資料３

徳田構成員提出資料

Letters

Invited Commentary

Challenges in Choosing Wisely's International Future: Support, Evidence, and Burnout

In the short time since its April 2012 launch by the American Board of Internal Medicine Foundation, the Choosing Wisely campaign has affected more than 60 US specialty societies. Now the campaign is becoming an international phenomenon, as evidenced by Selby et al[1] and Gupta and Detsky[2] in this issue. These publications should be considered in the context of other national efforts, the most prominent being Choosing Wisely Canada,[3] which identifies itself as being modeled after its American counterpart and having "spread to Australia, Germany, Italy, Japan, Netherlands, Switzerland and elsewhere." This rapid expansion is a heartening sign that there is increasing international sentiment against wasteful medical practices. However, actually decreasing wasteful and harmful health care will require both patient and physician commitment as well as objective evidence of effectiveness. If either is found wanting, the results will be underwhelming.

Related articles

Both Choosing Wisely and its global counterparts seek to reduce low-value health care by generating "top 5" lists of practices that should be questioned by patients and health care professionals; as such, effecting change from these suggested lists will require constituents' support of the lists. Therefore, it is fitting that the process should be designed to optimize support. The first such top 5 list, generated by the American Academy of Family Physicians and published in *Archives of Internal Medicine* in 2011,[4] was developed using a modified nominal group process. Three years later, the Swiss Society of General Internal Medicine used a process of literature review supplemented by expert opinion, followed by an electronic Delphi process in multiple rounds to identify the top 5 recommendations. Gupta and Detsky[2] chose to solicit recommendations from physicians, followed by a voting process to select the top recommendations. The above processes are quasi-systematic methods that focus on physician participation to increase support; however, they rely on subjective perceptions of feasibility and benefit to cost ratio rather than high-quality evidence. An alternative would be to develop a systematic process to identify the practices that will lead to the greatest improvement in patient outcomes and cost reductions. Doing so might be accomplished with traditional methods of evidence-based recommendations, such as systematic review and health technology assessment. Alternatively, one might leverage already-generated lists of practices that are known to have evidence of harm and are high in cost. Several such lists already exist, with groups having completed systematic reviews as well as sophisticated cost modeling to project potential cost reduction.[4-6]

Choosing Wisely and Choosing Wisely Canada aspired to initiate conversations about eliminating low-value health care,[3,7] and they have succeeded in realizing their goal. We are now ready and eager for the next steps—to realize a measurable decrease in low-value health care utilization. Currently, we are not aware of any evidence that the top 5 lists, in the United States or abroad, have reduced low-value medical practices. The American Board of Internal Medicine Foundation studied the effect of their campaign using a telephone survey of 600 US physicians and found that 21% had heard of the Choosing Wisely campaign and that, among this subgroup, 62% reported having reduced unnecessary testing in the past year.[8] These results suggest, at best, a modest effect; but because the results are self-reported, they cannot be used to estimate the net effect on cost-effective care. Building on the success of the Choosing Wisely campaign will require demonstration of a reduction in wasteful practices. As global enthusiasm for top 5 lists mounts, so will the desire to use the lists to shape policy and practices. Evidence of the effectiveness of top 5 lists must grow, not just the number of lists—otherwise, physicians may question the value of the campaigns. The resulting skepticism and cynicism are likely to lead to decreased support.

Even more dangerous to the movement than the present lack of evidence would be top 5 list "burnout." Survey studies[9] have shown that physicians who were faced with multiple guidelines on a single topic become less certain of how to proceed. Professional organizations around the world already publish guidelines that outline the best evidence-based practices. While top 5 lists are not guidelines, it is likely that the finding of guideline burnout is generalizable to top 5 lists. This potential seems more likely now that individual institutions are adopting their own top 5 lists. For example, Gupta and Detsky[2] describe the creation of a top 5 list for the general internal medicine inpatient service at Mount Sinai Hospital in Toronto, Ontario, Canada, that might be considered in addition to the top 5 lists from the 21 Canadian specialty societies that partnered with Choosing Wisely Canada. It is not hard to imagine a near future in which every service at an individual institution generates a top 5 list to be considered in the context of the national specialty society top 5 lists, all without specific evidence of effectiveness. Particularly, if some of these lists are discordant, they will be unlikely to change behavior.

Internationally, health care costs are increasing without a commensurate improvement in health outcomes. Therefore, we strongly believe in the global spirit behind the Choosing Wisely campaigns and movement; that is why we advocate that the priority in 2015 should be the thoughtful implementation and rigorous evaluation of existing top 5 lists. Changing behavior is more complex and challenging than writing a list, but clearly the will to change exists among physicians and patients. Systematic, repeated, delib-

erate effort is required, and tools such as dashboards, performance reporting, financial incentives, benchmarking, and repeated feedback loops may be useful. We believe all top 5 lists should be accompanied by an implementation plan and should be evaluated and continuously monitored to assess their effect on low-value health care utilization.

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1. Selby K, Gaspoz J-M, Rodondi N, et al. Creating a list of low-value health care activities in Swiss primary care [published online February 23, 2015]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2014.8111.

2. Gupta S, Detsky AS. Development of Choosing Wisely recommendations for an inpatient internal medicine service [published online February 23, 2015]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2014.8119.

3. Canadian Medical Association. What is CWC? Choosing Wisely Canada website. www.choosingwiselycanada.org/about/what-is-cwc. Accessed November 11, 2014.

4. Aguilar IBZ, Casher D, Choi RY, et al; Good Stewardship Working Group. The "top 5" lists in primary care: meeting the responsibility of professionalism. *Arch Intern Med*. 2011;171(15):1385-1390.

5. Elshaug AGWA, Watt AM, Mundy L, Willis CD. Over 150 potentially low-value health care practices: an Australian study. *Med J Aust*. 2012;197(10):556-560.

6. National Institute for Health and Care Excellence. NICE 'do not do' recommendations. National Institute for Health and Care Excellence website. www.nice.org.uk/proxy/?sourceurl=http://www.nice.org.uk/usingguidance/donotdorecommendations/index.jsp. Accessed November 11, 2014.

7. American Board of Internal Medicine Foundation. About. Choosing Wisely website. www.choosingwisely.org/about-us/. Accessed November 11, 2014.

8. Perry Undem Research/Communication. Unnecessary tests and procedures in the health care system: what physicians say about the problem, the causes, and the solutions: results from a national survey of physicians. www.choosingwisely.org/wp-content/uploads/2014/04/042814_Final-Choosing-Wisely-Survey-Report.pdf. Accessed November 11, 2014.

9. Gagliardi ARBM, Brouwers MC, Palda VA, Lemieux-Charles L, Grimshaw JM. How can we improve guideline use? a conceptual framework of implementability. *Implement Sci*. 2011;6(26):26.

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LETTERS

TOO MUCH MEDICINE

Direct to consumer unproved screening tests turn a profit in Japan

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Japanese doctors and patients face much the same problem of too much medicine outlined by Glasziou and colleagues.[1] The Japanese healthcare system is rightly lauded as a model of cost containment while achieving better outcomes on many key health indicators than the United States and other developed nations do. However, the use of unnecessary diagnostic tests driven by aggressive direct to consumer advertising has greatly increased in Japan over the past decade.

On the basis of data from the Japan Brain Dock Society and Japan PET Scan Net,[2 3] 220 screening centres in Japan provide brain magnetic resonance imaging (MRI) and 200 cancer screening centres offer positron emission tomography (PET). Healthy people without symptoms are urged to undergo MRI screening to detect possible asymptomatic stroke or unruptured aneurysms. PET screening is advocated to screen for asymptomatic occult cancers. Neither of these screening tests is supported by evidence, and both are likely to lead to harmful adverse effects from downstream invasive work-up of the results and unnecessary surgical procedures.

Most of the screening centres are operated by hospitals, including university hospitals and academic medical centres. The tests are advertised direct to consumers and the hospitals make a profit from direct payment for the test and the costly and usually unnecessary "self referrals" for work-up of the incidental findings. Japanese doctors and medical bodies should withdraw from the unethical business of promoting unproved and potentially harmful screening tests.

Competing interests: None declared.

1 Glasziou P, Moynihan R, Richards T, Godlee F. Too much medicine; too little care. *BMJ* 2013;347:f4247. (2 July.)
2 Japan Brain Dock Society.http://jbds.jp/nintei_list.html.
3 Japan PET Scan Net. http://www.pet-net.jp/pet_html/search.html.

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Editorial

Current Status of Choosing Wisely in Japan

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Editor-in-Chief, General Medicine

In January 2012, I had a chance to meet Dr Mitchell D. Feldman, who is a Professor of Medicine, University of California San Francisco and was a visiting faculty of Kyoto University at that time. At that time I explained some issues regarding Japanese healthcare to him. We had a good discussion about the development of a growing number of programs which provide education and research resources for generalist physicians in Japan. However, I also explained to him the Japanese situations of preventive medicine by unproven screening services for the general public, including human dock, PET-CT cancer dock, and brain dock.

While riding together on a local JR train, Dr Feldman suggested that, although these services are not covered by a national health insurance system but are paid by private payment, Japanese physicians should act against these services as advocates of patients as part of their professional role as physicians. He suggested that Japanese medical professions should follow choosing wisely campaigns that were developing internationally. This campaign was originally initiated by physicians with concerns on professionalism issues in American Board of Internal Medicine.

After I promised to start a campaign for Japanese people, Dr Feldman and I first published the need for such an activity to BMJ.[1] Japanese Consortium of Generalist Teachers kindly agreed to organize the first conference about choosing wisely Japan and we published a book (Choosing Wisely in Japan ～less is more～) describing five recommendations and the background of these recommendations from multiple US academic societies as well as our first five lists for choosing wisely Japan (**Table 1**).[2]

Meanwhile, international roundtables and conferences have been organized by influential societies. Articles and teaching case reports have also been published in major clinical journals such as *teachable moment* series by JAMA Internal Medicine.[3] Concept of High Value Care has been introduced as physicians' professional objective of choosing wisely campaigns.[4] This concept can be expressed as follows:

$$\text{Value} = \text{outcome}/(\text{side effect} \times \text{cost})$$

Table 1. The first five list of recommendations for choosing wisely Japan

1. Don't recommend PET-CT cancer screening for asymptomatic adults.
2. Don't recommend tumor marker screening for asymptomatic adults.
3. Don't recommend MRI brain screening for asymptomatic adults.
4. Don't perform routine abdominal CT for non-specific abdominal pain.
5. Don't place urinary catheters simply for provider convenience.

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Figure 1. Choosing Wisely Conference at Korea University, Seoul, South Korea

Japan is the fastest aging country in the world and thus we need effective healthcare with affordable cost and low risk for side effects. A generalist should play a leading role in aiming for higher value care throughout Japan.

In January 2015, Dr Shunzo Koizumi, Dr Kentaro Matsumoto and I were invited to a Korea-Japan joint conference for choosing wisely campaign, at Korea University, Seoul, South Korea at the kind courtesy of Dr Hyeong Sik Ahn, who is a Professor of Preventive Medicine, Korea University and other influential Korean clinicians, educators and researchers (**Figure 1**). Recently he published his analysis for probable overdiagnosis of thyroid cancer cases in his country.[5] As a recent review indicated good observational study as well as international collaborative study shows scientifically sound evidence for overdiagnosis in cancer screening.[6] Research collaboration between Korea and Japan will enhance public health in both countries. Since our journal would like to publish a good observational study on overdiagnosis, choosing wisely and high value care in Japan, I welcome submissions by generalists on these critical issues.

References

1 Tokuda Y, Feldman MD: Direct to consumer unproved screening tests turn a profit in Japan. BMJ. 2013;347:f4725.

2 Tokuda Y: Choosing Wisely in Japan ～less is more～. Kai Shorin; 2014.

3 Bowman C, Widera E: Feeding tube placement in patients with advanced cancer: a teachable moment. JAMA Intern Med. 2015;175(1):15–16.

4 Dhaliwal G: Bringing high-value care to the inpatient teaching service. JAMA Intern Med. 2014; 174(7):1021–1022.

5 Ahn HS, Kim HJ, Welch HG: Korea's thyroid-cancer "epidemic"—screening and overdiagnosis. N Engl J Med. 2014;371(19):1765–1767.

6 Carter JL, Coletti RJ, Harris RP: Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. BMJ. 2015;350:g7773.

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Original Article

Polypharmacy and Adverse Drug Events Leading to Acute Care Hospitalization in Japanese Elderly

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Background: Elderly patients are considered to be at risk of developing adverse drug events (ADEs) because they tend to receive a greater number of medications. The purpose of our study is to determine the prevalence of ADEs related to polypharmacy and causative admissions of patients in Japanese acute care hospitalization.

Methods: In retrospective cohort study, we analyzed 700 consecutive elderly patients admitted to the department of medicine of a Japanese community hospital in 2011. ADEs were defined by World Health Organization–Uppsala Monitoring Centre criteria. Polypharmacy was defined as five or more medications.

Results: The mean age was 79.5 years (men, 54%). The mean number of medications was 6.36 +/− 4.15 (maximum, 26). Polypharmacy was observed in 63% of cases. ADEs were identified in 4.9% (95% CI, 3.5–6.7%). The mean numbers of medications among patients with ADEs and those without ADEs were 9.3 +/− 3.4 and 6.2 +/− 4.1, respectively. A greater number of medications was significantly associated with ADEs ($p < 0.001$). Polypharmacy was identified in 91% of patients with ADEs, while it was noted in 62% of patients without ADEs ($p = 0.001$). Using logistic regression analysis, polypharmacy was significantly associated with ADEs (Odds ratio 5.89, 95% CI 1.74–19.9). The highest number of ADEs were identified among patients on antiplatelets or anticoagulants ($n = 8$), followed by benzodiazepines and NSAIDs ($n = 4$ for both). The most common ADEs were gastrointestinal bleeding, nausea and congestive heart failure.

Conclusion: ADEs complicated to about 5% of acute care elderly hospitalizations in Japan. Polypharmacy was significantly associated with these ADEs.

Keywords: adverse drug events, elderly, inpatients, polypharmacy

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INTRODUCTION

Adverse drug events (ADEs) are considered to be an important cause of admission to acute care hospitals. Multiple previous studies conducted in western countries during 1990s to 2000s showed ADEs were contributory factors for hospital admissions.[1–4]

ADEs are related to many factors, including polypharmacy. Although there are various definitions for polypharmacy from five or greater number of medications to seven or greater number of them, polypharmacy was identified as prevalent especially among elderly and as significantly associated factor with ADEs leading to emergency department visits or hospital admissions.[3,5–9]

In Japan, a study on ADEs in geriatric inpatients showed that the incidence of ADEs was 9.2% and it was significantly related to the number of drugs.[10] However, this study was conducted on admitted patients during their hospitalizations and the definition of ADEs was based on judgment by attending physicians. The prevalence of polypharmacy and its relations to ADEs have not been investigated for elderly patients who were admitted to hospitals in Japan. These data are likely to be important since Japan has the greatest proportion of elderly nationwide. In addition, detailed evaluation of medications responsible for ADEs is also important for educating Japanese physicians who prescribe these medications. Therefore, our goal was to determine the prevalence of ADEs, its relations to polypharmacy and causative effects of medications for patients admitted to acute care hospital in Japan.

METHODS

Data collection

We collected data retrospectively on 700 admitted patients, 65 years or older to the internal medicine service of a teaching hospital (270 beds) affiliated with University of Tsukuba in 2011. This hospital has department of emergency medicine, providing primary to secondary care for about 270,000 population in Mito city, Ibaraki, Japan. We included patients transferred from surgical service to medical service in our hospital. We recorded data of age, gender, number of medications, weight, serum creatinine concentration, and admission diagnosis. There are no clear definition of polypharmacy. We defined it as taking five or more medications since a number of previous studies have adopted the definition.[11] Two physician-investigators reviewed medical charts of all patients about possibility of ADEs. The primary outcome was occurrence of any ADEs. We used World Health Organization–Uppsala Monitoring Centre criteria[12] to define ADEs as being causal or contributory to hospital admission, consensus agreement of both of the two investigators was required. The secondary outcome was any deaths because of ADEs.

The sample size calculation was based on the results of a previous study by Leendertse et al[3] for estimation proportions of polypharmacy. We estimated the proportions of polypharmacy would be about 30% for control group and 40% for case group and obtained a total of about 700 patients based on a power of 80% and an alpha error of 5%.

Data analysis

Proportions were compared using chi-square test and continuous variables were compared by Student t-test. Multiple logistic regression analysis was used to determine whether ADEs were independently associated with the polypharmacy adjusted for age, gender and serum creatinine. SPSS version 21 (SPSS Inc, Chicago, Illinois) was used to analyze all data. Ethical approval was obtained from the hospital ethics committee.

RESULTS

In our study sample (N = 700), the mean age was 79.5 years and 54.0% (n = 378) were men. The mean number of medications was 6.36 (standard deviation, 4.15). The maximum number of medication was 26 (72 year old man). The frequency distribution of the number of medications is shown in **Figure 1**. Polypharmacy was identified in 443 patients (63%).

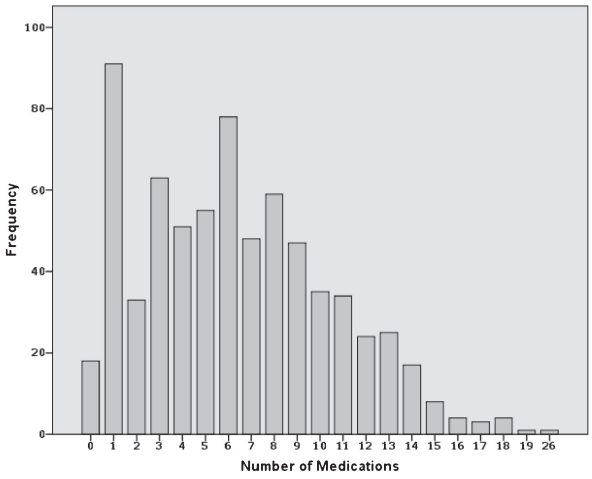
ADEs were identified in 4.9% (95% CI, 3.5–6.7%; n = 34) of this sample. The mean numbers of medications among patients with ADEs and that among patients without ADEs were $9.3 +/- 3.4$ and $6.2 +/- 4.1$, respectively. Bivariate analysis indicated that a greater number of medications was significantly associated

Table 1. Clinical characteristics

Variable	All patiens (N = 700)	Patients with ADE (n = 34)	Patients without ADE (n = 666)	p-value
Age	79.5 +/− 7.9	79.7 +/− 7.0	79.5 +/− 7.9	0.835
Male gender	322 (54.0%)	14 (41.2%)	364 (54.7%)	0.158
Serum creatinine (mg/dL)	1.27 +/− 1.40	1.14 +/− 0.79	1.28 +/− 1.42	0.596
♯ of medications	6.4 +/− 4.2	9.3 +/− 3.4	6.2 +/− 4.1	<0.001

ADE = Adverse Drug Events. Continuous variables: mean +/− standard deviation. Categorical variables: number (%)

Figure 1. The frequency distribution of the number of medications



with ADEs ($p < 0.001$). Polypharmacy was identified in 31 (91%) patients with ADEs, while it was noted in 412 (62%) patients without ADEs ($p = 0.001$). Age, gender and serum creatinine were not significantly associated with ADEs (**Table 1**). The number of medication was not associated with gender ($p = 0.222$) or age ($p = 0.692$), based on the linear regression analysis.

On logistic regression analysis, polypharmacy was significantly associated with ADEs (Odds ratio 5.89, 95% CI 1.74–19.9). Age, gender, and serum creatinine were not significantly associated with ADEs (**Table 2**).

Table 3 shows the list of patients with ADEs, including suspected medications, class of medications and specific events of ADEs. The highest number of ADEs were identified among patients on antiplatelets or anticoagulants (n = 8). The most common suspected medication was warfarin (n = 4). The second highest number of ADEs were seen among those on benzodiazepines (n = 4) and NSAIDs (n = 3). The most common ADEs were GI bleeding (n = 3), nausea (n = 3) and congestive heart failure (n = 3).

Table 2. Logistic regression analysis

Variable	OR	95%CI of OR	p-value
Age	0.97	0.93–1.02	0.278
Female Gender	1.78	0.80–3.98	0.158
Serum creatinine	0.87	0.61–1.24	0.432
Polypharmacy	5.89	1.74–19.90	0.004

OR = Odds ratio. CI = Confidence interval

Two patients among those with ADEs died during hospitalizations. One patient admitted for renal dysfunction from aspirin had died from aspiration pneumonia. The other patient admitted for gastrointestinal bleeding from NSAIDs had died from acute exacerbation of chronic obstructive lung disease. No one had died directly from ADEs.

DISCUSSION

The results of this study revealed that a greater number of medications was significantly associated with ADEs in elderly patients. Furthermore, our results showed that medications frequently involved in ADEs included antiplatelets, anticoagulants, benzodiazepines and NSAIDs. The most frequent ADEs were GI bleeding, nausea and congestive heart failure. This may be the first study which revealed the frequency of ADEs of hospitalized patients in the department of internal medicine, of a teaching hospital in Japan.

ADEs contributed to about 5% of elderly hospitalizations in the department of internal medicine of our hospital. This result confirmed our hypothesis that

Table 3. Details of ADEs

Age & gender	Class	Suspected medication	ADE
80 M	antiplatelet	aspirin	renal dysfunction
78 F	antiplatelet	aspirin	renal dysfunction
69 M	antiplatelet	cilostazol	lower gastrointestinal bleeding
82 M	antiplatelet	sarpogrelate	liver dysfunction
81 M	anticagulant	warfarin	gastric mucosa injury
85 F	anticagulant	warfarin	cerebral bleeding
74 M	antiplatelet, anticoagulant	aspirin, warfarin	gastrointestinal bleeding
75 F	antiplatelet, anticoagulant	ticlopidine, warfarin	gastric ulcer bleeding
85 F	benzodiazepine	brotizolam	weakness
68 F	benzodiazepine	loflazepate, diazepam, flunitrazepam, triazolam	nausea
88 F	benzodiazepine	etizolam	auditory hallucination
75 F	benzodiazepine	brotizolam	altered mental status
79 F	Chinese herbal medicine	Bupleuri radix	interstitial pneumonitis
73 F	Chinese herbal medicine	licorice	hypokalemia
91 F	Chinese herbal medicine	licorice	edema, hypokalemia
79 F	NSAIDs	celecoxib	nephrosis
78 F	NSAIDs	meloxicam	gastrointestinal bleeding
79 M	NSAIDs	loxoprofen	gastric ulcer
91 F	digitalis	digoxin	congestive heart failure
91 F	digitalis	digoxin	congestive heart failure
78 M	opioid analgesic	oxycodone	urinary retention
78 M	opioid analgesic	oxycodone	constipation
74 M	beta-adrenergic receptor blocker	bisoprolol	sick sinus syndrome
75 M	beta-adrenergic receptor blocker, antihypertensive	bisoprolol and/or nifedipine	nausea
90 F	diuretic	furosemide	cerebral infarction
77 M	antihypertensive, diuretic	nifedipine, furosemide	hypotension
74 F	antineoplastic	gemcitabine	nausea
85 F	antineoplastic	tegafur, gimeracil, oteracil	loss of appetite
86 F	antibiotic	azithromycin	liver dysfunction
76 M	anticholinergic	solifenacin	ileus
69 M	antipsychotic	unknown	ileus
86 M	beta-adrenoceptor agonist inhaler	procaterol inhaler	congestive heart failure
70 F	immunosuppressant	tacrolimus	hyperglycemia
69 M	steroid	prednisolone	diabetes

ADEs comprised significant number of admissions among elderly patients, although this number seemed to be lower than those of the previous studies, including 11% of all admissions and 7.9% of gastroenterology inpatients,[1,2] 6% of unplanned admissions[3] and 26% of all admitted elderly patients.[4]

However, the criteria for ADEs and observed populations used by previous studies might be different from that of ours. There was a report indicating a lower proportion of ADEs as a cause of admission. For

example, a Swiss study in 2000 indicated that only 3.3% of all hospitalizations were caused by ADEs.[12] In addition, a study on ED (Emergency Department) visiting elderly patients showed that ADEs accounted for about 11% of all ED visits.[6] Thus, there have been variations used for the criteria for ADEs and study populations, including age and admitting departments.

Our study revealed that polypharmacy was significantly associated with ADEs in older patients. In the aforementioned study, multivariate analysis showed that the likelihood of a serious avoidable ADE increased significantly when PIMs (Potentially Inappropriate Medicines) defined by STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria were more frequently prescribed, but this was not associated with the total number of medications.[4] An Italian study on elderly nursing home residents demonstrated a higher number of PIMs was a risk factor for hospitalization and was positively associated with the total number of drugs prescribed.[13] The study that was cited above also showed that the main determinants of preventable medication-related hospital admissions included impaired cognition, comorbidities, dependent living situation, impaired renal function and nonadherence to medication regimen and polypharmacy.[3] On the other hand, a study showed that polypharmacy was not associated with hospitalization, but that ADEs were associated with longer hospital stays, resulting in a higher mortality risk.[14]

Regarding the prevalence of polypharmacy in another Asian nation, a recent Chinese study in outpatient clinics showed that the average drug number per prescription was about 2.4, and the percentage of polypharmacy (five or more medications) was about 6%.[15] However, this study was conducted on patients with all ages between 1 month and 98 years (mean, 34 years). The prevalence in this study was low because this study included children and young adults, who might receive lower number of medications.

An inpatient study showed that the mean number of prescription drugs was 7.5 +/− 3.8.[9] Our data (with a mean number of medications, 6.4 +/− 4.2) indicated a similar number of medications among inpatients of internal medicine. This suggests that polypharmacy is likely to be prevalent among admitted patients to departments of internal medicine across international settings.

The medications frequently involved with ADEs included antiplatelets, anticoagulants, benzodiazepines and NSAIDs in our study. In a US study, in an elderly nursing facility in 1999, there were about 16% of residents that were hospitalized during 4-year study. The most common events were for nonsteroidal anti-inflammatory drugs (NSAIDs) (n = 30), psychotropic-related falls with a fracture (n = 14), digoxin toxicity (n = 5) and insulin hypoglycemia (n = 4).[17] These results suggest that NSAIDs could be a high risk factor for the elderly.

The most frequent ADEs were GI bleeding, nausea and congestive heart failure. With respect to GI bleeding, they were for antiplatelets, anticoagulants and NSAIDs. Many physicians prescribe these medications to prevent serious illness such as ischemic heart disease and stroke, knowing enough about the risk of GI bleeding. Physicians prescribe medications at the risk of ADEs and it is possible to investigate each prescription is appropriate or not by STOPP criteria[4] which evaluate qualities of prescriptions. However, the criteria does not cover all aspects of prescriptions. We evaluated the relation between the number of medications itself and ADEs in this study.

None of the patients died directly from ADEs in our study, although two patients who had died from aspiration pneumonia and chronic obstructive lung disease acute exacerbation, might have been affected by ADEs. ADEs may have led to admission with increased risk of mortality from complications along with poor functional status. However, our study sample was relatively small, including only 34 patients with ADEs. A study on patient fatalities during hospitalizations showed that about 18% of the deaths were classified as being directly or indirectly associated with one or more drugs.[7] Additional investigations of patient fatalities during hospitalizations, might identify more etiological factors associated with ADEs.

Our study has some limitations. Firstly, our study was conducted in single hospital. We have investigated consecutive sample of patients to minimize the possible sampling bias, however, there could be some confounders such as fragility of patients, underlying

conditions, recent admissions, and so on. We did not analyze them in this study. Therefore, these findings may not be generalizable to other hospitals in Japan. A multicenter study is needed for clarification on this point. Secondly, our study design was based on a retrospective analysis on medical charts. Thus, some patients with ADEs might not have been included into our study. A prospective study is required for more accurate description of ADEs in Japanese hospitals.

In conclusion, we examined the epidemiology of ADEs that contribute to hospitalization among elderly patients in the department of internal medicine of a teaching hospital in Japan. ADEs were associated with a greater number of medications which included GI bleeding, nausea and congestive heart failure. Our data highlight that, in order to prevent ADEs, physicians should exercise particular caution in prescribing antiplatelets, anticoagulants, benzodiazepines and NSAIDs.

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Conflict of Interest

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References

1 Hallas J, Harvald B, Gram LF, et al: Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med. 1990 Aug;228(2):83–90.

2 Hallas J, Jensen KB, Grodum E, Damsbo N, Gram LF: Drug-related admissions to a department of medical gastroenterology. The role of self-medicated and prescribed drugs. Scand J Gastroenterol. 1991 Feb;26(2):174–180.

3 Leendertse AJ, Egberts ACG, Stoker LJ, van den Bemt PMLA: Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008 Sep 22; 168(17):1890–1896.

4 Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D: Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med. 2011 Jun 13;171(11):1013–1019.

5 Linton A, Garber M, Fagan NK, Peterson MR: Examination of multiple medication use among TRICARE beneficiaries aged 65 years and older. J Manag Care Pharm. 2007 Mar;13(2):155–162.

6 Hohl CM, Dankoff J, Colacone A, Afilalo M: Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med. 2001 Dec;38(6):666–671.

7 Ebbesen J, Buajordet I, Erikssen J, et al: Drug-related deaths in a department of internal medicine. Arch Intern Med. 2001 Oct 22;161(19):2317–2323.

8 Buajordet I, Ebbesen J, Erikssen J, Brørs O, Hilberg T: Fatal adverse drug events: the paradox of drug treatment. J Intern Med. 2001 Oct;250(4):327–341.

9 Schuler J, Dückelmann C, Beindl W, Prinz E, Michalski T, Pichler M: Polypharmacy and inappropriate prescribing in elderly internal-medicine patients in Austria. Wien Klin Wochenschr. 2008 Jan;120(23–24):733–741.

10 Arai H, Akishita M, Teramoto S, et al: Incidence of adverse drug reactions in geriatric units of university hospitals. Geriatr Gerontol Int. 2005 Dec;5(4):293–297.

11 Rollason V, Vogt N: Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. Drugs Aging. 2003 Jan;20(11):817–832.

12 Uppsala Monitoring Centre: WHO-UMC system for standardised case causality assessment. [Internet]. [cited 2013 May 28]. Available from: http://www.who-umc.org/Graphics/26649.pdf.

13 Fattinger K, Roos M, Vergères P, et al: Epidemiology of drug exposure and adverse drug reactions in two swiss departments of internal medicine. Br J Clin Pharmacol. 2000 Feb;49(2):158–167.

14 Ruggiero C, Dell'Aquila G, Gasperini B, et al: Potentially inappropriate drug prescriptions and risk of hospitalization among older, Italian, nursing home residents: the ULISSE project. Drugs Aging. 2010 Sep 1;27(9):747–758.

15 Nobili A, Licata G, Salerno F, et al: Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. Eur J Clin Pharmacol. 2011 May; 67(5):507–519.

16 Dong L, Yan H, Wang D: Polypharmacy and its correlates in village health clinics across 10 provinces of Western China. J Epidemiol Community Health. 2010 Jun;64(6):549–553.

17 Cooper JW: Adverse drug reaction-related hospitalizations of nursing facility patients: a 4-year study. South Med J. 1999 May;92(5):485–490.