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To: Commissioners of Prefectural/Cities with Established Health Centers/Special District Health Department (Bureau)

Director of the Office of Medical Safety Promotion,
General Affairs Division, Health Policy Bureau, MHLW
(Official seal omitted)
Director of the Pharmaceutical Safety Division,
Pharmaceutical Safety and Environmental Health Bureau, MHLW
(Official seal omitted)

Guidance on Appropriate Medication for Elderly Patients (general)

We would like to express our deep appreciation for your special support of us to promote the medical government.

As the aging society progresses, safety issues are arising more readily in conjunction with multiple drug use (i.e., the concomitant use of multiple drugs) which aims to address symptoms associated with the various age-related physiological changes and co-morbidities. In light of this concern, MHLW established a Study Group on the Appropriate Medication for Elderly Patients (the Study Group) in April 2017 in order to promote safety measures related to drug therapies for geriatric patients, and it is currently assessing the factors necessary to ensure safety.

The Study Group prepared the Guidance on Appropriate Medication for Elderly Patients (general). Please inform the relevant medical institutions in your jurisdiction of this matter for practical use of the guidance.

Please note that the terms used in this guideline are defined as follows.

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1. The term “adverse drug events (ADE)” is used to denote untoward signs or symptoms appearing subsequent to use of drugs whether or not they are caused by such drugs.

2. The term “polypharmacy” denotes not simply using numerous medications concurrently, but rather the various concerns that this practice can lead to, such as increased risk of ADEs, medication errors and decreased medication adherence, among others.

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Guidance on Appropriate Medication for Elderly Patients (general)

Introduction

There have been more demands of medication for the elderly with an increase in the number of elderly people, specifically those aged 75 years or older. Meanwhile, they are prone to have adverse drug events* as their pharmacodynamics and drug response differ from those of younger adults due to physiological changes associated with aging and the drugs administered separately to treat comorbidities which tend to cause drug interactions. At the same time, medication itself tends to cause some problems due to changes in living function and environment. This guidance aims to optimize drug therapies for geriatric patients (avoidance of adverse drug events, improvement of medication adherence, avoidance of inadequate medical care) as a summary of fundamental points to consider in order to better administer drug therapies in consideration of the special characteristics of geriatric patients. This guidance is intended to provide reference information to be used in the course of clinical practice and in issuing prescriptions. This guidance concerns elderly people aged 65 years and older, and it places particular focus on elderly patients over the age of 75, a group in which the average number of types of medications used is increased.

Additionally, this guidance is aimed primarily at physicians, dentists, and pharmacists. It is expected that nurses and other occupations will refer to it to aid their understanding of patient medication adherence status and disease symptoms as well as their efforts to support adherence. However, it does not assume the use by patients and their families. Patients and their families should consult healthcare professionals if they have any questions or need clarification.

* In this guidance, the term “adverse drug event (ADE)” is used to denote untoward signs or symptoms appearing subsequent to the use of drugs whether or not they are caused by such drugs. If a causal relationship with the drugs used is suspected or cannot be ruled out, then the term “adverse drug reaction (ADR) is used.

1. Polypharmacy concept

An increase in adverse drug events is attributed to various disease-related, functional, and social factors, and the 2 biggest factors are changes in pharmacokinetics/pharmacodynamics due to aging and multiple drug use. What harms patients among multiple drug use is specifically called polypharmacy. Multiple drug use and polypharmacy are referred to as two different things in this guidance. Polypharmacy denotes not simply using numerous medications concurrently, but rather the various concerns to which this practice can lead, such as increased risk of ADEs, medication errors, decreased medication adherence, among others.

There is no strict definition as to how many medications used concurrently will constitute

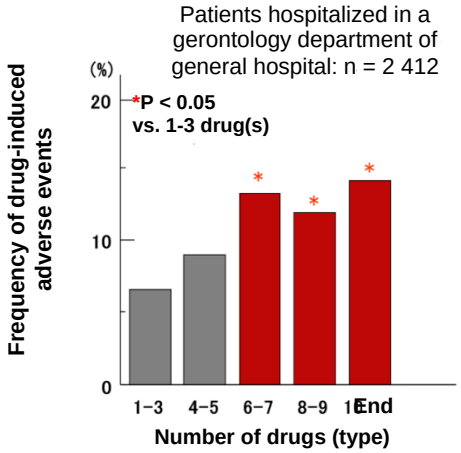
polypharmacy, and the prescriptions best suited to a particular patient may also change in light of her/his overall condition, life function, and living environment. Adverse drug events increase virtually in proportion to the number of drugs, and some data show that the use of 6 or more drugs was particularly related to an increase in adverse drug events (Figure 1). However, some patients need 6 or more drugs for treatment and other patients may have problems with 3 drugs. In essence, it is how the treatment goes for the patients that counts. Therefore, it is necessary not only to focus on a uniform number of drugs/drug types, but to optimize prescription details in terms of assured safety if polypharmacy is corrected.

2. Status of multiple-drug use

(1) The whole picture of medicines taken including those prescribed at multiple institutions

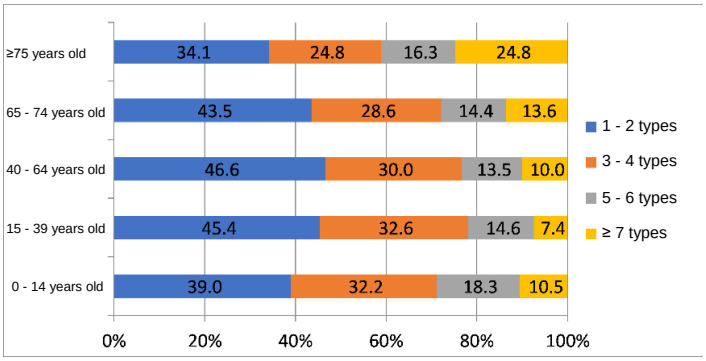
The elderly tend to suffer cumulative effects of lifestyle-related diseases and geriatric syndromes (see “4. Adverse events which require attention for multiple drug use, diagnosis, and chance for prescription revision”) and thereby use multiple drugs prescribed for treatment or alleviating increasing numbers of symptoms. As shown in Figure 2 of the nationwide prescription survey results at insurance pharmacies, approximately 25% of the elderly aged 75 years or older have been prescribed 7 drugs or more, and 40% have been prescribed 5 drugs or more.

Figure 1 Number of drugs taken and the frequency of adverse drug events



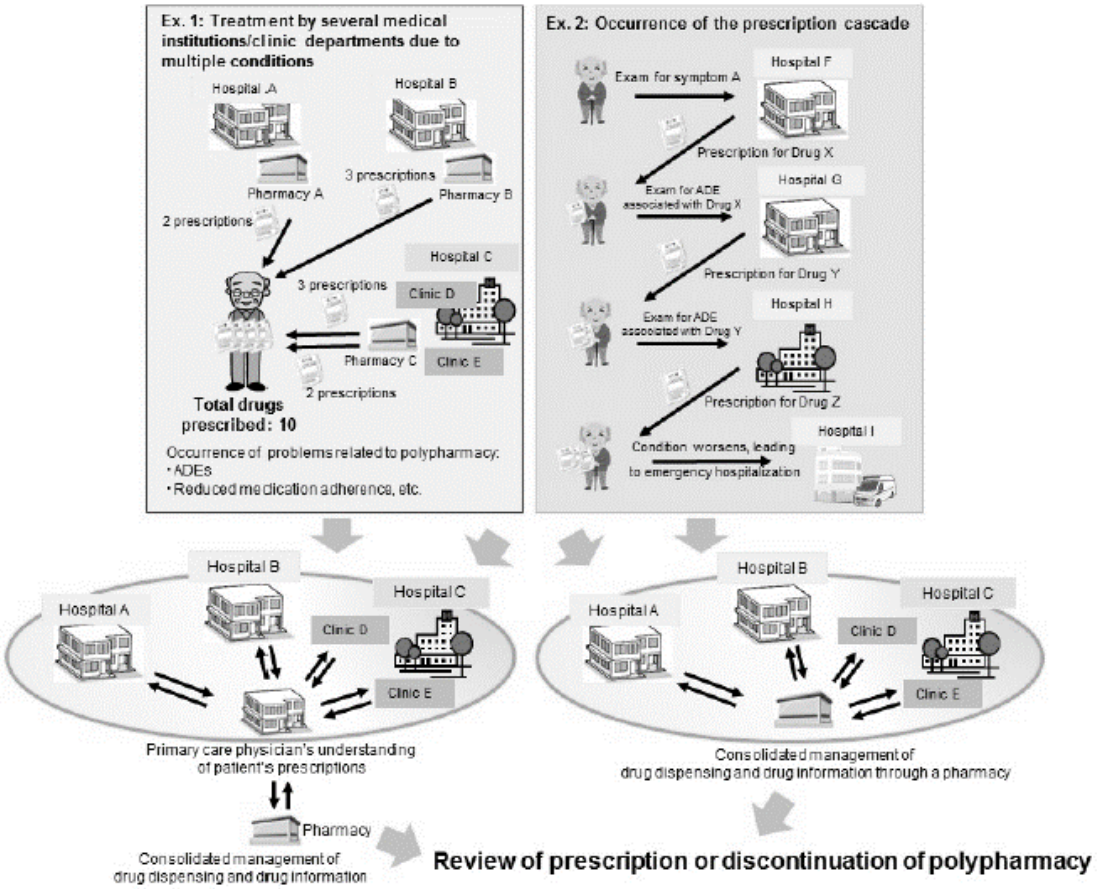
(quoted from the “Guidelines for Medical Treatment and its Safety in the Elderly 2015” (The Japan Geriatrics Society))

Figure 2 Number of drug types dispensed at a single insurance pharmacy (per month) (Statistics of Medical Care Activities in Public Health Insurance in 2016)



Discontinuation of polypharmacy requires cooperation among healthcare professionals and education to patients because it is related to a failure to grasp the whole prescription status and overlapped prescriptions due to an increase in comorbidities and medical consultation at multiple departments/medical institutions.

Figure 3 Sequence of formation and discontinuation of polypharmacy



(2) Polypharmacy formation

Figure 3 shows 2 typical examples of circumstances where polypharmacy is formed. Cumulative medications as a result of every new hospital or clinic visit due to every new symptoms even with just a couple of drugs prescribed per new visit, which can form polypharmacy (Figure 3, Example 1). In addition, when every new disease is treated with medication, the practice may fall into the “prescription cascade,” a vicious cycle where new prescriptions are issued to address ADEs associated with previously prescribed drugs (Figure 3, Example 2).

Progress towards eliminating polypharmacy arising from such circumstances is expected to be achieved as a result of factors such as primary care physicians ensuring they gain a comprehensive understanding of each patient’s existing prescriptions when initiating treatment, or through use of a single pharmacy (Figure 3, below).

3. Basic idea of medication review and flow chart

(1) General rules of prescription review

Medication can be reviewed in various treatment environments such as outpatient visit, hospital admission, nursing-facility entry or when a new acute disease develops and possible adverse drug events are observed.

○ **Comprehensive Geriatric Assessment**

The elderly may exhibit decreased medication adherence due to various reasons. Assessment of cognitive function, activities of daily living (ADL), living environment, drug preference of each patient, etc., which are the main components of the Comprehensive Geriatric Assessment (CGA), will contribute to understanding of their organ disorders, functional disorders, and the ability to manage their own medications. It is important to grasp all the departments/medical institutions the patient is visiting in this process and to check all prescribed drugs (including guidance-mandatory drugs/over-the-counter drugs, (hereinafter referred to as “over-the-counter drugs”), supplements, etc.) and medication adherence.

○ **Monitoring physiological functions, such as renal function**

For drugs that are mainly excreted by the kidneys, the patients should be monitored for decreased physiological functions such as renal function with aging as well as adverse drug events, etc. Careful administration should be considered, like dose reduction, and prolonged dosing interval.

○ **Prescription priority and dose reduction/drug discontinuation**

It is important to have a prescribing mindset which leads to polypharmacy prevention. Only the total number of prescribed drugs should not be focused on. A decrease in the number of tablets, such as less frequent dosing or use of combination drugs, is effective in improving medication adherence. On the other hand, for prevention adverse drug events, it is recommended to review each drug by prioritizing drugs based on the points in the table below. When a drug is discontinued, it should proceed step by step, taking into account an increased risk of sudden aggravation of diseases and adverse events.

Points to review the appropriateness of each drug
○ Whether the evidence of prophylaxis drugs is valid for the elderly ○ Whether symptomatic treatment is effective, or whether there are any other measures than medications ○ Whether it is the treatment policy according to treatment priority, etc.

(2) Importance of non-medication therapy

○ **Lifestyle-related disease**

In general, non-medication therapy which improves lifestyle may be useful in disease treatment for the elderly. In such a case, it should be provided prior to medication. For

example, sodium restriction and exercise therapy for patients with lifestyle-related diseases are recommended. Moderate exercise may resolve nocturnal insomnia, and sufficient sleep can be useful in treatment of depression.

○ **Behavioral and psychological symptoms of dementia (BPSD)**

The drugs used for BPSD may cause adverse drug events that affect ADL, such as extrapyramidal disorder and over-sedation. Therefore, non-medication therapy is recommended first. Meanwhile, an extreme change in lifestyle may decrease the quality of life (QOL); therefore, it should be limited to a level that does not interfere with the patients' life. Physical constraint without proper use of drugs is not recommended when BPSD occurs.

(3) Specialist perspective

When a disease is treated by specialists (including dentists), it is desirable to provide treatment with the maximum improvement in the disease as a goal. When the patient is under a serious disease condition and treatment is urgently needed, the medication aimed at better outcomes may be selected even if it is accompanied by a higher risk of adverse drug events. However, the elderly may have multiple comorbidities or be accompanied by dysfunction. In consideration of a risk of adverse drug events as well, specialists should consider the priority of disease treatment and understand the consideration on risk-benefit balance of medication, too. In addition, the elderly are sometimes excluded from the subject groups in clinical trials for new drugs. Therefore, new drugs should not easily be prescribed to the elderly.

Meanwhile, specialists in a certain area are not the specialists in other areas. It is necessary to understand the need in collaboration with other specialists, primary care physicians, and other types of professions for more appropriate medication.

(4) Flow of general ways of thinking

○ **Understanding and assessment of all drugs (including over-the-counter drugs, etc.)**

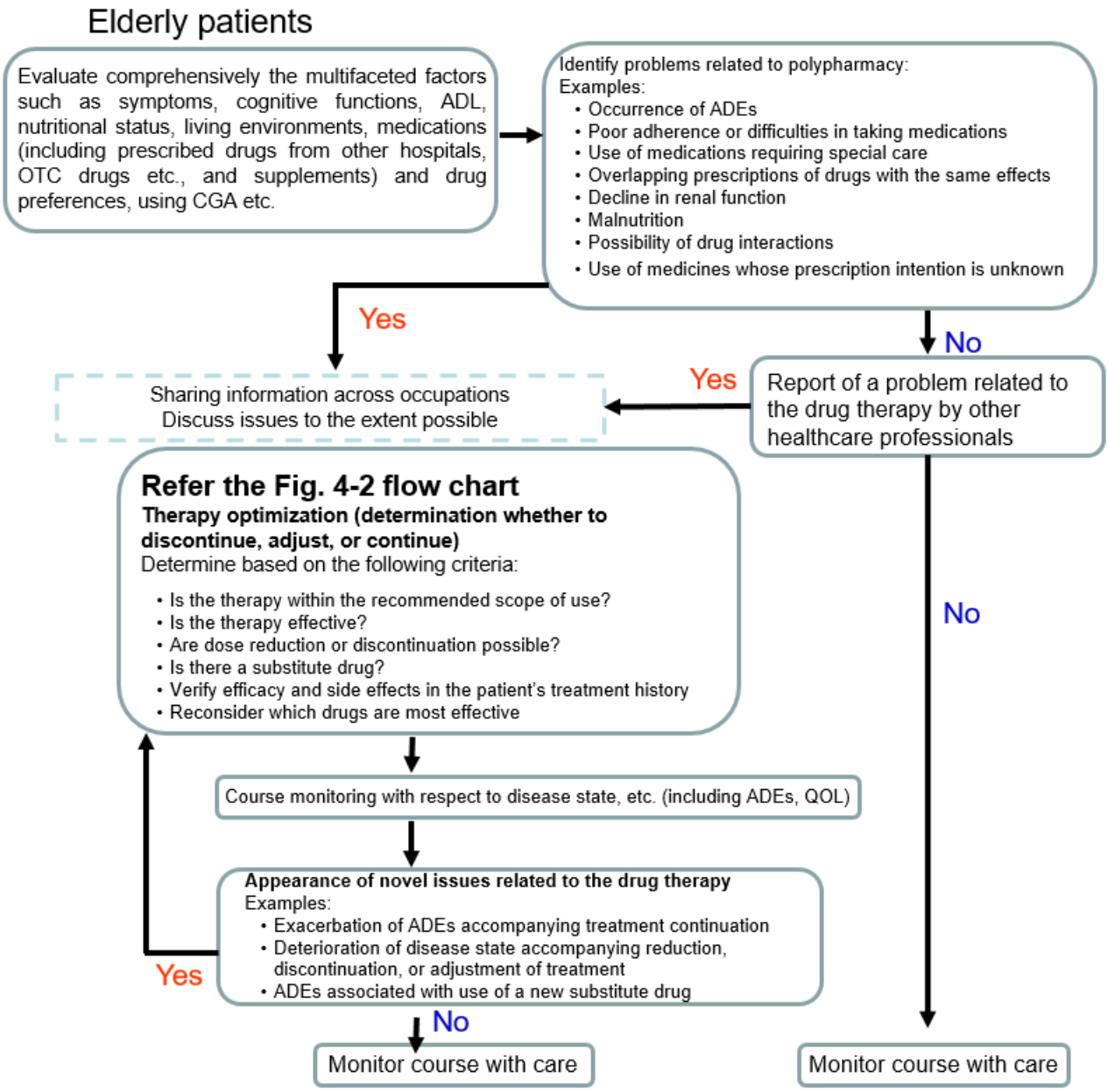
To consider more appropriate prescription, it is required to grasp all departments/medical institutions the patient visits and to fully understand patient's current diseases and concomitant diseases such as geriatric syndrome, ADL, life environment, and information on all drugs used, and CGA is recommended. As mentioned earlier, reconsider the necessity of medication regarding each drug used when necessary.

The flow chart in Figure 4-1 shows the prescription review process. **Appendix Tables 1 and 2*** provide a list of drugs that require attention in prescription. All the prescribed

drugs including those listed in the **Appendix Tables 1 and 2** should be assessed for their efficacy and safety, and the polypharmacy problems should be identified.

* Prepared in reference to “Drugs that require careful administration specifically to the elderly,” which is a list of drugs that potentially cause adverse events more often in the elderly in the guidelines, etc. edited by the Japan Geriatrics Society.

Figure 4-1 Prescription review process

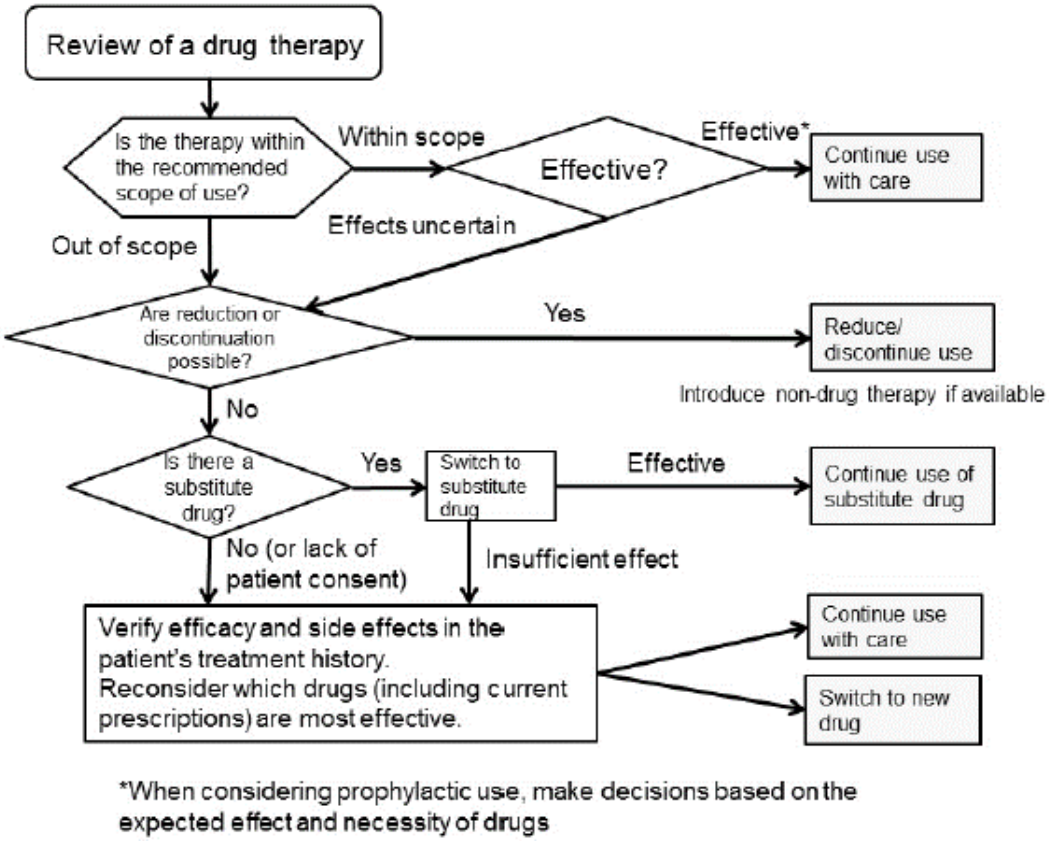


○ **Assessment of problems related to polypharmacy**

Prescription review is necessary for the patients with problems related to polypharmacy based on a result of CGA. For the patients with adverse drug events the

suspect drugs must be discontinued or the dose should be reduced. Moreover, it is recommended to discuss the problems among different professions led by physicians in order to assess the presence of daily-living problems, such as factors related to drug management, renal function, and nutrition status.

Figure 4-2 Flow chart for optimizing a patient's drug therapy regimen



(Excerpted from the Guidelines for Medical Treatment and its Safety in the Elderly 2015 (The Japan Geriatrics Society))

○ **Discussion about more appropriate prescription**

It should be considered whether the current treatment needs to be continued or changed based on the Figure 4-2 flow chart for individual drugs. It should be determined whether the drug can be discontinued, whether the use is within the scope of recommended usage in light of indications or proper doses, whether the drug is actually effective in improving the patient's clinical condition, or whether it can be switched to a more effective or safer alternative drug, etc.

(5) Precautions in reducing/changing the number of drugs

No procedures to reduce the number of drugs have been established for systematic

improvement of polypharmacy to date. Rather, some reports say that automatic reduction in the number of drugs aggravate existing diseases. To assess medication effects, it is effective to consider switching to other drugs or using alternative drugs based on information on changes in daily living.

In addition, careful observation of the clinical course is essential, such as whether changes in treatment have not aggravated the disease, whether no excessive treatment effects have been observed, whether any adverse events have not been caused by the alternative drugs patients were switched to, etc. It is recommended to share and review information on the presence of problems with nurses and other professions and to make prescription more appropriate when necessary.

4. Adverse events and their diagnosis that require attention in multiple drug use, and opportunities for prescription review

In the elderly, adverse drug events often occur as symptoms listed in Table 1 below. Careful attention is required because they tend to be overlooked as something usually associated with this population when they need medical treatment or long-term care/nursing (called “geriatric syndromes”). If there are any symptoms/findings including geriatric syndromes for which a relation with drugs is suspected, prescription should be checked and discontinuation/dose reduction should be considered first. If such responses are difficult, then switching to a safer drug should be considered. Specifically, when changes are noted in patient’s daily living or additional symptoms appear, firstly the possibility that drugs have caused such changes or symptoms should be suspected. For early detection of adverse events, information provided by the related professions is useful, too.

Table 1: Drug-induced Geriatric Syndromes and Major Drugs of Cause

Symptoms	Drug
Light-headed feeling/fall	Anti-hypertensives (especially, central anti-hypertensives, α blockers, β blockers), hypnotics, anti-anxiety drugs, antidepressants, antiepileptics, antipsychotics (phenothiazines), anti-Parkinson drugs (anticholinergic drugs), antihistamines (including H2 receptor antagonists), memantine
Memory impairment	Anti-hypertensives (central anti-hypertensives, α blockers, β blockers), hypnotics/anti-anxiety drugs (benzodiazepines), antidepressants (tricyclic), antiepileptics, antipsychotics (phenothiazine), anti-Parkinson drugs (anticholinergic drugs), antihistamines (including H2 receptor antagonists)
Delirium	Anti-Parkinson drugs, hypnotics, anti-anxiety drugs, antidepressants (tricyclic), antihistamines (including H2 receptor antagonists), hypertensives (central anti-hypertensives, β blocker), digitalis, antiarrhythmic drugs (lidocaine, mexiletine), bronchodilator drugs (theophylline, aminophylline), corticosteroids
Depression	Central anti-hypertensives, β blocker, antihistamines (including H2 receptor antagonists), antipsychotics, anti-thyroid drugs, corticosteroids
Impaired appetite	Nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, laxatives, anti-anxiety drugs, antipsychotics, anti-Parkinson drugs (anticholinergic drugs), selective serotonin reuptake inhibitor (SSRI), cholinesterase inhibitors, bisphosphonate, biguanide
Constipation	Hypnotics, anti-anxiety drugs (benzodiazepines), antidepressants (tricyclic), overactive bladder drugs (muscarine receptor antagonists), intestinal tract anticonvulsants (atropine, butylscopolamine), antihistamines (including H2 receptor antagonists), α-glucosidase inhibitor, antipsychotics (phenothiazine), anti-Parkinson drugs (anticholinergic drugs)
Impaired urination/incontinence	Antidepressants (tricyclic), overactive bladder drugs (muscarine receptor antagonists), intestinal tract anticonvulsants (atropine, butylscopolamine), antihistamines (including H2 receptor antagonists), hypnotics/anti-anxiety drugs (benzodiazepines), antipsychotics (phenothiazine), trihexyphenidyl, α blockers, diuretics

Table 1 lists drug-induced geriatric syndromes by monotherapy. Refer to the listing by therapeutic category in Tables 1 and 2, Appendix for adverse events caused by coadministration of drugs.
(Edited excerpt from “Wisdom” and “skill” to organize polypharmacy multiple drug use of the elderly, authored by Masahiro Akishita for editing)

5. Points to be considered as measures for multiple-drug use in medication to the elderly

(1) The initial dose and dose-adjustment method tailored to the drug characteristics (see the **Attachment for details)**

Since the elderly tend to experience an increase in the maximum blood concentration of a drug and its protracted elimination from the body, it is necessary to reduce doses and administer them at longer intervals. Therefore, in principle, the drug is started at a lower dose (e.g. 1/2 to 1/3 of usual dose), and it should be titrated up while its effectiveness and adverse events are monitored. The dose should be carefully set especially for so-called high-risk drugs (antidiabetic drugs, digitalis drugs, antiepileptic drugs, etc.). Typical drugs that are excreted by the kidneys are as shown in **Appendix Table 3**, and their doses and appropriateness of coadministered drugs should be

determined taking into account the renal function of the patient as specified in the **attached document of appendix**.

(2) Drug interactions and their management

Most of drug interactions involving drug metabolism are related to, especially, cytochrome P450 (CYP). **Appendix Table 4** provides typical examples of substrates, inhibitors, and inducers per CYP molecular species. The blood concentration of substrates is likely to be affected by interactions with inhibitors and/or inducers. Attention should be paid to the increases or decreases in the substrate actions when inhibitors and inducers are in the blood.

(3) Fundamental points to consider regarding use or concomitant use of drugs common in geriatric patients

1) Check of overlapping of prescriptions among drugs of the same type or with the same therapeutic effects

To prevent the risk of adverse drug events that may result in significant health damage, it is necessary to check at each medical institution and pharmacy for overlapping of prescriptions among drugs of the same type or with the same therapeutic effect for each therapeutic category.

2) Prevention and management of drug interactions

When a combination of drugs that may cause drug-induced actions is prescribed, it is important to correct the prescription by monitoring the efficacy and adverse effect, discontinuation, dose reduction, or switching to alternative drugs, taking into account prescription backgrounds, patient backgrounds, seriousness of actions that can be caused by drug interactions, and information on alternative drugs.

3) Fundamental points to consider regarding drug use and coadministration

Precautions in **Appendix Table 1** should be referred to when applicable for drug selection, dosage, dosing regimens accommodating the characteristics of the elderly, and precautions on drug interactions with other therapeutic categories, etc. based on the characteristics of each drug.

A. Hypnotics-sedatives/anxiolytics
B. Antidepressants (including sulpiride)
C. BPSD drugs
D. Anti-hypertensives
E. Antidiabetic drugs
F. Dyslipidemia drugs
G. Anticoagulant drugs
H. Drugs for peptic ulcer

(4) Basic precautions regarding the use and coadministration of other drugs intended across disease

1) Other drugs used across diseases

For the following drugs, their efficacy for each symptom should be assessed at an appropriate timing. Unnecessarily prolonged use should be avoided, and the use should be minimal. At the same time, application of non-medication therapy should be an option, depending on patents' symptoms. See **Appendix Table 1** for precaution details.

I. Anti-inflammatory analgesic drugs
J. Antimicrobial drugs (antibacterial drugs/antiviral drugs)
K. Laxative drugs
L. Anticholinergic drugs

2) Over-the-counter drugs, etc. (including Chinese medicines), so-called health food (including supplements)

○ **Grasping the over-the-counter drugs, etc. and so-called health food patients take without physician's prescription**

It is difficult to diagnose adverse drug events related to concomitant use of over-the-counter drugs and health food with prescription drugs if the patient does not visit a medical institution. Therefore, it is important to grasp how patients use such drugs or supplements (frequency and dose) to ensure safety by urging the patient, their family, nursing staff to be aware of the importance.

○ **Adverse drug events related to over-the-counter drugs, etc. and so-called health food**

Concomitant use of health food with drugs can greatly affect treatment effectiveness. Approximately 250 adverse drug events related to over-the-counter drugs, etc. are annually reported to MHLW and other related organizations. Even in over-the-counter drugs, inappropriate use, such as misuse by users or overlapping with prescription drugs, can cause serious adverse drug events.

There is a number of examples for such concomitant use including health food that contains a large amount of vitamin K and warfarin, calcium-containing drugs and drugs for osteoporosis, and Saint John's wort and antiepileptic drugs such as phenytoin or digitoxin, a cardiac glycoside, etc. Some over-the-counter drugs, etc. which often contain multiple ingredients such as multi-ingredient cold remedies, contain belladonna total alkaloids, a drug substance with a strong anticholinergic effect which is rarely used in prescription drugs, and other ingredients. Therefore, they should be carefully used.

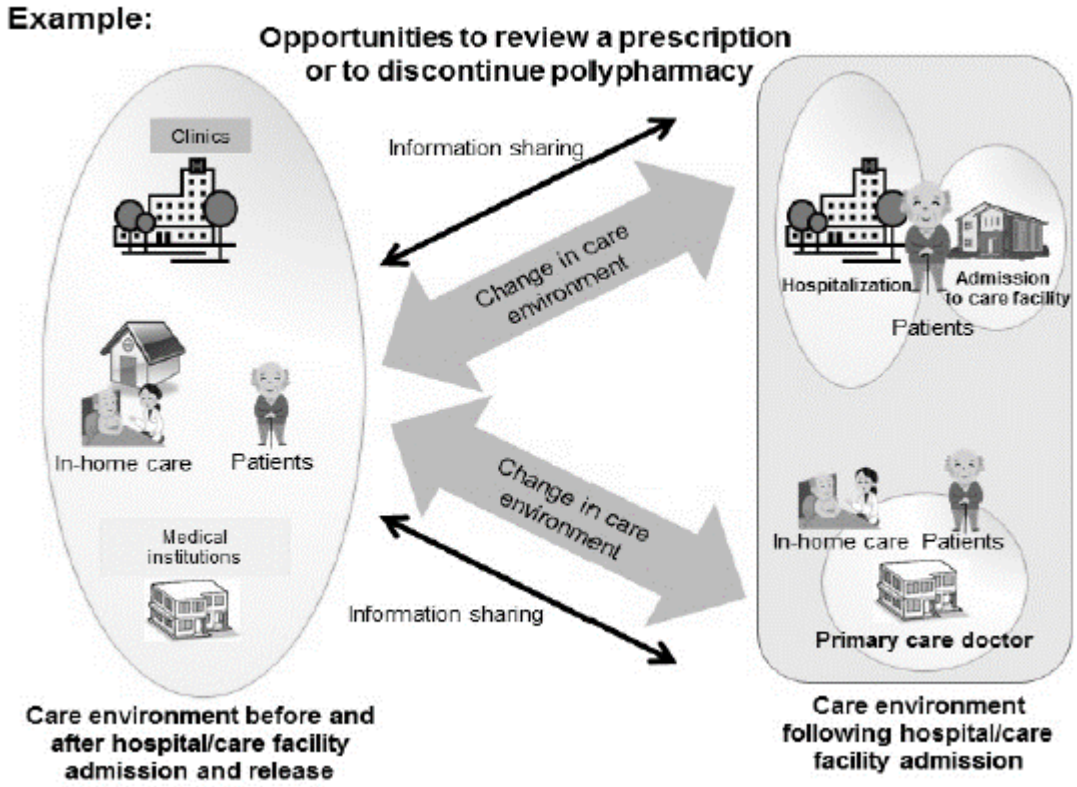
3) Drugs that need attention other than the above

Appendix Table 2 provides the summary as "a list of other drugs that require especially careful administration" for reference.

(5) Timing of prescription review

The general expectation concerning the review of prescriptions is that the review will be conducted at every opportunity in conjunction with monitoring of the patient's medical condition during the acute and chronic phases of the disease (Figure 5).

Figure 5 Diagram of prescription revision accompanying changes in care environment



○ **Acute phase**

The drugs administered for stable symptoms other than acute phase ones should be reviewed, taking into account the priority in order to prevent adverse drug events due to interactions, etc. Moreover, when adverse drug events are suspected as a cause of acute phase symptoms, as many drugs as possible should be discontinued and monitor the clinical course of patients.

○ **Upon changes in care environment**

When the acute symptom becomes stable, all medications should be reviewed including the resumption of drugs that were discontinued in the acute phase as well as the dose reduction/discontinuation of drugs added at the acute phase. In particular, at the time of changes in care environment, such as hospital discharge/transfer,

admission/relocation to a nursing-care facility, introduction to home-based medical care, and starting new treatment by a primary care physician, prescriptions must be reviewed assuming a continued management of the patient in the new environment (Figure 5).

○ **Chronic phase**

During a chronic phase, simpler prescriptions should be considered in view of better QOL for patients, their family and nursing staff as well as long-term safety, maintenance of medication adherence, and prevention of medication errors. To avoid being unnecessarily prolonged, prescription needs to be regularly reconsidered. This also applies to the prescription for outpatients.

6. Support for medication adherence

(1) Grasping patients' ability to manage medication

Medication adherence by geriatric patients often decreases along with complications caused by increased number of prescribed drugs and their ailing capacity to manage their medications. Support must be given to those patients to properly use their medications based on the understanding of the factors causing their medication adherence to decrease, which are shown in Table 2, and subsequent accurate assessment of their capacity to manage their medications.

○ **Checking factors that cause decreased medication adherence (cognitive function, deafness, decreased visual acuity, etc.)**

Since decreased cognitive function is difficult to be detected from conversation with the patient, it is preferable to check the patient's daily living, remaining drugs, and the medication status with his/her family, pharmacist, nurse, nursing staff, etc. In addition, it is necessary to check whether each factor shown in Table 2 affects proper drug adherence.

○ **Assessment of daily living**

It is important to assess a patient's daily living and link the assessment to the evaluation of the patient's drug adherence. An increase in the number of drugs and more complicated prescription may reduce the patient's understanding and motivation. In addition, the factors shown in Table 2 including those symptoms lead to decreased medication adherence.

Table 2 Factors of decreased medication adherence

- Ailing capacity to manage medications
  1. Decreased cognitive function
  2. Deafness
  3. Decreased visual acuity
  4. Finger dysfunction
  5. Decreased activities of daily living (ADL)
- Multiple-drug use
- Complicated prescription
- Dysphagia
- Depressed state
- Less self-perceived well-being (a condition where the patient does not feel healthy, like they do not feel the drug is working, etc.)
- Poor medical literacy
- Self-judged drug discontinuation (change in physical condition after medication, occurrence of adverse events, etc.)
- Living alone
- Aggravated living environment

(2) Consideration for better prescription and medication support

○ **Better prescription and medication support for dosage forms easy to take and to maintain medication adherence**

Table 3 provides considerations for better prescription for dosage forms that are easy to take and medication support to maintain patient medication adherence. Dosage forms that are easy to take or use are different from patient to patient. It is necessary to check whether a dosage form can be used by a patient correctly. It should be noted that a single-packaged dose containing multiple drugs does not always improve medication adherence.

○ **Patient's cognitive function and support**

If patients miss doses due to decreased cognitive function, their family, nurse, nursing staff, etc. should assist the patients by handing them the daily dose each time or in other appropriate manners. When the patients have to manage their medication by themselves, such related parties need to communicate with the patients in a supportive manner and consider feasible ways accommodating patients' remaining functions.

Table 3 Examples of consideration for better prescription and medication support

Reducing the number of drugs	● Multiple drugs with weaker potency should be replaced with a smaller number of drugs with stronger potency. ● Use of combination drugs ●Drugs for symptomatic treatment should be used on an as-needed basis only whenever possible. ● Active use a list of drugs that require specifically careful administration
Dosage form selection	● Selecting a formulation suitable for patient's decreased activities of daily living (ADL)
Simplification of use	● The dosing frequency should be reduced with a long-acting drug rather than a short-acting drug. ● Avoiding uneven administration whenever possible ● Utmost consistent medication timing among drugs, such as before meals, after meals, and between meals.
Considering suitable formulations	● A single-packaged dose ● Use of a medication set box or medication calendar ● Active use of available dosage forms (transdermal patch, etc.) ● Manner of dispensing suitable to each patient (mark or date on an individual wrapping) ● Proposal for change in dosage form or manner of taking medicines (simple suspension method, swallowing-aid jelly for oral medicines, etc.) for patients with dysphagia
Considering a better management method	● When patients cannot manage medication by themselves, drugs should be taken when their family can help manage it.
Consolidated management of prescription and dispensing	● Consolidated management of prescription/dispensing (including the use of a medication record book) should be sought.

7. Multi-occupational/institutional, and community cooperation

○ Roles of multi-occupational cooperation

Collaboration across or within the same occupations is important in various situations involving drug therapy. In particular, physicians, dentists, and pharmacists are required to play a central role in drug therapy. In addition, nurses, for example, are generally expected to collect information on patients' adherence, their ability to manage their medications, their symptoms suspected to indicate ADEs in the course of medication adherence support, and perceptions of patients or their families to share the information across occupations.

○ Collaboration at medical institutions, etc. according to medical care environment for both inpatients and outpatients

While a patient is hospitalized, the physicians, dentists, and pharmacists with different expertise as the core members can organize a team for prescription review with other professions such as nurses and nutritionists, centralize information and make the

prescription more appropriate in meetings, etc., and cooperate with the patient's primary care physician.

When a patient is to be admitted or released from a hospital, the patient's primary care physician prior to the admission and after the release can be involved in the collaboration in order to confirm the rationales behind the patient's prescriptions and any post-release policy. For short-term hospitalization, in particular, appropriate information should be provided to the primary care physician who takes care of the patient after hospital discharge so that it can lead to continuous prescription review and observation of the clinical course after the discharge.

Hospital pharmacists are also expected to provide information on drug prescription and other relevant information to the pharmacists of the local pharmacies as well as other healthcare professionals who are involved in the community-based integrated care system that the patient will use after hospital discharge. Ensuring the sufficient provision of prescription information from community pharmacists to hospital pharmacists is also necessary for a bilateral information sharing.

○ **Collaboration in the community beyond medical institutions**

Even in the nursing care facilities, home medical care, outpatient settings, it is possible to form a team with various professionals in an institution or an area with human resources available for each. Even if they do not gather at a place, collaboration/coworking function will work with the use of patients' medication records books, etc.

In any situation after hospitalization/discharge or in the applicable areas or outpatient departments, it is necessary to provide information which allows physicians to review prescriptions in cooperation with various professionals involved in the community-based integrated care system. For example, it is expected to check medication adherence, confirm and reorganize the remaining drugs, and provide medication support in collaboration with visiting nurses and pharmacists who support home visit.

8. Fostering public understanding

In order for this guidance to gain broad adoption in the medical practice, it is necessary to promote understanding by the general population, which includes patients receiving medical care and their families. It may be difficult for patients, families, and care workers to understand the concerns associated with polypharmacy, drug interactions, review of drugs used, and the necessity of providing appropriate medication adherence support. Meanwhile, each of these groups must understand that reducing the dosage or discontinuing a specific treatment in some cases can result in improvement, and knowledge of the proper uses of drugs should also be disseminated

widely among the public. This guideline should be used to provide medicine “centered on patients,” the spirit of this guideline, and for healthcare professionals to enlighten the general public. In addition, education materials for the general public are desired as well. For example, it is desired for the Japanese to understand more about the principles of drug use for the elderly, compliance with medication adherence, regular review process for drug use appropriateness by using an education leaflet for the general public titled “Too Many Drugs and Adverse Drug Reactions the Elderly Must Notice,” which was created jointly by the Japan Geriatrics Society and the Japanese Society of Geriatric Pharmacy, etc. Education on risks of polypharmacy and non-medication therapies is required as well in order to prevent polypharmacy.

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Appendix

Appendix Table 1 Fundamental points to consider regarding drugs frequently used by geriatric patients

(Therapeutic categories and non-proprietary names of representative drugs [Examples of branded names])

<table>
<tr><td rowspan="4">A.
Hypnotics-sedatives/anxiolytics</td><td colspan="2">Lifestyle instructions related to sleeping habits should be provided before prescribing drug therapy in light of the fact that sleeping time and quality are reduced as a result of aging. While use of hypnotics-sedatives or anxiolytics may be used as necessary, benzodiazepines have been identified as a drug class requiring particularly careful administration due to the likelihood of adverse events in geriatric patients associated with their use as well as their potential to formulate dependence.</td></tr>
<tr><td>Drug selection accounting for geriatric patient characteristics</td><td>Use of benzodiazepine-class hypnotics-sedatives (e.g., brotizolam [Lendormin], flunitrazepam [Rohypnol, Silece], nitrazepam [Benzalin, Nelbon], etc.) is associated with a greater risk of oversedation, deterioration of cognitive function, deterioration of motor functions, fall, bone fractures, or delirium. As such, special care is required when these drugs are prescribed to geriatric patients. Long-acting benzodiazepines (e.g., flurazepam [Dalmate], diazepam [Cercine, Horizon], haloxazolam [Somelin], etc.) should not be prescribed to geriatric patients because such patients commonly exhibit reduced metabolism of benzodiazepines as well as increased sensitivity. Additionally, triazolam [Halcion] carries a risk of causing amnesia and its use should be refrained from as much as possible.

An increased risk of falls and fractures has also been reported with respect to non-benzodiazepine hypnotics-sedatives (e.g., zopiclone [Amoban], zolpidem [Myslee], eszopiclone [Lunesta], etc.). Other adverse events similar to those associated with benzodiazepine use may also appear.

Benzodiazepine-class anxiolytics (e.g., alprazolam [Constan, Solanax], etizolam [Depas] etc.) may be used to address anxiety and feeling irritated during the day. However, elderly people are at a greater risk of developing the aforementioned adverse events and should refrain from their use as much as possible.</td></tr>
<tr><td>Precautions for dosage and administration</td><td>The drug should not be used unnecessarily long-term and be limited to a lower dose for example for careful use. Attention should be paid to the fact that even overseas guidelines require benzodiazepines to be administered for 4 weeks or shorter.

Additionally, attention should be paid to the risk that benzodiazepines can induce withdrawal symptoms after sudden drug discontinuation.</td></tr>
<tr><td>Precautions against interactions with other therapeutic-category products</td><td>Since many of the drugs are metabolized mainly by CYP3A, coadministration with drugs that inhibit CYP3A should be avoided as much as possible. See Appendix Table 4 for major interactions associated with CYP.

Ramelteon [Rozerem], a melatonin receptor agonist is contraindicated to coadministration with fluvoxamine [Depromel, Luvox], a selective serotonin reuptake inhibitor (SSRI) which strongly inhibits CYP1A2. In addition, since coadministration with suvorexant [Belsomra], or an orexin receptor antagonist inhibits metabolism by CYP3A and markedly increases the drug effect, coadministration with drugs which strongly inhibit CYP3A, such as clarithromycin [Clarith, Klaricid] is contraindicated.</td></tr>
<tr><td>B.
Antidepressants (including sulpiride)</td><td colspan="2">Treatment of depression in geriatric patients requires understanding of psychosocial factors and very careful handlings tailored to their clinical symptoms that differ from person to person. Tricyclic antidepressants are regarded as drugs that require specifically careful use when administered to geriatric patients with depression.</td></tr>
</table>

	Drug selection accounting for geriatric patient characteristics	**Tricyclic antidepressants** require specifically careful use to geriatric patients with depression because these drugs **(such as amitriptyline [Tryptanol], amoxapine [Amoxan], clomipramine [Anafranil], imipramine [Tofranil])** have induced anticholinergic symptoms (e.g. constipation, oral dryness, decreased cognitive functions), sleepiness, dizziness, etc. and led to discontinuation due to adverse drug reactions more frequently relative to SSRI. **Sulpiride [Abilit, Dogmatyl]** is used in patients with depression who had anorexia, but it should not be used as much as possible because it has a risk of extrapyramidal symptoms such as Parkinson's symptoms and tardive dyskinesia. **SSRIs (sertraline [Jzoloft], escitalopram [Lexapro], paroxetine [Paxil], and fluvoxamine [Depromel, Luvox])** induce a risk of fall, hemorrhage of digestive tract, etc. in geriatric patients as well.
	Precautions for dosage and administration	Most antidepressants require careful administration in patients with physical symptoms such as seizure, glaucoma, cardiovascular disease and impaired urination due to prostatic hypertrophy. **Tricyclic antidepressants** and **maprotiline [Ludiomil]** are contraindicated to glaucoma and the initial phase of recovery from myocardial infarction. **Tricyclic antidepressants** and **escitalopram** are contraindicated to long QT syndrome. **Sulpiride** should be used at 50 mg/day or less. Patients with decreased kidney function must be carefully monitored as the drug is excreted by the kidneys. Sulpiride is contraindicated to the use in patients with pheochromocytoma. Attention should be paid to the risk that **SSRI** can induce withdrawal symptoms after sudden discontinuation.
	Precautions against interactions with other therapeutic-category products	The patients who use **SSRI** should be carefully monitored for their coadministered drugs since they are likely to be affected by interactions associated with CYP. In particular, **fluvoxamine** and **paroxetine** strongly inhibit CYP1A2 and CYP2D6, respectively, and some drugs are contraindicated for coadministration, which require careful use. See Appendix Table 4 for major interactions associated with CYP. Attention should be paid to coadministration with nonsteroidal anti-inflammatory drugs or antiplatelet drugs since it may increase a bleeding risk.
C. **BPSD drugs**	**Any psychosomatic factors or environmental factors that could cause BPSD should be examined and some measures be taken. Drugs may induce BPSD. When any relations with drugs are suspected, discontinuation of the suspect drug should be firstly considered. Consider the start of medications when the above treatment was found ineffective.**	
	Drug selection accounting for geriatric patient characteristics	Consider selecting drugs as medication with the symptoms taken into account. The use of **antipsychotics** is an option against symptoms such as hallucination, delusion, irritated feeling, excitement, and attack. Remember that the use of antipsychotics for BPSD is off-label use. **The use of typical antipsychotics (haloperidol [Serenace], chlorpromazine [Contomin], levomepromazine [Hirnamin, Levotomin], etc.)** should be avoided as much as possible. **Atypical antipsychotics (risperidone [Risperdal], olanzapine [Zyprexa], aripiprazole [Abilify], quetiapine [Seroquel], etc.)** should be minimally used. **Yokukansan** may be used in some cases. As it contains licorice, the patient should be carefully monitored for hypokalemia due to pseudoaldosteronism. **Antidepressants** are sometimes used in dementia patients with depression. **Tricyclic antidepressants** should be avoided as much as possible since they can further aggravate cognitive disorder.
	Precautions	It has been reported that **antipsychotics** have increased the rate of

	for dosage and administration	cerebrovascular disorder and mortality when used in patients with dementia. The risks and benefits as well as possible adverse events should be taken into account when they are used. Attention should be paid to development of decreased cognitive function, extrapyramidal symptoms, fall, aspiration, over-sedation, etc. The drugs should be started at a lower dose, then be titrated up after the effect is confirmed. Even after the effect is confirmed, unnecessarily prolonged administration should be avoided. Gradual decrease in doses and discontinuation should be an option. Attention should be paid to long half-life drugs because they may help prolong the period of adverse events even after discontinuation. **Atypical antipsychotics** may increase glucose levels, and **quetiapine** and **olanzapine** are contraindicated to the use in patients with diabetes mellitus. **Butyrophenone-based drugs (e.g. haloperidol)** is contraindicated to Parkinson's disease. Most of **antipsychotics and antidepressants** are metabolized in the liver. Geriatric patients should start on the drugs at a lower dose than usual. They may decrease the threshold of epileptic seizure.
	Precautions concerning interactions with other therapeutic-category products	Most **antipsychotics** and **antidepressants** are mainly metabolized by CYP in the liver. Therefore, attention should be paid to interactions associated with CYP. See Appendix Table 4 for major interactions associated with CYP.
D. Anti-hypertensives	**The primary objective for geriatric patients is achievement of their antihypertensive goal, too. There is no limit to the number of drugs for concomitant therapy with anti-hypertensives, but it is recommended to reduce the number of drugs as much as possible in consideration of medication adherence, etc.**	
	Drug selection accounting for geriatric patient characteristics	For prophylaxis of cardiovascular disease, the first-line drugs for geriatric patients as well as younger patients include **calcium antagonists (amlodipine [Norvasc, Amlodin], nifedipine [Adalat-CR], benidipine [Coniel], cilnidipine [Atelec], etc.), ARB (olmesartan [Olmetec], telmisartan [Micardis], azilsartan [Azilva], etc.), ACE inhibitors (imidapril [Tanatril], enalapril [Renivace], perindopril [Coversyl], etc.), and a lower dose of thiazide diuretics (trichlormethiazide [Fluitran], etc.).** It is also important to select antihypertensives in light of complications for geriatric patients. **α blockers (urapidil [Ebrantil], doxazosin [Cardenalin], etc.)** may cause orthostatic hypotension and fall. The elderly should avoid using them whenever possible. **β blockers (metoprolol [Seloken], etc.)** should be considered in elderly hypertensive patients who experienced cardiac failure, tachycardia, angina on exercise, or myocardial infarction. **ACE blockers** are considered useful in the elderly patients who repeat aspiration pneumonia partly for aspiration prophylaxis. **The use of thiazide diuretics** should be considered in the elderly particularly who are at a higher risk of fracture with no better antihypertensives available.
	Precautions for dosage and administration	The blood pressure level which will prevent excessive hypotensive action cannot be specified uniformly. Administration should be started at a lower dose (a half volume). In addition, when organ ischemic symptoms appear due to hypotensive action or when adverse drug events occur, dose reduction, discontinuation, or change of the anti-hypertensives should be considered.
	Precautions against	Since many of the **calcium antagonists** are metabolized mainly by CYP3A, careful attention should be paid to coadministration with drugs that

	interactions with other therapeutic-category products	inhibit CYP3A. See Appendix Table 4 for major interactions associated with CYP.
E. **Antidiabetic drugs**	The elderly's diabetes mellitus requires treatment for which safety has been carefully considered. In particular, for the patients aged 75 years or older, who are frail or need to be nursed, the treatment goal* should be set for each cognitive function or ADL after their cognitive function, activities of daily living (ADL), and support system are evaluated. *Glucose control target (HbA1c level) for the elderly was established in 2016 by the joint committee of the Japan Diabetes Society/the Japan Geriatrics Society.	
	Drug selection accounting for geriatric patient characteristics	Attention should be paid to the elderly since they tend to have sick days and hypoglycemia. **Insulin agents** should also not be used whenever possible except for acute conditions including hyperglycemic coma. **Of SU drugs (glimepiride [Amaryl], gliclazide [Glimicron], glibenclamide [Euglucon, Daonil]),** the drugs that have a strong hypoglycemic effect, such as **glibenclamide** should not be administered, and other SU drugs should also be very carefully used and dose reduction or drug discontinuation should be an option when hypoglycemia is suspected. SU drugs should be replaced with DPP-4 inhibitors whenever possible. When using **metformin [Glycoran, Metgluco]**, attention should be paid to possible hypoglycemia, lactic acidosis, and diarrhea. **Thiazolidine derivative (pioglitazone [Actos])** should not be administered to patients at a higher risk of cardiac risks such as heart failure. The drug should not be used in some cases because the drug may increase the risk of decrease in bone density/fracture in elderly patients. When **α-glucosidase inhibitors (miglitol [Seibule], voglibose [Basen], acarbose [Glucobay])** are administered, attention should be paid to serious adverse drug reactions such as intestinal obstruction. **SGLT2 inhibitors (ipragliflozin [Suglat], dapagliflozin [Foxiga], luseogliflozin [Lusefi], tofogliflozin [Deberza, Apleway], canagliflozin [Canaglu], empagliflozin [Jardiance])** suppress cardiovascular events. Attention should be paid to their risks that may cause various adverse drug reactions such as dehydration, excessive body weight loss, and ketoacidosis. They are not expected to be effective in patients with severe renal impairment. Patients with moderate renal impairment may respond poorly to these drugs. The necessity of the administration should be carefully determined. SGLT2 inhibitors should not be used in patients with urinary tract infections/genital infection. Drug administration must be suspended when the patient has pyrexia/diarrhea/vomiting, or have not taken enough meal due to anorexia (sick days).
	Precautions for dosage and administration	As physiological functions have been decreased in the elderly, the patients' condition should be observed and the drugs should be carefully administered, such as starting on a lower dose. See Appendix Table 3 for patients with decreased renal functions.
	Precautions against interactions with other therapeutic-category products	Multiple drug use of **other than insulin agent or SU drugs also** increases the risk of severe hypoglycemia. Always consider the necessity of in the number of drugs while HbA1c and glucose level is monitored. **Since SU drugs** and **nateglinide [Fastic, Starsis]** are mainly metabolized by CYP2C9, attention should be paid to coadministration with CYP2C9 inhibitors. See Appendix Table 4 for major interactions associated with CYP. **SGLT2 inhibitors** should not be coadministered with diuretics in terms of the dehydration risk.
F.	**It is necessary to consider medications as well as to focus on the guidance for lifestyle.**	

Dyslipidemia drugs	Drug selection accounting for geriatric patient characteristics	Administration of **statin (rosuvastatin [Crestor], atorvastatin [Lipitor], pitavastatin [Livalo], etc.)** showed a significant decrease in cardiovascular events as both primary and secondary prevention in the elderly aged from 65 years to 74 years old. Therefore, the use of statins is recommended as the first-line drug for hyper LDL cholesterolemia, in particular. Statins' effects to significantly decrease cardiovascular events as secondary prevention have been proven in the elderly aged 75 years or older while no effects as the primary prevention have been proven. Therefore, the drugs should not be used for the primary prevention. **Drugs other than statins** should be carefully administered due to insufficient evidence.
	Precautions for dosage and administration	It is believed that the elderly also experience muscle pain, digestive symptoms and new development of diabetes mellitus after the use of statins. Therefore, attention should be paid to these events.
	Precautions against interactions with other therapeutic-category products	**Coadministration of statins and fibrates (fenofibrate [Lipidil, Tricor], bezafibrate [Bezatol], clinofibrate [Lipoclin], clofibrate)** can develop rhabdomyolysis and is relatively contraindicated to patients with decreased renal function. **Simvastatin [Lipovas] and atorvastatin** are mainly metabolized by CYP3A while **fluvastatin [Lochol]** is mainly metabolized by CYP2C9. Coadministration with these CYP inhibitors can increase the blood concentration of statins. Attention should be paid to the adverse effects caused by the mechanism. See Appendix Table 4 for major interactions associated with CYP. **Ciclosporin [Neoral]**, which inhibit OATP, the hepatic uptake transporter, increase the blood concentration of statins. In particular, **rosuvastatin and pitavastatin** are contraindicated to coadministration with ciclosporin.
G. Anticoagulant drugs	**Administration should be determined following risk/benefit assessment, taking into account a higher bleeding risk when anticoagulant drugs are administered to the elderly. A long-term (more than one year) coadministration of multiple anticoagulant drugs, etc. should be avoided whenever possible.**	
	Drug selection accounting for geriatric patient characteristics	**Direct oral anticoagulants (DOAC) (apixaban [Eliquis], dabigatran [Prazaxa], rivaroxaban [Xarelto], edoxaban [Lixiana])** are believed to have a lower risk of hemorrhage of digestive tract in Asians compared to that of warfarin, and considered to be used easily for the elderly patients. Of note, DOAC is contraindicated to patients with severe renal disorders.
	Precautions for dosage and administration	**Since concomitant therapy of DOACs with antiplatelet drugs** increase the bleeding risk, its long-term use should be avoided even when the therapy is essential following coronary stenting, etc. CHA2DS2-VASc score and HAS-BLED score are useful in risk assessment for stroke and for bleeding risk at administration of anticoagulant drugs, respectively. Moreover, a history of cancer or fall, and polypharmacy are considered to be a risk of major bleed. The anti-coagulant effect of **Warfarin [Warfarin]** can be monitored by regular PT-INR check while that of DOAC cannot be monitored. Therefore, the dose of DOAC should be checked to review whether the dose is appropriate by regular check of the renal function.
	Precautions against interactions with other drug-class products	For **warfarin** and **DOAC**, careful attention should be paid to their coadministered drugs and interaction. See Appendix Table 4 for major interactions associated with CYP. Rivaroxaban is contraindicated to coadministration with multiple drugs that are strong CYP3A (or P-glycoprotein) inhibitors. Attention should be paid to drug interaction between **dabigatran** or **edoxaban** and P-glycoprotein inhibitors. In particular, **dabigatran** is contraindicated to coadministration with

		itraconazole, which is a strong P-glycoprotein inhibitor. When **warfarin** is taken, the patients also need to be careful of food that contains much vitamin K and other health foods. They should not take natto, chlorella and green juice.
H. **Drugs for peptic ulcer**	**Drugs for peptic ulcer tend to be used long-term specifically for treatment of gastroesophageal reflux disease (GERD), for which the adverse drug events are known. Therefore, their long-term use should be avoided.**	
	Drug selection accounting for geriatric patient characteristics	The effectiveness of **proton pump inhibitors (PPIs) (esomeprazole [Nexium], lansoprazole [Takepron], rabeprazole [Pariet], omeprazole [Omepral])** has been substantially reported, and these drugs are used as the first-line drug. **H2 receptor antagonists** are also effective drugs. However, they are excreted by the kidneys, which may cause a higher blood concentration when the renal function is decreased and increase a risk of adverse events. The drugs increase the risk of delirium and decreased cognitive function in the elderly, and the use should be avoided whenever possible. **Vonoprazan [Takecab]** strongly inhibits gastric-acid secretion the same as PPIs. Therefore, the patient's clinical course should be monitored as carefully as when PPIs are used.
	Precautions for dosage and administration	Although **PPIs** are very safe drugs, it is reported that long-term use has increased not only fracture risks, such as fracture of the femoral neck, but also the risk of *Clostridium difficile* infection. It is also reported that long-term use of these drugs has increased the risk of Alzheimer's type dementia. **H2 receptor antagonists (famotidine [Gaster], nizatidine [Acinon], and ranitidine [Zantac])** are excreted by the kidneys. The patients with decreased renal function should be carefully monitored while on the drugs (see the Appendix Table 3 for the typical drugs that are excreted by the kidneys).
	Precautions against interactions with other therapeutic-category products	**PPIs** are metabolized by CYP2C19, and the enzyme's contribution level in metabolism differs depending on the drug. Administration should not last for more than 8 weeks except for the patients with refractory GERD, severe esophagitis, and a higher digestive-bleeding risk due to oral administration of NSAIDs and the risks should be always taken into account when they are continued. See Appendix Table 4 for major interactions associated with CYP. Since **cimetidine [Tagamet]**, one of the H2 receptor antagonists, inhibits multiple CYP molecular species, attention should be paid to drug interactions.
I. **Anti-inflammatory analgesic drugs**	**NSAIDs have a risk of adverse drug events such as upper digestive bleeding, renal impairment, and cardiovascular disorder, and should be very carefully administered to the elderly.**	
	Drug selection accounting for geriatric patient characteristics	**NSAIDs (celecoxib [Celecox], loxoprofen [Loxonin], lornoxicam [Lorcam], diclofenac [Voltaren], etc.)** should be used for as a short period as possible. Since they may cause bleeding of the upper digestive tract, they should be coadministered with proton pump inhibitors or misoprostol [Cytotec]. **Selective COX-2 inhibitors such as celecoxib, meloxicam [Mobic]**, etc. are expected to decrease the risk of NSAIDs-induced ulcer. Therefore, they should be considered for the elderly with a history of peptic ulcer who have no choice but to use NSAIDs. **Acetaminophen [Calonal]** is not classified into NSAIDs, but is regarded as an option when using analgesics in the elderly because the drug has a lower risk of adverse drug events such as digestive bleeding, renal impairment, and cardiovascular disorder compared to NSAIDs.
	Precautions	Since **NSAIDs** have a high risk of decreasing renal function, they should

	for dosage and administration	not be used in patients who often have mild renal impairment whenever possible. Even when they are the only option for treatment, they should be administered as low a dose as possible and for as short a period as possible. Since they also increase the risk of cardiovascular diseases, attention should be paid to administration to the elderly who have such concomitant underlying diseases. Bear in mind that coadministration of topical NSAIDs and oral NSAIDs, or coadministration with over-the-counter drugs, etc. containing NSAIDs can cause adverse drug events, too. Attention should be paid to the point that administration of **acetaminophen** at a high dose may increase the risk of hepatic impairment. Attention should be paid to the overlapped use of acetaminophen that is contained in a combination cold remedy, including an over-the-counter drug. For the use of any analgesics, it is important to provide the treatment tailored to details of the pain based on evaluation of its cause/type. Automatic, prolonged administration of analgesics should be avoided without appropriate assessment.
	Precautions against interactions with other therapeutic-category products	The patients who concomitantly use **antiplatelet drugs, anticoagulant drugs, or gluco-corticosteroid** may be at a higher risk of NSAIDs-induced ulcer. NSAIDs should be changed/discontinued early as soon as possible when these drugs are used. **Renin-angiotensin inhibitors (ARB, ACE inhibitors, etc.), diuretics (furosemide [Lasix], azosemide [Diart], spironolactone [Aldactone], trichlormethiazide [Fluitran], etc.) coadministered with NSAIDs** will increase the risk of decreased renal function and hyponatremia. Therefore, coadministration of these drugs should be avoided whenever possible.
J. **Antimicrobial drugs (antibacterial drugs/anti-virus drugs)**	**Antibacterial drugs are recommended against being administered to the patients with cold, adult acute sinusitis, acute pharyngitis without A group β-hemolytic *streptococcus*, underlying diseases such as chronic respiratory disease, etc., adult acute bronchitis without complications (pertussis excluded), and mild acute diarrhea among those with acute respiratory tract infection. On the other hand, attention should be paid to the fact that even the above infections may worsen in the elderly.**	
	Drug selection accounting for geriatric patient characteristics	When a bacterial disease is suspected and treatment with antibacterial drugs is started, it is necessary to select the antibacterial drugs to which the suspected or detected causative bacterial pathogens are susceptible in principle. Attention should be paid to the long-term use of bacterial drugs with unnecessarily broad spectrum because they can increase drug-resistant bacteria.
	Precautions for dosage and administration	For treatment periods, too, the standard treatment period per infection type must be followed, in principle. Attention should be paid to the fact that an excessively short treatment period can cause treatment failure or recurrence while an excessively and unnecessarily prolonged treatment may increase drug-resistant bacteria. For the doses, the standard doses should be followed per disease or type of bacterial drugs. The elderly often have decreased renal function or hepatic function, and the appropriate dosage and administration should be arranged based on the individual condition. Note that a sufficient dose should be administered to secure the efficacy for acute diseases, for which it is important not to miss the treatment timing among others. If the dose is too low just because the patient is elderly, not only insufficient efficacy can be expected but also it may increase drug-resistant bacteria. Be careful of that point. When a dose is adjusted, the determination on whether a dose should be reduced or the dose interval should be longer must be made based on the drug characteristics such as pharmacological action. For example, concentration-dependent antibacterial drugs such as **fluoroquinolone antibacterial drug (garenoxacin [Geninax], sitafloxacin [Gracevit], levofloxacin [Clavit], tosufloxacin [Ozex], etc.)**, etc. should not have the dose be reduced. Rather, the dosing interval should be prolonged.

		Vancomycin hydrochloride, aminoglycoside antibacterial drug (kanamycin), fluoroquinolone antibacterial drug, cefepime [Maxipime], aciclovir [Zovirax], etc. may increase the risk of adverse drug events in the elderly with decreased renal function. Be careful about this point.
	Precautions against interactions with other therapeutic-category products	**Macrolide antibacterial drugs (clarithromycin [Clarith, Klaricid], erythromycin [Erythrocin]), and azole antifungal drugs (itraconazole [Itrizole], miconazole [Florid], voriconazole [Vfend], fluconazole [Diflucan])** strongly inhibit CYP, help increase the blood concentration of other drugs which are metabolized through this channel, and thereby can cause adverse drug events. See Appendix Table 4 for major interactions associated with CYP. **Carbapenem antibiotics** are contraindicated to **coadministration with sodium valproate [Depakene]** because this combination decreases the blood concentration of valproic acid. Attention should be paid to the point that **fluoroquinolone antibacterial drug** may induce seizure when **coadministered with NSAIDs.** **Tetracycline antibacterial drugs (minocycline [Minomycin], Doxycycline [Vibramycin], achromycin), and fluoroquinolone antibacterial drugs** will form chelate which decreases their absorption **when administered at the same time with drugs containing aluminum or magnesium, or iron tablets**. Therefore, coadministration should be avoided or the drugs should be separately administered at a certain interval. When **warfarin** is coadministered with antibacterial drugs, vitamin K production is suppressed by bactericidal effects of antibacterial drugs on enterobacteria, which can potentiate the anti-coagulant effect. The blood coagulation ability should be carefully monitored and the dose be adjusted when necessary. **Anti-HIV drugs and anti-HCV drugs** have a variety of combinations that may cause drug interactions, many of which also cause substantial fluctuations in the blood concentration. Therefore, individual combinations should be carefully monitored regarding any problems.
K. Laxative drugs	**If the patient uses any of the drugs that may cause constipation (see Table 1), replacing the causative drugs with other drugs or discontinuation should be considered. If the disease does not require fluid restriction, patients should be instructed to take water and improve the constipation through a diet with dietary fiber and moderate exercise.**	
	Drug selection accounting for geriatric patient characteristics	**Magnesium drugs (magnesium oxide)** is frequently used since the dose can be easily adjusted as an osmotic laxative. However, when it is used for the elderly, who have decreased renal function, attention should be paid to hypermagnesemia. **Lubiprostone [Amitiza]** is a chloride channel activator and softens feces without an impact on serum electrolyte. Therefore, it should be considered for the condition of dyschezia due to hard feces. **Naldemedine [Symproic]** should be an option to treat opioid-induced refractory constipation.
	Precautions for dosage and administration	**Magnesium drugs** should be started at a low dose and not used at a high dose. Serum magnesium level should be measured on a regular basis. When the patient experiences such symptoms as nausea/vomiting, lowered blood pressure, bradycardia, muscle weakness, and somnolence, which are hypermagnesemia symptoms, the patients should be instructed to discontinue magnesium drugs and see a physician. **Irritant cathartics** may worsen constipation toward the refractory level if continuously used for a long time. Moreover, anthraquinones, which is contained in senna, etc., causes abnormal movement of the large intestine and pseudomelanosis. Irritant cathartics should be used on an as-needed basis.
	Precautions	When a **magnesium drug** is used with **fluoroquinolone/tetracycline**

<table>
<tr><td></td><td>against interactions with products from other therapeutic category</td><td>antibacterial drugs, they should be separately administered, at an approximately two-hour interval, because magnesium drugs reduce absorption of these antibacterial drugs.</td></tr>
<tr><td rowspan="3">L. Anticholinergic drugs</td><td colspan="2">Bear in mind that drugs with anticholinergic effect may cause decreased cognitive function, delirium, or other adverse events in the central nervous system in addition to dry mouth and constipation.</td></tr>
<tr><td>Precautions for dosage and administration</td><td>Development of cognitive dysfunction is related to multiple factors such as cognitive function at baseline, electrolyte imbalance, complications, and effects of coadministered drugs. For anticholinergic effects, in particular, the total cholinergic load of administered drugs is regarded as important, not an effect of a single agent. Therefore, the anticholinergic risk scale (ARS) is often used as an index to assess a risk of adverse events.
Attention should be paid to a risk of developing withdrawal symptoms due to sudden discontinuation for many anticholinergic drugs.</td></tr>
<tr><td>Precautions against interactions with other therapeutic-category products</td><td>A table provides a list of drugs with anticholinergic effect. If any of the drugs listed here are administered, it is recommended to consider discontinuation or dose ducton.
<table>
<tr><td>Antidepressants</td><td>Tricyclic antidepressants (imipramine [Imidol, Tofranil], clomipramine [Anafranil], amitriptyline hydrochloride [Tryptanol], etc.)
Paroxetine [Paxil]</td></tr>
<tr><td>Antipsychotics</td><td>Phenothiazine antipsychotics (chlorpromazine [Contomin], levomepromazine [Hirnamin, Levotomin], etc.)
Atypical antipsychotics (olanzapine [Zyprexa], clozapine [Clozaril])</td></tr>
<tr><td>Antiparkinson drugs</td><td>Trihexyphenidyl [Artane]
Biperiden [Akineton]</td></tr>
<tr><td>Antiarrhythmic drugs</td><td>Disopyramide [Rythmodan]</td></tr>
<tr><td>Skeletal muscle relaxants</td><td>Tizanidine [Ternelin]</td></tr>
<tr><td>Overactive bladder drugs (Muscarine receptor antagonists)</td><td>Oxybutynin [Pollakisu], propiverine [Bup-4], solifenacin [Vesicare], etc.</td></tr>
<tr><td>Intestinal tract anticonvulsants</td><td>Atropine, butylscopolamine [Buscopan], etc.</td></tr>
<tr><td>Antiemetics</td><td>Prochlorperazine [Novamin]
Metoclopramide [Primperan]</td></tr>
<tr><td>H2 receptor antagonists</td><td>All H2 receptor antagonists (cimetidine [Tagamet], ranitidine [Zantac], etc.)</td></tr>
<tr><td>H1 receptor antagonists</td><td>All first-generation H1 receptor antagonists (chlorpheniramine [Allergin, Neorestamin, Bismilla], diphenhydramine [Restamin], etc.)</td></tr>
</table>
* Prepared by limiting to drugs with anticholinergic effect listed in Guideline for Safe Medication of the Elderly Patients 2015, the drugs listed as strong for Anticholinergic risk scale, and the drugs that are listed in Drugs with Strong Anticholinergic Properties of Beers criteria 2015 and are available in Japan.</td></tr>
</table>

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Appendix Table 2 A list of drugs that require specifically careful administration

Category	Drug (Cluster or non-proprietary name)	Recommended use	Major adverse drug events, reasons
Antiparkinson drugs	Antiparkinson drugs (anticholinergic drugs) (Trihexyphenidyl [Artaine], Biperiden [Akineton])	Avoid using the drugs whenever possible. Alternative drug: L-dopa	Decreased cognitive function, delirium, oversedation, oral dryness, constipation, aggravated urination symptoms, urinary retention
Steroids	Oral steroids (Prednisolone, methylprednisolone [Medrol], betamethasone [Rinderon], etc.)	They must not be used in chronic stable COPD patients. If symptoms are aggravated, it is recommended to administer prednisolone 40 mg/day for 5 days to patients with stage III or higher or those who need to be controlled as inpatient.	Muscle weakness of respiratory muscle, prolonged respiratory failure, development of peptic ulcer
Digitalis	Digoxin [Digosin, Halfdigoxin]	A dose should be reduced to 0.125 mg/day or less. Since the elderly are at a risk of digitalis poisoning even if their dose is 0.125 mg/day or less. When monitoring the patients by blood concentration or by electrocardiogram is difficult, discontinuation should be considered.	Digitalis poisoning
Diuretics	Loop diuretics (Furosemide [Lasix], etc.)	Minimum necessary use should be sought. When a decreased circulating plasma volume is suspected, discontinuing or dose reduction of the drug should be considered. Electrolyte/renal function should be monitored. when required	Decreased renal function, orthostatic hypotension, fall, electrolyte abnormality
	Aldosterone antagonist (spironolactone [Aldactone-A], eplerenone [Selara])	Electrolyte/renal function should be monitored when required. In particular, the patients with a higher potassium level and decreased renal function should use the drugs at a lower dose.	Hyperkalemia
β blockers	Non-selective β blockers (Propranolol [Inderal], carteolol [Mikelan])	For bronchial asthma and COPD, only β_1-selective β blockers should be used. Even in this pattern, the indication itself should be carefully considered. Carvedilol [Artist] may be used in COPD patients with concomitant cardiac failure (there have been few reports on aggravated COPD, and the usefulness for heart failure outweighs the event. It is	Aggravated respiratory diseases and induced asthmatic attack

		contraindicated to bronchial asthma).	
α blockers	Receptor subtype non-selective α_1 receptor blockers (terazosin [Hytracin, Vasomet], prazosin [Minipress], urapidil [Ebrantil], doxazosin [Cardenalin], etc.)	Avoid using the drugs whenever possible. Alternative drugs: (hypertension) other anti-hypertensives (Prostatic hyperplasia) silodosin [Urief], tamsulosin [Harnal], naftopidil [Flivas], plant preparations	Orthostatic hypotension, fall
First generation H_1 receptor antagonists	H_1 receptor antagonists (first generation)	Avoid whenever possible.	Decreased cognitive function, delirium risk, oral dryness, constipation
Antiemetics	Metoclopramide [Primperan], prochlorperazine [Novamin], promethazine [Hiberna, Pyrethia]	Avoid whenever possible.	The effect to block dopamine receptors may induce or aggravate Parkinson's symptoms.
Overactive bladder drugs	Oxybutynin (oral) [Pollakisu]	The drug must be avoided for use whenever possible. As an alternative drug: Other muscarine receptor antagonists	It may cause urinary retention, decreased cognitive function, and delirium. A higher incidence of oral dryness and constipation
	Muscarine receptor antagonists (solifenacin [Vesicare], tolterodine [Detrusitol], fesoterodine [Toviaz], imidafenacin [Uritos, Staybla], propiverine [Bup-4], oxybutynin percutaneous absorption type [Neoxy tape])	They should be started at a low dose. In patients with prostatic hyperplasia, α_1 receptor blocker should be coadministered. Laxatives should be used when necessary.	Oral dryness, constipation, aggravated urination symptoms, urinary retention
Osteoporosis drugs	Activated vitamin D_3 drugs (alfacalcidol [Alfarol, Onealfa], eldecalcitol [Edirol])	Alfacalcidol should not be used at 1 μg/day or more.	Attention should be paid to the fact that coadministration with calcium preparations including supplements can cause decreased cognitive function and/or delirium associated with hypercalcemia.

(Edited and excerpted from the Guidelines for Medical Treatment and its Safety in the Elderly 2005 (The Japan Geriatrics Society), Guidelines for Medical Treatment and its Safety in the Elderly 2015 (The Japan Geriatrics Society))

Appendix Table 3 Typical renal excreted drugs

Therapeutic category	Drug name
Antibacterial drugs	fluoroquinolone antibacterial drugs (levofloxacin, etc.) Vancomycin hydrochloride Aminoglycoside antibacterial drugs (gentamicin sulfate), etc.
Anti-virus drugs	Valaciclovir hydrochloride Aciclovir Oseltamivir phosphate, etc.
H_2 receptor antagonists	Famotidine Ranitidine hydrochloride, etc.
Antidiabetic drugs	Metformin hydrochloride Sitagliptin phosphate hydrate Alogliptin benzoate, etc.
Antiarrhythmic drugs	Cibenzoline succinate Disopyramide Pilsicainide hydrochloride, etc.
Anticoagulant drugs	Dabigatran etexilate methanesulfonate Rivaroxaban, etc.
Hyperuricemia drugs	Allopurinol
Cardiac glycoside	Digoxin Metildigoxin, etc.
Psycho/neuro therapeutic drugs	Lithium carbonate Sulpiride Risperidone Amantadine hydrochloride Memantine hydrochloride, etc.

Appendix Table 4. Typical examples of substrates, inhibitors, and inducers associated with CYP (drugs that are expected to be used in the elderly and to which attention should be paid)

CYP molecular species	Substrate A drug that receives interactions of inhibitors or inducers	Inhibitor Drugs that increase the blood concentration of a substrate	Inducer Drugs that decrease the blood concentration of a substrate
CYP1A2	Tizanidine Ramelteon Duloxetine	Fluvoxamine Ciprofloxacin Mexiletine	
CYP2C9	Warfarin Phenytoin Glimepiride, Glibenclamide, Nateglinide Diclofenac, Celecoxib Fluvastatin	Miconazole, Fluconazole Amiodarone Bucolome	Rifampicin
CYP2C19	Voriconazole Omeprazole, Lansoprazole	Fluvoxamine Voriconazole, Fluconazole	Rifampicin
CYP2D6	Dextromethorphan Nortriptyline, Maprotiline Metoprolol Atomoxetine Tolterodine	Paroxetine Terbinafine Cinacalcet Mirabegron Duloxetine	
CYP3A note1, 2)	Triazolam, Alprazolam, brotizolam Suvorexant Simvastatin, Atorvastatin Nisoldipine, Felodipine, Azelnidipine, Nifedipine Rivaroxaban Ticagrelor Eplerenone	Itraconazole, Voriconazole, Miconazole, Fluconazole Clarithromycin, Erythromycin Diltiazem, Verapamil Grapefruit juice	Rifampicin, Rifabutin Phenobarbital, Phenytoin, Carbamazepine St. John's wort

* A substrate (a drug subject to interactions) is a drug metabolized by its CYP molecular species. The substrate drug may cause interactions when coadministered with an inhibitor (drugs that increase the blood concentration of a substrate) and/or an inducer (a drug, etc. which decreases the blood concentration) in the same metabolizing enzyme column. In general, the combination with an inhibitor which increases the blood concentration may cause adverse drug events due to stronger substrate effect while the combination with an inducer which decreases the blood concentration may reduce the efficacy. Of note, in many cases, coadministration of substrates does not affect each other.

* Reports on the above drugs basically provide interactions due to fluctuations in the blood concentration or AUC's change to double or more or half or less. Drugs for which the use in the elderly is expected, in particular, and considered important are listed. They do not necessarily include all the drugs which may cause interactions, such as anti-HIV drugs, anti-HCV drugs, and anti-cancer drugs. Some combinations may increase the blood concentration 5-fold or more, or 10 times or more in some cases.

* This list does not cover all the drugs. Whether attention should be actually paid to interactions should be determined for each combination by checking the descriptions in the package insert or the presence of reports on interactions.

Note 1 Most benzodiazepines and calcium antagonists are mainly metabolized by CYP3A. This list provides examples of drugs for which CYP3A is known to greatly contribute to metabolism among the drugs.

Note 2 CYP3A or P-glycoprotein's contribution to digestive absorption is not evident in many cases. Attention should be paid to the fact that some cases have been affected by both. Drugs that inhibit CYP3A often inhibit P-glycoprotein, too.

(Attachment) Pharmacokinetics, when renal function is decreased, and drug interactions

(1) Changes with aging in pharmacokinetics and pharmacodynamics

○ Pharmacokinetics

Pharmacokinetics are defined by the steps called ADME consisting of absorption, distribution, metabolism, and excretion. In each step, aging has the impacts mentioned below (in the table). In particular, metabolism and excretion are important because they tend to be particularly affected by aging and are related to drug elimination capacity (drug clearance).

In general, for many drugs, exposure in the body is highly related to their efficacy/adverse drug events. A factor that defines the exposure in the body is Area Under the Curve (AUC). When a drug is administered, the elderly can, in theory, maintain the same AUC as associated with normal hepatic or renal function by reducing the dose according to the residue rate of systemic (or oral) clearance level associated with decreased hepatic clearance and renal clearance because of the relationship that **AUC equals the dose/systemic (or oral) clearance**. This is the basis of the idea of the administration design for decreased renal function (Giusti-Hayton method) and changes in AUC by the inhibition of CYP as mentioned later.

Table 1. Physiological changes and pharmacokinetics changes with aging

	Physiological changes with aging	**General pharmacokinetics changes**
Absorption	Decreased digestive tract function Decreased blood flow in the digestive tract Increased intragastric pH	Prolonged T_{max} (increased or decreased blood concentration, depending on the drug)
Distribution	Increased body fat rate	Increased distribution volume of lipophilic drugs (Prolonged blood half-life)
	Decreased body water volume	Decreased distribution volume of water-soluble drugs
	Decreased plasma albumin concentration	Decreased protein binding rate of acidic drugs
Metabolism	Decreased liver weight	Decreased hepatic clearance ***Interaction's impact is also important**
	Decreased blood flow in the liver	
	Decreased activation of drug-metabolizing enzyme	

Excretion	Decreased blood flow in the kidneys	Decreased renal clearance ***The elderly are greatly affected, in particular.**
	Decreased glomerulus filtration rate	
	Decreased secretion from the renal tubules	

○ Pharmacodynamics

Some drugs may respond to target molecules differently with the aging of patients while exhibiting no fluctuation in their blood concentrations. Known examples are decreased sensitivity to β receptor agonists, increased sensitivity to anxiolytics, hypnotics, and anticholinergic drugs, etc.

(2) Renal function assessment with creatinine clearance

Appropriate renal function assessment is important to dose selection of drugs excreting by the kidneys. Inappropriate renal function assessment would lead to over- or under-dosing. Although it is ideal to assess the renal function with measured creatinine clearance (Ccr), it is unrealistic to measure all patients in the clinical settings. Moreover, even with decreased renal function, the elderly often have a serum creatinine level (SCr) within the normal range. Therefore, when setting doses of a drug, the decision should not be made based on the SCr alone. Estimation of Ccr with the Cockcroft-Gault method or renal function assessment with estimated glomerulus filtration rate (eGFR) is required. Of note, renal function is over-assessed with the CG method for obese patients, and, since this equation was established based on the SCr measured by the Jaffe method, 0.2 should be added to an actual SCr if measured with the enzyme method which is used by most institutions in Japan.

(3) Renal function assessment based on estimated glomerulus filtration rate (eGFR)

The standardized eGFR (unit: mL/min/1.73 m^2) provides a renal function when assuming that the body size of patients is uniformly 1.73 m^2. Such values are not applicable unadjusted especially to elderly female patients with a smaller body size because it will result in overdosing associated with over-assessment of renal function. Therefore, the eGFR calculated based on the body surface area of individual patients (personalized eGFR) must be used when eGFR is used to select the dose. Of note, since the dose of a drug that is set per body weight or body surface area has already considered the body size, the standardized eGFR (unit: mL/min/1.73 m^2) should be used for the corresponding renal function.

(4) Problems of the renal function assessment based on creatinine and usefulness of cystatin C

SCr often does not reflect the actual renal function in patients with decreased muscle mass, such as bedridden patients and those with sarcopenia/frailty in many cases. For such patients, it is useful to apply an estimation equation that employs cystatin C, which is not affected by the muscle mass.

Table 2. Various renal function assessment methods and their characteristics

Renal function assessment methods	Characteristics/points to be noted
Creatinine clearance (CG method) $\mathrm{Ccr} = \frac{(140 - \mathrm{Age}) \times \mathrm{Body\ weight}}{72 \times \mathrm{SCr}}$ *Multiplied by 0.85 for women	• When SCr measured with the enzyme method (the method in Japan) is used, 0.2 should be added to the actual value for substitution. • Renal function is over-assessed in patients with less muscle mass. • Renal function is over-assessed in obese patients.
Standardized eGFR (calculated with SCr) $\mathrm{eGFR} = 194 \times \mathrm{SCr}^{-1.094} \times \mathrm{Age}^{-0.287}$ *Multiplied by 0.739 for women	• This formula does not take the body size of each patient into account, and it is not suitable to drug dose selection in many cases. • Renal function is over-assessed in patients with less muscle mass.
Personalized eGFR (calculated with SCr) $\text{Personalized eGFR} = \text{Standardized GFR} \times \frac{\text{Patient's body surface area}}{1.73}$	• It is suitable to drug dose selection. • Renal function is over-assessed in patients with less muscle mass.
Standardized eGFR (calculated with cystatin C) $\text{Male: eGFR} = (104 \times \mathrm{CysC}^{-1.019} \times 0.996^{\mathrm{Age}})\text{-}8$ $\text{Female: eGFR} = (104 \times \mathrm{CysC}^{-1.019} \times 0.996^{\mathrm{Age}} \times 0.929)\text{-}8$	• This formula does not take the body size of each patient into account, and it is not suitable for drug dose selection in many cases. • Not affected by muscle mass • May be affected by HIV infection, abnormal thyroid function, and medication such as ciclosporin.
Personalized eGFR (calculated with cystatin C) $\text{Personalized eGFR} = \text{Standardized eGFR} \times \frac{\text{Patient's body surface area}}{1.73}$	• It is suitable to drug dose selection. • Not affected by muscle mass • May be affected by HIV infection, abnormal thyroid function, and medication such as ciclosporin.

(5) Simple way of drug dose selection (the Giusti-Hayton method)

The Giusti-Hayton method is a way to select the doses of drugs excreted by the kidneys in patients with decreased renal function. Optimal doses for such patients can be obtained by multiplying the usual dose by the correction coefficient (G) which can be obtained from the equation below and required increase of dosing interval by dividing the required increase of dosing interval can be obtained by the usual dosing interval by

dividing with G. In the following equation, the Ccr of persons with normal renal function is considered to be 100 mL/min, in general. Ccr can be replaced with eGFR.

$$\text{Correction coefficient(G)} = 1 - \text{the urinary excretion rate of unchanged drugs}^{*} \times \left(1 - \frac{\text{Ccr of the patient}}{\text{Ccr of the persons with normal renal function}}\right)$$

* When a value obtained at intravenous administration or at oral administration is used, the value should be corrected by dividing by bioavailability (F).

* If the metabolite is active, the urinary excretion rate should be considered as well.

E.g. when famotidine (usual dose: 40 mg/day, the urinary excretion rate of unchanged drugs: 80%) is administered to a patients with Ccr of 50 mL/min, the correction coefficient for administration (G) is 1 - 0.8 × 0.5 = 0.6. The correction coefficient provides approximately the same blood concentration in this patient as that of those with normal renal function if the patient receives 40 mg/day × 0.6 = 24 mg/day.

(6) Types of drug interactions

The mechanisms of action of drug interactions include pharmacokinetics interaction and pharmacodynamics interaction.

Pharmacokinetics interaction refers to a case where excessive effect appears (poisoning) or the effect is decreased through fluctuation in the blood concentration after the drug's absorption, distribution, metabolism, and excretion are affected by other drugs. A typical example is inhibition of drug-metabolizing enzyme activities in the liver. It has been reported that approximately 40% of drug interactions are the pharmacokinetics interaction at metabolized sites. Most of these interactions have the mechanism via cytochrome P450 (CYP) while reports on important interactions via transporter have been increasing. Pharmacodynamics interaction refers to a case where there is no change in the pharmacokinetics in the body (blood concentration), but the efficacy will be increased or decreased due to interactions at the activated site, such as receptors, or overlapped similar therapeutic effects. Examples are exacerbated asthma symptoms caused by concomitant use of bronchodilator drugs and β receptor blockers with a bronchoconstriction action, somnolence caused by concomitant use of central nervous system depressants, drug-induced parkinsonism caused by concomitant use of drugs with antidopaminergic effects, and thirst, impaired urination, constipation, etc. caused by concomitant use of drugs with an anticholinergic effect.

(7) Interactions involving CYP

The molecular species of CYP3A, CYP2D6, CYP2C, and CYP1A2 account for 90% or more in the CYP molecular species' contribution to drug metabolism. In particular, CYP3A is the major CYP in human small intestine and liver, and it is related to approximately 50% of CYP-metabolized drugs. Even the substrates (metabolized

drugs) in which a CYP molecular species greatly contributes to elimination (clearance), do not inhibit the CYP molecular species at a dose specified for clinical use in many cases. Therefore, the contribution level to metabolism and inhibition level should be considered separately.

For interactions due to changed activation of a drug metabolizing enzyme, it is important to assess how much the metabolizing enzyme contributes to elimination (clearance) of substrate drugs *in vivo* (when administered to humans) and to what extent the inhibitor or inducer reduces or increase the activity of the relevant metabolizing enzyme.

(8) Prevention and management of interactions

Drug interactions not only decrease or increase the treatment effect but also cause significant adverse effects in some cases. Therefore, assessment and prevention are important. It is necessary to examine how much the range of fluctuation in blood concentration due to interactions affect the efficacy and adverse drug events, per drug and per case. It is required to pay attention to interactions on a regular basis, strive to collect the latest information, and assess interactions in each patient in order to assure safe medication.

When a combination of drugs that can cause interactions is prescribed, it is important to take into account the seriousness of effects that can appear as a result of the prescription backgrounds, patient backgrounds, and interactions, as well as information on alternative drugs, to monitor the effect and adverse effects, and to make the prescription more appropriate through drug discontinuation, dose reduction, replacement with alternative drugs, etc.

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