筑　波　大　学

博 士 （医 学） 学 位 論 文

Potentially Inappropriate Medications in a Japanese Primary Care Setting

（プライマリ・ケアにおける潜在的不適切処方）

２０１７

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ABBREVIATIONS

ACE-I: angiotensin converting enzyme inhibitor

ADE: adverse drug event

ARB: angiotensin Ⅱ receptor blocker

BZA: benzodiazepine

CCB: calcium channel blocker

CCI: Charlson comorbidity index

CI: confidence interval

CKD: chronic kidney disease

ED: emergency department

eGFR: estimated glomerular filtration rate

GP: general practitioner

HADS: Hospital Anxiety and Depression Scale

IQR: interquartile range

NSAID: nonsteroidal anti-inflammatory drug

OR: odds ratio

PIM: potentially inappropriate medication

PPI: proton pump inhibitor

SD: standard deviation

STOPP: Screening Tool of Older Person's Prescriptions

ABSTRACT

Background: The use of potentially inappropriate medications (PIMs) in elderly patients is a major public health concern. However, there is little information concerning PIMs in Japanese primary care settings, and the association between PIMs and clinical outcomes has not been well evaluated. In addition, associations between PIMs and clinical outcomes can differ depending on the number of medications because PIMs and polypharmacy are highly correlated and result in confounding. This study was conducted to explore the prevalence of PIMs and predictors in elderly patients with chronic diseases in a Japanese primary care setting and to assess the association between PIMs and adverse clinical outcomes including falls, emergency department (ED) visits, and unplanned hospitalizations, comparing the difference between patients with and without polypharmacy.

Methods: The author performed a prospective observational cohort study in a Japanese outpatient clinic providing a primary care. Baseline data were collected from January 2016 to March 2016. A total of 740 patients aged 65 years and above with chronic diseases were enrolled and followed up after 1 year. Data regarding falls, ED visits, and unplanned hospitalizations were collected. A questionnaire and review of patient medical records were used to collect information regarding sociodemographic status, comorbidities,

prescribed medications, and psychological status. PIMs were defined using the Screening Tool of Older Person's Prescriptions (STOPP) criteria, version 2. Factors associated with PIMs were analyzed using chi-square test and logistic regression analysis. In addition, using chi-square test or Fisher's exact test for univariate analysis, and logistic regression analysis for multivariate analysis, the incidence of falls as well as ED visits and hospitalizations were compared between patients with and without PIMs stratified by the existence of polypharmacy, which was defined as being prescribed more than five medications.

Results: PIMs, as defined by STOPP criteria version 2, were found in 32.3% of patients, and 39.5% of patients were found to be prescribed five or more medications. Benzodiazepines, Z-hypnotic drugs, proton pump inhibitors, sulfonylureas, nonsteroidal anti-inflammatory drugs, and duplicate drug class prescription accounted for most PIMs. After adjusting for age, sex, comorbidities, estimated glomerular filtration rate, and the number of medications, anxiety was identified as a predictor for PIMs (adjusted odds ratio (OR) = 2.09, 95% confidence interval (CI) = 1.25–3.48). After stratification by the number of prescriptions, PIMs were significantly associated with falls in the group with polypharmacy (adjusted OR = 2.03, 95% CI = 1.11–3.69); this association was not seen in patients without polypharmacy. PIMs were not associated with ED visits or

hospitalizations at the 1-year follow-up upon multivariate analysis.

Conclusions: The findings of this study demonstrate that PIMs and polypharmacy are common in elderly patients with chronic diseases in a Japanese primary care setting. PIMs may be associated with anxiety; therefore, this association should be taken into account and addressed, to reduce PIMs. Furthermore, the combination of PIMs and polypharmacy might increase the risk of falls; therefore, clinicians need to consider both PIMs and polypharmacy.

1. INTRODUCTION

1.1. Potentially inappropriate medications and relevant criteria

Both the proportion and absolute number of older people in the global population is increasing dramatically.[1] According to the United Nations, the number of people worldwide aged 60 years or over is projected to grow by 56% between 2015 and 2030, from 901 million to 1.4 billion, and this population is projected to more than double its size in 2015, reaching nearly 2.1 billion by 2050.[2] This increase in the older population poses huge challenges to health care, as elderly populations tend to have chronic diseases, often with multimorbidity (the coexistence of multiple chronic diseases).[3] In such situations, clinicians are often faced with the need to prescribe a number of medications, depending on the patient's condition and complaints. Prescriptions for older patients must be chosen using special precautions because this population often has impaired drug metabolism and changes in kidney and liver function, altered pharmacokinetics and pharmacodynamics of drugs.[4] Potentially inappropriate medications (PIMs) are prescriptions whose potential risks outnumber the benefits. PIMs have recently been the focus of attention worldwide, especially among elderly populations, reflecting the rapidly aging global population.

To improve the quality of prescription behavior, several criteria for the

identification of PIMs have been developed; commonly used criteria include the Beers criteria and Screening Tool of Older Person's Prescriptions (STOPP) criteria. Developed in 1991[5] with several revised versions proposed thereafter,[6-9] the Beers criteria are the most widely used. The STOPP criteria were developed in Ireland in 2007[10] and updated in 2015.[11] STOPP comprises explicit criteria consisting of 81 items related to situations that are potentially inappropriate for elderly adults. The STOPP criteria have been validated through a Delphi consensus by experts in geriatric pharmacotherapy. Reflecting the increased concern in Japan regarding PIMs, the "Screening Tool for Older Person's Appropriate Prescriptions for Japanese (STOPP-J)" were published in Japan by the Japan Geriatrics Society in 2016.[12]

The STOPP and Beers criteria have several areas of overlap. Both sets of criteria focus on the higher risk of adverse drug events (ADEs) in older people with use of benzodiazepines (BZAs), tricyclic antidepressants, anticholinergic drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs). Comparisons among several criteria have been conducted in previous studies, and the STOPP criteria have been reported to identify a higher proportion of ADEs and hospitalizations.[13-15] Although all criteria should be modified and applied in each region according to approved prescriptions and dose regulations, the STOPP-J is currently not well validated and is not thought to be

suitable for research purposes.

1.2. Prevalence and details of PIMs

The prevalence of PIMs varies across regions and according to the criteria used.[16] Previous studies have indicated that the prevalence also differs across settings, accounting for 34.7% to 77.3% of hospitalized patients,[17, 18] 12% to 22.6% of community-dwelling older adults,[19-21] 40% to 50.3% of older adults living in long-term care facilities,[20, 22] and 19.8% to 82.7% of home care patients.[23, 24] In primary care settings, the prevalence of PIMs ranges from 19% to 59.2% by the 2003 or 2012 Beers criteria,[25-28] from 21.4% to 39.1% by the original STOPP criteria,[29-35] and from 39.1% to 56% by STOPP criteria version 2.[36, 37]

The most frequently used PIMs also differ by country and the criteria used. According to previous systematic reviews, propoxyphene, doxazosin, diphenhydramine, anxiolytics, antidepressants, NSAIDs and antirheumatic drugs, and antithrombotics are reported to be frequently overused or misused.[21, 38] In studies using the STOPP criteria, BZAs, Z-hypnotics, and other psychotropic drugs have been reported to be most frequent among PIMs.[17, 29] Calcium channel blockers (CCBs) for patients with constipation was a frequently defined PIM in the original STOPP criteria,[39, 40] but it was omitted from the list of PIMs in STOPP criteria version 2.[11]

1.3. PIMs in Japan

Currently, Japan has the most aged society in the world and its elderly population is rapidly increasing. In 2015, 26.6% of Japan's population was reported to be more than 65 years old, meaning that more than one in four people in Japan are elderly adults.[41] This report also states that by 2036, 33.3% of the total population, corresponding to one in three people, will be considered an elderly person. Reflecting concern about Japan's rapidly aging society, many studies on polypharmacy and PIMs have been conducted in the country. In 2011, a report by the Japan Geriatrics Society revealed that 72% of older patients have experienced ADEs caused by PIMs.[42]

Recent studies have suggested that the prevalence of PIMs in Japan is 56.1% in acute care hospitals,[43] 43.6% in outpatient clinics,[44] 21.1% in long-term care facilities,[45] and 40.4 to 48.4% in home health care.[46, 47] The most recent study revealed that 42.1% of patients admitted to a university hospital were identified as having been prescribed PIMs, according to STOPP criteria version 2.[48] However, in Japan, there are few studies on PIMs in the area of primary care, and the association between PIMs and clinical outcomes has not been sufficiently evaluated.

1.4. Predictors for PIMs

A recent systematic review in Europe reported that polypharmacy, poor functional status, and depression are associated with PIMs.[21] Many previous studies have also demonstrated that polypharmacy and advanced age are important predictors for PIMs.[25, 26, 29, 32, 35, 36, 40, 49-51] Other identified predictors for PIMs are reported to be female sex,[26, 49, 51] increased number of chronic diseases,[26, 36] fewer activities of daily life,[36, 49] self-medication,[28] and having psychiatric disorders[32, 44] or psychotropic drug use.[45, 52]

General practitioners (GPs) and family physicians often prescribe anxiolytics and antidepressants for patients with depression, anxiety, or other psychiatric disorders.[53] Although psychiatric disorders or psychotropic drug use has been suggested as a predictor for PIMs in several studies,[32, 44, 45, 52] other reports have claimed that subjective assessment of depression was not a significant factor in predicting PIMs.[36, 49] Therefore, it is inconclusive whether depression or anxiety are associated with PIMs.

1.5. PIMs and negative health outcomes

PIMs are reported to lead to negative health outcomes such as ADEs,[17, 54] hospitalizations,[26, 55-59] emergency department (ED) visits,[39, 54, 60] declining health-related quality of life,[39, 54] and increased health care costs;[51] however, whether PIMs are related to mortality remains controversial.[37, 61] Among several criteria, the STOPP criteria have

been reported to modestly predict ADEs, hospitalizations, and ED visits.[15] Moreover, recent randomized controlled trials have suggested that interventions using the STOPP criteria reduce polypharmacy and PIMs, which may reduce negative health outcomes.[62, 63]

1.6. Polypharmacy

Older people often have multiple chronic diseases: multimorbidity. A study conducted in the United States showed that 82% of elderly Medicare beneficiaries had one or more chronic disorders and 24% had four or more chronic disorders.[64] Such patients tend to be prescribed multiple medications concomitantly for treatment, especially if clinicians adhere to clinical guidelines. The use of multiple medications is called polypharmacy, which is common in older patients and is estimated to occur in 20 to 50% of older patients.[65-67] Moreover, the prevalence of polypharmacy is increasing.[68] There is no consensus with regard to the number of medications considered to be polypharmacy, although it is usually defined as five or more, as this is the number of medications demonstrated to be highly associated with adverse outcomes.[69, 70] Polypharmacy is strongly associated with PIMs and has been identified as a risk factor for PIMs.[71] Whereas reports regarding the benefits of polypharmacy are scarce, previous studies have reported

polypharmacy to be associated with ADEs; drug–drug interactions; falls; hospital admissions/readmissions; medication errors; and declining nutritional status, functional ability, cognitive capacity, and health-related quality of life,[69, 72-77] However, the findings of studies regarding these associations have been mixed because of confounding and heterogeneity in the definition of polypharmacy, according to a recent systematic review.[78] Moreover, polypharmacy poses a challenge for medication adherence among older patients as complex medication regimens are reported to be associated with medication nonadherence.[79]

Polypharmacy and PIMs are not synonymous but they are often present concomitantly and are highly correlated.[80] Although confounding is likely to exist between PIMs and polypharmacy, the effect of PIMs on clinical outcomes can differ depending on the number of medications. Previous studies have adjusted for the effect of the number of medications using statistical methods, when assessing the relationship between PIMs and clinical outcomes. However, it is considered that such a strategy is inadequate to reduce confounding between PIMs and polypharmacy.

1.7. Significance of the study

Although concerns regarding PIMs are skyrocketing owing to the rapidly aging society

in Japan, how PIMs are prescribed and what the predictors for PIMs are in Japanese primary care settings are not well known. In addition, the association between PIMs and clinical outcomes has not been sufficiently evaluated in previous studies in Japan. It is of critical importance to clarify the actual situation of PIMs in Japan, one of the most aged and developed countries in the world.

1.8. Purpose of this study

The present study was conducted with the following objectives. The first was to describe the prevalence of PIMs among elderly patients with chronic diseases in a Japanese primary care setting. The second aim was to identify factors associated with PIMs, especially to assess the association between depression or anxiety and PIMs among elderly patients with chronic diseases. The third objective was to follow a cohort of elderly patients with chronic diseases in a Japanese primary care setting for 12 months, to assess the relationship between PIMs and adverse clinical outcomes including falls, ED visits, and unplanned hospitalizations. Moreover, this study aimed to determine if patients in the cohort with polypharmacy were affected by PIMs differently than patients without polypharmacy.

2. METHODS

2.1. Study design and participants

This was a prospective observational cohort study, conducted in an outpatient clinic in the family medicine department of an urban general hospital (Kawakita Satellite Clinic) providing primary care in Tokyo, Japan. According to the definition in 1996 by Institute of Medicine, National Academy of Sciences in the United States, "Primary care is the provision of integrated accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients and practicing in the context of family and community".[81] Based on the definition, the clinic provides a wide range of integrated care to patients with the common chronic diseases, which includes hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary diseases, asthma, chronic kidney diseases, heart diseases, liver diseases, thyroid dysfunction, dementia, musculoskeletal disorders, and psychological disorders including anxiety and depression. A total of 23 doctors with various subspecialties, including part-time doctors, were working in the clinic when the study was started. To reduce information bias, the STOPP criteria were not explained to each doctor.

Participants were recruited from January to March in 2016. Patients who met the following criteria were included in the study: age 65 years or more, visiting the clinic on

a regular basis with presence of any chronic diseases, taking at least one prescribed medication. Written informed consent was sought from each participant and those who did not consent to participation were excluded. Patients who were not prescribed any medications from the clinic, those who had difficulty in communication, those with incomplete answers to the questionnaire, and those without identification of questionnaire were also excluded. Patients were asked to complete a questionnaire after a medical consultation.

Enrolled patients were divided into two groups, patients with PIMs and those without PIMs. All study participants were followed up after 1 year unless they dropped out of the study for any of the following reasons: death for unknown reason, left the facility because of hospitalization, change of hospital, transition to home visits, interruption of treatment, or failure to consent to the follow-up investigation. An analysis was conducted with stratification by the number of prescriptions (patients with five or more prescriptions and those with less than five prescriptions) to reduce confounding, because polypharmacy was assumed to strongly modify the relationship between PIMs and adverse clinical outcomes.

2.2. Data collection

Data from electronic medical records and responses to the questionnaires were used to obtain information regarding patient characteristics including age, sex, estimated glomerular filtration rate (eGFR; ml/min/1.73 m^2), smoking status, alcohol consumption, living circumstances, subjective economic status, education level, Hospital Anxiety and Depression Scale (HADS) score, and nonprescription medication use.

All medications were extracted and reviewed using medical records, and drugs prescribed in other facilities were confirmed by referring to patients' medication notebooks, used in Japan to record an individual's medication history. STOPP criteria version 2 was used to define PIMs because it seemed to better reflect the current practice in Japan than the original STOPP or Beers criteria. In cases where it was difficult to judge PIMs, two researchers discussed the case and decided if the specific case pertained to PIMs or not. When applying STOPP criteria version 2, criteria D5 (BZAs for more than 4 weeks) and K1 (BZAs could increase the risk of fall incidents) were considered to be similar and duplicated in the list; therefore, prescription of BZA was counted as one PIM, as in a previous study.[37]

As for the number of prescriptions, inhaled agents were counted as prescriptions. Combination products were counted as combined medicines. Topical drugs, such as

ointments or pasting agents, were excluded. Injection agents such as erythropoietin stimulating agents were not counted as prescriptions. Polypharmacy was defined as five or more medications per day prescribed by a physician, which is the most frequently used definition of polypharmacy.[69, 71]

2.2.1. Independent variables

Most independent variables were analyzed as categorical data. With regard to age, patients were divided into two groups, those aged less than 75 years and those aged 75 years and older. As to renal function, patients were dichotomized into either patients with eGFR less than 60 mL/min/1.73 m^2 or those with eGFR 60 mL/min/1.73 m^2 and greater. Each participant was asked to subjectively state their economic status, and patients were categorized into three groups based on their responses: those with economic status lower than average, average, or higher than average. Participants' education level was classified into two groups, those with educational background of high school or below, or more than high school. Daily use of nonprescription medications (defined to be daily use of dietary supplements or over-the-counter drugs) was queried and participants were categorized into three groups according to their responses: patients with

daily use of nonprescription medications, those without daily use of nonprescription medications, or those who did not provide a definite response.

Comorbidity was assessed using the Charlson comorbidity index (CCI), based on the information extracted from medical records and the questionnaire survey. The CCI was developed in 1987 and has been used as a tool for assessing the severity of chronic diseases.[82] The score ranges from 0 to 37, with lower score indicates less severity of comorbidities.

The HADS was developed by Zigmond and has been used worldwide for assessing anxiety and depression in patients with chronic diseases.[83] The Japanese version was validated in a previous study.[84] A score of 8 points was used as the cutoff for both anxiety and depression, i.e., patients with a score of 8 points or more on the anxiety scale were identified as having anxiety and those with a score of 8 points or more on the depression scale were identified as having a depressive mood.

2.2.2. Outcome variables

Primary adverse outcomes were considered to be any falls, ED visits, or unplanned hospitalizations identified at the 1-year follow-up. The follow-up survey was a questionnaire given to each patient 12 months after they were

enrolled in the study. Episodes of falls, ED visits, and hospitalizations were confirmed by reviewing patient medical records.

A fall was defined as an event that results in a person inadvertently coming to rest on the ground, floor, or other lower level, in accordance with the definition of the World Health Organization.[85] Participants were asked about the occurrence of falls at the 12-month follow-up investigation.

An ED visit was defined as at least one ED utilization at any medical facility without an appointment. The use of an outpatient clinic without an appointment was not considered an ED visit.

Hospital admission was defined as at least one unplanned hospitalization, usually as a result of an ED visit. Planned hospitalizations, such as planned surgery, were not considered in the study.

2.3. Ethical considerations

All procedures involving human participants were in accordance with the ethical standards of institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Before commencing, this study received approval by the ethical review board of Kawakita General Hospital. Written informed consent was obtained from all participants included

in the study.

2.4. Statistical analysis

Statistical analysis was performed with IBM SPSS ver. 22 (IBM Corp., Armonk, NY, USA). Descriptive analysis results were presented as mean values and standard deviation (SD) for normally distributed continuous variables, and as median values and interquartile range (IQR) for nonparametric variables. Categorical data were presented as number and percentage. Differences in the distributions of categorical variables were compared using the chi-square test or Fisher's exact test.

To assess the association between psychological status and PIMs, logistic regression analysis was performed by adjusting for age, sex, and variables with *P* value below 0.10.

The association between PIMs and clinical outcomes were also assessed by logistic regression analysis, stratifying by the number of prescriptions (with or without polypharmacy). Additional analyses without stratification by number of prescriptions were performed using logistic regression analysis, to assess the relationship between PIMs and clinical outcomes.

Results of the regression analysis were presented with odds ratios (ORs) and

95% confidence intervals (CIs). *P* values less than 0.05 were considered statistically significant.

3. RESULTS

3.1. Basic patient characteristics and prevalence of PIMs

A total of 740 patients were included in the analysis. Patient characteristics are given in Table 1. The mean age (±SD) of participants was 75.7 ± 7.5 years and 51.2% were women. The median number of prescriptions was 4 (IQR, 2–6), with a range of 1–22 medications per patient. Polypharmacy (five or more prescribed medications) was found in 292 (39.5%) patients. Use of nonprescription medications was found in 234 patients (32.1%). The types of nonprescription medication were mainly dietary supplements including vitamins/minerals, *aojiru* (Japanese vegetable juice), and chondroitin–glucosamine. The median CCI was 1 (IQR, 0–1), which indicated that many participants had relatively mild diseases. In descending order, the most common comorbidities were hypertension (71.9%), hyperlipidemia (50.9%), chronic kidney disease (CKD) with eGFR less than 60 mL/min/1.73 m^2 (49.0%), and diabetes mellitus (20.4%) (Table 2). The average eGFR was 60.8 mL/min/1.73 m^2, and 48.1% of patients were categorized those with eGFR less than 60.0 mL/min/1.73 m^2. Regarding smoking status, 9.8% were current smokers, 39.2% were past smokers, and 51.0% were never smokers. As to alcohol consumption, 32.8% were regular drinkers. With respect to living circumstances, 26.6% of patients lived alone. Regarding subjective economic status, 17.3% of participants reported having lower than

average economic status, 61.5% reported an average level, and 21.2% stated that they had a higher than average economic status. Regarding educational attainment, the proportion of patients with high school or below and more than high school level educations were 40.5% and 59.5%, respectively.

The percentage of patients with depression and anxiety (i.e., those who scored 8 points or more on the HADS) was 22.9% and 15.9%, respectively. Overall, 239 (32.3%) participants were prescribed at least one PIM, as defined by STOPP criteria version 2. Among patients with any PIMs, there were 193 cases with one PIM, 36 cases with two PIMs, 8 cases with three PIMs, and 2 cases with five PIMs.

3.2. Details of PIMs

Among 239 patients who were prescribed PIMs, 108 patients were prescribed BZAs for longer than 4 weeks; BZAs were the most frequently prescribed among the drugs on the list (STOPP criteria version 2). The second most frequently prescribed PIM was proton pump inhibitors (PPIs) for uncomplicated peptic ulcer disease or erosive peptic esophagitis, prescribed for 64 patients at full therapeutic dosage for > 8 weeks. The third most common prescription was hypnotic Z-drugs (zopiclone, zolpidem), which were prescribed for 47 patients. The fourth were sulfonylureas with long duration of action for type 2 diabetes mellitus, followed by duplicate drug class prescription (Table 3).

Inappropriate use of NSAIDs was also found in several patients and included long-term use of NSAIDs for symptom relief of osteoarthritis pain where paracetamol had not been tried or NSAIDs with eGFR < 50 mL/min/1.73 m^2.

3.3. Predictors for PIMs

Univariate analysis revealed that age of 75 years or more, polypharmacy, CCI of more than 2, eGFR < 60 mL/min/1.73 m^2, and presence of depressive mood or anxiety identified using the HADS score were positively associated with PIMs (Table 4).

Logistic regression analysis revealed that after adjusting for age, sex, CCI, and eGFR, anxiety (OR = 2.06, 95% CI = 1.24-3.44) was associated with PIMs (Table 5), and polypharmacy was strongly associated with PIM prescription (OR = 4.55, 95% CI = 3.08–6.75). However, barring BZAs and Z-hypnotics, other PIMs did not show a significant association with anxiety (OR = 1.62, 95% CI = 0.93–2.82, *P* = 0.09). Among 141 patients with prescriptions for BZAs and/or Z-drugs, 78 (47.9%) reported having anxiety or depression.

3.4. Association between PIMs and adverse clinical outcomes

All participants were followed for 1 year. Between the two groups of patients with and without PIMs, there was no significant difference for age, CCI, or eGFR in patients

without polypharmacy at the start of the study. However, for patients with polypharmacy, there were significant differences for age and eGFR between those with PIMs and those without PIMs (Table 6). Among the 239 patients identified as having PIMs at the baseline assessment, 177 patients were assessed after 1 year. In addition, of the 501 patients without PIMs at the baseline assessment, 415 patients were followed for 1 year. Regarding falls and ED visits, these data were unavailable for several patients because some were unable to respond to the follow-up questionnaire or the information could not be verified (Figure 1). Patients who could not be followed-up were older (77.5 vs 75.2, *P*=0.001) and with more prescriptions (5.01 vs 4.20, *P*=0.001) and PIMs (41.9% vs 29.9%, *P*=0.005) than those completed follow-up for 1 year. The average number of prescriptions was 4.19 at the start of the study and 4.16 after 12 months. The percentage of patients receiving PIMs decreased from 32.3% at the beginning of the study to 28.7% after 12 months.

After 12 months, 142 patients (24.7%) reported at least one fall, 74 patients (12.5%) had at least one ED visit, and 46 patients (7.8%) reported at least one unplanned hospitalization.

Based on univariate analysis, in patients without polypharmacy, PIMs were not associated with any falls, ED visits, or unplanned hospitalizations over the 12-month follow-up period (Table 7). However, in patients with polypharmacy, PIMs were

significantly associated with an increased risk of falls over the 12 months, but were not significantly associated with ED visits or unplanned hospitalizations (Table 7).

In multivariate analyses, no significant association was seen between PIMs and ED visits or unplanned hospitalizations in patients both with and without polypharmacy. However, PIMs were associated with falls in the group of patients with polypharmacy, even after adjusting for age, sex, and CCI (OR = 2.03, 95% CI = 1.11–3.69); such a relationship was not observed in patients without polypharmacy (OR = 0.94, 95% CI = 0.46–1.90) (Table 8).

3.5. Predictors for adverse clinical outcomes

Additional analyses were conducted to identify predictors for each clinical outcome without stratifying by the number of prescriptions, to evaluate risk factors for the clinical outcomes.

3.5.1. Risk factors for falls

In multivariate logistic regression analysis conducted in all patients who were followed up, only age more than 75 years was significantly associated with at least one fall during the 1 year of follow-up (Table 9a). Patients with either polypharmacy or PIMs had a tendency for any falls, although this did not reach

statistical significance.

3.5.2. Risk factors for ED visits

In multivariate logistic regression analysis, age more than 75 years and polypharmacy were identified as predictors for ED visits (Table 9b).

3.5.3. Predictors for unplanned hospital admission

Only age more than 75 years was found to be related to unplanned hospitalization in logistic analysis (Table 9c).

4. DISCUSSION

This study clarified the prevalence and predictors for PIMs in a primary care setting in Japan. PIMs were prescribed to 32.3% of patients in this study. The most frequently prescribed PIMs were BZAs, Z-hypnotics, PPIs, sulfonylureas, duplicate drug class prescription, and NSAIDs. Polypharmacy was found in 39.5% of participants. Multivariate analysis showed that polypharmacy and anxiety were associated with PIMs. Previous studies have rarely focused on the relationship between psychological status and PIMs. The present study sheds new light on this aspect, indicating a significant association between anxiety and PIMs. In addition, PIMs were associated with increased risk of falls in patients with polypharmacy. This suggests the additive risk for falls of PIMs and polypharmacy in elderly patients.

4.1. Prevalence of PIMs and polypharmacy

The prevalence of PIMs by STOPP criteria version 2 was 32.3%, which was consistent with those of previous reports on primary care.[29-33, 36] Because the STOPP criteria were updated in 2015, reports that use STOPP criteria version 2 are relatively recent.[36, 37, 86-88] In Japan, 42.1% of patients admitted to university hospitals were identified as having PIMs, using STOPP criteria version 2.[48] The present study results indicated a lower prevalence of PIMs among patients in primary care compared with hospital admitted patients. This may be because most patients in an outpatient setting have milder conditions as compared with hospitalized patients.

The prevalence of PIMs can differ depending on the criteria used. Ideally, the criteria should be modified and applied in each region by considering approved prescriptions and dose regulations. The STOPP-J could be a candidate for defining PIMs in the present study setting. Unfortunately, the validity of this criteria has not yet been established. At present, it would be more reasonable to use the STOPP criteria than STOPP-J to improve measurement validity and domestic and international comparability. However, the results would not change much even if other criteria were used, because the STOPP-J and Beers criteria also define BZAs and PPIs as PIMs.

Polypharmacy was found in 39.5% of patients in the present study. Differences

in how the data are collected and how polypharmacy is defined makes international comparisons challenging. However, the results of the present study are consistent with those of previous reports, which range from 26.7% among primary care patients with polypharmacy in Germany,[89] 42.2% among a Swedish elderly population aged ≥ 77 years,[90] and 60.4% among primary care patients in Ireland.[91]

4.2. Frequently used PIMs

In the present study, the majority of PIMs were BZAs, Z-hypnotics, PPIs, sulfonylureas, duplicate drug class prescription, and NSAIDs. Details of PIMs vary according to the criteria used, as well as the region and setting. Compared with the previous version, STOPP criteria version 2 can usually be used to identify more patients because the list includes patients prescribed all types of BZAs for more than 4 weeks as well as those prescribed hypnotic Z-drugs, both of which were not counted as PIMs in the previous version. On the other hand, compared with the previous version of STOPP, CCBs for chronic constipation, which was one of the most frequent PIMs, were deleted in version 2.[39, 40]

BZAs and hypnotic Z-drugs are commonly prescribed for insomnia or anxiety in primary care settings despite the possibility of developing dependence. Johnson reported that 12.1% of older people are prescribed BZAs or Z-hypnotics in Scotland.[53] BZAs in

elderly people are reported to be common and are associated with falls,[92] hip fractures,[93] cognitive impairment,[94, 95] and ED visits.[96, 97] In Japan, the rate of BZA prescription is reported to be higher (14.5%)[98] than that in the United States (5.2%).[96] A previous study in Japan demonstrated frequent prescription of BZAs as PIMs.[48] Reports from Ireland also revealed that many PIMs are BZAs,[17, 29] and recommended that unnecessary prescription of BZAs should be reduced. For GPs, the decision to prescribe BZAs is said to be complex, uncomfortable, and challenging when taken within the constraints of daily general medical practice.[99] Hypnotic Z-drugs have been considered to be safer than BZAs, but these have also been reported to be associated with the risk of falls, hip fractures, and hospitalization for fall-related injuries;[100, 101] therefore, Z-drugs are included on the list of PIMs in both the STOPP version 2 and Beers criteria 2015, although they were not included in the previous version of STOPP.

PPIs were first marketed in the late 1980s, and the volume of PPI prescriptions has been rising considerably.[102, 103] PPIs are commonly prescribed for gastric symptoms and are popularly used for prevention of peptic ulcers in patients taking antiplatelets or anticoagulants. Long-term, high-dose PPIs have also been identified as one of the most frequent PIMs and a cause of budgetary concern.[29, 103] However, PPIs are sometimes overprescribed for long-term use and beyond the indications,[104] which may cause acute

or chronic kidney disease, hypomagnesemia, *Clostridium difficile* infection, osteoporotic fractures, and pneumonia.[105, 106] GPs should regularly assess the potential risks and benefits of prescribing such drugs and should consider dose reduction or discontinuation.

Sulfonylureas are commonly used for the treatment of diabetes mellitus, despite the risk for hypoglycemia. Hypoglycemia is the most frequent ADE caused by sulfonylureas among elderly patients with diabetes.[107] Hypoglycemia may be very serious in elderly patients; the condition may cause serious events like myocardial infarction or stroke and can lead to permanent neurological damage and even death. Hypoglycemia has been especially associated with sulfonylureas with a long duration of action, such as chlorpropamide, glibenclamide, and glimepiride.[108]

Duplication of drugs, the concurrent use of drugs within the same therapeutic group, has been reported to be substantial, although it is sometimes appropriate in managing chronic diseases among elderly patients.[35, 109] However, in most cases, drug duplication is not deliberate and may increase the risk of ADEs. The present study revealed that a total of 13 patients (1.3%) were identified with drug duplication, which is lower than a report from the United Kingdom.[35] Among patients with drug duplication, 4 patients were concomitantly prescribed angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (ARB), 5 patients were prescribed two types of

CCBs, 3 patients were prescribed more than two types of BZAs, and one patient was prescribed two probiotics. Combination therapy with ACE-I and ARB is also not recommended because it has been reported to worsen major renal outcomes.[110] The duplication of CCBs can exacerbate ADEs induced by CCBs such as bradycardia and constipation.[111] Previous studies have found that duplication of psychotropic drugs including BZAs is common, which may increase the risk for falls and cognitive disturbances.[112]

PIMs related to NSAID prescriptions were substantial in the present study. Chronic pain is very common among elderly people and leads to a negative impact on quality of life and declining function. NSAIDs are a mainstay of chronic pain management, but they have been associated with risks of gastrointestinal, cardiovascular, renal, hematological, and other systemic ADEs.[113] NSAIDs are typically more effective than acetaminophen, but acetaminophen is considered first-line therapy for the management of chronic pain because of the ADEs associated with long-term use of NSAIDs.[114]

4.3. Association between anxiety and PIMs

Polypharmacy has been recognized as a risk factor for PIMs,[29, 49, 50] and this study showed findings compatible with previous evidence. It is likely that the risk of potentially

inappropriate medications increases as the number of prescriptions increases. Female sex and advanced age have been reported to be associated with PIMs in several studies,[26, 28, 30, 40, 49] but a significant association between these variables and PIMs has not been detected in the present study. This may be because female or elderly patients tend to have anxiety and previous studies have not assessed such variables as predictors. Although depression was identified as a predictor for PIMs in one study,[44] the association was significant only in univariate analysis and not in multivariate analysis in the present study. After adjusting for other factors, anxiety was a significant predictor for PIMs. To the author's best knowledge, this is the first study to have assessed the association between anxiety and PIMs. Anxiety can be explained as a predictor mainly through its association with the prescription of BZAs or Z-hypnotics.

4.4. PIMs and risk of falls, ED visits, and hospitalization

This study demonstrated that, over a 12-month period, PIMs were associated with an increased risk of falls among elderly Japanese patients with chronic diseases and polypharmacy; however, the relationship between PIMs and falls was not observed in patients without polypharmacy. This suggests that PIMs and polypharmacy may have an interactive effect on falls. PIMs have been reported to be associated with an increased

risk of falling, mainly due to long-acting BZAs and other inappropriate psychotropics, and anticholinergic medications.[115, 116] However, this study demonstrated that when combined with polypharmacy, PIMs increase an elderly person's risk of falling. Polypharmacy has also been demonstrated to be an independent risk factor for falls.[78, 117] Recent studies have reported that polypharmacy is associated with a greater risk of falling but only when including the fall risk increasing drugs, such as BZAs or antidepressants.[118, 119] Additional analysis has revealed that, among patients with polypharmacy, BZAs or Z-hypnotics significantly increase the patient's risk of falling (adjusted OR = 2.11, 95% CI = 1.13–3.95). This result may be attributed to potential drug–drug interactions between PIMs including BZAs, Z-hypnotics, or other medications. Logically, the risk of interactions would increase as the number of medications increased. In addition, prescriptions with more than two PIMs were not associated with increased risk of falling compared with one PIM. This may indicate that coexistence of PIMs and polypharmacy overweigh the risk of duplication of PIMs. On the other hand, the reason why PIMs were not associated with increased risk of falling among patients without polypharmacy is not clear. It is possible that the result was influenced by patients who could not be followed-up, because such patients tended to be older and with more prescriptions and PIMs. It is considered that negative clinical events are likely to occur in such patients and the

difference between the groups compared in this study could be underestimated. High loss to follow-up rate might influence the negative association between PIMs and ED visit or hospitalization as well. Considering such possibility, it should not be declared that PIMs are safe for those who without polypharmacy.

ED visits and hospitalizations are costly events and the association between these events and PIMs has been previously reported.[15, 22, 39, 56-58] However, in the present study, no significant association between PIMs and ED visits or hospital admissions was found. This may be because the follow-up period was too short to detect significant differences. Previous studies conducted over longer periods (2 years or more) have demonstrated increased risks of ED visits or hospital admissions related to PIMs.[54, 60] A longer follow-up period of greater than 1 year may reveal an association between PIMs and hospital admissions, which was not identified here.

Additional analyses conducted in all patients who were followed up revealed that older age is associated with all outcomes (falls, ED visits, and unplanned hospitalizations), which seems to be a natural consequence of aging. Polypharmacy was associated with ED visits after adjusting for other variables. However, an interactive relationship, such as the relationship seen between PIMs and polypharmacy and falls, was not observed.

Polypharmacy, PIMs, and drug–drug interactions often happen simultaneously;

Novaes et al. termed these three factors the “iatrogenic triad”.[80] Few studies have investigated these aspects concomitantly, although these factors relate to each other and are independently associated with negative health outcomes. The present study is quite important in that the association between PIMs and outcomes was evaluated, with reduced confounding between PIMs and polypharmacy.

4.5. Study limitations

There are some limitations of this study. First, recall bias could cause an underestimation of adverse clinical outcomes. However, this would not affect the results of the study because it would occur in both groups. Second, the application of the study results to other populations may be limited because this work was conducted among patients from only one facility in urban Tokyo. The prevalence of PIMs was relatively low compared with previous studies, which might reflect higher awareness to PIMs and polypharmacy of GPs at the studied clinic. Nevertheless, the basic patient characteristics are consistent with those in previous studies. In addition, the high prescription rate of BZAs observed here is consistent with previous research in Japan.[48] Therefore, the participants in this study are thought to be fairly representative of the general elderly patient population in the primary care setting in Japan. Third, identification of PIMs was conducted mainly by one researcher, which may lead to impaired reliability of data. In order to increase

reliability, the researcher confirmed the prescription twice on the STOPP criteria. Fourth, there might be a possibility of underestimation of medications prescribed by other hospitals or clinics, although we tried to collect all the information about medications by referring patients' medication notebooks. Finally, the study was limited by the inability to assess patients' adherence to prescriptions; thus, the actual drug use by patients is not known, which may be one of the causes of non-significant results.

4.6. Implications of the study

Previous studies have shown that medication reviews using the STOPP criteria are effective in reducing PIMs and the number of prescriptions.[63] However, reducing PIMs is not simple, as it is related to physicians' knowledge and acceptance.[120] A recent systematic review argued that prescriber barriers to and enablers of minimizing PIMs included awareness of the problem; inertia secondary to lower perceived value proposition for ceasing versus continuing PIMs; self-efficacy with regard to personal ability to alter prescribing behavior; and feasibility of altering prescribing behavior in routine care environments given external constraints.[121] A qualitative study conducted in Belgium mentioned that GPs are recognizing that polypharmacy is an important problem but they do not have a ready-made solution for polypharmacy.[122] In addition, another systematic review reported that the process of deprescribing is influenced by various

patient barriers: disagreement with cessation, the lack of a process in place for cessation, and fear of the consequences of cessation. This process is also influenced by the following enablers of deprescribing: understanding the appropriateness of cessation; having a process in place for cessation; a general dislike of medications, and tailoring deprescribing is affected by information obtained from family members, friends, and the media.[123]

In order to address PIMs and polypharmacy, it may be effective to focus on the most frequently prescribed PIMs, i.e., BZAs and PPIs, and to provide additional support for patients who are experiencing anxiety and depression. It may be challenging for GPs to reduce or discontinue BZAs or Z-hypnotics because of patient dependency, but the potential harm in continuing these medications cannot be overlooked. To reduce the ADEs caused by PIMs, there must be greater emphasis on managing anxiety and depression. Methods such as cognitive behavioral therapy, counseling, or treatment for dependency on BZAs used to alleviate anxiety may be effective in decreasing PIMs.

Our results indicated a synergetic effect on increasing the risk for falls by PIMs and polypharmacy. Medical practitioners need to recognize the additional risk of PIMs on polypharmacy and are recommended to try to reduce the burden of both PIMs and polypharmacy. Reducing or discontinuing BZAs in an effort to reduce the number of

drugs may lead to a reduction of falls among elderly patients.

GPs are recommended to familiarize themselves with frequently prescribed PIMs and to regularly assess the necessity of such prescriptions. It has been reported that use of an algorithm is effective and feasible for discontinuation of multiple medications in community-dwelling older patients.[124] Several studies have showed that educational interventions aimed at GPs,[125, 126] computer-assisted approaches,[127] and a multidisciplinary medication review,[128] can improve the appropriateness of prescribing behavior for elderly patients in different settings.[129] A recent study conducted in Japan also reported that intervention by pharmacists was effective in reducing inappropriate prescriptions.[130] In addition, a patient-centered deprescribing process is proposed, which involves understanding the barriers to and enablers of deprescribing and working collaboratively with patients to achieve the best possible outcome for deprescribing of PIMs.[123] In order to pursue this process, patients need to be provided with information about the potential harm from continued use of PIMs, and they must be supported to reduce dosages or discontinue medications in a manner that is approved by their primary health care providers.

In the present study, it was difficult to conclude that PIMs and polypharmacy are in fact associated with negative health outcomes. To confirm these results among a more

generalized population, a multicenter trial that includes solo clinics and with a longer follow-up period is warranted. Also, interventional studies to improve the quality of prescriptions are needed, to assess which approach is most effective in reducing PIMs and polypharmacy and to evaluate whether a reduction in PIMs or polypharmacy can improve patients' health outcomes, including their quality of life. In the face of the unprecedented and fast-approaching global ageing society, urgent efforts must be made to construct systematic approaches, such as multidisciplinary medication reviews or computer assisted systems that are based on the established evidence.

5. CONCLUSION

The findings of this study demonstrate that PIMs and polypharmacy are common in elderly patients with chronic diseases in the Japanese primary care setting. BZAs, Z-hypnotics, PPIs, sulfonylureas, duplicate drug class prescription, and NSAIDs were the most frequent PIMs. Anxiety and polypharmacy were significantly associated with PIMs in multivariate analysis, adjusting for other independent variables. The findings of this study also demonstrate that PIMs are associated with falls, especially in patients with polypharmacy, which suggests the synergistic effect of PIMs and polypharmacy. Considering the high prevalence of PIMs and polypharmacy, efforts must be made to reduce both PIMs and the number of prescriptions through multidisciplinary medication reviews, patient and doctor education, and improved doctor–patient relationships.

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8. LIST OF FIGURES AND TABLES

FIGURE

TABLES

Figure 1. Flowchart of participants throughout the study

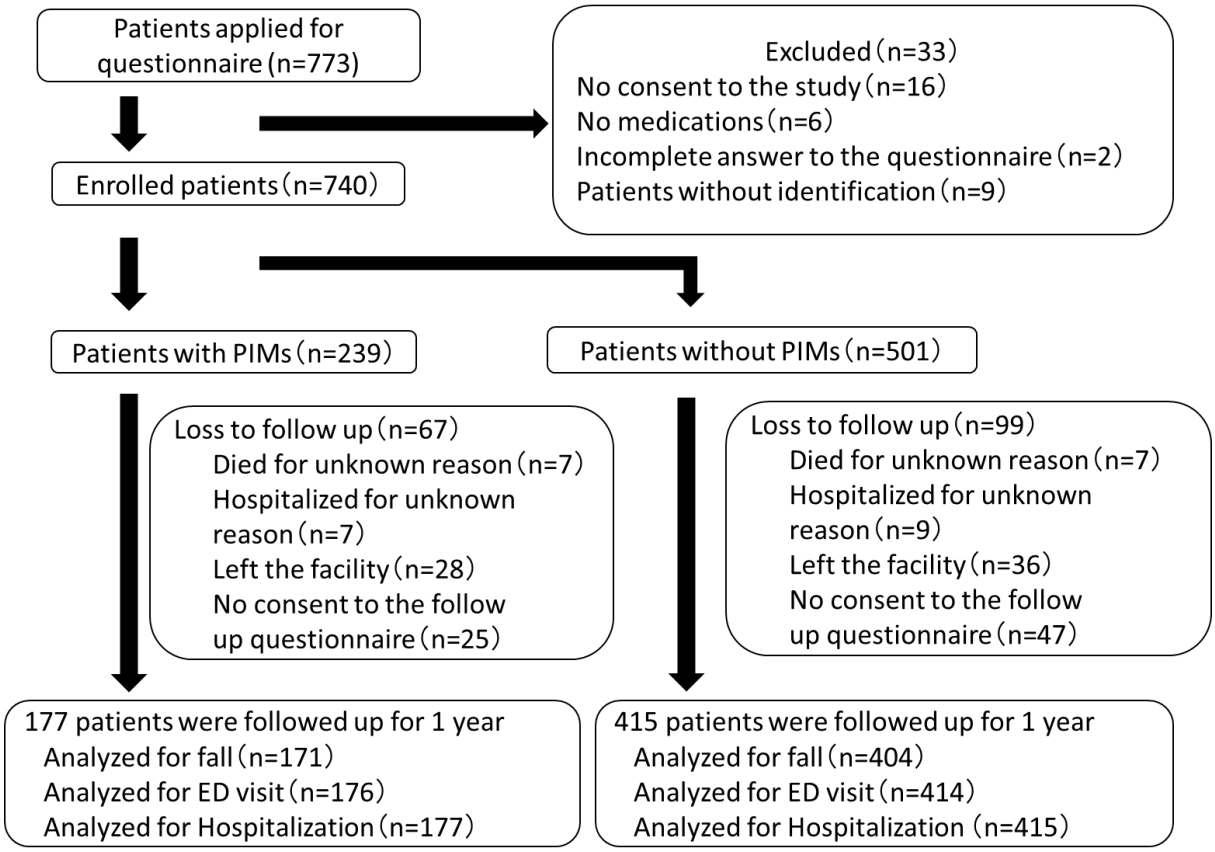

Table 1. Characteristics of the study population

Characteristics	Total (n=740)
Age, mean±SD	75.7±7.5
Sex, n (%)	
Male	361 (48.8)
Female	379 (51.2)
Drug prescriptions per patient, median (IQR)	4 (2-6)
Use of nonprescription medications, n (%)	234 (32.1)
Charlson comorbidity index, median (IQR)	1 (0-1)
eGFR, mean (mL/min/1.73m^2)	60.8
Smoking status, n (%)	
Current smoker	71 (9.8)
Past smoker	285 (39.2)
Never smoker	371 (51.0)
Regular drinker, n (%)	239 (32.8)
Lives alone, n (%)	192 (26.6)
Economic status, n (%)	
Less than average	125 (17.3)
Average	445 (61.5)
More than average	153 (21.2)
Educational attainment, n (%)	
≦High school	287 (40.5)
>High school	422 (59.5)
Anxiety by HADS, n (%)	106 (15.9)
Depression by HADS, n (%)	155 (22.9)
PIMs by STOPP version 2	239 (32.3)

Missing values were omitted from percentage calculation

SD = standard deviation, IQR = interquartile range, HADS = Hospital Anxiety and Depression Scale, PIMs = potentially inappropriate medications

Table 2. Underlying medical conditions of the study population

Underlying medical conditions	n (%)
Hypertension	532 (71.9)
Dyslipidemia	377 (50.9)
Chronic Kidney Disease	362 (49.0)
Diabetes mellitus	151 (20.4)
Hyperuricemia/gout	140 (18.9)
Cerebrovascular disease	131 (17.7)
Respiratory disease (Bronchial Asthma, COPD)	97 (13.1)
Gastric ulcer	96 (13.0)
Dementia	58 (7.8)
Cardiovascular disease	57 (7.7)
Liver disease	41 (5.5)

Table 3. Details of potentially inappropriate medications by STOPP criteria ver. 2

	Contents	n
A1	Any drug without an evidence-based clinical indication	1
A3	Any duplicate drug class prescription	13
B3	Beta-blocker in combination with verapamil or diltiazem	1
B7	Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	1
B10	Centrally-acting antihypertensives, unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	1
B11	ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia	1
B12	Aldosterone antagonists with concurrent potassium-conserving drugs without monitoring of serum potassium	2
C4	Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	2
C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation without a clear indication for aspirin	1
C7	Ticlopidine in any circumstances	3
C11	NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis	1
D5	Benzodiazepines for ≥ 4 weeks	108
D14	First-generation antihistamines	1
E4	NSAID's if eGFR < 50 ml/min/1.73m^2	6
E6	Metformin if eGFR < 30 ml/min/1.73m^2	2
F2	PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	64

G1	Theophylline as monotherapy for COPD	1
H1	Non-COX-2 selective non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	1
H3	Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried	5
H7	COX-2 selective NSAIDs with concurrent cardiovascular disease	1
I1	Antimuscarinic drugs for overactive bladder syndrome with concurrent dementia or chronic cognitive impairment or narrow-angle glaucoma, or chronic prostatism	1
I2	Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope	1
J1	Sulphonylureas with a long duration of action with type 2 diabetes mellitus	33
K1	Benzodiazepines	108
K3	Vasodilator drugs with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg	1
K4	Hypnotic Z-drugs	47

Table 4. Association between each variable and PIMs by univariate analysis

Variables	PIMs by STOPP version 2		*P* value
	Yes: n=239 (%)	No: n=501 (%)	
Sex			0.300
Male	110 (30.5)	251 (69.5)	
Female	129 (34.0)	250 (66.0)	
Age			<0.001
<75	94 (25.5)	275 (74.5)	
≧75	145 (39.1)	226 (60.9)	
Economic status			0.294
Less than average	48 (38.4)	77 (61.6)	
Average	138 (31.0)	307 (69.0)	
More than average	49 (32.0)	104 (68.0)	
Educational attainment			0.932
≦High school	92 (32.1)	195 (67.9)	
>High school	134 (31.8)	288 (68.2)	
Household composition			0.130
Living alone	70 (36.5)	122 (63.5)	
Others	162 (30.5)	369 (69.5)	
Prescription medications			<0.001
≦4 (Non-polypharmacy)	80 (17.9)	368 (82.1)	
≧5 (Polypharmacy)	159 (54.5)	133 (45.5)	
CCI			<0.001
0-1	155 (28.0)	499 (72.0)	
≧2	81 (44.5)	101 (55.5)	

Use of nonprescription medications			0.404
Yes	81 (34.6)	153 (65.4)	
No	156 (31.5)	339 (68.5)	
eGFR			0.002
eGFR<60ml/min/1.73m^2	134 (37.6)	222 (62.4)	
eGFR≧60ml/min/1.73m^2	103 (27.0)	279 (73.0)	
Anxiety by HADS			<0.001
≦7	156 (27.8)	405 (72.2)	
≧8	54 (50.9)	52 (49.1)	
Depression by HADS			<0.001
≦7	142 (27.3)	379 (72.7)	
≧8	71 (45.8)	84 (54.2)	

Missing values were omitted from percentage calculation

CCI = Charlson Comorbidity Index, HADS = Hospital Anxiety and Depression Scale

Table 5. Factors associated with PIMs by logistic regression analysis (n=649)

Variables	Univariate	Multivariate	***P* value**[†]
	Crude OR (95% CI)	**Adjusted OR**[‡] **(95% CI)**	
Female	1.18 (0.87-1.60)	1.32 (0.90-1.93)	0.157
Age≧75	1.88 (1.37-2.57)	1.06 (0.72-1.56)	0.767
Polypharmacy[§]	5.50 (3.94-7.68)	4.69 (3.18-6.93)	<0.001
CCI≧2	2.06 (1.46-2.92)	1.40 (0.90-2.16)	0.135
eGFR<60ml/min/1.73m^2	1.64 (1.20-2.23)	1.28 (0.87-1.88)	0.218
Anxiety by HADS	2.70 (1.77-4.12)	2.09 (1.25-3.48)	0.005
Depression by HADS	2.26 (1.56-3.27)	1.44 (0.91-2.27)	0.121

CCI = Charlson Comorbidity Index, HADS = Hospital Anxiety and Depression Scale

† *P* value was calculated for multivariate analysis.

‡ Gender, age, polypharmacy, CCI, eGFR, anxiety and depression were adjusted for multivariate analysis.

§Polypharmacy was defined to be prescription with more than 5 drugs by physicians

Table 6. Characteristics of the study population (stratified by number of prescriptions)

Variables	Polypharmacy† (+)			Polypharmacy† (-)		
	PIMs (+) n=159 (%)	PIMs (-) n=133 (%)	*P* Value	PIMs (+) n=80 (%)	PIMs (-) n=368 (%)	*P* Value
Sex			0.219			0.266
Male	77 (48.4)	74 (55.6)		33 (41.3)	177 (48.1)	
Female	82 (51.6)	59 (44.4)		47 (58.8)	191 (51.9)	
Age (years)	79.1	76.8	0.011	74.1	74.1	0.941
Economic status			0.521			0.176
>average	29 (18.5)	18 (14.2)		20 (25.6)	86 (23.8)	
average	98 (62.4)	87 (68.5)		40 (51.3)	220 (60.9)	
<average	30 (19.1)	22 (17.3)		18 (23.1)	55 (15.2)	
Educational attainment			0.733			0.967
≦high school	62 (41.6)	55 (43.7)		30 (39.0)	140 (39.2)	
>high school	87 (58.4)	71 (56.3)		47 (61.0)	217 (60.8)	
eGFR			0.004			0.154
eGFR<60 ml/min/1.73m^2	108 (68.4)	69 (51.9)		26 (32.9)	153 (41.6)	
eGFR≧60 ml/min/1.73m^2	50 (31.6)	64 (48.1)		52 (67.1)	215 (58.4)	
CCI	1.46	1.55	0.532	0.73	0.64	0.436

PIMs = potentially inappropriate medications, CCI = Charlson Comorbidity Index

†Polypharmacy was defined to be prescription with more than 5 drugs by physicians

Table 7. Association between PIMs and falls, ED visit, and hospitalization after 12 months of follow-up, by univariate analysis

Outcomes	Polypharmacy† (+)		*P* Value	Polypharmacy† (-)		*P* Value
	PIMs (+)	PIMs (-)		PIMs (+)	PIMs (-)	
Fall, n (%)	n=110	n=106	0.015‡	n=61	n=298	0.935‡
	44 (40.0)	26 (24.5)		12 (19.7)	60 (20.1)	
ED visit, n (%)	n=115	n=109	0.417‡	n=61	n=305	0.444§
	25 (21.7)	19 (17.4)		3 (4.9)	27 (8.9)	
Hospitalization, n (%)	n=116	n=109	0.872‡	n=61	n=306	0.146§
	12 (10.3)	12 (11.0)		1 (1.6)	21 (6.9)	

PIMs = potentially inappropriate medications, ED = emergency department

†Polypharmacy was defined to be prescription with more than 5 drugs by physicians

‡Chi-square test

§Fisher's exact test

Table 8. PIMs and risk of falls, ED visit, and hospitalization by multivariate analysis

Outcomes	Polypharmacy† (+)		Polypharmacy† (-)	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Fall	2.03 (1.11-3.69)	0.021	0.94 (0.46-1.90)	0.857
ED visit	1.31 (0.65-2.66)	0.448	0.52 (0.15-1.80)	0.304
Hospitalization	0.82 (0.34-2.00)	0.663	0.21 (0.03-1.65)	0.138

Odds ratios were adjusted for gender, age, and CCI

OR = odds ratio, CI = confidential interval, PIMs = potentially inappropriate medications, ED = emergency department, CCI = Charlson Comorbidity Index

†Polypharmacy was defined to be prescription with more than 5 drugs by physicians

Table 9a. Factors associated with falls by logistic regression analysis (n=575)

Variables	**Adjusted OR (95% CI)**	***P* value†**
Female sex	1.35 (0.90-2.01)	0.145
Age≧75	1.78 (1.19-2.65)	0.005
PIMs	1.44 (0.93-2.22)	0.100
Polypharmacy†	1.51 (0.97-2.35)	0.067
CCI≧2	1.07 (0.66-1.73)	0.781

Table 9b. Factors associated with ED visit by logistic regression analysis (n=590)

Variables	**Adjusted OR (95% CI)**	***P* value†**
Female sex	0.63 (0.37-1.07)	0.085
Age≧75	2.41 (1.40-4.15)	0.001
PIMs	0.99 (0.56-1.72)	0.951
Polypharmacy†	2.11 (1.18-3.75)	0.011
CCI≧2	1.20 (0.67-2.14)	0.540

Table 9c. Factors associated with unplanned hospitalization by logistic regression analysis (n=592)

Variables	**Adjusted OR (95% CI)**	***P* value†**
Female sex	0.63 (0.33-1.21)	0.167
Age≧75	4.23 (2.01-8.88)	<0.001
PIMs	0.61 (0.29-1.28)	0.190
Polypharmacy†	1.35 (0.66-2.76)	0.408
CCI≧2	1.70 (0.85-3.42)	0.136

OR = odds ratio, CI = confidential interval, PIMs = potentially inappropriate medications, CCI = Charlson Comorbidity Index

†Polypharmacy was defined to be prescription with more than 5 drugs by physicians

慢性疾患を持つ患者さまの内服薬と生活に関する調査

＜回答者の皆様のプライバシーを保護するために＞

本研究は慢性疾患を持つ65歳以上の患者様の内服薬と生活の実態を調査するための自己記入式アンケート調査です。お手数ですが、質問にご回答いただいた後、調査票を設置された回収箱に入れてください。

皆様には氏名をご記入いただきますが、回収後に切り離します。データの管理は河北家庭医療学センターの研究者のみが行い、個人情報が外部に漏れることはありません。アンケート調査の回答に加え、カルテ情報も解析に利用させて頂く予定です。調査結果は個人が特定できない形で関連学会・雑誌などに発表させていただきます。本研究で得られたすべての情報は研究目的以外に使用されることはありません。また、ご回答いただいた調査用紙は研究終了後にシュレッダー処理を行い破棄いたします。

本研究への参加は任意であり、研究に参加しないことによって診療上の不利益は発生しません。なお、同意後に調査を辞退していただいても構いません。

また、同意いただけた患者さまには、半年後、1年後にもアンケート調査をお願いいたします。

＜ご記入にあたってのお願い＞

◆質問は全部で32問です。 およそ10分で回答が終了します。回答が難しい質問もあるかもしれませんが、できるだけ全質問にご回答くださるようお願いいたします。

◆本研究に関し、ご不明な点は下記までお問い合わせ下さい。

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慢性疾患を持つ患者さまの内服薬と生活に関する調査

調査に関する説明をお読みいただいたうえで、調査に同意していただけますか？
（いずれかにチェックしてください）

☐同意する　　☐同意しない

同意していただける方は、氏名の記入をお願いいたします。
（この表紙は回収後すぐに切り離します）

氏名　（　　）

それでは、次ページからのアンケートのご回答をお願いいたします。

以下の質問について現在の状況ついてのご回答をお願いします。まず、あなたの生年月と性別を教えてください（該当する項目の□に✓をつけ、括弧内に数字を記入してください）。

生年月：□大正・□昭和（　　）年（　　）月

性別　：□男　　□女

Ⅰ　ご自身の状況ついて、それぞれの質問について該当する項目の□に１つ✓をつけ、括弧内にその詳細を記載してください。

1. あなたは、普段お薬手帳を利用していますか？

□0　はい

□1　いいえ

2. あなたは、当院以外の医療機関に定期的に通院していますか？「はい」、の場合は、当院以外にいくつ通院されているか括弧内に記載してください。

□0　はい　→（　　）

□1　いいえ

3. あなたは、現在当院以外の医療機関から定期的に処方を受けていますか？

□0　はい　→お薬手帳または処方内容のわかるものを回収時に受付にご提出下さい。ない場合は、次回外来時に持参をお願いいたします。

□1　いいえ

4. あなたは、現在の処方薬の数について、どう感じていますか？

□1 多すぎる

□2 ちょうどよい

□3 足りない

5. あなたは、できれば現在の処方薬の数を減らしたいと感じていますか？

□0 そう思う

□1 そうは思わない

6. あなたは現在医師からの処方以外の市販薬・サプリメント・健康食品・漢方薬などを定期的に使用していますか？

□0 はい

□1 いいえ

6. の設問で「1. はい」と回答された方は以下 7・8 の質問にご回答ください。

7. 以下のもののうち、現在定期的に使用しているものを教えてください（複数回答可）。どのようなものか括弧内に具体的に記載してください。

(ア) 市販薬　（解熱鎮痛薬、抗アレルギー薬、胃腸薬、便秘薬等）

□0 はい→（　　）

□1 いいえ

(イ) サプリメント（ビタミン剤、カルシウム、亜鉛、ヒアルロン酸等）または健康食品（青汁、クロレラ、プロポリス等）

□0 はい→（　　）

□1 いいえ

(ウ) 漢方薬（医師の処方ではなく薬局等で購入したもの）

□0 はい→（　　）

□1 いいえ

(エ) その他上記にあてはまらないもの

→（　　）

8. あなたは医師からの処方以外の市販薬・サプリメント・健康食品・漢方薬などを使用していることを、主治医に伝えていますか？

□0 はい

□1 いいえ

Ⅱ　病気と生活に関する質問です

9. あなたは、過去 1 年間で救急受診（救急外来の受診、救急車利用）をしましたか？

□0　はい→（　　）回

□1　いいえ

10. あなたは、過去 1 年間に緊急で入院しましたか？（手術や検査などの予定入院を除く）

□0　はい

□1　いいえ

11. あなたは過去 1 年間に転んだ（膝より上の部分が地面に付く）ことがありましたか？

□0　はい→ □1～2 回、□3～4 回、□5 回以上

□1　いいえ

12. あなたはタバコを吸ったことがありますか？

□1　現在喫煙している

□2　過去に喫煙していたが、現在は禁煙している

□3　吸ったことがない、もしくはほとんど吸ったことがない

13. あなたは、定期的に飲酒をしていますか？

□0　はい

□1　いいえ

14. あなたは現在何人暮らしですか？

（　　）人

15. あなたの最終学歴を教えてください。

□1 中学校

□2 高校

□3 専門学校

□4 大学以上

□5 その他

16. あなたの経済状況について教えてください

□1 かなり余裕がある

□2 平均より余裕がある

□3 平均的である

□4 平均より余裕がない

□5 全く余裕がない

17. あなたの普段の活動状況を教えてください

□1 ほとんど家の中で過ごし、介助なしでは外出しない

□2 隣近所に外出する

□3 交通機関等を利用して外出する

18. 以下の疾患の診断を受けたことがありますか？

病名	あり	なし
脳血管障害（脳梗塞・脳出血など）……	□0	□1
緑内障……	□0	□1
心不全……	□0	□1
心筋梗塞・狭心症……	□0	□1
認知症……	□0	□1
高血圧症……	□0	□1
糖尿病……	□0	□1
痛風または高尿酸血症……	□0	□1
肝炎・肝硬変……	□0	□1
脂質異常症または高脂血症……	□0	□1
末梢血管疾患（下肢閉塞性動脈硬化症など）	□0	□1
白血病・リンパ腫……	□0	□1
気管支喘息……	□0	□1
慢性呼吸器疾患（肺気腫、COPD など）‥	□0	□1
甲状腺疾患……	□0	□1
膠原病……	□0	□1
前立腺肥大症……	□0	□1
腎臓の病気……	□0	□1
胃・十二指腸潰瘍……	□0	□1
手足の麻痺症状……	□0	□1
癌……	□0	□1
静脈血栓症……	□0	□1

Ⅲ　これ以降の質問はあなたが最近どのように感じているかお尋ねします

次に挙げてある 14 の設問を読み、それぞれについて 4 つの答えのうち、あなたのこの１週間のご様子にもっとも近いものの□に✓をつけて下さい。

１.緊張感を感じますか？

□1　ほとんどいつもそう感じる

□2　たいていそう感じる

□3　時々そう感じる

□4　全くそう感じない

２.以前楽しんでいたことを今でも楽しめますか？

□1　以前と全く同じ位楽しめる

□2　以前より楽しめない

□3　すこししか楽しめない

□4　全く楽しめない

３.まるで何かひどいことが今にも起こりそうな恐ろしい感じがしますか？

□1　はっきりあって、程度もひどい

□2　あるが程度はひどくない

□3　わずかにあるが、気にならない

□4　全くない

4.笑えますか？いろいろなことのおかしい面が理解できますか？

□1　以前と同じように笑える

□2　以前と全く同じようには笑えない

□3　明らかに以前ほどには笑えない

□4　全く笑えない

5.くよくよした考えが心に浮かびますか？

□1　ほとんどいつもある

□2　たいていある

□3　時にあるが、しばしばではない

□4　ほんの時々ある

6.機嫌が良いですか？

□1　全くそうではない

□2　しばしばそうではない

□3　時々そうだ

□4　ほとんどいつもそうだ

7.のんびり腰かけて、そしてくつろぐことができますか？

□1　できる

□2　たいていできる

□3　できることがしばしばではない

□4　全くできない

８.まるで考えや反応がおそくなったように感じますか？

□1　ほとんどいつもそう感じる

□2　たいへんしばしばにそう感じる

□3　時々そう感じる

□4　全くそう感じない

９.胃が気持ち悪くなるような一種おそろしい感じがしますか？

□1　全くない

□2　時々感じる

□3　かなりしばしば感じる

□4　たいへんしばしば感じる

１０．自分の身なりに興味を失いましたか？

□1　明らかにそうだ

□2　自分の身なりに充分な注意を払っていない

□3　自分の身なりに充分な注意を払っていないかもしれない

□4　自分の身なりには充分な注意を払っている

１１．まるで終始動きまわっていなければならないほど落ちつきがないですか？

□1　非常にそうだ

□2　かなりそうだ

□3　余りそうではない

□4　全くそうではない

１２．これからのことが楽しみにできますか？

□1　以前と同じ程度にそうだ

□2　その程度は以前よりやや劣る

□3　その程度は明らかに以前より劣る

□4　ほとんど楽しみにできない

１３．急に不安に襲われますか？

□1　大変しばしばにそうだ

□2　かなりしばしばにそうだ

□3　しばしばでない

□4　全くそうでない

１４．良い本やラジオやテレビの番組を楽しめますか？

□1　しばしばそうだ

□2　時々そうだ

□3　しばしばでない

□4　ごくたまにしかない

全ての設問にお答え下さったでしょうか？もう一度見直して下さい。

質問は以上です。　ご協力ありがとうございました。

慢性疾患を持つ患者さまの内服薬と生活に関する調査-追跡調査②

本調査は 2016 年 1 月から 3 月にかけて行った「慢性疾患を持つ 65 歳以上の患者様の内服薬と生活に関する調査」の 1 年後の追跡調査です。本調査への参加は任意であり、辞退される場合も診療上の不利益は発生しません。追跡調査に同意いただける場合は、質問にご回答いただいた後、調査票を設置された回収箱に入れてください。

あなたの生年月と性別、氏名、体重、以下の質問についてご回答をお願いします。(該当する項目の□に✓をつけ、括弧内に数字を記入してください)。

生年月：□大正・□昭和（　　）年（　　）月

性別　：□男　　□女

氏名　：（　　）

1.あなたは、最近 1 年間に救急受診（救急外来の受診、救急車利用）をしましたか？

□0　はい→（　　）回

□1　いいえ

いつ　　どこに

いつ　　どこに

いつ　　どこに

2.あなたは、最近 1 年間に緊急で入院しましたか？（手術や検査などの予定入院を除く）

□0　はい→（　　）回

□1　いいえ

いつ　　どこに

いつ　　どこに

いつ　　どこに

3．あなたは、最近 1 年間に転んだ（膝より上の部分が地面に付く）ことがありましたか？

□0　はい→（　　）回

□1　いいえ

Appendix 3: Screening Tool of Older Person's Prescriptions (STOPP) version 2.

The following prescriptions are potentially inappropriate to use in patients aged 65 years and older.

Section A: Indication of medication

1. Any drug prescribed without an evidence-based clinical indication.

2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined.

3. Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).

Section B: Cardiovascular System

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).

2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).

3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).

4. Beta blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).

5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem).

6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).

7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).

8. Thiazide diuretic with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65

mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).

9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).

10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).

11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.

12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).

13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse).

Section C: Antiplatelet/Anticoagulant Drugs

1. Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).

2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).

3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).

4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high

grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).

5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin).

6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (No added benefit from dual therapy).

7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).

8. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).

9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).

10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).

11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease).

Section D: Central Nervous System and Psychotropic Drugs

1. TriCyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).

2. Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).

3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).

4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).

5. Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).

6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms).

7. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity).

8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).

9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).

10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).

11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).

12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).

13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy).

14. First-generation antihistamines (safer, less toxic antihistamines now widely available).

Section E: Renal System. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)

1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m^2 (risk of digoxin toxicity if plasma levels not measured).

2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m^2 (risk of bleeding).

3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m^2 (risk of bleeding).

4. NSAID's if eGFR < 50 ml/min/1.73m^2 (risk of deterioration in renal function).

5. Colchicine if eGFR < 10 ml/min/1.73m^2 (risk of colchicine toxicity).

6. Metformin if eGFR < 30 ml/min/1.73m^2 (risk of lactic acidosis).

Section F: Gastrointestinal System

1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).

2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).

3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).

4. Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day; no evidence of enhanced iron absorption above these doses).

Section G: Respiratory System

1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).

2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).

3. Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).

4. Non-selective beta-blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm).

5. Benzodiazepines with acute or chronic respiratory failure i.e. $pO2 < 8.0$ kPa ± $pCO2 > 6.5$ kPa (risk of exacerbation of respiratory failure).

Section H: Musculoskeletal System

1. Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).

2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).

3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).

4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthrtitis (risk of systemic corticosteroid side-effects).

5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).

6. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).

7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).

8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease).

9. Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture).

Section I: Urogenital System

1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).

2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).

Section J. Endocrine System

1. Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).

2. Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure).

3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).

4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).

5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).

6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).

Section K: Drugs that Predictably Increase the Risk of Falls in Older People

1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).

2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).

3. Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin Ⅱ receptor blockers) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20 mmHg (risk of syncope, falls).

4. Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

Section L: Analgesic Drugs

1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).

2. Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).

3. Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain).

Section N: Antimuscarinic/Anticholinergic Drug Burden

Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity).