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Original Article

A Unified Primary Care Approach for the Management of Insomnia and Confusion Using the Clinical Pathway

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Abbreviations: DZP: diazepam; CP: chlorpromazine; JPOS: Japanese Psycho-Oncology Society; JASCC: Japanese Association of Supportive Care in Cancer; CYP: cytochrome P450

Abstract

Background: Delirium and confusion are risk factors for falls and its related injuries. Therefore, we designed a unified clinical pathway to reduce the risk of delirium among hospitalized patients.

Methods: A unified approach of pharmacotherapy for managing insomnia and confusion, which is subdivided based on the patients' age (<70 versus ≥70 years) and presence of diabetes mellitus, was implemented in Nagoya Memorial Hospital, Japan. Risk factors for delirium were assessed via a multidisciplinary approach. For older high-risk patients, suvorexant or trazodone was prophylactically prescribed to promote sleep. If delirium occurred, either quetiapine or perospirone was administered prior to the usage of risperidone or haloperidol. The amounts of prescribed sleep inducers and antipsychotic agents were examined. The application rate of the clinical pathway and incidence of falls were compared before and after its introduction.

Results: The application of a unified approach for the management of insomnia and confusion significantly decreased the prescribed amounts of benzodiazepines and may be associated with the reduced incidence of falls among hospitalized patients.

Conclusions: A clinical pathway assisted the selection of sleep inducers and antipsychotic agents. This is useful for managing inpatients safely by preventing delirium and subsequent falls.

Background

Delirium is characterized by an acute or subacute decline in cognitive functioning and fluctuating disturbances in attention, circadian rhythm, emotion, and psychomotor functions [1]. Risk factors for delirium are classified into predisposing and precipitating factors [2,3]. Common predisposing factors include older age, comorbidities, and dementia. Precipitating factors include infections, sleep disruptions, and the usage of drugs including sedative hypnotics and histamine type-2 receptor antagonists [4]. Benzodiazepines have been established a principal contributor toward delirium and patient falls [5]. Furthermore, delirium and confusion are well established risk factors for patient falls and related injuries [6], and are associated with longer hospital stays [2,7] and increased caregiver burden [8,9]. Most delirium presentations are preceded by sleep disturbances and restlessness [4]. In Nagoya Memorial Hospital, prescriptions for insomnia and delirium were dependent on the relevant attending physician. In addition, the nursing observation items used to greatly vary among hospitalized patients. Accordingly, a unified clinical pathway of pharmacotherapy for insomnia and confusion was developed to promote a standardized approach to treating delirium.

Methods

We designed a clinical pathway for managing insomnia and confusion with reference to the Japanese Psycho-Oncology Society (JPOS) and Japanese Association of Supportive Care in Cancer (JASCC) clinical guidelines for delirium [10]. Patients were then subdivided according to age (<70 versus ≥70 years) and the presence of diabetes mellitus as shown in Table 1. The comments including the half-life of each drug and precautions as a reference for additional administration and the onset of effects were described in the clinical pathway. This current clinical pathway was introduced in July 2018. Either nurses, pharmacists, or attending physicians checked for the presence of delirium-inducing drugs and Parkinson's

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***Table 1**. A clinical pathway of pharmacotherapy for insomnia and confusion*

	≥70 years; DM(−)	<70 years; DM(−)	≥70 years; DM(+)	<70 years; DM(+)
Insomnia 1st choice	**Suvorexant (15mg)** 1tablet t1/2 10h p. o. early after dinner	**Suvorexant (20mg)** 1tablet t1/2 10h p. o. early after dinner	**Suvorexant (15mg)** 1tablet t1/2 10h p. o. early after dinner	**Suvorexant (20mg)** 1tablet t1/2 10h p. o. early after dinner
Insomnia 1st choice (High risk group*)	**Quetiapine** (25mg) 1tablet t1/2 3h		None	
Insomnia 2nd choice	**Trazodone** (25mg) 1tablet t1/2 6h	**Eszopiclone** (1mg) 2tablets t1/2 6h	**Trazodone** (25mg) 1tablet t1/2 6h	**Eszopiclone** (1mg) 2tablets t1/2 6h
Confusion 1st choice	**Quetiapine** (25mg) 1tablet t1/2 3h		**Perospirone** (4mg) 1tablet t1/2 2.3h	
Confusion 2nd choice	**Risperidone** (1mg) 1packet t1/2 21h ※kidney function attention			
Not orally possible 1st choice	**Haloperidol** (5mg) 1A/ saline water100mL 1V in 30 minutes, 202mL/h t1/2 14h sleep stop and go			
Not orally possible 2nd choice	**Haloperidol** (5mg) 0.5A/ **Flunitrazepam** (2mg) 0.5A/ saline water100mL 1V in 60 minutes, 101mL/h t1/2 14h sleep stop and go; ECG needed			

The specific clinical pathway for each patient was selected from the above four options, based on the patients' age (<70 versus ≥70 years) and the presence or absence of diabetes mellitus (DM).
*High risk group for delirium: medical history of delirium, dementia, and cerebrovascular disorder, the usage of delirium-inducing drugs.

***Table 2**. Outcomes and indications*

Name	**Insomnia/ confusion (≥70 years; DM-)**			
Phase	Day1	Day2	Day3	Day4
Date	/	/	/	/
Outcomes	1. Excellent sleep during the night			
	2. The outbreak of delirium is controlled			
	3. Fall prevention			
Indication	**Indication** **When using benzodiazepines, report to the attending physician.** **[≥70 years: benzodiazepines are generally prohibited]**			
	Indication **Parkinsonism (+) (−)** **Haloperidol: Parkinson's disease is contraindicated**			
	Indication **DM (+) (−)** **Quetiapine: DM is contraindicated**			
	Indication **Delirium-inducing drugs (+) (−)** **For example: benzodiazepines, histamine type-2 receptor antagonists**			

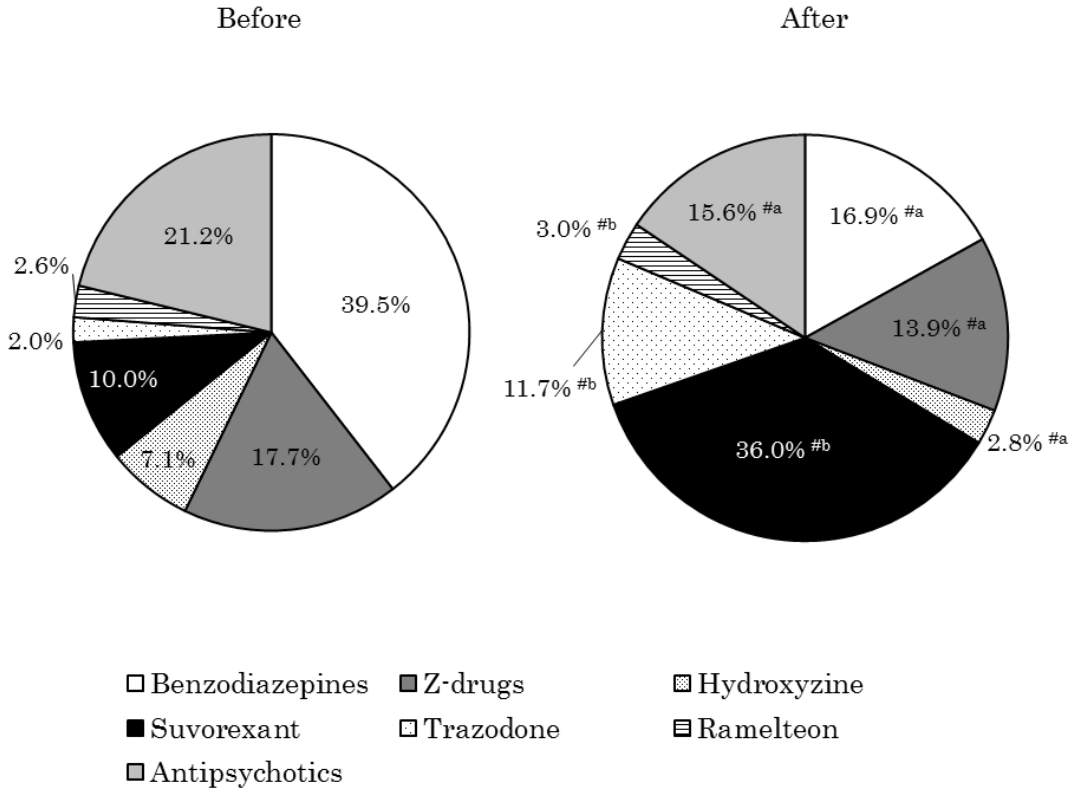
disease prior to issuing the clinical pathway and then the specific clinical pathway for each patient was selected from four options. As described in Table 2, outcomes were evaluated as 1st grade ("Excellent sleep during the night"), 2nd grade ("The outbreak of delirium is controlled"), and 3rd grade ("Fall prevention"). Table 3 showed that a unified format of nursing observation items was adopted to eliminate the disparities of nursing care provision.

We examined the prescribed amounts of hypnotics and antipsychotics for inpatients between 2012 and 2019. We compared the application rates, the usage ratio of the above-mentioned drugs, and the fall rates among the inpatients before and after the introduction of the current clinical pathway for insomnia and confusion. The prescribed amounts of benzodiazepines and Z-drugs were converted into those of diazepam (DZP conversion), and the amounts of antipsychotics were converted into those of chlorpromazine (CP conversion) [11]. This retrospective study was approved by the Research Ethics Committee of Nagoya Memorial Hospital (approval No. 2020-017) and conducted in accordance with the Declaration of Helsinki.

The data analysis was primarily performed using descriptive statistics. The results of a stratified analysis were compared using Fisher's exact test or Mann-Whitney U test between

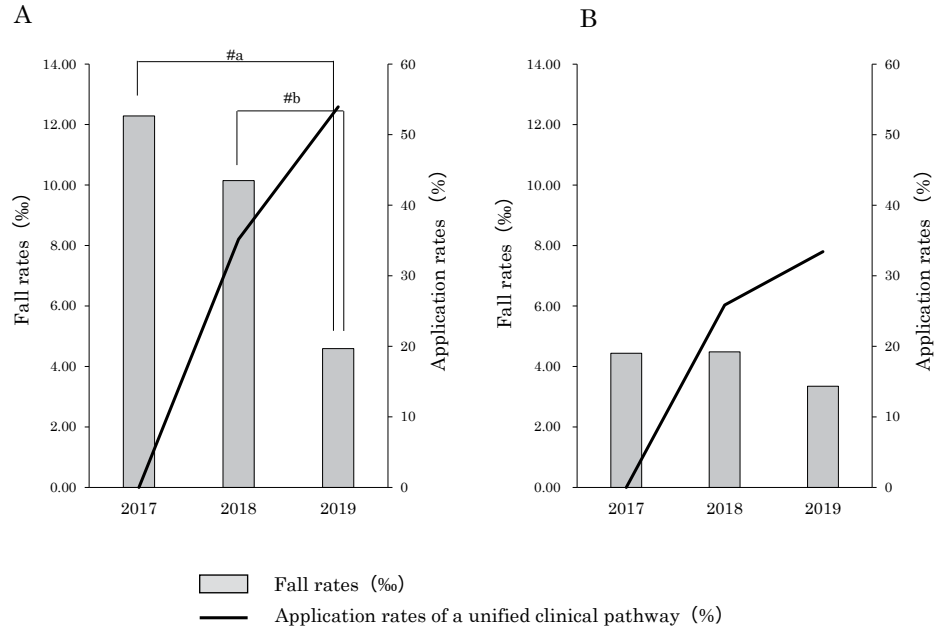
***Table 3**. A unified format of nursing observation items*

Evaluation items	Estimation method
SpO2	Measured value
Nocturnal awakening	+, −, ±
Early morning awakening	+, −, ±
Constipation	+, −, ±
Appetite	+, −, ±
Nausea	+, −, ±
Somnolence	+, −, ±
Excitation	+, −, ±
Restlessness	+, −, ±
Dangerous behavior (falls)	+, −, ±
Depression	+, −, ±
Environmental adjustment (setting a calendar, clock, or photograph)	○, ×
Toilet guidance	○, ×
Life rhythm collapses	○, ×



Before: January 2017 – June 2018
After: July 2018 – December 2019
#a indicates a significant decrease and #b indicates a significant increase compared to the usage ratio at baseline; $p < 0.05$ (Fisher's exact test).

***Figure 1.** The comparison of the usage ratio of hypnotics and antipsychotics before and after the introduction of a unified clinical pathway.*



A: Department of neurosurgery
B: Department of gastrointestinal medicine
#a indicates a significant difference compared to fall rates in 2017. #b indicates a significant difference compared to fall rates in 2018. $p < 0.05$ (Bonferroni's test).

Figure 2. *Chronological changes in fall rates and application rates of a unified clinical pathway which was introduced in July 2018.*

two groups, and Bonferroni's test among the three groups. All p-values were two-sided, and p-values of 0.05 or less were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, it is a modified version of the R commander, designed to add statistical functions frequently used in biostatistics [12].

Results

Prescribed amounts of hypnotics and antipsychotic drugs were shown in Table 4. Regarding sedative hypnotics, the number of prescriptions of brotizolam consistently decreased, while that of suvorexant and trazodone reciprocally increased during the study period. For antipsychotics, the number of prescriptions of risperidone (1mg) decreased in 2019, while that of quetiapine increased from 2016 and reached a plateau. Perospirone was not prescribed until 2016; however, the prescribed amounts then gradually increased. Among injection formulations, the prescribed amounts of hydroxyzine decreased, while that of haloperidol increased. The application of clinical pathway significantly reduced the usage ratios of benzodiazepines, Z-drugs, and hydroxyzine. Furthermore, it increased the usage ratios of suvorexant and trazodone (Figure 1). There was a notable decrease in the ratio of antipsychotics overall due to clinical pathway usage (21.2% versus 15.6%).

The average amounts of hypnotics and antipsychotics prescribed per month were compared before and after the introduction of a unified clinical pathway for insomnia and confusion in Table 5. The average amounts of hypnotics (DZP) and antipsychotics (CP) prescribed per month were reduced after the introduction of a unified clinical pathway for insomnia and confusion.

Application rate of the clinical pathway was highest in the department of neurosurgery, followed by gastrointestinal medicine. As the application rates increased, the fall rates decreased in both departments (Figure 2). The fall rates was significantly reduced in neurosurgery (2017; 12.3% vs 2019; 4.6%, 2018; 10.2% vs 2019; 4.6%, Bonferroni's test).

Discussion

Delirium is extremely distressing for patients, their families, and their professional caregivers [8,9]. We used suvorexant, a selective orexin receptor antagonist, as the primary choice of hypnotics in the current clinical pathway [13]. As a secondary choice, the Z-drugs eszopiclone and trazodone were administered for patients aged < 70 and ≥70 years, respectively. Thus, the prescribed amounts of benzodiazepines significantly decreased. However, it should be noted that suvorexant is metabolized by cytochrome P450 (CYP) 3A4. Since approximately 75% of marketed drugs are metabolized by CYP and approximately half of these are metabolized by CYP3A4 [14], the concomitant drug must be investigated to determine the drug interaction.

For the treatment of restlessness, quetiapine was selected due to its short half-life [15]. Perospirone was administered to the patients with diabetes mellitus, since quetiapine is contraindicated for this disorder [16]. While risperidone also has a short half-life of 4 hours, its active metabolite is excreted through the kidney, which has a half-life of 20 to 24 hours and may increase depending on renal function [17]. Renal functions often decline in elderly patients; therefore, risperidone was considered as a second choice. The application of the present

Table 4. *Prescribed amounts of hypnotics and antipsychotic drugs*

		Year							
Drugs		2012	2013	2014	2015	2016	2017	2018	2019
Benzodiazepines	Brotizolam 0.25mg	19415	17648	15706	14095	13119	9924	6939	5147
	Flunitrazepam 2mg	94	101	340	74	152	120	125	291
Z-drugs	Zolpidem 10mg	2286	2213	3133	2986	2282	1927	1338	2126
	Eszopiclone 1mg					301	2034	3416	2255
Hydroxyzine 25mg		3283	2537	2742	1761	1567	1932	1375	905
Suvorexant	Suvorexant 15mg				17	1114	1515	5796	11811
	Suvorexant 20mg				38	321	203	522	924
Trazodone 25mg		766	942	822	294	1035	430	1475	4417
Ramelteon 8mg		36	48	242	349	771	712	613	1057
Antipsychotics	Quetiapine 25mg	216	260	852	510	1296	1562	2480	2161
	Perospirone 4mg						44	289	322
	Risperidone 1mg	1742	2191	1494	2124	2338	2252	1906	1110
	Haloperidol 5mg	538	471	486	775	664	924	956	1181

Table 5. *The comparison of average amounts of hypnotics and antipsychotics prescribed per month before and after the introduction of a unified clinical pathway*

Drugs	Before	After	p-value
Hypnotics (DZP conversion)	16485.4 ± 884.1	9123.8 ± 343.4	#a
Benzodiazepines (DZP conversion)	15989.1 ± 898.5	8614.1 ± 338.7	#a
Z-drugs (DZP conversion)	496.2 ± 44.3	509.6 ± 30	
Hydroxyzine (mg)	3597.2 ± 163	1861.1 ± 114.1	#a
Suvorexant (mg)	3157.1 ± 467	14609.7 ± 777.1	#b
Trazodone (mg)	1035.4 ± 237.1	7743.8 ± 748.9	#b
Ramelteon (mg)	419.1 ± 33.8	639.1 ± 116.3	
Antipsychotics (CP conversion)	26475.6 ± 1362.9	20754.1 ± 1622.3	#a

Before: January 2017 – June 2018
After: July 2018 – December 2019
DZP conversion: The prescribed amounts of benzodiazepines and Z-drugs were converted into those of diazepam.
CP conversion: The amounts of antipsychotics were expressed in terms of the amounts of chlorpromazine.
#a indicates a significant decrease and #b indicates a significant increase compared to the prescription amounts before the introduction of a unified clinical pathway for insomnia and confusion; $p < 0.05$ (Mann-Whitney U test)

clinical pathway significantly decreased the usage ratio of antipsychotics overall. Additionally, higher application rates of the clinical pathway were associated with lower fall rates. These findings suggest that the proper choice of hypnotics is helpful for the prevention of confusion and subsequent falls.

Prior to the clinical pathway introduction, each doctor prescribed hypnotics and antipsychotics based on their own experiences. It was thus difficult for the multi-disciplinary staff to collaborate on the management of insomnia and confusion. Drug information, including half-life and precautions, were available upon commencing the clinical pathway. These were provided in the electronic medical record, enabling nursing staff to consult with it at any time. Ward pharmacists held a study session in each ward to diffuse knowledge on hypnotics and antipsychotics among the staff, which enhanced communication and prompted inquiry from the nurses. Accordingly, the doctors were confident in the use of the clinical pathway. Currently, there are several departments in which the clinical pathway for insomnia and confusion can be routinely applied for inpatients. When there is a lack of instructions for the management of insomnia and confusion on admission, nursing staff often request physicians to use this clinical pathway for high-risk patients.

Recently, pharmacovigilance data have been reported in palliative care [18,19]. Furthermore, non-pharmacologic interventions such as reorientation, maintaining hydration and nutrition, early mobilization, and hearing and visual adaptations are extremely effective in decreasing the occurrence of delirium among elderly persons [3,20]. The usage of the clinical pathway, along with interdisciplinary involvement, further improves the quality of sleep. This may eventually reduce the usage of antipsychotics and decrease the incidence of falls, enhancing daytime activity levels and the efficacy of rehabilitation.

Conclusions

A clinical pathway of pharmacotherapy for insomnia and confusion ensures appropriate prescription of sleep inducers and antipsychotics. This may contribute to the safe management of hospitalized patients by preventing delirium and subsequent falls.

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the ethics committee of Nagoya Memorial Hospital (approval No. 2020-017) and conducted in accordance with the Declaration of Helsinki.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Competing interests

The authors declare that they have no competing interests..

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Author contributions

MK, YT, and KI wrote the manuscript. MK, SK, and YK reviewed the medical records. MK and SY performed the computed analyses. All authors read and approved the final manuscript.

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