Author/s:
Wong, C;Ho, J;Ankravs, MJ;Sharrock, L;Kee, K;Goldin, J;MacIsaac, C;Presneill, JJ;Ali Abdelhamid, Y;Deane, AM

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Administration of pharmacological sleep aids prior to, during and following critical illness.

Authors (in order)

Dr. Cliff Wong

Qualifications:

M.D.

Affiliations:

1. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia

Contribution:

i) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
ii) Drafting the work or revising it critically for important intellectual content
iii) Final approval of the version to be published
iv) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Jankin Ho

Qualifications:

M.B.B.S. (Hons), B.Pharm (Hons)

Affiliations:

1. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia

Contribution:

i) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

Ms. Melissa J. Ankravs

Qualifications:

B.Pharm, GradCertPharmPrac, M.ClinPharm, M.S.H.P.

Affiliations:

1. The University of Melbourne, Melbourne Medical School, Department of Medicine and Radiology, Royal Melbourne Hospital, Parkville, Victoria.

2. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria.

3. Pharmacy Department, Royal Melbourne

Contribution:

i) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

Ms. Lucy Sharrock

Qualifications:

B.Pharm (Hons), M.H.A.

Affiliations:

1. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria.

2. Pharmacy Department, Royal Melbourne Hospital, Parkville, Victoria.

Contribution:

i) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

Dr. Kirk Kee

Qualifications:

M.B.B.S., F.R.A.C.P.

Affiliations:

1. Department of Respiratory and Sleep Medicine, Royal Melbourne Hospital, Parkville, Victoria.

Contribution:

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

A/Prof. Jeremy Goldin

Qualifications:

M.B.B.S., F.R.A.C.P.

Affiliations:

1. Department of Respiratory and Sleep Medicine, Royal Melbourne Hospital, Parkville, Victoria.

2. The University of Melbourne, Melbourne Medical School, Department of Medicine and Radiology, Royal Melbourne Hospital, Parkville, Victoria.

Contribution:

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

A/Prof. Christopher MacIsaac

Qualifications:

M.B.B.S.(Hons), F.R.A.C.P., F.C.I.C.M., Ph.D.

Affiliations:

1. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria.

2. The University of Melbourne, Melbourne Medical School, Department of Medicine and Radiology, Royal Melbourne Hospital, Parkville, Victoria.

Contribution:

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

A/Prof. Jeffrey J. Presneill

Qualifications:

M.B.B.S., Ph.D., M.Biostat, F.R.A.C.P., F.C.I.C.M.

Affiliations:

1. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria.

2. Department of Medicine, University of Melbourne, Parkville, Victoria.

Contribution:

i) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

Dr. Yasmine Ali Abdelhamid

Qualifications:

M.B.B.S., F.R.A.C.P., F.C.I.C.M.

Affiliations:

1. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria.

2. Centre for Integrated Critical Care, University of Melbourne, Parkville, Victoria.

Contribution:

i) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

A/Prof. Adam M. Deane

Qualifications:

M.B.B.S., Ph.D., F.R.A.C.P., F.C.I.C.M.

Affiliations:

1. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria.

2. The University of Melbourne, Melbourne Medical School, Department of Critical Care, Parkville, Victoria.

Contribution:

i) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

ii) Drafting the work or revising it critically for important intellectual content

iii) Final approval of the version to be published

iv) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Institution and department in which work was performed

Department of Intensive Care, Royal Melbourne Hospital, Parkville, Victoria.

Corresponding author

Cliff Wong

Department of Intensive Care, Royal Melbourne Hospital

300 Grattan St, Parkville, Victoria, Australia

T: (+61)412078081

E: cwongnt@gmail.com

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INTRODUCTION

Sleep is an important physiologic process and sleep deprivation can lead to adverse outcomes[1]. Sleep deprivation and its detrimental effect on recovery from critical illness has gained increasing attention as patients in ICU are known to experience poor sleep,

characterised by frequent disruptions, loss of circadian rhythms, and a paucity of time spent in restorative sleep stages[2,3].

Sleep aids can be categorised as non-pharmacological[4,5] or pharmacological[6,7]. While sleep deprivation impairs recovery, recent international Clinical Practice Guidelines do not make any recommendations about the administration of pharmacological sleep aids or what class of drug, if any, is preferred during critical illness due to a lack of evidence and potential adverse effects[8]. Moreover, the use of pharmacological sleep aids may diminish the periods of restorative phases of sleep[9].

Given the importance of sleep, that sleep deprivation occurs frequently in the critically ill, and the lack of recommendations about pharmacological sleep aid prescription, the objective of this study was to determine drug prescribing patterns for critically ill patients, prior to hospitalisation, throughout ICU admission and following ICU discharge. We hypothesized that pharmacological sleep aids would be infrequently prescribed in ICU but, once commenced, drug administration would continue for extended periods including the post-ICU setting.

METHODS

We conducted a single-centre period prevalence study between 24 June and 21 September 2019. The university-associated adult medical-surgical ICU supports a state trauma centre, and accepts approximately 2,900 admissions per year accommodated in 32 individual rooms. Morning and afternoon medical ward rounds each day are conducted by a consultant intensivist with senior critical care nurses who routinely cluster nocturnal care to minimise disruptions to sleep by reducing nocturnal noise and light to encourage usual circadian

patterns[10]. Clinical pharmacists also participate in the ICU morning rounds each weekday. The Melbourne Health Human Research Ethics Committee assessed the study as meeting the criteria for a Quality Assurance project (QA number 2019097) and the need for informed consent was waived.

Patient Selection

All patients admitted to the ICU of the Royal Melbourne Hospital for more than two nights between 24 June and 21 September 2019 were eligible. Exclusion criteria were age less than 18 years and patients admitted for consideration of organ donation or palliative care during the study period. We defined a night as being present in the ICU at 0000hrs.

For patients with two or more admissions to ICU during the study period, only the index ICU admission was used.

Study Procedure

Suitable patients were identified via daily screening rounds with subsequent cross checking and confirmation using the locally held Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD)[11]. Data extracted from the ANZICS APD included demographics (age and sex), ICU length of stay, baseline chronic health evaluation as defined by the Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores and requirement of specific ICU interventions (i.e. invasive ventilation, inotropic support, renal replacement therapy or tracheostomy).

We manually reviewed ICU and hospital discharge summaries and linked data to International Classification of Diseases (ICD-10) coding summaries for documentation of a

history of psychiatric illness (defined as any of schizophrenia/schizoaffective disorder, bipolar disorder, depression, anxiety or related conditions, personality disorders, eating disorders or a history of substance abuse); a history of cognitive impairment/intellectual disability/dementia; or a history of insomnia or other sleep orders (e.g. restless leg syndrome, narcolepsy, obstructive sleep apnoea).

Two authors who are hospital pharmacists (MA or LS) determined each patient's pharmacological sleep aid use prior to hospital admission. This process involved obtaining a medication history from the patient, the patient's carer or medical treatment decision maker or a current medication chart if the patient was a resident of a Residential Care Facility. This information was then cross-referenced with at least one other source, such as the local pharmacy's dispensing record, the patient's local doctor, any recent hospital discharge prescriptions, or the patient's medication supply if available. Medications such as benzodiazepines and Z-class hypnotics (i.e. zopiclone and zolpidem) were also crosschecked against a state-wide centralised database (Safescript, Victorian Government Department of Health and Human Services).

Pharmacological sleep aids administered during the inpatient stay were identified by a manual search of all ICU and general hospital medication charts for each patient, extracting the type, dosage and frequency of sleep aids received by patients. Frequency was classified as one of three categories: regular (administered at a set time each night), as required (administered by nursing or medical staff when indications were met), or once only. For each sleep aid, dosage was recorded as Maximum Daily Dose (MDD), defined as the highest total dose received by a patient in a single day.

Patients were nursed in a 1:1 ratio for ICU-level care and 1:2 for high dependency unit (HDU)-level care. All patients were assessed at least once a nursing shift for delirium using the Confusion Assessment Method for the ICU (CAM-ICU)[12].

Definition of a pharmacological sleep aid

Because drugs may be prescribed for indications other than promoting sleep (e.g. anxiety, alcohol withdrawal or to prevent delirium)[13], we prospectively developed a criteria to define a pharmacological sleep aid. Drugs were identified as pharmacological sleep aids if they were: (i) melatonin; or (ii) Z-class hypnotics (e.g. zopiclone or zolpidem). Drugs belonging to four other groups were also classified as sleep aids when only administration for that 24-hour period occurred between 2000-0600hrs. These comprised (iii) benzodiazepines (e.g. temazepam or diazepam); (iv) sedating antihistamines (e.g. diphenhydramine or doxylamine), (v) clonidine and (vi) atypical antipsychotics (e.g. quetiapine or olanzapine).

Outcomes

Major outcomes of interest were the proportion of patients who had a pharmacological sleep aid administered in ICU and the proportion of prescribed sleep aids that were initiated in ICU.

Outcomes of secondary interest were class, dosage, frequency and duration of sleep aid therapy in ICU. Sleep aid use in the ICU was compared to that in the community and in patients recovering from critical illness in the hospital wards. Persistent prescription of pharmacological sleep aids on ICU discharge (defined as the presence of a sleep aid that was administered in ICU on medications charts on the first night post ICU discharge) was also examined.

Data Analysis

Using a binary patient classification according to non-receipt or receipt of pharmacological sleep aids, continuous data were compared using a Mann-Whitney-U test and categorical variables compared using a Chi-square or Fisher exact test, as appropriate. A subsequent multivariate logistic regression model using purposeful selection of variables[14] returned adjusted estimates of associations between selected patient factors and sleep aid prescription in the ICU. The finally applied model included patient sex, patient age (per decile), binary classifications of three other variables (a history of psychiatric illness, prehospital sleep aid use, and CAM-ICU positive status), and quartiles of two variables (the APACHE III score and the ICU length of stay). Age and psychiatric history were included as potential predictors of sleep aid prescription in the community setting[15-17] and also as likely contributing factors to sleep disruption in ICU[2,18]. A positive CAM-ICU assessment was also included to account for the relationship between delirium and sleep aid prescription[19]. Less than ten events-per-variable did not preclude our fitted model, as described[20], and the overall fit of the finally applied model was assessed by the Hosmer-Lemeshow test[14].

All statistical analysis was performed using R (version 4.0.2)[21] with the user interface Rstudio (version 1.3.1056)[22]. Regression models were created using the 'glm' function. Additional packages and functions used include 'DescTools::Cstat'[23] and 'ResourceSelection::hoslem.test'[24].

RESULTS

During the study period there were 726 patient admissions to the ICU of whom 370 met all inclusion criteria and none of the exclusion criteria. Among these were 340 ICU survivors

(8.1% ICU mortality), of whom 292 patients remained in the same hospital to receive post-ICU ward-based care, thus forming the post-ICU ward patient cohort (Figure 1).

Pre-hospital pharmacological sleep aids

Baseline patient characteristics are summarised in Table 1. Other than obstructive sleep apnoea, premorbid sleep disturbances were rare but pharmacological sleep aids were prescribed not uncommonly prior to hospitalization (n=34, 9%). Of the 38 separate prescriptions for pharmacological sleep aids in the community, 23 (61%) were prescribed regularly and 15 (39%) prescribed to be taken as required. There was wide variation in the drug class used (Supplemental material, Table S1).

Pharmacological sleep aids administered in ICU

Sixty-two (17%) patients received a pharmacological sleep aid during ICU admission (Table 2). The majority of patients (51/62, 82%) received only one class of drug but 7 (11%) received two classes, 3 (5%) patients received three classes and one patient received four classes of pharmacological sleep aids during their ICU admission. Patients who received two or more drugs usually only received one drug on any given night (79/113 nights of sleep aid administered). Of those receiving more than one drug, 81% (9/11) were receiving melatonin as one of the agents.

Pharmacological sleep aids were most frequently administered as a single once only dose (Figure 2). Regular dosing was more common than taken as required (Figure 2). The duration of prescription of all sleep aids in ICU is presented in Figure 3; with the majority administered for one or two nights (58/78 – 74% of all sleep aid prescribed) with a median duration of 1 night. The longest duration of treatment with melatonin was 39 nights and the

longest duration of treatment with temazepam was 15 nights. Seven patients (11%) received sleep aids for 5 or more nights during their ICU admission. Of the 11 individual sleep aids prescribed for 5 or more nights, 81% (9/11) were initiated in ICU.

Patient and admission characteristics associated with sleep aid use in ICU.

The applied multivariate logistic model returned strong evidence of an independent association between prehospital sleep aid use and sleep aid use in ICU (adjusted OR: 6.2, 95% CI: 2.5-15). There was also evidence to support independent associations between sleep aid use in ICU and male sex, longer duration of ICU admission and higher APACHE III scores (Table 3). While a positive CAM-ICU score was associated with sleep aid prescription in univariate analysis, the apparent strength of that association decreased after adjustment for the influence of other variables included in the model (Table 3). Of the 30 patients receiving a sleep aid and scoring positive on CAM-ICU assessment during their ICU admission, the first pharmacological sleep aid was administered prior to a positive CAM-ICU in 12 patients and after in 18 patients.

Persistence of pharmacological sleep aids prescription on ICU discharge.

Of the 292 (79%) patients who were able to be followed through their post-ICU hospital ward care (Figure 1), 25 (9%) patients were discharged from ICU with an order for a pharmacological sleep aid. Thirteen (4%) patients continued to be charted melatonin as monotherapy, 6 (2%) patients received nocturnal antipsychotic monotherapy, 4 (1%) patients received temazepam monotherapy and one patient was charted zopiclone as monotherapy. One patient received combination therapy with melatonin and temazepam (Supplemental material, Table S2). Of the 26 separate sleep aids prescribed on ICU discharge, 65% (17/26) were initiated in ICU.

Pharmacological sleep aids administered in the ward after discharge from ICU.

After ICU discharge to the ward 96/292 (33%) of patients received a sleep aid at some time during their ward admission. Of patients receiving pharmacological sleep aid on the ward, 35 received melatonin monotherapy, 17 temazepam monotherapy, 6 benzodiazepine monotherapy that was not temazepam (i.e. diazepam, lorazepam or clonazepam) and 24 patients received combination therapy. Of patients receiving combination therapy, 96% (23/24) were receiving melatonin, with the most popular combination being melatonin and temazepam. Of the 121 separate prescriptions for pharmacological sleep aids on the ward only 31 (25%) were also prescribed during the patient's ICU stay (Supplementary Material, Table S3).

Pharmacological sleep aids on hospital discharge

One hundred and thirty-eight (37%) patients were discharged directly home following hospital admission, with the majority transferred to another acute hospital or in-patient rehabilitation facility (193, 52%) and a small proportion not surviving to hospital discharge (39, 11%). Of those discharged home, 14/138 (10%) were prescribed a sleep aid (Table S4) with 9 prescribed to a patient who was not previously receiving a pharmacological sleep aid before hospital admission.

DISCUSSION

To our knowledge there are limited studies regarding the prevalence of sleep aid prescription for patients who are in an ICU. At our centre we observed that patients in ICU frequently (17%) received a pharmacological sleep aid. However, the majority of patients received no

more than two nights of treatment, which likely reflects a conservative approach to prolonged administration of pharmacological sleep aids, particularly given that the prevalence of poor sleep in the intensive care unit has been reported to be as high as 70% of patients[25]. We also observed no robust relationships between administration of pharmacological sleep aids in the ICU and adverse patient-centred outcomes such as delirium.

The most frequently prescribed pharmacological sleep aids in ICU were melatonin and temazepam but a number of other drug classes were used. The variation in classes and dosage of prescribed pharmacological sleep aids probably reflects the inadequate evidence base to inform clinicians. There are at least three published, small, single-centre, randomised clinical trials (n=32, n=24 and n=8) that compare the effects of melatonin and placebo administration in the ICU on sleep outcomes[7,26,27] with other trials ongoing[28]. Given the lack of evidence or recommendations from clinical practice guidelines it is, perhaps, not surprising that there was such variation in practice.

We observed that administration of pharmacological sleep aids increased substantially after ICU discharge to the hospital ward. The markedly lower sleep aid use in ICU relative to post-ICU discharge is likely strongly influenced by the severity of illness for many patients during their acute phase of ICU care, and the very common use of intravenous sedation for mechanical ventilator support in ICU. It is also possible that sleep disturbances occurring associated with critical illness and the ICU environment may contribute to a pattern of poor sleep that persists after discharge in ICU survivors[29-32]. Factors such as shared rooms on hospital wards may also increase noise, exacerbating sleep fragmentation[33,34].

Limitations

Important limitations of data derived from this investigation include the uncontrolled nature of the sleep aid therapy recorded within this single centre observational study. In particular the evidence of associations between more severe illness and longer ICU admissions and the receipt of a sleep aid in ICU are likely to be confounded by the influence of ICU mortality (survivor bias) and the widespread use of intravenous sedation for mechanically-ventilated patients. Patients with higher severity of illness scores have both an elevated risk of the occurrence of mechanical ventilation and ICU mortality relatively soon after ICU admission, before sleep aids are usually prescribed, while survivors of acute severe illness may be more likely to require protracted ICU care during the latter part of which sleep aid prescription may be more common. Similarly, those patients admitted to ICU with relatively low severity of illness may be more likely to be discharged to hospital wards relatively soon after ICU admission before insomnia becomes a clinical problem. Other potential limitations include the simple definitions of pharmacological sleep aids used in this study. Our definition of a pharmacological sleep aid was based on our anecdotal experience that some clinicians occasionally prescribe drugs such as antihistamines, clonidine and atypical antipsychotics at night for multiple indications including an added benefit of drowsiness or increasing sleep. While we established this definition prior to study commencement, it should be recognised that such drugs are more likely to be administered for an alternative indication that is unrelated to sleep. Moreover, this definition of a pharmacological sleep aid may not have been exhaustive, as some drugs, e.g. tricyclic antidepressants (amitriptyline) and gabapentinoids (gabapentin and pregabalin), were not included in our definition and a side-effect of these drugs may include drowsiness and sleep.

Future directions

Our observations that new pharmacological sleep aids are not uncommonly prescribed in the ICU, with widespread variation as to class and dose of drug administered, suggest controlled trials of the effect of pharmacological sleep aids on sleep quality and quantity are merited. Furthermore, given the increase in administration of pharmacological sleep aids after ICU discharge, studies utilising objective measures of sleep during recovery from critical illness are warranted.

CONCLUSIONS

This single centre observational study found treatment with a pharmacological sleep aid was relatively common at some point in the ICU stay of adult patients, and that such treatment was more common if there was a history of pre-ICU sleep aid medication use. The most commonly used drugs were melatonin or temazepam. In ICU survivors, short term pharmacological sleep aid prescription on the hospital ward exceeded the frequency of their prescription in ICU.

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Figure 1. Patient Inclusion

Figure 2. Frequency of Sleep Aid Administration in ICU

Figure 2. Frequency of Sleep Aid Administration in ICU. Combination refers to a combination of administration regimens (e.g. a medication that was initially prescribed at a once only regimen which was then increased to regular administration).

Figure 3. Duration of Pharmacological Sleep Aid Therapy in the ICU

Figure 3. Duration of Pharmacological Sleep Aid Therapy in the ICU.

Table 1. ICU Patient Characteristics

Table 1. ICU Patient characteristics	Total (N=370)	Sleep aids (n=62)	No sleep aids (n=308)	p-value
Baseline Demographics				
Age, year	63.8 [48.8-72.6]	63.4 [51.0-70.1]	63.9 [48.4-73.5]	0.56
Sex				0.02*
Female	151 (40.8)	16 (25.8)	135 (43.8)	
Male	219 (59.2)	46 (74.2)	173 (56.2)	
Coexisting illness				
Comorbidity†	130 (35.1)	31 (50.0)	99 (32.1)	0.01*
Diabetes	90 (24.3)	19 (30.6)	71 (23.1)	0.27
Chronic Respiratory Disease	5 (1.4)	2 (3.2)	3 (1.0)	0.20
Chronic Renal Disease	4 (1.1)	1 (1.6)	3 (1.0)	0.52
Immune Disease	24 (6.5)	7 (11.3)	17 (5.5)	0.10
Immunosuppression	29 (7.8)	11 (17.7)	18 (5.8)	<0.01*
Hepatic Failure/Cirrhosis	10 (2.7)	3 (4.8)	7 (2.3)	0.48
Lymphoma/Leukaemia	17 (4.6)	6 (9.7)	11 (3.6)	0.08
Metastatic Cancer	5 (1.4)	0	5 (1.6)	0.59
Cognitive Impairment‡	18 (4.9)	3 (4.8)	15 (4.9)	1
Psychiatric Illness	93 (25.1)	20 (32.3)	73 (23.7)	0.21
Schizophrenia/Schizoaffective	9 (2.4)	2 (3.2)	7 (2.3)	1
Depression	48 (13.0)	8 (12.9)	40 (13.0)	1
Anxiety	22 (5.9)	2 (3.2)	20 (6.5)	0.55
Substance Misuse	43 (11.6)	11 (17.7)	32 (10.4)	0.13
Sleep Disorder				
Obstructive sleep apnoea	14 (3.8)	1 (1.6)	13 (4.2)	0.48
Insomnia	1 (0.3)	1 (1.6)	0	0.17
Restless leg syndrome	1 (0.3)	1 (1.6)	0	0.17
Narcolepsy	0	0	0	-
Parasomnia	0	0	0	-
Prehospital Sleep Aid Use	34 (9.2)	15 (24.2)	19 (6.2)	<0.01*
Severity of illness score				
Apache II Score	16 [12-21]	19.5 [13-25]	16 [12-21]	<0.01*
Apache III Score	60 [45-76]	69.5 [55-86.7]	59.5 [44-74]	<0.01*
ICU interventions				
Intubated in first 24 hours	225 (60.8)	36 (58.1)	189 (61.4)	0.73
Intubated during ICU stay	231 (62.4)	41 (66.1)	190 (61.7)	0.61
Inotropes	266 (71.9)	48 (77.4)	218 (70.8)	0.36
Renal Replacement Therapy	24 (6.5)	9 (14.5)	15 (4.9)	0.01*
Tracheostomy	12 (3.2)	5 (8.1)	7 (2.3)	0.04*
ICU outcomes				
ICU length of stay (days)	3.2 [2.1-5.1]	5.4 [2.9-8.6]	3.0 [2.1-4.5]	<0.01*
CAM-ICU positive	118 (31.9)	30 (48.4)	88 (28.6)	<0.01*

† Any of the chronic health diseases defined in the APACHE scoring systems.
‡ Mild Cognitive Impairment, Dementia or Intellectual Disability.
* p-value<0.05

Data are median [25th-75th percentile] or n (%) unless indicated. P-values were calculated by Mann-Whitney U test, Chi-square test or Fisher's exact test, as appropriate. CAM-ICU = Confusion Assessment Method for the Intensive Care Unit, ICU = Intensive Care Unit

Table 2. Count of patients prescribed sleep aids in ICU (N=370)

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Drug	Total Count (n/370, %)	Initiated in ICU, n	MDD, mg (Count)
Melatonin	25 (6.8)	21	2 (14) 4 (9) 6 (1) 8 (1)
Temazepam	23 (6.2)	20	10 (19) 20 (3) 30 (1)
Any antipsychotic	18 (4.9)	14	-
Quetiapine	11 (3.0)	11	12.5 (5) 25 (2) 50 (3) 75 (1)
Olanzapine	5 (1.4)	3	2.5 (2) 5 (2) 10 (1)
Risperidone	2 (0.5)	0	1 (1) 1.5 (1)
Diazepam	9 (2.4)	9	2.5 (1) 5 (6) 10 (2)
Lorazepam	2 (0.5)	1	1 (1) 2.5 (1)
Zopiclone	1 (0.3)	0	15 (1)

MDD = Maximum daily dose

Table 3. Factors associated with sleep aid prescription in ICU

Table 3. Factors associated with sleep aid prescription in ICU				
	Univariate OR (95%CI)	p-value	Multivariate OR†,‡,§ (95%CI)	p-value
Age (per 10-year increase)	0.98 (0.84-1.1)	0.78	0.96 (0.79-1.2)	0.65
Male sex (vs female)	2.2 (1.2-4.3)	0.01*	2.2 (1.2-4.5)	0.02*
Psychiatric History* (vs not present)	1.5 (0.83-2.8)	0.16	1.0 (0.48-2.1)	0.98
Prehospital Sleep Aid Use (vs no pre-hospital sleep aid)	4.9 (2.3-10)	<0.01*	6.2 (2.5-15)	<0.01*
CAM-ICU positive (vs not present)	2.3 (1.3-4.1)	<0.01*	1.5 (0.76-2.9)	0.24
APACHE III score				
≤45	Reference	-	Reference	-
46-60	2.0 (0.80-5.2)	0.15	1.9 (0.69-5.5)	0.22
61-75	2.3 (0.99-6.2)	0.06	1.7 (0.60-5.0)	0.33
≥76	3.7 (1.6-9.2)	<0.01*	2.9 (1.1-8.1)	0.04*
ICU LOS, days				
≤2	Reference	-	Reference	-
>2 to ≤3	2.4 (0.81-8.9)	0.14	1.9 (0.59-7.3)	0.31
>3 to ≤5	2.1 (0.68-7.8)	0.22	1.9 (0.57-7.2)	0.33
>5	9.0 (3.4-32)	<0.01*	6.9 (2.3-26)	<0.01*

† adjusted for all other variables in the table
‡ C statistic - Area Under the Receiver Operating Characteristic Curve = 0.79
§ Hosmer and Lemeshow goodness of fit test - P-value = 0.96, Chi-square = 2.44, Degrees of Freedom = 8
* p-value<0.05

APACHE III = Acute Physiology and Chronic Health Evaluation III, CAM-ICU = Confusion Assessment Method for the Intensive Care Unit, ICU = Intensive Care Unit, LOS = Length of stay, OR = Odds Ratio