Addition of Suvorexant to Ramelteon Therapy for Improved Sleep Quality with Reduced Delirium Risk in Acute Stroke Patients

Kei Kawada, MS,* Tsuyoshi Ohta, MD, PhD,† Koudai Tanaka, MS,* Mitsuhiko Miyamura, MS, PhD,‡ and Satoshi Tanaka, BS*

Background and Purpose: Delirium in acute stroke is associated with poor clinical outcome. The purpose of this study was to examine the effect of sleep medications on sleep quality and delirium in acute stroke. *Methods:* In this retrospective cohort study, sleep disturbances, and delirium were investigated in acute stroke patients treated in April 2013-March 2017 who were prescribed ramelteon plus either an alpha-aminobutyric acid receptor (GABAR) agonist or a selective dual orexin receptor antagonist (suvorexant). *Results:* Of the patients included, 104 received a GABAR agonist and 128 received suvorexant in addition to ramelteon. Patient characteristics did not differ significantly between the groups, except for a higher proportion of cerebral infarction in suvorexant group ($P = .033$). Subjective sleep quality was significantly improved in suvorexant group compared to GABAR agonist group (difficulty staying asleep: 6.3% versus 34%, $P < .001$; daytime sleepiness: 33% versus 63%, $P < .001$). Delirium was significantly less frequent in suvorexant group than GABAR agonist group (7.0% versus 31%, $P < .001$). The length of hospital stay was significantly shorter in suvorexant group than in GABAR agonist group (in days, 21 [15-29] versus 25 [18-33]; $P = .019$). Multivariable logistic regression analysis revealed that the addition of suvorexant was significantly associated with a reduced occurrence of delirium (odds ratios .19, 95% confidence interval .085-.43, $P < .001$). *Conclusions:* Addition of suvorexant to ramelteon therapy, rather than a GABA receptor agonist, can improve subjective sleep quality without inducing delirium in acute stroke patients.

Key Words: Delirium—stroke—suvorexant—ramelteon—sleep quality

Introduction

Sleep disturbances are frequently observed in acute stroke patients and are associated with delirium.[1-7] Patients with delirium exhibit increased morbidity and mortality.[8-10] Patients with sleep disturbances are often prescribed sleep medications. However, some sleep medications also increase delirium risk. The melatonin receptor agonist ramelteon has been reported to reduce the occurrence of delirium in elderly acute care patients with sleep disturbances, including acute stroke patients, but some did not exhibit improved sleep quality.[11,12] The purpose of the present study was to investigate if the addition of an alpha-aminobutyric acid receptor (GABAR) agonist, or the selective dual orexin receptor antagonist suvorexant, can improve subjective sleep quality without inducing delirium in acute stroke patients unresponsive to ramelteon alone.

From the *Pharmaceutical Department, Kochi Health Sciences Center, Kochi, Japan; †Department of Neurosurgery, Kochi Health Sciences Center, Kochi, Japan; and ‡Pharmaceutical Department, Kochi Medical Graduate School, Kochi, Japan.

Received July 25, 2018; revision received August 28, 2018; accepted September 14, 2018.

Address correspondence to Tsuyoshi Ohta, MD, PhD, Department of Neurosurgery, Kochi Health Sciences Center, Ike 2125-1, Kochi City, Kochi, Japan. E-mail: tsuyoshi@ya2.so-net.ne.jp

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.09.024

Methods

Patient Selection

This was a retrospective, nonblinded, cohort study involving acute stroke patients treated at a single center between April 2013 and March 2017. Acute stroke was defined as cerebral infarction or hemorrhagic stroke (intracerebral hemorrhage or subarachnoid hemorrhage) diagnosed by stroke specialist physicians within 7 days of onset. Patients with transient ischemic attack were not included in this study.

Acute stroke patients who received ramelteon plus an additional agent within 14 days of admission were included. Patients in a comatose state on admission or who died within 3 days of admission were excluded. The requirement for informed consent was waived because of the retrospective and anonymous nature of this study. The study protocol was approved by the institutional ethics review board of the hospital (identifier: 171005).

Prescription of Sleeping Medications

At our institution, acute stroke patients with sleep disturbances are treated primarily with 8 mg/d ramelteon (Takeda Pharmaceutical Co., Ltd., Osaka, Japan), and subjective sleep quality is evaluated for 3 consecutive days. If no satisfactory improvement is found,[13] the addition of another sleep medication is considered at the physician's discretion. These include either a GABAR agonist (5 mg/d zolpidem [Astellas Pharmaceutical Co., Ltd., Tokyo, Japan] or .25 mg/d brotizolam [Boehringer Ingelheim Japan, Inc., Ltd., Tokyo, Japan]), or 15 mg/d suvorexant (Belsomra, Merck & Co. Inc., Whitehouse Station, New Jersey).

Patient Characteristics and Clinical Outcomes

Patients were divided into 2 groups according to the type of sleep medication added to ramelteon (suvorexant or a GABAR agonist). We compared the following patient characteristics, all considered independent risk factors for delirium,[14-25] between the treatment groups: age,[14,15] sex,[16] body mass index, type of stroke,[15] aphasia,[17] infection,[18] hemodynamic failure,[19] National Institute of Health Stroke Scale score on admission,[18] habitual use of alcohol,[20] frequent use of sleeping medications,[21] regular use of antipsychotics,[22,23] history of dementia,[20] use of opioids and sedative drugs,[15,24] emergency surgical or endovascular interventions,[25,26] and use of artificial respiration.[27] Infection was defined as a fever of more than 38 degrees treated with antibiotics. Hemodynamic failure was defined as hypotension requiring vasopressors to maintain circulatory dynamics.

Subjective sleep quality was evaluated according to established guidelines[13] as difficulty falling and staying asleep, waking too early, poor sleep quality, and daytime sleepiness during study drug administration. Subjective sleep quality was checked by nurses daily at around 6 o'clock AM.

Outcomes and Measurements

The primary outcome measure was an improvement of sleep disturbances during the acute period. Factors related to subjective sleep quality were recorded retrospectively based on nursing observations and hospital records.[11,13] The secondary outcome was the incidence of severe delirium. Delirium was diagnosed according to the Confusion Assessment Method for the Intensive Care Unit.[28] Subsequently, the severity of delirium was classified according to the Richmond Agitation Sedation Scale, and grade 2 or higher was diagnosed as severe.[12,29,30] The frequency of severe delirium was compared between groups (GABAR versus suvorexant). The third outcome was the length of hospital stay, which has been shown to increase with the incidence of delirium.[10,31] The length of hospital stay was measured as days from admission to discharge or hospital transfer.

Statistical Analysis

All statistical analyses were performed using EZR version 1.29 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[32] Fisher's exact test was used to compare categorical variables and Mann-Whitney U-test was employed to compare ratios or ordinal variables. Explanatory variables included in multivariable logistic regression models were limited to those with occurrence (n) in at least one-tenth of cases in the category with the lowest frequency.[33] Variables were chosen a priori on the basis of clinical relevance[34] due to significant P values on univariable analysis, or to exclude confounding factors. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for each variable included in the multivariable model. A P less than .05 was considered statistically significant for all tests. All P values of less than .001 are expressed as P less than .001. Continuous or ordinal variables are presented as median (25%-75% interquartile range).

Results

Patient Selection

During the study period, 1603 patients were assessed for eligibility. Of these, 70 survived less than 72 hours, 655 did not receive any sleep medications during hospitalization, and 646 received only a single sleep medication (507 received ramelteon, 129 a GABAR agonist, and 10 suvorexant). The remaining 232 patients who received ramelteon plus an additional agent (suvorexant or GABAR agonist) were included in the analysis. The patients were divided into 2 groups: 128 patients taking ramelteon plus suvorexant (suvorexant group) and 104 patients taking ramelteon plus a GABAR agonist (GABAR agonist group)

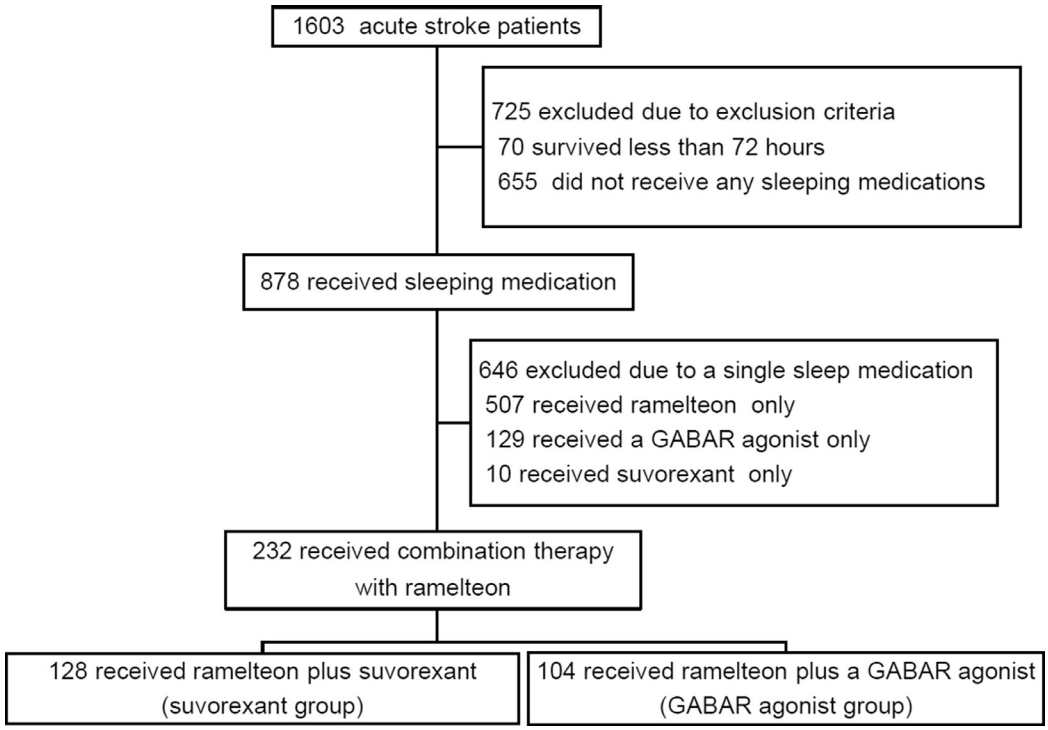

Figure 1. *Trial profile.*

A total of 232 acute stroke patients treated with ramelteon and either suvorexant (n = 128) or a GABAR agonist (n = 104) were included in this study.

Abbreviation: GABAR, alpha-aminobutyric acid receptor.

Fig 1. As shown in Table 1, patient characteristics did not differ significantly between the 2 groups except for a higher proportion of cerebral infarction patients in the suvorexant group ($P = .033$).

Effects on Sleep Disturbances

All examined factors related to subjective sleep quality were significantly improved in the suvorexant group

Table 1. *Demographic and clinical characteristics of suvorexant and GABAR agonist treatment groups*

Characteristic	Suvorexant group (n = 128)	GABAR agonist group (n = 104)	*P*
Age (years), median [IQR]	79.0 [72.0-84.0]	75.5 [67.0-84.0]	.10
Sex, female, n (%)	56 (44)	50 (48)	.60
BMI (kg/m^2), median [IQR]	23.0 [20.0-25.5]	22.8 [20.9-25.7]	.27
Type of stroke, cerebral infarction, n (%)	82 (64)	52 (50)	.033
Aphasia, n (%)	53 (41)	54 (52)	.12
Infection, n (%)	21 (16)	15 (14)	.72
Hemodynamic failure, n (%)	3 (2.3)	2 (1.9)	1
NIHSS on admission, median (IQR)	7 [3−13]	6.5 [3.8-13]	.71
Habitual use of alcohol, n (%)	48 (38)	40 (40)	.68
Regular use of any tranquilizers, n (%)			
Seeping medications	27 (21)	22 (21)	1
Antipsychotics	4 (3.1)	3 (2.9)	1
Dementia, n (%)	10 (7.8)	4 (3.8)	.27
Other prescribed medications, n (%)			
Opioids	19 (15)	16 (16)	1
Sedative drugs	20 (16)	17 (19)	1
Surgical intervention, n (%)	17 (13)	14 (13)	1
Endovascular surgery, n (%)	24 (18.8)	10 (9.6)	.062
Artificial respirator, n (%)	15 (12)	14 (13)	.70

Abbreviations: BMI, body mass index; GABAR, alpha-aminobutyric acid receptor; ICH, intracerebral hemorrhage; IQR, interquartile range; SAH, subarachnoid hemorrhage; NIHSS, National Institute of Health Stroke Scale.

compared to the GABAR agonist group (difficulty staying asleep: 6.3%, 8 of 128 versus 34%, 35 of 104; $P < .001$; daytime sleepiness: 33%, 42 of 128 versus 63%, 66 of 104; $P < .001$; Table 2).

Clinical Outcomes

The proportion of patients showing delirium was significantly lower in the suvorexant group than the GABAR agonist group (7%, 9 of 128 versus 31%, 32 of 104; $P < .001$). Also, the length of hospital stay was significantly shorter in the suvorexant group than the GABAR agonist group (in days, 21 [15-29] versus 25 [18-33]; $P = .019$).

Factors associated with delirium by univariable analyses were aphasia (OR 2.1, 95% CI .99-4.4; $P = .039$), habitual use of alcohol (OR 2.2, 95% CI 1.0-4.7; $P = .03$), and treatment with ramelteon plus suvorexant (OR .17, 95% CI .068-.39; $P < .001$; Table 3). Multivariable logistic regression analysis of delirium was performed for the factors of age, sex, aphasia, habitual use of alcohol, and treatment with ramelteon plus suvorexant. The addition of suvorexant to ramelteon (OR .19, 95% CI .085−.44; $P < .001$) was the sole factor showing a significant and independent association with a reduced occurrence of delirium (Table 4).

Discussion

In this large cohort of acute stroke patients, the addition of suvorexant to ramelteon therapy significantly improved subjective sleep quality compared to the addition of a GABA receptor agonist. Further, the incidence of delirium, a known predictor of higher morbidity and mortality,[8-10] was significantly lower in the suvorexant group compared to the GABAR agonist group despite similar clinicodemographic characteristics, including stroke severity. In this study, there were significantly more number of patients with acute cerebral infarction in the suvorexant group than in the GABAR agonist group. However, stroke severity, as measured using the NIHSS score, did not significantly differ between the groups.

Risk Factors for Delirium

Sleep disturbances are frequently observed in acute stroke patients and are a risk factor for delirium.[1-7] Delirium worsens clinical outcome,[8-10] and acute stroke patients generally exhibit a higher incidence of delirium (10%-66%) than patients admitted to general internal medicine wards (10%-25%).[8,35,36] Many proposed risk factors for delirium, including age,[14,15] sex,[16] primary diseases,[14] symptoms,[17] drug habituations,[20-23] medical history,[20] and invasive treatment,[15,24-27] are unalterable. Sleep disturbances is also a risk factor for delirium,[3,5,7,37] and is affected by the type of sleep medication.[38] Therefore, selection of appropriate sleep medications may reduce the incidence of delirium.[11,12,39]

Sleep Medications

Ramelteon regulates the sleep cycle and improves subjective sleep quality in patients with chronic insomnia.[40] Ramelteon also reduced the occurrence of delirium in elderly acute care patients with sleep disturbances.[11,12] In the current study, 69% of patients (507 of 739) demonstrated improved subjective sleep quality with ramelteon alone. However, ramelteon does not improve the subjective sleep quality of some emergency patients,[11] and the addition of adjunct sleep medications is sometimes required.

GABAR agonists are frequently used for the treatment of insomnia, and short periods of use could improve sleep quality in younger patients with insomnia.[41] However, prolonged use of GABAR agonists is associated with numerous drug class effects, including daytime sedation, ataxia, anterograde memory disturbance, fractures, falls, motor vehicle accidents, and rebound insomnia.[42-44] The use of GABAR agonists is also associated with delirium in older patients, particularly in the acute phase of treatment.[20,38] In the present study, 31% of patients in the GABAR agonist group exhibited delirium, suggesting that GABAR agonists are inappropriate for the treatment of acute stroke patients with sleep disturbances.

Suvorexant is a new type of sleep medication that has no affinity for GABARs,[45,46] and can be safely used for the treatment of insomnia in older adults.[47] Additionally, suvorexant was shown to prevent the occurrence of delirium in emergency patients.[37] This current study suggests that suvorexant can be added to ramelteon for acute stroke patients poorly responsive to ramelteon alone. In the present study, 63% of patients in the GABAR agonist group exhibited daytime sleepiness, higher than in

Table 2. *Comparison of subjective sleep quality between the suvorexant and GABAR agonist groups*

	Suvorexant group (n = 128)	GABAR agonist group (n = 104)	P
Difficulty in falling asleep, n (%)	24 (19)	15 (14)	.38
Difficulty in staying asleep, n (%)	8 (6.3)	35 (34)	< .001
Waking too early, n (%)	1 (.78)	5 (4.8)	.094
Poor sleep quality, n (%)	13 (10)	20 (19)	.06
Daytime sleepiness, n (%)	42 (33)	66 (63)	< .001

Abbreviations: GABAR, alpha-aminobutyric acid receptor.

Table 3. *Univariable analysis of possible factors associated with delirium in acute stroke patients*

Factor	Delirium (n = 41)	No delirium (n = 191)	*P*
Age (years), median [IQR]	74.0 [64.0-84.0]	78.0 [70.0-84.0]	.061
Sex, female, n (%)	15 (37)	91 (48)	.23
BMI (kg/m^2), median [IQR]	22.6 [20.7-25.4]	23.0 [20.3-25.6]	.65
Type of stroke, cerebral infarction, n (%)	23 (56)	111 (58)	.86
Aphasia, n (%)	25 (61)	82 (43)	.039
Infection, n (%)	9 (22)	27 (14)	.24
Hemodynamic failure, n (%)	1 (2.4)	4 (2.1)	1
NIHSS on admission, median [IQR]	8 [4-14]	7 [3-12.5]	.51
Habitual use of alcohol, n (%)	21 (51)	67 (35)	.03
Regular use of any tranquilizers, n (%)			
Sleeping medications	7 (17)	42 (22)	.67
Antipsychotics	2 (4.9)	5 (2.6)	.61
Dementia, n (%)	3 (7.3)	11 (5.8)	.72
Other prescribed medications, n (%)			
Opioids	8 (20)	27 (14)	.47
Sedative drugs	6 (15)	24 (13)	.80
Surgical intervention, n (%)	8 (20)	23 (12)	.21
Endovascular surgery, n (%)	4 (9.8)	30 (16)	.47
Artificial respirator	6 (14)	24 (13)	.19
Treatment with ramelteon and suvorexant	9 (22)	119 (62)	< .001

Abbreviations: BMI, body mass index; ICH, intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; SAH, subarachnoid hemorrhage.

previously published studies (45%-50%).[2,48] In contrast, the frequency of daytime sleepiness in the suvorexant group was lower (33%). Therefore, cotreatment with ramelteon and suvorexant was safe and effective, without inducing daytime sleepiness. Additionally, the addition of suvorexant to ramelteon therapy decreased the incidence of delirium independent of other patient characteristics. The improvement of sleep quality may be responsible for the reduction in delirium because poor sleep quality is a known risk factor for delirium.[5-7,49]

Limitations

The present study has several limitations. Selection bias was inevitable because of the retrospective nature of the study. However, most patient characteristics, including stroke severity, did not differ significantly between groups. Additionally, multivariable logistic regression analysis was performed to determine the relative contributions of different causes to a single event.[50] A second limitation is our institutional prescription policy. In this study, suvorexant or a GABAR agonist was added to ramelteon for sleep disturbances in acute stroke patients. However, the replacement of ramelteon with another drug rather than cotreatment may also be useful. A randomized controlled trial is warranted to compare the efficacy and safety of suvorexant alone to suvorexant plus ramelteon. However, a trial with GABAR agonist alone is not required because GABAR agonist is a known risk factor for delirium.[21,30] Nonetheless, this study demonstrates that suvorexant can be safely coadministered with ramelteon. Finally, although previous reports suggested an association of delirium with more extended hospital stay,[10,31] lengths of hospital stay could be inappropriate for the assessment of outcomes associated with delirium because it is influenced by multiple unrelated factors such as socio-economic background.

Conclusions

Treatment with ramelteon and suvorexant is safe and effective for acute stroke patients with sleep disturbances compared to treatment with ramelteon and GABAR agonist.

Table 4. *Independent factors for reduced delirium incidence according to a multivariable logistic regression model*

	Odds ratio	95% confidence interval	*P*
Ramelteon and suvorexant	.19	.085-.44	< .001*
Age (years)	.98	.94-1.0	.16
Female sex	1.0	.44-2.5	.93
Aphasia	1.8	.81-3.8	.15
Habitual use of alcohol	1.8	.75-4.2	.19

References

1. Koo DL, Nam H, Thomas RJ, et al. Sleep disturbances as a risk factor for stroke. J Stroke 2018;20:12-32.
2. Pasic Z, Smajlovic D, Dostovic Z, et al. Incidence and types of sleep disorders in patients with stroke. Med Arh 2011;65:225-227.
3. Salah S, Rekik M, Boudokhane S, et al. A comparative cross-sectional study of the prevalence of sleep disorders in ischemic stroke patients. Ann Phys Rehabil Med 2016;59S:e77.
4. Siarnik P, Klobucnikova K, Surda P, et al. Excessive daytime sleepiness in acute ischemic stroke: association with restless legs syndrome, diabetes mellitus, obesity, and sleep-disordered breathing. J Clin Sleep Med 2018;14:95-100.
5. Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, et al. Sleep and delirium in ICU patients: a review of mechanisms and manifestations. Intensive Care Med 2009;35:781-795.
6. Weinhouse GL, Schwab RJ, Watson PL, et al. Bench-to-bedside review: delirium in ICU patients—importance of sleep deprivation. Crit Care 2009;13:234.
7. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
8. Shi Q, Presutti R, Selchen D, et al. Delirium in acute stroke: a systematic review and meta-analysis. Stroke 2012;43:645-649.
9. Young J, Inouye SK. Delirium in older people. BMJ 2007;334:842-846.
10. McCusker J, Cole MG, Dendukuri N, et al. Does delirium increase hospital stay? J Am Geriatr Soc 2003;51:1539-1546.
11. Hatta K, Kishi Y, Wada K, et al. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA Psychiatry 2014;71:397-403.
12. Ohta T, Murao K, Miyake K, et al. Melatonin receptor agonists for treating delirium in elderly patients with acute stroke. J Stroke Cerebrovasc Dis 2013;22:1107-1110.
13. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4:487-504.
14. Muangpaisan W, Wongprikron A, Srinonprasert V, et al. Incidence and risk factors of acute delirium in older patients with hip fracture in Siriraj Hospital. J Med Assoc Thai 2015;98:423-430.
15. Sheng AZ, Shen Q, Cordato D, et al. Delirium within three days of stroke in a cohort of elderly patients. J Am Geriatr Soc 2006;54:1192-1198.
16. Oh ES, Sieber FE, Leoutsakos JM, et al. Sex differences in hip fracture surgery: preoperative risk factors for delirium and postoperative outcomes. J Am Geriatr Soc 2016;64:1616-1621.
17. Carin-Levy G, Mead GE, Nicol K, et al. Delirium in acute stroke: screening tools, incidence rates and predictors: a systematic review. J Neurol 2012;259:1590-1599.
18. Oldenbeuving AW, de Kort PL, Jansen BP, et al. Delirium in the acute phase after stroke: incidence, risk factors, and outcome. Neurology 2011;76:993-999.
19. Yang Y, Zhao X, Dong T, et al. Risk factors for postoperative delirium following hip fracture repair in elderly patients: a systematic review and meta-analysis. Aging Clin Exp Res 2017;29:115-126.
20. Kanova M, Sklienka P, Roman K, et al. Incidence and risk factors for delirium development in ICU patients—a prospective observational study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2017;161:187-196.
21. Airagnes G, Pelissolo A, Lavallee M, et al. Benzodiazepine misuse in the elderly: risk factors, consequences, and management. Curr Psychiatry Rep 2016;18:89.
22. Linszen MM, Brouwer RM, Heringa SM, et al. Increased risk of psychosis in patients with hearing impairment: review and meta-analyses. Neurosci Biobehav Rev 2016;62:1-20.
23. Khanra S, Sethy RR, Munda SK, et al. An unusual case of delirium after restarting clozapine. Clin Psychopharmacol Neurosci 2016;14:107-108.
24. Gaudreau JD, Gagnon P, Harel F, et al. Psychoactive medications and risk of delirium in hospitalized cancer patients. J Clin Oncol 2005;23:6712-6718.
25. Raats JW, van Eijsden WA, Crolla RM, et al. Risk factors and outcomes for postoperative delirium after major surgery in elderly patients. PLoS One 2015;10:e0136071.
26. van der Sluis FJ, Buisman PL, Meerdink M, et al. Risk factors for postoperative delirium after colorectal operation. Surgery 2017;161:704-711.
27. Limpawattana P, Panitchote A, Tangvoraphonkchai K, et al. Delirium in critical care: a study of incidence, prevalence, and associated factors in the tertiary care hospital of older Thai adults. Aging Ment Health 2016;20:74-80.
28. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703-2710.
29. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289:2983-2991.
30. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104:21-26.
31. Emond M, Boucher V, Carmichael PH, et al. Incidence of delirium in the Canadian emergency department and its consequences on hospital length of stay: a prospective observational multicentre cohort study. BMJ Open 2018;8:e018190.
32. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-458.
33. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373-1379.
34. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753-1762.
35. Alvarez-Perez FJ, Paiva F. Prevalence and risk factors for delirium in acute stroke patients. A retrospective 5-years clinical series. J Stroke Cerebrovasc Dis 2017;26:567-573.
36. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006;35:350-364.
37. Hermann DM, Bassetti CL. Sleep-related breathing and sleep-wake disturbances in ischemic stroke. Neurology 2009;73:1313-1322.
38. Schroeck JL, Ford J, Conway EL, et al. Review of safety and efficacy of sleep medicines in older adults. Clin Ther 2016;38:2340-2372.
39. Hatta K, Kishi Y, Wada K, et al. Preventive effects of suvorexant on delirium: a randomized placebo-controlled trial. J Clin Psychiatry 2017.

40. Liu J, Wang LN. Ramelteon in the treatment of chronic insomnia: systematic review and meta-analysis. Int J Clin Pract 2012;66:867-873.
41. Glass J, Lanctot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005;331:1169.
42. Kamel NS, Gammack JK. Insomnia in the elderly: cause, approach, and treatment. Am J Med 2006;119:463-469.
43. Winkelman JW. CLINICAL PRACTICE. Insomnia disorder. N Engl J Med 2015;373:1437-1444.
44. Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. Pharmacotherapy 2007;27:89-110.
45. Winrow CJ, Renger JJ. Discovery and development of orexin receptor antagonists as therapeutics for insomnia. Br J Pharmacol 2014;171:283-293.
46. Winrow CJ, Gotter AL, Cox CD, et al. Promotion of sleep by suvorexant-a novel dual orexin receptor antagonist. J Neurogenet 2011;25:52-61.
47. Tampi RR, Manikkara G, Balachandran S, et al. Suvorexant for insomnia in older adults: a perspective review. Drugs Context 2018;7:212517.
48. Medeiros CA, de Bruin PF, Paiva TR, et al. Clinical outcome after acute ischaemic stroke: the influence of restless legs syndrome. Eur J Neurol 2011;18:144-149.
49. Van Rompaey B, Elseviers MM, Van Drom W, et al. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. Crit Care 2012;16:R73.
50. Katz MH. Multivariable analysis a practical guide for clinicians and public health researchers. Cambridge: Cambridge University Press; 2011.