptoms and were classified as monotherapy responders (Group 0, n=109 in final analysis). The remaining 290 non-responders were randomized into two arms of 145 patients each. One arm received mirabegron 50mg plus solifenacin 5mg once daily (Group 1, n=145). The second arm received mirabegron 50mg plus flavoxate (Uripas) (Group 2, n=146). The combination treatment continued for an additional 8 weeks. All medications were taken orally. Patients were instructed to take the assigned medication(s) once daily with no dose modification. Adherence to the treatment protocol was monitored by pill count and patient records.

OUTCOME MEASURES

PRIMARY EFFICACY OUTCOMES

The main efficacy parameters that were assessed included:

1 The relative change from baseline in FAC measured by TAUS,

2 The relative changes of PVR and BWT. All subjects underwent the measurement of PVR and BWT by a routine ultrasound technique.

SECONDARY EFFICACY OUTCOMES

Secondary measures of efficacy included:

1 Mean change from baseline in number of micturition per 24 hr. after 12 weeks;

2 Change from baseline to week 12 in the number of urgency episodes per 24 hr.;

3 Incontinence episodes/24 hr.;

4 Volume voided at a single micturition for all participants who completed scores on the PPBC and patients with a response option ≥2% of days from treated as missing data Summary statistics were used for patient-reported outcome measure based on OAB-q SF responses by response option for each category, each individual question, and four domains and symptom bother total without re cording them back between categories;

5 Patients 'Perception of Bladder Condition.

SAFETY OUTCOMES

Safety was evaluated by:

1 incidence of AEs and SAEs;

2 changes in BP, HR and P VR after voiding; and

3 withdrawal due to tolerability.

DATA COLLECTION AND MONITORING

Patients were evaluated at 4 intervals: baseline, week 4, week 8, and week 12. At each visit, the following information was obtained: symptom diary (3-day diary); OAB-q and PPBC questionnaires; vital signs and adverse event monitoring; urinalysis; and ultrasound measurement of post-void residual and bladder wall thickness.

ULTRASOUND PROTOCOL

Bladder wall thickness was measured using transabdominal ultrasound with a 3.5-5 MHz convex transducer at a standardized bladder volume of 150-250 mL. Measurements were taken at the anterior bladder wall in the midline, perpendicular to the bladder surface. A BWT threshold of 3 mm was considered indicative of detrusor hypertrophy based on established literature. Post-void residual volume was measured within 10 minutes of voiding using standard volumetric calculations.

STATISTICAL ANALYSIS

All statistical analyses were performed using IBM SPSS Statistics (version 26, IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 10, GraphPad Software, San Diego, CA, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Normality of distribution was assessed using the Shapiro-Wilk test. For normally distributed continuous variables, comparisons between baseline and follow-up within groups were conducted using paired-samples t-tests, while independent-samples

Table 1. Symptom prevalence and ranking (N=400)

Rank	Symptom	n/N	Prevalence	95% CI
1	Urgency	371/400	92.8%	90.3-95.3%
2	Polyuria/Frequency	354/400	88.5%	85.4-91.6%
3	Nocturia	306/400	76.5%	72.3-80.7%
4	Intermittent stream	257/400	64.3%	59.6-69.0%
5	Dribbling	245/400	61.3%	56.5-66.1%
6	Loin pain	166/400	41.5%	36.7-46.3%
7	Incontinence	36/400	9.0%	6.2-11.8%
8	Hematuria	0/400	0.0%	-

Notes: CI = confidence interval
Source: Compiled by authors of this study

Table 2. Baseline patient characteristics by treatment group

Characteristic	Group 0 (n=109)	Group 1 (n=145)	Group 2 (n=146)	p-value
Age, years (mean ± SD)	38.68 ± 8.96	39.06 ± 7.06	38.18 ± 6.10	NS
Male sex, n (%)	82 (75.2%)	145 (100%)	113 (77.4%)	<0.001
Married, n (%)	72 (66.1%)	116 (80.0%)	128 (87.7%)	<0.001
Symptom duration, months	10.69 ± 10.71	16.75 ± 13.55	10.30 ± 9.17	<0.05
Severity, n (%)				<0.001
Mild	24 (22.0%)	0 (0%)	0 (0%)	
Moderate	44 (40.4%)	0 (0%)	43 (29.5%)	
Severe	41 (37.6%)	145 (100%)	103 (70.5%)	
Ultrasound parameters				
BWT, mm	2.44 ± 0.75	2.49 ± 0.50	3.56 ± 1.74	<0.001
Pre-void volume, mL	244.33 ± 41.28	220.51 ± 28.33	232.21 ± 36.97	0.003
PVR, mL	24.27 ± 10.32	34.28 ± 3.91	32.42 ± 6.50	<0.001

Notes: Group 0 = monotherapy responders; Group 1 = mirabegron + Solifenacin; Group 2 = mirabegron + Flavoxate. BWT = bladder wall thickness; PVR = post-void residual; NS = not significant. Data presented as mean ± SD or n (%)
Source: Compiled by authors of this study

t-tests were employed for between-group comparisons. In cases where assumptions of normality were not met, equivalent non-parametric tests (Wilcoxon signed-rank test or Mann-Whitney U test) were applied. Categorical outcomes were analyzed using the Chi-square test of independence (or Fisher's exact test when cell counts were <5). For repeated measurements across treatment stages (baseline, post-monotherapy, post-combination), repeated-measures ANOVA was used with post hoc Bonferroni correction for multiple comparisons. Where sphericity was violated, the Greenhouse-Geisser correction was applied. Effect sizes were reported as Cohen's dz for within-group paired comparisons and Cohen's d for between-group contrasts, with 95% confidence intervals (CIs) calculated for mean changes. Adjustment for multiple pairwise contrasts was performed using the Holm-Bonferroni correction to control family-wise error. Statistical significance was defined as a two-tailed p-value < 0.05.

RESULTS

PATIENT ENROLLMENT AND DISPOSITION

The final group consisted of 400 patients who were eligible. After the 8 weeks of monotherapy with mirabegron 50mg, patients were classified by response: 109 (27.3%) continued with only one drug (Group 0) and 291 patients (72.7%) switched to combination therapy. Mirabegron plus Solifenacin was administered to one hundred and forty five patients (Group 1) while mirabegron plus Flavoxate/Uripas received by one hundred and forty six of them (Group2).

DURATION OF OVERACTIVE BLADDER SYMPTOMS

Among the sample (n=400), the median symptom duration was 6.0 months (IQR: 2.5-21.0), and the mean and median of symptom presence were 12.74 ± 11.71 and 1-41 months,

Table 3. Within-group changes after β3-agonist monotherapy phase

Group	Outcome	Mean Change [95% CI]	t (df)	p	dz
Group 1 (n=145)	BWT [mm]	-0.38 (-0.71, -0.06)	-2.34 (144)	0.021	-0.20
	Pre-void [mL]	+57.38 (52.17, 62.60)	21.76 (144)	<0.001	+1.81
	PVR [mL]	-5.90 (-6.51, -5.29)	-19.10 (144)	<0.001	-1.59
Group 2 (n=146)	BWT [mm]	-0.15 (-0.30, -0.01)	-2.07 (145)	0.040	-0.18
	Pre-void [mL]	+37.54 (30.78, 44.31)	10.97 (145)	<0.001	+0.91
	PVR [mL]	-2.83 (-3.49, -2.16)	-8.39 (145)	<0.001	-0.70

Notes: BWT = bladder wall thickness; PVR = post-void residual; dz = Cohen's effect size for paired comparisons. Negative changes in BWT and PVR indicate improvement; positive changes in pre-void volume indicate increased bladder capacity
Source: Compiled by authors of this study

respectively. A bias to the right was found because most patients had early access to medical review shortly after their illness onset. Symptoms lasted ≤6 months in 50.2% of the entire cohort (n=201) and >36 months in 5.0% only (n=20).

SYMPTOM PREVALENCE AND PATTERNS

Frequency OAB syndrome symptoms were the most common (Table 1). Urgency (92.8%, n=371) was reported as being the predominant symptom, followed by polyuria/ frequency (88.5, n=354), with nocturia (76.5%, n=306) coming third. The most frequent voiding symptoms were not non-associated with storage, and intermittent stream (64.3%, n = 257) and dribbling (61.3%, n = 245), respectively, were the most common among them. Note that only 9.0% of the patients were on UI (n=36) indicating a prevalence for OAB-dry phenotype. Loin pain describers.

SYMPTOM BURDEN AND CLUSTERING

The mean value for the reported number of symptoms was 4.34 ± 1.24 (median, 5.0). The majority of patients (n=329, 82.3%) reported an intermediate number of symptoms (3–5), with 45 CSF-positive patients experiencing a high symptom burden (≥6; 11.3%). Low burden (≤2 symptoms) was observed in 6.5% of all patients only (n=26). Three sets of clusters of symptoms were discovered: the storage core triad (urgency + nocturia + polyuria), which presented in 69.3% (n=277); voiding stimuli bundle (intermittent stream - dribbling), 53.8% (n=215); and men with pure storage complaints but an absence of any voiding-related complaints, only seen in 15.0% with acute urinary retention symptom presentation (n=60).

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS BY TREATMENT GROUP

All groups showed significant differences at baseline (Table 2). Comparison is the crucial lens through which we should be viewing all those other effect findings. All male patients were 100% in group I (mirabegron & Solifenacin, both drugs). All these had very high symptoms. Symptom duration in Group 1 (16.75 ± 13.55 months) was significantly longer compared with both Group 0 (10.69 ± 10.71 months) and Group 2 (10.30 ± 9.17 months). The average age of the groups were compared and found not to be statistically different (Group 0: 38.68 ± 8.96, Group 1: 39.06 ±7.06, Group 2: 38.18 ± 6.10). The rate of incidence in the severe cases was higher 70.5% than that in Group 0 (37.6%), and now we can understand why monotherapy might not be enough. The only meaningful objective difference was observed for BWT: the BWT mean in G2 (3.56 ±1.74 mm) appeared to be significantly different from group O and group I (p<0.001). Baseline pre-void residual volumes differed significantly: Group 0 had the highest values (244.33 ± 41.28 mL), followed by Group 2 (232.21 ± 36.97 mL) and Group 1 (220.51 ± 28.33 mL). Baseline PVR was lowest in Group 0 (24.27 ± 10.32 mL) and higher in Groups 1 (34.28 ± 3.91 mL) and 2 (32.42 ± 6.50 mL).

THERAPEUTIC EFFICACY OF B3-AGONIST MONOTHERAPY

The multimodal efficacy of beta-3 agonist was histometric in OAB pathophysiology (Table 3). Summary of Results (continued) Variable Key: M = Mean; SD = Standard Deviation Outcomes Placebo Details Placebo Adjusted mirabegron Efficacy All 3 treatment groups 25 mg b.d.50 mg q.d.100 mg q.d.P value NE Enrolment NE Yes (P>0.0007 It is clear from Table 1 that statistically significant and clinically meaningful improvements in the primary UDS variables have been found, for each group of interventions). Pre-void residual was elevated in both groups. Effect sizes in all groups were large: Group 1 (dz = +1.81, p<0.0002); Group 2 (dz = +1.51; p<0.005) and; Group 3 (d=+4.82; p<0.000001). 18; p=0.040).

Table 4. Combination therapy outcomes: Final values and total change from baseline

Parameter	Group 1 (Mirabegron + Solifenacin)	Group 2 (Mirabegron + Flavoxate)	p-value†
Bladder Wall Thickness [mm]			
Baseline	2.49 ± 0.50	3.59 ± 1.74	<0.001
Post-combination	1.86 ± 0.39	2.63 ± 1.11	<0.001
Mean change [95% CI]	-0.64 (-0.72, -0.55)	-0.96 (-1.15, -0.77)	0.002
Pre-void Residual Volume [mL]			
Baseline	220.51 ± 28.33	232.58 ± 36.84	0.003
Post-combination	328.69 ± 48.68	332.47 ± 40.72	0.521
Mean change (95% CI)	+108.19 (99.95, 116.42)	+99.89 (93.82, 105.96)	0.110
Post-void Residual Volume [mL]			
Baseline	34.28 ± 3.91	32.43 ± 6.52	0.052
Post-combination	22.86 ± 6.58	24.40 ± 6.94	0.081
Mean change (95% CI)	-11.42 (-12.35, -10.49)	-8.03 (-9.03, -7.03)	<0.001

Notes: Data presented as mean ± SD or mean change (95% CI). †Between-group comparison using independent t-test. Within-group comparisons all p<0.001 by paired t-test

Source: Compiled by authors of this study

COMBINATION THERAPY OUTCOMES

Following escalation to combination therapy, both regimens demonstrated robust efficacy with distinct differential effects (Tables 4 and 5).

FINAL TREATMENT OUTCOMES

Significant baseline differences persisted between the two combination groups. Group 2 started with significantly higher BWT (3.59 ± 1.74 mm *vs.* 2.49 ± 0.50 mm, p<0.001) and pre-void residual volume (232.58 ± 36.84 mL *vs.* 220.51 ± 28.33 mL, p=0.003). Following combination therapy, both groups demonstrated substantial improvement. For BWT, Group 1 achieved a final value of 1.86 ± 0.39 mm compared to Group 2's 2.63 ± 1.11 mm (p<0.001). The total change from baseline was significantly greater in Group 2 (-0.96 mm) compared to Group 1 (-0.64 mm), with a between-group difference of p=0.002. For pre-void residual volume, final values were comparable between groups (328.69 ± 48.68 mL *vs.* 332.47 ± 40.72 mL, p=0.521). Both groups showed large, equivalent increases: Group 1 increased by +108.19 mL and Group 2 by +99.89 mL, with no significant between-group difference (p=0.110). For PVR, final values were similar between groups (22.86 ± 6.58 mL *vs*. 24.40 ± 6.94 mL, p=0.081). However, the reduction was significantly greater in Group 1 (-11.42 mL) than in Group 2 (-8.03 mL), with a between-group difference of p<0.001

ADDITIONAL THERAPEUTIC EFFICACY OF COMBINATION THERAPY ESCALATION

The additional change in urodynamic parameters following escalation from monotherapy to combination therapy revealed distinct group-dependent effects (Table 5). For BWT, Group 1 showed a non-significant additional reduction of -0.25 mm (dz = -0.13, p=0.133). In contrast, Group 2 demonstrated a highly significant additional reduction of -0.76 mm (dz = -0.70, p<0.001). For pre-void residual volume, both groups showed significant additional increases: Group 1 increased by +50.46 mL (dz = +1.32, p<0.001) and Group 2 by +62.55 mL (dz = +1.78, p<0.001). Both groups showed significant additional PVR reductions: Group 1 reduced by -5.55 mL (dz = -1.44, p<0.001) and Group 2 by -5.21 mL (dz = -0.92, p<0.001).

PRIMARY ENDPOINT ANALYSIS: BETWEEN-GROUP COMPARISON

Non inferiority of both combination therapies was not demonstrated in the between-group analysis presented in (Table 6) based on justifiable use using the primary outcome item (post-void residual volume at final visit). The adjusted mean PVR was 1.48 mL higher in group 2 than in group 1 (adjusted MD = -1.48 ml, SE=0.80 and CI 95% = -3.05 to ≈ +0.09). This 'negative' delta value relates to a (small), however, "positive" tendency of better voiding efficiency in Group 1. This differed from control [(t = −2.23, p = 0.040), but this did not reach the conventional threshold of alpha = 0.05 when corrected for multiple comparisons using Holm procedure (t = −1.85, Holm-adjusted p = 0.065)]. Post void residuals (23-24 ml) determined in the two study groups were close to being very low, clinically and obviously below the 50-ml safety limit. 2014 Service At least at the time of this analysis, based on primary PVR reduction the

Table 5. Additional change after escalation to combination therapy

Group	Outcome	Mean Change [95% CI]	t (df)	p	dz
Group 1 (n=145)	BWT [mm]	-0.25 (-0.57, 0.08)	-1.51 (144)	0.133	-0.13
	Pre-void [mL]	+50.46 (44.16, 56.75)	15.85 (144)	<0.001	+1.32
	PVR [mL]	-5.55 (-6.19, -4.92)	-17.32 (144)	<0.001	-1.44
Group 2 (n=146)	BWT [mm]	-0.76 (-0.94, -0.58)	-8.35 (145)	<0.001	-0.70
	Pre-void [mL]	+62.55 (56.79, 68.31)	21.46 (145)	<0.001	+1.78
	PVR [mL]	-5.21 (-6.14, -4.29)	-11.11 (145)	<0.001	-0.92

Notes: Paired t-tests quantify additional benefit after adding combination agent, dz = Cohen's effect size (mean difference / SD of differences)
Source: Compiled by authors of this study

Table 6. Primary endpoint: Pairwise adjusted mean differences at final visit (Holm-corrected)

Contrast	Adjusted Mean Difference (mL)	SE	t	p (Holm)
Group 1 vs. Group 2	-1.48	0.80	-1.85	0.065

Notes: Negative values favor Group 1 (lower = better PVR). Holm adjustment controls family-wise error across pairwise contrasts. At final visit, Group 1 had 1.5 mL lower mean PVR compared with Group 2; this did not reach significance after correction
Source: Compiled by authors of this study

two combination therapies would hence be regarded as equivalent in result.

DISCUSSION

These results have an impact on the treatment hierarchy and offer valuable evidence for stratified management of OAB. Our results demonstrate that while baseline demographics and potential performance indicators such as BWT are important confounders (the subject of the study is simply not only fit to be studied) in an unbalanced study, they also make good predictor(s) for response rate against time-to-escalation. It may be helpful to have more personal information of the medical history, disease symptoms and consultation habit to better understand 400 cases enrolled in our series; therefore its application value could be determined whether these information are consider as important or tenable. The right-skewed symptom-duration distribution (median, 6 mo) suggests that most patients experienced their symptoms and presented to our clinic in relatively short order (e.g., bothersome enough for seeking evaluation fairly soon after becoming symptomatic). The symptom prevalence pattern (92.8% urgency, 88.5% frequency, 76.5% nocturia) is characteristic for the classical OAB syndrome complex. Also, the low rate of UUI (9.0%) and the tendency toward the OAB-dry subtype were remarkable. This further supports the fact that it is urgency and frequency which is motivating patients to care, giving early disease a chance. The presence of widely associated voiding symptoms (53.8% storage-voiding dysfunction overlap) does not favor a dichotomous diagnostic separation. Such a clinical overlap also reflects the practice at which we treat male patients suffering both (BPH) and OAB, when already today it makes sense if somehow that benign prostatic hyperplasia (BPH) and OAB are in bad company in most patients who will need combined treatments for storage and voiding lUTS [12]. The beneficial differences in baseline characteristics between groups are a key consideration in interpreting treatment effectiveness. The significant additional BWT in Group 2 (3.56 ± 1.74 mm compared with 2.44 ± 0.75 mm for Group 0) is anatomical evidence of marked detrusor hypertrophy and forms a pathoanatomical basis for combined therapy in excess of an effort to discontinue treatment alone, while observational are only one method of (WHOERS) who allow such differences in funnel plot symp analyzing clinical data, and differences between groups tometry at baseline to be quantified. Our data indicate that BWT is a candidate for an objective criterion that will enable clinicians to select patients at risk of requiring step-up of combination therapy sooner. This strategy is consistent with the 2024 AUA/SUFU guideline, i.e., we should individualize treatment by taking note of patient features and phenotypes [13-14]. For the β-3 agonist (mirabegron), a multi-modal effect as monotherapy was observed for great improvement of BLC along with substantial decrease in PVR and BWT. This suggests that treatment with mirabegron confers positive structural remodeling in addition to the symptomatic relief. But the difference in their reactions was extreme. The modest decrement in BWT experienced by nonresponders meant that monotherapy "worked" for them to some level but they remained unmet clinically and they were a rational biological foundation for escalating. This model of escalating the intensity of Management in

response to failure aligns well with emerging emphasis on moving away from step therapy and back towards a personalized patient centered approach together via shared-decision making, as underscored by 2024 AUA/SUFU guideline [13-14]. The finding that both combination regimens lead to significant increases in bladder capacity (approximately + 100 mL) indicates that they were equally efficacious at one of the most important OAB end points. This parallels pharmacodynamics synergy of drugs shown in trials such as SYNERGY where combination therapy with mirabegron and Solifenacin were more effective than monotherapy [15-16]. Heterogeneity in secondary end points is informative. The significantly higher BWT reduction with mirabegron/Flavoxate reflects a giant myogenic synergy driving the favorable picture of muscle hypertrophy turn-around. On the other hand, the more prominent reduction in PVR pressure with mirabegron + Solifenacin seems to make patients feel less threatened about retention by making voiding protocol presumably little more organized. The potential for phenotype-specific therapy is therefore an attractive clinical concept in light of this finding. When the bladder wall thickening was severe (BWT >3 mm), mirabegron and Flavoxate can be combined for structural normalization. Combination mirabegron and Solifenacin Combination therapy with mirabegron + Solifenacin may be of value in the patient with high PVR or voiding dysfunction to improve voiding. This specific assumption is consistent with the general premise of 2024 guidelines, which emphasizes the choice of personalized intervention according to patient clinical condition, symptoms and priority.

RELEVANCE

Clinical rational for balance presented with main outcome. It hint that a B3-agonist + MR min combination would have equivalent or greater efficacy to the comparator NMJ-min-combination as far as primary efficacy variables. This is further support for the paradigm shift advocated in the new 2024 AUA/SUFU guideline of step fixed therapy to individualized therapy [14]. The present equipoise provided herein could impact clinical practice for MCOs. Flavoxate combination is an evidence based approach for patients intolerant to anticholinergic AEs (a clinically relevant concern in view of real-world medication persistence and risk profiles 1) [17]. Possibility to perform shared decision-making between clinicians and patients by using combination regimens according to patient-related variables, symptom complex and over-ruling specific intolerances [13]. Several limitations warrant consideration. Observational design at first sight, we noticed that in this analysis there were important differences at baseline. Secondly, this post-hoc stratification of the patient cohort is exposed to selection bias. Third, long-term follow-up is limited by the relatively short follow-up period. Fourth, PROs findings on QoL could not be obtained for this analysis. Fifth, the study was a single-center study and results may not be generalizable. Such limitations would obviously be overcome by subsequent prospective (with stratification), large RCTs, with patients randomized to the intervention arm based on BWT at presentation.

CONCLUSIONS

The β-3 agonists have the clearest evidence base for multi-modality benefit as effective monotherapy and first-line treatment, but less so in patients with high symptom intensity. Both complex regimens are equally effective in promoting a phenotype-selective drive to increase bladder capacity. The MBG/Flavoxate response is better at structural remodeling in unashamed detrusor hypertrophy (BWT high) group, and the MBG/Solifenacin treatment has a higher voiding efficiency. Such findings strengthen a phenotype-model-based personalized therapy with objective biomarkers such as BWT and PVR for combination therapeutics, conditioning toward the ultimate goal of precision medicine in OAB.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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