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Original Article

Relationship between cognitive function affecting motor Functional Independence Measure and hypnotics

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ABSTRACT

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Purpose: The purpose of this study was to examine the relationship between cognitive dysfunction affecting motor Functional Independence Measure (FIM) and hypnotics.

Methods: This was a retrospective study involving 509 patients aged ≥ 65 years who were discharged from a convalescent rehabilitation ward.

Results: Multiple regression analysis was performed with motor FIM efficiency and motor FIM effectiveness (motor FIM-e) as independent variables and the presence or absence of cognitive dysfunction as the dependent variable. The use of hypnotics in patients with cognitive dysfunction showed a positive relationship with motor FIM efficiency (β = 0.147, P = 0.019) and motor FIM-e (β = 0.141, P = 0.026). Multiple regression analyses were performed after further classifying hypnotics by therapeutic class into hypnotics with new mechanisms, non-benzodiazepine (BZ) hypnotics, and BZ hypnotics. Non-BZ hypnotics (β = 0.141, P = 0.021) showed a positive relationship with motor FIM efficiency. Non-BZ hypnotics (β = 0.158, P = 0.009) and BZ hypnotics (β = 0.178, P = 0.003) showed a positive relationship with motor FIM-e, whereas hypnotics with new mechanisms of action did not. In contrast, none of the three combinations of hypnotics showed any significant relationship with either motor FIM efficiency or motor FIM-e in patients without cognitive dysfunction.

Conclusion: The results suggested that the use of hypnotics in patients with cognitive dysfunction increases motor FIM efficiency and motor FIM-e.

Key words: convalescent rehabilitation ward, motor FIM, cognitive function, hypnotics

Introduction

Convalescent rehabilitation wards play an important role in the transition from acute stage treatment to home care. About 85% of inpatients are elderly, aged ≥ 65 years [1], most of whom have underlying diseases such as hypertension and diabetes mellitus. Furthermore, they are at higher risk of polypharmacy (the number of drugs used exceeds 5 to 6) because of the use of anticoagulants, analgesics, and anti-ulcer drugs in the acute stage ward, and sleep disorders during hospitalization [2, 3]. Convalescent rehabilitation wards are more appropriate than acute stage wards for pharmacists to examine the types, use, and dosage of medical drugs for patients with long-term hospitalization. However, our previous survey of the activities of pharmacists in Japanese hospitals revealed fewer cases of individual active treatment in convalescent rehabilitation wards than in general wards [4].

Some studies have examined the relationship between functional independence measure (FIM) and the number of drugs, anticholinergic agents, or potentially inappropriate medications (PIMs) [3, 5–7]. However, none of the patients in the convalescent rehabilitation wards were analyzed in these studies; instead, patients were analyzed by disease such as fracture and stroke.

Our previous exploratory study on factors affecting motor FIM in 294 adult patients aged ≥ 20 years in the

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convalescent rehabilitation ward [8] suggested that hypnotics increase motor FIM efficiency in patients with cognitive dysfunction. However, the findings were not consistent with those of previous studies [6, 7] and the Japan Geriatrics Society's Guidelines for Medical Treatment and its Safety in the Elderly 2015 [9]. Therefore, the purpose of the present study was to examine the relationship between cognitive dysfunction that affects motor FIM and drugs (mainly hypnotics) using a large sample size (509 elderly patients aged ≥ 65 years in our convalescent rehabilitation ward).

Methods

1. Subjects

Patients aged ≥ 65 years who were discharged from our convalescent rehabilitation ward between April 2018 and March 2021 were included in this retrospective study. Patients who were transferred, died, or hospitalized within 7 days were excluded.

This study was conducted with the approval of the ethics committee of Ichigao Hospital (approval number: 1) and that of the School of Pharmacy and Graduate School of Pharmaceutical Sciences, Showa University (approval number: 369) and was in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects (2014).

2. Study items

Complications, anticholinergic agents, and body mass index (BMI), which showed less significant relationships with motor FIM in our previous study [8], were excluded from this study. The study items were as follows: period of hospitalization, gender, age, diseases requiring hospitalization, presence or absence and severity of cognitive dysfunction, normal estimated glomerular filtration rate (eGFR), number of drugs at admission and discharge, and usage of frequently used hypnotics and sedatives among PIMs.

Hypnotics, which were continued for more than two-thirds of the total hospitalization period, were classified by therapeutic class into three types: hypnotics with new mechanisms (suvorexant, lemborexant, and ramelteon), non-benzodiazepine [BZ] hypnotics (zolpidem, eszopiclone, zopiclone), and BZ hypnotics (brotizolam, etc.). Similar to hypnotics, sedatives, which were continued for more than two-thirds of the total hospitalization period as sleeping aids, were trazodone, risperidone, mirtazapine, and yokukansan [10].

eGFR was calculated by the standardized eGFR (mL/min/1.73) formula, and if the serum creatinine (Cr) level was less than 0.6 mg/dL and the patient was judged to be in a sarcopenic state with decreased muscle mass and strength, the serum recalculated eGFR was calculated by the rounding-up method of substituting 0.6 for the Cr value [11]. Patients were considered to have cognitive dysfunction if they met the following criteria: Mini Mental State Examination (MMSE) score at admission of 23 points or less (severity 1: 20−23, 2: 11−19, 3: 10 or less), Hasegawa Dementia Scale (HDS-R) score at admission of 20 points or less (severity 1: 16−20, 2: 5−15, 3: 4 or less), or cognitive FIM at admission of 24 points or less (severity 1: 20−24, 2: 10−19, 3: 9 or less). In case of patients who underwent all tests, cognitive function was evaluated using the MMSE score. When only HDS-R and cognitive FIM scores were determined, cognitive function was evaluated using the HDS-R score. The outcomes used in this study were motor FIM efficiency and motor FIM effectiveness (motor FIM-e) [= motor FIM gain/(91 − motor FIM at admission)] [12].

3. Statistical analysis

The numerical data were presented as median [quartile 1, quartile 3]. Univariate analysis was performed with diseases requiring hospitalization, age, gender, period of hospitalization, cognitive dysfunction (presence or absence), renal function, number of drugs at admission and discharge, presence or absence of hypnotics, and presence or absence of sedatives as independent variables, and motor FIM efficiency and motor FIM-e as the dependent variables. Continuous data without normality were analyzed using Spearman's rank correlation coefficient. Comparisons between the two groups were performed using the Wilcoxon signed rank test. Multiple comparison was performed using Dunn's method for joint ranking. Factors affecting motor FIM efficiency and motor FIM-e were identified based on the results of univariate analysis ($P < 0.10$ for either criterion) as well as the effect size (r). Our previous study identified cognitive function as the most significant factor that affects motor FIM [8]. Therefore, after dividing the patients into groups based on the presence or absence of cognitive dysfunction, multiple regression analysis was performed with diseases requiring hospitalization, age, renal function, number of drugs at discharge, presence or absence of hypnotics, and presence or absence of sedatives as independent variables. Furthermore, an additional multiple regression analysis was performed with additional independent variables (use or no use of different therapeutic classes of hypnotics).

Multicollinearity was evaluated using variance inflation factors (VIFs). The reliability of the multiple regression analysis was evaluated using P values from the analysis of variance. All statistical analyses were performed using JMP® Pro version 14 (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant.

4. Cognitive dysfunction and hypnotics

The effect of the presence or absence of cognitive dysfunction on the use of different therapeutic classes of hypnotics (new mechanism, non-BZ, BZ) was examined. In terms of side effects, patients using a combination of a BZ hypnotic and a non-BZ hypnotic were classified as the BZ hypnotic group, whereas

patients using a combination of a non-BZ hypnotic and a hypnotic with a new mechanism were classified as the non-BZ hypnotic group. Subsequently, the chi-squared test and residual analysis were performed.

In addition, patients with cognitive dysfunction were divided into two groups based on the severity of cognitive dysfunction (severity 1, and 2 or above) to analyze the use of hypnotics by therapeutic class. Patients using a combination of hypnotics of different therapeutic classes were also included in the analysis.

Results

1. Patient characteristics

The patient characteristics are shown in Table 1. The number of target patients was 509, and the causative diseases of admission to the rehabilitation ward were "cerebrovascular" group (n = 226, 44.4%), "orthopedic surgery" group (n = 254, 49.8%), and "other" (postoperative disuse syndrome, etc.) group (n = 29, 5.7%). The median age (quartile 1, quartile 3) was 82 years (range, 77−86 years). Among the inpatients, 325 (63.8%) were female. The median standardized eGFR was 67.1 (range, 53.9−81.8).

The median number of drugs at discharge was 7 (range, 5−9). The use of hypnotics at discharge was 33.6% (171/509). The use of sedatives at discharge was 14.5% (74/509).

The median values of motor FIM, motor FIM gain, motor FIM efficiency, and motor FIM-e at admission were 41 (range, 25−53), 29 (range, 20−39), 0.41 (range, 0.24−0.56), and 0.69 (range, 0.46−0.85), respectively. The mean values for all these variables varied depending on the presence or absence of cognitive dysfunction.

2. Factors affecting motor FIM

The following factors were selected as factor candidates based on the results of the univariate analysis (Table 1): diseases requiring hospitalization, age, cognitive function, renal function, number of drugs at discharge, and presence or absence of sedatives and hypnotics. Length of hospital stay was excluded from the analysis, as it was included as a variable in the motor FIM efficiency calculation and was strongly related to diseases requiring hospitalization.

Analysis of the severity of dementia and motor FIM in patients with cognitive dysfunction (Figure 1) showed that patients with severity level 1 accounted for 37.6% (95/253), while those with severity level 2 accounted for 56.1% (142/253) of the patients. The results showed a significant negative relationship between the severity of cognitive dementia and motor FIM efficiency and motor FIM-e in all groups.

Multiple regression analysis of motor FIM according to the presence or absence of cognitive dysfunction (Table 2) did not show multicollinearity for any of the variables (VIF < 1.3). In patients with cognitive dysfunction, the number of drugs showed a negative relationship with motor FIM efficiency ($\beta = -0.152$, $P = 0.018$) and motor FIM-e ($\beta = -0.127$, $P = 0.049$). In patients without cognitive dysfunction, the number of drugs showed a negative relationship with motor FIM efficiency ($\beta = -0.150$, $P = 0.022$). In patients with cognitive dysfunction, the use of hypnotics showed a positive relationship with motor FIM efficiency ($\beta = 0.147$, $P = 0.019$) and motor FIM-e ($\beta = 0.141$, $P = 0.026$). Renal function by standardized eGFR showed a negative relationship with motor FIM efficiency (with dementia, $\beta = -0.116$, $P = 0.06$; without dementia, $\beta = -0.255$, $P < 0.001$), motor FIM-e (with dementia, $\beta = -0.172$, $P = 0.006$; without dementia, $\beta = -0.296$, $P < 0.001$) irrespective of the presence or absence of cognitive dysfunction. Diseases requiring hospitalization showed a positive relationship with motor FIM efficiency ($\beta = 0.375$, $P = 0.001$) and motor FIM-e ($\beta = 0.307$, $P = 0.001$) only in the cognitive dysfunction group.

The results of multiple regression analysis with additional independent variables (i.e., hypnotics of different classes) are shown in Table 3. Out of 87 patients with cognitive dysfunction using hypnotics, 7 were using a combination of hypnotics of different therapeutic classes. Two patients were using a combination of a BZ hypnotic and a non-BZ hypnotic. Two patients were using a combination of a BZ hypnotic and a hypnotic with new mechanism of action. Three patients were using a combination of a non-BZ hypnotic and a hypnotic with new mechanism of action. Motor FIM efficiency showed a positive relationship with non-BZ hypnotics ($\beta = 0.141$, $P = 0.021$). Motor FIM-e showed a positive relationship with non-BZ hypnotics ($\beta = 0.158$, $P = 0.009$) and BZ hypnotics ($\beta = 0.178$, $P = 0.003$). Motor FIM efficiency and motor FIM-e did not show any significant relationship with hypnotics with new mechanisms of action. In contrast, among patients without cognitive dysfunction, 84 were using hypnotics, out of whom 8 were using a combination of hypnotics of different therapeutic classes. One patient was using a combination of a BZ hypnotic and a non-BZ hypnotic. Three patients were using a combination of a BZ hypnotic and a hypnotic with new mechanism of action. Three patients were using a combination of a non-BZ hypnotic and a hypnotic with new mechanism of action. One patient was using a combination of all three hypnotics. Motor FIM efficiency and motor FIM-e did not show any significant relationship with hypnotics of different classes without cognitive dysfunction.

The relationship between the presence or absence of cognitive dysfunction and types of hypnotics are shown in Table 4. The presence or absence of cognitive dysfunction did not affect the presence or absence of the use of hypnotics [with dementia: 34.4% (87/253), without dementia: 32.8% (84/256)]. However, the presence or absence of cognitive dysfunction significantly affected the types of hypnotics the patients were using (chi-squared and Fisher's exact tests: $P = 0.005$). Residual analysis showed that patients with cognitive dysfunction

Table 1. Patient characteristics (2018.4–2021.3).

Item	All patients (n = 509)	Motor FIM efficiency (P value)	Motor FIM effectiveness (P value)
Diseases requiring hospitalization: persons (%)		<0.001**[d] (r = 0.35)	<0.001**[d] (r = 0.20)
Cerebrovascular group	226 (44.4)		
Orthopedic surgery group	254 (49.8)		
Others	29 (5.7)		
Age (years)	82 [77, 86]	0.596[c]	<0.001**[c]
Cerebrovascular group	81 [75, 86]	P = 0.001**[b]	
Orthopedic surgery group	84 [77, 87]		
Woman: persons (%)	325 (63.8)	0.407[b]	0.662[b]
Cerebrovascular group /226	118 (52.0)	P < 0.001**[a]	
Orthopedic surgery group /254	192 (75.9)		
Length of stay (days)	80 [54, 105]	<0.001**[c]	<0.001**[c]
Cerebrovascular group	106 [63, 146]	P < 0.001**[b]	
Orthopedic surgery group	70 [50, 86]		
Cognitive impairment: persons (%)	yes: 253 (49.7)	<0.001**[b] (r = 0.32)	<0.001**[b] (r = 0.47)
Cerebrovascular group /226	yes: 130 (57.5)	P < 0.001**[a]	
Orthopedic surgery group /254	yes: 107 (42.1)		
Renal function: eGFR	67.1 [53.9, 81.8]	<0.001**[c]	<0.001**[c]
Cerebrovascular group	69.8 [55.6, 84.3]	P = 0.027*[b]	
Orthopedic surgery group	64.4 [52.6, 79.3]		
Number of drugs at admission	7 [5, 9]	0.446[c]	0.899[c]
Cerebrovascular group	6 [4, 8]	P < 0.001**[b]	
Orthopedic surgery group	7 [5, 10]		
Number of drugs at discharge	7 [5, 9]	0.094[c]	0.404[c]
Cerebrovascular group	6 [5, 8]	P < 0.001**[b]	
Orthopedic surgery group	7 [5, 10]		
Use of hypnotics: persons (%)			
At admission	yes: 157 (30.8)		
At discharge	yes: 171 (33.6)	0.040*[b]	0.250[b]
Cerebrovascular group /226	yes: 63 (27.9)	P = 0.020*[a]	
Orthopedic surgery group /254	yes: 96 (37.8)		
Use of sedatives: persons (%)			
At discharge	yes: 74 (14.5)	0.006**[b]	<0.001**[b] (r = 0.18)
Cerebrovascular group /226	yes: 33 (14.5)	P = 0.792[a]	
Orthopedic surgery group /254	yes: 34 (13.4)		
Motor FIM at admission	41 [25, 53]		
Without cognitive dysfunction	48 [36, 60]	P < 0.001**[b]	
With cognitive dysfunction	32 [19, 46]		
Motor FIM gain	29 [20, 39]		
Without cognitive dysfunction	33 [25, 40]	P < 0.001**[b]	
With cognitive dysfunction	26 [17, 37]		
Motor FIM efficiency	0.41 [0.24, 0.56]		
Without cognitive dysfunction	0.45 [0.33, 0.68]	P < 0.001**[b]	
With cognitive dysfunction	0.32 [0.18, 0.48]		
Motor FIM effectiveness	0.69 [0.46, 0.85]		
Without cognitive dysfunction	0.81 [0.07, 0.90]	P < 0.001**[b]	
With cognitive dysfunction	0.54 [0.29, 0.73]		

1) Numbers in median [1st quartile, 3rd quartile], number of people (%).
2) Statistical analysis a, Fisher's exact test; b, Wilcoxon rank sum test; c, Spearman's rank correlation coefficient test; d, Dunn's test; based on merge order; *, $P < 0.05$; **, $P < 0.01$; r, Effect size.
3) Standardized eGFR: Male = 194 × Serum creatinine [mg/dL]$^{-1.094}$ × Age$^{-0.287}$, Female = Male eGFR × 0.739.
4) Motor FIM gain = motor FIM score at discharge − motor FIM score at admission, Motor FIM efficiency = motor FIM gain / length of stay.
Motor FIM effectiveness: motor FIM gain / (91 − motor FIM at admission)

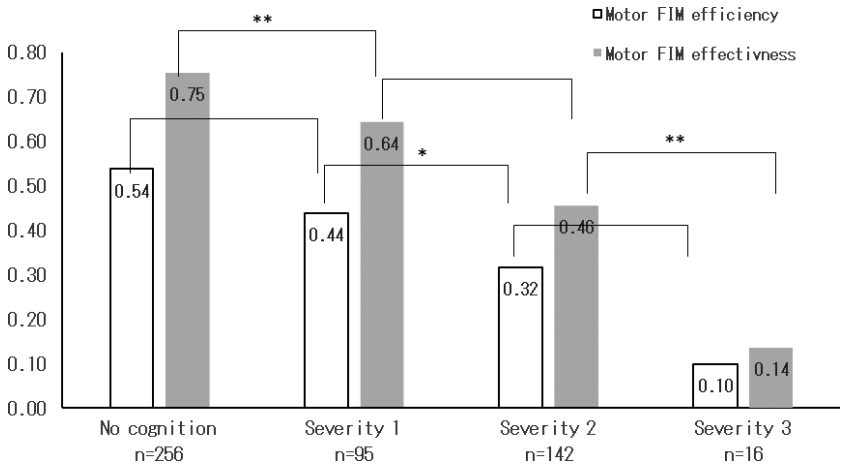

Figure 1. Relationship between dementia severity and motor FIM (n = 509).
Vertical axis: motor FIM efficiency and motor FIM-e value.
Horizontal axis: Number of applicable patients in each group (No cognition, severity 1, severity 2, severity 3).
Analysis: Dunn's test by merge order; $^{*}P < 0.05$, $^{**}P < 0.01$.

Table 2. Multiple regression analysis for Motor FIM efficiency and Motor FIM effectiveness.

A With cognitive dysfunction n = 253	Motor FIM efficiency				Motor FIM effectiveness			
	Partial regression coefficient	Standard error	Standard regression coefficient	P value	Partial regression coefficient	Standard error	Standard regression coefficient	P value
Diagnosis	0.188	0.032	0.375	0.001**	0.168	0.036	0.307	0.001**
Age	−0.003	0.003	−0.079	0.205	−0.006	0.003	−0.126	0.048*
Renal function (eGFR)	−0.001	0.001	−0.116	0.060	−0.002	0.001	−0.172	0.006**
Number of drugs	−0.012	0.005	−0.152	0.018*	−0.011	0.006	−0.127	0.049*
Hypnotics (No 0, Yes 1)	0.039	0.016	0.147	0.019*	0.041	0.018	0.141	0.026**
Sedatives (No 0, Yes 1)	−0.011	0.019	−0.034	0.570	−0.028	0.021	−0.083	0.173

1) Analytical evaluation: Motor FIM efficiency (R^2 = 0.17, Analysis of variance $P < 0.001$)
Motor FIM effectiveness (R^2 = 0.15, Analysis of variance $P < 0.001$)
2) $^{*}P < 0.05$, $^{**}P < 0.01$.

B Without cognitive dysfunction n = 256	Motor FIM efficiency				Motor FIM effectiveness			
	Partial regression coefficient	Standard error	Standard regression coefficient	P value	Partial regression coefficient	Standard error	Standard regression coefficient	P value
Diagnosis	0.051	0.043	0.075	0.238	0.052	0.027	0.118	0.057
Age	−0.001	0.003	−0.013	0.845	−0.007	0.002	−0.225	<0.001**
Renal function (eGFR)	−0.004	0.001	−0.255	<0.001**	−0.003	0.001	−0.296	<0.001**
Number of drugs	−0.015	0.006	−0.150	0.022*	−0.007	0.004	−0.113	0.074
Hypnotics (No 0, Yes 1)	0.005	0.022	0.014	0.826	0.012	0.014	0.052	0.400
Sedatives (No 0, Yes 1)	−0.063	0.035	−0.112	0.073	−0.043	0.022	−0.118	0.051

1) Analytical evaluation: Motor FIM efficiency (R^2 = 0.10, Analysis of variance $P < 0.001$)
Motor FIM effectiveness (R^2 = 0.15, Analysis of variance $P < 0.0001$)
2) $^{*}P < 0.05$, $^{**}P < 0.01$.

Table 3. Multiple regression analysis of motor FIM with additional hypnotics of different classes.

A With cognitive dysfunction $n = 253$	Motor FIM efficiency				Motor FIM effectiveness			
	Partial regression coefficient	Standard error	Standard regression coefficient (β)	*P* value	Partial regression coefficient	Standard error	Standard regression coefficient (β)	*P* value
Diagnosis	0.083	0.027	0.197	0.002**	0.083	0.029	0.182	0.004**
Age	−0.003	0.003	−0.075	0.232	−0.005	0.003	−0.122	0.051
Renal function (eGFR)	−0.001	0.001	−0.129	0.036*	−0.002	0.001	−0.182	0.003**
Number of drugs	−0.012	0.005	−0.154	0.017*	−0.013	0.006	−0.145	0.024*
New mechanism (No 0, Yes 1)	0.005	0.019	0.016	0.792	0.002	0.020	0.007	0.907
Non-benzo (No 0, Yes 1)	0.060	0.026	0.141	0.021*	0.074	0.028	0.158	0.009**
Benzo (No 0, Yes 1)	0.041	0.031	0.080	0.181	0.100	0.033	0.178	0.003**
Sedatives (No 0, Yes 1)	−0.089	0.019	−0.028	0.640	−0.027	0.020	−0.077	0.197

1) Analytical evaluation: Motor FIM efficiency ($R^2 = 0.17$, Analysis of variance $P < 0.001$)
Motor FIM effectiveness ($R^2 = 0.18$, Analysis of variance $P < 0.001$)
2) $^{*}P < 0.05$, $^{**}P < 0.01$.
3) New mechanism hypnotics: Ramelteon, Suvorexant, Lembolexant.
4) Non-benzodiazepine hypnotics: Zolpidem, Eszopiclone, Zopiclone.
5) Benzodiazepines hypnotics: Brotizolam, Etizolam, Flunitrazepam, Alprazolam, Diazepam.

B Without cognitive dysfunction $n = 256$	Motor FIM efficiency				Motor FIM effectiveness			
	Partial regression coefficient	Standard error	Standard regression coefficient (β)	*P* value	Partial regression coefficient	Standard error	Standard regression coefficient (β)	*P* value
Diagnosis	0.024	0.037	0.042	0.526	0.015	0.023	0.041	0.529
Age	−0.001	0.003	−0.003	0.959	−0.005	0.002	−0.212	0.001**
Renal function (eGFR)	−0.004	0.001	−0.260	<0.001**	−0.003	0.001	−0.299	<0.001**
Number of drugs	−0.016	0.005	−0.160	0.016*	−0.008	0.004	−0.127	0.049*
New mechanism (No 0, Yes 1)	−0.019	0.031	−0.038	0.540	−0.003	0.019	−0.009	0.877
Non-benzo (No 0, Yes 1)	0.019	0.031	0.038	0.542	0.025	0.019	0.077	0.204
Benzo (No 0, Yes 1)	0.026	0.033	0.051	0.424	0.022	0.021	0.066	0.287
Sedatives (No 0, Yes 1)	−0.062	0.035	−0.109	0.080	−0.043	0.022	−0.117	0.054

1) Analytical evaluation: Motor FIM efficiency ($R^2 = 0.11$, Analysis of variance $P < 0.001$)
Motor FIM effectiveness ($R^2 = 0.20$, Analysis of variance $P < 0.001$)
2) $^{*}P < 0.05$, $^{**}P < 0.01$.

Table 4. Relationship between the presence or absence of cognitive dysfunction and types of hypnotics.

	With cognitive dysfunction ($n = 253$)		Without cognitive dysfunction ($n = 256$)	
	Patient (persons)	%	Patient (persons)	%
New mechanism	49**	19.4	25**	9.8
Non-benzodiazepine	22	8.7	30	11.7
Benzodiazepines	16*	6.3	29*	11.3
Not used	166	65.6	172	67.2

1) Statistical analysis: Fisher's χ^2 exact test $P = 0.005$.
Comparison between groups by residual analysis: $^{*}P < 0.05$, $^{**}P < 0.01$.
2) Priority in combination: Benzo > Non-Benzo > New mechanism.
3) New mechanism hypnotics: Ramelteon, Suvorexant, Lembolexant.
4) Non-benzodiazepine hypnotics: Zolpidem, Eszopiclone, Zopiclone.
5) Benzodiazepines hypnotics: Brotizolam, Etizolam, Flunitrazepam, Alprazolam, Diazepam.

were using hypnotics with new mechanisms more frequently than patients without cognitive dysfunction ($P < 0.01$). Patients without cognitive dysfunction were using BZ hypnotics more frequently than those with cognitive dysfunction ($P < 0.05$).

Comparisons between the group with severity level 1 and severity level 2 or above showed that the group with severity level 1 was using BZ hypnotics more frequently [group with severity level 1, 10.5% (10/95); group with severity level 2 or above, 3.8% (6/158); $P < 0.05$]. Groups with severity levels 1 and 2 or above did not differ significantly regarding the use of non-BZ hypnotics [group with severity level 1, 12.6% (12/95); group with severity level 2 or above, 6.3% (10/158)]. In contrast, the group with severity level 2 or above was using hypnotics with new mechanisms of action more frequently than the group with severity level 1, although the result was not statistically significantly [group with severity level 1, 16.9% (16/95); group with severity level 2 or above, 20.9% (33/158)].

Discussion

The outcomes of this study were motor FIM efficiency (which was not affected by the length of hospital stay) and motor FIM-e (with less ceiling effect due to the reduced effects of motor FIM compared to that on admission). Motor FIM gain, motor FIM efficiency, and motor FIM-e have been widely used as indicators of motor FIM. However, no consensus has been reached regarding the validity of the variables. Therefore, this study used motor FIM efficiency and motor FIM-e.

From the results of this study, cognitive dysfunction was negatively associated with both motor FIM efficiency and motor FIM-e (Table 1), and decreased according to the severity of dementia (Figure 1).

The results suggested that an increase in the number of drugs and standard eGFR leads to reduction in motor FIM efficiency and motor FIM-e. Similar to that observed in previous studies, hypnotics increased motor FIM efficiency and motor FIM-e (Table 2-A). Among hypnotics, non-BZ hypnotics showed a positive relationship with motor FIM efficiency and motor FIM-e, whereas BZ hypnotics showed a positive relationship with motor FIM-e. However, hypnotics with new mechanisms of action did not show any significant association with motor FIM efficiency and motor FIM-e (Table 3-A). A significant relationship between hypnotics and motor FIM was not observed in patients without cognitive dysfunction (Tables 2-B and 3-B). Among the 15 patients using a combination of hypnotics of different therapeutic classes in this study, 7 patients (7/87) had cognitive dysfunction and 8 (8/84) did not. Therefore, the proportion of patients in different categories in this study would not affect the results.

Among the hypnotics with new mechanisms of action, ramelteon, a melatonin receptor agonist, suvorexant and lemborexant, the orexin receptor antagonists, were introduced to the Japanese market in 2010, 2014, and July 2020, respectively. Lemborexant has higher selectivity for the orexin 2 receptor agonist, which plays an important role in the control of sleep-wake cycle [13]. A study that compared the time of sleep onset, total sleep time, and awakening after sleep onset between lemborexant and suvorexant treatments [14] showed promising benefits of lemborexant. However, owing to the small number of patients who were using lemborexant in the present study period, the results may not reflect the efficacy. In addition, hypnotics with new mechanisms of action tend to be more frequently used by patients with moderate to severe dementia than by patients with mild dementia. This may be responsible for the non-significant results for hypnotics with new mechanisms of action.

A previous study evaluated drug therapy for sleep disorders in patients with dementia using the Cochrane Database [15]. The results revealed uncertainty regarding the efficacies of BZ and non-BZ hypnotics, which warranted studies using larger cohorts, although it showed the benefits of orexin receptor antagonists with new mechanisms of action.

A study regarding the relationship between sleep quality and recovery of motor function in patients undergoing rehabilitation after brain surgery [16] showed an association between reduced sleep quality and delayed recovery. This may support the results of the present study, which showed a positive relationship between the use of hypnotics and motor FIM efficiency and motor FIM-e in patients with cognitive dysfunction.

However, studies [15, 16] using sleep quality as an outcome did not directly examine the relationship between the use of hypnotics and motor FIM in patients with dementia. Reports have shown that short-term sleep deprivation in the elderly, compared to that in young people, significantly affects the functions of the cognitive domain such as attention, working memory, processing speed, short-term memory, and reasoning [17]. The effect of sleep deprivation may be stronger in patients with cognitive dysfunction.

In general, elderly patients with insomnia not using hypnotics are initially administered drugs with new mechanisms of action that have relatively fewer side effects; they are switched to non-BZ drugs if they do not respond to the initially administered drugs. However, 30% of inpatients use some hypnotics (Table 1). These patients switch to drugs of the same class and are followed up even after admission. Subsequently, dose reduction and switching to drugs with new mechanisms of action are considered. The number of inpatients who used BZ hypnotics in our hospital decreased. However, many of them used BZ hypnotics for a long period of time. Therefore, drug switching and dose reduction are difficult in the absence of side effects. The use of hypnotics not only improves sleep quality and cognitive

function, but also supports active daytime rehabilitation.

This study has certain limitations. First, this was a single-center retrospective study. Second, we considered patients to have cognitive dysfunction if they met the following less rigorous criteria: MMSE at admission of 23 points or less, HDS-R at admission of 20 points or less, or a total cognitive FIM score at admission of 24 points or less. Third, the use of sedating or hypnotic agents was considered based on whether the patients had continued using sedative or hypnotic agents for more than two-thirds of the total duration of hospitalization. The study did not directly examine the relationship between rehabilitation and drug dose or the presence or absence of medication. Fourth, serum Cr in the elderly with prolonged bed rest, women, patients with malnutrition, and patients with lower muscle mass was corrected using the rounding-up approach, but renal function was evaluated using standard eGFR.

Many patients in convalescent rehabilitation wards complain of problems regarding sleep and excretion. Although avoiding the easy use of hypnotics in the elderly and prioritizing the use of sleep hygiene guidelines are preferred, these are difficult, considering the constraints of hospitalization. However, our observations suggested that the use of hypnotics that do not affect rehabilitation does not reduce, but rather increases, the effects of rehabilitation on patients with cognitive dysfunction. Evaluation of the cause of insomnia, the level of satisfaction with the currently used hypnotics, and the presence or absence of daytime sleepiness and dizziness can be best accomplished by a multidisciplinary medical team.

In future, prospective multicenter studies with larger sample sizes and additional variables, such as sleep quality, should be performed to examine the relationship between cognitive function affecting motor FIM and hypnotics.

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