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Anticholinergic burden in the Japanese elderly population: Use of antimuscarinic medications for overactive bladder patients

Masaki Yoshida,1 Daisuke Kato,2 Takuya Nishimura,2 James Van Schyndle,3 Satoshi Uno2 and Tomomi Kimura2

1Department of Urology, National Center for Geriatrics and Gerontology, Obu, 2Astellas Pharma Inc., Tokyo, Japan, and 3Astellas Pharma, Northbrook, Illinois, USA

**Objectives:** To assess anticholinergic use, especially the use of antimuscarinics, in the elderly (aged ≥65 years) Japanese overactive bladder and non-overactive bladder populations.

**Methods:** Patient records were sourced from a large, nationwide Japanese pharmacy claims database. Anticholinergic use on a random day in 2016 (index date) was investigated through the Anticholinergic Cognitive Burden scale (primary scale), the Anticholinergic Drug Scale, the Anticholinergic Risk Scale and Beers criteria. The prevalence of anticholinergic use and anticholinergic scores at the index date were summarized descriptively. The overactive bladder population was defined as patients who had at least one prescription record for any antimuscarinic (fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin or tolterodine) or the β3-adrenoreceptor agonist, mirabegron, within the 1-year pre-index period.

**Results:** Among 1,216,126 outpatients, 35,138 (2.9%) were included in the overactive bladder group. In total, 112 (68.7%) of the anticholinergics listed in the scales were identified. In those who received any Anticholinergic Cognitive Burden scale-listed anticholinergic, the mean scores were higher in overactive bladder patients versus non-overactive bladder patients (3.2 ± 1.3 and 1.6 ± 1.1, respectively). Similarly, overactive bladder patients who received antimuscarinics had higher Anticholinergic Cognitive Burden scores (3.3 ± 1.2) than patients who received mirabegron only (1.7 ± 1.1). In 58.8% of the overactive bladder patients, ≥80% of the total Anticholinergic Cognitive Burden score was exclusively attributable to antimuscarinics.

**Conclusions:** Anticholinergic use was higher in overactive bladder patients versus non-overactive bladder patients. This increased use was largely attributable to antimuscarinics. The alternative use of mirabegron could therefore be considered to reduce the burden experienced by patients in Japan.

**Key words:** anticholinergics, antimuscarinics, elderly, Japan, overactive bladder.

**Introduction**

AC medications are extensively used to treat a variety of conditions, including OAB.1,2 An association between AC use and an increased risk of falls, and cognitive, physical and functional impairment has been reported.3–5 In contrast, other investigations have not identified an association between AC burden and specific clinical adverse effects (e.g. delirium).6,7 Although differences exist between findings, the Beers criteria, from the American Geriatrics Society, state that the use of medications that are classified as strong ACs should be avoided in the elderly due to an increased risk of confusion, dry mouth, constipation and other AC effects or toxicity.8 If alternative treatments with similar efficacy, but no associated AC side effects, are available for use in a particular therapeutic area, it might be possible to reduce the AC burden experienced by the patient.9

Several scales have been developed to estimate AC score by giving points to each medication according to the risk of AC effects. The ACB scale was devised to provide the clinician with a simple score that captures the accumulative AC cognitive burden resulting from the medications administered to the patient.10 The ADS was developed to identify patients at risk...
of adverse events and provide guidance for therapeutic interventions.11 The ARS was derived to assess the risk of falls, delirium and cognitive impairment.12 In the ARS, topical, ophthalmic, otologic or inhaled AC medications are not included. The Beers criteria were formulated to improve the care of older adults by reducing their exposure to potentially inappropriate medications using the criteria as an educational tool and quality measure.8 Only strong ACs are listed as potentially inappropriate medications in the Beers criteria. Investigations from the primary, secondary and community settings in the USA, UK and France have estimated that between 17.1% and 48.4% of elderly patients receive at least one AC listed in these scales.12–14

A number of AM medications, which show AC properties, have been the mainstay of pharmacotherapy approaches for treating patients with OAB symptoms.8,15 As the prevalence of OAB increases with age,16 and older age is associated with polypharmacy,17 elderly individuals with OAB might experience a higher AC burden. However, an alternative OAB medication is available that is not associated with AC side effects, the β3-adrenoceptor agonist, mirabegron. As there have been only a limited number of studies from Japan, the current investigation was carried out to assess AC use, including the attribution of AMs, in the elderly Japanese OAB or non-OAB populations. The ACs investigated in the present study were defined as those listed in any of the following AC scales: the ACB scale, ADS, ARS and Beers criteria (Table S1). The AMs were defined according to Table 1.

Methods

Data source

The data source was the Medi-Trend pharmacy claims database provided by Kyowa Kikaku (https://www.kk-kyowa.co.jp/), which contained prescription records from approximately 900 pharmacies throughout Japan and was comprised of out-of-hospital prescription records for 3.9 million outpatients when the study was carried out. The raw data were purchased from Kyowa Kikaku, who obtained prescription and dispensing records from their contracted pharmacies and de-identified the data for research purposes.

AC scales

The four scales used in the present study vary by the selection of ACs, specific therapeutic areas and scores for each AC. In total, 99, 114, 49 and 52 ACs are listed in the ACB scale, ADS, ARS and the Beers criteria, respectively. The ACB scale was selected as the primary scale, as it is the only measure that captures all of the AMs, except for imidafenacin. We added imidafenacin to the ACB scale (but not to the other scales), given the widespread use of the drug in Japan.18 Imidafenacin was afforded a score of 3 after consultation with a specialist and in accordance with the other AMs included.

The dataset was reviewed to identify all ACs listed in the scales (see below). Each AC product was defined according to the first seven digits of the YJ code (Japanese drug coding system).

Study design

All patients born on or before 31 December 1950 (i.e. aged ≥65 years as of 1 January 2016) with at least one prescription record for any medication between 23 September 2015 and 31 December 2016 were included. Similar to previous studies,3,11 where data were acquired on medications that patients were taking at a specific time, a random date between 1 January and 31 December 2016 was assigned to each patient (index date). Using a timeframe of −99 days to the index date (total 100 days), prescription records for the ACs from each of the scales were acquired and included in the analysis if the days of supply encompassed the index date. If more than one prescription of the same medication was found, it was counted only once. The study design is shown in Figure S1.

The OAB patient population was defined as those who had at least one prescription record for fesoterodine, imidafenacin, mirabegron, oxybutynin (including oxybutynin patch), propiverine, solifenacin or tolterodine during the 1-year pre-index period (darifenacin is not approved in Japan). Therefore, it was possible that patients might have been included in the OAB group without receiving any OAB medication on their index date. The OAB patients who received mirabegron only during the pre-index period were categorized as “mirabegron-only patients,” and all other OAB patients were categorized as “AM patients.” AM patients might have also received mirabegron during the pre-index period. Patients who did not receive any OAB medications during the 1-year pre-index period were categorized as non-OAB patients.

AC use was evaluated in terms of the prevalence of AC use and the AC scores for three of the scales (ACB scale, ADS and ARS). Scores were not included for the ACs listed

| Table 1 | AMs included in each scale |
|---------|-----------------------------|
| Scale   | Listed AMs                  | AMs added to the scale in this study |
| ACB scale | Fesoterodine, oxybutynin (oral and patch), propiverine, solifenacin, tolterodine (all score = 3), darifenacin† | Imidafenacin (score = 3) |
| ADS     | Oxybutynin (oral and patch), tolterodine (all score = 3) | – |
| ARS     | Oxybutynin (oral; score = 3), tolterodine (score = 2) | – |
| Beers criteria | Fesoterodine, oxybutynin (oral and patch), solifenacin, tolterodine | – |

†Not approved in Japan.
in the Beers criteria and therefore only prevalence was estimated for this scale. For the other scales, each AC has a score of 1–3; the higher the score, the greater the burden. Cumulative scores for each patient were calculated through the summation of the score for each AC medication. Dosage, dosing frequency and days on AC medication were not considered in the calculations.

The protocol was approved by the sponsor’s internal committee (review number MAJ-PRC_20161222).

Results

Study population

Overall, 1 216 126 patients were identified who had at least one prescription record during the study period. The median age of the patients was 75.0 years (IQR 70.0–82.0 years) and 56.8% of the patients were women (Table 2). The age distribution was generally similar to the Japanese population (Fig. 1). Among the study population, 35 138 (2.9%) patients were included in the OAB group and 9247 (0.8%) were included in the mirabegron-only group. Overall, OAB patients were typically older than non-OAB patients (Fig. 2), and those who received mirabegron only were slightly younger and more likely to be men versus patients who had received AMs (Table 2).

Prevalence of AC use

In total, 112 (68.7%) of the ACs listed in any of the scales were used in this analysis. For each of the scales, 75 of 99 (75.8%), 81 of 114 (71.1%), 39 of 49 (79.6%) and 33 of 52 (63.5%) of the ACs listed in the ACB scale, ADS, ARS and the Beers criteria, respectively, were prescribed to the patients (63.5%) of the ACs listed in the ACB scale, ADS, ARS and the Beers criteria (1.9%; Table 3), a finding that reflects the number of listed ACs in each scale. The prevalence of AC prescriptions increased with age and was higher in OAB patients versus non-OAB patients. Similarly, a higher prevalence of AC use was observed in the AM group versus the mirabegron-only group. For example, 56.7% patients in the AM group received an AC listed in the ACB scale versus 15.0% of patients in the mirabegron-only group.

AC scores and attribution of AMs

ACB score was higher in OAB patients versus non-OAB patients (mean ± SD: 1.5 ± 1.8 and 0.1 ± 0.6, respectively; Table 4). When the results were evaluated in terms of patients who had received any ACB scale-listed AC, mean scores were also higher in OAB patients (3.2 ± 1.3 and 1.6 ± 1.1, respectively). Furthermore, out of these patients, higher ACB scores were obtained for the AM group (3.3 ± 1.2) versus the mirabegron-only group (1.7 ± 1.1). Overall, ACB scores were similar between the mirabegron-only group and the non-OAB group.

As stated above, OAB patients were older than non-OAB patients, and when these individuals were stratified according to age, OAB patients consistently had higher mean ACB scores (Fig. S2). Furthermore, in each age strata, higher ACB scores were observed for the AM group versus the mirabegron-only group.

Using ADS and ARS, where a limited number of AMs are listed, mean AC scores were only slightly higher in OAB patients versus non-OAB patients. Similar findings were observed between patients who had received mirabegron only and those who received AMs. For example, slightly higher mean scores were observed for the AM group (1.9 ± 1.3) versus the mirabegron-only group (1.6 ± 1.0) in patients who had received any ADS-listed AC.

In 51.8% of OAB patients, ≥80% of the total ACB score was attributable to AMs (Fig. 3). This percentage increased when the data were evaluated for the OAB patients who

| Parameter          | Total       | Non-OAB patients | OAB patients† | Mirabegron only | AMs‡ |
|--------------------|-------------|------------------|---------------|----------------|------|
| n (% of total)     | 1 216 126 (100) | 1 180 988 (97.1) | 35 138 (2.9) | 9247 (0.8)§ | 25 891 (2.1)§ |
| Age (years)        |             |                  |               |                |      |
| Mean (SD)          | 76.3 (7.5)  | 76.2 (7.5)       | 79.7 (7.4)    | 78.9 (7.1)    | 80.0 (7.5) |
| Median (IQR)       | 75.0 (70.0–82.0) | 75.0 (70.0–81.0) | 80.0 (74.0–85.0) | 79.0 (74.0–84.0) | 80.0 (74.0–85.0) |
| Age group, n (% of patient population) |            |                  |               |                |      |
| 65–74 years        | 557 005 (45.8) | 547 614 (46.4) | 9391 (26.7)  | 2711 (29.3) | 6680 (25.8) |
| 75–84 years        | 466 667 (38.4) | 450 508 (38.1) | 16 159 (46.0) | 4425 (47.9) | 11 734 (45.3) |
| ≥85 years          | 192 454 (15.8) | 182 866 (15.5) | 9588 (27.3)  | 2111 (22.8) | 7477 (28.9) |
| Female, n (% of patient population) | 691 356 (56.8) | 672 240 (56.9) | 19 116 (54.4) | 3946 (42.7) | 15 170 (58.6) |

†Includes any patient who had at least one prescription record for fesoterodine, mirabegron, oxybutynin, propiverine, solifenacin or tolterodine in the 1-year period before their index date. ‡Can include patients who received mirabegron before, after or concomitantly with AMs in the 1-year period before their index date. Overall, fesoterodine was prescribed to 3376 (0.3%) patients, imidafenacin to 6185 (0.5%) patients, mirabegron to 12 659 (1.0%) patients, oxybutynin to 734 (0.1%) patients, oxybutynin patch to 1089 (0.1%) patients, propiverine to 4579 (0.4%) patients, solifenacin to 10 958 (0.9%) patients and tolterodine to 1041 (0.1%) patients. Patients who were prescribed mirabegron might have also received an AM, and AM patients might have received more than one AM.

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received AMs; 64.4% of these patients had a total ACB score that was ≥80% attributable to AMs alone.

**Discussion**

This is the first nationwide study in Japan to quantify AC use in individuals aged ≥65 years who were either OAB or non-OAB patients. The present study principally showed that higher ACB scores were observed in the OAB population. Within this group of patients, the ACB scores were higher for those who received AMs versus patients who received mirabegron only. The negative clinical effects associated with increased ACB scores have been previously reported; an investigation involving 3344 community-dwelling adults found that a 1-point increase in total ACB score was associated with a 13% increased risk of cognitive impairment and a greater need for healthcare resources. A further study showed that the use of an ACB scale-listed AC was associated with a decline in Mini-Mental State Examination score of 0.33 points, and a 1 point increase on the ACB scale enhanced the risk of death by 26%. Therefore, there is a clinical need to reduce the AC burden experienced by patients. To help achieve this aim, further studies are required that accurately clarify the specific ACB scores that are associated with cognitive impairment in Japanese patients.

Although the present study population only included patients who had at least one prescription for any medication, the age distribution was very similar for the study population and the general Japanese population. Therefore, the patients involved in this study were judged to be representative of the overall situation in Japan. However, in-hospital prescriptions were not captured and therefore the AC use identified in this study would have been an underestimate of the real-world situation experienced by the elderly population.

Overall, 2.9% of the study population was included in the OAB group. This proportion is considerably lower than the prevalence of OAB in the Japanese population, which has been estimated at approximately 12%. This difference is probably due to the different nature of the investigations. The present study was a database analysis involving patients who received OAB medication, whereas the prevalence study was an epidemiological investigation where patients with urinary frequency and urgency symptoms were diagnosed with OAB.

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Fig. 1  Age distribution in the study population versus the national Japanese census. The Japanese population data were obtained from the 2015 census and subsequently age-adjusted to obtain 2016 results.

Fig. 2  Age distribution of OAB and non-OAB patients.
Other reasons for the differences between the two results include the fact that not all patients will seek medical treatment; the initial management of OAB will frequently involve conservative therapy;21 persistence with OAB medication is typically low,18 and therefore a significant proportion of patients might discontinue OAB medication and also patients might receive alternative treatment options.22

The scales utilized in the present study varied according to the selection of ACs.8,10–12 In terms of AMs available in Japan, the ACB scale lists six, the Beers criteria include five AMs with strong AC activity, whereas ADS and ARS include only oxybutynin (including the patch for ADS) and tolterodine. Owing to the differences in ACs included in each scale, it is not surprising that the results also varied considerably. For example, similar proportions of patients received an AC listed in the ACB scale (10.3%) and ADS (11.6%). However, substantially lower proportions of patients received an AC that was listed in the ARS (2.9%) and Beers criteria (1.9%). This finding was due to the lower number of ACs that are listed in the ARS and Beers criteria. Regardless of the scale used, lower proportions of patients received a prescription for AMs with strong AC activity, whereas ADS and ARS include only oxybutynin (including the patch for ADS) and tolterodine. Importantly, the present study showed that similar ACB scores were observed for OAB patients who had received mirabegron only and non-OAB patients. This finding suggests that using mirabegron as an alternative to AMs could potentially reduce AC burden and hence lower the risk of the associated negative AC effects.

When the ADS and ARS were utilized, similar results were observed for the OAB and non-OAB patients, and in the AM group and mirabegron-only group. This is predominately because the ADS and ARS only include two AMs, oxybutynin and tolterodine, neither of which are widely used in Japan.18 Indeed, the present study showed that just 3.1%, 2.1% and 3.0% of the patients in the OAB group were prescribed oxybutynin patch, oral oxybutynin or tolterodine, respectively.

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Table 4 ACB, ADS and ARS scores at index date in the total patient population and patients who received any of the drugs listed in the scales

| Parameter | Total | Non-OAB patients | OAB total | Mirabegron only | AMs‡ |
|-----------|-------|------------------|-----------|-----------------|------|
| **ACB scale** |       |                  |           |                 |      |
| Total patient population | 1 216 126 (100) | 1 180 988 (97.1) | 35 138 (2.9) | 9247 (0.8) | 25 891 (2.1) |
| Score | Mean (SD) | 0.2 (0.7) | 0.1 (0.6) | 1.5 (1.8) | 0.3 (0.7) | 1.9 (1.9) |
| Median (IQR) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) |
| Range | 0–19 | 0–19 | 0–17 | 0–9 | 0–17 |      |
| Patients who have received any ACB scale-listed AC§ | 125 426 (100) | 109 353 (87.2) | 16 073 (12.8) | 1388 (1.1) | 14 685 (11.7) |
| Score | Mean (SD) | 1.8 (1.3) | 1.6 (1.1) | 3.2 (1.3) | 1.7 (1.1) | 3.3 (1.2) |
| Median (IQR) | 1 (1–3) | 1 (1–2) | 3 (3–3) | 1 (1–2) | 3 (3–3) |      |
| Range | 1–19 | 1–19 | 1–17 | 1–9 | 1–17 |      |
| Proportion of patients, n (% of patients who received any ACB scale-listed AC) |       |                  |           |                 |      |
| Score = 1 | 76 134 (60.7) | 74 282 (67.9) | 1852 (11.5) | 887 (63.9) | 965 (6.6) |
| Score = 2 | 17 298 (13.8) | 16 881 (15.4) | 417 (2.6) | 194 (14.0) | 223 (1.5) |
| Score = 3 | 21 840 (17.4) | 12 023 (11.0) | 9817 (61.1) | 215 (15.5) | 9602 (65.4) |
| Score ≥ 4 | 5998 (4.8) | 3611 (3.3) | 2387 (14.9) | 57 (4.1) | 2330 (15.9) |
| Score ≥ 5 | 4156 (3.3) | 2556 (2.3) | 1600 (10.0) | 35 (2.5) | 1565 (10.7) |
| **ADS** |       |                  |           |                 |      |
| Total patient population | 1 216 126 (100) | 1 180 988 (97.1) | 35 138 (2.9) | 9247 (0.8) | 25 891 (2.1) |
| Score | Mean (SD) | 0.2 (0.6) | 0.2 (0.6) | 0.5 (1.0) | 0.3 (0.8) | 0.5 (1.1) |
| Median (IQR) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) |      |
| Range | 0–22 | 0–22 | 0–14 | 0–8 | 0–14 |      |
| Patients who have received any ADS-listed AC§ | 140 634 (100) | 131 959 (93.8) | 8675 (6.2) | 1763 (1.3) | 6912 (4.9) |
| Score | Mean (SD) | 1.5 (1.0) | 1.5 (1.0) | 1.8 (1.2) | 1.6 (1.0) | 1.9 (1.3) |
| Median (IQR) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–3) |      |
| Range | 1–22 | 1–22 | 1–14 | 1–8 | 1–14 |      |
| Proportion of patients, n (% of patients who received any ADS-listed AC) |       |                  |           |                 |      |
| Score = 1 | 94 676 (67.3) | 89 681 (68.0) | 4985 (35.7) | 1165 (66.1) | 3820 (55.3) |
| Score = 2 | 27 631 (19.6) | 26 094 (19.8) | 1535 (17.7) | 319 (18.1) | 1216 (17.6) |
| Score = 3 | 12 107 (8.6) | 10 733 (8.1) | 1374 (15.8) | 193 (10.9) | 1181 (17.1) |
| Score = 4 | 3763 (2.7) | 3287 (2.5) | 476 (5.5) | 54 (3.1) | 422 (6.1) |
| Score ≥ 5 | 2457 (1.7) | 2152 (1.6) | 305 (3.5) | 32 (1.8) | 273 (3.9) |
| **ARS** |       |                  |           |                 |      |
| Total patient population | 1 216 126 (100) | 1 180 988 (97.1) | 35 138 (2.9) | 9247 (0.8) | 25 891 (2.1) |
| Score | Mean (SD) | 0.1 (0.4) | 0.1 (0.4) | 0.2 (0.7) | 0.1 (0.5) | 0.2 (0.8) |
| Median (IQR) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) |      |
| Range | 0–16 | 0–16 | 0–12 | 0–7 | 0–12 |      |
| Patients who have received any ARS-listed AC§ | 35 628 (100) | 32 353 (90.8) | 3275 (9.2) | 529 (1.5) | 2746 (7.7) |
| Score | Mean (SD) | 2.0 (1.2) | 2.0 (1.2) | 2.2 (1.1) | 2.0 (1.1) | 2.2 (1.2) |
| Median (IQR) | 2 (1–3) | 2 (1–3) | 2 (1–3) | 2 (1–3) | 2 (1–3) |      |
| Range | 1–16 | 1–16 | 1–12 | 1–7 | 1–12 |      |
| Proportion of patients, n (% of patients who received any ARS-listed AC) |       |                  |           |                 |      |
| Score = 1 | 15 340 (43.1) | 14 287 (44.2) | 1053 (32.2) | 221 (41.8) | 832 (30.3) |
| Score = 2 | 9437 (26.5) | 8457 (26.1) | 980 (29.9) | 125 (23.6) | 855 (31.1) |
| Score = 3 | 8729 (24.5) | 7729 (23.9) | 1000 (30.5) | 156 (29.5) | 844 (30.7) |
| Score = 4 | 956 (2.7) | 843 (2.6) | 113 (3.5) | 12 (2.3) | 101 (3.7) |
| Score ≥ 5 | 1166 (3.3) | 1037 (3.2) | 129 (3.9) | 15 (2.8) | 114 (4.2) |

†Includes any patient who had at least one prescription record for fesoterodine, imidafenacin, mirabegron, oxybutynin, propiverine, solifenacin or tolterodine in the 1-year period before their index date. ‡Can include patients who received mirabegron before, after or concomitantly with AMs in the 1-year period before their index date. §In total, 99, 114 and 49 ACs are included in the ACB scale, ADS and ARS, respectively. Each of the drugs included in the scales had a score of 1–3 depending on the degree of AC activity (higher score = higher activity).
not shown), and therefore we believe that the lack of in-hospital data in our study had a minimal impact on the results obtained. In addition, not all ACs used in Japan are listed in these scales. Therefore, the AC burden highlighted in this study is likely to be a conservative estimate. Furthermore, daily dose and length of use were not taken into consideration, and therefore the cumulative effect of the AC drugs might have reflected AC burden more accurately. In addition, OAB patients were defined according to their medication, rather than by diagnosis, and therefore the OAB population might have been underestimated. Finally, the present study did not examine the consequences of AC use on patient outcomes, therefore we do not know if the OAB patients who were prescribed AMs had a greater risk of experiencing adverse effects.

In conclusion, OAB patients showed a higher prevalence of AC use and increased AC scores than non-OAB patients when the results were assessed using the ACB scale. This difference was largely attributable to the prescribing of AMs. The AC score was similarly low for mirabegron-only and non-OAB patients. As an alternative to AMs, the use of mirabegron as a pharmacological agent could therefore be potentially considered to reduce the AC burden experienced by patients with OAB symptoms in Japan.

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Conflict of interest

Masaki Yoshida has received consultancy, lectureship and advisory board membership fees, and editorial assistance from Astellas Pharma; consultancy and lectureship fees from Kyorin and Kissui and lectureship fees from Pfizer. Daisuke Kato, Takuya Nishimura, James Van Schuyld, Satoshi Uno and Tomomi Kimura are all employees of Astellas Pharma.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Figure S1. Study design. (a) Selecting patients and assigning an index date, (b) extracting AC use data and (c) identifying the OAB population.

Figure S2. ACB scores by age group in the (a) total patient population and (b) patients who received any ACB scale-listed AC.

Table S1. ACs according to the ACB scale, ADS, ARS and Beers criteria.