J Nutr Health Aging. 2019;23(4):381-385

INFLUENCE OF ANTIPSYCHOTICS ON FUNCTIONAL PROGNOSIS AFTER GERIATRIC HIP FRACTURE

M. NAKAMICHI[1], H. WAKABAYASHI[2], S. NISHIOKA[3], R. MOMOSAKI[4]

1. Department of Pharmacy, Haradoi Hospital, Higashi ward, Fukuoka city, Japan; 2. Department of Rehabilitation Medicine, Yokohama City University Medical Center, Minami ward, Yokohama city, Japan; 3. Department of Clinical Nutrition and Food Service, Nagasaki Rehabilitation Hospital, Nagasaki, Japan; 4. Department of Rehabilitation Medicine, Teikyo University School of Medicine University Hospital, Takatsu ward, Kawasaki city, Japan. Corresponding author: Mariko Nakamichi, Department of Pharmacy, Haradoi Hospital 6-40-8 Aoba, Higashi ward, Fukuoka city, Japan, 813-8588 Tel: +81-92-691-3881, Fax: +81-92-691-1059, E-mail: m.nakamichi.09@gmail.com

Abstract: *Objective:* To investigated the effects of antipsychotics on rehabilitation outcomes for geriatric hip fracture inpatients. *Design:* Retrospective cohort study. *Setting:* The registry data from the Japan Rehabilitation Nutrition Database for analysis. *Participants:* Of the 234 patients in the Japan Rehabilitation Nutrition Database admitted between November 2015 and March 2018, 214 met the eligibility criteria. *Measurements:* The antipsychotics were phenothiazine, butyrophenone, benzamide, and atypical antipsychotics. For hip fracture patients, the following information was registered: (a) admission data: age, sex, Charlson Comorbidity Index, Functional Independence Measure (FIM) at admission, medications, height, body weight, and Mini Nutritional Assessment-Short Form score (MNA-SF) and (b) discharge data: discharge destination, FIM at discharge, MNA-SF, and total units of provided rehabilitation therapy (one unit = 20 minutes based on the national healthcare insurance policy). *Results:* Thirteen patients (6.1%) were prescribed antipsychotics. According to the multiple linear regression analysis, antipsychotics negatively affected FIM efficiency (β=-0.190, 95% confidence interval, -0.652 to -0.104, *p*=0.007). Furthermore, on logistic regression analysis, fall during hospitalization was correlated with the use of antipsychotics (odds ratio=4.376, 95% confidence interval: 1.153 to 16.612, *p*=0.030). *Conclusion:* The use of antipsychotics impaired the improvement of the activities of daily living (ADL) and increased the incidence of fall during hospitalization. Reviewing medication therapies at admission may further improve ADL.

Key words: Activities of daily living, antipsychotics, fall, geriatric, hip fracture.

Introduction

Hip fracture is of concern in Japan as it becomes an aging society due to the increased risk of mortality, functional decline, and decreased quality of life (1). The incidence of hip fracture is steadily increasing in Japan (2). The total population of Japan is projected to decrease until 2050, but a substantial increase in the proportion of the population aged 85 years and over is expected. Goals for self-reliance in early activities of daily living (ADL) are desired in order to improve functional dysfunction related to hip fractures.

Pharmacotherapy is also one of the considerations for the aging society (3). Polypharmacy poses a severe problem for many older patients with hip fracture who are frail and at risk for falls (4-5). Polypharmacy refers to taking five or more medications, and potentially inappropriate medications (PIM) may be given to outpatients and inpatients, and at nursing homes and all disease stages. However, 22% of older people with hip fracture were reported to be taking five or more medications, which was related to readmission (6). In addition, older people are characterized by impairment of the regulatory processes that allow functional integration between cells and organs (7). Kojima et al demonstrated that older people become susceptible to adverse effects. They revealed that five or more medications for outpatients, or six or more medications for inpatients increased the adverse effects of pharmacotherapy (8).

Rehabilitation pharmacotherapy is considered for disabled people and frail older people (9-10). Based on the rehabilitation status, disabled people and frail older people take multiple drugs, and PIM are related to the risk of fall, cognitive disability, and functional disability (11). Rehabilitation pharmacotherapy includes approach against iatrogenic sarcopenia (12). In two recent study for hip fracture, the high prevalence of PIM use associate with time to full functional recovery (13) and anticholinergic drug use associate with rehabilitation outcome (14). Of 144 stroke patients with chronic kidney disease in the convalescent rehabilitation ward, 48(33.3%) took six or more drugs and were divided into the polypharmacy group. Improvement in ADL as assessed by the Functional Independence Measure (FIM) in the polypharmacy group was significantly lower than that in the nonpolypharmacy group (15). In particular, an increase in the Anticholinergic Risk Scale score by 2 points was correlated with a 2.86-fold greater risk for hip fracture (16). Increased psychotropic drug use while in the convalescent rehabilitation ward may predict limited improvement of the cognitive ADL in geriatric patients (17). However, the effects of antipsychotics on ADL are unclear.

This study investigated the effects of antipsychotic use on rehabilitation outcomes in geriatric hip fracture inpatients.

Received November 12, 2018
Accepted for publication December 4, 2018

Published online February 19, 2019, http://dx.doi.org/10.1007/s12603-019-1173-2

Methods

Study design and participants

In this retrospective cohort study, we used the registry data from the Japan Rehabilitation Nutrition Database (JRND) (18) for analysis. The JRND was established in March 2016 by the Committee of the JRND as a part of the Japanese Association of Rehabilitation Nutrition. The JRND aims to clarify the relationship between rehabilitation and nutrition, and the effectiveness of rehabilitation nutrition (19). Patients comprise those with stroke or hip fracture aged 20 years or older in convalescent rehabilitation wards, or those with pneumonia aged 40 years or older in an acute care hospital. The JRND was constructed by the Research Electronic Data Capture (REDcap) (20) using free electronic data capture. Participating facilities were recruited from the JARN network, and 11 facilities comprising 234 patients were involved at the end of March 2018. This study included patients with hip fracture aged 65 years or older. Exclusion criteria were patients transferred to acute hospitals (suspected aggravation of clinical condition) or those who had missing data for the FIM score. The ethics committee of the Jikei University School of Medicine approved this study. Receipt number: 27-150(8035).

Main outcome measurement

The primary outcomes were FIM efficiency and the use of antipsychotics. The secondary outcome was the risk of fall during hospitalization. Antipsychotic use was defined as the use of one or more antipsychotics. FIM gain was the difference in the total FIM at the time of discharge from that at the time of admission. FIM efficiency was calculated as FIM gain divided by the length of stay. ADL were evaluated by FIM. FIM is composed of 13 motor domains: eating, grooming, bathing, dressing the upper body, dressing the lower body, going to the toilet, bladder management, bowel management, transfer to bed/ chair/ wheelchair, to toilet, to tub/ shower, locomotion by walking/ wheelchair, on the stairs, and five cognitive domains: comprehension, expression, social interaction, problem solving, and memory. Each item was scored from 1 (total assistance) to 7 (complete independence); therefore, the total FIM score ranged from 18 to 126 (21).

Measurements

The antipsychotics were phenothiazine, butyrophenone, benzamide, and atypical antipsychotics (22). For the hip fracture patients, the following information was registered: (a) admission data: age, sex, Charlson Comorbidity Index (CCI) (23), FIM at admission, medications, height, body weight, and Mini Nutritional Assessment-Short Form (MNA-SF) (24) score; and (b) discharge data: discharge destination, FIM at discharge, MNA-SF, and total units of provided rehabilitation therapy (one unit = 20 minutes based on the national healthcare insurance policy).

Nutritional status was assessed using the MNA-SF. The MNA-SF is composed of 6 questions aimed at addressing a possible decline in food intake, weight loss over the past 3 months, mobility, psychological stress and/or acute disease in the past 3 months, neuropsychological problems, and body mass index (24).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 23 software (IBM Corporation; Armonk, NY, USA). Normally distributed variables were reported as the mean ± standard deviation (SD), and variables with a skewed distribution were reported as the median and interquartile range (IQ). The Chi-square test, t-test, the Mann-Whitney U test, and Fisher's exact test were used, as appropriate, to compare variables between the groups. Spearman's rank correlation was used for univariate analysis. Multiple linear regression analysis was performed for FIM efficiency, and multiple logistic regression analysis was carried out for the incidence of fall during hospitalization. Variables were independently associated with the presence of antipsychotics. As the number of subjects taking antipsychotics was small, the number of variables included in the logistic model had to be reduced. Propensity scores were calculated by logistic regression analysis including age, sex, CCI, rehabilitation unit, and FIM or MNA-SF at admission as explanatory variables. A *P*-value less than 0.05 was considered significant.

Results

Of the 234 patients in the JRND admitted to each facility between November 2015 and March 2018, 214 met the eligibility criteria (mean age: 85.0±7.2 years; Female: 79.9%). Table 1 shows the clinical and demographic data for the patients. Thirteen patients (6.1%) were prescribed antipsychotics. Patients on antipsychotics comprised a smaller proportion of those discharged home (p=0.009), and had lower FIM scores at admission and discharge (p=0.005, p=0.002), a lower FIM efficiency (p=0.010), and a higher fall rate during hospitalization (p=0.002) than those not using antipsychotics. The Spearman's rank correlation results are shown in Table 2. Antipsychotics were correlated with FIM at admission and discharge, FIM efficiency, and fall during hospitalization. FIM efficiency was correlated with the use of antipsychotics and total rehabilitation units, but not with age, CCI, or MNA-SF.

The results of the multiple linear regression analysis for FIM efficiency after propensity score matching for antipsychotic use or non-use are shown in Table 3. Propensity scores were calculated by logistic regression analysis including age, sex, CCI, rehabilitation units, and FIM or MNA-SF at admission as explanatory variables. Antipsychotics negatively affected the FIM efficiency (β=-0.190, 95% confidence interval, -0.652 to -0.104, p=0.007).

The results of the logistic regression analysis are shown in Table 4. The incidence of fall during hospitalization was

Table 1
Clinical characteristics of the study groups at baseline

	Overall	Antipsychotic non-use	Antipsychotic use	*p*-value
Number of participants, N (%)	214 (100)	201 (93.9)	13 (6.1)	
Age, mean ± SD	85.0 ± 7.2	84.9 ± 7.1	86.3 ± 8.7	0.485[d]
Female, N (%)	171 (79.9)	162 (80.6)	9 (69.2)	0.300[g]
Fracture type, N (%)				
Femoral neck fracture	111 (51.9)	105 (52.2)	6 (46.2)	
Trochanteric fracture	103 (48.1)	96 (47.8)	7 (53.8)	
Surgical procedure, N (%)				
Non-surgical treatment	12 (5.6)	12 (6.0)	0	
Femoral head replacement	74 (34.6)	69 (34.3)	5 (38.5)	
Osteosynthesis	121 (56.5)	114 (56.7)	7 (53.8)	
Others	7 (3.3)	6 (3.0)	1 (7.7)	
Onset-admission duration, days, median (IQR)	67.5 (49.0-85.0)	66.0 (49.0-85.0)	76.0 (54.5-88.0)	0.308[f]
CCI, median (IQR)	1 (0-2.0)	1 (0-2.0)	2 (0-2.5)	0.248[f]
Discharge destination, N (%)[a]				
Home	153 (71.5)	148 (73.6)	5 (38.5)	0.009[e]
Care facilities	51 (23.8)	45 (22.4)	6 (46.2)	
General wards	6 (2.8)	5 (2.5)	1 (7.7)	
Convalescent wards	2 (0.9)	1 (0.5)	1 (7.7)	
Others	1 (0.5)	1 (0.5)	0	
Admission FIM, median (IQR)	71 (50.8-89.0)	73 (54.0-89.5)	45 (27.5-65.0)	0.005[f]
Discharge FIM, median (IQR)	102 (75.8-116.0)	103 (77.0-116.0)	65 (35.5-90.0)	0.002[f]
FIM gain, median (IQR)	23 (12.0-33.0)	23 (12.0-33.0)	13 (1.5-33)	0.111[f]
FIM efficiency, (IQR)	0.37 (0.20-0.55)	0.39 (0.20-0.55)	0.20 (0.02-0.41)	0.010[f]
Total units of rehabilitation, median (IQR)	354 (230.8-457.0)	350 (230-461)	388 (224.0-449.0)	0.959[f]
BMI, kg/m^2, mean ± SD[b]	20.1 ± 3.2	20.1 ± 3.2	21.4 ± 3.4	0.136[d]
Admission MNA-SF, median (IQR)	6 (4.0-8.0)	6 (4.0-8.0)	4 (3.5-8.5)	0.550[f]
Normal nutritional status, N (%)	0	0	0	
At risk of malnutrition, N (%)	63 (29.4)	59 (29.4)	4 (30.8)	
Malnourished, N (%)	151 (70.6)	142 (70.6)	9 (69.2)	
Oral intake (route of nutrition), N (%)	201 (93.9)	189 (94.0)	12 (92.3)	0.540[g]
Energy intake, median (IQR)	1400.0 (1200.0-1472.0)	1400.0 (1200.0-1475.0)	1379.0 (1165.5-1475.0)	0.993[f]
Fall during hospitalization, N (%)[c]	28 (13.1)	22 (10.9)	6 (46.2)	0.002[g]

Abbreviation: SD, standard deviation; IQR, interquartile range; CCI, Charlson comorbidity index; FIM, Functional Independence Measure; BMI, body mass index; MNA-SF, Mini Nutritional Assessment Short-Form; a. Data analyzed from 213 participants (one had missing data); b. 212 participants (Two missing data); c. 208 participants (six had missing data); d. unpaired t-test, e. Chi-squared test, f. Mann-Whitney U test, g. Fisher's exact test.

correlated with the use of antipsychotics (odds ratio=4.376, 95% confidence interval: 1.153 to 16.612, p=0.030). Propensity scores were calculated by logistic regression analysis including age, sex, CCI, rehabilitation units, and FIM or MNA-SF at admission as explanatory variables.

Discussion

The findings of this retrospective observational cohort study regarding antipsychotic use, and improvement of ADL and risk after hip fracture were two-fold. First, this study suggested antipsychotics as a possible factor for the reduced ADL of older patients after hip fracture. Second, antipsychotics may increase the risk of fall after hip fracture for inpatients. This study supports the hypothesis that antipsychotics reduce the ADL

Table 2
Spearman's rank coefficients among the different factors

	Antipsychotics	FIM at admission	FIM at discharge	FIM efficiency	Fall during hospitalization	Total rehabilitation units	Age	CCI	MNA-SF at admission
MNA-SF at admission	-0.041	0.489*	0.344*	0.013	-0.052	-0.237*	-0.165	-0.231*	1
CCI	0.079	-0.258*	-0.275*	-0.102	0.110	0.101	0.053	1	-0.231*
Age	0.093	-0.321*	-0.310*	-0.080	0.160	0.128	1	0.053	-0.165*
Total rehabilitation units	0.003	-0.269*	-0.210*	-0.292*	-0.007	1	0.128	0.101	-0.237*
Fall during hospitalization	0.265*	-0.324*	-0.399*	-0.248*	1	-0.007	0.160*	0.110	-0.052
FIM efficiency	-0.177*	0.080	0.453*	1	-0.248*	-0.292*	-0.080	-0.102	0.013
FIM at discharge	-0.212*	0.842	1	0.453*	-0.399*	-0.210*	-0.310*	-0.275*	0.344*
FIM at admission	-0.194*	1	0.842	0.080	-0.324*	-0.269*	-0.321*	-0.258*	0.489*
Antipsychotics	1	-0.194*	-0.212*	-0.177*	0.265*	0.003	0.093	0.079	-0.041

*p-value <0.05; Abbreviation: FIM, Functional Independence Measure; CCI, Charlson comorbidity index; MNA-SF, Mini Nutritional Assessment Short-Form.

Table 3
Linear regression analysis for FIM efficiency

Variables	β	95% confidence interval		*P*-value
		Lower	Upper	
PS	-0.008	-1.224	1.093	0.911
Antipsychotics	-0.190	-0.652	-0.104	0.007

PS (log-transformed propensity score) was calculated from log transformation of the propensity score for age, sex, Charlson comorbidity index, rehabilitation units, and Functional Independence Measure or Mini Nutritional Assessment Short-Form at admission for antipsychotics

Table 4
Logistic regression analysis for fall during hospitalization

Variables	Odds ratio	95% confidence interval		*P*-value
		Lower	Upper	
PS	110374.514	183.285	66467622.730	<0.001
Antipsychotics	4.376	1.153	16.612	0.030

PS (log-transformed propensity score) was calculated from log transformation of the propensity score for age, sex, Charlson comorbidity index, rehabilitation units, and Functional Independence Measure or Mini Nutritional Assessment Short-Form at admission for antipsychotics

for older patients after hip fracture during the rehabilitation phase. To the best of our knowledge, this is the first study to demonstrate a negative relationship between antipsychotics, and FIM efficiency and discharge to home.

First, we found that antipsychotics may lower the ADL of older patients after hip fracture. Antipsychotics were recommended as a medication to be stopped by STOPP-J in older patients (25). Antipsychotic use by younger patients requires chronic therapy. Currently, antipsychotics are commonly used off-label as therapy not just for schizophrenia, but also for behavioral and psychological symptoms of dementia (BPSD) such as fantasies, delusions, loitering, behavior disorder, delirium, fretting, and depression (22). Antipsychotics cause drug-induced parkinsonism, anticholinergic effects, and cardiovascular compromise, which increase the mortality risk (26, 27). The reason for side effects is that as many antipsychotics are soluble in oil, they accumulate substantially more in older patients, and the drug half-life and duration of effectiveness become prolonged (7). In a previous study, the concentrations of an antipsychotic drug were found to increase via drug-drug interactions involving CYP3A4 and CYP2D6 metabolism (28). Antipsychotic treatment for the elderly with cognitive impairment is associated with ADL, which is important for the quality of life (QOL) (29).

Second, antipsychotics may increase the risk of fall after hip fracture for inpatients. According to the previous meta-analysis, patients taking more than one psychotropic drug, including neuroleptics, sedatives/hypnotics and antidepressants, fell more often (30, 31). In a study of patients over 65, receiving a new prescription of an atypical antipsychotic was associated with a 52% increase in the risk of serious fall and a 50% increase in the risk of nonvertebral osteoporotic fracture (31). This study revealed that atypical and typical antipsychotics increased the risk of fall. Geriatric syndrome, such as falls and wobbling, is one of the drug-induced characteristics of the elderly. Atypical antipsychotics were reported to be associated with hypotension, sedation, and gait disorder, which increase clinic visits and subsequent prescriptions (31). Multiple drugs increase the adverse effect risk, and five or more prescriptions require considerable attention (32). Polypharmacy also increases the risk of fall (28).

Rehabilitation pharmacotherapy is defined as helping patients with disabilities and frail older people achieve the highest possible body function, activity, participation, and QOL using holistic evaluation by the International Classification of Functioning, Disability, and Health, "pharmacotherapy in consideration of rehabilitation", and "rehabilitation in consideration of pharmacotherapy" (9). "Pharmacotherapy in consideration of rehabilitation" includes medications to treat

impairments, activity limitations, and participation restriction, as well as medication adjustment to reduce adverse drug events. Consideration should also be given to therapy because antipsychotics may increase the risk of adverse drug events in elderly patients who require rehabilitation (33).

This study has some limitations. First, the type and amount of prescriptions of each antipsychotic were not clarified. However, there was no difference between typical and atypical antipsychotics as both affected rehabilitation pharmacotherapy. Second, information regarding polypharmacy was missing.

Conclusion

The use of antipsychotics impairs ADL improvement and increases the incidence of fall during hospitalization in geriatric hip fracture inpatients. Reviewing medication therapies at admission may further improve ADL. The potential of medications to cause disabilities in frail older people must be considered.

Acknowledgments: The authors thank the staff of Atagawa Hospital, Nagasaki Rehabilitation Hospital, Miharu Hospital, Tsurumaki Onsen Hospital, Haradoi Hospital, Nanko Hospital, Nishi Hiroshima Rehabilitation Hospital, Yasuoka Hospital, Kanazawa Nishi Hospital, Sakurakai Medical Corporation Sakurakai Hospital, Sapporo Nishi-Maruyama Hospital, Mihono Hospital, Tamana Regional Health Medical Center, Jikei University Daisan Hospital, Nakanoshima Iwaki Hospital, Nishinomiya Kyoritsu Neurosurgical Hospital, and Minamisoma Municipal General Hospital for providing patient data to the JRND.

Disclosure statement: Ryo Momosaki was funded by a grant from the Japan Society for the Promotion of Science (grant number: 15K01395). Hidetaka Wakabayashi reports grants from The Ministry of Education, Science, Culture, Sports, Science, and Technology of Japan, outside the submitted work. Mariko Nakamichi and Shinta Nishioka have no conflicts of interest.

Ethical standards: This study has been performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and amendments. The ethics committee of the Jikei University School of Medicine approved this study. Receipt number: 27-150(8035).

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