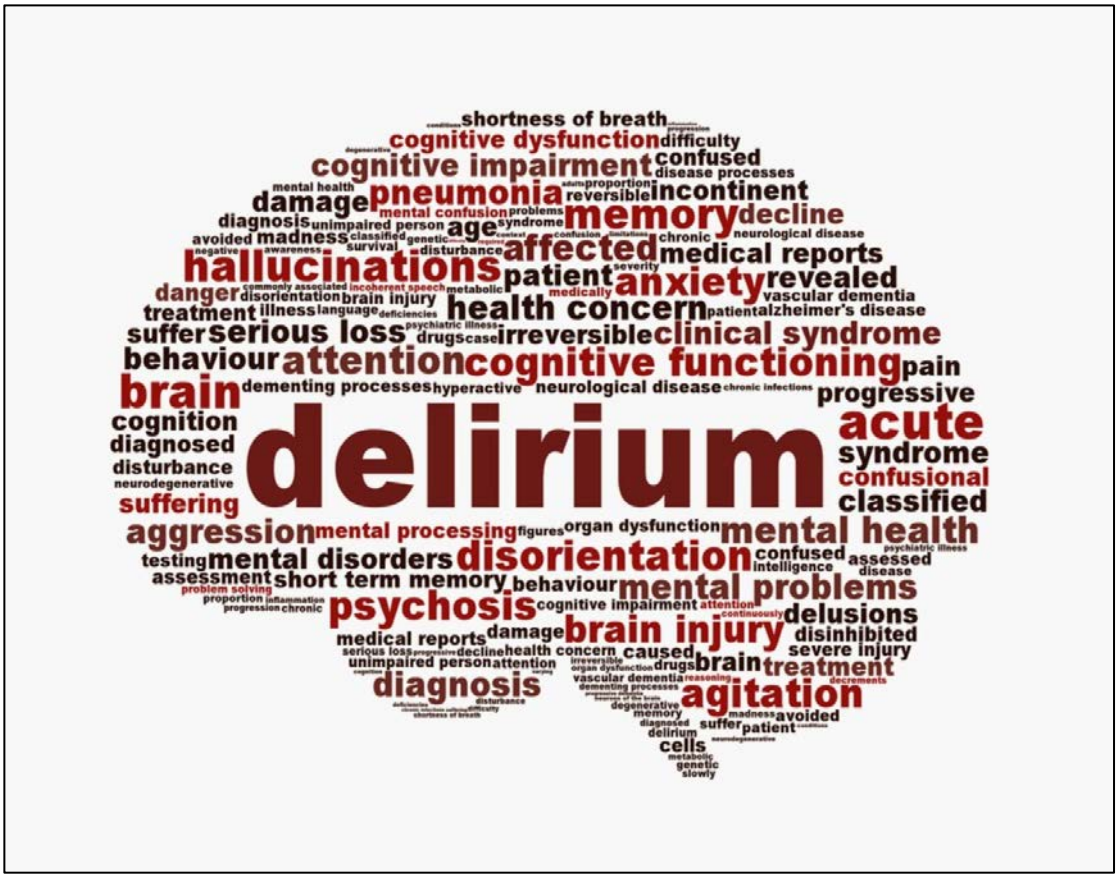
Evaluation of Sleep Aids for Prevention of ICU Delirium: Time to Hit the Snooze?



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Pharmacist Learning Objectives:

1. Evaluate the correlation between the sleep-wake cycle and development of delirium in the intensive care unit (ICU).
2. Identify risk factors and potential consequences of ICU delirium.
3. Discuss the PADIS guideline recommendations for prevention and treatment of ICU delirium.
4. Assess a patient's risk for ICU delirium and determine if melatonin or ramelteon may aid in prevention.

Technician Learning Objectives:

1. Evaluate the correlation between the sleep-wake cycle and development of delirium in the intensive care unit (ICU).
2. List the risk factors and potential consequences of ICU delirium.
3. Summarize the PADIS guideline recommendations for prevention and treatment of ICU delirium.
4. Identify a patient at risk for ICU delirium and determine if melatonin or ramelteon may aid in prevention.

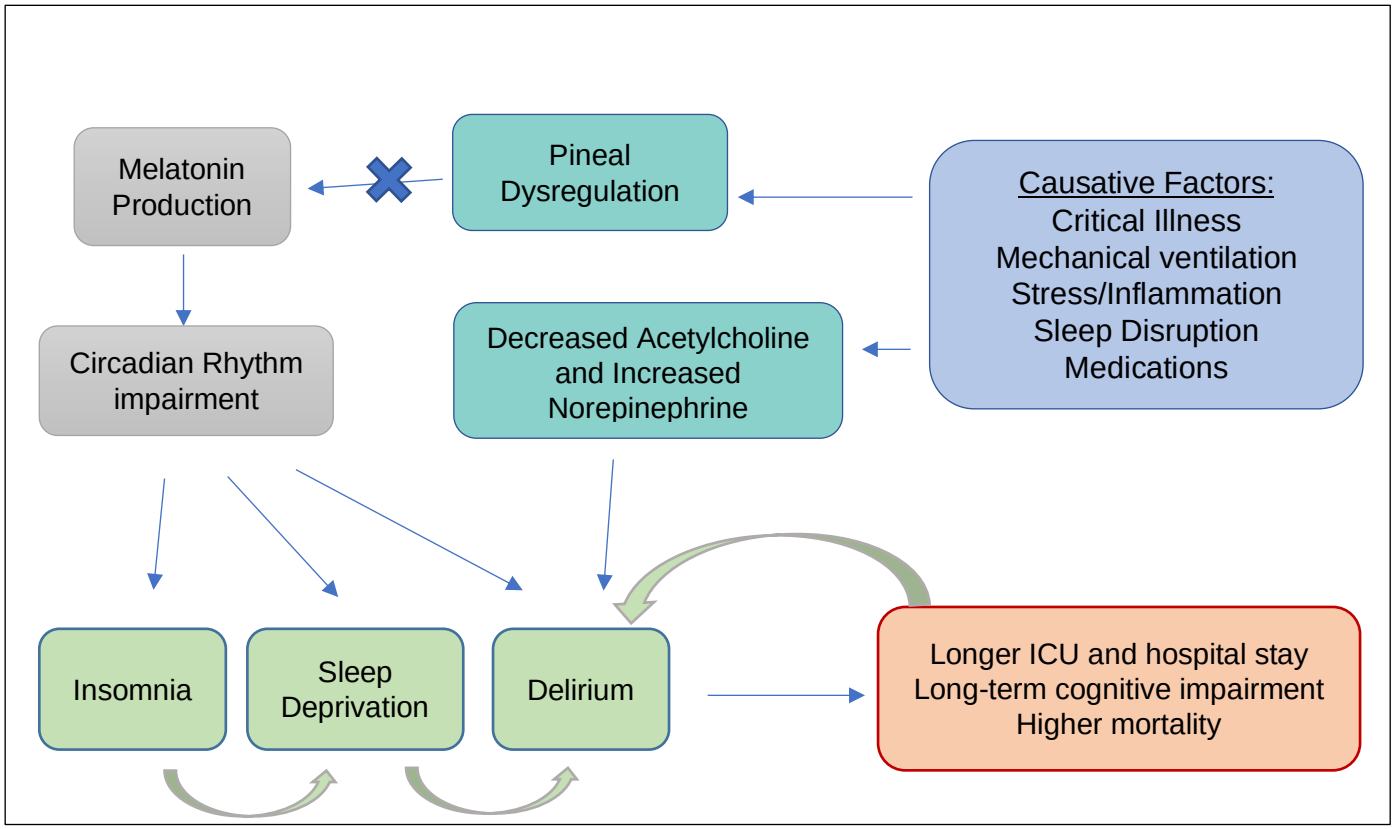
1. Delirium
    a. Background[1-3]
        i. Delirium is a mental disorder characterized by acute cognitive changes including loss of focus or disorientation.
        ii. In Latin, delirium means “to go off the furrowed path” which is translated to “madness” and was first coined in the first century.
        iii. Current Diagnostic Criteria
            1. DSM-5

A	Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B	The disturbance develops over a short period (hours to days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C	An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
D	The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal.
E	Evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies.

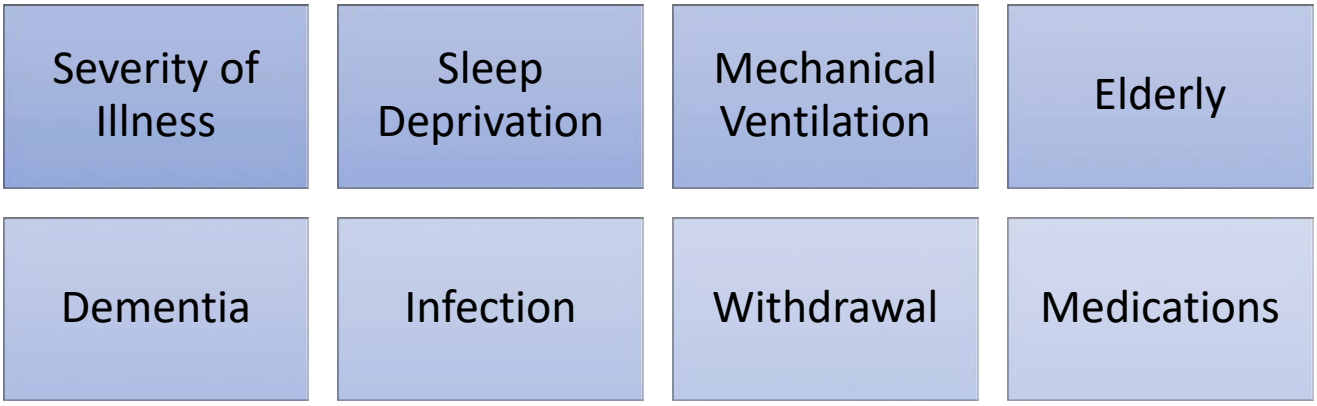
    b. Sub-Types[4,5]
        i. Definitions
            1. Hypoactive: withdrawn, quiet, decreased responsiveness
            2. Hyperactive: marked agitation, irritable, disruptive
            3. Mixed-Motor Type: fluctuation between quiet and agitated states
    c. Prevalence[6,7]
        i. In the general population, delirium is very rare and occurs in about 1-2%, predominantly in patients over 65 years of age
        ii. In the hospital, delirium is more common
            1. In the acute care units:
                a. 29-31% of patients admitted to hospital without symptoms of delirium develop delirium during hospital stay
            2. In the intensive care unit (ICU):
                a. Variable depending on severity of illness, ICU duration, medication use, and mechanical ventilation
                b. Rates reported between 20-80%

2. ICU delirium
    a. Epidemiology[8]
        i. Highest rates occur in elderly and those on mechanically ventilation
        ii. In one prospective cohort study of 614 patients conducted in medical ICU, hypoactive delirium and mixed delirium were most prevalent, occurring in 43.5% (267/614) and 54.9% (337/614), respectively
    b. Consequences of ICU delirium[9-13]
        i. Increased mortality rates, especially in the elderly
            1. A prospective cohort study of over 6,000 elderly patients found that patients with delirium had an in-hospital mortality of 8% vs 1% in those with vs. without delirium
            2. This increased risk of mortality remained high with a 3-year mortality rate of 75% vs 51%, respectively.
        ii. Increased ICU length of stay
            1. A hospital-wide evaluation study of delirium prevalence and effect on length of stay found that out of more than 10,000 patients, 28% developed delirium
            2. A significantly higher number of patients who developed delirium also had longer ICU and hospital stays ($P<0.001$)
            3. Average cost of a day in the ICU is around $3000 according to 2017 American Hospital Association annual survey but can be upwards of $3500 depending on severity of illness and mechanical ventilation
        iii. Long-term cognitive impairment
            1. Increased rates of prolonged cognitive impairment at 3- and 12-months post-discharge (79% and 71% respectively) in patients with a history of delirium and mechanical ventilation during ICU stay
    c. Common Assessment Tools for Diagnosis in the ICU[14-16]
        i. Confusion Assessment Method – Intensive Care Unit (CAM-ICU): a highly reliable and validated tool recommended by 2018 Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption guidelines to assess mental status, inattention, altered consciousness and disorganized thinking
            1. Specificity: 96%
            2. Sensitivity: 80%
        ii. Intensive Care Delirium Screening Checklist (ICSDC): highly validated tool which assesses level of consciousness, inattention, disorientation, hallucinations, psychomotor agitation, speech, and sleep/wake disturbances
            1. Specificity: 81%
            2. Sensitivity: 74%

d. Pathophysiology[3]



e. Risk Factors[17]



i. Medications Cont.[18]
   1. Benzodiazepines
   2. Antiarrhythmics (Disopyramide)
   3. Antibiotics (ex. Fluoroquinolones)
   4. Anticholinergic medication
      a. Antihistamines
      b. Anti-parkinsonian agents
      c. Anti-spasmodic agents
      d. Barbiturates
   5. Non-steroidal Anti-inflammatory Drugs (NSAIDs)
   6. Opiates

f. 2018 Pain, Agitation, Delirium, Immobility and Sleep Disruption Guidelines for Adult Patients in the ICU on the prevention and management of ICU delirium (PADIS) [19-22]
    i. Prevention:
        1. Pharmacotherapy:
            a. Pharmacotherapy options are NOT recommended for the prevention of delirium.
            b. There has been a multitude of studies done with pharmacologic options over the years, however, data for agents such as haloperidol, quetiapine, dexmedetomidine, or an HMG-CoA reductase inhibitor (ie. statin medications) have not showed beneficial reduction in the rate of delirium
                i. The REDUCE trial
                    1. Prospective, multicenter study
                    2. Assessed prophylactic haloperidol use vs placebo in patients with a high risk of delirium in the ICU
                    3. Nonsignificant differences noted in mortality, delirium occurrence, and ICU length of stay between groups
                ii. The HOPE-ICU trial
                    1. Prospective, multicenter study
                    2. Assessed prophylactic haloperidol use vs placebo in critically ill patients in the ICU despite their delirium status
                    3. Nonsignificant differences noted in mortality or days free of delirium
                    4. More patients in the haloperidol group remained over-sedated
        2. Non-Pharmacologic Therapy:
            a. A multi-modal approach to prevention of delirium is recommended with a focus on risk reduction including increasing mobility, avoiding excess noise/light avoidance, reorientation to person, place, and time, and choosing the most appropriate pain and sedation medications.
                i. The most well-known and well-studied approach to a multi-modal prevention strategy is the ABCDEF (A2F) bundle.
                ii. Prospective, multicenter cohort study
                    1. Included across 68 academic centers with over 15,000 ICU patients
                    2. A2F bundle associated with significant improvements in mortality, mechanical ventilation, coma, ICU readmission rates and occurrence of delirium (Pun, CCM 2019).
            b. Light therapy is NOT recommended due to lack of evidence for efficacy.

A2F Bundle					
Assess, prevent, and manage pain	Both spontaneous awakening trials and spontaneous breathing trials	Choice of analgesia and sedation medication	Delirium assessment, prevention, and management	Early mobility	Family engagement

ii. Treatment:
    1. Pharmacotherapy:
        a. Dexmedetomidine
            i. Only recommended therapy based off a single randomized controlled trial evaluating use for agitation preventing weaning from mechanical ventilation
            ii. Dexmedetomidine associated with decreased ventilator time but no effect of ICU or hospital length of stay
        b. All other agents: haloperidol, quetiapine, and HMG-COA reductase inhibitors
            i. Little to no evidence supporting their use in ICU delirium management
    2. Non-Pharmacologic Therapy:
        a. Current guidelines recommend same non-pharmacotherapy options used for prevention
        b. May shorten length of delirium

3. Sleep/Wake Cycle
    a. Melatonin's role[23]
        i. Melatonin is a hormone that is released by the pineal gland to regulate the sleep-wake cycle
        ii. In darkness, the pineal gland releases melatonin which then stimulates drowsiness and stimulates the body that it is time for relaxation and sleep
        iii. In light, the pineal gland stops the production of melatonin which then stimulates wakefulness
        iv. Exogenous melatonin promotes this pathway alone without changing the architecture of sleep allowing for reduced risk of daytime drowsiness or "hangover" effects
    b. Causes of disruption[24-27]
        i. Many things can disrupt the sleep wake cycles such as excess noise, stimulation, stress or caffeine
        ii. In the ICU, the sleep wake cycle is disrupted by a variety of factors including:
            1. Bodily stress from acute illness,
            2. Pain,
            3. Medical professionals, or
            4. Constant noise from monitoring devices

Table 1: Freedman et al. (2001)	
Population	22 mechanically ventilated patients in the medical ICU
Intervention	Sleep/wake cycles assessed with a continuous polysomnography (PSG) (gold standard assessment tool for sleep)
Outcome	• All patients (N=22) demonstrated some sleep abnormality during study period • Large fluctuations were noted in total sleep time • Most patients demonstrated fragmented sleep cycles leading to decreased quality of sleep

Table 2: Elliott et al. (2013)	
Population	57 patients in the adult ICU
Intervention	Sleep/wake cycles assessed with a continuous PSG over a 24-hour period for both quantity and quality of sleep
Outcome	• Median sleep time (5 hours) and staging of sleep were low in all 57 patients, demonstrating poor quantity and quality of sleep • Low stage sleep was reported as stage 1 and 2 indicating little REM sleep • Patients self-reported poor sleep throughout stay

c. Consequence[28]
    i. Delirium may be a consequence of sleep deprivation, although causality uncertain
    ii. Assessing plausibility
        1. Melatonin levels noted in ICU patients are much lower than normal
        2. Higher rates of sleep disturbance in the ICU
        3. Rates of delirium are highest in the critically ill, particularly in the ICU

4. Controversy
    a. ICU patients have the highest rates of delirium, especially if elderly and those who are mechanically ventilated
    b. Currently no quality pharmacotherapy options to prevent delirium; focus is on risk reduction
    c. One link associated with development is the disrupted sleep-wake cycle and lower level melatonin at baseline
    d. Therefore, what is the role of melatonin and derivatives in prevention of ICU delirium?

	Melatonin [29-30]	Ramelteon[29,31-32]
Mechanism	Over the counter product (OTC) Mimics melatonin produced by pineal gland	Prescription product (Rx) Acts at the same M1 and M2 receptors as melatonin but is 10x times more potent
Regulation	Regulation is controlled by U.S Food and Drug Administration (FDA) while advertising is controlled by Federal Trade Commission (FTC)	Regulation and advertising are controlled by the FDA
Safety	OTC medications require a wider margin of safety in order to be sold directly to patient but require less precise standards with amount of active ingredient in each product	Rx medications have a narrower margin of safety and require prescription by a provider and dispensing by a pharmacy for patient to receive
Cost	Average cost is $0.04 - $0.10 per tablet	Average cost of ramelteon is $3.00-$4.00 per tablet

5. Literature Evaluation

Effectiveness of Melatonin for the Prevention of Intensive Care Unit Delirium

Baumgartner et al. Pharmacotherapy 2019;39(3):280–287. doi: 10.1002/phar.2222

<table>
<tr><th colspan="2">STUDY OVERVIEW</th></tr>
<tr><td>Objectives</td><td>• Primary objective: determine effect of melatonin on rate of delirium within 7 days
• Secondary objective: compare the rate of delirium-free days without coma at day 28 in those with ICU delirium, hospital and ICU length of stay, duration of mechanical ventilation, and mortality</td></tr>
<tr><th colspan="2">METHODS</th></tr>
<tr><td>Design</td><td>• Retrospective, single-center, observational cohort study conducted from 2013-2017
• Patients identified via hospital's electronic medical record using ICU order sets or an order for melatonin
• CAM-ICU was measured every 12 hours by trained nursing staff per floor protocol
• Delirium was defined as two consecutive positive CAM-ICU assessments within 14 days of inclusion
• Patients followed for 7 days with the first day of melatonin being day 0 for intervention group and the 4th day of admission to the ICU being day 0 for the control group
• Unit standards of care included adherence to ABCDEF bundle including spontaneous awakening and breathing trials (SAT/SBTs), use of first line propofol and dexmedetomidine for sedation as well as early mobilization and family engagement</td></tr>
<tr><td>Inclusion criteria</td><td>• Adults ≥ 18 years-old admitted to medical-surgical or cardiac ICU
• Two consecutive negative CAM-ICU scores</td></tr>
<tr><td>Exclusion criteria</td><td>• Positive CAM-ICU score prior to receiving melatonin
• Prescribed antipsychotic or sleep aid prior to admission
• Admitted for neurologic condition or injury
• History of hepatic encephalopathy or end stage liver disease
• Acutely withdrawing from alcohol
• Presence of a condition limiting effectiveness of CAM-ICU screening</td></tr>
<tr><td>Statistical analysis</td><td>• Estimated sample size of 115 patients per group was calculated based on the assumption melatonin would reduce the rate of delirium from 30% to 15% with 80% power and alpha of 0.05
• Continuous variables: Student t test or Mann-Whitney U test depending on distribution
• Categorical variables: Chi-square or Fisher exact test
• Study team used a multivariate logistic regression model to evaluate predictors of ICU delirium as well as control for variables known to be higher risk for delirium</td></tr>
<tr><th colspan="2">RESULTS</th></tr>
<tr><td>Baseline Characteristics</td><td>
<table>
<tr><th colspan="4">Demographic and Characteristics</th></tr>
<tr><th></th><th>Melatonin (n=117)</th><th>Placebo (n=115)</th><th>P-value</th></tr>
<tr><td>Mean age, years (SD)</td><td>60.5 (± 16.8)</td><td>59.5 (± 16.5)</td><td>0.63</td></tr>
<tr><td>Men (%)</td><td>63</td><td>60</td><td>0.69</td></tr>
<tr><td>Delirium risk factors
Median APACHE score (IQR)
Mechanical ventilation (%)
Emergent Surgery (%)</td><td>
17.5 (13-22)
49
57</td><td>
16 (11-20)
54
38</td><td>
0.2
0.51
<0.01</td></tr>
<tr><td>Type of ICU (%)
Medical-surgical
Cardiac</td><td>
78
39</td><td>
81
34</td><td>
0.57
0.57</td></tr>
<tr><td>Hypertension (%)</td><td>64</td><td>60</td><td>0.43</td></tr>
</table>
</td></tr>
<tr><td>Primary and Secondary outcomes</td><td>
<table>
<tr><th></th><th>Melatonin (n=117)</th><th>Placebo (n=115)</th><th>P-value</th></tr>
<tr><td>Delirium (%)</td><td>7.7</td><td>24.3</td><td>0.001</td></tr>
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Delirium-free days without coma, day 28 (SD)	19.9 (± 6.9)	20.9 (± 7.2)	0.72
Duration of Mechanical ventilation (hours)	491.8 (± 1027.3)	358.3 (± 491.9)	0.4
Hospital Mortality (%)	15	22	0.24
Length of Stay (days) Hospital ICU	 30.1 (± 40.1) 15.6 (± 30.5)	 24 (± 37) 17.1 (± 37.3)	 0.24 0.75

- Dose of melatonin used varied between patients with a range of 1-10mg; median dose used was 3.5mg/day
- Average duration of melatonin was 6.3 days (± 6.9)
- Initially the investigators chose to look at use of as needed antipsychotic medication as a secondary outcome but took it off later as the majority of patient who developed delirium were the ones who also received antipsychotics
- Multivariate logistic regression analysis found that both mechanical ventilation, APACHE II score and melatonin for ≥ 48 hours significantly affected rates of delirium (P<0.01, P=0.05, and P<0.01 respectively)
    - In contrast, age, ICU length of stay, sedation agents, hypertension, and emergent surgery did not prove to affect rate of delirium significantly

AUTHOR CONCLUSIONS

"In this single-center, retrospective cohort study involving critically ill patients, melatonin appeared to be a promising agent for the prevention of ICU delirium".

CRITIQUE

Study strengths	• Primary outcome assessed rate of delirium • Met power • Larger sample size • Assessed only those in the ICU setting which is where the highest rates of delirium are present in the hospital • Well balanced baseline characteristics • Utilized a well validated tool for assessment of delirium • Strictly adhered to current guideline recommended non-pharmacologic therapy for the prevention of delirium throughout study • Conducted a multivariate analysis to control for individual delirium risk factors
Study limitations	• Retrospective, single-centered • Variable dosing of melatonin without stratifying the results based on dose (decreased internal validity) • Inability to verify accurate measurement of CAM-ICU based retrospective design
Take home points	• Patients in the medical/surgical or cardiac ICU demonstrated lower rates of delirium when taking melatonin versus no melatonin • Retrospective study design that evaluated outcomes over a short duration • Difficult to assess dosing strategies as prescribers used varying doses of melatonin, which may have varying amounts of the active ingredient at baseline given decreased regulation

Potential Role of Exogenous Melatonin Supplement in Delirium Prevention in Critically Ill Patients: A Double-Blind Randomized Pilot Study

Abbasi et al. Iranian Journal of Pharmaceutical Research. 2018;17 (4): 1571-1580

STUDY OVERVIEW

Objectives	• **Primary objective:** Evaluate effect of melatonin on the rate of delirium in the ICU within 8 days • **Secondary objective:** Compare the length of stay in the ICU and hospital, rate of prescribed haloperidol, mortality, and length of delirium between melatonin and placebo

METHODS

Design

- Randomized, prospective, double-blinded, placebo-controlled trial conducted from October 2014 to May 2016
- Patient's randomly assigned to each group via computerized number generator
- Each patient was given a code and the codes were generated on the bottle of 5 tablets of the study medications and they were administered in a double-blind manner
- Each patient was given the study medication within the first 24 hours of admission at 9:00PM and every night for a subsequent 5 days
- Patients were followed for a minimum of 8 days to assess delirium occurrence
- Delirium was assessed via the CAM-ICU assessment tool
- Appropriate training was given to all research personnel and tested for reliability
- PRE-DELIRIC model used for predicting the chance of developing delirium in each patient by assessing 10 separate delirium risk factors

Inclusion criteria

- Age > 18 years
- Tolerated oral medications/healthy GI tract
- Richmond agitation sedation scale (RASS) > - 4
- Glasgow coma score (GCS) > 8
- Negative delirium or mental changes prior to start of study

Exclusion criteria

- Heart Failure as defined as an NYHA class III or IV
- ICU stay of < 5 days
- Sensitivity reaction to melatonin
- Pregnancy
- History of seizure

Statistical analysis

- Categorical data: chi-square and presented as frequency/percentage
- Continuous data: Independent sample t-test and presented as mean/SD
- Alpha = 0.05
- Logistic regression to evaluate melatonin use, frequency of delirium and mortality rate
- SPSS for data analysis

RESULTS

Baseline Characteristics

Demographic and Characteristics

	Melatonin (N=67)	Placebo (N=70)	P-value
Mean age (years)	52.5 ± 18.4	49.9 ± 19.0	0.46
Women (%)	46.3	40	0.49
Chronic diseases (%)			
Cardiovascular Disease	38.8	24.2	0.13
Diabetes Mellitus	20.9	8.6	0.05
Neurologic Disease	7.5	7.1	1.00
Respiratory Disease	0	4.3	0.50
Chronic Organ Insufficiency	10.4	0	0.06
Delirium risk factors			
APACHE II score, mean	8.1 ± 4.3	7.3 ± 4.6	0.32
SOFA score, mean	3.1 ± 2.0	3.2 ± 2.3	0.76
Chance of delirium during 8 days in ICU, % (mean ± SD)	8.6 ± 7.8	6.0 ± 5.1	0.01
Reason for admission, %			
Medical	34.3	15.7	N/A
Surgical	53.7	62.9	N/A
Trauma	11.9	21.4	N/A

Primary outcome

	Melatonin (N=67)	Placebo (N=70)	P-value
Incidence of delirium, n (%)	3 (4.5)	1 (1.4)	0.36
Medical	0 (0.0)	1 (9.1)	NA
Surgical	3 (8.3)	0 (0.0)	NA
Trauma	0 (0.0)	0 (0.0)	NA

<table>
<tr><td>Secondary outcomes</td><td>
<table>
<tr><th></th><th>Melatonin (N=67)</th><th>Placebo (N=70)</th><th>P-value</th></tr>
<tr><td>Mean duration of delirium, days ± SD</td><td>3.0 ± 1.7</td><td>2.0 ± 1.7</td><td>0.28</td></tr>
<tr><td>Cumulative dose of haloperidol, mg ± SD</td><td>4.0 ± 5.3</td><td>2.0 ± 5.3</td><td>0.32</td></tr>
<tr><td>Length of Stay, days ± SD
Hospital
ICU</td><td>
18.1 ± 13.5
8.8 ± 5.9</td><td>
18.6 ± 15.6
9.8 ±</td><td>
0.85
0.50</td></tr>
<tr><td>Mortality (%)</td><td>13.4</td><td>11.4</td><td>0.80</td></tr>
</table>
Regression analysis noted no significant reductions in duration of delirium, the rate of prescribed haloperidol, duration of ICU or hospital stay, or rate of mortality (P = 0.86, 0.98, 0.195, 0.48, and 0.92 respectively)
</td></tr>
<tr><td colspan="2">AUTHOR CONCLUSIONS</td></tr>
<tr><td colspan="2">“This double-blind, randomized, controlled clinical trial showed no treatment effect of melatonin to decline the frequency and duration of delirium in ICU patients.”</td></tr>
<tr><td colspan="2">CRITIQUE</td></tr>
<tr><td>Study strengths</td><td>Design (double-blinded, prospective, placebo-controlled)
Assessed rate of delirium as the primary outcome
Utilized a well validated tool to assess primary outcome
Adhered to current guideline recommended non-pharmacologic therapy for the prevention of delirium throughout study
Assessed reliability of research personnel</td></tr>
<tr><td>Study limitations</td><td>Small sample size
Did not address power
Baseline characteristics indicated low severity of illness which is a potential reason for low rates of delirium seen
Assessed delirium less than recommended in guidelines
At baseline, all admission types (medical, surgical, trauma) had significantly higher risk of delirium in the melatonin group</td></tr>
<tr><td>Take home points</td><td>Melatonin at a dose of 3mg/day did not prove to significantly reduce to rate of delirium in patients in the medical, surgical, or trauma ICUs
Regression analysis also demonstrated a non-significant reduction in delirium
Disparity in delirium risk at baseline between medical, surgical, and trauma admissions
No significant differences were noted in the duration of delirium, mortality, or ICU and hospital length of stay
Power not addressed</td></tr>
</table>

Effect of Administration of Ramelteon, a Melatonin Receptor Agonist, on the Duration of Stay in the ICU: A Single-Center Randomized Placebo-Controlled Trial

Nishikimi et al. Crit Care Med 2018; 46:1099–1105

STUDY OVERVIEW	
Objectives	• **Primary objective:** evaluate the effect of ramelteon on duration of stay in the ICU • **Secondary objective:** evaluate the rate of delirium, duration of delirium and clinical status of the patient at discharge
METHODS	
Design	• Randomized, triple-blinded, placebo-controlled single-centered trial conducted from May 2015 to April 2017 • Randomly assigned to treatment or control group in a 1:1 ratio • Patients were administered the study drug each day at 20:00 until discharge • Visitation by family was only allowed twice daily between 11:00-12:00 and 15:00-16:00 • Patients were evaluated every 4 hours by trained nursing staff using the RASS and the CAM-ICU for secondary endpoints

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In situations where patients were actively experiencing delirium and emergent therapy needed, prescribers administered haloperidol
Randomization occurred using a block size of four; randomized list made by an outsider prior to enrollment
Groups stratified by age ≥ 60 or <60, intubation status and APACHE II score ≥ 30 or <30

</td></tr>
<tr><td>Inclusion criteria</td><td>

Age ≥ 20
Admission into emergency and medical ICU
Working GI tract and ability to take medications orally or nasogastric tube

</td></tr>
<tr><td>Exclusion criteria</td><td>

Previous or existing use of ramelteon or fluvoxamine
Known allergy to ramelteon

</td></tr>
<tr><td>Statistical analysis</td><td>

A sample size of 91 per group was calculated to reach an 80% power
All tests were two-sided with an alpha of 0.05
Intention to treat analysis
Categorical variables were assessed with Fisher exact test
Continuous variables were assessed with student t tests
Multivariate linear regression was used to evaluate factors that may independently affect duration of ICU stay

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<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Baseline Characteristics</td><td>
Demographic and Characteristics:
<table>
<tr><th></th><th>Ramelteon (N=45)</th><th>Placebo (N=43)</th></tr>
<tr><td>Mean age, years (IQR)</td><td>68 (57-75)</td><td>68 (52-78)</td></tr>
<tr><td>Women (%)</td><td>67</td><td>76</td></tr>
<tr><td>Admission Diagnosis (%)
Heart failure/Myocardial infarction
Respiratory failure
Sepsis
Other</td><td>
20.0
17.8
26.7
35.6</td><td>
25.6
23.3
20.9
30.2</td></tr>
<tr><td>Past medical history (%)
Habitual heavy use of alcohol
Habitual use of sleeping medication
Habitual use of psychiatric medication</td><td>
6.7
15.6
4.4</td><td>
2.3
11.6
2.3</td></tr>
<tr><td>Delirium risk factors
APACHE II score (mean ± SD)
SOFA score (mean ± SD)
Dementia (%)
Mechanical ventilation (%)</td><td>
24.0 ± 7.3
8.0 ± 4.16
13.3
40.0</td><td>
23.9 ± 8.61
8.5 ± 3.89
2.3
46.5</td></tr>
<tr><td>Mean RASS score</td><td>-1.15</td><td>-1.12</td></tr>
</table>
</td></tr>
<tr><td>Primary outcome</td><td>
<table>
<tr><th></th><th>Ramelteon</th><th>Placebo</th><th>P-value</th></tr>
<tr><td>Duration of ICU stay, days (IQR)</td><td>4.56 (2.1-7.07)</td><td>5.86 (2.97-14.16)</td><td>0.082</td></tr>
</table>

Through a multivariate analysis to control for prespecified risk factors, ramelteon use, mechanical ventilation, and mean RASS score did prove to significantly affect length of stay (P=0.028, 0.004, and 0.018 respectively)
Age > 60, dementia, and APACHE II score did not prove significant (p=0.56, 0.371, and 0.176 respectively)

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Secondary outcomes

	Ramelteon	Placebo	P-value	Odds Ratio
Rate of delirium (%)	24.4	46.5	0.044	2.69 (1.09-6.65)
Mean duration of delirium, days (± SD)	0.78 ± 1.8	1.40 ± 2.3	0.048	N/A
ICU mortality (%)	6.7	7.5	0.999	N/A
Awakenings per night (n)	0.8	1.31	0.045	N/A
Nights without awakenings (%)	51	31	0.048	N/A

AUTHOR CONCLUSIONS

"Ramelteon administration was associated with a tendency toward a decreased duration of ICU stay, as well as significant decreases in the occurrence rate and duration of delirium in patients admitted to the ICU."

CRITIQUE

Study strengths

- Design (triple-blinded, placebo-controlled)
- Appropriate statistical tests used
- Assessed known consequences of ICU delirium such as increased length of stay and mortality
- Utilized well-validated tools for both primary and secondary outcomes
- Adhered to guideline recommended non-pharmacologic therapy for the prevention of delirium throughout study

Study limitations

- Single-centered
- Small sample size
- Did not meet power
- Higher risk patients in the treatment group
- Rate of delirium was a secondary outcome
- Retrospective assessment of sleep duration via chart review
- Potential for less vigorous non-pharmacologic strategies as description less clear and family visitation very restrictive

Take home points

- Ramelteon significantly reduced the rate of delirium as well as the duration of delirium
- Adhered to guideline recommended non-pharmacologic therapy however, unsure if to the full extent
- Neither rate nor duration of delirium were the primary outcome; not powered to assess
- No statistically significant difference in length of stay in the ICU or ICU mortality

Ramelteon for Prevention of Postoperative Delirium: A Randomized Controlled Trial in Patients Undergoing Elective Pulmonary Thromboendarterectomy

Jaiswal et al. Crit Care Med 2019; e1-e8

STUDY OVERVIEW

Objectives

- **Primary objective:** the effect of ramelteon on delirium incidence in the 5 days post-surgical intervention
- **Secondary objectives**: the effect of ramelteon on rate of mortality, antipsychotic use, and ventilator-free days
- **Safety objective:** the effect of ramelteon on duration of delirium and coma

METHODS

Design

- Randomized, placebo-controlled, single centered trial conducted from March 2016 to December 2017
- Investigators were required for all study processes from start to finish which caused some gaps in enrollment
- Primary outcome was total sleep duration but was switched to delirium incidence prior to data collection due to funding restraints on equipment needed for sleep monitoring
- Only the investigational pharmacists who dispensed the medication knew the group assignment, but all other personnel and patients were blinded until trial completion
- Assessed delirium every 4 hours via the CAM-ICU assessment tool
- Each group was given the study medication for a maximum of seven days starting the night prior to surgery up until post-operation day 5

<table>
<tr><td></td><td>

If patients were discharged prior to post-operation day 5, they halted study medication
A 4x4 block randomization was used to split patients up into each treatment arm

</td></tr>
<tr><td>Inclusion criteria</td><td>

Age ≥ 18
Admitted for elective pulmonary thromboendarterectomy (PTE)

</td></tr>
<tr><td>Exclusion criteria</td><td>

Pregnancy
Cirrhosis
Fluvoxamine use
Non-English speaking

</td></tr>
<tr><td>Statistical analysis</td><td>

Estimated sample size of 48 subjects per group needed to detect 20% relative reduction in delirium with 90% power
Normally distributed variables compared using t-test while non-normally distributed variables were compared using a Mann-Whitney U test
Categorical data: Chi-square analysis or Fisher Exact test
Post-hoc analyses completed for patients at high risk including: age > 65 years and greater than one positive CAM assessment
Two-way, unbalanced analysis of variance used to compare differences in sedation scores

</td></tr>
<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Baseline Characteristics</td><td>
<u>Demographics and Characteristics:</u>
<table>
<tr><th></th><th>Ramelteon (N=59)</th><th>Placebo (N=58)</th><th>P-value</th></tr>
<tr><td>Mean age (years)</td><td>58.1</td><td>56.1</td><td>0.47</td></tr>
<tr><td>Women (%)</td><td>50.8</td><td>50.0</td><td>0.93</td></tr>
<tr><td>Body mass index, kg/m² (±SD)</td><td>31.2 (± 9.8)</td><td>33 (± 8.7)</td><td>0.30</td></tr>
<tr><td>Charlson Comorbidity Index (CCI)</td><td>3.3</td><td>3.2</td><td>0.82</td></tr>
<tr><td>Median operating room time, min (IQR)</td><td>510.0 (480-540)</td><td>526.0 (480-540)</td><td>0.84</td></tr>
<tr><td>Delirium risk factors
Duration of ventilation, days (IQR)
Benzodiazepine use (%)
Benzodiazepine use in lorazepam equivalents, mg (IQR)
Opiate use in morphine equivalents (mg)</td><td>
2.0 (2-3)
8.5
2.0 (1-2)
31.7</td><td>
2.0 (2-3)
10.3
33.9 (2-84)
42.0</td><td>
0.46
0.73
0.52
0.76</td></tr>
<tr><td>ICU length of stay, days (IQR)</td><td>4.0 (3-6)</td><td>4.0 (3-5)</td><td>0.35</td></tr>
<tr><td>Hospital length of stay, days (IQR)</td><td>12.0 (10-16)</td><td>12.0 (10-14)</td><td>0.72</td></tr>
</table>
</td></tr>
<tr><td>Primary and Secondary outcomes</td><td>
<table>
<tr><th></th><th>Ramelteon (N=59)</th><th>Placebo (N=58)</th><th>P-value</th><th>Relative Risk</th></tr>
<tr><td>Rate of delirium (%)
Per protocol
Intention-to-treat
> 1 CAM Assessment
Age ≥ 65 years, n (%)</td><td>
38
36
16
9/19 (47)</td><td>
32
32.2
15
6/20 (30)</td><td>
0.52
0.66
0.97
0.27</td><td>
0.8 (0.5-1.4)
0.9 (0.5-1.4)
1.0 (0.4-2.3)
0.6 (0.3-1.4)</td></tr>
<tr><td>Mortality (%)</td><td>6.9</td><td>5.1</td><td>0.72</td><td>0.7 (0.2-3.2)</td></tr>
<tr><td>Antipsychotic use (%)</td><td>12.1</td><td>11.9</td><td>0.97</td><td>0.9 (0.4-2.6)</td></tr>
<tr><td>Ventilator-free days (IQR)</td><td>2.0 (2-3)</td><td>2.0 (2-3)</td><td>0.29</td><td>0.3 (-0.4-0.9)</td></tr>
</table>

Adherence was measured and reported to be ≥ 95% for each study medication
40% of the CAM-ICU assessments were positive for coma (RASS -4 or -5)

</td></tr>
</table>

Safety	

	Ramelteon	Placebo	P-value	Relative Risk
Median duration of delirium and coma, days (IQR)				
Delirium/coma-free	2.0 (2-3)	3.0 (2-5)	0.18	0.4 (-1.1-0.3)
Coma-free	2.0 (1-3)	3.0 (2-4)	0.21	0.3 (-1.0-0.3)
Delirium	0.0 (0-1)	0.0 (0-1)	0.58	0.0 (-0.4-0.4)
Coma	2.0 (1-3)	2.0 (1-2)	0.29	0.3 (-0.4-0.9)

AUTHOR CONCLUSIONS

"Ramelteon did not reduce incident delirium in patients undergoing cardiopulmonary bypass surgery for thromboendarterectomy, nor did it improve delirium duration."

CRITIQUE

Study strengths	• Design (randomized, placebo-controlled) • Met power • Primary outcome assessed for rate of delirium • Assessed post-operative patients in the ICU setting which is a high-risk patient population • Utilized the CAM-ICU assessment tool by a trained staff • Appropriate statistical tests utilized • Adhered to guideline recommended non-pharmacologic therapy for the prevention of delirium throughout study
Study limitations	• Design (single-centered) • Selection bias due to using patients undergoing an elective surgery which likely decreases probability of delirium due to severity of illness • Small sample size • Less than 10% of patients received benzodiazepines which does not quite represent the typical ICU patient population
Take home points	• Ramelteon was shown to be a safe option for use in post-surgical ICU patients • Ramelteon did not significantly affect the rate of ICU delirium in the per protocol, intention to treat, or high-risk population • Potential selection bias due to patients undergoing elective surgery • No difference noted between groups in ventilation status or mortality • Though trial met power, sample size was small

6. Trials in progress[37-38]

Author/Date	Population	Intervention	Comparator	Results
Burry et al.	Adults with expected ICU stay > 48 hours. Expected: 69 ICU patients	Melatonin 2mg vs 5mg	Placebo	Pending Expected finish: Oct 12 2019
Martinez et al.	Adult ICU patient with an ICU LOS of minimum 72 hours of admission. Expected: 850 adult ICU patients	Melatonin 4mg	Placebo	Pending Expected finish: 2019

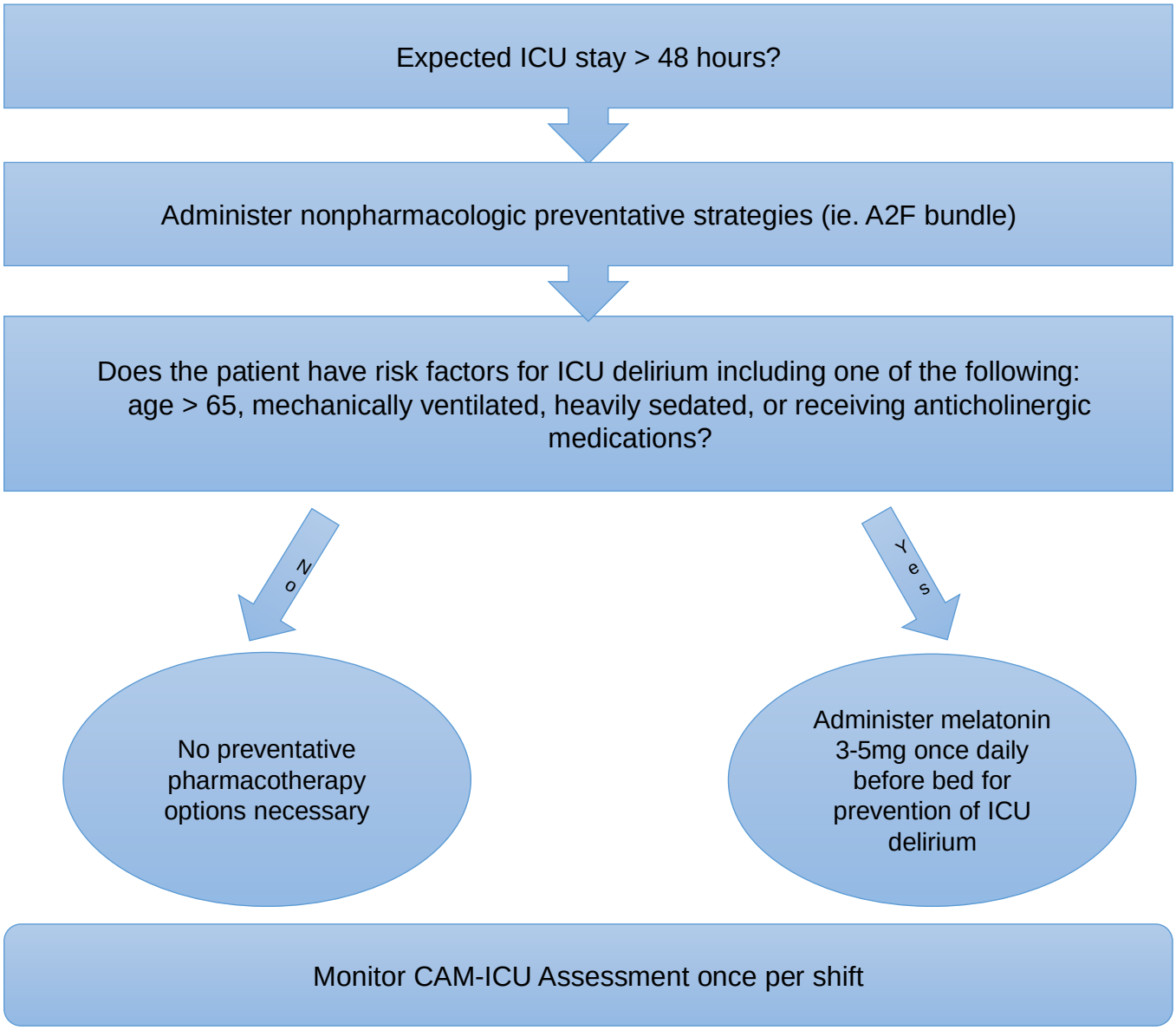
7. Putting it all together

	Baumgartner et al. (melatonin)	Abbasi et al. (melatonin)	Nishikimi et al. (ramelteon)	Jaiswal et al. (ramelteon)
What was the population size?	N= 232	N= 137	N= 88	N= 117
Did the population of the study adequately represent the typical ICU patient?	Yes	No	Yes	No
Were the patients in the study at high risk for ICU delirium?	Yes	No	Yes	No
Was a well validated tool used to assess delirium?	Yes	Yes	Yes	Yes
Did the study appropriately use non-pharmacologic options (ie. A2F bundle)?	Yes	Yes	Yes/No	Yes
What dose of melatonin or ramelteon was used?	Varying doses Median dose: 3.5mg	3mg	8mg	8mg
Was incidence of delirium the primary outcome?	Yes	Yes	No	Yes
Did the trial meet power?	Yes	Not addressed	No	Yes
Did melatonin or ramelteon significantly reduce ICU delirium?	Yes	No	Yes	No
Did melatonin or ramelteon improve outcomes such as ICU Length of stay?	No	No	No	No
Was the use of melatonin or ramelteon deemed safe to use (i.e. no ADEs)?	Yes	Yes	Yes	Yes

8. Conclusion
    a. Missing Data:
        i. Currently no trials assess cost-effectiveness of either melatonin or ramelteon
        ii. Melatonin has limited generalizability due to lack of standardization in active ingredient between manufacturers. Therefore, no dose can truly be recommended which further limits the data available

    b. My conclusion based on the research and my clinical judgement
        i. Low risk with melatonin or ramelteon: Little evidence of ADE's with either medication
            1. Melatonin and ramelteon are lower in cost compared to that of a day in the ICU
            2. Lack of consistent data, however some benefits have been noted in the larger prospective trials
            3. If at high risk and expected ICU stay of > 48 hours, give 3mg of melatonin once nightly along with non-pharmacologic strategies
        ii. Larger, multicentered, prospective studies needed

Figure 2: Algorithm



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