Intensive Care Med (2022) 48:479–481
https://doi.org/10.1007/s00134-022-06656-7

EDITORIAL

Melatonin in ICU delirium: shining light on the hormone of darkness

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Delirium represents a form of acute brain dysfunction predictive of excess death and long-term cognitive impairment in critically ill patients [1, 2]. For many years, we have wondered whether pharmacological doses of melatonin would help prevent the onset or mitigate the duration of this calamity in the life of our sickest patients. The data are growing to help us realize answers.

Melatonin is a pleiotropic neurohormone produced by the pineal gland during the hours of darkness [3]. Understanding of the pineal gland and the biological effects of melatonin has evolved from its historical conceptualization as the "tranquilizing organ" and the "seat of the soul" to knowledge of their pivotal role in the regulation of circadian rhythm. Melatonin is synthesized from tryptophan via a sequence of enzymatic reactions. The rate-limiting enzyme is *N*-acetyltransferase (AA-NAT) whose synthesis is promoted by darkness with its activity modulated by the suprachiasmatic nucleus in the hypothalamus. Darkness stimulates the pineal gland to secrete melatonin with peak concentrations of ~ 100 pg/mL between 02:00 and 04:00 h, while strong light suppresses production.

Melatonin works as a hypnotic by accelerating sleep initiation and improving sleep maintenance and efficiency [3]. Unlike other hypnotics, melatonin causes no significant changes in sleep architecture, nor does it have hangover effects or abuse potential, nor has it been associated with delirium. Although sleep–wake cycle disturbances are not a diagnostic criterion for delirium, they are incorporated into delirium assessment tools with studies indicating sleep alterations are present in 75% of delirious patients [4]. Disturbances in the circadian pattern of melatonin secretion have been described in various critically ill populations [4–6]. Advances in our understanding of the association of delirium and devastating outcomes of critically ill patients has prompted the flurry of prevention trials with pharmacological and non-pharmacological interventions and more recently, these include melatonin or melatonin receptor agonists and strategies for sleep (e.g., reducing noise or light) [7].

In this issue of the journal, Wibrow et al. report the results of the large double-blind multicenter randomized Pro-MEDIC trial on the usefulness of prophylactic melatonin for delirium in intensive care unit (ICU) [8]. The study compared melatonin with placebo among 847 patients across 12 Australian ICUs. The primary outcome was the proportion of delirium-free assessments within 14 days or before ICU discharge, as assessed by the Confusion Assessment Method for ICU (CAM-ICU). Secondary outcomes were sleep quality and quantity, delirium and coma-free days, length of stay, mortality, adverse events, and use of rescue therapies for delirium and agitation (e.g., antipsychotics, physical restraint). Patients aged ≥ 18 years with expected ICU stay of ≥ 72 h were randomized to enteral liquid melatonin 4 mg or matched placebo *qHS* until ICU discharge or up to 2 weeks. The authors found no difference between groups in the proportion of delirium-free assessments (melatonin 79.2% vs. placebo 80%, $p = 0.457$). This finding was consistent across all subgroups including age, gender, diagnostic category, and delirium risk. There was no difference for any secondary outcome including measures of sleep quality or quantity, as scored on Richards-Campbell Sleep Questionnaire (RCSQ) and Little's questionnaires, or delirium and coma-free days.

The authors should be commended for the execution of one of the largest pharmacological delirium prevention trials to date. The current trial ticks the boxes for

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Table 1 ICU delirium prevention randomized trials with melatonin or melatonin receptor agonist

Author year	ICU population *N*	Intervention	Control	Delirium rate -intervention	Delirium rate -control	*p* value
Wibrow 2022 [8]	Multi-center *N* = 847 mixed ICU patients	Melatonin 4 mg × 14 days	Placebo	147/419 (35.1%)	138/422 (32.7%)	0.466
Ford 2020 [10]	Multi-center *N* = 210 cardiac surgery	Melatonin 3 mg × 7 days	Placebo	21/98 (21.4%)	21/104 (20.2%)	NR
Abassi 2018 [9]	Single-center *N* = 172 mixed ICU patients	Melatonin 5 mg × 5 days	Placebo	3/67 (4.5%)	1/70 (1.4%)	0.36
Vijaya-kumar 2016 [13]	Single-center *N* = 56 Organo-phosphate poisoning patients	Melatonin 3 mg × ICU stay	Placebo	13/26 (50%)	26/30 (85%)	< 0.001
Nishikimi 2018 [12]	Single-center *N* = 88 mixed ICU patients	Ramelteon 8 mg × ICU stay	Placebo	11/45 (24.4%)	20/43 (46.5%)	0.044
Hatta 2014 [11]	Multi-center *N* = 67 mixed medical hospital and ICU patients ≥ 65 years	Ramelteon 8 mg × 7 days	Placebo	1/33 (3%)	11/34 (32%)	0.003

NR not reported

quality about trial interventions, including a clear rationale for the melatonin dose selection, protocol compliance checks, and serum melatonin concentrations measured in a subset of patients. Key limitations in performing a prevention trial include difficulties to confirm negative delirium status pre-enrollment, early in ICU stay in the setting of sedation, coma, and mechanical ventilation. Therefore, the authors took a pragmatic approach to enrollment and planned an a priori analysis based on initial delirium status. The PRISMA diagram highlights challenges with delirium screening early in the ICU admission with 17% excluded due to "not expected to improve within 14 days to perform CAM-ICU" or "preceding reason could not perform CAM-ICU". Approximately 9% of subjects enrolled had initial delirium assessment as positive. Also, while the sample size calculations attempted to account for anticipated missing or non-assessable delirium assessments that are commonly experienced in ICU practice, the amount missing was higher than projected with ~ 17% missed time points in both arms. Although the authors reported exposures to sedatives and analgesics that may impact delirium burden in both arms, sedation and ventilator weaning protocols [9], that are known to impact delirium or coma burden in ICU, were not standardized in participating centers. Other environmental factors that may impact melatonin activity or sleep quality such as eye mask and ear plugs to modify exposure to light and noise, were rarely used.

Should the results of the Pro-MEDIC trial lead clinicians to abandon melatonin for delirium prophylaxis in ICU? The data are certainly compelling, yet other multicenter trials are ongoing (NCT03524937, NCT02615340, NCT03013790, NCT047216913). Previous randomized trials that explored the use of melatonin or melatonin receptor agonists for delirium prophylaxis in the ICU found mixed results (Table 1) [10–14]. We often think simple things will fix complicated problems in the ICU; they rarely do. Of note, we have not yet found any single prophylactic drug that acts on a specific pathway to prevent delirium consistently [7]. What we do know is that bundled interventions (i.e., ABCDEF) reduce risk of delirium [15] showing us multifaceted approaches are likely key. One of the next important steps in delirium research may include studies investigating specific pharmacological interventions such as melatonin to restore sleep layered on top of bundled interventions that have been proven successful. These studies should not only focus on delirium burden in ICU, but also other clinically relevant outcomes including cognitive disturbances, anxiety and depression, and sleep disorders that are frequently observed in ICU survivors [16].

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Declarations

Conflicts of interest
LB is the principal investigator of the MELLOW trial (NCT02615340) which is supported by grants from the University of Toronto and Canadian Critical Care Trials Group. RS received grants from the French Ministry of Health. RS is member of the scientific committee of the DEMEL trial (NCT03524937) and

the principal investigator of the R2D2 trial (NCT04273360). EWE has ongoing funding from the NIH and the Veteran's Affairs.

Publisher's Note

Published: 7 March 2022

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