RESEARCH ARTICLE

South Korean geriatrics on Beers Criteria medications at risk of adverse drug events

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Abstract

Background
The Beers Criteria released by the American Geriatrics Society includes a list of drugs to avoid in the geriatric population and is frequently used as a safety resource in geriatric pharmacotherapy.

Objective
To evaluate the exposure of South Korean geriatrics to potentially inappropriate medications according to the Beers Criteria and the risk of adverse events from these medications.

Methods
This study included medications recommended to be avoided in patients 65 years or older regardless of concomitant drug therapy or disease. The exposure of South Korean geriatrics to each of the study medications were examined using health claims data of 2011. The number of South Korean geriatrics at risk of experiencing adverse drug events from the study medications were estimated by multiplying the number of patients exposed to the medication in 2011 and the incident rate of the event obtained from literature sources.

Results
This study examined 166,822 geriatrics for Beers Criteria medication exposure and adverse drug event risk. The most prevalent Beers Criteria medication prescribed in South Korean geriatrics >1 day was chlorpheniramine (53.9%) and the adverse drug event with the highest number of this geriatric population at risk of was amitriptyline related dry mouth (4.9%). The proportion of South Korean geriatrics on chronic Beers Criteria medications >1 day at risk of adverse drug events from these medications was significantly higher than in US geriatrics (0.005 vs. 0.001, 2-way ANOVA post hoc pairwise t-test P<0.0001).
Conclusions

In 2011, over half of South Korean geriatrics was exposed to medications recommended to be avoided in geriatrics and their adverse drug event risk warrants close monitoring of their occurrence.

Introduction

The geriatric population is at risk for drug related adverse events as they tend to have acute illnesses and are exposed to several medications [1, 2]. A previous study revealed that around half of older populations take five or more medications [2]. This population also has physiological changes attributed to aging and this may influence the pharmacokinetics and pharmacodynamics of drugs increasing the risk of drug therapy [3, 4]. There were studies showing that inappropriate medication prescribing was common in the geriatric population with rates up to 40.0% [3]. Inappropriate prescribing are those practices where the risk of adverse drug events (ADEs) from prescribing the medication is higher than the benefit [3].

This type of inappropriate prescribing is known to be associated with ADEs and hospitalization and around 12% of elderly hospital admissions are caused by adverse drug reactions [5]. ADEs are a significant problem as these increase the morbidity and mortality of patients, and in Western countries, make up 3–5% of hospital admissions and around 10% of hospitalization costs [6].

Beers et al. made criteria with drugs considered inappropriate in the elderly in 1991 [7]. This criteria lists drugs or drug classes to avoid in patients aged 65 years or more due to risk of ADEs including anticholinergic effects, physical dependence, cognitive impairment as well as those that have drug-disease interactions that worsen the disease of the geriatric patient [5]. The goal of the criteria was to improve geriatric pharmacotherapy through decreasing the exposure of the elderly to potentially inappropriate medications. These medications were seen to be commonly prescribed in hospitals and were known to decrease the health of the elderly [6, 7]. This criteria was updated in year 2003, 2012, and 2015 and is now frequently used as a safety resource in geriatric pharmacotherapy, education, and research [8].

The aim of this study was to assess the exposure of South Korean geriatrics to potentially inappropriate medications in the Beers Criteria and their risk of ADEs from the medications. This was performed to measure the extent of ADE risk that South Korean geriatric patients were exposed to and the need of safety measures to prevent the ADEs.

Materials and methods

Study population

This was a cross-sectional study including South Korean patients 65 years of age or older. The claims data of this population issued in year 2011 was used to extract the medication use of these patients (claims dataset serial number, HIRA-2011-0133). The dataset used was collected by the Health Insurance Review and Assessment service (HIRA) and includes the health claims data for 3% of the total South Korean population. This population was selected in the dataset using stratified sampling using gender and 5-year age group and was shown to be representative of 95% of the total South Korean population [9, 10]. The total number of patients in this dataset was 1,375,842 and the number of geriatrics 65 years of age or older was 166,822 (12.13%).
Study medications
The 2015 Beers Criteria medication (BCM) list was used for this study. BCMS to be avoided in patients 65 years or older were included for analysis regardless of concomitant disease or meds. The reason for this was because the health claims data did not provide sufficient information to extract patients who satisfy when to avoid the BCM considering concomitant disease or drug therapy of the patient. The number of medications in the 2015 BCM list was 115 and among these, the number of medications that were to be avoided in the elderly over 65 years of age regardless of concomitant disease or drug therapy was 82.

Population exposure to study medication
The exposure of the South Korean geriatric study patients to each of the 82 BCMS was examined by counting the number of patients who had a claim for each BCM with a prescription duration of more than one day according to the 2011 HIRA claims data. The count of patients on the med was denoted as $N_{med}$. For comparison of South Korean geriatric exposure to BCM with that of US geriatrics, the Part D Prescriber National Summary Report, Calendar Year 2014 was downloaded from the Centers for Medicare & Medicaid Services website. This data included the number of Medicare Part D beneficiaries who had claims to medications [11]. The total number of Medicare beneficiaries in 2014 was 54,095,565 and this was used to estimate the proportion of US geriatrics aged 65 years or older exposed to BCMS [12]. The number of South Koreans on a BCM for one day or less was examined separately to account for ADEs that may have occurred from or short term meds. The number of patients on BCMS for this duration were denoted as $N_{med, short}$.

The overall workflow for this study is in Fig 1.

Population at risk of ADE
A literature search in PubMed was performed to extract the incident rate of adverse drug events (ADEs) from the study meds in Asians and the US population for calculating the number of populations at risk of ADEs in South Korea and US, respectively. The literature sources preferred for analysis were those in English or translated in English, included subjects of age 65 years and older, studied subjects of Asian race (or subjects in the US if obtaining rates for US population), and were a meta-analysis. If there was no literature source for the ADE incident rate exclusively in geriatrics 65 years or over, studies including subjects aged <65 years as well as those ≥65 years if available were used. In the case were there were no meta-analyses, single studies were included. If there were multiple studies satisfying the above criteria, the more recent study was used to extract the ADE incident rate. The PubMed search term was "study drug AND elderly (or geriatric) AND side effect (or adverse event) AND Asia" for extracting ADE rates in the South Korean population and "study drug AND elderly (or geriatric) AND side effect (or adverse event)" for extracting ADE rates in the US population. Using the number of exposed South Korean geriatrics to each study med and the med-related ADE incident rates extracted from the literature, the number of geriatrics at risk of the BCM related ADE was calculated. The formula for this calculation was

$$ N_{med-ADE} = N_{med} \times \Pr(\text{ADE}|med),$$

where $med$ indicates the BCM of our study, $N_{med-ADE}$ the number of geriatrics at risk of an ADE from a $med$, $N_{med}$ the number of geriatrics exposed to a $med$, and $\Pr(\text{ADE}|med)$ the incidence rate of ADE from the $med$ in geriatrics.
Statistical analysis

The Chi-squared test was used to evaluate the difference in frequency of BCMs prescribed in South Korean geriatrics for >1 day versus ≤1 day or versus the BCM prescription frequency in US geriatrics. The proportions of South Koreans on BCMs >1 day versus ≤1 day at risk of ADEs grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) was compared using 2-way ANOVA using the factors prescription duration and MedDRA SOC, with pairwise t-test for post hoc analysis. In addition, 2-way ANOVA was used to compare the proportions of South Koreans on BCMs >1 day and US geriatrics at risk of ADEs again grouped by MedDRA SOC using two factors, the national location of the patients and the SOCs, with pairwise t-test for post hoc analysis. The South Korean geriatrics on BCMs for >1 day were used for ADE risk comparison with US geriatrics due to the data source used for US geriatrics including prescription data of chronic disease Medicare beneficiaries [11, 13]. The mean risk of ADEs grouped by SOCs were compared between South Korean geriatrics on BCMs >1 day and ≤1 day as well as South Korean geriatrics on BCMs for >1 day and US geriatrics using the two sample t-test. Each of the BCM ADEs were grouped into SOCs using the
BioPortal ontology library [14]. All statistical tests were carried out with a significance level of $P<0.05$ using R version 3.3.2 [15].

**Ethical approval**

The personal identification information of samples in the South Korean HIRA service and the CMS Part D Prescriber National Summary Report, Calendar Year 2014 was removed prior to data download for this study. Therefore, formal consent of the study sample was not required.

**Results**

**Study population**

The demographics of the study population are in Table 1. The number of the target geriatric population who were ≥65 years of age was 166,822. The mean (standard deviation, SD) age of the study population was 73.1 (6.5) years and 98,714 (59.2%) were women. The mean (SD) number of medications prescribed per patient was 30 (20.1). The number of people prescribed at least one prescription for a BCM inappropriate in the elderly of 65 years of age or older regardless of concomitant disease or drug was 128,749 (77.2%). The number of people prescribed two or more of such prescriptions was 107,430 (64.4%) and three or more was 91,427 (54.8%).

**Population exposure to study medications**

The prevalence of South Koreans on BCMs is shown in Table 2. The meds were sorted by prevalence of prescribing BCMs >1 day in South Korean geriatrics. This prevalence was compared with that of US geriatrics. The most prevalent BCM prescribed in South Korean geriatrics for >1 day was chlorpheniramine (53.9%), a first-generation antihistamine, followed by the benzodiazepines, diazepam (23.7%), and alprazolam (13.0%). The most prevalent BCM prescribed in South Korean geriatrics for ≤1 day was chlorpheniramine (21.9%), a first-generation antihistamine, followed by a benzodiazepine, diazepam (4.6%), and ketorolac, a nonsteroidal anti-inflammatory drug (3.4%). In US geriatrics, alprazolam (4.7%) was most prevalently prescribed, followed by lorazepam (4.0%), and zolpidem (3.9%). Out of the 82 BCMs, 35 were prescribed at least once in South Korean geriatrics for >1 day and 33 prescribed for ≤1 day while 66 were prescribed in US geriatrics. Comparing prescription rates between the South Korean geriatrics on >1 day or ≤1 day of BCMs, 31 meds were prescribed at a significantly higher rate in South Korean geriatrics prescribed BCMs >1 day, 2 meds at a significantly higher rate in geriatrics prescribed BCMs ≤1 day, and 2 meds were unknown as the prescribing frequency was not available for at least one of the population groups. Comparing

| Variable                        | Total (n = 166,822) |
|---------------------------------|---------------------|
| Age, y (mean±SD)                | 73.1±6.5            |
| Female gender, n (%)            | 98,714 (59.2)       |
| Medications per person, n (mean±SD) | 30±20.1            |
| Population prescribed at least X BCM prescriptions, n (%) | 128,749 (77.2) |
| 1                               | 107,430 (64.4)      |
| 3                               | 91,427 (54.8)       |

SD standard deviation, BCM Beers Criteria medication.

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Table 2. Exposure of South Korean and US geriatrics to Beers Criteria medications not recommended in geriatrics regardless of concomitant disease or drugs.

| BCM (n = 82) | No. South Korean sample population (% total sample no. 166,822) | Minimum no. US patients on Medicare Part D on BCM in 2014 (% total no. 54,095,565) |
|-------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|
|             | On BCM for >1 day                                            | On BCM for ≤1 day                                                               |
| Chlorpheniramine† | 89,923 (53.9)                                                   | 36,474 (21.9)                                                                  | NA |
| Diazepam †   | 39,467 (23.7)                                                   | 7,659 (4.6)                                                                     | 1,077,677 (2.0) |
| Alprazolam † | 21,705 (13.0)                                                   | 1,605 (1.0)                                                                     | 2,544,993 (4.7) |
| Dimenhydrinate† | 19,419 (11.6)                                                    | 1,990 (1.2)                                                                     | 27 (0.0) |
| Hydroxyzine † | 17,719 (10.6)                                                   | 1,406 (0.8)                                                                     | 478,644 (0.9) |
| Zolpidem †   | 14,278 (8.6)                                                    | 1,856 (1.1)                                                                     | 2,134,655 (3.9) |
| Orphenadrine † | 11,271 (6.8)                                                    | 571 (0.3)                                                                       | 48,876 (0.1) |
| Amitriptyline † | 10,913 (6.5)                                                    | 551 (0.3)                                                                       | 805,092 (1.5) |
| Methocarbamol † | 6,747 (4.0)                                                     | 1,565 (0.9)                                                                     | 376,405 (0.7) |
| Lorazepam †  | 6,375 (3.8)                                                     | 2,237 (1.3)                                                                     | 2,139,238 (4.0) |
| Triazolam †  | 4,625 (2.8)                                                     | 497 (0.3)                                                                        | 45,044 (0.1) |
| Nifedipine † | 3,779 (2.3)                                                     | 1,255 (0.8)                                                                     | 528,204 (1.0) |
| Clonazepam † | 3,471 (2.1)                                                     | 204 (0.1)                                                                        | 1,488,470 (2.8) |
| Ketorolac †  | 1,878 (1.1)                                                     | 5,594 (3.4)                                                                     | 543,586 (1.0) |
| Megestrol †  | 1,775 (1.1)                                                     | 327 (0.2)                                                                        | 263,577 (0.5) |
| Paroxetine † | 1,343 (0.8)                                                     | 39 (0.0)                                                                         | 852,918 (1.6) |
| Cyclobenzaprine † | 1,335 (0.8)                                                   | 67 (0.0)                                                                         | 1,296,038 (2.4) |
| Imipramine † | 1,307 (0.8)                                                     | 51 (0.0)                                                                         | 67,450 (0.1) |
| Phenobarbital † | 889 (0.5)                                                      | 105 (0.1)                                                                        | 77,327 (0.1) |
| Clemastine † | 771 (0.5)                                                        | 83 (0.0)                                                                         | 3,457 (0.0) |
| Chlordiazepoxide † | 743 (0.4)                                                    | 63 (0.0)                                                                         | 30,182 (0.1) |
| Benztropine (oral) † | 743 (0.4)                                                    | 51 (0.0)                                                                         | 306,664 (0.6) |
| Ticlopidine † | 713 (0.4)                                                        | 32 (0.0)                                                                         | 3,375 (0.0) |
| Flurazepam † | 632 (0.4)                                                        | 120 (0.1)                                                                        | 18,289 (0.0) |
| Clidinium-Chlordiazepoxide † | 418 (0.3)                                                      | 27 (0.0)                                                                         | NA |
| Trihexyphenidyl † | 398 (0.2)                                                      | 22 (0.0)                                                                         | 47,580 (0.1) |
| Clorazepate † | 365 (0.2)                                                        | 14 (0.0)                                                                         | 70,224 (0.1) |
| Triprolidine † | 301 (0.2)                                                        | 23 (0.0)                                                                         | NA |
| Doxylamine † | 212 (0.1)                                                        | 17 (0.0)                                                                         | NA |
| Atropine (excludes ophthalmic) † | 182 (0.1)                                                      | 3,542 (2.1)                                                                     | 368,693 (0.7) |
| Clomipramine † | 86 (0.1)                                                         | 1 (0.0)                                                                           | 17,988 (0.0) |
| Amoxapine † | 20 (0.0)                                                         | 1 (0.0)                                                                           | 2,099 (0.0) |
| Pentazocine † | 10 (0.0)                                                         | 2 (0.0)                                                                           | 5,483 (0.0) |
| Dipyridamole (oral, short-acting) † | 4 (0.0)                                                      | 0 (0.0)                                                                            | 135,045 (0.2) |
| Pentobarbital | 1 (0.0)                                                          | 0 (0.0)                                                                           | NA |
| Amobarbital | 0 (0)                                                             | 0 (0.0)                                                                           | NA |
| Brompheniramine | 0 (0)                                                              | 0 (0.0)                                                                           | NA |
| Dextromethorphan | 0 (0)                                                                | 0 (0.0)                                                                           | NA |
| Dextropheniramine | 0 (0)                                                                | 0 (0.0)                                                                           | NA |
| Guanabenz | 0 (0)                                                            | 0 (0.0)                                                                           | NA |
| Isoxsuprine | 0 (0)                                                            | 0 (0.0)                                                                           | NA |
| Mepobarbital | 0 (0)                                                            | 0 (0.0)                                                                           | NA |
| Mineral oil, given orally | 0 (0)                                                             | 0 (0.0)                                                                           | NA |

(Continued)
| BCM (n = 82) | No. South Korean sample population (% total sample no. 166,822) | Minimum no. US patients on Medicare Part D on BCM in 2014 (% total no. 54,095,565) |
|-------------|------------------------------------------------------------|----------------------------------------------------------------------------------|
|             | On BCM for > 1 day | On BCM for ≤ 1 day | NA                                      |
| Quazepam    | 0 (0)             | 0 (0)               | NA                                     |
| Meclizine*  | 0 (0)             | 0 (0)               | 1,069,961 (2.0)                        |
| Temazepam*  | 0 (0)             | 0 (0)               | 714,706 (1.3)                          |
| Promethazine* | 0 (0)          | 0 (0)               | 695,648 (1.3)                          |
| Dicyclomine* | 0 (0)             | 0 (0)               | 535,628 (1.0)                          |
| Glyburide*  | 0 (0)             | 0 (0)               | 346,562 (0.6)                          |
| Nortriptyline* | 0 (0)           | 0 (0)               | 324,594 (0.6)                          |
| Carisoprodol* | 0 (0)           | 0 (0)               | 287,184 (0.5)                          |
| Indomethacin* | 0 (0)            | 0 (0)               | 193,060 (0.4)                          |
| Eszopiclone* | 0 (0)             | 0 (0)               | 113,047 (0.2)                          |
| Scopolamine* | 0 (0)             | 0 (0)               | 101,220 (0.2)                          |
| Metaxalone* | 0 (0)             | 0 (0)               | 80,983 (0.1)                           |
| Zaleplon*   | 0 (0)             | 0 (0)               | 72,811 (0.1)                           |
| Cyproheptadine* | 0 (0)       | 0 (0)               | 63,651 (0.1)                           |
| Desiccated thyroid* | 0 (0)    | 0 (0)               | 51,167 (0.1)                           |
| Chloroxazine* | 0 (0)            | 0 (0)               | 30,151 (0.1)                           |
| Guanfacine* | 0 (0)             | 0 (0)               | 29,973 (0.1)                           |
| Butalbital* | 0 (0)             | 0 (0)               | 29,554 (0.1)                           |
| Hyoscyamine* | 0 (0)             | 0 (0)               | 24,939 (0.0)                           |
| Oxazepam*   | 0 (0)             | 0 (0)               | 21,717 (0.0)                           |
| Desipramine* | 0 (0)             | 0 (0)               | 20,551 (0.0)                           |
| Estazolam*  | 0 (0)             | 0 (0)               | 16,951 (0.0)                           |
| Diphenhydramine (oral)* | 0 (0)     | 0 (0)               | 16,007 (0.0)                           |
| Methyldopa* | 0 (0)             | 0 (0)               | 13,878 (0.0)                           |
| Meperidine* | 0 (0)             | 0 (0)               | 13,199 (0.0)                           |
| Disopyramide* | 0 (0)             | 0 (0)               | 4,729 (0.0)                            |
| Carboxamine* | 0 (0)             | 0 (0)               | 4,192 (0.0)                            |
| Meprobamate* | 0 (0)             | 0 (0)               | 3,595 (0.0)                            |
| Protriptyline* | 0 (0)            | 0 (0)               | 2,340 (0.0)                            |
| Propantheline | 0 (0)             | 0 (0)               | 1,058 (0.0)                            |
| Chlorpropamide | 0 (0)             | 0 (0)               | 634 (0.0)                              |
| Belladonna alkaloids | 0 (0)        | 0 (0)               | 565 (0.0)                              |
| Ergoloid mesylates | 0 (0)          | 0 (0)               | 500 (0.0)                              |
| Trimipramine | 0 (0)             | 0 (0)               | 323 (0.0)                              |
| Butobarbital | 0 (0)             | 0 (0)               | 283 (0.0)                              |
| Secobarbital | 0 (0)             | 0 (0)               | 61 (0.0)                               |
| Reserpine   | 0 (0)             | 0 (0)               | 11 (0.0)                               |
| Doxepin >6 mg/d | NA               | NA                  | NA                                     |
| Insulin, sliding scale | NA           | NA                  | NA                                     |

NA not available, BCM Beers Criteria medication

* Med prescribing frequency is significantly different between South Korean geriatrics on BCM >1 day and US geriatrics according to Chi-square test (P<0.05).
† Med prescribing frequency is significantly different between South Korean geriatrics on BCM >1 day and ≤1 day according to Chi-square test (P<0.05).

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prescription rates between the two countries, 22 meds were prescribed at a significantly higher rate in South Korean geriatrics prescribed BCMs >1 day, 35 meds at a significantly higher rate in US geriatrics, and 16 were unknown as the prescribing frequency was not available in the geriatric population of one or either countries.

Population at risk of ADE from study medications

We estimated the number as well as proportion of geriatrics at risk of ADEs using the incidence rate of ADEs from BCMs in the literature and the exposure of the geriatrics to the BCMs. The number of study BCMs with ADE rates available in the literature was 16 out of 82 for Asians and 44 out of 82 for the US population. The ADE incidence rates and the number of South Korean patients at risk of the ADEs calculated using Eq (1) are in Table 3 and of the US patients in Table 4. The BCMs and ADEs in Tables 3 and 4 were sorted by the number of geriatrics at risk of the ADE. Specifically, for Table 3 the BCMs and ADEs were sorted by the number of South Korean geriatrics on BCMs >1 day at risk of ADEs. The BCM-ADE pair with the highest number of South Koreans on BCMs >1 day at risk of its occurrence was amitriptyline related dry mouth (n = 8,185, 4.9%) followed by amitriptyline related sleepiness (n = 7,508, 4.5%). In addition, dizziness and constipation from amitriptyline and rash/urticaria/pruritus, dizziness/somnolence, dyspnea, and nausea/vomiting from diazepam were among the ten most frequent ADEs that were predicted occur in this South Korean geriatric population on BCMs for for more than 1 day. The BCM-ADE pair with the highest number of South Koreans on BCMs ≤1 day at risk of its occurrence was diazepam related rash/urticaria/pruritus (n = 1,081, 0.6%). This was followed by lorazepam related dizziness/somnolence (n = 1,040, 0.6%), diazepam related dizziness/somnolence (n = 1,021, 0.6%), and diazepam related dyspnea (n = 873, 0.5%). The ADE from BCMs that the highest number of US geriatrics was at risk of was cyclobenzaprine related somnolence (n = 1,296,038, 2.4%). This was followed by cyclobenzaprine related dry mouth (n = 751,702, 1.4%), dicyclomine related dizziness/blurring of vision/dry mouth (n = 368,512, 0.7%), cyclobenzaprine related headache (n = 349,930, 0.6%), and lorazepam related restlessness (n = 320,886, 0.6%).

The mean proportion of South Korean on BCMs for >1 day versus ≤1 day at risk of ADEs grouped according to MedDRA SOC is in Fig 2. The mean proportion of South Korean on BCMs for >1 day and US geriatrics at risk of ADEs grouped according to MedDRA SOC is in Fig 3. Out of the total 26 SOCs in MedDRA, the BCM ADEs which South Korean geriatrics (regardless of duration of BCM prescription) may be at risk from corresponded to 15 single SOCs and 4 multiple SOC combinations. The 15 single SOCs were “cardiac disorders”, “eye disorders”, “gastrointestinal disorders”, “general disorders and administration site conditions”, “hepatobiliary disorders”, “injury, poisoning and procedural complications”, “investigations”, “metabolism and nutrition disorders”, “Musculoskeletal and connective tissue disorders”, “nervous system disorders”, “psychiatric disorders”, “renal and urinary disorders”, “reproductive system and breast disorders”, “skin and subcutaneous tissue disorders”, and “vascular disorders”. Seven BCM-ADE pairs included ADEs that were a composite of multiple ADEs that were grouped into more than one SOC.

The BCM ADEs which US geriatrics were at risk from corresponded to 17 single SOCs and 8 multiple SOC combinations. The single SOCs were “blood and lymphatic system disorders”, “cardiac disorders”, “eye disorders”, “gastrointestinal disorders”, “general disorders and administration site conditions”, “injury, poisoning and procedural complications”, “investigations”, “metabolism and nutrition disorders”, “Musculoskeletal and connective tissue disorders”, “nervous system disorders”, “psychiatric disorders”, “renal and urinary disorders”, “reproductive system and breast disorders”, “respiratory, thoracic and mediastinal disorders”, “skin and subcutaneous tissue disorders”, and “vascular disorders”. Seven BCM-ADE pairs included ADEs that were a composite of multiple ADEs that were grouped into more than one SOC.
Table 3. Rate and number of the geriatric population in South Korea at risk of adverse drug events from Beers Criteria medications (80 BCM-ADE pairs).

| BCM (n = 16) | ADE (n = 56) | Incidence of ADE in Asians (%) | No. South Korean geriatrics with risk of ADE (total no. 166,822) | SOC of ADE (per MedDRA ontology) | Reference of ADE incidence |
|--------------|--------------|-------------------------------|---------------------------------------------------------------|----------------------------------|---------------------------|
|              |              |                               | on BCM for >1 day | on BCM for ≤1 day |                                      |                          |
| Amitriptyline| Dry mouth    | 75                            | 8,185             | 413               | Gastrointestinal disorders          | [16]                     |
| Amitriptyline| Sleepiness   | 68.8                          | 7,508             | 379               | Psychiatric disorders               | [16]                     |
| Diazepam     | Rash/urticaria/pruritus | 14.1                     | 5,569             | 1,081             | Skin and subcutaneous tissue disorders/immune system disorders/skin and subcutaneous tissue disorders | [17]                     |
| Diazepam     | Dizziness/somnolence | 13.3                     | 5,261             | 1,021             | Nervous system disorders/psychiatric disorders | [17]                     |
| Dimenhydrinate| Weakness   | 26                            | 5,049             | 517               | General disorders and administration site conditions | [18]                     |
| Diazepam     | Dyspnea      | 11.4                          | 4,499             | 873               | Cardiac disorders                   | [17]                     |
| Lorazepam    | Dizziness/somnolence | 46.5                     | 2,964             | 1,040             | Nervous system disorders/psychiatric disorders | [17]                     |
| Amitriptyline| Dizziness    | 25                            | 2,728             | 138               | Nervous system disorders            | [16]                     |
| Diazepam     | Nausea/vomiting | 6.3                       | 2,467             | 479               | Gastrointestinal disorders          | [17]                     |
| Amitriptyline| Constipation  | 18.8                          | 2,052             | 104               | Gastrointestinal disorders          | [16]                     |
| Lorazepam    | Hypotension  | 27.1                          | 1,728             | 606               | Vascular disorders                  | [17]                     |
| Lorazepam    | Dyspnea      | 26.3                          | 1,678             | 589               | Cardiac disorders                   | [17]                     |
| Dimenhydrinate| Dizziness   | 8                             | 1,554             | 159               | Nervous system disorders            | [18]                     |
| Lorazepam    | Rash/urticaria/pruritus | 22.6                     | 1,439             | 505               | Skin and subcutaneous tissue disorders/skin and subcutaneous tissue disorders | [17]                     |
| Clonazepam   | Drowsiness   | 36.8                          | 1,277             | 75                | Psychiatric disorders               | [19]                     |
| Lorazepam    | Nausea/vomiting | 14.2                     | 902               | 317               | Gastrointestinal disorders          | [17]                     |
| Amitriptyline| Palpitations | 6.3                           | 688               | 35                | Cardiac disorders                   | [16]                     |
| Amitriptyline| Malaise      | 6.3                           | 688               | 35                | General disorders and administration site conditions | [16]                     |
| Diazepam     | Hypotension  | 1.4                           | 560               | 109               | Vascular disorders                  | [17]                     |
| Dimenhydrinate| Drowsiness | 2                             | 388               | 40                | Psychiatric disorders               | [18]                     |
| Zolpidem     | Impaired balance/falls | 1.8                        | 257               | 33                | Nervous system disorders/injury, poisoning and procedural complications | [20]                     |
| Nifedipine   | Mild headache | 6.7                        | 253               | 84                | Nervous system disorders            | [21]                     |
| Zolpidem     | Morning drowsiness | 1.3                       | 186               | 24                | Psychiatric disorders               | [20]                     |
| Clonazepam   | Dizziness    | 5.3                           | 184               | 11                | Nervous system disorders            | [19]                     |
| Phenobarbital| Weight gain  | 14.7                          | 131               | 15                | Investigations                      | [22]                     |
| Paroxetine   | Loss of appetite | 8.7                        | 117               | 3                 | Metabolism and nutrition disorders  | [23]                     |
| Paroxetine   | Nausea and vomiting | 8.7                       | 117               | 3                 | Gastrointestinal disorders          | [23]                     |
| Zolpidem     | Amnesia      | 0.8                           | 114               | 15                | Nervous system disorders            | [20]                     |
| Zolpidem     | Agitation/confusion/somnambulism | 0.7                     | 100               | 13                | Nervous system disorders/psychiatric disorders/nervous system disorders | [20]                     |
| Phenobarbital| Nausea, vomiting | 10.3                     | 92                | 11                | Gastrointestinal disorders          | [22]                     |
| Paroxetine   | Dry mouth    | 6.5                           | 87                | 3                 | Gastrointestinal disorders          | [23]                     |
| Paroxetine   | Sweating     | 6.5                           | 87                | 3                 | General disorders and administration site conditions | [23]                     |
| Zolpidem     | Twilight state | 0.5                        | 71                | 9                 | Nervous system disorders            | [23]                     |
| Paroxetine   | Dizziness    | 4.3                           | 58                | 2                 | Nervous system disorders            | [20]                     |
| Zolpidem     | Dizziness    | 0.4                           | 57                | 7                 | Nervous system disorders            | [20]                     |
| Zolpidem     | Dependence   | 0.4                           | 57                | 7                 | Psychiatric disorders               | [20]                     |
| Paroxetine   | Weight gain  | 2.2                           | 30                | 1                 | Investigations                      | [23]                     |

(Continued)
Table 3. (Continued)

| BCM (n = 16) | ADE (n = 56) | Incidence of ADE in Asians (%) | No. South Korean geriatrics with risk of ADE (total no. 166,822) | SOC of ADE (per MedDRA ontology) | Reference of ADE incidence |
|-------------|-------------|-------------------------------|---------------------------------------------------------------|---------------------------------|-----------------------------|
|             |             |                               | No. South Korean geriatrics with risk of ADE for >1 day | No. South Korean geriatrics with risk of ADE for ≤1 day |
|             |             |                               | on BCM | on BCM |                             |                                   |
| Paroxetine  | Blurred vision | 2.2                          | 30     | 1     | Nervous system disorders    | [23]                             |
| Zolpidem    | Headache    | 0.2                          | 29     | 4     | Nervous system disorders    | [20]                             |
| Zolpidem    | Nightmare   | 0.2                          | 29     | 4     | Psychiatric disorders       | [20]                             |
| Zolpidem    | Malaise     | 0.2                          | 29     | 4     | General disorders and administration site conditions | [20]                             |
| Zolpidem    | Weakness    | 0.2                          | 29     | 4     | General disorders and administration site conditions | [20]                             |
| Ticlopidine | Cerebral infarction | 2.5                       | 18     | 1     | Nervous system disorders    | [24]                             |
| Zolpidem    | Dysgeusia   | 0.1                          | 14     | 2     | Nervous system disorders    | [20]                             |
| Phenobarbital | Hepatitis  | 1.5                          | 13     | 2     | Hepatobiliary disorders    | [22]                             |
| Ticlopidine | Transient ischemic attack | 0.5                   | 4      | 0     | Vascular disorders         | [24]                             |
| Ticlopidine | Angina pectoris | 0.4                       | 3      | 0     | Coronary artery disorders  | [24]                             |
| Ticlopidine | Peripheral arterial occlusion | 0.1                  | 1      | 0     | Vascular disorders         | [24]                             |
| Estazolam   | Falls       | 16.1                         | 0      | 0     | Injury, poisoning and procedural complications | [25]                             |
| Eszopiclone | Dysgeusia   | 16.2                         | 0      | 0     | Nervous system disorders    | [26]                             |
| Eszopiclone | Somnolence  | 5.9                          | 0      | 0     | Psychiatric disorders       | [26]                             |
| Eszopiclone | Dizziness   | 2.9                          | 0      | 0     | Nervous system disorders    | [26]                             |
| Eszopiclone | Dermatitis contact | 2.9                  | 0      | 0     | Injury, poisoning and procedural complications | [26]                             |
| Eszopiclone | Feeling abnormal | 4.3                       | 0      | 0     | General disorders and administration site conditions | [26]                             |
| Isoxsupr in | Decreased arterial pressure | 22.2                   | 0      | 0     | Investigations              | [27]                             |
| Isoxsupr in | Headache    | 19.4                         | 0      | 0     | Nervous system disorders    | [27]                             |
| Isoxsupr in | Trembling   | 8.3                          | 0      | 0     | Nervous system disorders    | [27]                             |
| Isoxsupr in | Nervousness | 11.1                         | 0      | 0     | Psychiatric disorders       | [27]                             |
| Isoxsupr in | Gastrointestinal problems | 25.0                 | 0      | 0     | Gastrointestinal disorders  | [27]                             |
| Isoxsupr in | Skin rash   | 11.1                         | 0      | 0     | Skin and subcutaneous tissue disorders | [27]                             |
| Isoxsupr in | Facial redness | 11.1                    | 0      | 0     | Skin and subcutaneous tissue disorders | [27]                             |
| Isoxsupr in | Tachycardia | 5.6                          | 0      | 0     | Cardiac disorders          | [27]                             |
| Meperidine  | Shivering   | 9.1                          | 0      | 0     | Musculoskeletal and connective tissue disorders | [28]                             |
| Meperidine  | Nausea      | 21.2                         | 0      | 0     | Gastrointestinal disorders  | [28]                             |
| Meperidine  | Pruritus    | 3.0                          | 0      | 0     | Skin and subcutaneous tissue disorders | [28]                             |
| Nortriptyline | Dysarthria | 36.8                         | 0      | 0     | Psychiatric disorders       | [29]                             |
| Nortriptyline | Orthostatic dizziness | 42.1                | 0      | 0     | Nervous system disorders    | [29]                             |
| Nortriptyline | Sleepiness/sedation | 47.4                | 0      | 0     | Psychiatric disorders/nervous system disorders | [29]                             |
| Nortriptyline | Accommodation disturbance | 36.8           | 0      | 0     | Eye disorders              | [29]                             |
| Nortriptyline | Reduced salivation | 60.5                    | 0      | 0     | Gastrointestinal disorders  | [29]                             |
| Nortriptyline | Diarrhea   | 23.7                         | 0      | 0     | Gastrointestinal disorders  | [29]                             |
| Nortriptyline | Constipation | 50.0                     | 0      | 0     | Gastrointestinal disorders  | [29]                             |
| Nortriptyline | Micturition disturbance | 39.5               | 0      | 0     | Renal and urinary disorders | [29]                             |
| Nortriptyline | Nausea/vomiting | 15.8                   | 0      | 0     | Gastrointestinal disorders  | [29]                             |
| Nortriptyline | Weight gain | 39.5                         | 0      | 0     | Investigations              | [29]                             |

(Continued)
skin and subcutaneous tissue disorders”, “surgical and medical procedures”, and “vascular disorders”. Eight BCM-ADE pairs included ADEs that were a composite of multiple ADEs that were grouped into more than one SOC.

The SOC with the BCM related ADE which most South Korean geriatrics on BCMs for >1 day were at risk of was the “composite of multiple SOCs” group (mean proportion = 0.0134). The reason for this was because the third and fourth most common ADEs in this population which were rash/urticaria/pruritus and dizziness/somnolence from diazepam corresponded to multiple adverse events. Excluding the “composite of multiple SOCs” group, this geriatric population was most at risk of ADEs in the “cardiac disorders” SOC (mean proportion = 0.0082). This was followed by the “gastrointestinal disorders” SOC (mean proportion = 0.0064) and “general disorders and administration site conditions” SOC (mean proportion = 0.0059). The SOC with the BCM related ADE which most South Korean geriatrics on BCMs for ≤1 day were at risk of was the “composite of multiple SOCs” group (mean proportion = 0.0032). The reason for this was because the first and second most common ADE in this population which were rash/urticaria/pruritus from diazepam and dizziness/somnolence from lorazepam corresponded to multiple adverse events. Excluding the “composite of multiple SOCs” group, this population was most at risk of ADEs in the “cardiac disorders” SOC (mean proportion = 0.0018) followed by the “vascular disorders” SOC (mean proportion = 0.0011) and “gastrointestinal disorders” SOC (mean proportion = 0.0006). The SOC with the BCM related ADE which most US geriatrics were at risk of was “psychiatric disorders” (mean proportion = 0.0013). This was because the most common ADE in US geriatrics, cyclobenzaprine related somnolence, corresponded to the SOC “psychiatric disorders”. This was followed by the “composite of multiple SOCs” (mean proportion = 0.0011) and the “gastrointestinal disorders” SOC (mean proportion = 0.0010) and. The SOC including the most BCM-ADE pairs was “nervous system disorders” for both South Koreans on BCMs for more than 1 day and US geriatric cases at 18 pairs and 33 pairs, respectively.

Using the 16 SOCs where South Koreans had ADE rates available, the proportion of South Korean geriatrics prescribed a BCM >1 day versus ≤1 day were compared. The mean overall proportion of South Korean geriatrics on BCMs >1 day at risk of experiencing an ADE of 0.005 was significantly higher than that of South Korean geriatrics on BCMs ≤1 day of 0.001 (2-way ANOVA post hoc pairwise t-test, P = 0.001). Although not significant, South Korean geriatrics on BCMs >1 day were shown to have a higher mean risk of ADEs grouped into 10 SOCs “cardiac disorders”, gastrointestinal disorders”, “general disorders and administration site conditions”, “hepatobiliary disorders”, “investigations”, “metabolism and nutrition

### Table 3. (Continued)

| BCM (n = 16) | ADE (n = 56) | Incidence of ADE in Asians (%) | No. South Korean geriatrics with risk of ADE (total no. 166,822) | SOC of ADE (per MedDRA ontology) | Reference of ADE incidence |
|--------------|--------------|-------------------------------|---------------------------------------------------------------|-----------------------------------|-----------------------------|
| Nortriptyline | Weight loss  | 10.5                          | 0                                                             | Investigations                    | [29]                         |
| Nortriptyline | Diminished sexual desire | 36.8 | 0 | 0 | Reproductive system and breast disorders | [29] |
| Doxepin >6 mg/d | Somnolence  | 14.2                          | NA                                                            | NA                                | NA                          |
| Doxepin >6 mg/d | Nervousness  | 2.9                           | NA                                                            | NA                                | NA                          |

NA not available, BCM Beers Criteria medication.

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Table 4. Rate and number of the geriatric population in the US at risk of adverse drug events from Beers Criteria medications (159 BCM-ADE pairs).

| BCM (n = 44) | ADE (n = 104) | Incidence of ADE in US (%) | No. US geriatrics with risk of ADE (total no. 54,095,565) | SOC of ADE (per MedDRA ontology) | Reference of ADE incidence |
|--------------|---------------|----------------------------|----------------------------------------------------------|---------------------------------|-----------------------------|
| Cyclobenzaprine | Somnolence     | 100                        | 1,296,038                                                | Psychiatric disorders           | [31]                        |
| Cyclobenzaprine | Dry mouth      | 58                         | 751,702                                                  | Gastrointestinal disorders      | [31]                        |
| Dicyclomine    | Dizziness/blurring of vision/dry mouth | 68.8                      | 368,512                                                   | Nervous system disorders/nervous system disorders/gastrointestinal disorders | [32]                        |
| Cyclobenzaprine | Headache       | 27                         | 349,930                                                   | Nervous system disorders        | [31]                        |
| Lorazepam      | restlessness   | 15                         | 320,886                                                   | Nervous system disorders        | [33]                        |
| Atropine (excludes ophthalmic) | Fatigue | 84.6                       | 311,914                                                   | General disorders and administration site conditions | [34]                        |
| Cyclobenzaprine | Dizziness      | 19                         | 246,247                                                   | Nervous system disorders        | [31]                        |
| Atropine (excludes ophthalmic) | Dyspnea | 53.8                       | 198,357                                                   | Cardiac disorders               | [34]                        |
| Benztropine (oral) | Dry mouth | 63                         | 193,198                                                   | Gastrointestinal disorders      | [35]                        |
| Cyclobenzaprine | Blurred vision | 12                        | 155,525                                                   | Nervous system disorders        | [31]                        |
| Benztropine (oral) | Blurred vision | 42                        | 128,799                                                   | Nervous system disorders        | [35]                        |
| Atropine (excludes ophthalmic) | Dry mouth | 34.6                       | 127,568                                                   | Gastrointestinal disorders      | [34]                        |
| Clonazepam     | Fatigue        | 8                          | 119,078                                                   | General disorders and administration site conditions | [36]                        |
| Cyclobenzaprine | Dry throat     | 8                          | 103,683                                                   | Gastrointestinal disorders      | [31]                        |
| Cyclobenzaprine | Nausea         | 8                          | 103,683                                                   | Gastrointestinal disorders      | [31]                        |
| Paroxetine     | Hyponatremia   | 12                         | 102,350                                                   | Metabolism and nutrition disorders | [37]                      |
| Clonazepam     | Hypotonia      | 6                          | 89,308                                                    | Musculoskeletal and connective tissue disorders | [36]                        |
| Benztropine (oral) | Decreased motor activity | 26                       | 79,733                                                    | Nervous system disorders        | [35]                        |
| Benztropine (oral) | Dizziness      | 26                         | 79,733                                                    | Nervous system disorders        | [35]                        |
| Benztropine (oral) | Drowsiness     | 24                         | 73,999                                                    | Psychiatric disorders           | [35]                        |
| Benztropine (oral) | Anorexia       | 20                         | 61,333                                                    | Metabolism and nutrition disorders | [35]                      |
| Imipramine     | Constipation   | 65                         | 43,843                                                    | Gastrointestinal disorders      | [38]                        |
| Atropine (excludes ophthalmic) | Angina | 11.5                       | 42,400                                                    | Cardiac disorders               | [34]                        |
| Benztropine (oral) | Nausea         | 13                         | 39,866                                                    | Gastrointestinal disorders      | [35]                        |
| Cyproheptadine | Sedation       | 62.5                       | 39,782                                                    | Nervous system disorders        | [39]                        |
| Nifedipine     | Edema          | 7.5                        | 39,615                                                    | Metabolism and nutrition disorders | [40]                      |
| Triazolam      | Next-day memory impairment/amnesia | 83.3              | 37,522                                                    | Nervous system disorders        | [41]                        |
| Imipramine     | Dry mouth      | 55                         | 37,098                                                    | Gastrointestinal disorders      | [38]                        |
| Zolpidem       | Nonvertebral fracture | 1.7                      | 36,289                                                    | Injury, poisoning and procedural complications | [42]                        |
| Cyproheptadine | Dry mouth      | 56.3                       | 35,836                                                    | Gastrointestinal disorders      | [39]                        |
| Nortriptyline  | Sinus tachycardia | 10                      | 32,459                                                    | Cardiac disorders               | [43]                        |
| Atropine (excludes ophthalmic) | Palpitations | 7.7                        | 28,389                                                    | Cardiac disorders               | [34]                        |
| Imipramine     | Tremor         | 40                         | 26,980                                                    | Nervous system disorders        | [38]                        |
| Imipramine     | Drowsiness     | 40                         | 26,980                                                    | Psychiatric disorders           | [38]                        |
| Diazepam       | Headache       | 2.5                        | 26,942                                                    | Nervous system disorders        | [44]                        |
| Diazepam       | Agitation      | 2.5                        | 26,942                                                    | Psychiatric disorders           | [44]                        |
| Imipramine     | Sweating       | 35                         | 23,608                                                    | General disorders and administration site conditions | [38]                        |

(Continued)
Table 4. (Continued)

| BCM (n = 44) | ADE (n = 104) | Incidence of ADE in US (%) | No. US geriatrics with risk of ADE (total no. 54,095,565) | SOC of ADE (per MedDRA ontology) | Reference of ADE incidence |
|--------------|---------------|---------------------------|-----------------------------------------------------------|---------------------------------|-----------------------------|
| Imipramine   | Vertigo       | 35                        | 23,608                                                     | Nervous system disorders        | [38]                        |
| Imipramine   | Headache      | 35                        | 23,608                                                     | Nervous system disorders        | [38]                        |
| Imipramine   | Cardiovascular symptoms | 35          | 23,608                                                     | Cardiac disorders               | [38]                        |
| Zolpidem     | Hip fracture  | 1.1                       | 23,481                                                     | Injury, poisoning and procedural complications | [42]                        |
| Benztropine (oral) | Sweating | 7                         | 21,466                                                     | General disorders and administration site conditions | [35]                        |
| Imipramine   | Disturbance of accommodation | 50           | 20,235                                                     | Eye disorders                   | [38]                        |
| Ketorolac    | Tachycardia   | 3.5                       | 19,026                                                     | Cardiac disorders               | [45]                        |
| Desipramine  | Tiredness     | 89.5                      | 18,393                                                     | General disorders and administration site conditions | [46]                        |
| Clonazepam   | Drowsiness     | 26                        | 18,258                                                     | Psychiatric disorders           | [47]                        |
| Nifedipine   | Headache      | 3.4                       | 17,959                                                     | Nervous system disorders        | [40]                        |
| Desipramine  | Dry mouth     | 84.2                      | 17,304                                                     | Gastrointestinal disorders      | [46]                        |
| Desiccated thyroid | Hypertriiodothyroninemia | 33.3       | 17,039                                                     | Investigations                  | [48]                        |
| Temazepam    | Fatigue/sensation of heaviness/ somnolence/eye irritation | 2.3          | 16,367                                                     | General disorders and administration site conditions/gastrointestinal disorders/psychiatric disorders/eye disorders | [49]                        |
| Nortriptyline | Intractable constipation | 5                         | 16,230                                                     | Gastrointestinal disorders      | [43]                        |
| Nortriptyline | Proarrhythmic event | 5                         | 16,230                                                     | Cardiac disorders               | [43]                        |
| Ketorolac    | Hypotension   | 2.8                       | 15,220                                                     | Vascular disorders              | [45]                        |
| Eszopiclone  | Unpleasant taste | 12.5                     | 14,131                                                     | Nervous system disorders        | [50]                        |
| Nifedipine   | Dizziness     | 2.6                       | 13,733                                                     | Nervous system disorders        | [40]                        |
| Imipramine   | Disturbance of micturition | 20               | 13,490                                                     | Renal and urinary disorders    | [38]                        |
| Imipramine   | Nausea        | 20                        | 13,490                                                     | Gastrointestinal disorders      | [38]                        |
| Diazepam     | Somnolence    | 1.2                       | 12,932                                                     | Nervous system disorders        | [44]                        |
| Megestrol    | Deep vein thrombosis | 4.9                      | 12,915                                                     | Vascular disorders              | [51]                        |
| Cyproheptadine | Dizziness | 18.8                      | 11,966                                                     | Nervous system disorders        | [39]                        |
| Cyproheptadine | Nausea and vomiting | 18.8         | 11,966                                                     | Gastrointestinal disorders      | [39]                        |
| Hyoscyamine  | Dry mouth/constipation/dizziness/ tiredness/headaches/vaginal dryness/night sweats | 61.3         | 11,912                                                     | Gastrointestinal disorders/ gastrointestinal disorders/nervous system disorders/general disorders and administration site conditions/nervous system disorders/reproductive system and breast disorders/general disorders and administration site conditions | [52]                        |
| Ketorolac    | Hypertension  | 2.1                       | 11,415                                                     | Vascular disorders              | [45]                        |
| Ketorolac    | Thrombophlebitis | 2.1                      | 11,415                                                     | Vascular disorders              | [45]                        |
| Desipramine  | Constipation  | 55.3                      | 11,365                                                     | Gastrointestinal disorders      | [46]                        |
| Glyburide    | Edema         | 3.2                       | 11,090                                                     | Metabolism and nutrition disorders | [53]                        |
| Imipramine   | Sexual dysfunctions | 15                        | 10,118                                                     | Psychiatric disorders           | [38]                        |
| Eszopiclone  | Dry mouth     | 8.8                       | 9,948                                                      | Gastrointestinal disorders      | [50]                        |
| Flurazepam   | Hangover symptoms | 50                         | 9,145                                                      | General disorders and administration site conditions | [54]                        |

(Continued)
| BCM (n = 44) | ADE (n = 104) | Incidence of ADE in US (%) | No. US geriatrics with risk of ADE (total no. 54,095,565) | SOC of ADE (per MedDRA ontology) | Reference of ADE incidence |
|-------------|--------------|-----------------------------|----------------------------------------------------------|----------------------------------|-----------------------------|
| Dipyridamole (oral short-acting) | Chest pain/headache/nausea/dizziness/pain (not chest)/dyspnea/vomiting/wheezing/syncope/severe hypotension | 36 | 8,766 | Cardiac disorders/nervous system disorders/gastrointestinal disorders/nervous system disorders/general disorders and administration site conditions/cardiac disorders/gastrointestinal disorders/respiratory, thoracic and mediastinal disorders/vascular disorders/vascular disorders | [55] |
| Nifedipine | Constipation | 1.6 | 8,451 | Gastrointestinal disorders | [40] |
| Glyburide | Weight gain | 2.4 | 8,317 | Investigations | [53] |
| Nortriptyline | Persistent myoclonic jerks | 2.5 | 8,115 | Nervous system disorders | [43] |
| Nortriptyline | Severe angina | 2.5 | 8,115 | Cardiac disorders | [43] |
| Nifedipine | Fatigue | 1.5 | 7,923 | General disorders and administration site conditions | [40] |
| Chlordiazepoxide | Drowsy | 25.8 | 7,787 | Psychiatric disorders | [56] |
| Eszopiclone | Dizziness | 6.6 | 7,461 | Nervous system disorders | [50] |
| Eszopiclone | Somnolence | 6.6 | 7,461 | Psychiatric disorders | [50] |
| Guanfacine | Fatigue | 23.5 | 7,044 | General disorders and administration site conditions | [57] |
| Desipramine | Insomnia | 34.2 | 7,028 | Psychiatric disorders | [46] |
| Desipramine | Increased sweating | 34.2 | 7,028 | General disorders and administration site conditions | [46] |
| Clorazepate | Depression | 10 | 7,022 | Psychiatric disorders | [47] |
| Imipramine | Ataxia | 10 | 6,745 | General disorders and administration site conditions | [38] |
| Imipramine | Vomiting | 10 | 6,745 | Gastrointestinal disorders | [38] |
| Eszopiclone | Pain | 5.9 | 6,670 | General disorders and administration site conditions | [50] |
| Diphenhydramine (oral) | Delirium symptoms | 41.2 | 6,595 | Psychiatric disorders | [58] |
| Desipramine | Headache | 28.9 | 5,939 | Nervous system disorders | [46] |
| Desipramine | Lightheadedness | 28.9 | 5,939 | Nervous system disorders | [46] |
| Clomipramine | Dry mouth | 32.2 | 5,792 | Gastrointestinal disorders | [59] |
| Estazolam | Drugged feeling | 33.3 | 5,645 | Nervous system disorders | [60] |
| Nifedipine | Chest pain | 1 | 5,282 | Cardiac disorders | [40] |
| Nifedipine | Flushing | 1 | 5,282 | Vascular disorders | [40] |
| Nifedipine | Abdominal pain | 1 | 5,282 | Gastrointestinal disorders | [40] |
| Nifedipine | Nausea | 0.9 | 4,754 | Gastrointestinal disorders | [40] |
| Eszopiclone | Nervousness | 3.7 | 4,183 | Psychiatric disorders | [50] |
| Eszopiclone | Rash | 3.7 | 4,183 | Skin and subcutaneous tissue disorders | [50] |
| Cyproheptadine | Blurred vision | 6.3 | 4,010 | Nervous system disorders | [39] |
| Ketorolac | Angina pectoris | 0.7 | 3,805 | Cardiac disorders | [45] |
| Ketorolac | Cardiac failure congestive | 0.7 | 3,805 | Cardiac disorders | [45] |
| Ketorolac | Supraventricular tachycardia | 0.7 | 3,805 | Cardiac disorders | [45] |
| Ketorolac | Flashing | 0.7 | 3,805 | Vascular disorders | [45] |
| Imipramine | Increased energy | 5 | 3,373 | General disorders and administration site conditions | [38] |

(Continued)
### Table 4. (Continued)

| BCM (n = 44) | ADE (n = 104) | Incidence of ADE in US (%) | No. US geriatrics with risk of ADE (total no. 54,095,565) | SOC of ADE (per MedDRA ontology) | Reference of ADE incidence |
|--------------|--------------|-----------------------------|-------------------------------------------------------------|-------------------------------|----------------------------|
| Eszopiclone  | Accidental injury | 2.9 | 3,278 | Injury, poisoning and procedural complications | [50] |
| Clomipramine | Dizziness | 15.9 | 2,860 | Nervous system disorders | [59] |
| Glyburide | Hypoglycemia | 0.8 | 2,772 | Metabolism and nutrition disorders | [53] |
| Clomipramine | Constipation | 14.6 | 2,626 | Gastrointestinal disorders | [59] |
| Pentazocine | Drowsy/sleepy | 47.2 | 2,588 | Psychiatric disorders | [61] |
| Indomethacin | Cardiovascular and cerebrovascular events | 1.33 | 2,568 | Vascular disorders/nervous system disorders | [62] |
| Eszopiclone | Back pain | 2.2 | 2,487 | Musculoskeletal and connective tissue disorders | [50] |
| Eszopiclone | Peripheral edema | 2.2 | 2,487 | Metabolism and nutrition disorders | [50] |
| Eszopiclone | Arthralgia | 2.2 | 2,487 | Musculoskeletal and connective tissue disorders | [50] |
| Eszopiclone | Anxiety | 2.2 | 2,487 | Psychiatric disorders | [50] |
| Estazolam | Dizziness | 13.3 | 2,254 | Nervous system disorders | [60] |
| Clomipramine | Erectile dysfunction | 10.4 | 1,871 | Reproductive system and breast disorders | [59] |
| Disopyramide | Dry mouth | 37 | 1,750 | Gastrointestinal disorders | [63] |
| Eszopiclone | Emotional lability | 1.5 | 1,696 | Psychiatric disorders | [50] |
| Eszopiclone | Memory impairment | 1.5 | 1,696 | Nervous system disorders | [50] |
| Desipramine | Orthostatic symptoms | 7.9 | 1,624 | Vascular disorders | [46] |
| Desipramine | Palpitations | 7.9 | 1,624 | Cardiac disorders | [46] |
| Amoxapine | Composite of anticholinergic symptoms/ cardiovascular/neurological/sedative complaints | 68.1 | 1,429 | Nervous system disorders/cardiac disorders | [64] |
| Clorazepate | Headache | 2 | 1,404 | Nervous system disorders | [47] |
| Disopyramide | Headache | 29.6 | 1,400 | Nervous system disorders | [63] |
| Disopyramide | Bowel changes | 29.6 | 1,400 | Gastrointestinal disorders | [63] |
| Diphenhydramine (oral) | Required new urinary catheter | 7.9 | 1,265 | Surgical and medical procedures | [58] |
| Disopyramide | Urinary complaints | 25.9 | 1,225 | Renal and urinary disorders | [63] |
| Disopyramide | Weakness | 22.2 | 1,050 | General disorders and administration site conditions | [63] |
| Disopyramide | Nausea | 22.2 | 1,050 | Gastrointestinal disorders | [63] |
| Disopyramide | Palpitations | 22.2 | 1,050 | Cardiac disorders | [63] |
| Disopyramide | Lightheadedness | 22.2 | 1,050 | Nervous system disorders | [63] |
| Clomipramine | Insomnia | 4.2 | 755 | Psychiatric disorders | [59] |
| Propantheline | Dry mouth | 56.3 | 596 | Gastrointestinal disorders | [65] |
| Diphenhydramine (oral) | Behavioral disturbance | 3.5 | 560 | Psychiatric disorders | [58] |
| Estazolam | Headache | 3.3 | 559 | Nervous system disorders | [60] |
| Estazolam | Hangover | 3.3 | 559 | General disorders and administration site conditions | [60] |
| Clomipramine | Nervousness | 2.9 | 522 | Psychiatric disorders | [59] |
| Promethazine | Dystonia/extrapyrimidal symptoms/ oversedation/delirium/ respiratory depression | 0.1 | 401 | Nervous system disorders/nervous system disorders/ psychiatric disorders/nervous system disorders | [66] |
| Butalbital | Somnolence | 1 | 296 | Psychiatric disorders | [67] |

(Continued)
disorders”, “nervous system disorders”, “psychiatric disorders”, “vascular disorders”, and “composite of multiple SOCs” than geriatrics on BCMs ≤1 day. There were no SOCs where South Korean geriatrics on BCMs ≤1 day had a higher mean risk of ADEs than geriatrics on BCMs >1 day. There were no SOCs where South Korean geriatrics on BCMs for 1 day or less were of higher risk than South Korean geriatrics on BCMs >1 day. Comparing the mean risk of SOC-grouped ADEs between SOCs, the mean risk of ADEs grouped into the “composite of multiple SOCs” group was significantly higher than the ADEs grouped into the SOCs “investigations”, “nervous system disorders”, and “skin and subcutaneous tissue disorders” respectively in the South Korean geriatrics on BCMs.

Using the 15 SOCs where both South Korean and US populations had ADE rates available, the proportion of South Korean and US geriatrics at risk of SOC-grouped ADEs from BCMs were also compared. The mean proportion of geriatrics at risk of experiencing the ADEs was significantly higher in South Korean geriatrics on BCMs >1 day at 0.005 compared to US geriatrics at 0.001 (2-way ANOVA post hoc pairwise t-test \( P < 0.0001 \)). Although not significant, for 8 out of the 15 SOCs where ADEs were grouped into (“cardiac disorders”, “gastrointestinal disorders”, “general disorders and administration site conditions”, “metabolism and nutrition disorders”, “nervous system disorders”, “psychiatric disorders”, “vascular disorders”, and “composite of multiple SOCs” than geriatrics on BCMs ≤1 day. There were no SOCs where South Korean geriatrics on BCMs ≤1 day had a higher mean risk of ADEs than geriatrics on BCMs >1 day. There were no SOCs where South Korean geriatrics on BCMs for 1 day or less were of higher risk than South Korean geriatrics on BCMs >1 day. Comparing the mean risk of SOC-grouped ADEs between SOCs, the mean risk of ADEs grouped into the “composite of multiple SOCs” group was significantly higher than the ADEs grouped into the SOCs “investigations”, “nervous system disorders”, and “skin and subcutaneous tissue disorders” respectively in the South Korean geriatrics on BCMs.

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disorders”, “nervous system disorders”, “psychiatric disorders”, “vascular disorders”, “composite of multiple SOCs”), South Korean geriatrics on BCMs >1 day were shown to have a higher mean risk of ADEs than the US geriatrics while the US geriatric population had a higher mean risk of ADEs than the South Korean geriatric population for 7 SOCs which were “eye disorders”, “injury, poisoning and procedural complications”, “investigations”, “musculoskeletal and connective tissue disorders”, “renal and urinary disorders”, “reproductive system and breast disorders”, and “skin and subcutaneous tissue disorders”. Finally, the mean risk of ADEs grouped into the “composite of multiple SOCs” group was significantly higher than the ADEs grouped into the SOCs “cardiac disorders”, “gastrointestinal disorders”, “general disorders and administration site conditions”, “injury, poisoning and procedural complications”, “investigations”, “metabolism and nutrition disorders”, “nervous system disorders”, “psychiatric disorders”, “renal and urinary disorders”, “skin and subcutaneous tissue disorders”, and “vascular disorders” respectively in the South Korean geriatrics on BCMs >1 day and US geriatric populations combined.

Discussion

This study discovered that the exposure of South Korean geriatrics to BCMs was prevalent in that over half of this population was exposed to these medications and the proportion of the
population at risk of the ADEs from BCMs was around three-fold higher in South Korean geriatrics (limited to those prescribed BCMs >1 day) compared to US geriatrics. BCM classes that were most prevalently prescribed in South Korean geriatrics in year 2011 regardless of duration of BCM prescription were first generation antihistamines and benzodiazepines. Specific medications of the first generation antihistamines were chlorpheniramine, dimenhydrinate, and hydroxyzine. These medications have risk of ADEs such as dizziness or drowsiness and this may be debilitating in the elderly as the ADEs may lead to falls or fractures. The benzodiazepines were diazepam and alprazolam and use of these medications in geriatrics increases their risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes. The high prescribing rate of these medications in South Korean geriatrics is concerning and this warrants heightened awareness in prescribers regarding the risk of ADEs from BCMs. This issue is becoming more important due to the increased lifespan of the population and use of multiple medications in the geriatric population.

Notable differences in BCM exposure patterns between South Korean geriatrics prescribed chronic (in present study >1 day) and short duration (in present study, 1 day or less) BCMs
were that ketorolac and atropine were prescribed more frequently in a short duration of 1 day or less instead of chronically. This may be due to ketorolac being indicated for short term pain or surgical procedures and atropine is indicated acutely for cardiac arrest or organophosphate poisoning [74]. Although other than atropine and ketorolac, the absolute number of South Korean geriatrics prescribed BCMs short term were smaller than geriatrics prescribed BCMs longer term, the relative prescribing trend of the latter BCMs were similar in both populations. The trend of BCM prescribing between South Korea and the US was also similar. The most prevalently prescribed meds for US geriatrics in 2014 were benzodiazepines including alprazolam, lorazepam, zolpidem, and clonazepam. Alprazolam was one of the most commonly prescribed medications in both South Korea and the US.

In South Korean geriatrics prescribed BCMs for >1 day, the ADE rates from amitriptyline were among the highest out of all BCM ADEs examined in this study. Specifically, dry mouth from amitriptyline was the ADE with the highest number of geriatrics at risk of experiencing. Sleepiness, dizziness, and constipation related to amitriptyline were other ADEs that many South Korean geriatrics were at risk of. The reasons for this trend was because the number of patients on amitriptyline and the incidence of ADEs from this drug were high. Diazepam related rash/urticaria/pruritus was the 3rd most common ADE predicted to occur in South Korean geriatrics after amitriptyline ADEs and this also reflects the high number of geriatrics on diazepam. Thus, monitoring geriatrics for anticholinergic changes or toxicities after prescribing medications is important and necessary. The SOCs of ADEs that most of this South Korean population was at risk of were “cardiac disorders” (mean proportion = 0.0082), “gastrointestinal disorders” (mean proportion = 0.0064), and “general disorders and administration site conditions” (mean proportion = 0.0059), after excluding “composite of multiple SOCs” (mean proportion = 0.0134). This shows that monitoring geriatrics for their change in cardiac system or gastrointestinal condition for the possibility of ADEs from medications and adjusting their drug treatment accordingly may improve the safety of drug therapy in geriatrics.

Similarly, for geriatrics of South Korea prescribed BCMs for 1 day or less, ADEs from the benzodiazepines diazepam and lorazepam including rash/urticarial/pruritus, dizziness/somnolence, and dyspnea were those that most of these geriatrics were at risk of. Dry mouth from amitriptyline was also one of the high risk ADEs in this population. Therefore, monitoring geriatrics for their neuropsychiatric, cardiac, and anticholinergic symptoms after medication use and prevention of these ADEs is necessary. Considering that ADEs of the SOC “cardiac disorders” was the most prevalent ADEs this population was at risk of (mean proportion of population at risk = 0.0018) excluding the “composite of multiple SOCs” group, care to avoid medications with cardiotoxicity in this population may be needed.

Examining ADEs predicted in US geriatrics, the trend of ADEs that geriatrics were at risk of were not similar to those in South Korean geriatrics. The ADE that the highest number of US geriatrics was at risk of having was somnolence from cyclobenzaprine. The other ADEs that many US geriatrics were at risk of experiencing were dry mouth, headache, dizziness, and blurred vision from cyclobenzaprine, restlessness from lorazepam, and dizziness/blurring of vision/dry mouth from dicyclomine, and fatigue and dyspnea from atropine (excluding ophthalmic). The most common SOCs of ADEs that US geriatrics were at risk of were “psychiatric disorders” (mean proportion = 0.0013), “gastrointestinal disorders” (mean proportion = 0.0010), and “nervous system disorders” (mean proportion = 0.0009), after excluding “composite of multiple SOCs” (mean proportion = 0.0011).

Comparing the mean proportion of patients at risk of ADEs in 15 SOC groups, South Korean geriatrics on BCMs >1 day were at a higher risk of ADEs in 7 single SOCs plus the “composite of multiple SOCs” group than US geriatrics, although not statistically significant.
The 7 single SOCs were “cardiac disorders”, “gastrointestinal disorders”, “general disorders and administration site conditions”, “metabolism and nutrition disorders”, “nervous system disorders”, “psychiatric disorders”, and “vascular disorders”. However, the proportion of geriatrics at risk of the 15 SOC-grouped ADEs combined was statistically significantly higher in South Korea than in the US, showing that medication prescribing for geriatrics in South Korea may require modification or further monitoring regarding its safety outcomes. Although not statistically significant, US geriatrics were at a higher risk of experiencing ADEs in the SOCs “eye disorders”, “injury, poisoning and procedural complications”, “investigations”, “musculoskeletal disorders”, “renal and urinary disorders”, “reproductive system and breast disorders”, and “skin and subcutaneous tissue disorders” than South Korean geriatrics on BCMs >1 day.

This study was the first to systematically examine the exposure of all BCMs in South Korean and US geriatrics and the risk of ADEs from these medications. This analysis enabled a comprehensive overview of the extent of geriatric risk of ADEs using population data. These results may be generalizable to the total national population as the South Korean HIRA national patient sample dataset was shown to represent the total South Korean population [9] and the US Medicare Part D data includes prescription information of American geriatrics 65 years or older [75]. Therefore, the results of this study may be used as a reference to evaluate the current drug therapy in geriatrics.

As this study was cross sectional, there were some limitations. Firstly, the results of this study present medication exposure and ADE risk data for a one-year range providing only a snapshot of BCM exposure and ADE risk. Data of a longer period would enable examination of the change in med exposure or ADE risk over time providing stronger evidence for risk of ADEs from BCMs and enable the inclusion of additional BCMs. The latter is due to the fact that some BCMs were permitted to be used as an alternate to a med used for a certain indication. In this study, as the medication history of a patient was infeasible to determine over a year, we excluded BCMs that were to be avoided under particular medication use or disease histories. Secondly, it was not possible to determine if the patients actually took the drugs as this study used claims data. Thirdly, follow up of patients’ clinical status was not possible. Confirming if the patients on BCMs had an ADE with the claims data would provide direct evidence of ADE risk from the med. However, whether the patients exposed to BCMs experienced ADEs is unknown with our study as the patients in the study data were anonymized and linking the claims data of patients in this study to other data was not possible. Lastly, considering that approximately 0.2% of the South Korean geriatric population are using hospice care, our study may have overestimated the exposure of geriatrics exposed to BCMs as this criteria applies to geriatrics not receiving hospice or palliative care. This population could not be excluded from this study sample because information on whether the geriatric was having this type of care was not discernable from our study data. However, this overestimation did not alter the trend or direction of the study results.

Conclusions

To conclude, this study found that there is room for improvement in South Korean geriatric drug therapy through enhanced awareness and education of clinicians regarding medications that may be potentially inappropriate for geriatrics. This was known from the fact that at least half of South Korean geriatrics were exposed to medications recommended to be avoided in geriatrics according to the Beers Criteria and a significantly higher proportion of South Korean geriatrics on BCMs >1 day were at risk of ADEs from the BCMs compared to US geriatrics. Heightened awareness from clinicians regarding safe geriatric drug therapy may contribute to increased quality of drug treatment in South Korean geriatrics.
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