OPEN

Characterization of Nocturnal Neuroactive Medication Use and Related Sleep Documentation in Critically Ill Adults

Arzo Hamidi, PharmD[1]
Russel J. Roberts , PharmD, FCCM[1,2]
Gerald L. Weinhouse, MD, FCCM[3]
Paul M. Szumita, PharmD, FCCM[4]
Jeremy R. Degrado , PharmD[4]
Kevin M. Dube, PharmD[4]
Mary P. Kovacevic, PharmD[4]
Mia Choi, PharmD[5]
Regan Sevinsky, PharmD[1]
Matthew S. Duprey, PharmD, PhD[2]
John W. Devlin, PharmD, MCCM[2–4]

ABSTRACT: We retrospectively characterized scheduled, newly initiated, nocturnal neuroactive medication use, and related clinician documentation, in a cohort of consecutive adults admitted greater than or equal to 24 hours to seven different medical/surgical ICUs at two academic centers who had not received a scheduled nocturnal neuroactive medication prior to admission, over a 5-month period (April 1, 2017, to August 31, 2017). A total of 207 different newly initiated, scheduled nocturnal neuroactive medication orders were written (melatonin agonist 101 [48.8%], antipsychotic 80 [38.6%], antidepressant 17 [8.2%], benzodiazepine 9 [4.3%]) in 189 (9.7%) of the 1,955 patients. Among the 1,553 nights, the 189 patients spent in the ICU, a scheduled nocturnal neuroactive medication was administered on 1,103 (71%), an "as needed" nocturnal neuroactive medication was solely administered on 183 (11.8%), delirium occurred on 736 (47.4%), and nurses were twice as likely as physicians (28.8% vs 11.4%; $p < 0.0001$) to document a note about sleep quality. Among the 69.8% of patients discharged to the floor, and the 64.5% from the hospital, the scheduled nocturnal neuroactive medication was continued in 85.6% and 87.3%, respectively. Scheduled nocturnal neuroactive medication initiation is common, often continued beyond hospital discharge, and poorly documented.

KEY WORDS: antipsychotics; delirium; intensive care; melatonin; ramelteon; sleep

To the Editor:

Sleep is frequently disrupted during critical illness; poor sleep is a common source of distress for patients (1). Delirium is also prevalent in the ICU and has been postulated to be both a cause and sequelae of disrupted sleep, although the inter-relationship between the two remains poorly researched (1–3). Polypharmacy is a common sequelae of ICU admissions and is associated with increased adverse events and costs (4). Patients frequently ask for sleep-enhancing medications and ICU providers report they commonly prescribe them (5). Best-evidence and practice guidelines do not support the routine, scheduled use of any nocturnal neuroactive medication (NNM) to initiate, maintain, or improve sleep (1, 6–10). It is suspected these medications (e.g., antipsychotics, melatonin agonists, and antidepressants) are often continued after hospital discharge. While protocolized delirium assessment efforts are established at many centers (11), it is suspected sleep quality is not routinely documented by the ICU care team when medications to improve it are prescribed (1). We therefore sought to characterize newly initiated, scheduled,

DOI: 10.1097/CCE.0000000000000367

NNM use both during and after the ICU admission at two academic medical centers and evaluate ICU nurse and physician documentation regarding sleep quality in the context of NNM use.

MATERIALS AND METHODS

We retrospectively characterized scheduled, newly initiated NNM use (only administered between 18:00 and 02:00 hr) and related clinician documentation in a cohort of consecutive adults admitted greater than or equal to 24 hours to seven different medical/surgical ICUs at two academic centers (the 1,035-bed Massachusetts General Hospital and the 793-bed Brigham and Women's Hospital), over a 5-month period (April 1, 2017, to August 31, 2017). All data were extracted from the Mass General Brigham (MGB) Epic (Verona, WI) electronic health record (EHR) by trained research personnel. The study was approved by the MGB Institutional Review Board (Number 2017P002269/PHS). At the time of the study, each ICU had implemented the ICU Liberation bundle (11); none had implemented a formal sleep improvement protocol (12). Twice daily delirium screening by bedside nurses using the Confusion Assessment Method for the ICU was well-established (13).

The NNMs evaluated (i.e., antidepressants, antihistamines, antipsychotics, benzodiazepines, melatonin agonists, and nonbenzodiazepine hypnotics) are the medications ICU physicians most frequently report using to improve sleep (5). Data on "as needed" NNM use was also collected. The proportion of patients discharged to the floor (and from the hospital) on a scheduled NNM was also recorded. On nights a scheduled NNM was administered, all primary ICU physician and bedside nurse EHR documentation regarding sleep quality that night (or the following day) was recorded. Statistical analyses were conducted using SPSS Version 22.0 (IBM, Armonk, NY).

RESULTS

A total of 207 different new, scheduled NNM orders were written (melatonin agonist 101 [48.8%], antipsychotic 80 [38.6%], antidepressant 17 [8.2%], and benzodiazepine 9 [4.3%]) for 189 (9.7%) of the 1,955 evaluated patients. No patient was prescribed a scheduled antihistamine or nonbenzodiazepine hypnotic at night. The 189 patients were 63 ± 16.1 years old, mostly male (62.4%), and half surgical (57.1%). A history of obstructive sleep apnea (6.3%) or insomnia (3.7%) was rare. Half (56.9%) were mechanically ventilated for greater than or equal to 1 day, 52.9% had delirium on greater than or equal to 1 ICU day, and 12.7% died in the ICU.

The 189 patients received at least one newly initiated, scheduled NNM on 71.0% (1,103/1,553) of the nights they spent in the ICU. Among the NNM orders, the median (interquartile range) time from ICU admission to first initiation was 4 days (2–7 d) (**Table 1**). The average first-prescribed nocturnal dose for quetiapine, melatonin, and ramelteon was 44.3 ± 44.8 mg, 5.5 ± 3.1 mg, and 8.9 ± 2.0 mg, respectively. Delirium occurred on 736 (47.4%) ICU nights. Use of a scheduled antipsychotic was more likely on a delirium night ($p < 0.0001$); use of a scheduled melatonin agonist ($p < 0.0001$) or antidepressant ($p < 0.0001$) was more likely on a delirium-free night. The characteristics of newly initiated "as needed" NNM use in the ICU are presented in **Table 2**. Of the 132 patients (69.8%) who survived their ICU stay and were transferred to the floor (vs another institution), the newly initiated, scheduled NNM was continued on the first-floor night in 113/132 (85.6%). Of the 126 (95.5%) floor transfer patients who survived to hospital discharge, 110 of 126 (87.3%) were continued on the scheduled NNM (**Table 3**).

On nights a scheduled NNM was administered, nurses (354 [22.8%]) were twice as likely as physicians (177 [11.4%]; $p < 0.0001$) to document a note in the EHR about sleep quality. On nights where sleep was documented, nurses (as compared to physicians) were more likely to document sleep quality as improved (38.2% [135/354] vs 22.6% [40/177]; $p = 0.01$), less likely to document sleep quality as unchanged (42.9% [152/354] vs 58.2% [103/177]; $p = 0.05$), and just as likely to document sleep quality as worse (18.9% [152/354] vs 19.2% [34/177]; $p = 0.52$). On ICU night (days) where the nurse documented a note in EHR regarding sleep quality, and either an antipsychotic or melatonin agonist was administered, nurses and physicians were each more likely to document sleep as being improved (vs not improved or worse) when a melatonin agonist (vs an antipsychotic) was administered (nurses 48.6% vs 26.6% [$p = 0.01$]; physicians 30.7% vs 10.8% [$p = 0.02$]).

DISCUSSION

Our study, the first published, large-scale, evaluation of newly initiated, scheduled NNM use in critically ill adults has a number of key findings: 1) Nearly 10% of critically

TABLE 1.
Characterization of Time to Scheduled Nocturnal Neuroactive Medication Initiation and Comparison of ICU Nights Spent With and Without Delirium

NNM Medication	Time From ICU Admission to Initiation (d)[a]	Average Dose on the First ICU Night the NNM Was Initiated (mg)	Proportion of ICU Nights ($n = 1,553$) the NNM Was Administered, *n* (%)	Delirium Present on a Night a Scheduled NNM Was Administered		
				Yes, $n = 736$, Nights, *n* (%)	No, $n = 817$, Nights, *n* (%)	*p*
Any NNM medication	3.8 (2.1–7.1)	Not applicable	1,103 (71.0)	483 (66.0)	620 (75.9)	< 0.0001
Quetiapine	4.5 (2.3–6.8)	44.3 ± 22.4	333 (21.4)	211 (28.9)	122 (14.9)	< 0.0001
Melatonin	2.2 (1.9–4.7)	5.5 ± 2.3	320 (20.6)	103 (14)	217 (26.6)	< 0.0001
Ramelteon	3.0 (1.7–5.9)	8.0 ± 3.2	251 (16.2)	162 (22)	89 (10.9)	< 0.0001
Trazodone	6.0 (2.5–12)	46.2 ± 18.8	86 (5.5)	30 (4.1)	56 (6.9)	0.02
Olanzapine	7.0 (4.0–6.0)	4.3 ± 1.6	21 (1.4)	12 (1.6)	9 (1.1)	0.37
Lorazepam	2.8 (1.9–8.2)	0.7 ± 0.3	28 (1.8)	9 (1.2)	19 (2.3)	0.10
Haloperidol	6.0 (5.0–11.0)	3.1 ± 0.8	42 (2.7)	36 (4.9)	7 (0.9)	< 0.0001
Mirtazapine	4.0 (2.1–12.0)	17.5 ± 6.4	8 (0.5)	4 (0.5)	4 (0.5)	1.0
Clonazepam	4.5 (1.0–8.5)	1.5 ± 0.4	10 (0.6)	8 (1.1)	2 (0.2)	0.12
Midazolam	9.0 (5.5–12.0)	4 ± 1.9	4 (0.3)	2 (0.3)	2 (0.2)	1.0

NNM = nocturnal neuroactive medication.
[a]Presented as median (interquartile range).

TABLE 2.
Characterization of "As Needed" Nocturnal Neuroactive Medication Administration

Medication	ICU Nights the PRN NNM Was Prescribed, *n* (%)	ICU Nights the PRN NNM Was Administered, *n* (%)	ICU Nights the PRN NNM Was Administered With ≥ 1 Scheduled NNM, *n* (%)
Quetiapine	160 (10.3)	70 (4.5)	44 (2.8)
Trazodone	52 (3.3)	30 (1.9)	23 (1.5)
Ramelteon	46 (3.0)	14 (0.9)	4 (0.2)
Haloperidol	45 (2.9)	12 (0.7)	7 (0.4)
Lorazepam	29 (1.9)	25 (1.6)	9 (0.6)
Melatonin	24 (1.5)	8 (0.5)	2 (0.1)
Olanzapine	23 (1.4)	9 (0.6)	4 (0.2)

NNM = nocturnal neuroactive medication.
PRN "as needed."

ill adults were newly initiated on a scheduled NNM; 2) Melatonin agonists (49.3%) and antipsychotics (36.7%) accounted for more than 85% of the scheduled NNM orders; 3) Antipsychotics were more likely to be administered on nights with delirium; melatonin agonists on nights without delirium; 4) scheduled NNM therapy, when newly initiated in the ICU, is frequently continued on the floor and after ICU discharge; and 5) Sleep quality is infrequently documented by either the ICU nurse or physician on days a scheduled NNM is administered.

TABLE 3.
Continuation of Scheduled Newly Initiated Nocturnal Neuroactive Medication Use After ICU and Hospital Discharge

Medication	Scheduled NNM Use on the Last ICU Night, *n* (%)	Scheduled NNM Use on the First-Floor Night, *n* (%)	Floor Continuation Rate (%)	Discharged From Hospital on a Scheduled NNM, *n* (%)	Post-Hospital Continuation Rate (%)
Any NNM	122 (92.4)	115 (87.8)	94.3	110 (87.3)	90.2
Melatonin	46 (34.8)	44 (33.3)	95.6	43 (34.1)	93.5
Ramelteon	31 (23.4)	28 (21.2)	90.3	27 (21.4)	87.1
Quetiapine	29 (21.9)	29 (21.9)	100.0	28 (22.2)	96.6
Trazodone	8 (6.1)	5 (3.8)	62.5	5 (3.9)	62.5
Olanzapine	4 (3.0)	3 (2.3)	75.0	3 (2.7)	75.0
Mirtazapine	2 (1.5)	2 (1.5)	100.0	2 (1.9)	100.0
Clonazepam	1 (0.8)	1 (0.8)	100.0	1 (0.8)	100.0
Haloperidol	1 (0.8)	1 (0.8)	100.0	1 (0.8)	100.0
Lorazepam	1 (0.8)	1 (0.8)	100.0	1 (0.8)	100.0
Midazolam	1 (0.8)	0 (0.8)	0.0	0 (0.0)	0.0

NNM = nocturnal neuroactive medication.

The frequency of newly initiated, scheduled NNM use in the ICU we report is a potential concern given the current paucity of controlled evidence demonstrating the use of a NNM improves sleep or reduces delirium in critically ill adults (1, 6–10). Practice guidelines do not support the routine use of any of the NNMs evaluated in our study (1). Important potential safety concerns exist with ICU NNM use, particularly among older adults and when they are continued after hospital discharge (14). The very low prevalence of nocturnal-only benzodiazepine use we observed is noteworthy and may be a result of high clinician awareness regarding their deliriogenic potential (15) and guidelines advocating against their routine use (1). Nonbenzodiazepine hypnotics like zolpidem were not used in our cohort, as they are not on formulary at MGB Health. The frequent continuation of newly initiated, scheduled NNM's after transfer to the floor or beyond hospital discharge, suggests ICU teams may not be discussing the continued role for these agents during interprofessional rounds. Medication reconciliation efforts regarding NNM use at ICU discharge that consider persistent insomnia, nocturnal wakefulness, or nocturnal delirium-associated agitation are needed.

The low frequency by which sleep quality or quantity was documented in the patient record by physicians or nurses may also be related in part to the current lack of a standard objective or subjective method to evaluate sleep on a routine basis in the ICU (1, 2). Sleep, with its many domains and the current lack of a valid and feasible assessment method, is challenging to evaluate in the ICU setting, particularly in patients who are mechanically ventilated or sedated. Current guidelines do not advocate the routine assessment of sleep in critically ill adults (1).

Our study has important limitations. The retrospective design did not allow us to collect data on the nocturnal symptoms (e.g., insomnia, wakefulness, or agitation) that could drive scheduled NNM initiation or the specific prescribing rationale of the physician. It is therefore impossible to determine whether the NNM prescribing we report was appropriate. Certain baseline conditions including psychiatric comorbidities that could have influenced NNM use were not collected. The use and success of nonpharmacologic sleep improvement/delirium reduction strategies may have influenced NNM use, but a sleep improvement protocol was not in use in any ICU at the time of the study and data on the use of other delirium-reducing efforts was not able to

be collected (1, 12). Although we only included scheduled NNMs administered between 6:00 PM and 2:00 AM period, it is possible that some of these orders were not prescribed with an intent to improve sleep. NNM prescribing practices and ICU clinician documentation may have changed since 2017 and after publication of the Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption guidelines in 2018 (1). Results from a single health system might reflect local care patterns and not be generalizable to other centers.

CONCLUSIONS

Scheduled NNMs (particularly antipsychotics and melatonin agonists) are frequently newly initiated in the ICU, often continued beyond hospital discharge and poorly documented by clinicians. Our results highlight the importance for critical care clinicians to evaluate current NNM prescribing practices at their institution and better document the rationale for why they are being initiated. They also underscore the need for more research regarding the role of medications to improve sleep in critically ill adults.

1 *Department of Pharmacy, Massachusetts General Hospital, Boston, MA*

2 *Department of Pharmacy and Health Systems Sciences, Bouve College of Health Sciences, Northeastern University, Boston, MA*

3 *Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA*

4 *Department of Pharmacy, Brigham and Women's Hospital, Boston, MA*

5 *Department of Pharmacy, Riverside University Health System, Moreno Valley, CA*

This study was supported by departmental funds.

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: jwdevlin@bwh.harvard.edu

REFERENCES

1. Devlin JW, Skrobik Y, Gélinas C, et al: Executive summary: Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018; 46:e825–e873
2. Pisani MA, D'Ambrosio C: Sleep and delirium in adults who are critically ill: A contemporary review. *Chest* 2020; 157:977–984
3. Duprey MS, Devlin JW, Skrobik Y: Is there an association between subjective sleep quality and daily delirium occurrence in critically ill adults? A post hoc analysis of a randomised controlled trial. *BMJ Open Respir Res* 2020; 7:e000576
4. Garpestad E, Devlin JW: Polypharmacy and delirium in critically ill older adults: Recognition and prevention. *Clin Geriatr Med* 2017; 33:189–203
5. Kamdar BB, Knauert MP, Jones SF, et al; Sleep in the ICU (SLEEPii) Task Force: Perceptions and practices regarding sleep in the intensive care unit. A survey of 1,223 critical care providers. *Ann Am Thorac Soc* 2016; 13:1370–1377
6. Zhang Q, Gao F, Zhang S, et al: Prophylactic use of exogenous melatonin and melatonin receptor agonists to improve sleep and delirium in the intensive care units: A systematic review and meta-analysis of randomized controlled trials. *Sleep Breath* 2019; 23:1059–1070
7. Hatta K, Kishi Y, Wada K, et al; DELIRIA-J Group: Preventive effects of ramelteon on delirium: A randomized placebo-controlled trial. *JAMA Psychiatry* 2014; 71:397–403
8. Nishikimi M, Numaguchi A, Takahashi K, et al: Effect of administration of ramelteon, a melatonin receptor agonist, on the duration of stay in the ICU: A single-center randomized placebo-controlled trial. *Crit Care Med* 2018; 46:1099–1105
9. Jaiswal SJ, Vyas AD, Heisel AJ, et al: Ramelteon for prevention of postoperative delirium: A randomized controlled trial in patients undergoing elective pulmonary thromboendarterectomy. *Crit Care Med* 2019; 47:1751–1758
10. Nikooie R, Neufeld KJ, Oh ES, et al: Antipsychotics for treating delirium in hospitalized adults: A systematic review. *Ann Intern Med* 2019; 171:485–495
11. Pun BT, Balas MC, Barnes-Daly MA, et al: Caring for critically ill patients with the ABCDEF bundle: Results of the ICU liberation collaborative in over 15,000 adults. *Crit Care Med* 2019; 47:3–14
12. Andrews JL, Louzon PR, Torres X, et al: Impact of a pharmacist-led intensive care unit sleep improvement protocol on sleep duration and quality. *Ann Pharmacother* 2020 Nov 9. [online ahead of print]
13. Ely EW, Margolin R, Francis J, et al: Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; 29:1370–1379
14. The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel: American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *JAGS* 2019; 54:674–694
15. Zaal IJ, Devlin JW, Hazelbag M, et al: Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med* 2015; 41:2130–2137