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Polypharmacy and changes in prescribing medication in elderly inpatients due to pharmacological intervention in an acute care hospital : a single center study

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Abstract

Aim : This study aims to understand the polypharmacy conditions in one department of an acute care hospital in Japan, as well as details of intervention by physicians and pharmacists, to educate and provide meaningful information for healthcare professionals.

Methods : Participants were 345 hospitalized adults older than 75 years, admitted to the Department of Geriatrics at Tokyo Medical University Hospital between April 2017 and March 2018, who were taking one or more chronic medications. Patients were categorized into a polypharmacy group (PG ; six or more medications) and a non-polypharmacy group (nPG ; fewer than six medications). Factors such as age, sex, renal function, and drugs requiring special administration were retrospectively compared. We then investigated the number of interventions performed by physicians and pharmacists during the participants' hospitalization and the nature of these interventions.

Results : Most participants were admitted for malignant lymphoma, pneumonia, gastrointestinal bleeding, and dementia observation. The univariate comparison between groups showed that the percentage of PG patients using angiotensin receptor antagonists, calcium channel blockers, antiplatelet agents, magnesium oxide, dipeptidyl peptidase-4 inhibitors, loop diuretics, biguanide hypoglycemic agents, nonselective β-blockers, and oral digoxins was higher than that of the nPGs ($p < 0.01$). Between hospitalization and discharge, the details of prescription changes were reduction or discontinuation (71 medications), drug dosage adjustment (20 medications), adherence improvement interventions (e.g., single packaging), and usage adjustment (12 medications).

Conclusions : The results demonstrate that physicians and pharmacists can enable pharmacological intervention to address polypharmacy by understanding the drugs to be aware of and the contents of the interventions, as well as future issues to be addressed.

1. Introduction

Polypharmacy among older adults can be described as the inappropriate use of several medications. It is typified by adverse drug reactions, use of potentially inappropriate medications (PIMs), high medical expenses, and decreased medication adherence[1)]. Polypharmacy is difficult to avoid[2)3)], particularly among older adults who have more comorbidities, or "multimorbidity." This results in a greater number of medications to administer continuously, side effects, and medications for geriatric syndromes that may not be needed.[4,5)]

In the United States and Europe, there are criteria such as the Beers criteria[6)] and the Screening Tool for Older People's Prescriptions (STOPP)[7)] to address polypharmacy-related challenges and listed PIMs. To date,

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Japan does not have similar standards ; however, considering its super-aging society, the problem definitely warrants attention. It recommends that doctors and pharmacists actively work on this issue to appropriate polypharmacy. The Japanese Society of Geriatrics and Gerontology has published the STOPP measures in Japan, also known as "STOPP-J"[8], which lists PIMs in relation to drugs for non-essential geriatric syndromes. In addition, the Ministry of Health, Labor and Welfare (MHLW) has issued guidelines for the appropriate use of drugs given to older adults, advocating that both physicians and pharmacists, in both acute and convalescent care hospitals, actively address this concern in order to optimize polypharmacy.

Acute care hospitals in Japan have an environment that facilitates the prevention of polypharmacy, because patient medication information is easily centralized. It has been reported that the number of drug-induced adverse events decrease when healthcare professionals, including pharmacists, regularly promote the appropriate use of medications[9)10)]. However, we suspect that healthcare professionals' perceptions of polypharmacy in older adults may not be high. In our Department of Geriatric Medicine at Tokyo Medical University Hospital, our approach begins with the evaluation of geriatric syndromes and the elucidation of their causes, which eventually leads to the development of prevention, treatment, and care methods, as well as the comprehensive care of individual older adults. As part of this effort, physicians and pharmacists work together to facilitate and manage drug therapy. Such interventions by healthcare professionals are rarely reported upon in Japan, however we consider that understanding how these interventions affect inappropriate drug therapy will provide important information that will lead to countermeasures and help to raise awareness within hospitals. Therefore, we investigated the current situation of polypharmacy as well as possible prescription suggestions by physicians and pharmacists in one department of an acute care hospital in Japan.

2. Materials and methods

2.1. Study Methods and Participants

The study group for this retrospective observational study comprised 462 patients admitted to the Department of Geriatric Medicine at the Tokyo Medical University Hospital, from April 2017 to March 2018 who were using one or more regular medications. Of these patients, 345 participants were included. Information about the purpose of the study and procedures was provided, and participants (or their family members, in cases of dementia or inability to confirm their wishes) were given the opportunity to decline participation. Consent was obtained whenever feasible. Further, patient anonymity was preserved at all stages of the study design by omitting personal details. Details of those who were excluded from the study include : 27 individuals who were transferred to other departments, 38 individuals who did not have a clear record of the medication they were taking from admission to discharge (e.g., as a result of unconsciousness or cognitive decline), 44 individuals who had no oral medications prescribed at the time of admission, and 8 individuals who were discharged as a result of death. There were 33 patients who were hospitalized at different times during the study period ; these patients were considered to be different participants each time they were admitted. This is because their drug evaluation may differ each time, depending on symptoms.

The following information was extracted from their medical and pharmacy records : (1) regular medications upon admission — this means whether six or more drugs were orally administered and whether, among them, they were taking proton pump inhibitors[11] (PPIs) or one of 36 drugs whose improper use has been reported in STOPP-J. Other data included (2) age, (3) sex, (4) disease that led to their hospital admission, (5) hospitalization duration, (6) renal function estimated Creatinine Clearance [CCr] and glomerular filtration rate (eGFR) as measured from their blood collected on the day closest to the date of admission, and (7) liver function including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), and γ-Glutamyl TransPeptidase (γ-GTP).

To calculate medical costs in Japan, polypharmacy is defined and calculated as concurrently "taking six or more medications for four weeks or more[12]." The same definition was used in this study : the polypharmacy group (PG) was defined as patients who were taking six or more regular medications concurrently, as specified in the STOPP-J list, for four weeks or more. The non-polypharmacy group (nPG) was defined as patients taking fewer than six regular medications from the list. This definition was formulated based on the medications administered at the time of admission.

2.2. Analysis of the Reasons for Medication Reduction and Status of Intervention by Physicians and Pharmacists

We investigated the total number of drugs that were discontinued to moderate polypharmacy during hospitalization, the total number of physician and pharmacist interventions, the specific reasons, and the intervention items (as explained below). The STOPP-J, which is issued by the Japanese Geriatrics Society[12], was used as a reference to develop the following 14 intervention items : (1) improvement of disease symptoms, (2) non-adherence to the dosage indicated by the package insert, (3) renal or hepatic dysfunction, (4) low medication

adherence, (5) no drug effects, (6) no need for long-term administration, (7) dysphagia due to disease and aging, (8) decline in cognitive function, (9) changed to other effective drugs, (10) changes or discontinuation of a drug(s) during hospitalization, (11) suspected adverse drug events, (12) consideration of disadvantages, (13) overlapping drug efficacy, and (14) no longer required owing to nonpharmacological interventions.

2.3. Statistical Analysis

Background comparisons for the patients included in the study were conducted utilizing the Mann-Whitney U test to compare median PG and nPG, respectively, and the χ-square test for comparing categorical variables. Regarding reasons for hospitalization, descriptive statistics were presented for the PG and nPG groups. In the case of univariate analysis of the proportion of medications taken by PG and nPG, the data were categorical and the χ2 test or Fisher's direct comparison test was utilized. Overall, descriptive statistics were performed for the number of drugs discontinued after hospitalization and reasons for discontinuation. All analyses were performed using IBM's Statistical Package for Social Sciences (SPSS) Statistics version 27 (IBM Corp., Armonk, NY).

2.4. Ethics Approval

This study was approved by the Medical Ethics Committee of the Tokyo Medical University (study approval number : TS2021-0093) and its ethical considerations were consistent with the Declaration of Helsinki.

3. Results

The reasons for hospitalization of the 345 participants are shown in Table 1. Most patients were admitted for malignant lymphoma, pneumonia, gastrointestinal bleeding, and dementia observation. In terms of blood test results, the eGFR values were significantly lower in the PG group than in the nPG group ($p < 0.01$). Liver function (AST, ALT, T-Bil, γ-GTP), and CCr were not significantly different for all items examined (Data not shown).

The results of the univariate comparison between the PG and the nPG groups are shown in Table 2. The percentage of PG patients using angiotensin receptor antagonists (ARBs), calcium channel blockers (CCBs), antiplatelet agents, magnesium oxide (MgO), dipeptidyl peptidase-4 (DPP-4) inhibitors, loop diuretics, biguanide hypoglycemic agents, nonselective β-blockers, and oral

Table 1 Reasons for the patients' hospitalization

Patient background		nPG (n = 149)	PG (n = 196)	p-value
Age	Median (min-max)	83.5 (75-98)	84 (75-98)	0.93
Sex (female)	% (n)	55.7 (84)	52.5 (103)	0.48
Body weight (kg)	Median (min-max)	49.3 (30-76)	52 (28-86)	0.96
Number of hospitalization days	Median (min-max)	12 (1-182)	12 (1-372)	0.81
eGFR (mL/min/1.73 m2)	Median (min-max)	65 (19-144)	57 (4-130)	<0.01※

Reason for admission	nPG	PG	N
Malignant lymphoma	16	24	40
Pneumonia	13	25	38
Investigation of cause of gastrointestinal bleeding	10	25	35
Close examination of dementia	22	12	34
Cerebral hemorrhage	14	19	33
Infectious diseases†	12	15	27
Gastrointestinal diseases‡	9	15	24
Brain and nerve diseases§	12	11	23
Solid tumor	5	10	15
Anemia	2	7	9
Chronic cardiac insufficiency	7	2	9
Diabetes	2	6	8
Lung diseases‖	2	5	7
Suspected rheumatic disease	3	2	5
Chronic renal insufficiency	0	2	2
Others	20	16	36
Total			345

†excluding pneumonia ; ‡excluding infectious diseases and malignant tumors ; §excluding dementia and stroke ; ‖excluding pneumonia
N : number of patients

Table 2 Univariate analysis of the proportion of medications taken by the polypharmacy (PG) and non-polypharmacy groups (nPG)

Drug class	Total % (n/N)	nPG % (n/N)	PG % (n/N)	*p*-value
Proton pump inhibitors	46.3 (160/345)	27.5 (41/149)	60.7 (119/196)	< 0.01※※
Angiotensin receptor blockers	39.4 (136/345)	29.5 (44/149)	46.9 (92/196)	< 0.01※※
Calcium channel blockers	37.7 (130/345)	28.2 (42/149)	44.9 (88/196)	< 0.01※※
Antiplatelet agents	33.3 (115/345)	22.8 (34/149)	41.3 (81/196)	< 0.01※※
Magnesium oxide	19.1 (66/345)	8.1 (12/149)	27.6 (54/196)	< 0.01※※
DPP-4 inhibitors	14.2 (49/345)	7.4 (11/149)	19.4 (38/196)	< 0.01※※
Loop diuretics	14.2 (49/345)	7.4 (11/149)	19.4 (38/196)	< 0.01※※
Anticoagulant drugs	10.7 (37/345)	7.4 (11/149)	13.3 (26/196)	0.08
Benzodiazepines	10.1 (35/345)	6.7 (10/149)	12.8 (25/196)	0.66
Biguanides	6.4 (22/345)	1.3 (2/149)	10.2 (20/196)	< 0.01※※
Selective beta-blocker	6.4 (22/345)	2.7 (4/149)	9.2 (18/196)	0.02※
NSAIDs	5.5 (19/345)	3.4 (5/149)	7.1 (14/196)	0.13
Histamine 1 receptor antagonists	5.2 (18/345)	3.4 (5/149)	6.6 (13/196)	0.18
Nonbenzodiazepines (Z-type)	4.9 (17/345)	4.0 (6/149)	5.6 (11/196)	0.5
ACE inhibitors	4.3 (15/345)	2.7 (4/149)	5.6 (11/196)	0.19
Sulfonylureas	4.1 (14/345)	2.7 (4/149)	5.1 (10/196)	0.26
Steroids	4.1 (14/345)	3.4 (5/149)	4.6 (9/196)	0.56
Aldosterone antagonists	4.1 (14/345)	2.7 (4/149)	5.1 (10/196)	0.26
Nonselective beta-blockers	3.8 (13/345)	0 (0/149)	6.6 (13/196)	< 0.01※※
α-glucosidase inhibitors	3.2 (11/345)	2.0 (3/149)	4.1 (8/196)	0.22
SSRIs	2.6 (9/345)	2.7 (4/149)	2.6 (5/196)	0.6
Digoxin	2.6 (9/345)	0 (0/149)	4.6 (9/196)	< 0.01※※
Histamine 2 receptors antagonist	2.6 (9/345)	2.7 (4/149)	2.6 (5/196)	0.6
Alpha blockers	2.0 (7/345)	0 (0/149)	3.6 (7/196)	0.02※
Atypical antipsychotics drugs	1.7 (6/345)	0.67 (1/149)	2.6 (5/196)	0.19
Muscarinic receptor antagonists	1.7 (6/345)	2.0 (3/149)	1.5 (3/196)	0.52
SNRIs	1.4 (5/345)	0 (0/149)	2.6 (5/196)	0.06
NaSSA	1.4 (5/345)	0.67 (1/149)	2.0 (4/196)	0.28
SGLT inhibitors	1.4 (5/345)	1.3 (2/149)	1.5 (3/196)	0.62
Thiazolidinedione hypoglycemic drugs	1.2 (4/345)	0.67 (1/149)	1.5 (3/196)	0.42
Insulins	1.2 (4/345)	0 (0/149)	2.0 (4/196)	0.1
Typical antipsychotics	0.29 (1/345)	0 (0/149)	0.5 (1/196)	0.57
Tricyclic antidepressants	0.29 (1/345)	0 (0/149)	0.5 (1/196)	0.57
Sulpiride	0.29 (1/345)	0 (0/149)	0.5 (1/196)	0.38

n : number of patients ; N : total number of patients ; DPP-4 : dipeptidyl peptidase-4 ; NSAIDs : non-steroidal anti-inflammatory drugs ; SSRIs : selective serotonin reuptake inhibitor ; SNRIs : serotonin and noradrenaline reuptake inhibitor ; NaSSA : noradrenergic and specific serotonergic antidepressant ; SGLT : sodium-glucose transporter 2
※$p < 0.05$; ※※$p < 0.01$
The X^2 test and Fisher's exact test were used to compare the groups. $p < 0.05$ was considered to indicate a statistically significant difference.

digoxins was higher than that of the nPGs ($p < 0.01$).

Physicians and pharmacists intervened after consultation with the physician and discontinued a total of 326 oral medications taken by 345 participants, as depicted in Table 3. The most common reasons for discontinuing medication were the improvement of disease symptoms (59 medications), adverse drug events (39 medications), and suspected adverse drug events (17 medications). More detailed results are as follows :

1. Discontinuations due to symptom relief included mostly gastrointestinal drugs, including gastroprokinetic agents in 7 medications, intestinal agents in 5 medications, and laxatives in 4 medications. Antihypertensive and analgesic drugs that were discontinued were 4 and 3 medications, respectively.
2. Nine medications were discontinued because the patients' use did not correspond to the dosage and administration instructions on the package insert ; of these, 3 were antiplatelet agents and 3

Table 3 Number of drugs discontinued after hospitalization and reasons for discontinuation

Reason for discontinuation	Number of drugs discontinued
Improvement of disease symptoms	59
Consideration of disadvantages	39
Suspected adverse drug event	33
Low medication adherence	17
Decline in cognitive function	12
No need for long-term administration	10
Nonadherence to the dosage given in the instructions	9
Changed to other effective drugs	6
Change or discontinuation due to hospitalization	4
Renal and hepatic dysfunction	4
Changed to nonpharmacological interventions	2
Overlapping drug efficacy	2
No medicinal effects	2
Dysphagia due to disease and aging	127
Total	326

were PPIs.

3. Considering the issue of long-term administration, the main medications that were discontinued were 3 PPIs.
4. The drugs that were discontinued due to their disadvantageous properties were anticoagulants in 8 cases, antiplatelet agents in 4 cases, and anti-Parkinson's agents in 5 cases.
5. Regarding drugs discontinued due to adverse drug events, ARBs were discontinued in 10 cases, CCBs in 5 cases, and antiplatelet agents in 5 cases.
6. Lastly, there were 127 medications that were not directly related to adverse drug events, but were discontinued due to the risk of acute medical conditions or age-related dysphagia. Of these, 56 medications were discontinued in 20 patients because they were difficult to take, due to issues such as aspiration pneumonia.

4. Discussion

This study suggests that physicians and pharmacists should be involved in measures to improve polypharmacy among older adults by collecting older adult patients' medication status upon admission to hospital wards in acute care hospitals, and offering prescription suggestions, based on pharmacological judgment of appropriate use. Furthermore, the implications of the PIMs prescribing ratio and intervention status were examined in detail, and the results were utilized to raise awareness of the issue.

The results of the patients' background analyses showed that many patients were admitted to the hospital for detailed examination for suspected dementia, gastrointestinal bleeding and anemia, and treatment of malignant lymphoma. This indicates the unique characteristics of our hospital's geriatric department. In Japanese general hospitals, each department has its own specialty area where they mainly treat different diseases related to their specialty. The purpose of a patient's hospitalization would, of course, affect the duration of observation, which would also affect the course of the patient's quality of life after appropriate treatment. Considering the two participant groups, eGFR values from the univariate analysis were lower in the PG than in the nPG group. This is consistent with previous reports[13]. Naturally, these results suggest that it is necessary to consider reducing or discontinuing the dose of some medications, depending on renal function.

Compared with the nPG group, the PG group took a higher percentage of antihypertensive drugs, gastrointestinal drugs (PPIs, gastrointestinal drugs, or laxatives), magnesium oxide, and antiplatelet drugs. These are commonly reported factors of polypharmacy[12]. This result has been reported in existing literature as a factor in polypharmacy, as well as in drugs causing geriatric syndromes[12]. Antihypertensive medications were discontinued in a significant number of cases, after blood pressure was measured as needed, and the need for continuation was confirmed with the physician or nurse. It is thought that the above measures were taken because of improved blood pressure control during hospitalization and the progress of the patient's falling and unsteady movements. With regard to laxatives and other gastrointestinal medications, it is believed that determining the patient's symptoms and the observation of their progress during hospitalization led to the appropriate use of these medications.

Healthcare professionals may need to confirm the

appropriate use of PPIs. In this study, the long-term administration of PPIs in a number of patients was determined to be unnecessary and was discontinued. PPIs are effective and safe for older patients ; however, it has recently been reported that long-term administration increases the risk of bone fractures and *Clostridioides difficile* infections[14]. One study reported that doctors tend to prescribe PPIs for a longer period of time than necessary for reflux esophagitis ; hence, doctors and pharmacists should pay attention to the duration of use[15]. In addition, an increased risk of kidney damage has been reported with PPIs[16]. We have not been able to determine this in the current study, but we intend to discuss it in the future.

Interventions regarding antiplatelet and coagulant medications were made in all cases. This is sometimes discussed by the physician at the time of admission, and sometimes by other hospital personnel. It is crucial for hospital personnel to continue their work without having to investigate a suspected gastrointestinal bleed and anemia, considering that there were many cases of anemia in the hospital. Antiplatelet agents for secondary prophylaxis are not prescribed to many patients who need them[17][18]. In this study, the comorbidities related to antiplatelet agents as well as dosages were also confirmed, leading to their appropriate use.

As dysphagia was the most common factor leading to geriatric interventions, the swallowing function should be closely monitored. Medication management and changing medicines to other dosage forms, such as patches, should be considered accordingly. Doctors, pharmacists, nurses, and other healthcare professionals should assess patients' general conditions and living conditions, including the degree of progression of the geriatric syndrome dysphagia, and consider sustainable treatments.

Despite its clear contributions, there are four limitations to this study : (1) The definition of polypharmacy is challenging. This study, and the Japanese medical insurance system, define polypharmacy as taking 6 or more oral medications simultaneously. Some reports from other countries define it as 5 drugs, whereas others describe it as multiple prescriptions with inappropriate use, regardless of the number of drugs[19]. It is therefore difficult to clearly define polypharmacy. (2) This was a cross-sectional retrospective study of patients during their hospitalization period. We did not conduct subsequent studies on patients' conditions and discontinued medications after patients were discharged. This is partially due to Japan's medical system, by which patients can visit any of the local medical institutions after being discharged from acute care hospitals, which hinders the acquisition of medical information and medication history. (3) Lastly, patients' medication adherence was only verbally confirmed by physicians and pharmacists. The pill counting method and the drug blood level assay have been reported as methods to check adherence[20]. As hospital pharmacists in Japan mainly focus on activities within the hospital, it is necessary to acquire a detailed medication history, check patients' medication adherence, and adjust their remaining medications in cooperation with local pharmacies. Residual medication due to unused prescription medications is a challenge, and further investigation and interventions must be proposed. (4) In this study, we focused solely on the reason for hospitalization and did not investigate other medical conditions or the presence of multimorbidity. This decision was made as a result of the substantial complexity that would arise from analyzing multiple comorbidities for each individual.

Implementing initiatives based on interventions such as this study in each medical facility has significant implications. It is crucial to raise awareness regarding appropriate medication including PIMs use among older adult patients, healthcare professionals including nursing staff, caregivers or family members caring for older adults and other relevant actors. Explanations provided by healthcare professionals can help patients and caregivers understand and use medicines appropriately, leading to improved adherence. Our study may contribute to shedding light on some of these aspects.

5. Conclusion

This study reported on drugs that caused problems with polypharmacy. This demonstrated that countermeasures should be developed to address polypharmacy, particularly among older adults. We believe that our results will contribute to the solving of polypharmacy challenges in the future.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Yoshiyuki Furumi, Yusuke Sekine, Yusuke Takata, Tomohiko Sato, and Kentaro Hirao. The first draft was written by Yoshiyuki Furumi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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急性期病院の高齢入院患者におけるポリファーマシーと薬学的介入による処方の変化に関する研究 : 単一施設での検討

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[2)]東京医科大学高齢総合医学分野

【要旨】本研究は、日本の急性期病院のある診療科におけるポリファーマシーの状況およびその対策を把握し、医療従事者への教育および有意義な情報提供を行うことを目的とする。

2017 年 4 月から 2018 年 3 月までに東京医科大学病院高齢診療科に入院し、1 種類以上の薬剤を服用していた 75 歳以上の成人 345 名を対象とし、患者をポリファーマシー群（PG ; 6 種類以上の薬剤）と非ポリファーマシー群（nPG ; 5 種類以下の薬剤）に分類した。年齢、性別、腎機能、特別な投与を必要とする薬剤などの因子を後方視的に比較し、入院中に医師、薬剤師共同で薬剤に介入した件数とその内容を調査した。

群間単変量比較では、PG においてアンジオテンシン受容体拮抗薬、カルシウム拮抗薬、抗血小板薬、酸化マグネシウム、ジペプチジルペプチダーゼ 4 阻害薬、ループ利尿薬、ビグアナイド血糖降下薬、非選択性 β ブロッカー、ジゴキシン経口の使用割合は nPG より多かった（p<0.01）。入院から退院までの間で処方の変更詳細は、減量・中止（71 薬剤）、用量調整（20 薬剤）、アドヒアランス向上介入（一包化など）、使用量調整（12 薬剤）であった。

これらの結果から、注意すべき薬剤、また介入内容が把握できたことで、医師、薬剤師がポリファーマシー対処するための薬学的介入が可能になること、また今後の課題について示すことができた。

〈キーワード〉 臨床医学、社会医学、薬剤学、ポリファーマシー、老年医学