DOI: 10.4081/aiua.2022.4.451

ORIGINAL PAPER

The choice of therapeutic agent in female overactive bladder patients in real-world practice

Hiroshi Masuda, Kosuke Mikami, Kotaro Otsuka, Kyokusin Hou, Takahito Suyama, Kazuhiro Araki, Satoko Kojima, Yukio Naya

Department of Urology, Teikyo University Chiba Medical Center, 3426-3 Anesaki, Ichihara, Chiba 299-0111, Japan.

Summary *Objective: The reasons why anticholinergic drugs or β3 adrenergic agonists are selected as treatments for overactive bladder (OAB) are unclear. The aim of this study was to investigate the background data of female OAB patients that were prescribed anticholinergic drugs or β3 adrenergic agonists in a real-world setting.*

Materials and methods: Between January 2013 and December 2014, 75 patients who had been diagnosed with OAB were included in this study. Administered medications, age, the persistence on treatment rate at one-year, medical history, pretreatment total Overactive Bladder Symptom Score (OABSS), pretreatment score for each OABSS factor, body mass index (BMI), and various comorbidities were evaluated retrospectively. Since there were many types of anticholinergic drugs and few patients, we grouped the patients into those that were prescribed anticholinergic drugs (group A) and those that were prescribed β3 adrenergic agonists (group B).

Results: 75 patients (29 in group A and 46 in group B) were included in this study. There were no significant differences in age, BMI, obesity, medical history, pretreatment total OABSS, or pretreatment score for each OABSS factor. There was a significant difference in the post-voiding residual urine volume (PVR) between the groups (group A: 22 ml, group B: 9 ml; p = 0.0252). The 1-year persistence on treatment rate was 28% in both groups.

Conclusions: There were no significant differences in clinical characteristics of patients who were prescribed anticholinergics and β3 adrenergic agonists for OAB treatment, but a marginal difference of PVR value before treatment.

The 1-year persistence rates of anticholinergic drugs and β3 adrenergic agonists were considered to be almost equivalent.

KEY WORDS: *Overactive bladder; Anti-cholinergic drugs; β3 adrenergic agonists; Post-voiding residual urine volume.*

Submitted 28 October 2022; Accepted 10 November 2022

INTRODUCTION

Overactive bladder (OAB) is a condition with characteristic symptoms of urinary urgency, usually accompanied by increased urinary frequency and nocturia, with or without urge incontinence, in the absence of a *urinary tract infection* (UTI) or any other obvious pathology (1). It was observed that the prevalence of OAB among Japanese adults aged ≥ 40 years is 12.4%, and the estimated number of patients with OAB is 8.1 million (2). OAB affects 11.8-24.7% of adults in North America and Europe, and its prevalence increases with age (3). In addition to age, the risk factors for OAB include diabetes, UTI, and obesity (4, 5). Pharmacotherapy is the main treatment for OAB in Japan, and anticholinergic drugs are considered to be first-line drugs (6). Recently, β3 adrenergic agonists, which have completely different mechanism of action from anticholinergic drugs, have become available and have been shown to be effective.

β3 adrenergic agonists were awarded a grade-A recommendation in the Japanese OAB treatment guidelines. However, no study on the criteria for choosing between anticholinergics and β3 adrenergic agonists has been published. When treating patients with OAB, how do clinicians choose among these medications, which both have grade-A recommendations and exhibit comparable therapeutic efficacy? Are there any factors that influence the selection of these medications?

In the present study, we investigated the factors that influence the selection of anticholinergic drugs or β3 adrenergic agonists for OAB in the real world practice.

MATERIALS AND METHODS

This was a retrospective study, which used data extracted from electronic records. Seventy-five who were diagnosed with OAB at the *Department of Urology, Teikyo University Chiba Medical Center* (*Ichihara, Japan*), between January 2013 and December 2014 were included in this study.

The *Overactive Bladder Symptoms Score* (OABSS) was calculated for each patient, and all of the patients met the diagnostic criteria for OAB. OAB was diagnosed based on the OABSS or the presence of urinary urgency (6).

The OABSS is a validated self-assessed questionnaire created by the *Japanese Continence Society* and consists of four questions about OAB symptoms (Q1: daytime frequency, Q2: nighttime frequency, Q3: urgency, and Q4: urge incontinence) (6).

We retrospectively evaluated various factors, including age, administered treatments, *body mass index* (BMI), pretreatment total OABSS, pretreatment score for each OABSS factor, *post-voiding residual* volume (PVR), smoking habits, presence or absence of hypertension, diabetes mellitus, and dyslipidemia.

The post-voiding residual (PVR) urine was measured on a transabdominal ultrasonic echogram in all cases.

No conflict of interest declared.

Regarding the administered medications, since many kinds of anticholinergic drugs were administered in small groups of patients, patients were categorized into two groups as those treated with anticholinergic drugs (group A) and those treated with β3 adrenergic agonists (group B).
The patients were allowed to discontinue their medication during the follow-up period, according to their desires and the judgement of the attending physician. We investigated the continuation/discontinuation of anticholinergic drug and β3 adrenergic agonist treatment. although we could not examine the reasons for discontinuation.

Statistical analysis

Statistical analyses were carried out to identify clinical parameters that differed significantly between groups A and B. The results are shown as mean ± SE or percentage. The Mann-Whitney U test and Chi-squared test were used for the statistical analyses. All analyses were performed with JMP version 10 (*SAS Institute Inc., Cary, NC, USA*). A probability value of < 0.05 was considered statistically significant.
Ethical approval. The institutional review board of Teikyo University approved this study (TUIC-COI 21-1218).

RESULTS

Table 1 shows the patients' background characteristics.
We evaluated 75 patients (29 in group A and 46 in group B) that were prescribed anticholinergic drugs or β3 adrenergic agonists by our department.
There were no significant differences in age, BMI, obesity, medical history, the pretreatment total OABSS, or the pretreatment scores for individual OABSS factors. The mean pretreatment PVR was significantly greater in group A than in group B (22 ml vs. 9 ml, respectively; P = 0.0252) (Table 2).
A younger age, a lower pretreatment total OABSS score,

Table 1.
Patient characteristics.

No. of patients	N = 75
Age (years, mean ± SE)	70 ± 1.4
Medication	
Anticholinergics (N)	29
Propiverine	3
Imidafenacin	9
Fesoterodine	6
Solifenacin	11
β3 adrenergic agonists	46
Body mass index (kg/m^2, mean ± SE)	28.2 ± 0.3
OABSS	
Daytime frequency	1.0 ± 0.1
Nighttime frequency	2.4 ± 0.1
Urgency	2.9 ± 0.2
Urge incontinence	1.7 ± 0.2
Total score	8.1 ± 0.5
PVR (ml, mean ± SE)	14 ± 2.6
Smoking	
Positive/Negative	7/68
Alcohol consumption	
Positive/Negative	7/68
Hypertension	
Positive/Negative	38/37
Diabetes mellitus	
Positive/Negative	10/65
Dyslipidemia	
Positive/Negative	24/51

OABSS: Overactive Bladder Symptom Score; PVR: Post-voiding residual urine volume.

Table 2.
Comparisons between the groups.

Variable	Group A (n = 29)	Group B (n = 46)	P-value
Age (years, mean ± SE)	69 ± 1.4	71 ± 1.7	0.5029
Body mass index (kg/m^2, mean ± SE)	28.2 ± 0.5	28.3 ± 0.3	0.6414
OABSS			
Daytime frequency	1.1 ± 0.1	1.0 ± 0.1	0.2736
Nighttime frequency	2.5 ± 0.1	2.4 ± 0.1	0.7708
Urgency	3.1 ± 0.2	2.8 ± 0.3	0.5017
Urge incontinence	2.1 ± 0.2	1.5 ± 0.3	0.1298
Total score	8.8 ± 0.7	7.7 ± 0.6	0.1639
PVR (ml, mean ± SE)	22 ± 5.8	9.2 ± 2.2	0.0247
0-50 ml/51-100 ml/100 ml<	26/3/0	45/1/0	0.1251
Smoking			
Positive/Negative	4/25	3/43	0.151
Alcohol consumption			
Positive/Negative	2/27	5/14	0.3061
Hypertension			
Positive/Negative	13/16	25/21	0.4219
Diabetes mellitus			
Positive/Negative	3/26	7/39	0.5455
Dyslipidemia			
Positive/Negative	7/22	17/29	0.2465

OABSS: Overactive Bladder Symptom Score; PVR: Post-voiding residual urine volume.

Table 3.
Assessment of the factors affecting the continuation of medical treatment.

Variable	Continuation group (n = 21)	Discontinuation group (n = 54)	P-value
Age (years, mean ± SE)	74 ± 1.4	68 ± 1.7	0.2328
Medication			0.9495
Anticholinergics	8	21	
Mirabegron	13	33	
Body mass index (kg/m^2, mean ± SE)	28.0 ± 0.5	28.3 ± 0.3	0.5236
OABSS			
Daytime frequency	1.2 ± 0.1	1.0 ± 0.1	0.201
Nighttime frequency	2.6 ± 0.3	2.4 ± 0.1	0.2912
Urgency	2.8 ± 0.4	3.0 ± 0.3	0.5301
Urge incontinence	1.9 ± 0.4	1.7 ± 0.3	0.614
Total score	8.6 ± 0.9	8.1 ± 0.5	0.8093
PVR (ml, mean ± SE)	18 ± 5.6	12 ± 3.0	0.3325
Smoking			
Positive/Negative	0/21	7/47	0.151
Alcohol consumption			
Positive/Negative	2/19	5/49	0.3061
Hypertension			
Positive/Negative	9/12	29/25	0.3989
Diabetes mellitus			
Positive/Negative	4/17	6/48	0.364
Dyslipidemia			
Positive/Negative	6/15	18/36	0.6914

OABSS: Overactive Bladder Symptom Score; PVR: Post-voiding residual urine volume.

and a lower PVR were associated with a tendency towards medication discontinuation. However, no potential predictors of discontinuation differed significantly between the groups (Table 3). The one-year persistence rate of prescriptions from our department was 28% in both groups.

Discussion

In the Japanese guidelines for OAB, anticholinergic drugs and β3 adrenergic agonists are given grade-A recommendations as treatments for OAB (6). However, while there has been some debate about the usage of different anticholinergic drugs, there was insufficient discussion and there are no clear indicators or guidelines regarding the usage of anticholinergic drugs versus β3 adrenergic agonists. Therefore, individual medications are being administered for OAB without any particular reason in real-world practice, and it seems that choices between anticholinergic drugs and β3 adrenergic agonists are based on the treating doctor's preferences and experience. In the present study, we investigated the factors that influence the selection of anticholinergic drugs and β3 adrenergic agonists in the real-world. To the best of our knowledge, this is the first study to investigate this among OAB patients.

Safety

Safety is the first consideration when selecting a drug, and avoiding adverse events should be prioritized over efficacy. β3 adrenergic agonists cause side effects, such as dry mouth and constipation, less frequently than anticholinergic drugs. This should favor the selection of β3 adrenergic agonists. Regarding dry mouth, it has been reported that β3 adrenergic agonists cause this symptom in 33% fewer cases than tolterodine (7). In another study, it was reported that the incidence of dry mouth during β3 adrenergic agonist treatment was similar to that produced by a placebo, and that it was associated in one-fifth of cases with anticholinergic drugs (8). It has been observed that dry mouth is an important factor influencing oral medication discontinuation (9). Therefore, there is an advantage in choosing β3 adrenergic agonists over anticholinergic drugs. It has also been reported that β3 adrenergic agonists have higher persistence rates than anticholinergics drugs and should be considered for first-line pharmacological treatment for OAB (10).

Furthermore, it should be considered that elderly patients would be more likely to be prescribed β3 adrenergic agonists than anticholinergics because of their high frequency of abnormal bowel movements.

Finally, it is likely that medications that involve fewer oral doses should be selected for elderly patients because they may already be taking a large number of medications.

Post-voiding residual urine

In a comparative study of anticholinergic drugs and β3 adrenergic agonists, it was reported that there was no significant difference in the increase in the PVR seen during the study period (0.86 ml for the placebo, 0.80 ml for β3 adrenergic agonists, and 0.44 ml for tolterodine) (11). Moreover, *Stöhrer et al.* reported that the PVR increased significantly from 50 ml to 87 ml in patients treated with propiverine (12). Also, *Khullar et al.* reported that a PVR exceeding 300 ml was seen in 0.2% of patients treated with β3 adrenergic agonists (7).

These studies suggest that the PVR is not a determining criterion during the selection of anticholinergic drugs or β3 adrenergic agonists.

Regarding the frequency of urinary retention, it has been reported that it was < 1% in patients treated with anticholinergic drugs, while it was almost negligible in patients treated with β3 adrenergic agonists (13).

In the present study the pretreatment PVR was significantly higher in patients who were prescribed anticholinergics compared to those who were treated with β3 adrenergic agonists, but this finding seemed to be of limited clinical significance because it was related to only three patients with high PVR taking anticholinergics.

Compliance to treatment

It has been reported that the 1-year persistence rates of anticholinergic drugs and mirabegron ranged from 17% to 35% (14) and 19-38% (9, 15, 16), respectively.

The 1-year persistence rates of anticholinergic drugs and β3 adrenergic agonists at our institution were similar. It has been reported that treatment discontinuation is also seen in younger age groups, and our study showed a similar trend (17).

We suggest that this could be explained by the fact that the drugs were administered at hospital, and an appointment was required to visit the hospital.

However, a recent study suggested that β3 adrenergic agonists have very high 1-year persistence rates of 63% in females and 67% in males (18). It was considered that this was probably because β3 adrenergic agonists are safe and well tolerated.

Non-medical factors

Recently, a study reported that when physicians received complimentary meals and hospitality by a pharmaceutical company they increased their prescriptions of drugs marketed by that company (19). Although this may have affected our prescription patterns, we do not have any information about this in the present study. This could be an important subject for further study, including other oral medications.

Limitations

Our study presented some limitations:

1) It was a retrospective cohort study, which involved the extraction of electronically stored clinical data, and it had a small sample size. Thus, it will be necessary to validate the findings of this retrospective analysis in prospective studies, including a randomized study, with larger populations in future. We expect that such studies will provide new perspectives on how decisions regarding the selection of anticholinergic drugs and β3 adrenergic agonists are made.

2) Since this study only involved females, the factors influencing the selection of anticholinergic drugs or β3 adrenergic agonists in male OAB patients were not evaluated.

3) The patients' complications and the other types of medications they were taking were not investigated, and hence, more detailed patient background information is needed.

4) The two-year observation period was relatively short,

and hence, it may not have been long enough to allow appropriate evaluations to be performed.
5) Patients assuming anticholinergics were analyzed collectively because the small number of patients taking different anticholinergics did not allow to analyze them separately. Collection of larger populations taking different anticholinergics could give information about difference of outcomes between them.
6) Untreated patients were not investigated.
7) We did not investigate refractory OAB separately.

Conclusions

There were no significant differences in clinical characteristics of patients who were prescribed anticholinergics and β3 adrenergic agonists for OAB treatment, but a marginal difference of PVR value before treatment.
The 1-year persistence rates of anticholinergic drugs and β3 adrenergic agonists were considered to be almost equivalent.

References

1. Abrams P, Cardozo L, Fall M Paul Abrams, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urody. 2002; 21:167-178.

2. Homma Y, Yamaguchi O, Hayashi K. Neurogenic bladder society committee. An epidemiological survey of overactive bladder symptoms in Japan. BJU Int. 2005; 96:1314-1318.

3. Eapen RS, Radomski SB. Review of the epidemiology of overactive bladder. Res Rep Urol. 2016; 8:71-76.

4. Brown JS, McGhan WF, Chokroverty S. Comorbidities associated with overactive bladder. Am J Manag Care. 2000; 6:S574-579.

5. Subak LL, Richter HE, Hunskaar S. Obesity and urinary incontinence: epidemiology and clinical research update. J Urol. 2009; 182:S2-7.

6. Yamaguchi O, Nishizawa O, Takeda M, et al. Clinical guidelines for overactive bladder. Int J Urol 2009; 16:126-142.

7. Khullar V, Amarenco G, Angulo J, et al. Efficacy and tolerability of mirabegron, a β (3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. Eur Urol. 2013; 63:283-295.

8. Yamaguchi O, Marui E, Kakizaki H, et al. Phase III, randomised, double-blind, placebo-controlled study of the β3-adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder. BJU Int. 2014; 113:951-960.

9. Chapple CR, Nazir J, Hakimi Z, et al. Persistence and adherence with mirabegron versus antimuscarinic agents in patients with overactive bladder: a retrospective observational study in UK clinical practice. Eur Urol. 2017; 72:389-399.

10. Yeowell G, Smith P, Nazir J. et al. Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB): a systemic literature review. BMJ open. 2018; 8:e021889.

11. Yamaguchi O, Ikeda Y, Ohkawa S. Phase III study to assess long-term (52-week) safety and efficacy of mirabegron, a β3-adrenoceptor agonist, in Japanese patients with overactive bladder. LUTS. 2017; 9:38-45.

12. Stöhrer M, Madersbacher H, Richter R, et al. Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia-a double-blind, placebo-controlled clinical trial. Spinal Cord. 1999; 37:196-200.

13. Nitti VW, Khullar V, van Kerrebroeck P, et al. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. Int J Clin Pract. 2013; 67:619-632.

14. Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimusucarinic therapy for overactive bladder: a UK experience. BUJ Int. 2012; 110:1767-1774.

15. Wagg A, Franks B, Ramos B, Berner T. Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus antimuscarinics in overactive bladder: Early experience in Canada. Can Urol Asso J. 2015; 9:343-350.

16. Sussman D, Yehoshua A, Kowalski J, et al. Adherence and persistence of mirabegron and anticholinergic therapies in patients with overactive bladder: a real-world claims data analysis. Int J Clin Prac. 2017; 71:e12824.

17. Kalder M, Pantazis K, Dinas K, et al. Discontinuation of treatment using anticholinergic medications in patients with urinary incontinence. Obstet Gynecol. 2014; 124:794-800.

18. Wada N, Watanabe M, Banjo H, et al. Long-term persistence with mirabegron in a real-world clinical setting. Int J Urol. 2018; 25:501-506.

19. DeJong C, Aguilar T, Tseng CW, et al. Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries JAMA Intern Med. 2016; 176:1114-1122.

Correspondence
Hiroshi Masuda, MD, PhD (Corresponding Author)
hrsmasuda@yahoo.co.jp
Kosuke Mikami, MD
Kotaro Otsuka, MD
Kyokusin Hou, MD
Takahito Suyama, MD
Kazuhiro Araki, MD
Satoko Kojima, MD
Yukio Naya, MD
Department of Urology, Teikyo University Chiba Medical Center, 3426-3 Anesaki, Ichihara, Chiba, 299-0111, Japan