Section: ICU

Review Article

CIRCADIAN DISRUPTION AND DELIRIUM IN CRITICAL ILLNESS: A NARRATIVE REVIEW OF THE EVIDENCE FOR A CHRONOBIOLOGICAL HYPOTHESIS

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ABSTRACT

Background: Circadian disruption has been proposed as a modifiable cause of delirium in critically ill adults. Whether it is causal, and whether circadian-directed interventions prevent delirium, remains unresolved. **Materials and Methods:** Narrative review guided by the Scale for the Assessment of Narrative Review Articles (SANRA). Studies published between January 2016 and July 2026 were identified in PubMed, with AI-assisted discovery and record-by-record verification. Thirty core studies were appraised. **Result:** Melatonin rhythms are altered in critically ill patients, but the alterations track encephalopathy, catecholamine exposure and sedation, and a 58-study systematic review found melatonin levels and rhythms were not reliably linked with delirium. The largest light trial (n=734) found no benefit. The two largest ICU melatonin trials were null (n=841 and n=334), and a meta-analysis restricted to lower-risk-of-bias trials gave a risk ratio of 0.89 (95% CI 0.73 to 1.09). Estimates for ramelteon and orexin antagonists derive from small, predominantly Japanese trials; the largest orexin antagonist trial missed its primary outcome (16.8% vs 26.5%, P=0.13). Multicomponent bundles are associated with less delirium but cannot be attributed to circadian action. Few trials tested whether an intervention engaged a circadian target. **Conclusion:** Circadian disruption is a plausible but unproven contributor to ICU delirium. Light and noise hygiene and benzodiazepine avoidance are reasonable on general grounds. Timed feeding, orexin antagonists, ramelteon and phase-timed melatonin should be confined to research. Future trials should measure circadian phase and test whether the intervention moves it.

INTRODUCTION

Delirium is common in the intensive care unit (ICU) and carries a high price. In a meta-analysis of 42 studies, 31.8% of 16,595 critically ill patients developed delirium, and those who did had higher mortality during admission (risk ratio 2.19, 95% CI 1.78 to 2.70).[1] In mechanically ventilated patients, delirium predicted six-month mortality after adjustment for coma, sedatives and analgesics (adjusted hazard ratio 3.2, 95% CI 1.4 to 7.7).[2] Among 821 survivors in the BRAIN-ICU cohort, 34% had global cognition at 12 months similar to moderate traumatic brain injury and 24% similar to mild Alzheimer disease, and longer delirium was associated with worse cognition at 3 and 12 months.[3]

The ICU removes most of the cues that normally entrain the human circadian system. Days are dim, nights are lit, feeding is continuous and patients are often immobile. Illness and treatment add further disturbance. Oldham and colleagues argued in 2016 that these changes produce circadian arrhythmia that impairs cognition and recovery, and that lighting and melatoninergic interventions deserved full-scale trials.[4] The idea is attractive because it points to inexpensive, low-risk interventions.

Since then, the evidence has grown. A scoping review of 50 ICU intervention studies described the association between sleep or circadian interventions and delirium as mixed.[5] A systematic review of 58

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human studies concluded that the circadian-delirium link remains complex and incompletely characterised.[6] Meta-analyses of melatonin, ramelteon and orexin antagonists in hospitalised adults report discordant results,[7] and a recent editorial argues that the next step is to show target engagement.[8]

This review adds an ICU-focused appraisal that places physiology, competing explanations and each intervention class side by side, and that sets the largest light trial and the two largest ICU melatonin trials against the pooled estimates that dominate secondary summaries. It also considers ICU-specific drug safety and proposes a trial blueprint. Our aims were to (1) summarise human evidence that circadian disruption occurs in critical illness and relates to delirium; (2) examine alternative explanations; (3) appraise each intervention class with attention to certainty of evidence; and (4) derive graded practical statements and research priorities. We treat the circadian account as a hypothesis.

MATERIALS AND METHODS

This is a narrative review. We used the Scale for the Assessment of Narrative Review Articles (SANRA) as a design and reporting guide, and a self-assessment is provided in Supplementary File S3. Searches covered January 2016 to July 2026 and were run on 1st October 2026. PubMed was searched with the strings listed in Supplementary File S1. Consensus, an AI-assisted discovery tool, was used to find additional candidates, and every candidate was confirmed in PubMed before use. Reference lists of key reviews and trials were screened by hand. Five earlier publications (2004 to 2015) are cited as foundational anchors.

We included adult studies set in ICUs, or in mixed hospital populations that included ICU patients, that examined circadian or melatonin physiology in relation to delirium, or that tested light, noise control, bundles, melatonin, ramelteon, orexin receptor antagonists or nocturnal dexmedetomidine for delirium prevention. Randomised trials, meta-analyses, observational human studies and guidelines were eligible. Rodent studies were cited only where they underpin the proposed mechanism. Eligibility did not require a circadian framing, so trials that did not describe their question in circadian terms were retained.

Two reviewers screened titles and abstracts. Thirty studies form the core evidence set (Table 1); the remainder are supporting references. Effect estimates were extracted from PubMed records and, for one editorial, from the full text, and are reported as published. We did not re-analyse data or apply a formal risk-of-bias tool; certainty ratings are those of the original authors.

Is the circadian system disrupted in critical illness?: Environmental cues are clearly abnormal. In a prospective cohort of 112 critically ill patients (53 with sepsis, 59 with intracerebral haemorrhage), light exposure was dim, feeding was reduced or mistimed and arousal stimuli were increased and mistimed.[9] Melatonin amplitude and acrophase were generally preserved in awake patients but were dampened and delayed as encephalopathy, measured by the Glasgow Coma Scale, worsened. Catecholamine vasopressor infusions were associated with melatonin hypersecretion, and the authors found no effect of sedatives on the rhythm.[9]

That last finding sits uneasily with a randomised substudy of 79 patients allocated to sedation or non-sedation, in which serum melatonin was suppressed in sedated patients.[10] The studies differ in design, timing and case-mix, and neither resolves the question of whether sedation alters the circadian signal or merely the amount of melatonin secreted. A third source of tension concerns the urinary melatonin metabolite 6-sulphatoxymelatonin (aMT6s). A weaning-trial substudy of 70 patients linked delirium to lower aMT6s excretion,[11] whereas Maas and colleagues concluded that aMT6s is not a reliable measure of the central rhythm in critical illness.[9]

Two conceptual points limit interpretation. First, sleep-wake state and circadian phase are related but separable. True circadian phase is assessed by dim-light melatonin onset or the core temperature nadir, and it is usually masked at the bedside by behaviour and environment.[8] Most ICU studies measure sleep or surrogate rhythms, not phase. Second, the abnormalities observed in critical illness correlate with encephalopathy, vasopressor exposure and sedation, which are themselves delirium risk factors.

Does circadian disruption contribute to delirium?

Human association studies: The human evidence for a link is inconsistent. In the sedation substudy, suppressed melatonin was not related to delirium (odds ratio 1.004, 95% CI 0.997 to 1.010).[10] Because Maas and colleagues graded encephalopathy by Glasgow Coma Scale score, attenuation of the melatonin rhythm in patients with lower scores may track coma and sedation depth more than delirium.[9] In the 58-study systematic review, melatonin levels and rhythms in saliva, serum and cerebrospinal fluid were not reliably linked with delirium, whereas cortisol and aMT6s fluctuations were more often connected with its onset or course, although both were studied infrequently.[6]

Competing explanations: At least four explanations overlap with the circadian account. Sedative exposure is the first. In a network meta-analysis of 80 trials, dexmedetomidine was associated with lower delirium than benzodiazepines (odds ratio 0.21, 95% credible interval 0.08 to 0.51; low certainty).[12] Sleep loss itself is the second: orexin antagonists act mainly by promoting sleep, whereas melatonin agonists have modest effects on sleep and act principally as chronobiotics that shift circadian phase.[8] Illness severity and systemic inflammation are the third and fourth. None of the human studies reviewed here separates these contributions from circadian

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misalignment, and the interventional literature mostly targets sleep-wake homeostasis rather than circadian phase.[8] A positive trial therefore cannot, by itself, confirm a circadian mechanism, and a null trial cannot be dismissed as failed circadian restoration unless engagement was measured.

Mechanistic data (rodent models): The most direct mechanistic report in delirium comes from mouse models. Chen and colleagues reported disrupted clock gene expression in patients with delirium and in mouse delirium models, and identified the clock-controlled factor E4BP4 as a regulator of delirium-associated cognitive impairment through microglial signaling in mice.[13] This is a single-group study in rodents, the human component is limited to clock gene expression, and we found no independent replication. A separate line of work in an amyloid precursor protein knock-in mouse model of Alzheimer disease linked microglial clock disturbance to pro-inflammatory gene expression, but the REV-ERB agonist SR9009 increased microglial activation and cognitive decline in those animals.[14] These models differ in species, insult and disease context, and they should not be merged into a single human mechanism. The second finding also argues against proposing REV-ERB agonists for delirium.

Interventions

Light, noise and multicomponent bundles: The largest light trial randomised 734 ICU patients to dynamic light of up to 1,700 lux between 09:00 and 16:00 or to usual lighting of about 300 lux. Delirium occurred in 38% and 33% respectively (odds ratio 1.24, 95% CI 0.92 to 1.68), and the trial was stopped for futility.[15] Its authors concluded that bright light alone does not reduce delirium and should be assessed within multicomponent strategies. Illuminance in lux is a poor proxy for circadian effect, and expert consensus now recommends the melanopic equivalent daylight illuminance as the metric, although the recommendations were derived for healthy adults.[16] Consensus guidance also calls for standardised light metrics in ICU trials.[17] Why a light-only trial failed is unknown; unmeasured corneal dose, eye closure and sedation, and mistimed exposure are candidate explanations, not findings.

A Berlin pilot compared two redesigned ICU rooms, which combined stress-relief changes with dynamic lighting, against standard rooms in 74 ventilated patients. Delirium occurred in 76% of patients in standard rooms and 46% in modified rooms (P=0.017).[18] This was a non-randomised pilot with a multicomponent change, not a randomised trial, although it has been described as one elsewhere.[17] It cannot isolate an effect of light.

Earplugs, alone or within bundles, were associated with lower delirium in a meta-analysis (risk ratio 0.59, 95% CI 0.44 to 0.78), but delirium was reported in only five of nine studies and all studies were at high risk of bias.[19] A staggered pre-post quality improvement study in two surgical ICUs (646 admissions) found fewer delirium days after a nighttime and daytime sleep-wake bundle (adjusted decrease 4.9 percentage points, 95% CI 0.5 to 9.2), without a change in perceived sleep quality.[20]

Network meta-analyses favour multicomponent strategies. One network meta-analysis of 29 randomised trials (7,005 patients) reported an odds ratio of 0.43 for multicomponent strategies (95% CI 0.22 to 0.84), with larger effects when early mobilisation and family participation were included.[21] In postoperative ICU patients, multicomponent sleep interventions gave a risk ratio of 0.32 (95% CI 0.20 to 0.51) and circadian-focused single interventions 0.61 (95% CI 0.39 to 0.96).[22] By contrast, the larger network meta-analysis of 80 trials reported that single and multicomponent non-pharmacological interventions did not connect to any evidence network, and pairwise comparisons found no difference from standard care.[12] The scoping review adds that bundle components with an effect cannot be identified.[5] Bundles are therefore best regarded as non-specific delirium prevention. Their benefit, where present, cannot be assigned to circadian action.

Melatonin and ramelteon: Three recent ICU trials bear directly on the question. Pro-MEDIC randomised 841 patients in 12 Australian ICUs to enteral melatonin 4 mg at 21:00 or placebo and found no difference in the primary delirium outcome (79.2% vs 80%, P=0.547).[23] DEMEL, in 334 mechanically ventilated patients, compared 0.3 mg, 3 mg and placebo. An optimal pharmacokinetic profile at 24 hours was reached in 12 of 24 patients on 0.3 mg, 6 of 25 on 3 mg and none of 26 on placebo, yet delirium incidence did not differ between 0.3 mg and placebo (54.4% vs 55.2%; risk ratio 0.986, 95% CI 0.803 to 1.211).[24] A three-arm feasibility trial of 0.5 mg, 2 mg and placebo enrolled 71 patients, recruiting slowly, and found no between-group differences in delirium.[25]

Pooled analyses disagree [Figure 2]. A meta-analysis of 32 trials reported a risk ratio of 0.72 (95% CI 0.58 to 0.89; low certainty) and a possible slight reduction in adverse events.[26] A meta-analysis restricted to trials at low or moderate risk of bias (six trials, 2,209 patients) found 0.89 (95% CI 0.73 to 1.09), and 0.86 (95% CI 0.70 to 1.04) with all 13 trials.[27] A smaller review of nine trials (six reporting delirium) gave 0.76 (95% CI 0.54 to 1.07), with a sensitivity analysis at 0.67 (95% CI 0.48 to 0.92).[28] An updated dose-response analysis reported 0.77 (95% CI 0.62 to 0.94), stronger in surgical ICUs (0.64) and with a suggested optimal cumulative dose of 22 mg, but with low certainty and moderate heterogeneity.[29] Across hospital settings, randomised trials of melatonin gave 0.94 (95% CI 0.72 to 1.22),[7] and a network meta-analysis found the melatonin association more evident in non-ICU and surgical populations.[30] These estimates overlap heavily in their underlying trials and are not independent. A reasonable summary is that ICU melatonin evidence is inconsistent, that apparent benefit is concentrated in lower-quality and surgical studies, and that the question is one of heterogeneity, not simple efficacy.

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A recent editorial addresses why such meta-analyses disagree.[31]

Dose and timing are unresolved. Doses in trials span a wide range, and no study assessed circadian phase to choose the time of administration.[8] Mistimed melatonin could be ineffective or counterproductive in principle, but this is inference from phase-response physiology, not trial evidence. DEMEL suggests that lower doses produce better pharmacokinetic profiles, yet better pharmacokinetics did not translate into benefit.[24]

For ramelteon, a multicentre rater-blinded placebo-controlled trial in 67 patients aged 65 to 89 from ICUs and acute wards reported delirium in 3% versus 32% (adjusted odds ratio 0.07, 95% CI 0.008 to 0.54).[32] A single-centre ICU trial (n=88) found a trend towards shorter ICU stay as the primary outcome (4.56 vs 5.86 days; P=0.082 unadjusted, 0.028 adjusted), with less delirium as a secondary outcome (24.4% vs 46.5%).[33] A trial of 117 patients after pulmonary thromboendarterectomy found no benefit (risk ratio 0.8, 95% CI 0.5 to 1.4).[34] The pooled randomised estimate was 0.63 (95% CI 0.39 to 1.03).[7]

Guidelines point in different directions. The 2025 Society of Critical Care Medicine focused update issued a conditional recommendation to administer melatonin,[35] whereas the American Psychiatric Association guideline, as summarised by Oldham, suggests that melatonin and ramelteon not be used for prevention or treatment, citing inconsistent, low-quality evidence.[8] We did not retrieve the latter guideline directly.

Dual orexin receptor antagonists: The randomised evidence consists of three suvorexant trials, all Japanese. The first, in 72 patients aged 65 to 89 from ICUs and acute wards, reported delirium in none of 36 suvorexant patients and six of 36 on placebo.[36] A single-centre trial of 70 medical ICU patients compared suvorexant with conventional treatment rather than placebo and reported a longer time to delirium.[37] The largest, in 203 older adults with mild cognitive impairment, mild dementia or prior delirium across 50 hospitals, did not meet its primary outcome: delirium occurred in 16.8% on suvorexant and 26.5% on placebo (difference -8.7%, 95% CI -20.1 to 2.6; P=0.13).[38] The abstract frames a possible effect on hyperactive delirium as a direction for further study; we could not verify that this was a pre-specified subgroup, and we do not treat it as one. Pooling three such trials gave a risk ratio of 0.55 (95% CI 0.35 to 0.87) for orexin antagonists, but the authors found no reliable difference between drug classes in meta-regression.[7] Oldham raises several methodological concerns: no delirium in the suvorexant arm of the earliest trial, as-needed trazodone use in a comparator arm, restricted eligibility in the largest trial, absent objective sleep outcomes and an exclusively Japanese population.[8] The earlier class-level estimate of a 40% to 46% reduction pooled ramelteon, suvorexant and lemborexant together, was of low certainty, and showed no effect on ventilator days, mortality or length of stay.[39] It should not be read as a DORA-specific result. A network meta-analysis reported a risk ratio of 0.51 (95% CI 0.27 to 0.95) for suvorexant.[30] Two registered trials may add information: REPOSE (130 older non-cardiac surgery patients; primary outcome total sleep time, delirium severity secondary),[40] and an ICU trial of suvorexant on sleep architecture and delirium.[41] We found no published results for either. Orexin antagonists remain hypothesis-generating in the ICU.

Nocturnal dexmedetomidine: Low-dose nocturnal dexmedetomidine in 100 delirium-free sedated ICU patients increased the proportion remaining delirium-free (80% vs 54%; risk ratio 0.44, 95% CI 0.23 to 0.82), without a difference in patient-reported sleep or in hypotension or bradycardia.[42] An overnight infusion after cardiac surgery in 331 patients aged 65 or older did not reduce delirium (12.6% vs 12.4%) and caused more hypotensive events (7.3% vs 0.6%).[43] In the broader network meta-analysis, dexmedetomidine was the only agent probably reducing delirium against placebo (odds ratio 0.43, 95% credible interval 0.21 to 0.85; moderate certainty).[12] Whether any benefit is sedative-sparing, sleep-related or circadian is not established, and we found no supporting evidence for claims that it preserves melatonin production.

Practical implications

The evidence supports graded, modest statements [Table 2]. Avoiding benzodiazepines where alternatives exist is reasonable on general sedation grounds, with low-certainty delirium evidence.[12] Reducing nocturnal noise and light and protecting daytime light exposure are low-risk and low-cost, and are justifiable for comfort and sleep protection, but should not be presented as proven delirium prevention. Melatonin may be considered under the conditional guideline recommendation,[35] with the understanding that no dose or time of administration is supported by outcome evidence and that the two largest ICU trials were null.[23,24]

Several practices belong in research protocols for now. Timed enteral nutrition has no delirium outcome data in the studies reviewed, and its interaction with glycaemic control, insulin infusion and calorie delivery in critically ill patients has not been tested. Ramelteon and orexin antagonists rest on small, mostly non-ICU or single-country trials. Phase-timed melatonin requires phase assessment that is not available at the bedside.

Drug safety deserves explicit attention [Table 3]. Ramelteon is metabolised mainly by CYP1A2, should not be combined with fluvoxamine and should not be used in severe hepatic impairment.[44] Suvorexant labelling recommends 5 mg with moderate CYP3A inhibitors, does not recommend use with strong CYP3A inhibitors, advises dose reduction with other central nervous system depressants and carries a Schedule IV classification.[45] Enteral absorption in shock, ileus or continuous feeding is unstudied for these agents.

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Nocturnal dexmedetomidine carries a hypotension risk.[43]

Research priorities and a trial blueprint: The central gap is target engagement. Future delirium prevention trials should measure circadian phase or a validated surrogate at baseline and after intervention, and should report whether the intervention moved it.[8] Phase assessment in the ICU is difficult, so feasibility work on serial melatonin sampling, core temperature or actigraphy-based methods is a legitimate first step. Recruitment is also a barrier, as the three-arm feasibility trial showed.[25]

Sample size depends heavily on the assumed effect. With a control-arm delirium incidence of 30%, two-sided alpha of 0.05, 80% power and an unadjusted two-proportion comparison, a 40% relative reduction needs about 390 patients in total, a 30% reduction about 730 and a 25% reduction about 1,075. If the true effect resembles the ICU melatonin estimate from lower-risk-of-bias trials (relative reduction 11%), about 5,850 patients would be required. The 40% planning figure rests on low-certainty pooled data and should not be used without justification. Trials should pre-specify stratification by sedation exposure and delirium motor subtype, include patient-centred and long-term cognitive outcomes, and pre-specify mediation analyses linking circadian change to delirium change. Dose-finding with ICU pharmacokinetics should precede efficacy trials, as DEMEL illustrates.[24]

Limitations: This is a narrative review with no formal risk-of-bias assessment. Searching was centred on PubMed and other databases were not searched, and records not indexed in PubMed may be missed. Several pooled analyses overlap in their trials and cannot be combined. Many trials were conducted outside the ICU or in single countries, and the orexin antagonist and ramelteon evidence is especially limited in this respect. Other recent narrative reviews that overlap with this work were not retrieved by our searches. Two pooled analyses and several trials were published close to the search cut-off, and further studies may have appeared since.

RESULTS

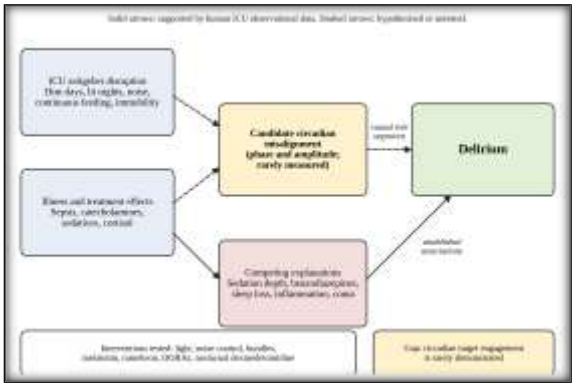

Figure 1: Conceptual model of the circadian hypothesis of ICU delirium. Solid arrows indicate associations supported by human ICU observational data; dashed arrows indicate hypothesised or untested relationships. The central gap is demonstration of circadian target engagement by interventions.

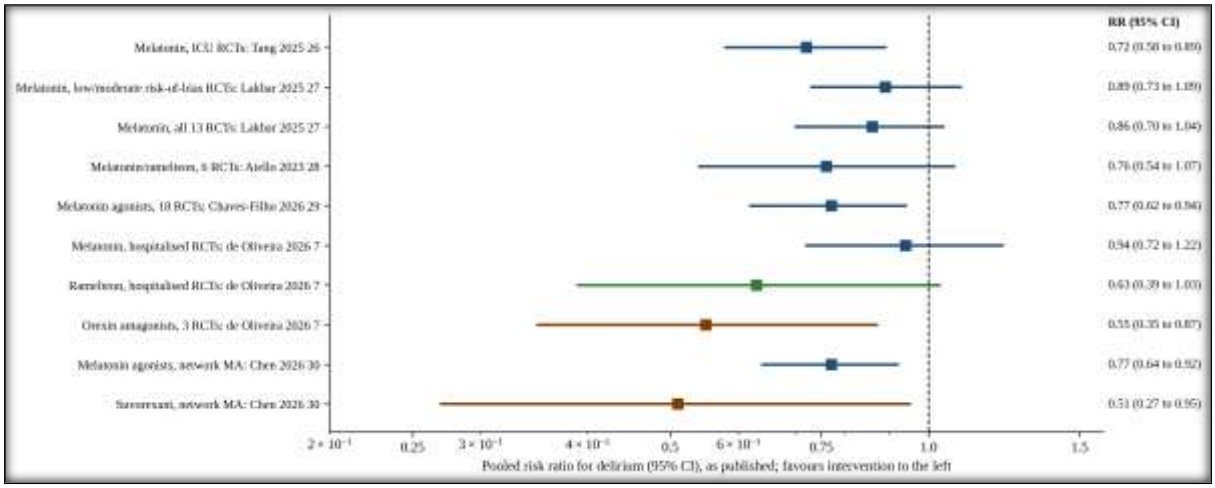

Figure 2: Published pooled risk ratios for delirium from meta-analyses of melatonin, ramelteon and orexin antagonists. Estimates are reproduced as published, not re-analysed, and the underlying trials overlap substantially. Populations differ (ICU only for the first five rows; hospitalised adults for the remainder).

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Table 1: Core evidence set (30 studies, 2016 to 2026) on circadian physiology and interventions for delirium in critically ill adults

#	Study	Design and population	Key finding	Certainty note
1	Maas 2020,[9]	Prospective cohort, 112 ICU patients (sepsis, intracerebral haemorrhage)	Melatonin rhythm preserved in awake patients; dampened and delayed with worse encephalopathy; hypersecretion with catecholamines	Observational; sedatives not associated with rhythm
2	Oxlund 2021,[10]	Randomised substudy, 79 patients, sedation vs non-sedation	Melatonin suppressed with sedation; melatonin not related to delirium (OR 1.004, 0.997 to 1.010)	Substudy; sedation confounds
3	Black 2026,[6]	Systematic review, 58 human studies	Melatonin levels and rhythms not reliably linked with delirium; cortisol and aMT6s more often linked	Heterogeneous, mostly observational
4	Spies 2024,[18]	Non-randomised pilot, 74 ventilated patients, redesigned rooms	Delirium 46% vs 76% (P=0.017)	Multicomponent; cannot isolate light
5	Simons 2016,[15]	RCT, 734 ICU patients, dynamic light	Delirium 38% vs 33% (OR 1.24, 0.92 to 1.68); stopped for futility	Largest light trial; null
6	Litton 2016,[19]	Meta-analysis, 9 studies (5 reporting delirium)	Earplugs: delirium RR 0.59 (0.44 to 0.78)	All studies high risk of bias
7	Tonna 2021,[20]	Pre-post quality improvement, 646 surgical ICU admissions	Fewer delirium days (adjusted -4.9 points, 0.5 to 9.2); sleep quality unchanged	Uncontrolled design
8	Chen 2022,[21]	Network meta-analysis, 29 RCTs, 7,005 patients	Multicomponent OR 0.43 (0.22 to 0.84)	Non-specific bundles
9	Li 2025,[22]	Network meta-analysis, postoperative ICU	Multicomponent RR 0.32; circadian-focused RR 0.61 (0.39 to 0.96)	Postoperative ICU only
10	Wilcox 2024,[5]	Scoping review, 50 ICU studies	Sleep and circadian interventions: mixed association with delirium	Descriptive
11	Perry 2024,[17]	Narrative review	Consensus call for standardised light metrics; ICU design may help	Expert opinion
12	Wibrow 2022,[23]	RCT, 841 patients, 12 ICUs, melatonin 4 mg	No difference (79.2% vs 80%, P=0.547)	Largest ICU melatonin trial; null
13	Mekontso 2025,[24]	Adaptive RCT, 334 ventilated patients, 0.3 mg vs 3 mg vs placebo	Delirium 54.4% vs 55.2% (RR 0.986, 0.803 to 1.211); best PK at 0.3 mg	PK benefit without clinical benefit
14	Burry 2025,[25]	Feasibility RCT, 71 patients, 0.5 mg vs 2 mg vs placebo	No between-group differences; slow recruitment	Feasibility only
15	Tang 2025,[26]	Meta-analysis, 32 RCTs, 3,895 patients	RR 0.72 (0.58 to 0.89)	Low certainty
16	Lakbar 2025,[27]	Meta-analysis, 13 RCTs; 6 at lower risk of bias	RR 0.89 (0.73 to 1.09) lower-risk trials; 0.86 (0.70 to 1.04) all	Sensitivity to bias
17	Aiello 2023,[28]	Meta-analysis, 9 RCTs (6 reporting delirium)	RR 0.76 (0.54 to 1.07)	Small review
18	Chaves-Filho 2026,[29]	Dose-response meta-analysis, 18 primary studies	RR 0.77 (0.62 to 0.94); suggested cumulative dose 22 mg	Low certainty; moderate heterogeneity
19	de 2026,[7]	Meta-analysis, 37 studies, hospitalised adults	Melatonin 0.94; ramelteon 0.63 (0.39 to 1.03); orexin antagonists 0.55 (0.35 to 0.87)	Mixed hospital settings
20	Nishikimi 2018,[33]	RCT, 88 ICU patients, ramelteon 8 mg	ICU stay 4.56 vs 5.86 days (P=0.082; adjusted 0.028); delirium 24.4% vs 46.5% (secondary)	Single centre; primary outcome not significant unadjusted
21	Jaiswal 2019,[34]	RCT, 117 patients after pulmonary thromboendarterectomy	Ramelteon RR 0.8 (0.5 to 1.4)	Null
22	Hatta 2017,[36]	RCT, 72 patients, ICUs and acute wards, suvorexant	Delirium 0/36 vs 6/36	Small; Japan
23	Azuma 2018,[37]	RCT, 70 medical ICU patients, suvorexant vs conventional treatment	Longer time to delirium	Single centre; no placebo
24	Hatta 2024,[38]	RCT, 203 older hospitalised adults, 50 hospitals, suvorexant	Delirium 16.8% vs 26.5% (difference -8.7%, -20.1 to 2.6; P=0.13)	Primary outcome missed
25	de 2025,[39]	Meta-analysis, 24 studies, ramelteon, suvorexant, lemborexant	RCTs RR 0.60 (0.38 to 0.97); no effect on ventilator days, mortality, length of stay	Low certainty; pooled drug classes
26	Chen 2026,[30]	Network meta-analysis, 33 trials, 5,045 patients	Melatonin agonists RR 0.77 (0.64 to 0.92); suvorexant 0.51 (0.27 to 0.95)	Effect more evident outside ICU and in surgical patients
27	Skrobik 2018,[42]	RCT, 100 sedated ICU patients, nocturnal dexmedetomidine	Delirium-free 80% vs 54% (RR 0.44, 0.23 to 0.82)	Two centres
28	Huet 2024,[43]	RCT, 331 cardiac surgery patients aged 65 or older	Delirium 12.6% vs 12.4%; hypotension 7.3% vs 0.6%	Null; harm signal
29	Burry 2021,[12]	Network meta-analysis, 80 trials	Dexmedetomidine vs placebo OR 0.43 (0.21 to 0.85); non-pharmacological interventions did not connect to the network	Moderate certainty for dexmedetomidine
30	Lewis 2025,[35]	Guideline focused update	Conditional recommendation to administer melatonin	Low certainty evidence

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Abbreviations: CI, confidence interval; OR, odds ratio; PK, pharmacokinetic; RCT, randomised controlled trial; RR, risk ratio. Results are as published and not re-analysed.

Table 2: Graded practical statements based on the reviewed evidence

Practice	Position	Basis	Sources
Avoid benzodiazepines where alternatives exist	Reasonable on general grounds	Lower delirium with dexmedetomidine than benzodiazepines (low certainty)	[12]
Reduce nocturnal noise and light; protect daytime light	Reasonable; low risk	Associated with less delirium in uncontrolled or high-risk-of-bias studies; largest light trial null	[19], [20], [15]
Multicomponent sleep-wake bundle	Reasonable as non-specific prevention	Benefit in network meta-analyses; component effects not identifiable	[21], [22], [12]
Melatonin for delirium prevention	Optional; conditional guideline recommendation, inconsistent trials	Two largest ICU trials null; lower-risk pooled RR 0.89 (0.73 to 1.09)	[35], [23], [24], [27]
Ramelteon	Research setting	Small trials; mixed populations; pooled interval includes no effect	[32], [33], [34], [7]
Orexin receptor antagonists	Research setting	Small Japanese trials; largest missed primary outcome	[36], [37], [38]
Nocturnal dexmedetomidine	Selected patients only; hypotension risk	One positive and one null RCT	[42], [43]
Timed enteral feeding and phase-timed dosing	Research setting	No delirium outcome data in the reviewed studies	[8]

Positions are the reviewers' summary of the evidence and are not formal guideline recommendations.

Table 3: Drug safety and interaction considerations relevant to ICU use

Agent	Consideration	Source
Ramelteon	CYP1A2 substrate; contraindicated with fluvoxamine; avoid in severe hepatic impairment	[44]
Suvorexant	Strong CYP3A inhibitors not recommended; 5 mg suggested with moderate CYP3A inhibitors; Schedule IV; additive effects with other CNS depressants	[45]
Lemborexant and daridorexant	Not covered by labels retrieved; confirm against local prescribing information	No source retrieved
Melatonin (exogenous)	No ICU safety signal in pooled data, with possible slight reduction in adverse events; formulations and doses vary	[26]
Dexmedetomidine (nocturnal)	Hypotension more frequent in overnight infusion after cardiac surgery (7.3% vs 0.6%)	[43]
All oral agents	Absorption in shock, ileus or continuous enteral feeding has not been studied for these indications	No source retrieved

Label information may change; confirm against current local prescribing information before clinical use.

CONCLUSION

Circadian disruption is a biologically plausible contributor to ICU delirium, and ICU environments and illness alter the cues and signals that support the circadian system. The human evidence that disruption causes delirium is, however, associational and confounded by sedation, illness severity and coma, and the interventional evidence is inconsistent. Light alone failed in the largest trial, the largest ICU melatonin trials were null, and encouraging pooled estimates for ramelteon and orexin antagonists come from small, mostly non-ICU or single-country studies. Practice should reflect that uncertainty. The most useful next step is a trial that measures whether an intervention shifts circadian phase and whether that shift mediates any change in delirium.

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