Real-World Preventive Effects of Suvorexant in Intensive Care Delirium:
A Retrospective Cohort Study

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ABSTRACT

Objective: This study aimed to examine the effects of suvorexant on delirium prevention in a real-world setting. Previous studies have demonstrated the efficacy of suvorexant for delirium prevention in limited randomized clinical trial settings; however, its effectiveness in everyday clinical settings remains unknown.

Methods: A single-center, retrospective cohort study was conducted in the intensive care unit of an academic hospital. Patients (aged ≥ 3 years) admitted from January 2016 to December 2018 were eligible if they stayed in the intensive care unit for at least 72 hours. Suvorexant was prescribed by the attending physician for insomnia as part of everyday clinical practice. A Cox proportional hazards regression analysis was conducted on delirium-free survival for suvorexant users, adjusting for delirium-related covariates. As part of routine clinical practice, the Confusion Assessment Method for the Intensive Care Unit was used to detect the existence of delirium at least twice daily throughout the intensive care unit stay.

Results: There were 699 patients—84 suvorexant users and 615 suvorexant nonusers. Delirium was detected in 214 patients. Delirium prevalence was significantly lower in suvorexant users than in nonusers (17.9% vs 32.4%, respectively; $P = .007$). Cox regression analysis revealed a significantly lower hazard ratio (0.472; 95% CI, 0.268–0.832; $P = .009$) of delirium in suvorexant users than in nonusers. Trazodone also had a preventive effect on delirium (hazard ratio 0.345; 95% CI, 0.149–0.802; $P = .013$).

Conclusions: The present study extends to real-world settings previous findings that suvorexant is effective for delirium prevention.

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Delirium is a common, serious problem in clinically ill patients.[1] A diagnosis of delirium is associated with increased mortality and decreased long-term cognitive and physical functions.[2] Delirium prevention strategies are therefore urgently needed. However, there is no convincing, reproducible evidence that pharmacologic treatments are effective for the prevention of delirium,[3] and a non-pharmacologic, multimodal strategy is currently recommended. Pharmacologic treatment of delirium is considered only when a patient's agitation endangers medical staff or the patient himself or herself, such as by interrupting essential medical therapies.[1]

The causes of delirium are complicated and multifactorial. Sleep and circadian rhythm disruption may play an important role in delirium development.[4] Recently, the American College of Critical Care Medicine updated their Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium (PAD)[5] to include guidelines for PAD, immobility, and sleep.[6] The relationship between delirium and sleep has recently received global attention. Traditionally, the pharmacologic treatment of sleep problems in the intensive care unit (ICU) is controversial, because typical hypnotics, including benzodiazepines or propofol, disrupt sleep architecture[7] and eventually evoke delirium.[8]

Some randomized studies have reported that suvorexant, which is prescribed for insomnia, is effective in preventing delirium. Hatta et al[9] reported its efficacy in both ICU and acute care settings, and Azuma et al[10] demonstrated its efficacy in the ICU. However, a network meta-analysis[11] failed to show a preventive effect of suvorexant for delirium because of a lack of conclusive evidence. Additionally, Masuyama et al[12] retrospectively analyzed ICU patients (33 patients who had used suvorexant and 85 patients who had not used suvorexant), but they failed to replicate a delirium-preventing effect of suvorexant with crude data. Hatta et al[13] prospectively observed delirium development in 734 ramelteon and/or suvorexant users compared with 214 nonusers. Of the 119 suvorexant users who were delirium-free the night before observation started, 17 (14.3%) developed delirium. Meanwhile, among 125 nonusers, 30 (24.0%) developed delirium. This previous study was the first to show that suvorexant users are less likely to develop delirium compared with nonusers in a clinical setting. However, these results were not compared statistically and were given as secondary information. When we performed an ad hoc statistical analysis, the difference between users and nonusers was not significant ($P = .054$). Therefore, a study investigating the

Clinical Points

- Although some placebo-controlled, randomized studies have shown the efficacy of suvorexant for preventing delirium, few investigations have examined the effectiveness of delirium prevention by suvorexant in everyday clinical settings.
- This study showed a delirium-preventing effect of suvorexant in clinically ill patients in a real-world setting and suggests that treating insomnia with suvorexant can prevent delirium occurrence.

real-world effectiveness of suvorexant in delirium prevention as its main outcome is needed to confirm its usefulness in routine clinical settings.

In the current study, using retrospective data from everyday ICU situations, we examined whether suvorexant prevented delirium in a relatively large sample of patients in a real-world setting.

METHODS

Study Design

We conducted a retrospective cohort study to compare delirium occurrence between suvorexant users (patients who had used suvorexant before delirium development) and nonusers. We also explored the association between delirium occurrence and other drugs that can be prescribed for insomnia or delirium. The study was approved by the Shimane University Hospital Ethics Board (approval number: 20171113–2). Data were collected anonymously; therefore, the ethics board waived the need for informed consent from individual patients. An opt-out option was provided through our website.

Data Collection

We retrospectively collected all data from electronic medical records (ACTIS; Canon Medical Systems; Tochigi, Japan) and the electronic ICU chart system (PIMS; Philips; Tokyo, Japan).

Study Population

The study population included all patients hospitalized in the 20-bed ICU of Shimane University Hospital in Shimane, Japan, between January 2016 and December 2018. Patients were excluded based on the following criteria: (*a*) they stayed in the ICU < 72 hours (to exclude patients with delirium at administration[14]); (*b*) they were aged ≤ 2 years (to exclude patients who could not be evaluated using the Confusion Assessment Method for the ICU [CAM-ICU]); (*c*) data were missing.

Delirium Diagnosis

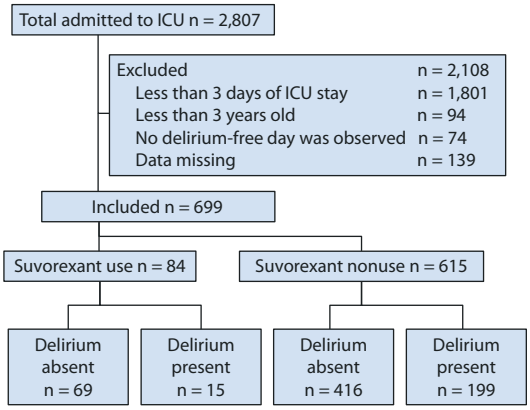
Each patient's wakefulness was evaluated every 2 hours using the Richmond Agitation-Sedation Scale (RASS).[15] In the RASS assessment, an assessor first observed each patient's alertness, restlessness, or agitation and scored from 0 (alert and calm) to +4 (combative). If the patient was not alert, the assessor stated the patient's name and said "open your eyes" and "look at the speaker" to the patient, and, according to the reaction, scored –1 (sustained eyes open and eye contact), –2 (no sustained eyes open or eye contact), or –3 (any movement in response but no eye contact). When no response to the verbal stimulation was observed, the assessor physically stimulated the patient by shaking his or her shoulder and/or rubbing his or her sternum and scored –4 (any movement in response to physical stimulation) or –5 (no response to any stimulation). If the RASS score was evaluated as –4 or –5, the patient was assumed to be in a coma and was later reassessed using the RASS. When the RASS score was –3 or greater, the CAM-ICU was scored every 12 hours.

Delirium was diagnosed if the CAM-ICU score was positive. To evaluate delirium with the CAM-ICU, the assessor first detected both (*a*) acute mental status changes and (*b*) inattention. If these were detected, the assessors assessed (*c*) disorganized thinking (such as rambling or irrelevant conversation) and (*d*) altered levels of consciousness (any level of consciousness other than "alert"). If (*c*) or (*d*) was present, in addition to (*a*) and (*b*), then the CAM-ICU was scored as positive. We administered the CAM-ICU in a clinical setting from 8:00 AM to 9:00 AM and from 6:00 PM to 7:00 PM until the patient was discharged from the ICU. This procedure was continually conducted before our study was performed.

The CAM-ICU was administered by bedside nurses. Each nurse received an on-the-job training course, taught by experienced nurses, at least 2 hours before they started working in the ICU and before they carried out any assessments. The CAM-ICU was scored by at least two nurses, of whom one had ICU experience of at least 3 years. ICU doctors and psychiatrists shared the CAM-ICU results in their regular meetings. Additional delirium evaluation training courses were held by psychiatrists at least once per year.

A single CAM-ICU assessment by a bedside nurse is very accurate for detecting delirium; thus, patients were classified

Figure 1. Flowchart of Patient Selection



Abbreviation: ICU = intensive care unit.

as delirious when 1 CAM-ICU assessment was positive. We adopted the Japanese version of the CAM-ICU (translation downloadable from Tsuruta et al[16]), which has a reported sensitivity of 78%–83% and specificity of 95%–98%.[17]

We defined a delirium-free day as a day in which (*a*) no positive CAM-ICU score was obtained, (*b*) no coma was detected, and (*c*) a negative CAM-ICU score was obtained. We started the analysis from the first delirium-free day and stopped once a positive CAM-ICU score was obtained or the patient was discharged from the ICU.

Measurement of Covariates

To evaluate the influence of previously detected delirium-related covariates,[3,18] baseline demographic information was collected, including age, history of coma, dementia, cognitive impairment, past history of delirium, severity of illness, use of mechanical ventilation, and emergency hospitalization. Severity of illness was evaluated using the modified Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system[19] and Sepsis-related Organ Failure Assessment (SOFA).[20] The Charlson Comorbidity Index was used to evaluate comorbidity.[21]

Statistics

We conducted Cox regression analyses to explore the preventive effects of suvorexant and other medications on delirium. For the other medications, we included sedative-hypnotics and antipsychotics that had been previously reported to prevent delirium[3,11] and excluded medications that were prescribed only in a small number of patients.

To confirm our results, the non–covariate-adjusted and fully covariate-adjusted Cox models were used to check whether the results were observed consistently.

Mann-Whitney *U* tests and χ^2 tests were used to compare characteristics between suvorexant users and nonusers.

SPSS v23 (March 2015; IBM; Tokyo, Japan) was used for statistical analysis. The level of significance was set as .05.

RESULTS

Study Cohort and Patient Characteristics

As shown in Figure 1, 2,807 patients were hospitalized in the ICU during the study period, and all patients' medical records were reviewed. Of these, 2,108 patients were excluded. There were 1,801 patients who had an ICU stay shorter

Table 1. Patient Baseline Characteristics and Clinical Outcomes[a]

Characteristic	Suvorexant Users (n = 84)	Suvorexant Nonusers (n = 615)	*P* value
Female	20 (23.8)	231 (37.6)	.014
Age, median (IQR), y	73.0 (65.3–78.8)	70.0 (62.0–79.0)	.104
BMI, median (IQR), kg/m^2	22.9 (20.4–25.0)	22.0 (19.5–24.5)	.077
Height, median (IQR), m	1.60 (1.53–1.68)	1.59 (1.50–1.66)	.179
Weight, median (IQR), kg	58.8 (50.4–65.5)	54.6 (47.0–63.7)	.024
Lifestyle factors			
Alcohol			.286
Nondrinker	57 (67.9)	366 (59.5)	
Drinker	18 (21.4)	150 (24.4)	
Past drinker	9 (10.7)	99 (16.1)	
Smoking habits			.070
Nonsmoker	63 (75.0)	385 (62.6)	
Smoker	8 (9.5)	70 (11.4)	
Past smoker	13 (15.5)	160 (26.0)	
Comorbidity and severity of illness			
Charlson Comorbidity Index score, median (IQR)	3.0 (1.3–3.8)	3.0 (2.0–4.0)	.153
Myocardial infraction	13 (15.5)	90 (14.6)	.838
Congestive heart failure	9 (10.7)	47 (7.6)	.331
Peripheral vascular disease	4 (4.8)	20 (3.3)	.476
Cerebrovascular disease and TIA	13 (15.5)	73 (11.9)	.345
Dementia	3 (3.6)	38 (6.2)	.340
COPD	2 (2.4)	7 (1.1)	.343
Connective tissue disease	2 (2.4)	22 (3.6)	.572
Peptic ulcer disease	4 (4.8)	45 (7.3)	.390
Liver disease (mild)	56 (66.7)	465 (75.6)	.078
Diabetes mellitus	12 (14.3)	132 (21.5)	.127
Severe diabetes mellitus	0 (0.0)	24 (3.9)	.065
Hemiplegia	6 (7.1)	105 (17.1)	.020
Chronic kidney disease	12 (14.3)	46 (7.5)	.034
Solid tumor	33 (39.3)	247 (40.2)	.878
Leukemia	0 (0.0)	13 (2.1)	.179
Lymphoma	3 (3.6)	11 (1.8)	.274
Severe liver disease	4 (4.8)	25 (4.1)	.764
Metastasis	3 (3.6)	17 (2.8)	.677
AIDS	0 (0.0)	0 (0.0)	…
APACHE II score, median (IQR)	18.5 (15.0–26.0)	20.0 (15.0–25.0)	.964
SOFA score, median (IQR)	7.0 (4.0–10.0)	7.0 (4.0–9.0)	.959
Physiologic factors, median (IQR) concentration			
Serum albumin, g/dL	2.8 (2.3–3.3)	2.7 (2.2–3.1)	.272
Serum urea nitrogen/creatinine ratio	19.3 (14.1–27.0)	19.7 (14.7–26.5)	.998
Serum sodium, mmol/L	139.0 (137.0–141.8)	139.0 (136.0–142.0)	.842
Serum potassium, mmol/L	4.2 (3.8–4.6)	4.1 (3.8–4.5)	.060
Total bilirubin, mg/dL	0.8 (0.5–1.2)	0.8 (0.6–1.3)	.257
History during ICU stay			
Surgery	48 (57.1)	335 (54.5)	.644
Infection	20 (23.8)	139 (22.6)	.804
Mechanical ventilation	67 (79.8)	479 (77.9)	.697
Emergency hospitalization	65 (77.4)	469 (76.3)	.821
Coma	5 (6.0)	8 (1.3)	.003
Existence of pain	32 (38.1)	222 (36.1)	.721
Etiology of admission in ICU			.244
Surgery			
Cardiovascular	22 (26.2)	112 (18.2)	
Digestive	12 (14.3)	108 (17.6)	
Brain surgery	9 (10.7)	74 (12.0)	
Injury	2 (2.4)	15 (2.4)	
Other	3 (3.6)	26 (4.2)	
Heart failure	9 (10.7)	63 (10.2)	
Sepsis	6 (7.1)	57 (9.3)	
Respiratory failure	9 (10.7)	36 (5.9)	
After cardiopulmonary arrest	4 (4.8)	22 (3.6)	
Injury	2 (2.4)	20 (3.3)	
Pneumonia	2 (2.4)	16 (2.6)	
Liver failure	1 (1.2)	10 (1.6)	
Stroke	1 (1.2)	10 (1.6)	
Other	2 (2.4)	46 (7.5)	

(continued)

Table 1 (continued).

Characteristic	Suvorexant Users (n = 84)	Suvorexant Nonusers (n = 615)	*P* value
Patient demography			
Performance status			.867
Median (IQR)	1.5 (0.0–3.0)	2.0 (0.0–3.0)	
0	25 (29.8)	186 (30.2)	
1	17 (20.2)	96 (15.6)	
2	9 (10.7)	67 (10.9)	
3	17 (20.2)	139 (22.6)	
4	16 (19.0)	127 (20.7)	
Dementia	3 (3.6)	38 (6.2)	.340
Cognitive impairment	9 (10.7)	80 (13.0)	.554
Past delirium	3 (3.6)	10 (1.6)	.216
Visual impairment	22 (26.2)	168 (27.3)	.828
Hearing impairment	15 (17.9)	128 (20.8)	.529
Functional disability	4 (4.8)	98 (15.9)	.007
Sleep problem	29 (34.5)	187 (30.4)	.444
Difficulty initiating sleep	18 (21.4)	97 (15.8)	.125
Difficulty maintaining sleep	7 (8.3)	74 (12.0)	.320
Waking up too early	1 (1.2)	1 (0.2)	.098
Circadian rhythm disruption	0 (0.0)	3 (0.5)	.521
Sleepiness	6 (7.1)	44 (7.2)	.977
Hypnotic use	21 (25.0)	113 (18.4)	.148
Medication use in the ICU before delirium development[b]			
Propofol	60 (71.4)	441 (71.7)	.958
Anesthesia (inhaled)	22 (26.2)	146 (23.7)	.622
Benzodiazepines (oral)	5 (6.0)	24 (3.9)	.377
Benzodiazepines (intravenous)	40 (47.6)	303 (49.3)	.777
Z drugs	9 (10.7)	45 (7.3)	.274
Dexmedetomidine	66 (78.6)	415 (67.5)	.040
Trazodone	14 (16.7)	34 (5.5)	.000
Risperidone	16 (19.0)	39 (6.3)	.000
Quetiapine	5 (6.0)	14 (2.3)	.052
Hydroxyzine	4 (4.8)	35 (5.7)	.728
Haloperidol	13 (15.5)	46 (7.5)	.013
Ramelteon	35 (41.7)	72 (11.7)	.000
No. of medications used, median (IQR)			
All type of medications	43.5 (28.3–53.8)	37.0 (29.0–48.0)	.051
CNS drugs	5.5 (4.0–8.0)	4.0 (3.0–6.0)	.000
Outcome			
Delirium in ICU	15 (17.9)	199 (32.4)	.007
Death in ICU	5 (6.0)	43 (7.0)	.724
Length of ICU stay, median (IQR), d	5.5 (4.0–9.0)	6.0 (4.0–10.0)	.988
Delirium-free length of observational period, median (IQR), d	3.0 (2.0–5.8)	3.0 (1.0–4.0)	.002

[a]Values shown as n (%) unless otherwise noted. Information about patient characteristics was collected before and after the ICU stay by a nurse.
[b]Inhaled anesthesia included desflurane and sevoflurane. Oral benzodiazepine was brotizolam. Intravenous benzodiazepines included diazepam and midazolam. Z drugs included zolpidem and eszopiclone.
Abbreviations: AIDS = acquired immunodeficiency syndrome, APACHE II = modified Acute Physiology and Chronic Health Evaluation scoring system, BMI = body mass index, CNS = central nervous system, COPD = chronic obstructive pulmonary disease, ICU = intensive care unit, IQR = interquartile range, IV = intravenous, SOFA = Sepsis-related Organ Failure Assessment, TIA = transient ischemic attack.

than 3 days, 94 patients who were 2 years old or younger, and 74 patients who did not have a detectable delirium-free day. In addition, 139 patients were excluded because of insufficient data. We examined the medical records of the remaining 699 patients and divided the patients into 2 groups: there were 84 suvorexant users and 615 suvorexant nonusers. Delirium was detected in 214 patients, while the remaining 485 patients were delirium-free during the observational period. The dose of suvorexant was 15 mg for patients ≥ 65 years of age and 20 mg for patients < 65 years of age. Of the 84 suvorexant users (69 who did not develop delirium and 15 who did), 18 patients (11 and 7, respectively) continuously used suvorexant before their ICU admission.

The CAM-ICU was administered at least once in 87.3% of person-days (441 of 505) and at least twice in 64.6% of person-days (326) for suvorexant users. For suvorexant nonusers, the CAM-ICU was administered at least once in 86.7% of person-days (2,725 of 3,142) and at least twice in 59.1% of person-days (1,856).

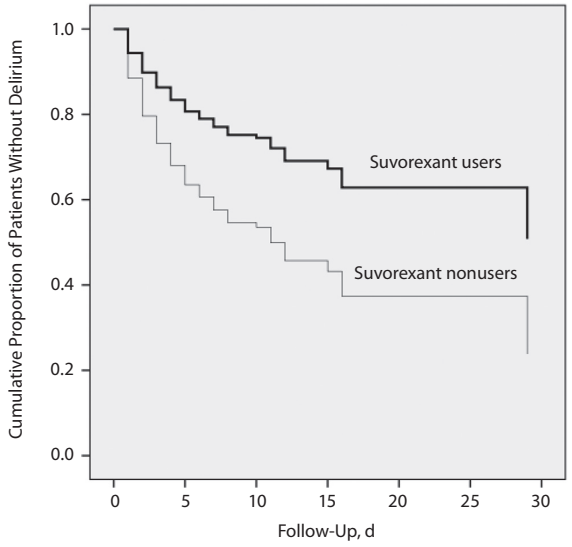
Patient characteristics are shown in Table 1. Suvorexant users were significantly more likely to be prescribed dexmedetomidine, trazodone, risperidone, haloperidol, or ramelteon; to have an observed coma; to have a higher body weight; and to be male. Hemiplegia and functional disability were less prevalent in suvorexant users. With regards to medication, 727 types of drugs were prescribed. There was no significant difference between suvorexant users and nonusers in the number of medications used, with medians of 43.5 (interquartile range [IQR], 28.3–53.8) and 37.0 (IQR, 29.0–48.0), respectively ($P = .051$). Suvorexant users took significantly more central nervous system agents compared with nonusers, with medians of 5.5 (IQR, 4.0–8.0) and 4.0 (IQR, 3.0–6.0), respectively ($P = .000$). Cox regression models should be used with a minimum of 10 events per predictor variable.[22] Of the 699 patients, 214 patients developed delirium. Therefore, 21 or 22 predictor variables were adequate for the Cox regression model. We included 9 patients' background covariates in the Cox model. We then entered 13 frequently prescribed drugs (including suvorexant) that prevent delirium into the Cox regression analysis (Table 1 and Table 2).

As shown in Table 1, delirium was significantly less prevalent in suvorexant users compared with nonusers (17.9% for suvorexant users vs 32.4% for suvorexant nonusers, $P = .007$). Length of ICU stay and ICU mortality were not related to suvorexant use. Suvorexant users had a longer delirium-free observation period; the median number of delirium-free days was 3.0 (IQR, 2.0–5.8) for suvorexant users and 3.0 (IQR, 1.0–4.0) for nonusers ($P = .002$).

Cox Regression Analysis

As shown in Figure 2 and Table 2, Cox regression analysis indicated that suvorexant users had a low hazard ratio (HR = 0.472; 95% CI, 0.268–0.832; $P = .009$) for delirium occurrence. Trazodone also had a low HR (0.345; 95% CI, 0.149–0.802; $P = .013$) for delirium occurrence. Other drugs, including dexmedetomidine, ramelteon, Z drugs (ie, non-benzodiazepine medications for insomnia such as zolpidem and eszopiclone), haloperidol, inhaled anesthesia, benzodiazepines, propofol, and risperidone,

Figure 2. Cox Regression Analysis for Delirium-Free Survival



Patients at risk, n							
Suvorexant users	84	26	8	4	3	2	1
Suvorexant nonusers	615	148	42	18	7	4	3

Table 2. Cox Regression Analysis for Delirium-Free Survival[a]

Covariate	Hazard Ratio (95% CI)	*P* Value
Age	1.009 (0.999–1.020)	.070
Coma (RASS score of –4 or –5)	1.003 (0.382–2.634)	.995
Dementia	0.826 (0.390–1.751)	.618
Cognitive impairment	1.217 (0.763–1.940)	.410
Past delirium	0.751 (0.228–2.473)	.638
APACHE II score	1.018 (0.996–1.041)	.108
SOFA score	1.037 (0.991–1.085)	.114
Mechanical ventilation	0.849 (0.583–1.237)	.394
Emergency hospitalization	1.139 (0.788–1.646)	.489
Propofol	1.198 (0.854–1.682)	.296
Anesthesia (inhaled)	0.833 (0.589–1.177)	.300
Benzodiazepine (oral)	1.036 (0.554–1.939)	.911
Benzodiazepine (IV)	1.116 (0.834–1.495)	.460
Z drugs	0.539 (0.289–1.006)	.052
Dexmedetomidine	1.215 (0.879–1.681)	.239
Trazodone	0.345 (0.149–0.802)	.013
Risperidone	0.839 (0.400–1.760)	.643
Quetiapine	1.806 (0.885–3.684)	.104
Hydroxyzine	0.708 (0.358–1.401)	.321
Haloperidol	0.854 (0.514–1.419)	.543
Ramelteon	1.184 (0.794–1.764)	.407
Suvorexant	0.472 (0.268–0.832)	.009

[a]Cox regression analysis showed that suvorexant use increased the probability of delirium-free survival in the intensive care unit. Trazodone also increased the delirium-free survival probability.
Abbreviations: APACHE II = modified Acute Physiology and Chronic Health Evaluation scoring system, IV = intravenous, RASS = Richmond Agitation-Sedation Scale, SOFA = Sepsis-related Organ Failure Assessment.

did not have significant effects on delirium occurrence. Suvorexant had a preventive effect for delirium, both in the Cox model without covariate adjustment (HR = 0.452, 95% CI, 0.263–0.778; *P* = .004) and in the fully (over)-adjusted Cox model (HR = 0.491; 95% CI, 0.277–0.870; *P* = .015; Table 3).

DISCUSSION

We retrospectively observed delirium occurrence and found that suvorexant had a possible delirium-preventing effect in the real-world setting of the Shimane University Hospital ICU.

Table 3. Cox Regression Analysis for Delirium-Free Survival With Full Covariate Adjustments[a]

Covariate	Hazard Ratio (95% CI)	*P* Value
Sex	1.119 (0.832–1.505)	.456
Age	1.008 (0.997–1.018)	.153
Coma	0.943 (0.353–2.521)	.907
Alcohol	1.035 (0.855–1.254)	.721
Dementia	0.859 (0.394–1.871)	.702
Cognitive impairment	1.246 (0.769–2.021)	.372
Past delirium	0.746 (0.225–2.476)	.632
Visual impairment	0.867 (0.626–1.202)	.393
Hearing impairment	0.937 (0.664–1.321)	.709
Functional disability	1.286 (0.844–1.959)	.243
Sodium	0.990 (0.959–1.022)	.538
Potassium	0.965 (0.756–1.232)	.776
Albumin	0.753 (0.600–0.945)	.014
Serum urea nitrogen/creatinine ratio	0.993 (0.980–1.007)	.337
BMI	1.056 (1.024–1.089)	.000
Surgery	1.040 (0.748–1.448)	.814
APACHE II score	1.018 (0.996–1.041)	.110
SOFA score	1.019 (0.972–1.068)	.438
Infection	1.617 (1.139–2.294)	.007
Mechanical ventilation	0.793 (0.539–1.165)	.237
Emergency hospitalization	1.010 (0.671–1.522)	.960
Charlson Comorbidity Index	0.941 (0.865–1.024)	.162
Propofol	1.203 (0.847–1.709)	.301
Anesthesia (inhaled)	0.738 (0.517–1.054)	.095
Benzodiazepine (oral)	0.981 (0.523–1.840)	.952
Benzodiazepine (IV)	1.144 (0.848–1.543)	.377
Z drugs	0.593 (0.315–1.114)	.104
Dexmedetomidine	1.152 (0.827–1.605)	.402
Trazodone	0.294 (0.126–0.684)	.004
Risperidone	0.764 (0.371–1.572)	.465
Quetiapine	1.927 (0.938–3.959)	.074
Hydroxyzine	0.510 (0.250–1.043)	.065
Haloperidol	0.848 (0.508–1.416)	.528
Ramelteon	1.197 (0.793–1.806)	.392
Suvorexant	0.491 (0.277–0.870)	.015

[a]Ignoring the instability of the Cox model, we included all delirium-relevant covariates in this model. Suvorexant and trazodone increased the probability of delirium-free survival in the fully (over)-adjusted Cox model.
Abbreviations: APACHE II = modified Acute Physiology and Chronic Health Evaluation scoring system, BMI = body mass index, IV = intravenous, SOFA = Sepsis-related Organ Failure Assessment.

Our results are consistent with those of previous randomized controlled trials (RCTs) showing a preventive effect of suvorexant for delirium in critically ill patients. Previously, Hatta et al[9] and Azuma et al[10] reported the efficacy of suvorexant for preventing delirium (36 suvorexant users vs 36 nonusers in intensive or acute care units, and 34 vs 36 in the ICU, respectively). Our results take the previous findings from experimental trial settings and expand our knowledge to include real-world settings. In previous RCTs, patients had to give informed consent, and sedated or comatose patients were therefore excluded. To overcome this bias from RCTs, our study examined consecutive patients. Consequently, we examined patients who were treated in routine daily clinical practice. Previous retrospective observational studies have also examined postoperative patients. For example, Booka et al[23] and Kawada et al[24] examined the effectiveness of a combination of ramelteon and suvorexant for postoperative delirium prevention. However, our study separated the effects of suvorexant from the effects of its combination with

ramelteon. Furthermore, Hatta et al[13] showed that suvorexant users were less likely than nonusers to develop delirium at consultation-liaison psychiatric services. Our findings support this previous result and confirm the effectiveness of suvorexant for delirium prevention in real-world settings. Whereas Tamura et al[25] examined postoperative patients (36 suvorexant users vs 52 nonusers), the present study was not limited to patients who underwent surgery or did not. Similar to our study, Masuyama et al[12] retrospectively analyzed intensive care patients. However, in this previous study, only 8 covariates were examined, including age, duration of mechanical ventilation, alcoholism, hypertension, APACHE II scores, and medication use (propofol, dexmedetomidine, and midazolam), because of the limited number of patients. In contrast, our study included 699 patients; in addition to suvorexant we investigated 21 covariates in the main analysis and 34 covariates in the supplemental analysis, based on previously reported delirium-related factors.[3,18] Thus, the present, relatively large sample of patients might have overcome some of the limitations of these previous studies.

Suvorexant increases slow-wave sleep and rapid eye movement (REM) sleep.[26,27] Previous studies have reported that REM reduction is correlated with delirium occurrence.[28,29] Furthermore, neuroinflammation can also cause delirium,[30] and sleep regulates inflammation through the sympathetic system.[31] However, further studies examining the mechanisms of the delirium-preventing effects of suvorexant are warranted.

The current study revealed no significant delirium-preventing effects of ramelteon or dexmedetomidine. The delirium-preventing effects of ramelteon remain controversial.[32] Similar to those of a previous study,[33] our results support a negative correlation between delirium prevention and ramelteon use. In addition, our results showed no delirium-preventing effect of dexmedetomidine. The effects of dexmedetomidine on delirium have been compared with placebo in just two randomized studies: in patients who underwent non-cardiac surgery[34] and in those with low-dose dexmedetomidine use.[35] Thus, further studies of larger samples in several different settings are needed to ascertain the effects of dexmedetomidine in delirium prevention in real-world settings. In the present study, trazodone showed a delirium-preventing effect. No previous reports have shown a delirium-preventing effect of trazodone; therefore, an RCT to examine the effect of trazodone in delirium prevention should be conducted in the future.

There are a number of limitations to our study, which are summarized in the following 9 points. First, this study was retrospective. We tried to examine possible delirium-related factors according to previous studies; however, unknown covariates might have affected the results. Moreover, there were several covariates that were significantly different between suvorexant users and nonusers, including the existence of chronic kidney disease, coma, hemiplegia, and functional disability. To exclude the effects of these factors, we used fully covariate-adjusted analyses in addition to the main analysis, and the models consistently revealed a delirium-preventing effect of suvorexant. Second, in our study population, patients had a clinical need for suvorexant treatment. Physicians may have prescribed suvorexant for insomnia rather than prescribing it intentionally for delirium prevention. Consequently, suvorexant users in the present study may not completely coincide with patients at high risk of delirium and those who really need delirium prevention. Third, in the present study, all data were collected from medical charts. There may therefore be some information that was mistakenly not registered. For example, there was a shortage of CAM-ICU reports. Approximately 10% of person-days did not have CAM-ICU data. Consequently, delirium might have been mistakenly not registered. Fourth, we used the CAM-ICU to detect delirium, but assessors and patients were not blinded. Fifth, delirium was scored by bedside nurses using the CAM-ICU. Compared with the detection of delirium by a psychiatrist using the *DSM-5*, the accuracy of delirium detection in the present study may have been compromised. Sixth, we examined patients who were treated in the ICU. However, not all of the patients may have been critically ill. Seventh, in the present study, the effects of the central nervous system agents and antipsychotics that were used were unable to be excluded. Although there have been several reports that antipsychotics are effective for the treatment of delirium, there is no conclusive evidence that antipsychotic use actually prevents delirium occurrence. Furthermore, in the present study, Cox regression analysis showed no significant effects of antipsychotics on delirium prevention. However, the possible effects of antipsychotic use might be a limitation for the interpretation of our results that suvorexant alone can prevent delirium. Furthermore, there is a possibility that the attending physicians prescribed antipsychotics or suvorexant because they thought the patient was delirious, even if the CAM-ICU was negative. Therefore, our results need to be interpreted carefully. Eighth, in the present study population, the numbers of suvorexant users and nonusers were unequal. To increase statistical power, we included as many patients as possible in each group, resulting in unequal numbers of subjects in the two groups. More suvorexant users would strengthen the results. Finally, several antipsychotics or hypnotics were prescribed for only a small number of patients, and we could therefore not examine the effects of these medications on delirium prevention.

CONCLUSIONS

The current study revealed that suvorexant prevents delirium in real-world settings. A large, multicenter study is required to raise the quality of the intensive care system.

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