Epidemiology

Risks of Dementia After Treatment with an Anticholinergic, Beta-3 Agonist, or Combination of Both for an Overactive Bladder: A Korean National Cohort Study

Jee Soo Park [a,b,c], Soo Beom Choi [d], Won Sik Jang [a], Jongchan Kim [a,e], Won Sik Ham [a,*]

[a] Department of Urology and Urological Science Institute, Yonsei University College of Medicine, Seoul, Republic of Korea; [b] Department of Urology, Sorokdo National Hospital, Goheung, Republic of Korea; [c] Incheon Airport National Quarantine Station, Capital Regional Centers for Disease Control and Prevention, Korea Disease Control and Prevention Agency, Incheon, Republic of Korea; [d] Division of Urban Society Research, Seoul Institute, Seoul, Republic of Korea; [e] Department of Urology, Yongin Severance Hospital, Yonsei University Health System, Yongin, Republic of Korea

Article info

Abstract

Background and objective: An overactive bladder (OAB) is primarily managed with behavioural therapy and using anticholinergics and beta-3 agonists. Reports have shown that the use of anticholinergics by OAB patients was associated with an increased risk of new-onset dementia compared with those using beta-3 agonists. This study compares the risks of dementia among patients with an OAB starting on a beta-3 agonist alone, an anticholinergic alone, or a combination treatment.
Methods: Using data from the Korean National Health Insurance Service database, we studied a nationwide population cohort comprising patients newly diagnosed with an OAB who initiated their OAB medications between 2015 and 2020. The treatment types were categorised as anticholinergics (oxybutynin, solifenacin, tolterodine, trospium, fesoterodine, flavoxate, and propiverine) alone, a beta-3 agonist (mirabegron) alone, and combination therapy (an anticholinergic plus the beta-3 agonist). To evaluate the impact of cumulative drug exposure, we quantified the cumulative exposure to solifenacin and mirabegron as cumulative defined daily doses (cDDDs) using proportional hazards regression analyses, adjusted for factors known to be associated with dementia.
Key findings and limitations: Among the study's 3 452 705 patients, 671 974 were new users of a beta-3 agonist alone (19.5%), 1 943 414 new users of anticholinergics alone (56.3%), and 837 317 receiving combination therapy (24.3%). The most common anticholinergic used both alone and as part of a combination treatment was solifenacin (42.9% and 56.3%, respectively). There was an increased risk of dementia between the users of an anticholinergic alone (adjusted hazard ratio [aHR] = 1.213; 95% confidence interval [CI], 1.195–1.232) and those taking a combination treatment (aHR = 1.345; 95% CI, 1.323–1.366) compared with the users of beta-3 agonists alone after the adjustment of covariates. However, the incidence of dementia was also significantly higher, with an increase in the cumulative dose of mirabegron (aHR = 1.062 [1.021–1.106] for 28–120 cDDDs and aHR = 1.044 [1.004–1.084]) for patients who received >121 cDDDs

* Corresponding author. Department of Urology and Urological Science Institute, Yonsei University College of Medicine, Seoul 03722, Republic of Korea. Tel. +82-10-6242-7938; Fax: +82-2-312-2538. E-mail addresses: jsparkysmed@gmail.com (J.S. Park), plains7@si.re.kr (S.B. Choi), sindakjang@yuhs.ac (W.S. Jang), lumpakcef@yuhs.ac (J. Kim), uroham@yuhs.ac (W.S. Ham).

compared with those who received <27 cDDDs). A marked increased risk of dementia was associated with the use of solifenacin, tolterodine, fesoterodine, and propiverine, both separately and in combination with mirabegron.

Conclusions and clinical implications: In this large Korean cohort, the use of anticholinergics with or without a beta-3 agonist increased the risk of new-onset dementia compared with the use of a beta-3 agonist alone. Given that the risk of dementia was most significantly elevated with combination treatments, care should be taken when considering combination treatment for OAB patients with risk factors for dementia. Furthermore, there could be a possible association between beta-3 agonists and dementia, although future studies are needed.

Patient summary: This study investigated the risk of dementia induced by overactive bladder (OAB) treatment in a large Korean cohort. Two representative OAB treatment drugs, anticholinergics and beta-3 agonists, both increased the risk of new-onset dementia. Clinicians should be cautious in using OAB treatment drugs since no drugs could be concluded as safe.

1. Introduction

An overactive bladder (OAB), one of several clinical presentations of lower urinary tract syndrome [1,2], has been reported in 10–15% of the population with symptoms of urinary urgency, according to the International Continence Society [3]. The primary treatment options consist of behavioural therapy and medical management [4,5]. The most widely used medications for an OAB are anticholinergics and beta-3 agonists [4,6]. Studies have suggested that both anticholinergics and beta-3 agonists demonstrate equivalent efficacy and are recommended equally as the first treatment options for an OAB by the American Urology Association (AUA) and European Association of Urology [7,8].

Several studies have reported an association between anticholinergic medications (when all drug classes are combined) and the risk of new-onset dementia [6-8], while other studies have reported contradictory results [9,10]. The effects of dementia induced by anticholinergics differ according to the level of anticholinergic activity, receptor sensitivity, central nervous system (CNS) penetration, and drug class [11-13], and the drugs used for an OAB exhibit strong anticholinergic activity [14]. Five observational studies have shown an association between anticholinergics and an increased risk of dementia [11,12,15-17]. However, none of these studies specifically examined the effects of the different anticholinergics, each of which has distinct pharmacological specificities [18]. Recently, the AUA emphasised the need for further research on the long-term cognitive side effects of anticholinergics overall and for each drug separately when used to treat an OAB [4]. Malcher et al [19] and Matta et al [13] reported differential effects of individual anticholinergics with respect to the incidence of dementia.

Beta-3 agonists, which involve mechanisms that differ from those of anticholinergics, reportedly reverse memory deficits in a mouse model [20], and a recent population-based cohort study in Canada found that the use of anti-cholinergic medications by patients with an OAB was associated with an increased risk of new-onset dementia compared with users of beta-3 agonists [17]. However, the Canadian study did not address the effects of the use of a beta-3 agonist alone on the incidence of dementia. Although beta-3 agonists are not known to have any cognitive effects [21], the follow-up period was too short to determine the cognitive effects of beta-3 agonists.

As a combination treatment of a beta-3 agonist and an anticholinergic is reportedly more effective in improving multiple OAB symptoms than either a beta-3 agonist alone or an anticholinergic [22-27], AUA guidelines recommend pharmacotherapy with beta-3 agonists or anticholinergics (or both) after and in conjunction with behavioural treatments [4,7]. Moreover, increasing the anticholinergic dosing for patients with previous suboptimal responses to anticholinergic drugs alone only leads to a greater risk of anticholinergic-related adverse events [23]. However, any association between combination therapy consisting of beta-3 agonists plus anticholinergics and dementia has yet to be evaluated.

Our study comprehensively analysed the relationship between beta-3 agonists and/or anticholinergics used to treat an OAB and the risk of new-onset dementia for overall anticholinergics, both together and for each drug separately.

2. Patients and methods

2.1. Data source

Data for the study were obtained from the claims database of the Korean National Health Insurance System (NHIS). Korea has a single-payer, universal-coverage, health care system, in which the NHIS provides insurance to >99% of the population and maintains comprehensive health records of all covered in- and outpatient visits, diagnoses, treatments, procedures, and prescriptions [28]. The database also provides information on comorbidities and concomitant medications. The institutional review board of the Sorokdo National Hospital approved this study and granted a waiver of informed consent from study participants due to the use of deidentified data (approval no. 2021-0009).

2.2. Study population

We used the NHIS database to identify patients who had an OAB as defined by code N32.81 of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). Among these patients, we identified all users of either an OAB anticholinergic or a beta-3 agonist between January 1, 2015 and December 31, 2020. We included the following anticholinergics: oxybutynin, solifenacin, tolterodine, trospium, fesoterodine, flavoxate, and propiverine (Supplementary Table 1). The only marketed beta-3 agonist during the study period was mirabegron (Supplementary Table 1). For the combination treatment of anticholinergics and mirabegron, we included only those patients who newly started to receive both anticholinergics and mirabegron on the same date. We only included patients who did not switch or add OAB medications after the first OAB medication prescription. The index date was the first OAB medication prescription during the study period. Patients were observed from that date forward. Patients were excluded in the event of poor data quality indicators or the use of an OAB medication before the index date. Patients with a previous diagnosis of dementia before the index date were excluded. A flow diagram of the study population selection is shown in Figure 1.

2.3. Exposure to OAB medications

We focused on the seven OAB anticholinergics and the single beta-3 agonist with marketing authorisation in Korea and reimbursed by the NHIS during our study period: flavoxate (G04BD02), oxybutynin (G04BD04), propiverine (G04BD06), tolterodine (G04BD07), solifenacin (G04BD08), trospium (G04BD09), fesoterodine (G04BD11), and mirabegron (G04BD12) based on World Health Organization Anatomical Therapeutic Chemical codes [29]. OAB medications were analysed individually and pooled together.

We quantified exposure using defined daily doses (DDDs), which are recommended by the World Health Organization Collaborating Center for Drug Statistics Methodology (https://www.whocc.no) and reflect the assumed average maintenance dose per day for a drug used for its main indication in adults [29].

We analysed drug exposure using three methods. First, we compared the differences between patients with anticholinergics alone, mirabegron alone, and combination therapy. Second, the cumulative DDD (cDDD) of an OAB medication use during the study period was quantified

for each patient using a DDD. We stratified the cumulative use of mirabegron and solifenacin using tertiles as follows: low-cDDD ($\leq$27 for mirabegron and $\leq$10 for solifenacin), medium-cDDD (28–120 for mirabegron and 10.5–45 for solifenacin), and high-cDDD ($\geq$121 for mirabegron and $\geq$45.5 for solifenacin) groups. Third, we have set fixed time intervals (<30, 30–120, 120–360, and >360 d), which allow a direct comparison (Supplementary Table 2). The calculation method for cDDD has been described in detail elsewhere (Supplementary material). For the low-cDDD group, we have assumed the harmful stochastic effects of an OAB medication.

2.4. Study outcomes and adjustment factors

Our primary outcome was dementia. Our hypothesis was that the risk of dementia would be significantly higher among patients taking an anticholinergic medication with or without a beta-3 agonist. Dementia was identified using ICD-10 codes or a new prescription of a cholinesterase medication (Supplementary Table 3).

The at-risk period began at the index date, and patients were censored at death. We have set 3 mo as the buffer period since it is not plausible that a short period after initial OAB medication exposure could lead to dementia. We have additionally set 1 yr as the buffer period to evaluate whether the risk of dementia persists even though some of the pre-existing subclinical dementia has been removed (Supplementary Table 4). Meanwhile, there are no relationships between the buffer period and cDDD, that is, the buffer period does not account for continuous OAB medications in that period.

To identify potential differences between groups, we compared demographic variables and medical comorbidities that are potentially associated with a risk of dementia (seizure, stroke, transient ischaemic attack [TIA], congestive heart failure, coronary artery disease or angina, hypertension, diabetes mellitus, and alcoholism; full coding details are listed in Supplementary Table 5).

2.5. Statistical analysis

Statistical analyses were performed in SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). The characteristics of the participants were reported as numbers (%) for categorical variables. The ages of patients were chan-
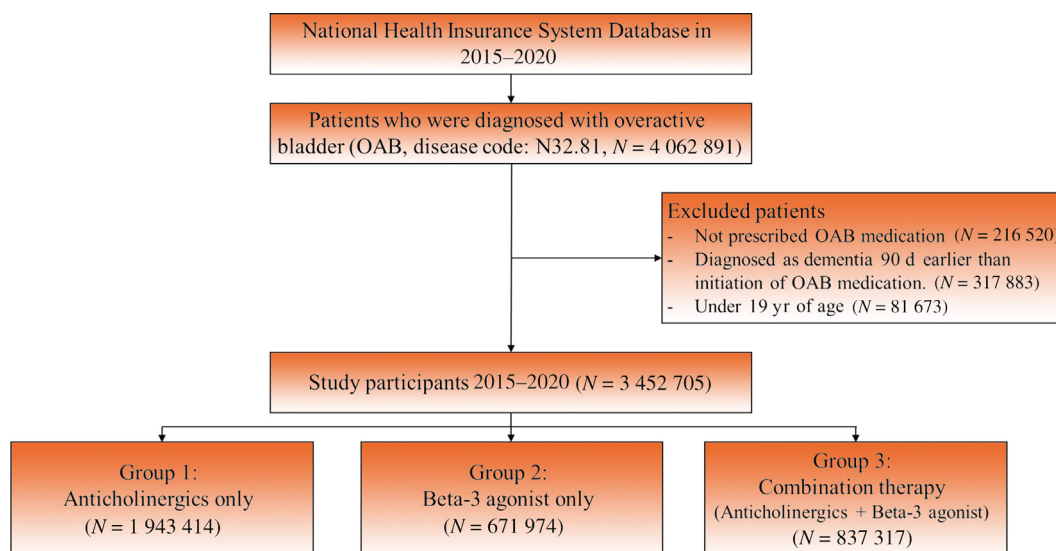

Fig. 1 – Flowchart for the selection of the study population using the National Health Insurance System Database in South Korea. OAB = overactive bladder.

Table 1 – Baseline characteristics of the matched patients with overactive bladder who used a beta-3 agonist alone, anticholinergics alone, or combination therapy

	Beta-3 agonist alone (N = 671 974)	Anticholinergics alone (N = 1 943 414)	Combination therapy (N = 837 317)	p value [a]
Demographics, n (%)				
Age <30	39 946 (5.9)	186 565 (9.6)	35 535 (4.2)	<0.0001
30 ≤ age < 40	53 277 (7.9)	209 893 (10.8)	47 961 (5.7)	
40 ≤ age < 50	88 462 (13.2)	318 437 (16.4)	93 640 (11.2)	
50 ≤ age < 60	145 801 (21.7)	427 182 (22.0)	171 946 (20.5)	
60 ≤ age < 70	177 022 (26.3)	374 578 (19.3)	221 948 (26.5)	
70 ≤ age < 80	124 494 (18.5)	290 938 (15.0)	198 821 (23.8)	
Age ≥80	42 972 (6.4)	135 821 (7.0)	67 466 (8.1)	
Male	451 757 (67.2)	483 495 (24.9)	369 024 (44.1)	<0.0001
Medical comorbidities, n (%)				
Seizure	40 417 (6.0)	114 022 (5.9)	70 281 (8.4)	<0.0001
Stroke or TIA	90 084 (13.4)	242 529 (12.5)	151 369 (18.1)	<0.0001
Congestive heart failure	63 572 (9.5)	162 992 (8.4)	103 506 (12.4)	<0.0001
Coronary artery disease or angina	146 386 (21.8)	346 974 (17.9)	220 069 (26.3)	<0.0001
Hypertension	341 165 (50.8)	861 906 (44.4)	488 712 (58.4)	<0.0001
Diabetes mellitus	292 608 (43.5)	739 026 (38.0)	424 504 (50.7)	<0.0001
Alcoholism	46 900 (6.9)	92 418 (4.8)	54 961 (6.6)	<0.0001
Dementia	21 091 (3.1)	122 617 (6.3)	56 301 (6.7)	<0.0001

TIA = transient ischaemic attack.

[a] Comparison of groups between a beta-3 agonist alone, anticholinergics alone, and combination therapy using the chi-square test.

ged to age groups (<30 yr, 40s, 50s, 60s, 70s, and ≥80 yr). A chi-square test was performed for each categorical variable (Table 1). All statistical tests were two tailed, and statistical significance was set at $p < 0.05$.

We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for developing dementia using a proportional hazards regression model based on OAB treatment type (anticholinergics alone, a beta-3 agonist alone, and combination therapy) or categories of mirabegron-solifenacin cDDDs, and adjusted this analysis to assess for potential confounding variables (either OAB treatment type or categories of mirabegron-solifenacin cDDDs, age, sex, and medical comorbidities [seizure, stroke or TIA, congestive heart failure, coronary artery disease or angina, hypertension, diabetes mellitus, and alcoholism]).

3. Results

The study cohort comprised 3 452 705 patients. Among these patients, 1 943 414 (56.3%) started anticholinergics alone, while 671 974 (19.5%) started beta-3 agonists alone and 837 317 (24.2%) started combination therapy. During 1.81 yr (interquartile range [IQR] = 0.93–2.99) of median follow-up, 200 009 patients (5.8%) developed dementia after starting their OAB medications. Significant differences ($p < 0.0001$) in age, sex, medical comorbidities, use of OAB medications, and cDDDs of OAB medications were evident between patients with or without new-onset dementia. The most frequently used anticholinergics were solifenacin (42.9%), propiverine (28.5%), and tolterodine (14.5%).

For patients who started with the beta-3 agonist alone, a 3.1% incidence of dementia was reported, while for patients using anticholinergics alone, a 6.3% incidence was observed, which was significantly higher than that for the beta-3 agonist alone ($p < 0.0001$; Table 1). However, the dementia incidence rate in the combination therapy group was still significantly higher, at 6.7% ($p < 0.0001$; Table 1).

After adjustments for age, sex, and medical comorbidities, an HR of 1.213 for anticholinergics and that of 1.345 for combination therapy were observed (Table 2). Similar results were observed even when the buffer period was

Table 2 – Cox proportional hazards regression analyses for the risk of dementia

	HR [a] (95% CI)	p value
OAB treatment type		
Beta-3 agonist alone	Reference	
Anticholinergics alone	1.213 (1.195, 1.232)	<0.0001
Combination therapy	1.345 (1.323, 1.366)	<0.0001
Confounding variables		
Age < 30	Reference	
30 ≤ age < 40	2.016 (1.644, 2.472)	<0.0001
40 ≤ age < 50	5.320 (4.443, 6.371)	<0.0001
50 ≤ age < 60	16.8 (14.1, 19.9)	<0.0001
60 ≤ age < 70	55.5 (46.6, 66.1)	<0.0001
70 ≤ age < 80	167.3 (140.6, 199.1)	<0.0001
Age ≥80	377.9 (317.7, 449.8)	<0.0001
Sex (female)	1.248 (1.235, 1.260)	<0.0001
Seizure	2.027 (2.004, 2.050)	<0.0001
Stroke or TIA	2.001 (1.983, 2.020)	<0.0001
Congestive heart failure	1.231 (1.218, 1.244)	<0.0001
Coronary artery disease or angina	1.053 (1.043, 1.063)	<0.0001
Hypertension	1.224 (1.208, 1.241)	<0.0001
Diabetes mellitus	1.193 (1.181, 1.205)	<0.0001
Alcoholism	1.380 (1.355, 1.405)	<0.0001

CI = confidence interval; HR = hazard ratio; OAB = overactive bladder; TIA = transient ischaemic attack.

[a] Adjusted for OAB treatment type, age, sex, and medical comorbidities (seizure, stroke or TIA, congestive heart failure, coronary artery disease or angina, hypertension, diabetes mellitus, and alcoholism).

set as 1 yr, with an HR of 1.186 for anticholinergics and that of 1.346 for combination therapy (Supplementary Table 4)

Table 3 presents the associations between the cDDDs of mirabegron alone and solifenacin alone, and the risk of dementia. Solifenacin was the most frequently used anticholinergic. The incidence of dementia increased proportionally with the levels of cDDDs in the beta-3 agonist–alone group ($p < 0.0001$), with a dementia incidence of 18.7% in the low-cDDD mirabegron group (≤27 cDDDs), 30.3% in the medium-cDDD mirabegron group (28–120 cDDDs), and 50.9% in the high-cDDD mirabegron group (≥121 cDDDs; Table 3). Even after multiple adjustments,

Table 3 – Hazard ratios for dementia by category of cumulative defined daily doses of mirabegron or solifenacin

Categories	Low	Medium	High
Mirabegron			
cDDDs (range)	≤27	28–120	≥121
Total cases (N)	216 438	232 504	223 032
Incidence of dementia, N (%)	3951 (18.7)	6399 (30.3)	10 741 (50.9)
HR [a] (95% CI)	Reference	1.062 (1.021, 1.106)	1.044 (1.004, 1.084)
Solifenacin			
cDDDs (range)	≤10	10.5–45	≥45.5
Total cases (N)	191 115	191 046	189 614
Incidence of dementia, N (%)	4252 (16.1)	6681 (25.3)	15 486 (58.6)
HR [a] (95% CI)	Reference	1.075 (1.035, 1.117)	1.330 (1.284, 1.377)

cDDD = cumulative defined daily dose; CI = confidence interval; HR = hazard ratio; TIA = transient ischaemic attack.
[a] Adjusted for categories of mirabegron or solifenacin cDDDs, age, sex, and medical comorbidities (seizure, stroke or TIA, congestive heart failure, coronary artery disease or angina, hypertension, diabetes mellitus, and alcoholism).

the increase in cDDDs of mirabegron was proportional to the increased risk of developing dementia (adjusted hazard ratio [aHR] = 1.062; 95% CI, 1.021–1.106 for the medium-cDDD mirabegron group, and aHR = 1.044; 95% CI, 1.004–1.084 for the high-cDDD mirabegron group, compared with the low-cDDD mirabegron group; Table 3). Moreover, an increase in the cDDDs of solifenacin was proportionally associated with an increased risk of developing dementia (aHR = 1.075; 95% CI 1.035–1.117 for the medium-cDDD solifenacin group, and aHR = 1.330; 95% CI; 1.284–1.377 for the high-cDDD solifenacin group, compared with the low-cDDD mirabegron

group). According to the fixed cDDD (ie, <31, 31–120, 121–360, and >360 d), similar findings were observed (Supplementary Table 2), except for no significant difference in mirabegron between the >360 cDDD group and the <31 cDDD group.

Associations between the use of specific OAB anticholinergics and dementia are shown in Table 4 and Figure 2. The incidence of dementia was significantly higher in patients using solifenacin (aHR = 1.173; 95% CI, 1.151–1.196 for monotherapy and aHR = 1.231; 95% CI, 1.205–1.258 for combination therapy), tolterodine (aHR = 1.170; 95% CI,

Table 4 – Risk of dementia according to different types of OAB anticholinergics with or without a beta-3 agonist in comparison with a beta-3 agonist alone

Oxybutynin			
OAB medications	Beta-3 agonist alone	Oxybutynin alone	Combination therapy
Total cases (N)	671 974	43 555	6079
Incidence of dementia, N (%)	21 091 (3.1)	2026 (4.6)	265 (4.4)
HR [a] (95% CI)	Reference	1.024 (0.975–1.075)	1.136 (1.006–1.283)
Solifenacin			
OAB medications	Beta-3 agonist alone	Solifenacin alone	Combination therapy
Total cases (N)	671 974	571 775	274 956
Incidence of dementia, N (%)	21 091 (3.1)	26 419 (4.6)	14 461 (5.3)
HR [a] (95% CI)	Reference	1.173 (1.151–1.196)	1.231 (1.205–1.258)
Tolterodine			
OAB medications	Beta-3 agonist alone	Tolterodine alone	Combination therapy
Total cases (N)	671 974	171 518	38 425
Incidence of dementia, N (%)	21 091 (3.1)	10 991 (6.4)	2122 (5.5)
HR [a] (95% CI)	Reference	1.170 (1.140, 1.200)	1.228 (1.175, 1.285)
Trospium			
OAB medications	Beta-3 agonist alone	Trospium alone	Combination therapy
Total cases (N)	671 974	10 695	3105
Incidence of dementia, N (%)	21 091 (3.1)	423 (3.9)	193 (6.2)
HR [a] (95% CI)	Reference	1.067 (0.967–1.176)	1.300 (1.128–1.498)
Fesoterodine			
OAB medications	Beta-3 agonist alone	Fesoterodine alone	Combination therapy
Total cases (N)	671 974	76 993	30 096
Incidence of dementia, N (%)	21 091 (3.1)	4867 (6.3)	1909 (6.3)
HR [a] (95% CI)	Reference	1.178 (1.139–1.218)	1.226 (1.170–1.285)
Flavoxate			
OAB medications	Beta-3 agonist alone	Flavoxate alone	Combination therapy
Total cases (N)	671 974	183 423	37 071
Incidence of dementia, N (%)	21 091 (3.1)	4457 (2.4)	999 (2.7)
HR [a] (95% CI)	Reference	0.861 (0.831–0.892)	0.989 (0.927–1.054)
Propiverine			
OAB medications	Beta-3 agonist alone	Propiverine alone	Combination therapy
Total cases (N)	671 974	382 244	98 479
Incidence of dementia, N (%)	21 091 (3.1)	23 601 (6.2)	5746 (5.8)
HR [a] (95% CI)	Reference	1.196 (1.171, 1.220)	1.216 (1.181, 1.252)

CI = confidence interval; HR = hazard ratio; OAB = overactive bladder; TIA = transient ischaemic attack.
[a] Adjusted for OAB medication class, age, sex, and medical comorbidities (seizure, stroke or TIA, congestive heart failure, coronary artery disease or angina, hypertension, diabetes mellitus, and alcoholism).
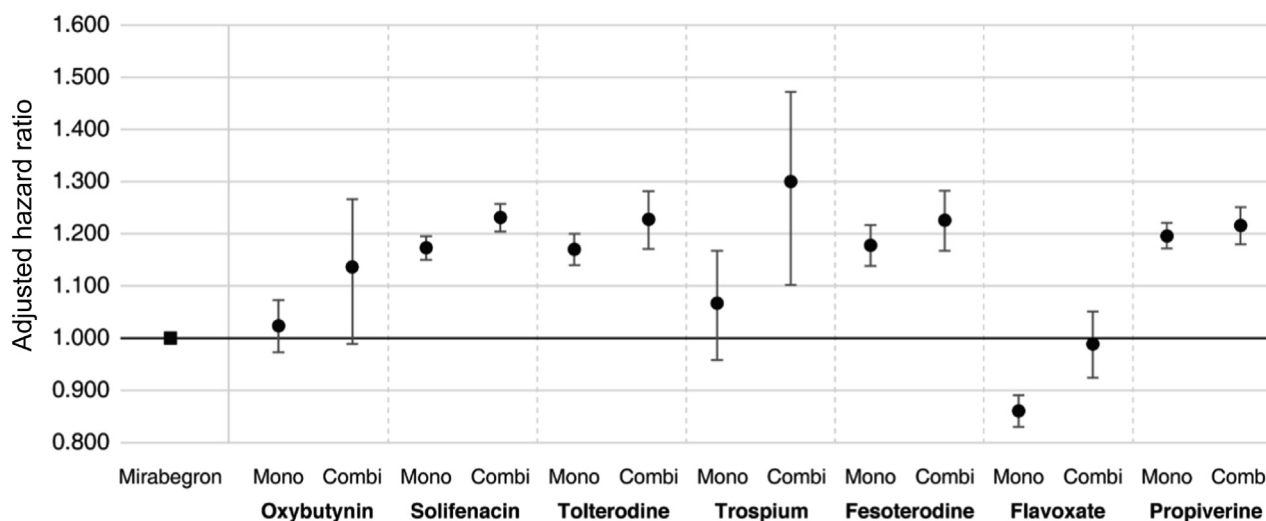
Fig. 2 – Association between overactive bladder anticholinergic drugs used alone or in combination with mirabegron and dementia compared with mirabegron alone (adjusted [a] hazard ratio with 95% confidence interval). Combo = combination therapy; Mono = monotherapy; OAB = overactive bladder; TIA = transient ischaemic attack. [a] Adjusted for OAB medication class, age, sex, and medical comorbidities (seizure, stroke or TIA, congestive heart failure, coronary artery disease or angina, hypertension, diabetes mellitus, and alcoholism).

1.140–1.200 for monotherapy and aHR = 1.228; 95% CI, 1.175–1.285 for combination therapy), fesoterodine (aHR = 1.178; 95% CI, 1.139–1.218 for monotherapy, and aHR = 1.226; 95% CI, 1.170–1.285 for combination therapy), and propiverine (aHR = 1.196; 95% CI, 1.171–1.220 for monotherapy, and aHR = 1.216; 95% CI, 1.181–1.252 for combination therapy), both used alone or in combination with mirabegron, compared with mirabegron alone, even after multiple adjustments. However, the incidence of dementia was significantly lower in patients who received flavoxate alone (aHR = 0.861; 95% CI, 0.831–0.892; $p < 0.0001$).

4. Discussion

Our study demonstrated that treatment consisting of anticholinergics with or without a beta-3 agonist increased the risk of new-onset dementia compared with the use of a beta-3 agonist alone. As we found that the risk of dementia significantly increased the most with a combination of treatments, care should be taken when combining anticholinergics and beta-3 agonists, particularly among those with risk factors for dementia. Furthermore, there were some tendencies of an increased incidence of dementia with the use of a beta-3 agonist alone, with a potentially cumulative dose-response relationship. Although not clearly validated in our study, there could be some possible associations between beta-3 agonists and dementia.

A case-control study using data from the UK found a similarly significantly increased risk of dementia among patients with urological anticholinergics (aHR = 1.18), with large gaps between exposure and diagnosis [12]. A similar study from the UK found that bladder anticholinergic users had a significantly increased risk of dementia (aHR = 1.19) [11]. A Canadian cohort study of patients with an OAB showed an increased risk of dementia in new users of OAB

anticholinergics compared with the new users of mirabegron (HR = 1.23) [17]. In addition, two Taiwanese studies also found a higher risk of dementia among users of OAB anticholinergics [15,16].

The findings in these studies are consistent with our results: OAB anticholinergic use was associated with an increase in the risk of dementia [11,12,15-17], although the previous studies' authors analysed all anticholinergics without differentiating between specific anticholinergics. Two studies, by French and Canadian researchers, analysed the association between individual anticholinergics and dementia [13,19]. When Malcher et al [19] differentiated each anticholinergic, they found that the two most frequently used OAB anticholinergics, oxybutynin and solifenacin, were associated with an increased risk of dementia. In our study, oxybutynin was not associated with a risk of dementia after multiple adjustments. This finding was similar to that of a study by Matta et al [13], which reported no association between oxybutynin and dementia. Matta et al [13] reported that the receipt of solifenacin and darifenacin was associated with an increased incidence of dementia during the 6 mo to 1 yr period prior to a diagnosis of dementia. Our results suggest that the use of solifenacin, tolterodine, fesoterodine, and propiverine increases the risk of dementia. Solifenacin was associated with an increased incidence of dementia in both a study by Matta et al [13] and our study. We should, therefore, at least exercise caution when prescribing solifenacin to those at risk of developing dementia.

Furthermore, although most studies reported the association between OAB anticholinergics and dementia [15-17], including studies by Coupland et al [11] and Richardson et al [12], which have focused on the long-term effects of anticholinergics taken before advanced age and the risk of late-life dementia according to class-based associations and reported an increased rate of dementia especially for

antidepressants, urological drugs, and antipsychotics, a recent study using UK Biobank reported no significant association in urological drugs and antipsychotics [30].

Although the results of mouse-model experiments reported that mirabegron is associated with memory-deficit reversal [20], no proper prospective clinical studies have evaluated the incidence of dementia according to the use of mirabegron. PILLAR is the first prospectively designed investigation of mirabegron specifically designed to assess the effects in patients aged 65 yr [21]; however, the follow-up period was only 3 mo, which was insufficient to measure the effects on cognitive function. In addition, only two observational studies compared the incidence of dementia in patients receiving anticholinergics and mirabegron, setting mirabegron as the reference to reduce protopathic bias [13,17]. However, the fact that the use of anticholinergics was associated with an increase in dementia compared with mirabegron does not imply that mirabegron is safe for dementia patients.

In the mouse model, mirabegron was found to be beneficial in terms of dementia [20]. The authors used CL-316,243, a specific β3-adrenergic receptor (AR) agonist [20]. They showed that β3-AR agonists can reverse memory deficits by decreasing body weight and improving peripheral glucose metabolism and brown adipose tissue (BAT) thermogenesis [20]. However, Blondin et al [31] recently revealed that therapeutic doses of mirabegron, which is a β3-AR agonist, do not stimulate human BAT. Human brown adipocytes lack β3-AR and primarily express β2-ARs, in which norepinephrine-induced respiration is driven by β2-AR [31]. Therefore, the action of the β3-AR agonist in the mouse model cannot be applied to humans, and the action of the β3-AR agonist in those with dementia should be explored further. Moreover, unlike CL-316,243, a specific β3-AR agonist, mirabegron has selectivity to some β2 and low-β1 activity [32]. The action of mirabegron on dementia should, therefore, not be considered equal to that of CL-316,243.

We found that the use of combination therapy dramatically increases the incidence of dementia compared with the use of anticholinergics alone. As the pharmacological mechanisms of anticholinergics and beta-3 agonists differ, with anticholinergics inhibiting bladder contraction and beta-3 agonists mediating relaxation, they are expected to enhance the treatment effect by complementing one another [33]. Several clinical trials (SYMPHONY, SYNERGY, BESIDE, and MILAI) have shown that combination therapy achieved significantly superior efficacy to anticholinergic monotherapy, although no additive effects on safety parameters were noted and no new clinically relevant safety concerns arose [24-27] in these studies. However, the long-term effects of combination therapy on cognition were not examined. The safety of combination therapy for cognitive impairment should therefore be revisited before expanding the use of combination therapy and the development of combination therapies from these two classes of drugs.

The cyclic adenosine 3,5-monophosphate (cAMP)/protein kinase A (PKA) signalling pathway plays a vital role in long-term memory [34]. In addition, the cAMP/PKA signalling pathway causes the accumulation of Aβ and neuronal apoptosis [35]. Since β-AR activation increases the cAMP/PKA pathway [36], potential links between adrenergic activation and amyloidogenesis, a crucial event in Alzheimer's disease, exist [35,37].

The pharmacological effects of anticholinergics on the CNS depend on their ability of CNS penetration, which depends on the permeability properties of the blood-brain barrier [38]. Solifenacin and tolterodine demonstrated significant CNS penetration, while trospium demonstrated poor CNS penetration [38]. These findings were in line with our results that a strong association of dementia with solifenacin and tolterodine but no association with trospium were reported. However, although oxybutynin is known for its extensive CNS penetration, there was no significant association between oxybutynin and dementia in our study. The significant association of oxybutynin and dementia has been reported by several studies even with small sample size [39,40]. This might be due to the well-known harmful effects of oxybutynin on cognition, which have affected the low-prescription tendency in patients at risk of dementia. Although we tried to adjust the overall confounder bias that is available, we could not adjust the preferences of prescription by clinicians, and this would have affected our results.

Furthermore, flavoxate was associated with a significantly lower incidence of dementia in our study. Malcher et al [19] also reported a decreased risk of dementia (adjusted odds ratio = 0.92; 95% CI, 0.57–1.49) in a French population, although the effect was not significant (p = 0.38). They concluded that the low frequency of use (121 patients) of flavoxate did not provide sufficient statistical power to detect any association with dementia [19]. The reason for the low frequency of flavoxate use would probably be the limited therapeutic efficacy of an OAB. Therefore, although our results suggest that flavoxate may be the only OAB drug with beneficial effects on cognitive function, the results might have been affected by the small number of flavoxate users.

Our study has several strengths. First, it was based on a large and representative sample of the Korean population, which allowed us to investigate the relationship between the use of different OAB anticholinergics and a beta-3 agonist, alone or in combination, and dementia. This is the largest study population among six observational studies to explore the association between OAB anticholinergics and dementia (Supplementary Table 6). The size of the study population was large enough to provide statistical power to reach conclusions not reported in other studies. However, this large sample size could have led to a relatively small proportionate difference as statistically significant. Second, this is the first study to analyse the effect of combination therapy on dementia. In addition, we are the first to report the effects of a beta-3 agonist prescribed for dementia. Third, information regarding prescription information for specific anticholinergics was obtained and analysed.

However, several limitations are noteworthy. First, this study lacks a comparator group neither using an anticholinergic nor a beta-3 agonist. The reason we did not include this comparator group was due to the validity concerns regarding the accuracy of diagnosis codes of studies using

claims databases [41]. One of the recommended methods is to include the records of both diagnosis and related medications to increase the accuracy of diagnosis [41]. Therefore, we have chosen this method. Second, due to the absence of a comparator group receiving no OAB medications, the association of dementia and beta-3 agonist was based on the indirect evidence from the cumulative exposure data and from the comparison of monotherapy with an anticholinergic with combination treatment. Therefore, future studies are needed to confirm this association. Third, there was a lack of information on treatment adherence. Since cognition and memory are reversible upon withdrawal of anticholinergics [42], no information regarding treatment adherence could affect the association between anticholinergics and dementia. Fourth, we were unable to differentiate specific types of dementia as genetic variables related to dementia, and baseline cognitive function was not measured. Fifth, although we attempted to adjust for several confounding factors, only a limited number of factors were available in the NHIS database. Therefore, the factors that might dictate prescription of OAB medications, such as availability, and social determinants of health, could not be controlled.

5. Conclusions

This is the first largest cohort study to compare the effects of different OAB medications on dementia. Prescribers tend to prescribe a nonanticholinergic OAB medication, a beta-3 agonist, as previous studies have found an association between anticholinergics and cognition. However, our study found that combination therapy increased the risk of dementia dramatically compared with anticholinergics alone. Furthermore, there could be some effects of a beta-3 agonist on dementia. We should therefore be cautious when prescribing combination therapy and discontinue the use of anticholinergics or beta-3 agonists as soon as possible. Finally, investigations on finding the association between an OAB and dementia will be done in the future to understand the pathophysiology more accurately.

Author contributions: Jee Soo Park and Won Sik Ham had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Park, Ham.
Acquisition of data: Park, Choi.
Analysis and interpretation of data: Park, Choi.
Drafting of the manuscript: Park.
Critical revision of the manuscript for important intellectual content: Jang, Kim.
Statistical analysis: Park, Choi.
Obtaining funding: Park, Ham.
Administrative, technical, or material support: Jang, Kim.
Supervision: Park, Ham.
Other: None.

Data sharing statement: All data are available from the National Health Insurance Sharing Service (NHISS; https://nhiss.nhis.or.kr). NHISS allows access to all these data for any researcher who promises to follow the research ethics at some cost. If you want to access the data from this paper, you can download it from the website after promising to follow the research ethics. Releasing of the data by the researcher is not legally permitted.

Ethics statement: This study was approved by the Institutional Review Board of the Sorokdo National Hospital (2021-0009). The NHIS-customised database was fully anonymised for privacy protection. Owing to the retrospective nature and use of deidentified data, this study was approved with a waiver of the requirement to obtain informed consent from participants by the Institutional Review Board of the Sorokdo National Hospital (2021-0009). The study was performed in accordance with approved guidelines and regulations for medical research expressed in the Declaration of Helsinki.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2024.02.002.

References

[1] Harding CK, Lapitan MC, Arlandis S, et al. EAU guidelines on management of non-neurogenic female lower urinary tract symptoms (LUTS). 2021. uroweb.org/wp-content/uploads/EAU-Guidelines-on-Non-Neurogenic-Female-LUTS-2021.pdf.

[2] Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006;50:1306–15.

[3] Rahanama'i S, editor. ICS standardisation committee terminology discussions: overactive bladder. http://www.ics.org/committees/standardisation/terminologydiscussions/overactivebladder.

[4] Lightner DJ, Gomelsky A, Souter L. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2019;202:558–63.

[5] Mostafaei H, Salehi-Pourmehr H, Jilch S, et al. Choosing the most efficacious and safe oral treatment for idiopathic overactive bladder: a systematic review and network meta-analysis. Eur Urol Focus 2022;8:1072–89.

[6] Su S, Liang L, Lin J, Liu L, Chen Z, Gao Y. Systematic review and meta-analysis of the efficacy and safety of vibegron vs antimuscarinic monotherapy for overactive bladder. Medicine (Baltimore) 2021;100:e2317.

[7] Gormley EA, Lightner DJ, Faraday M, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2015;193:1572–80.

[8] Nambiar AK, Bosch R, Cruz F, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. Eur Urol. 2018;73:596–609.

[9] Cai X, Campbell N, Khan B, et al. Chronic anticholinergic use and the aging brain. Alzheimers Dement 2013;9:377–85.

[10] Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Nondegenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ 2006;332:455–9.

[11] Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. JAMA Intern Med 2019;179:1084–93.

[12] Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case control study. BMJ 2018;361:l6213.

[13] Matta R, Gomes T, Juurlink D, Jarvi K, Herschorn S, Nam RK. Receipt of overactive bladder drugs and incident dementia: a population-based case-control study. Eur Urol Focus 2022;8:1433–40.

[14] Lozano-Ortega G, Johnston KM, Cheung A, et al. A review of published anticholinergic scales and measures and their applicability in database analyses. Arch Gerontol Geriatr 2020;87:103885.

[15] Wang YC, Chen YL, Huang CC, et al. Cumulative use of therapeutic bladder anticholinergics and the risk of dementia in patients with lower urinary tract symptoms: a nationwide 12-year cohort study. BMC Geriatr 2019;19:380.

[16] Harnod T, Yang YC, Chiu LT, Wang JH, Lin SZ, Ding DC. Use of bladder antimuscarinics is associated with an increased risk of dementia: a retrospective population-based case-control study. Sci Rep 2021;11:4827.

[17] Welk B, McArthur E. Increased risk of dementia among patients with overactive bladder treated with an anticholinergic medication compared to a beta-3 agonist: a population-based cohort study. BJU Int 2020;126:183–90.

[18] Chancellor MB, Staskin DR, Kay GG, Sandage BW, Oefelein MG, Tsao JW. Blood-brain barrier permeation and efflux exclusion of anticholinergics used in the treatment of overactive bladder. Drugs Aging 2012;29:259–73.

[19] Malcher MF, Droupy S, Berr C, et al. Dementia associated with anticholinergic drugs used for overactive bladder: a nested case-control study using the French National Medical-Administrative Database. J Urol 2022;208:863–71.

[20] Tournissac M, Vu TM, Vrabic N, et al. Repurposing beta-3 adrenergic receptor agonists for Alzheimer's disease: beneficial effects in a mouse model. Alzheimers Res Ther 2021;13:103.

[21] Wagg A, Staskin D, Engel E, Herschorn S, Kristy RM, Schermer CR. Efficacy, safety, and tolerability of mirabegron in patients aged ≥ 65 yr with overactive bladder wet: a phase IV, double-blind, randomized, placebo-controlled study (PILLAR). Eur Urol 2020;77:211–20.

[22] Kelleher C, Hakimi Z, Zur R, et al. Efficacy and tolerability of mirabegron compared with antimuscarinic monotherapy or combination therapies for overactive bladder: a systematic review and network meta-analysis. Eur Urol Focus 2018;74:324–33.

[23] Fogaing C, Mossa AH, Campeau L. Are beta 3 adrenergic agonists now the preferred pharmacologic management of overactive bladder? Curr Urol Rep 2020;21:49.

[24] Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomized, double-blind, dose-ranging, phase 2 study (Symphony). Eur Urol 2015;67:577–88.

[25] Herschorn S, Chapple CR, Abrams P, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU Int 2017;120:562–75.

[26] Drake MJ, Chapple C, Esen AA, et al. Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: a randomized double-blind multicentre Phase 3b study (BESIDE). Eur Urol 2016;70:136–45.

[27] Yamaguchi O, Kakizaki H, Homma Y, et al. Safety and efficacy of mirabegron as 'add-on' therapy in patients with overactive bladder treated with solifenacin: a post-marketing, open-label study in Japan (MILAI study). BJU Int 2015;116:612–22.

[28] Choi J, Kim HJ, Lee J, Cho S, Ko MJ, Lim YS. Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: a Korean nationwide cohort study. JAMA Oncol 2019;5:30–6.

[29] Norwegian Institute of Public Health. WHO Collaborating Centre for Drug Statistics and Methodology. https://www.fhi.no/en/hn/drug/who-collaborating-centre-for-drug-statistics-methodology/.

[30] Mur J, Russ TC, Cox SR, Marioni RE, Muniz-Terrera G. Association between anticholinergic burden and dementia in UK Biobank. Alzheimers Dement 2022;8:e12290.

[31] Blondin DP, Nielsen S, Kuipers EN, et al. Human brown adipocyte thermogenesis is driven by β2-AR stimulation. Cell Metab 2020;32:287–300.e7.

[32] Brucker BM, King J, Mudd Jr PN, McHale K. Selectivity and maximum response of vibegron and mirabegron for β3-adrenergic receptors. Curr Ther Res Clin Exp 2022;96:100674.

[33] O'Kane M, Robinson D, Cardozo L, Wagg A, Abrams P. Mirabegron in the management of overactive bladder syndrome. Int J Womens Health 2022;14:1337–50.

[34] Lonze BE, Ginty DD. Function and regulation of CREB family transcription factors in the nervous system. Neuron 2002;35:605–23.

[35] Li H, Yang S, Wu J, et al. cAMP/PKA signaling pathway contributes to neuronal apoptosis via regulating IDE expression in a mixed model of type 2 diabetes and Alzheimer's disease. J Cell Biochem 2018;119:1616–26.

[36] Anderson DB, Moody DE, Hancock DL. Beta adrenergic agonists. Encycl of Anim Sci 2004:104–8.

[37] Yang JH, Lee EO, Kim SE, Suh YH, Chong YH. Norepinephrine differentially modulates the innate inflammatory response provoked by amyloid-β peptide via action at β-adrenoceptors and activation of cAMP/PKA pathway in human THP-1 macrophages. Exp Neurol 2012;236:199–206.

[38] Callegari E, Malhotra B, Bungay PJ, et al. A comprehensive non-clinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder. Br J Clin Pharmacol 2011;72:235–46.

[39] Donnellan CA, Fook L, McDonald P, Playfer JR. Oxybutynin and cognitive dysfunction. BMJ 1997;315:1363–4.

[40] Kay G, Crook T, Rekeda L, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. Eur Urol 2006;50:317–26.

[41] Kao WH, Hong JH, See LC, et al. Validity of cancer diagnosis in the National Health Insurance database compared with the linked National Cancer Registry in Taiwan. Pharmacoepidemiol Drug Saf 2018;27:1060–6.

[42] Muderrisoglu AE, Becher KF, Madersbacher S, Michel MC. Cognitive and mood side effects of lower urinary tract medication. Expert Opin Drug Saf 2019;18:915–23.