Sleep, sedation and delirium in the ICUs

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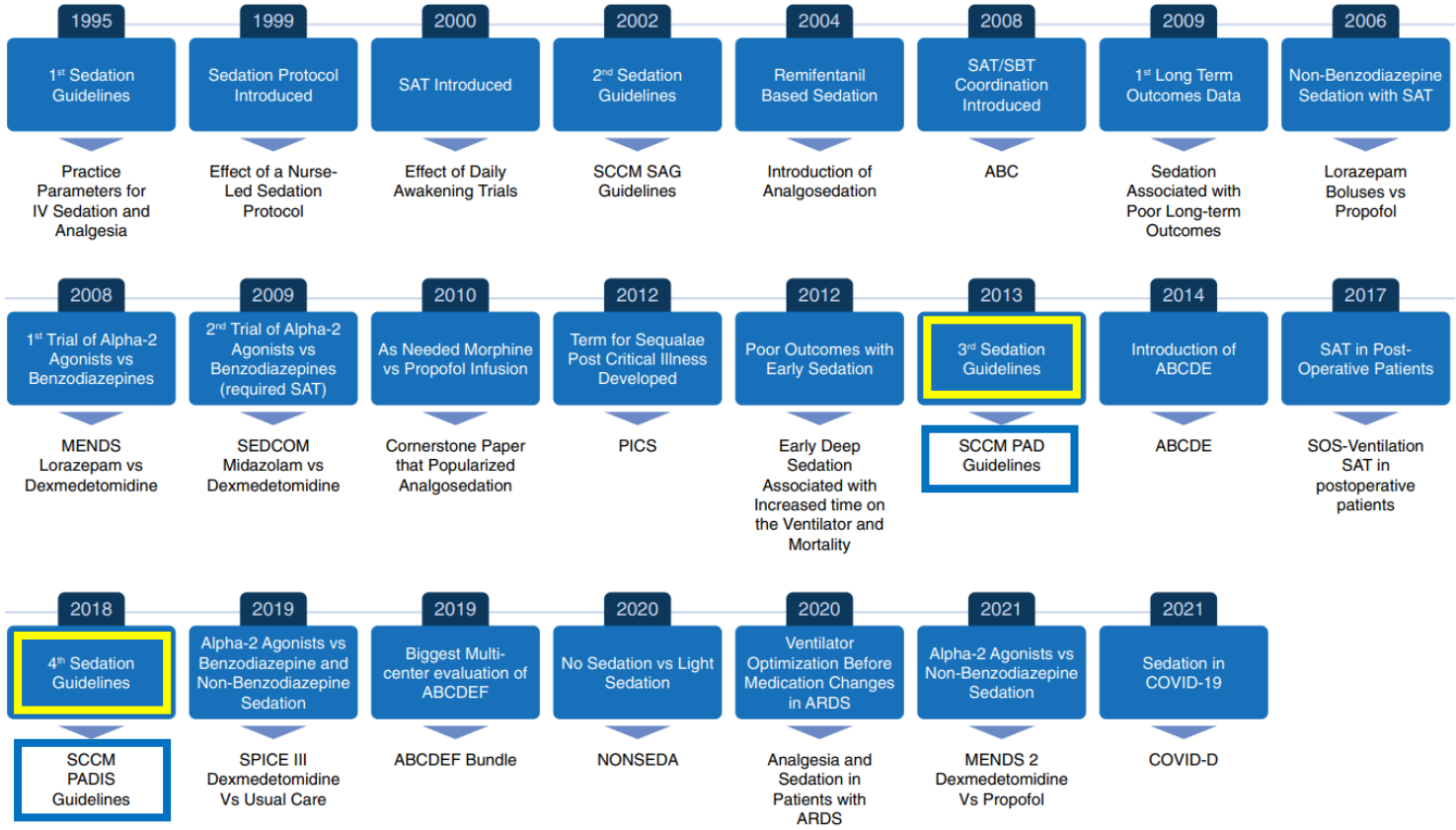
Evolution of sedation in the ICU

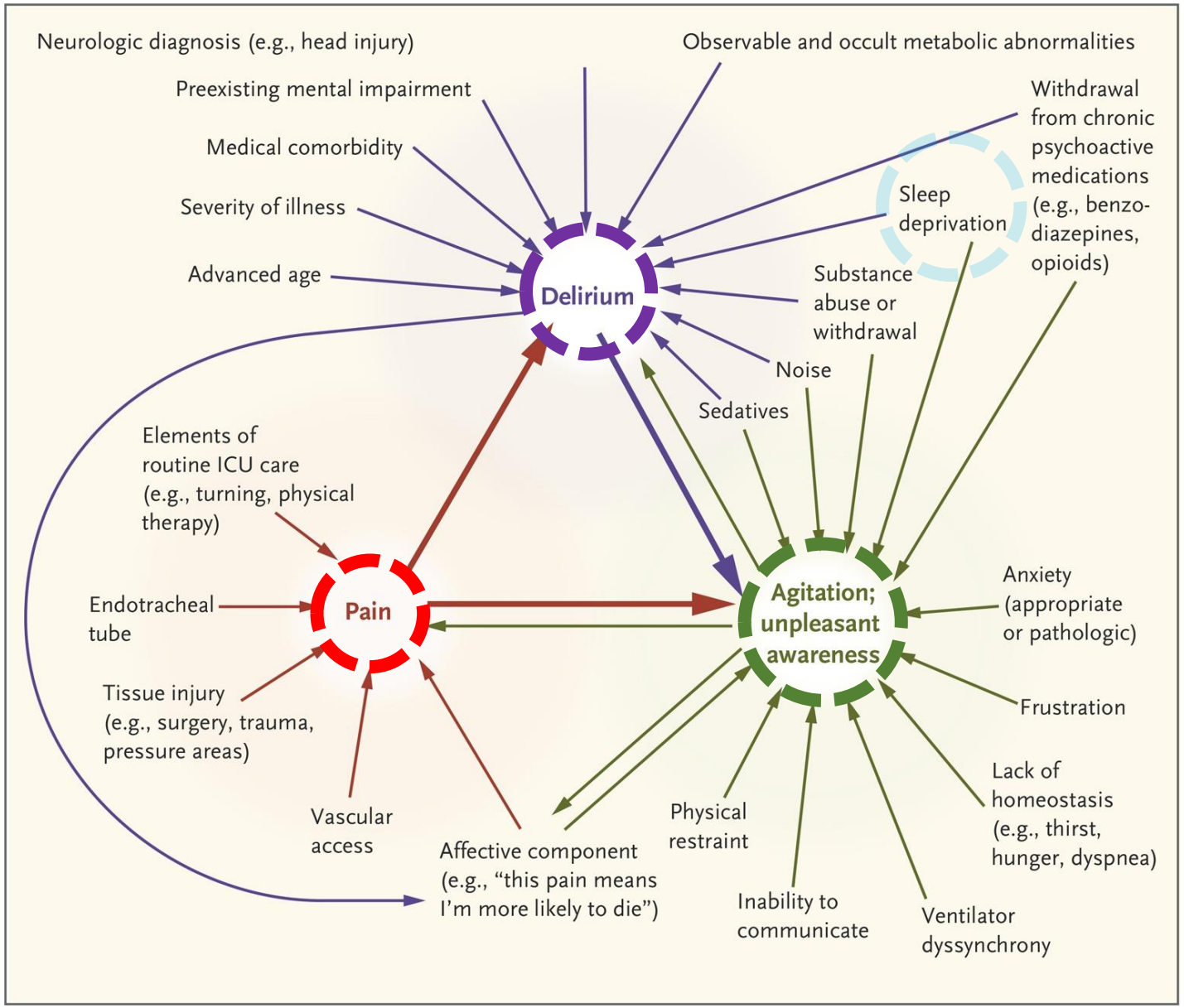


2013 Clinical practice guidelines for the management of **pain, agitation, and delirium** in adult patients in the intensive care unit

2018 Clinical Practice Guidelines for the Prevention and Management of **Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption** in Adult Patients in the ICU

Intensive Care Med. 2022 Nov;48(11):1625-1628.

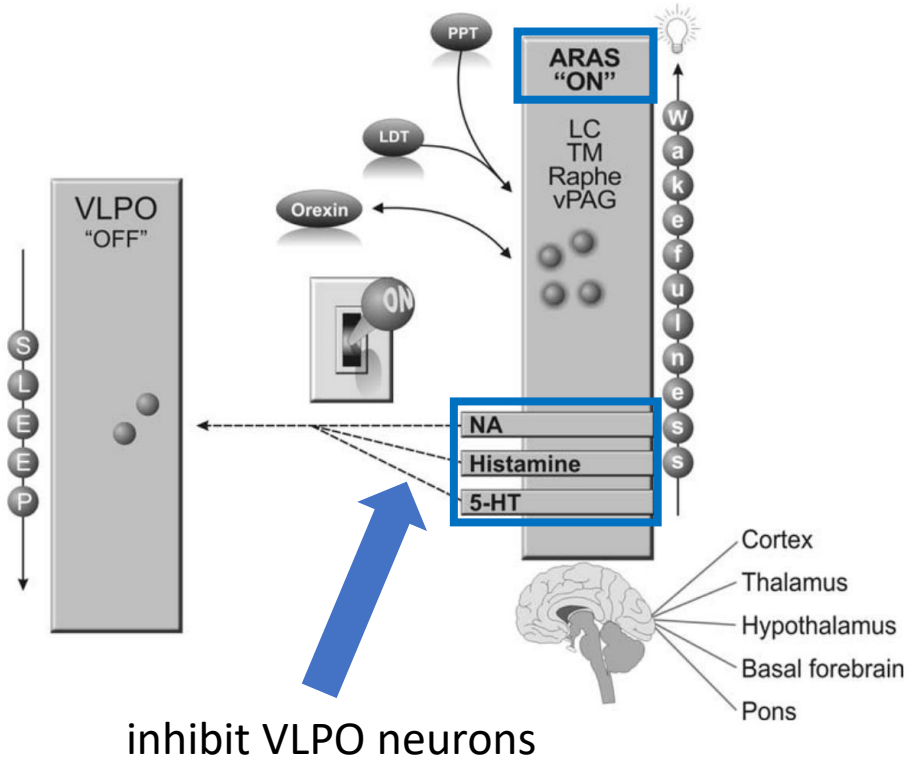
ICU triad



N Engl J Med. 2014 Jan 30;370(5):444-54.

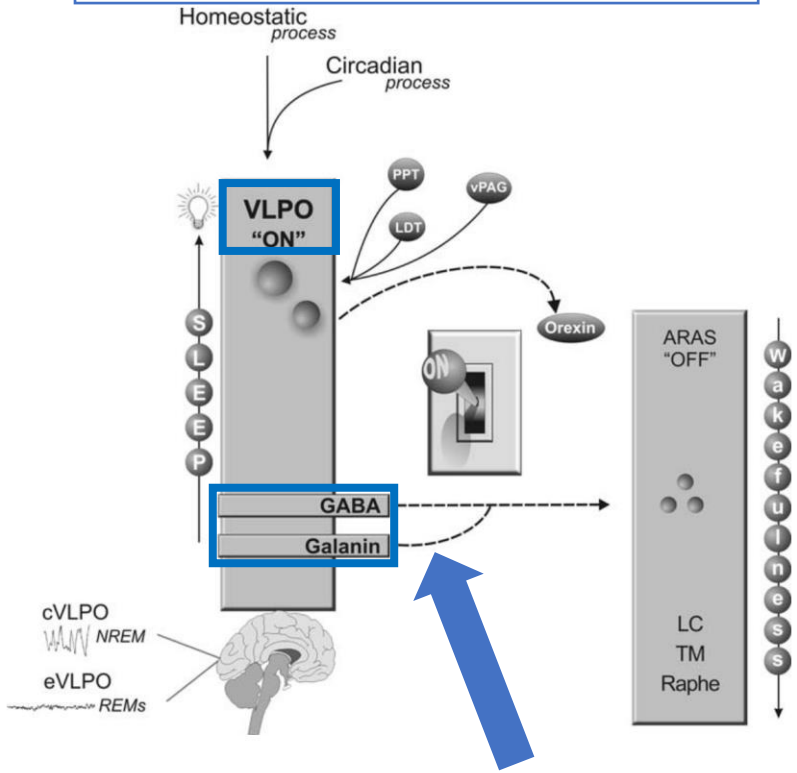
Sleep–wake-cycle: Flip-flop switch mechanism

ARAS is **On** during wakefulness



inhibit VLPO neurons

VLPO nucleus is **On** during sleep



inhibit ARAS neurons

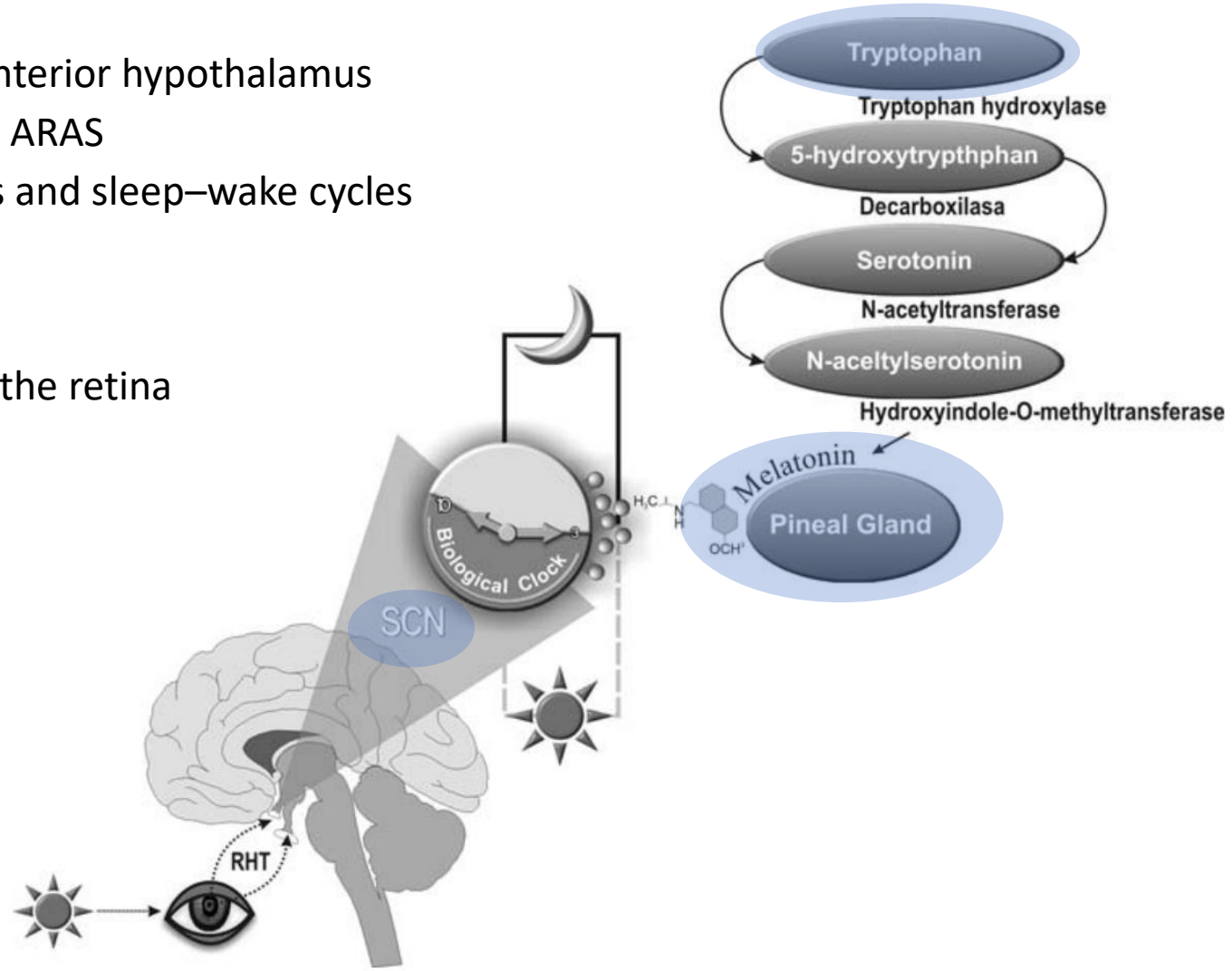
- Neural pathway that regulates the sleep–wake cycle
  - Ascending reticular activating system (ARAS)
  - Basal forebrain and lateral hypothalamus areas
  - Ventrolateral preoptic nucleus (VLPO) in the anterior hypothalamus→ sleep onset

Intensive Care Med. 2009 May;35(5):781-95.

Sleep–wake-cycle: Circadian rhythms

- Circadian rhythms
  - Regulation: suprachiasmatic nucleus (SCN), anterior hypothalamus
  - Input: retinal ganglion cells, pineal gland, and ARAS
  - Melatonin: maintenance of circadian rhythms and sleep–wake cycles

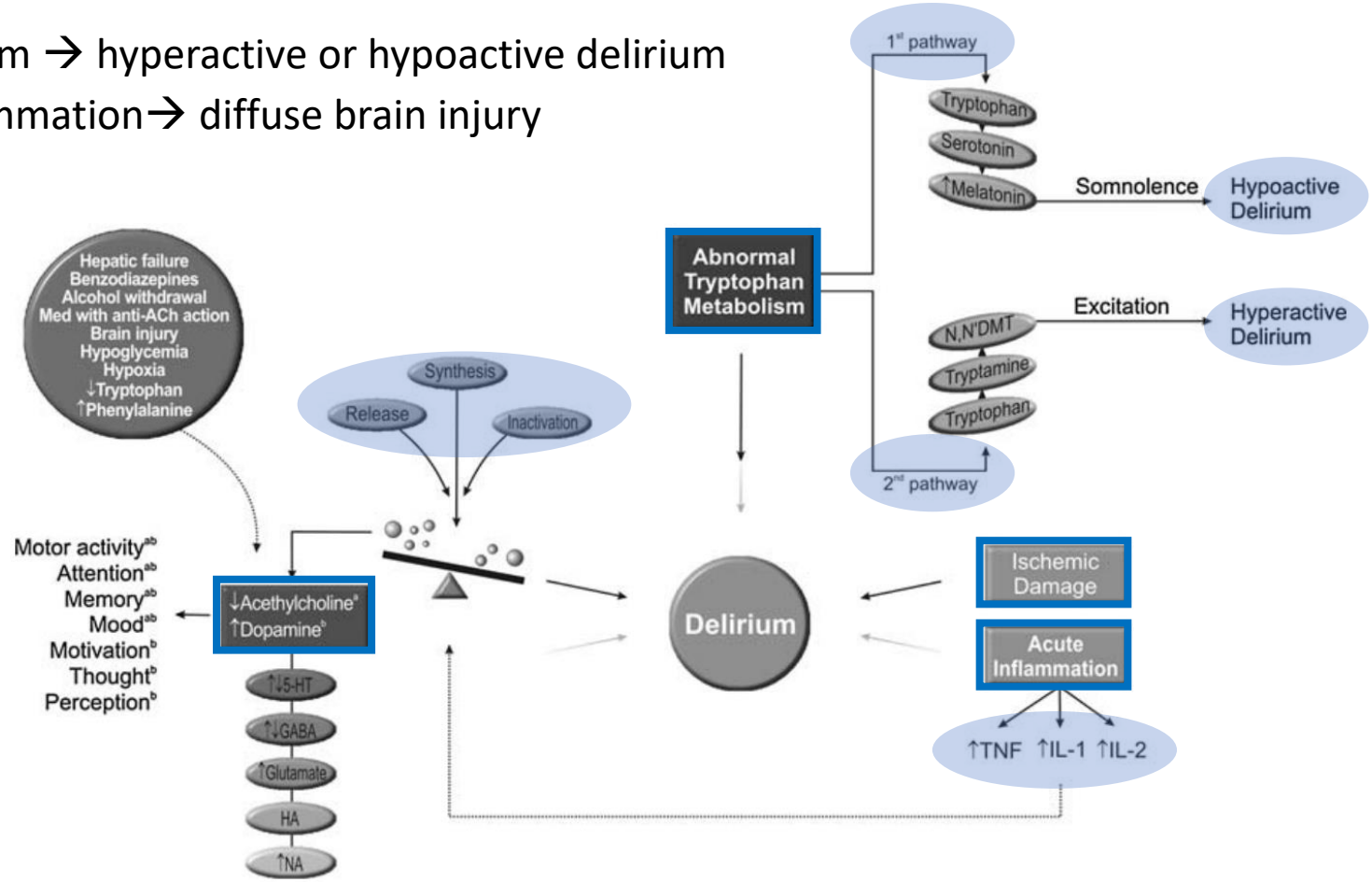
- SCN
  - light and dark environmental stimuli through the retina
  - regulates the secretion of melatonin



Intensive Care Med. 2009 May;35(5):781-95.

Delirium

- Hypotheses of delirium mechanisms
  - (1) imbalance in neurotransmitters
  - (2) abnormal tryptophan metabolism → hyperactive or hypoactive delirium
  - (3) ischemic damage or acute inflammation→ diffuse brain injury

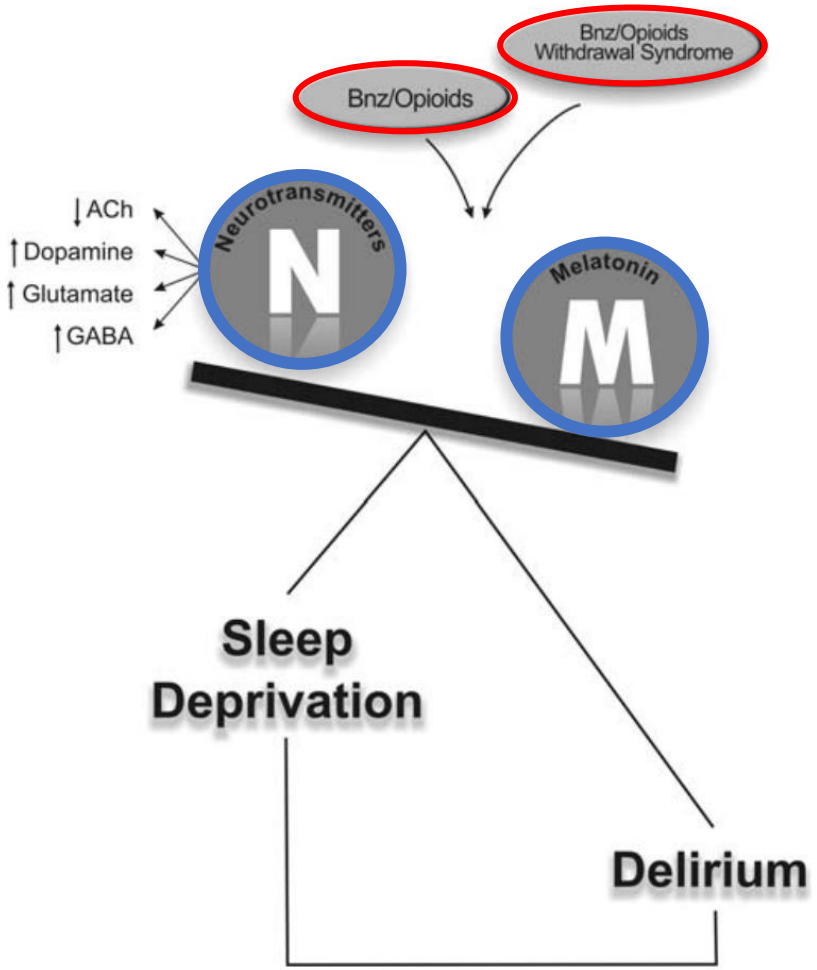


Intensive Care Med. 2009 May;35(5):781-95.

Sleep deprivation and delirium

- Similar mechanisms between sleep deprivation and delirium
  - imbalances in neurotransmitters
  - alteration of melatonin production

- Benzodiazepines and opioids
  - SWS ↓, REM sleep ↓, Delirium ↑
- Sudden discontinuation
  - Benzodiazepine withdrawal
    - GABA activity ↓ → hyperactive delirium, REM rebound
  - Opioid withdrawal
    - alterations in sleep architecture, REM rebound



Intensive Care Med. 2009 May;35(5):781-95.

Sleep and delirium

- January ~ September 2004
- ALI or ARDS with MV in SICU (n=29)
- Delirium assessment with CAM-ICU
- REM reduction: <6% of TST↓
- Severe REM reduction: >6% of TST↓

- In critically ill patients
  - fragmentation of sleep↑
  - arousals and awakenings↑
  - REM sleep↓

- Delirium is a risk factors of severe REM sleep reduction

	ALL (N.=29)	Severe REM reduction (N.=15)	REM reduction (N.=14)	P
Total sleep time (minutes)	343 (11-673)	355 (11-673)	331 (47-565)	NS
Stage 1 (minutes)	100 (11-206)	99 (11-174)	128 (21-206)	NS
Stage 2 (minutes)	162 (0-441)	228 (0-442)	120 (0-341)	NS
Stage 3 (minutes)	1 (0-377)	2 (0-377)	0 (0-27)	NS
Stage 4 (minutes)	0 (0-106)	0 (0-106)	0 (0-3)	NS
NREM (minutes)	263 (11-678)	329 (0-452)	248 (0-301)	NS
NREM (% total sleep time)	94 (29-99)	99	56 (45-83)	0.05
REM (minutes)	18 (0-72)	2 (0-36)	44 (16-72)	0.0001*
REM (% total sleep time)	6 (0-55)	1 (0-4)	11 (10-55)	0.0014*
REM periods (N.)	4 (0-6)	2 (0-2)	5 (3-6)	0.0014*
Arousals per hr	21 (4-187)	17 (4-84)	21 (5-187)	NS
Awakenings per hr	5 (2-86)	5 (2-24)	5 (2-86)	NS

TABLE V.—*Multivariate analysis* with sleep ("Severe REM reduction" vs. "REM reduction") as the a priori dependent factor.*

	Mean, SE	Odds ratio (95% CI)	P value
Delirium	119	34.5 (3.9-330.2)	0.0001*
Lorazepam	7	1.9 (1.8-1.2)	0.01*

Minerva Anestesiol. 2011 Jun;77(6):604-12.

Sleep and delirium

- 1996 ~ 2003
- major elective or urgent thoracic surgery operations (n=432)
- Postoperative delirium: 23 patients (5.32%) between postoperative days 2 to 12

- Sleep deprivation is a risk factors of postoperative delirium

Table 4. Factors in the Logistic Regression Model Associated With Postoperative Delirium

	Beta Coefficients	Standard Error	Wald	df	*p*	Exp (B) = Odds Ratio
Constant	−6.539	1.289	25.750	1	0.000	0.001
Markedly abnormal serum chemistry values	1.102	0.532	4.287	1	0.038	3.011
Sleep deprivation	1.730	0.881	3.856	1	0.05	5.642
Age	0.039	0.018	4.559	1	0.033	1.040
Operation time	0.252	0.123	4.178	1	0.041	1.287
Nagelkerke $R^2 = 0.128$						

Ann Thorac Surg. 2005 Mar;79(3):1004-9.

Delirium assessment

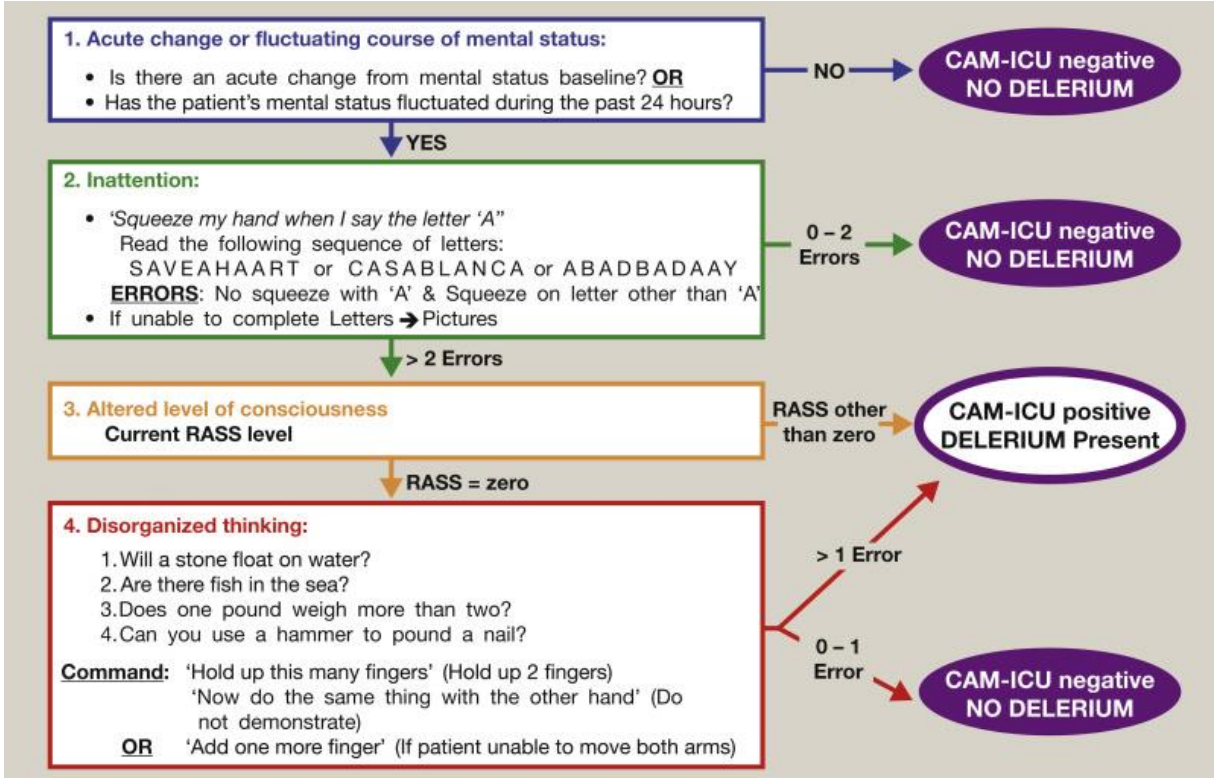
ICDSC

Item of the ICDSC	Description	Score
Altered LOC (with RASS or SAS)	• Deep sedation/coma (not assessable) • Agitation/light sedation without recent sedatives (1 point) • Normal wakefulness/light sedation with recent sedatives (0 point)	1 or 0
Inattention	• Difficulty following instructions or conversation; easily distracted by external stimuli. • Will not reliably squeeze hands to spoken letter "A": SAVEAHAART	1 or 0
Disorientation	• In addition to name, place, and date, does the patient recognize ICU caregivers? • Does patient know shat kind of place they are in? (list examples such as dentist's office, home, work, hospital)	1 or 0
Hallucination, delusion, or psychosis	• Ask the patient if they are having hallucination or delusion (e.q. trying to catch an object that isn't there) • Are they afraid of the people or things around them?	1 or 0
Psychomotor agitation or retardation	• Hyperactivity requiring the use of sedatives or restrains to control potentially dangerous behavior • Hypoactive or clinically noticeable psychomotor slowing or retardation	1 or 0
Inappropriate speech or mood	• Patient displays inappropriate emotion, disorganized or incogerent speech, sexual or inappropriate interactions or is apathetic or overtly demanding	1 or 0
Sleep-wake cycle disturbance	• Frequent awakening/<4 hours sleep at night or sleeping during much of the day	1 or 0
Symptom fluctuation	• Fluctuation of any of the above symptoms over a 24-hour period	1 or 0

ICDSC score ranges from 0 (minimum: normal) to 8 (maximum: overt delirium).

Some domains can be difficult to assess or can be misinterpreted

CAM-ICU



Developed to identify delirium in MV and non-ventilated ICU patients

J Neurocrit Care 2015;8(2):39-45
JAMA. 2001 Dec 5;286(21):2703-10.

Assessment of the sedation level

Sedation-Agitation Scale

SAS Score	Status
7	Dangerous agitation
6	Very agitated
5	Agitated
4	Calm and cooperative
3	Sedated
2	Very sedated
1	Unarousable

Richmond Agitation–Sedation Scale (RASS)

RASS Points	Term	Descriptions
+4	Combative	• Overtly combative, violent, immediate danger to staffs
+3	Very agitated	• Pulls or remove tube(s) or catheter(s): verbally aggressive
+ 2	Agitated	• Frequent non-purposeful movements: fight ventilator
+1	Restless	• Anxious, but movements are not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	• Not fully alert, but has sustained awakening (eye-openig/eye contact) to voice (>10 sec)
-2	Light sedation	• Briefly awakens with eye contact to voice (<10 sec)
-3	Moderate sedation	• Movement or eye opening to voice (but no eye contact)
-4	Intense sedation	• No response to voice, but movement or eye opening to physical stimulation
-5	Does not wake	• No response to verbal or physical stimulation

arousal state, cognitive function, response sustainability

J Neurocrit Care 2015;8(2):39-45

Measuring Sleep in the ICU

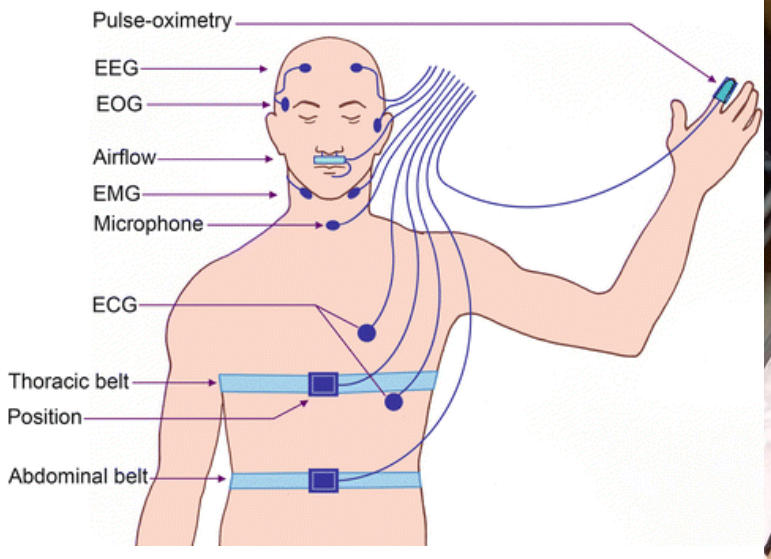
Measurement Tool	Outcome Measured	Advantages	Disadvantages
Traditional			
Subjective[a]	Patients' or surrogate's subjective assessment of their sleep	Most accessible, least costly	Recall bias. Altered recall due to delirium or sedation. Variable relationship with results of polysomnography
Actigraphy	Motion detector	Simple, not intrusive, little cost	Measures only motion so the effects of sedation and ICU care on motion not considered
Electroencephalogram-focused			
Processed electroencephalogram	Analysis of electroencephalogram waveform as surrogate for depth of sedation	Easy to use and available	Not validated against polysomnography as a measure of sleep
Polysomnography	Electroencephalogram Electrooculogram Electromyogram	Gold standard for measuring sleep in all patient settings	Limited by cost, requires skilled personnel to apply, interpretation difficult in the ICU, very intrusive
Single-channel electroencephalogram	Mostly delta power Frontal electrode	Uses delta waves to detect acute encephalopathy and/or ICU "depth of sleep" Mildly intrusive, easily applied. Real-time data	Crude assessment of level of consciousness. Likely cannot distinguish between different states of altered consciousness
Multichannel electroencephalogram	Several channel electroencephalogram (frontal) and also capable of collecting electrooculogram and electromyogram	Includes electroencephalogram but also with ability to do sleep staging Mildly intrusive, easily applied. Real-time data	Not as good as polysomnography for sleep staging
Newer physiologic-based methods of sleep assessment: not yet tested in the critically ill			
Functional imaging	CNS blood flow (functional MRI) CNS metabolism (positron emission tomography)	Records very specific physiologic measurements	Costly. Difficult/even risky to transport critically ill adults to conduct these studies. Studied in the critically ill for disorders of consciousness but not specifically sleep
MicroRNA	Experimental use for detecting or predicting poor sleep quality	Could become available serum biomarker	Currently untested for clinical use and in the critically ill

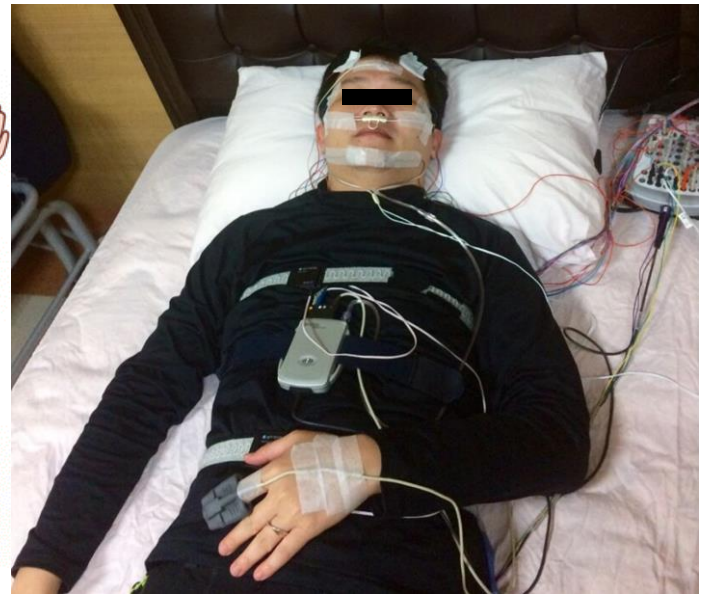
- Challenging
- **No** widely accepted **gold standard**
- medications, organ dysfunction, and critical illness itself can affect sleep classification and quantification

Crit Care Explor. 2022 Feb 7;4(2):e0628.

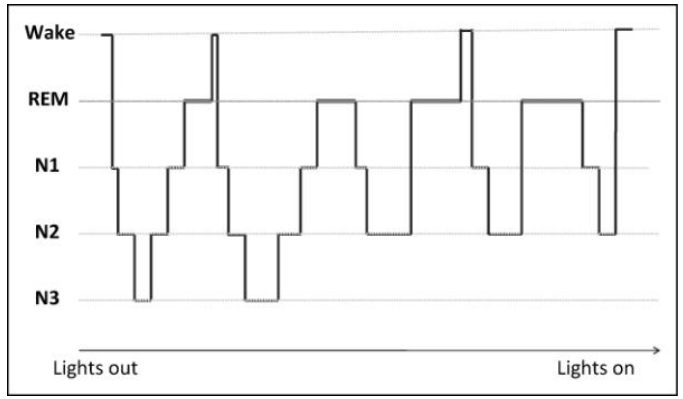
Polysomnography (PSG)

- Gold standard for sleep evaluation in **noncritically ill patients**





Normal adult hypnogram



REM: rapid eye movement

NREM: non-rapid eye movement

- N1, N2, and N3/slow wave sleep (SWS)

- Inaccurate in critically ill patients
- Expensive, labor intensive, often poorly tolerated by patients
- Interfere with beside care
- Recording at least 24 hours

Semin Respir Crit Care Med 2019;40:614–628.

Polysomnography (PSG)

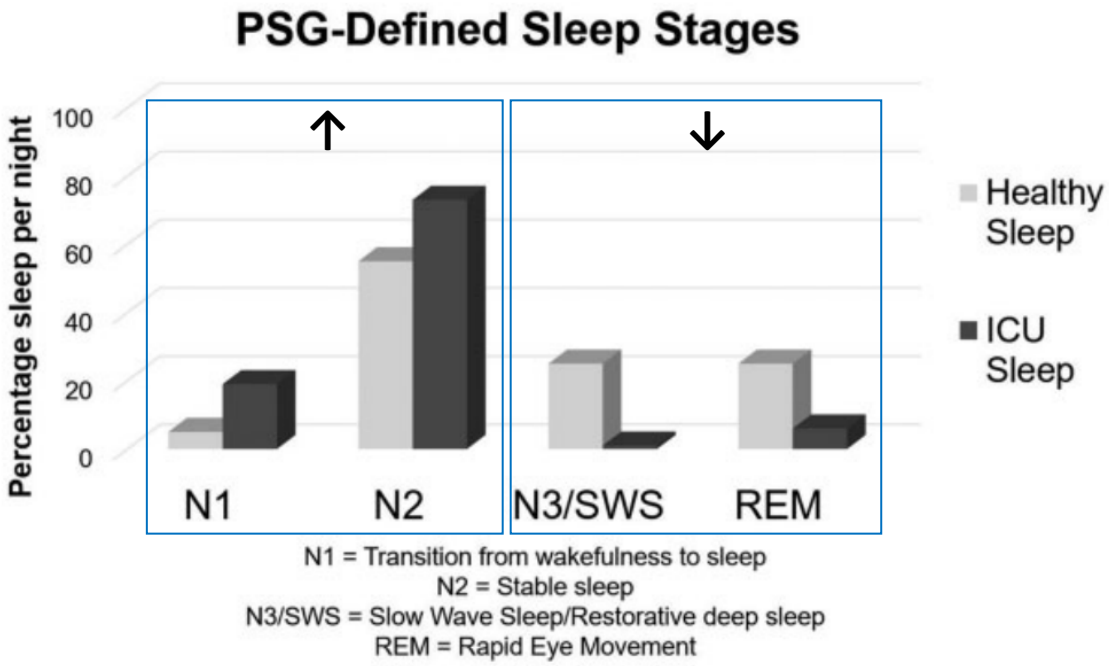
Table 1 Characteristics of NREM and REM sleep

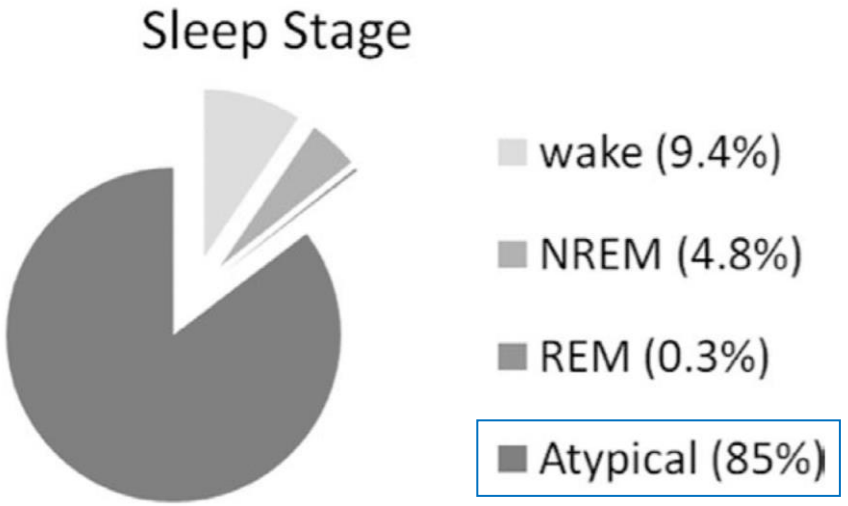
Characteristics	Sleep stages			
	NREM			REM
	Stage 1	Stage 2	SWS	
EEG				
% of the TST	2–5%	45–55%	15–20%	20–25%
Wave	Low-voltage Mixed frequency activity	Intermittent sleep spindles and K-complexes	High voltage Slow delta waves	Low-voltage amplitude Saw-tooth waves high frequency EEG
Physiologic	↓ CBF (brain stem and cerebellum in stages 1 and 2)↓ CBF (cortex in SWS) ↑ GH and ↓corticosteroids and catecholamines (SWS) ↓ HR, ↓ BP, ↓ RR (more regular than REMs) ↑ PAP ↓ CO ↓ Brain temperature Arousal threshold increase through the stages			↑ CBF Cardio-respiratory irregularities[a] (↑ HR, ↑ RR and BP variations) ↑ Brain temperature[b] Pupil change[b] High arousal threshold[b]
Behavioral	Leg movement Changes in posture Talking Sleep walking Dreams (at sleep onset and stage 2)			Muscle atonia[b] Muscle twitches[a] Rapid eye movement[a] Dreams

Intensive Care Med. 2009 May;35(5):781-95.

Polysomnography (PSG)

- Critically ill ICU patients
  - deranged sleep
  - atypical EEG patterns ~85%
  - no clearly assignable traditional sleep stage

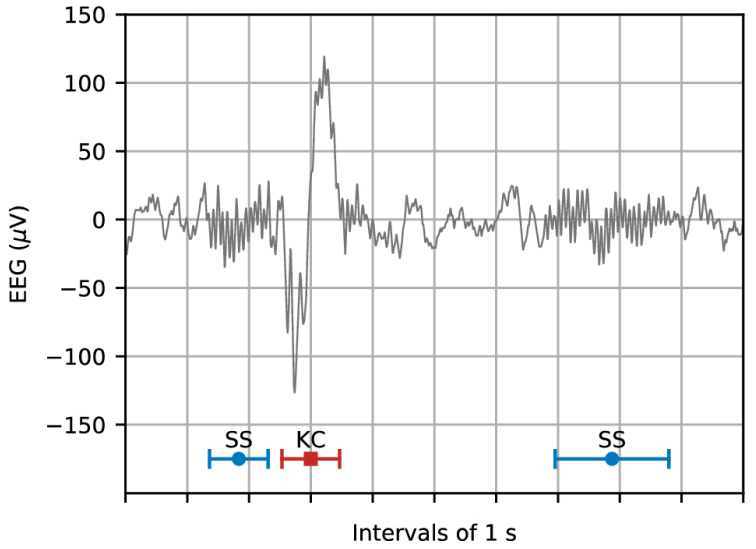




Semin Respir Crit Care Med 2019;40:614–628.
Sleep Med. 2012 Jan;13(1):7-14.

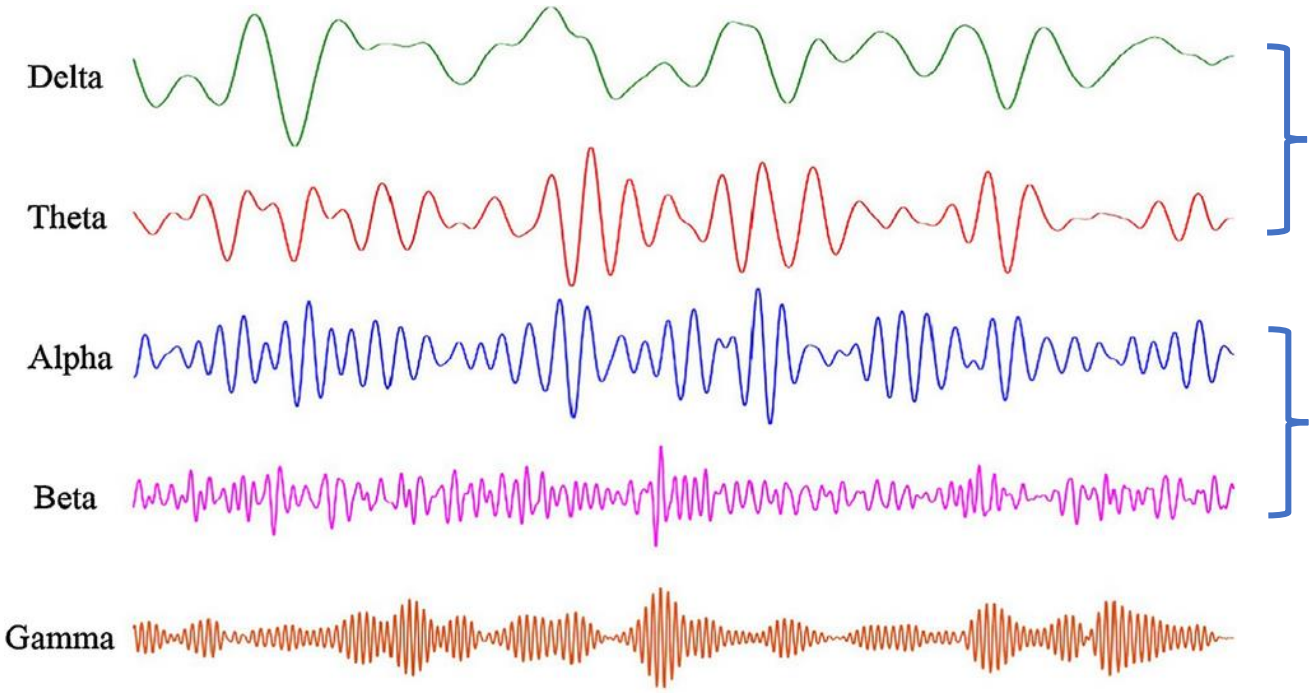
Sleep alterations in critical illness

- Abnormal sleep patterns
  - behaviorally **awake**, but dissociative EEG (**theta and delta waves**)
  - **Coma**, but EEG with **beta and alpha waves**
  - Pathologic wakefulness
  - Atypical sleep: NREM sleep without spindles or K complexes



Sleep spindles and K-complexes: during N2, cognitive functions

Sleep EEG waves



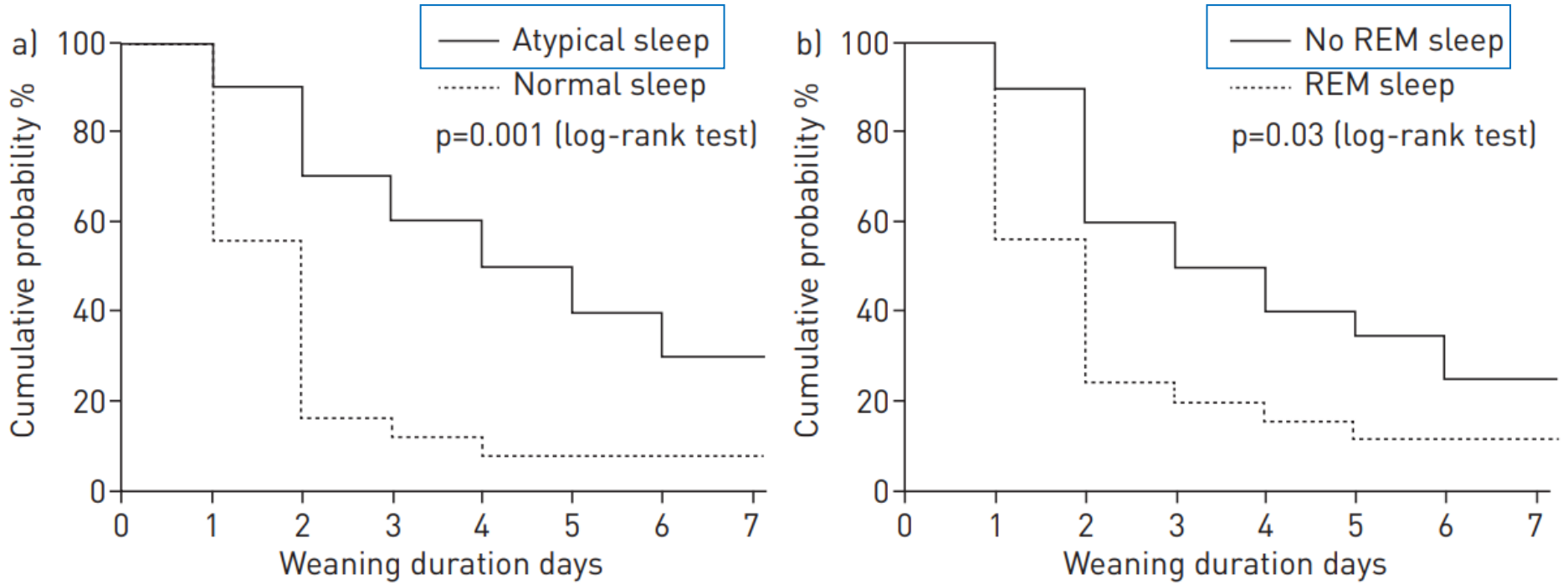
low frequencies: **sleep**

higher frequencies: **wakefulness**

Crit Care Explor. 2022 Feb 7;4(2):e0628.

Impact of sleep alterations

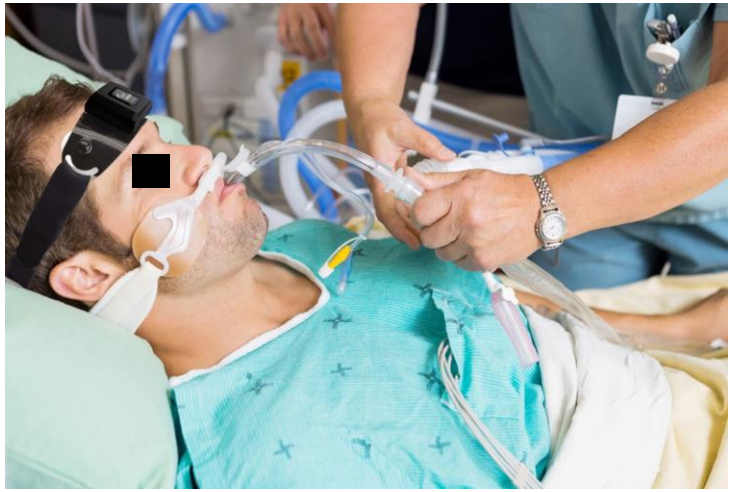
- Prospective physiological study (n=45)
- PSG: after the first SBT failure
- Altered sleep (atypical sleep or absence of REM sleep): weaning duration ↑



Eur Respir J. 2018 Apr 19;51(4):1702465.

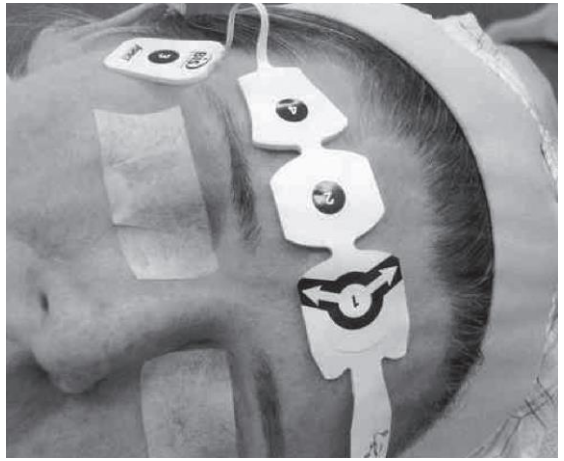
Partial PSG and Bispectral index (BIS)

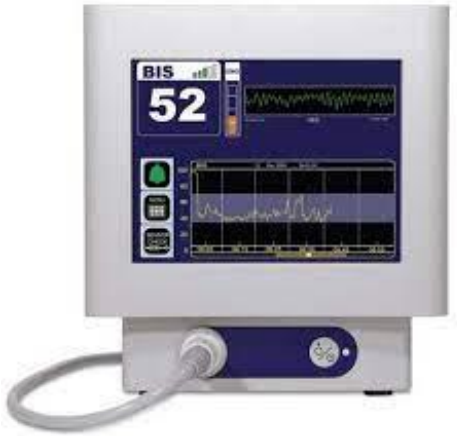
- Single-Channel Electroencephalogram
- Multichannel Electrophysiologic Devices



Single channel EEG monitoring in MV patient

- Processed Electroencephalogram
- EEG-derived parameter to monitor the hypnotic effects
- Usually in OR, monitoring of depth of sedation
- not validated for sleep measurement in critically ill patients





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Semin Respir Crit Care Med 2019;40:614–628.

Actigraphy

- Small noninvasive device
- Wristwatch-like **accelerometer** → continuously measures spontaneous limb activity/movement
- Limited use in critically ill patients
  - activity levels are impacted by sedation, weakness, delirium, bathing, myopathy

J. Clin. Med. 2023, 12(3), 1182;

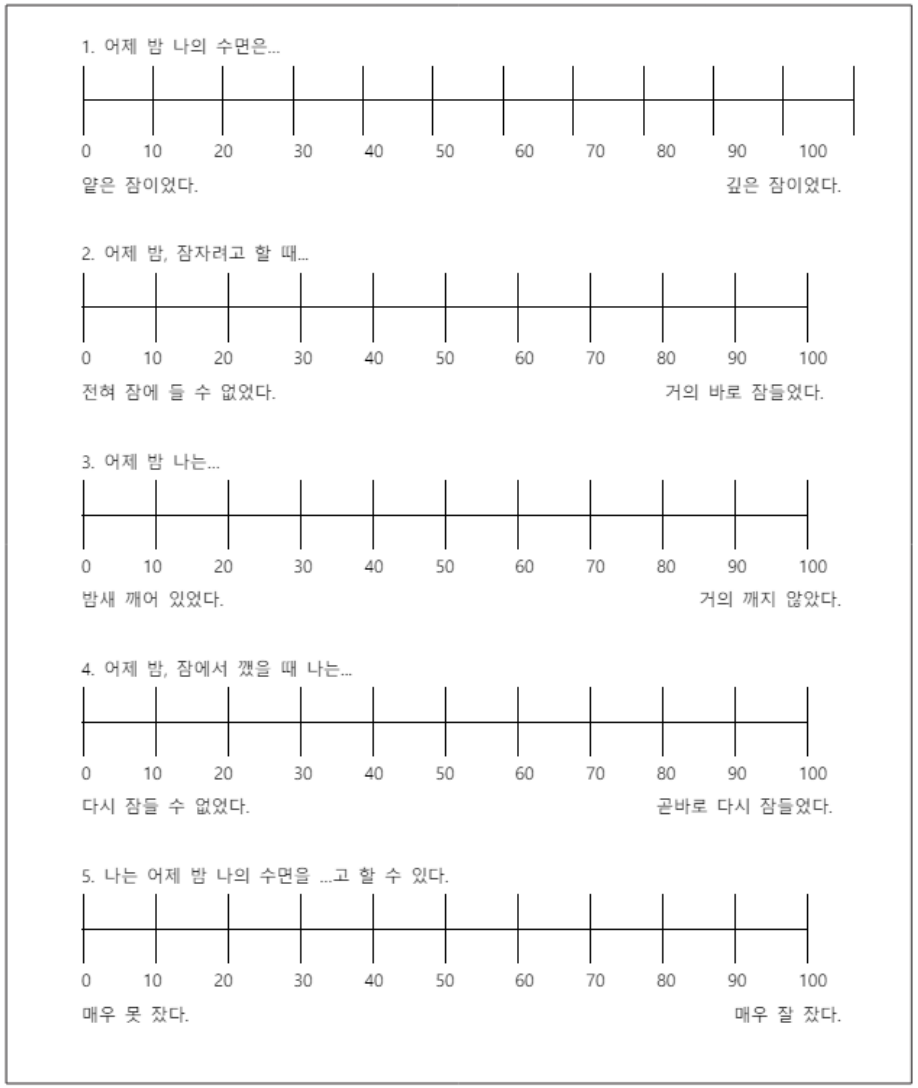
Questionnaires

- Richards Campbell Sleep Questionnaire (RCSQ): **by patients**
  - use in awake, alert, and responsive patients
- Sleep Observation Tool (SOT): **by nurse**
  - conducted in awake, low severity of illness ICU patients

- Easy to complete, low cost, feasible for large-scale use

- Limited reliability due to
  - recall bias
  - altered patient cognition
  - rater fatigue
  - inability to capture daytime sleep

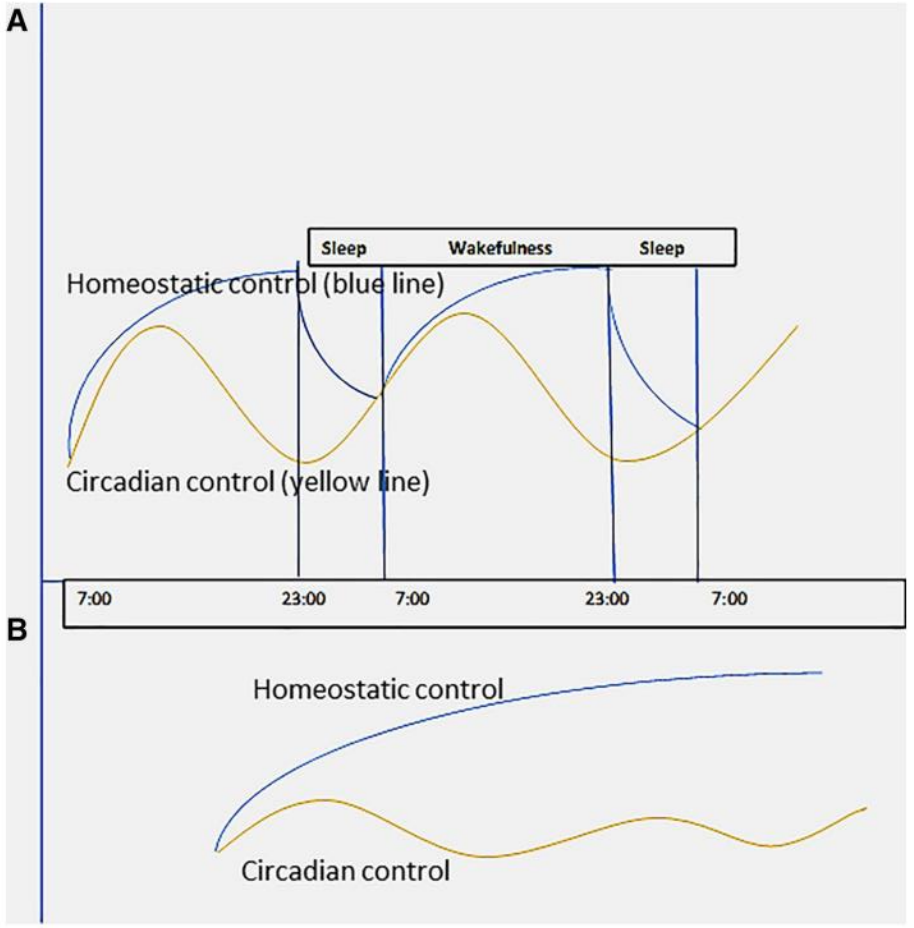
Supplementary Figure 2. Korean version of Richards-Campbell Sleep Questionnaire (K-RCSQ)



Crit Care Explor. 2022 Feb 7;4(2):e0628.

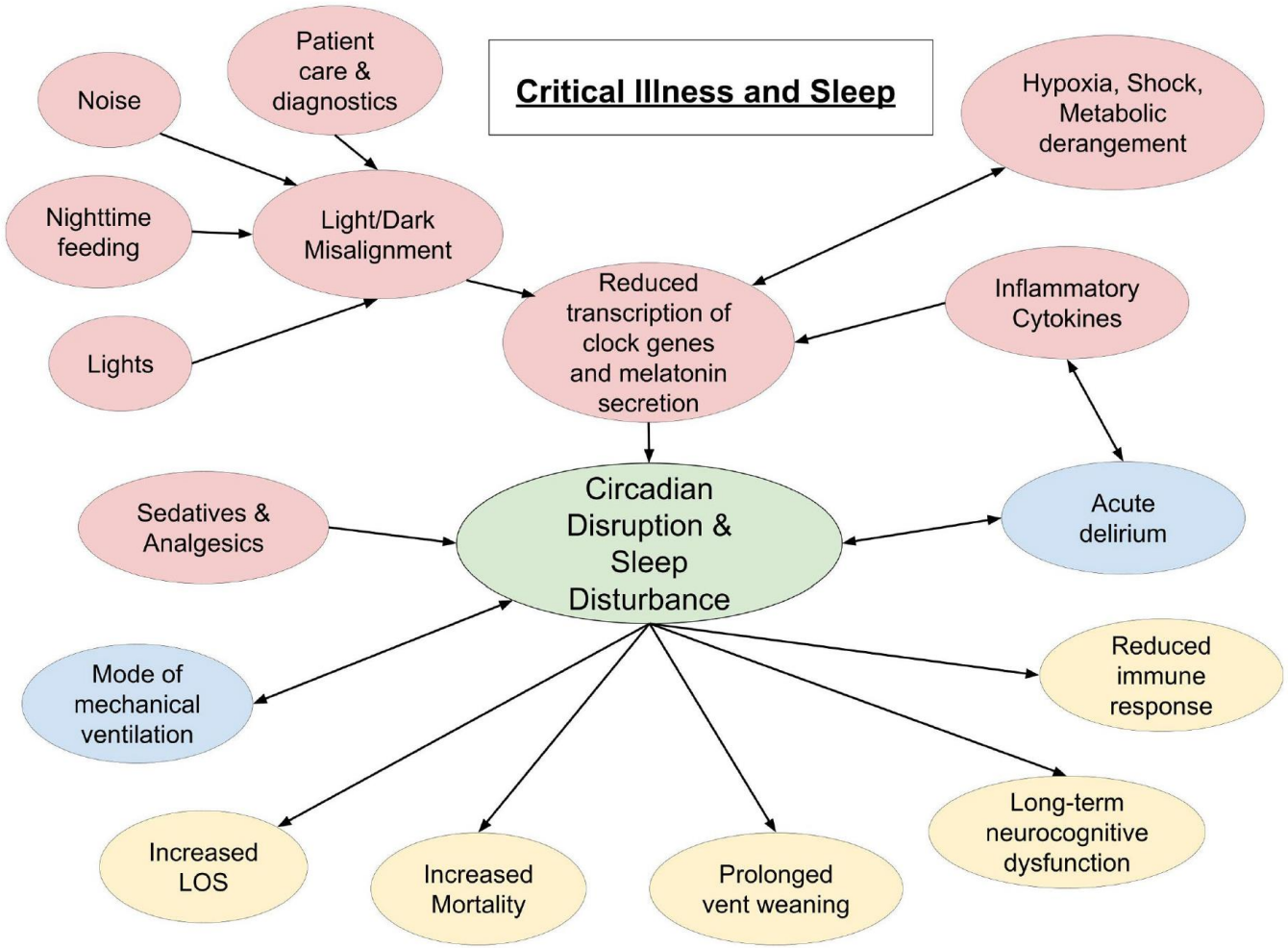
Sleep alterations in critical illness

- Two forces control the sleep-wake cycle
  - 1) Homeostatic drive
  - 2) Circadian rhythms
- Maintained circadian rhythm, but later sleep onset
  - Total sleep time (TST): normal
  - Sleep efficiency ↓, fragmentation (disruption) ↑
  - Light sleep >>> deep NREM, REM sleep



Crit Care Explor. 2022 Feb 7;4(2):e0628.

Causes and consequences of sleep disturbance in the ICU



Semin Respir Crit Care Med 2019;40:614–628.

Light in the ICU

- Abnormal light levels
  - dim light during the day
  - bright light at night
- Nocturnal light levels <20 lux
  - high-lux light exposure↑ → sleep fragmentation

Light Exposure in the ICU

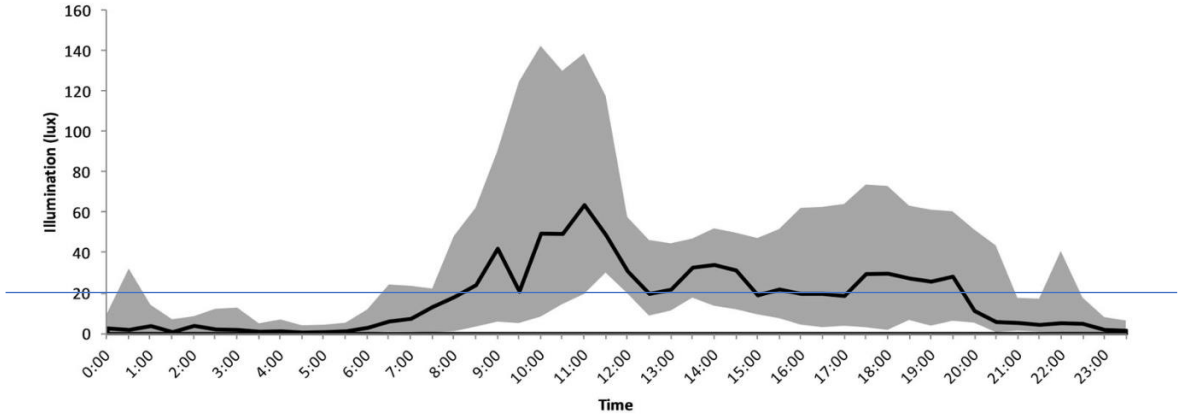


Table 5. Comparison of scores of sleep quality domains in the studied groups before the intervention

Domains	Test Control mean (SD)	Test mean (SD)	P*
Subjective sleep quality	0.83 (0.59)	1.46 (0.77)	0.000
Sleep latency	1.16 (0.53)	1.46 (0.77)	0.000
Sleep duration	1.2 (0.61)	1.66 (0.75)	0.000
Habitual sleep efficiency	0.93 (0.58)	1.53 (0.86)	0.000
Sleep disturbance	1.06 (0.44)	1.33 (0.8)	0.001
Use of sleeping medications	0.86 (0.57)	1.4 (0.8)	0.000
Daytime dysfunction	1.3 (0.53)	1.63 (0.71)	0.000

* Independent t-test

improved subjective sleep with the use of eye masks in cardiac ICU

J Crit Care. 2017 Aug;40:11-14.
J Caring Sci. 2012 Aug 25;1(3):135-43.

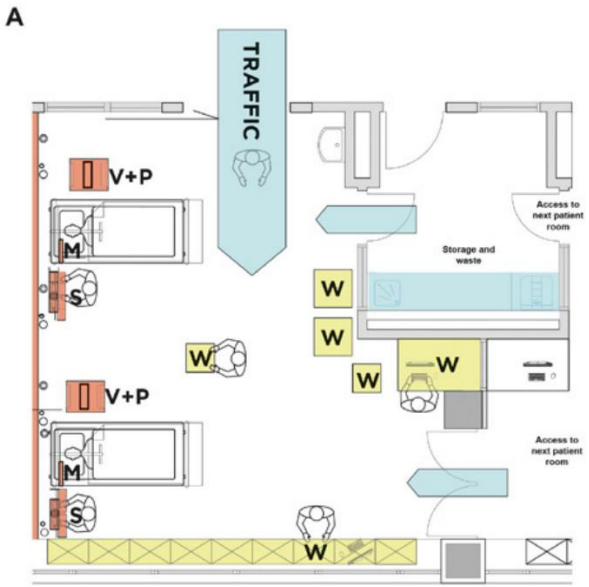
Sound in the ICU

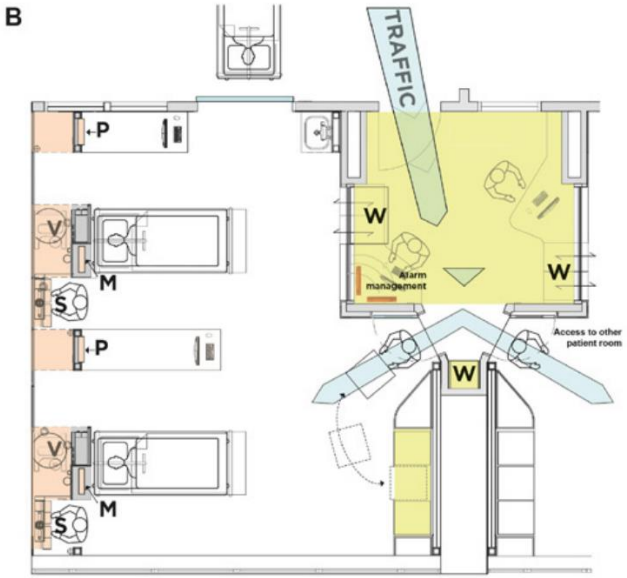
- WHO recommendations: continuous background sound < 30 dB, peak nocturnal sounds < 40 dB
  - ventilator (51 dB), suction (53 dB), syringe pump alarms (63 dB)
- Sound attenuation in the ICU

  (1) behavioral interventions: minimizing conversations, reducing unnecessary alarms

  (2) sound masking: white noise

  (3) sound blocking: earplugs





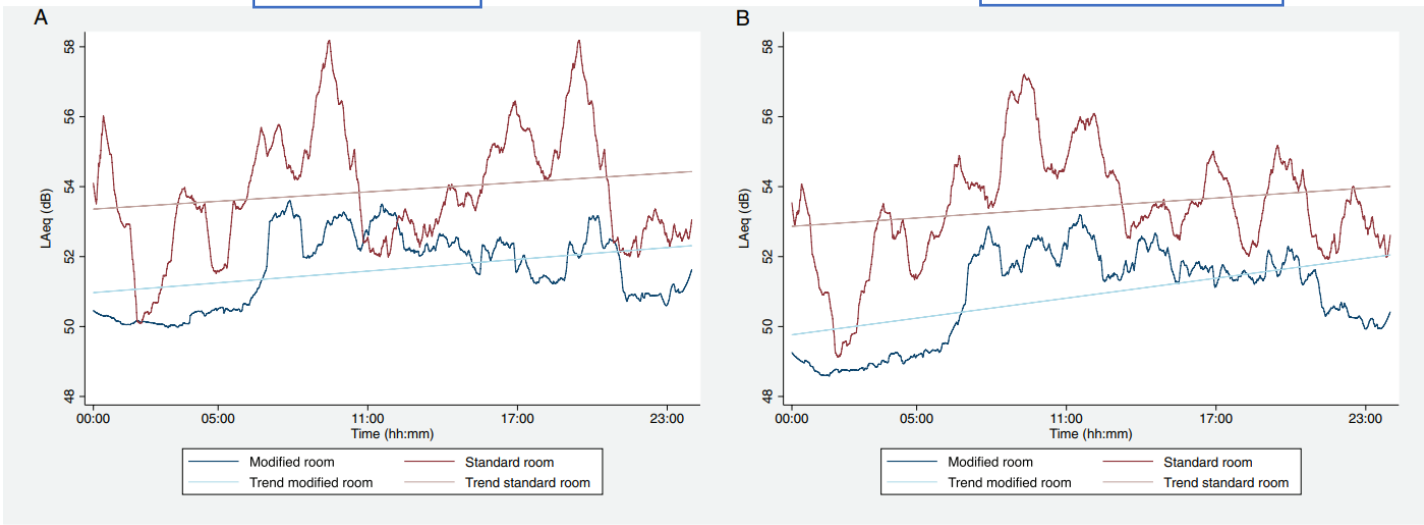
Semin Respir Crit Care Med 2019;40:614–628.

Sound in the ICU

- Behavior-based sound reduction: staff education, education with sound monitoring, education with environmental modifications

Door side

Window side

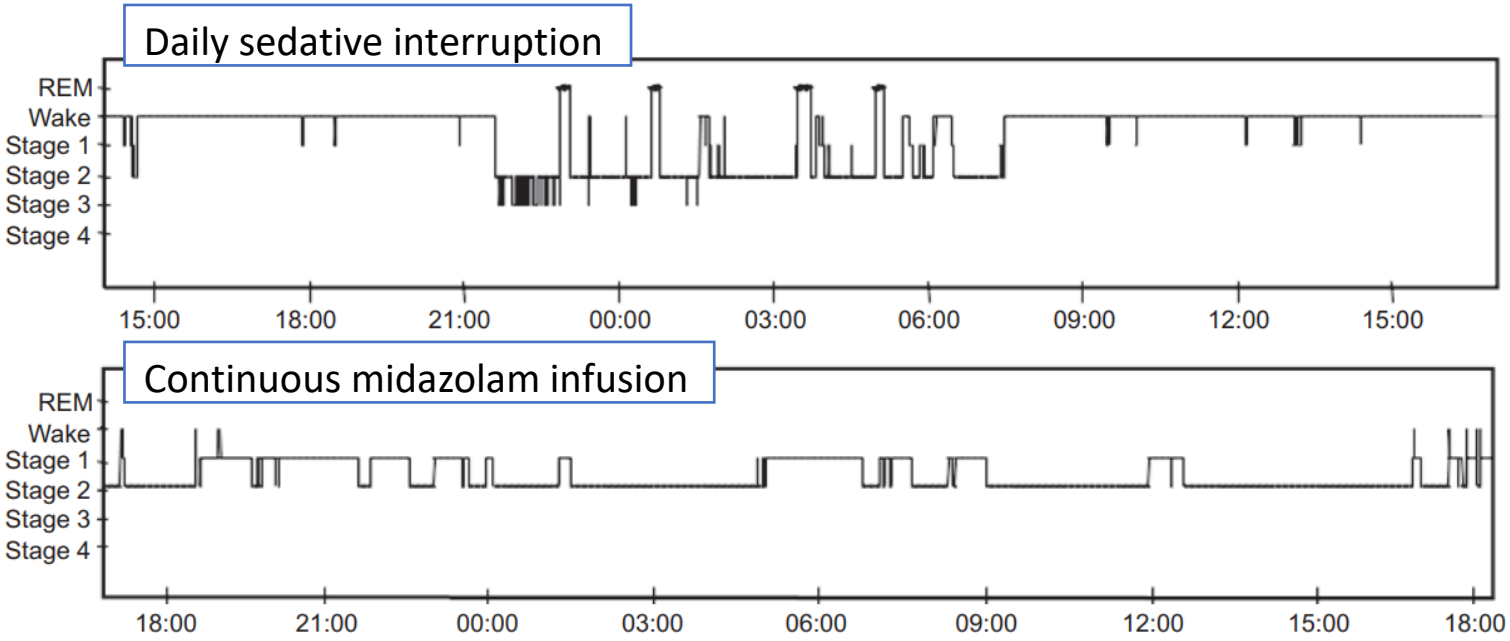


During night-time, significant decrease in 50 dB threshold overruns

Physiol Meas. 2016 Jul;37(7):1041-55.

Daily sedative interruption and sleep

- MV patients receiving midazolam (n=22)
- MV patients: abnormal sleep architecture
- DSI increased SWS and REM sleep



Sleep architecture during study period between two groups

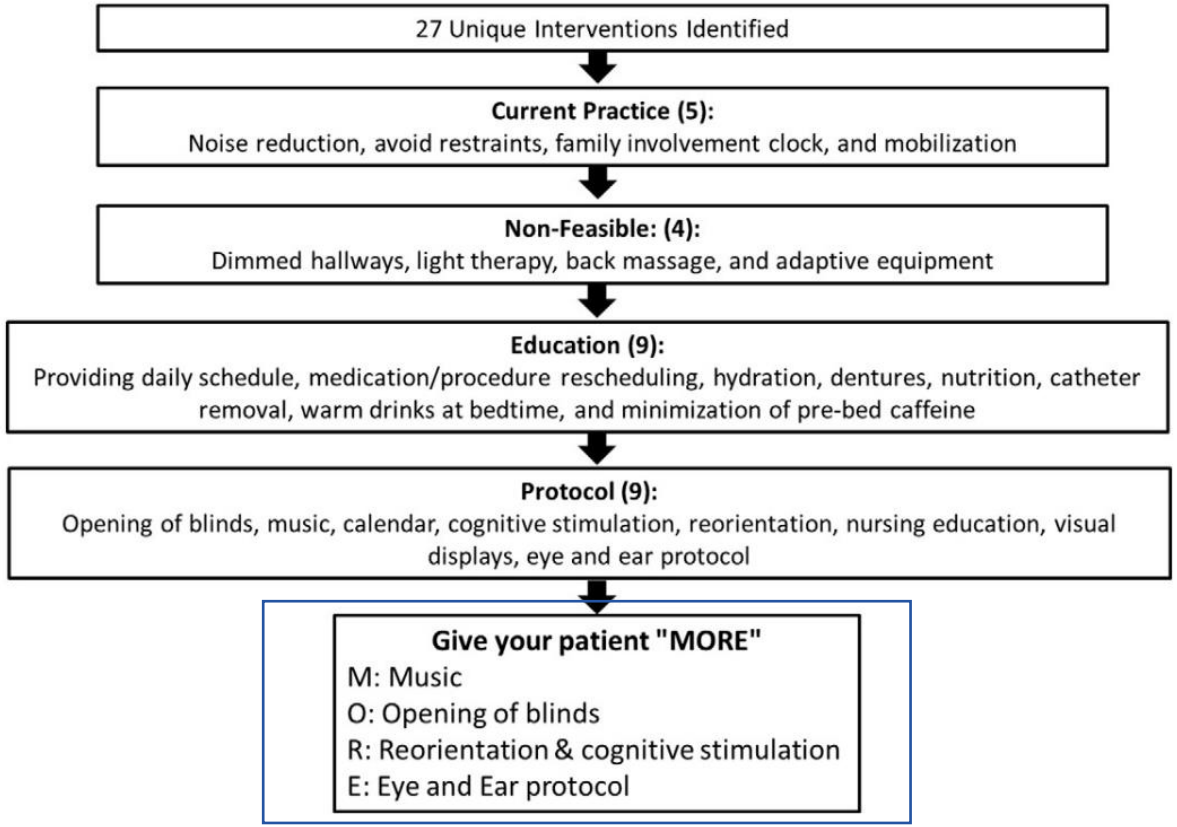
Variables	DSI group	CS group	*P* value
Whole day, 24 h			
Total sleep time, h	12.3 (9.0,14.6)	23.3 (22.1, 23.5)	0.002
Stage 1, min	222 (186, 246)	474 (168, 846)	0.16
Stage 2, min	408 (312, 462)	654 (306, 1242)	0.27
Stage 3, 4, min	6 (6, 7.2)	0 (0, 0)	0.04
REM, min	54 (24, 84)	0 (0, 12)	0.02
Arousal index, n/h	3.4 (2.6, 6.7)	2.2 (0, 2.8)	0.04
Night-time period, 9 h			
Total sleep time, h	7.3 (6.6, 8.2)	8.7 (8.2, 8.8)	0.047
Stage 1, min	96 (60, 144)	180 (54, 342)	0.46
Stage 2, min	264 (222, 360)	282 (66, 468)	0.55
Stage 3, 4, min	1.8 (0.6, 4.2)	0 (0, 0)	0.03
REM, min	30 (12, 48)	0 (0, 9)	0.01
Arousal index, n/h	4.4 (2.5, 8.3)	2.2 (0, 2.6)	0.03

Data were presented as median (quartile) unless otherwise noted. REM=rapid eye movement. DSI=daily sedative interruption, CS=continuous sedation, REM=rapid eye movement.

Anaesth Intensive Care. 2011 May;39(3):392-400.

Nonpharmacologic protocol to prevent delirium

- Phase 1: before protocol implementation (3-month)
- Phase 2: post–protocol implementation (3-month)



A comparison of delirious patient outcomes in phase 1 to phase 2

Delirium-related outcomes	Phase 1 (n = 230)	Phase 2 (n = 253)	*P*
Time delirious of ICU length of stay, h	20 (9.5-37)	16 (8-24)	<.001
Incidence of delirium (n, %)	36, 15.7	24, 9.4	.04
ICDSC screening frequency, h	6.3 (4.7-8.9)	9.3 (6.3-15.5)	<.001
Patients unable to be assessed at ICU presentation (n, %)	33, 14.5	58, 23.0	.02
ICU length of stay, h	188.3 (103.5-253)	153.5 (89-291)	.79
Time from ICU admission to delirium development, h	58.5 (12.3-110)	53.8 (21.5-113.5)	.74
Time unable to be assessed of ICU length of stay, h	0 (0-33)	0 (0-10)	.57

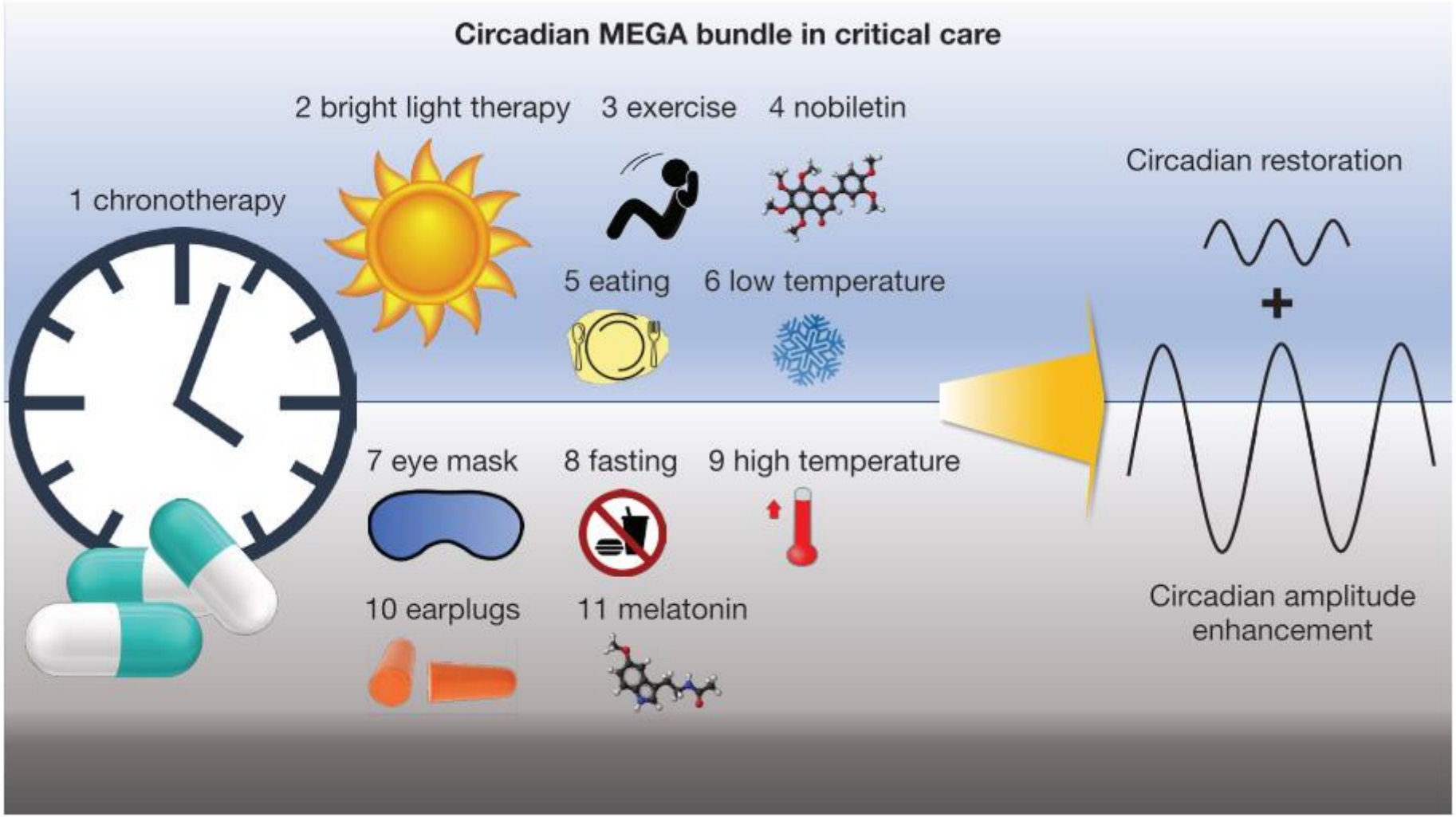
A multivariate logistic regression analysis of risk factors that were shown to be predictors of delirium

	OR	95% CI	*P*
Age	1.00	0.98-1.02	.91
Baseline dementia[a]	5.12	1.8-14.3	.002
APACHE II	1.07	1.02-1.11	.002
Mechanical ventilation of any duration during MICU stay	2.09	1.11-3.91	.022
Nonpharmaceutical protocol phase	0.43	0.24-0.77	.005
Home antipsychotic use[b]	2.11	0.85-5.2	.11

Nonpharmacologic delirium prevention protocol reduce the risk of development of delirium

J Crit Care. 2016 Feb;31(1):206-11.

Bundled Interventions enhancing circadian rhythms

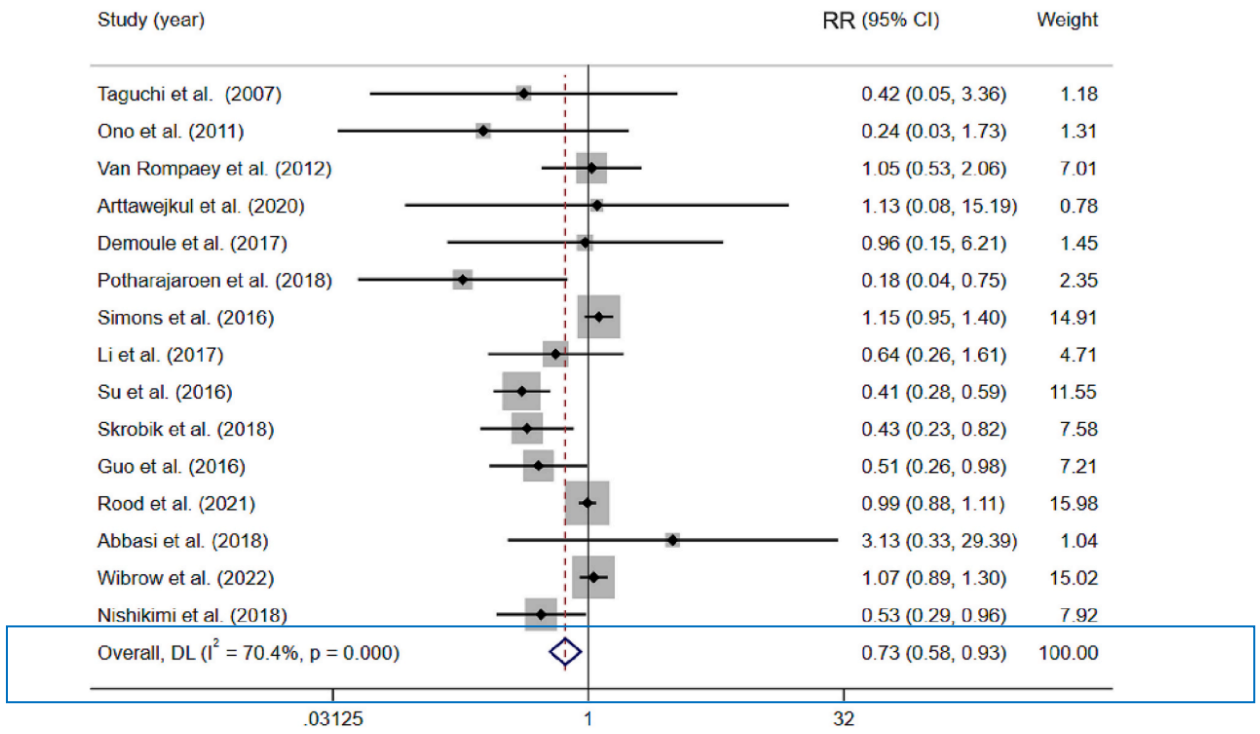


Ann Transl Med. 2023 Jun 30;11(9):319.

Sleep interventions and delirium in critically ill patients

- Systematic review and meta-analysis or 15 RCTs (n=5041)
- ~August 2022
- Sleep interventions: pharmacologic, nonpharmacologic, or mixed interventions

Sleep interventions on the incidence of ICU delirium



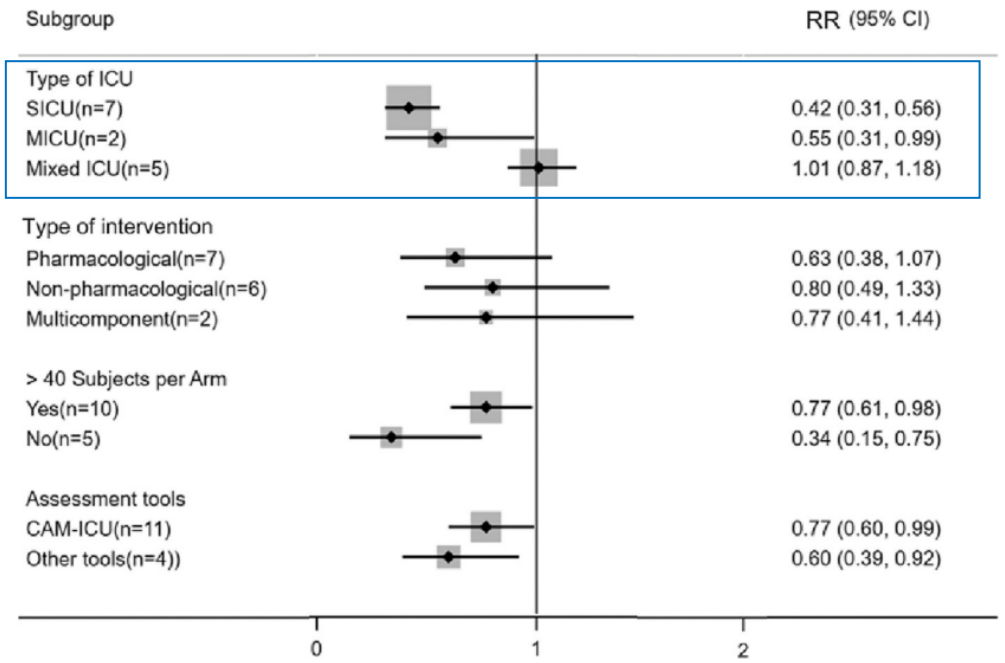


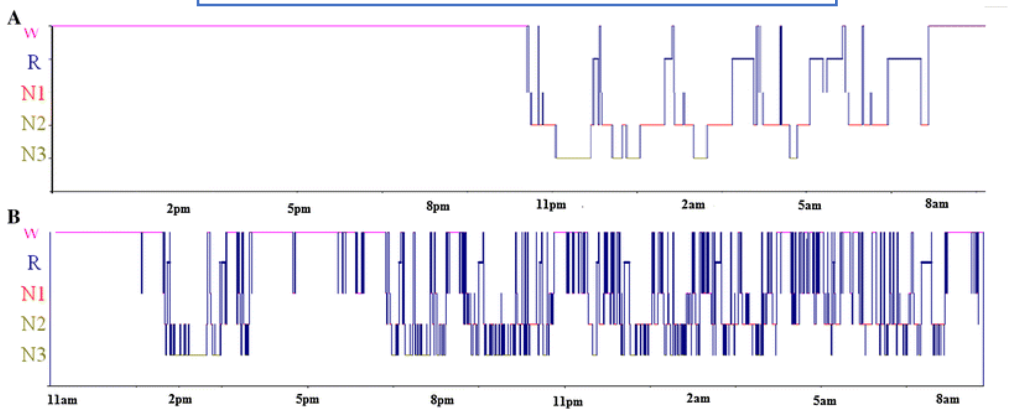
Fig. 7. Subgroup analysis results for sleep intervention in reducing the incidences of ICU delirium.

J Crit Care. 2023 Dec;78:154342.

MV and sleep in the ICU

- Disrupted sleep in MV
  - ↑1 and 2 NREM, ↓SWS, ↓REM sleep, sleep fragmentation
  - lower melatonin secretion, alarms, patient–ventilator asynchrony
  - Uncomfortable modes and/or inadequate settings with under- or over-assistance

Healthy vs. MV weaning phase



highly fragmented
30 % of sleep occurring during the day

Optimizing ventilator settings to prevent nocturnal sleep disruptions

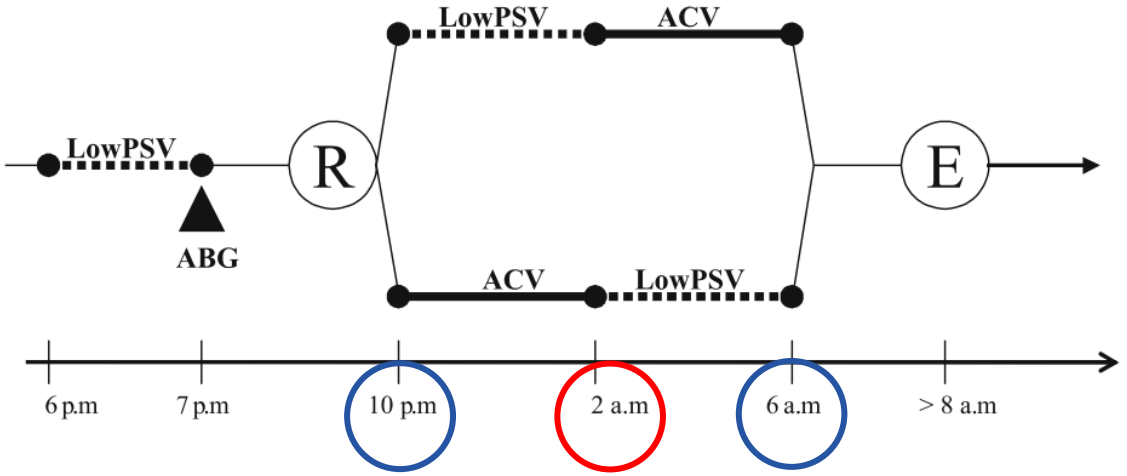
- work of breathing↓
- gas exchange↑→ respiratory drive ↓
- anxiety and dyspnea↓ (during spontaneous breathing)

Intensive Care Med (2016) 42:531–541

Sleep quality: ACV vs. PSV

- Prospective randomized cross-over study
- acute on chronic respiratory failure (n=20)
- ACV (VT 10 ml/kg, RR 12 bpm) vs. low PSV (6 cmH2O) on sleep quality
- Patients
  - enrolled at the end of the weaning period
  - planned extubation
  - No sedative, narcotic, analeptic drugs

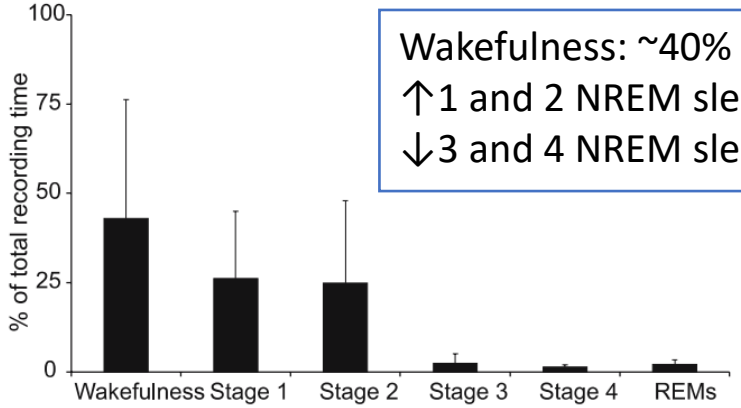
Study protocol



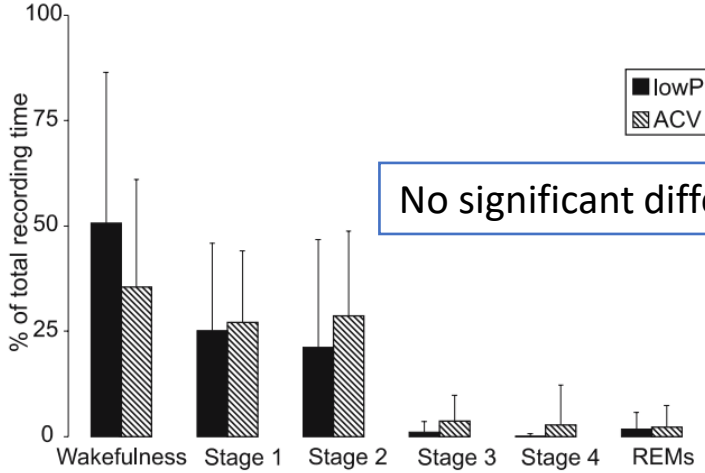
Intensive Care Med. 2007 Jul;33(7):1148-1154.

Sleep quality: ACV vs. PSV

Global sleep quality

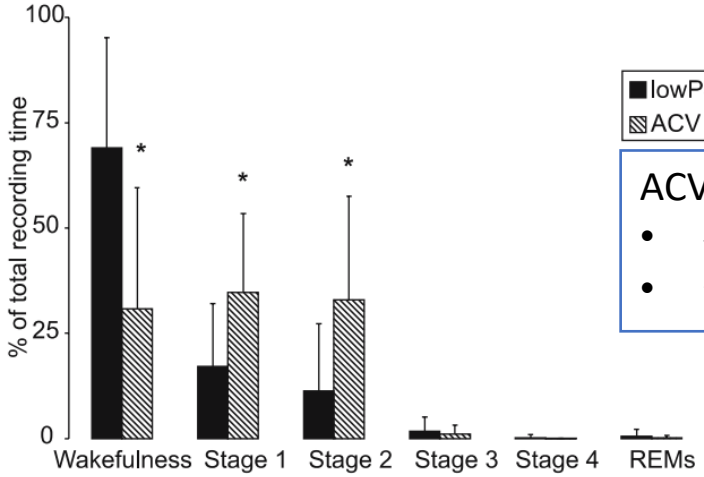


Wakefulness: ~40% of the night
↑1 and 2 NREM sleep
↓3 and 4 NREM sleep, REM sleep



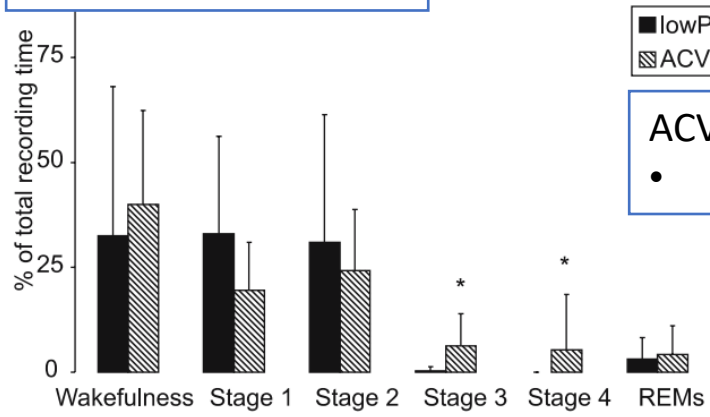
No significant differences

During the first 4-h



ACV group (*p < 0.05)
- **↓wakefulness**
- ↑1 and 2 NREM

During the second 4-h



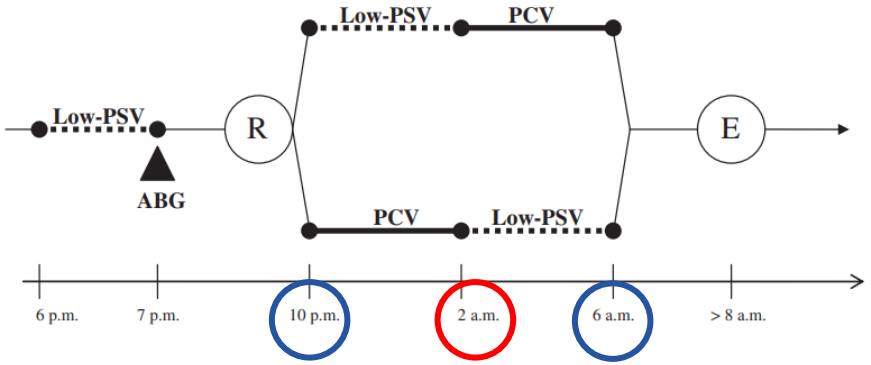
ACV group (*p < 0.05)
- **↑stages 3 and 4 NREM**

- ACV: better sleep quality than those recorded during PSV

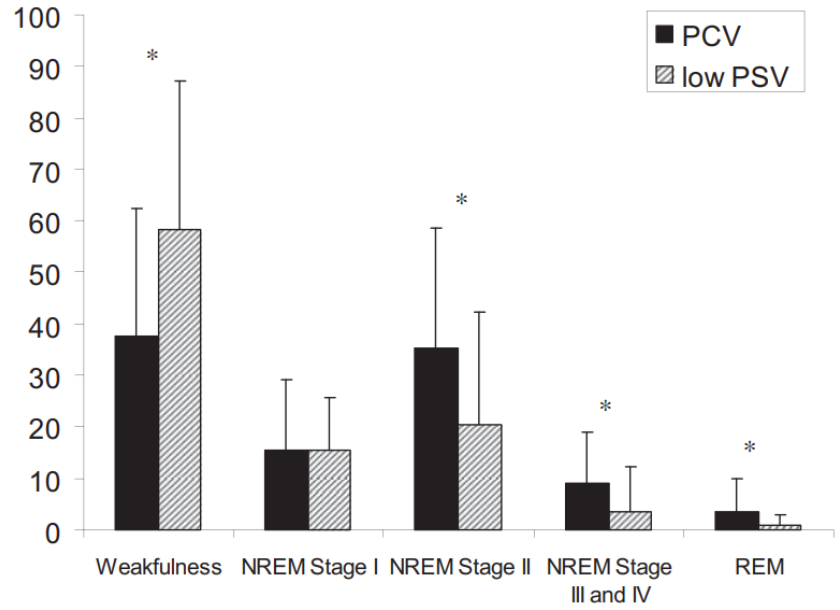
Intensive Care Med. 2007 Jul;33(7):1148-1154.

Sleep quality: PCV vs. PSV

- Prospective randomized cross-over study
- acute on chronic respiratory failure (n=26)
- PCV (Pins 20 cmH2O, RR 12 bpm) vs. low PSV (6 cmH2O)
- Patients: severe COPD

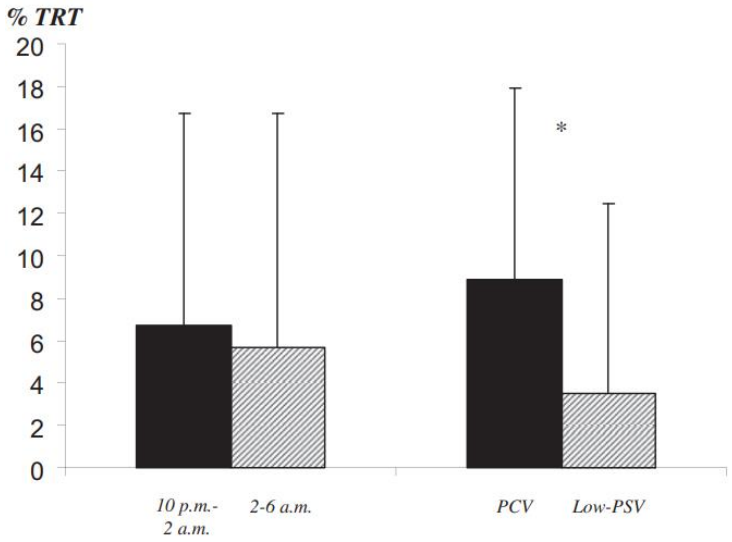


Comparison of quantity of sleep stages



Wakefulness: 37.7±24.7% (PCV) vs. 58.3±28.8% (PSV)

Quantity of stage 3 and 4 NREM sleep



Nocturnal respiratory muscles rest
→ improve sleep during PCV

Respir Med. 2013 Apr;107(4):534-41.

Sleep quality: NAVA vs. PSV

- Mismatch between patient respiratory drive and level of assistance

→patient-ventilator asynchronies → Quality of sleep ↓

- Neurally adjusted ventilatory assist (NAVA)
  - delivers a pressure that is proportional to the electrical activity of the diaphragm

- Prospective comparative crossover study
- NAVA vs. PSV
- Patients (n=14)
  - No sedation and opiate analgesia
  - PSV mode (FIO2 < 60%, PEEP = 5 cmH2O)
  - SpO2 ≥ 90%
- NAVA: improves the quality of sleep
  - ↑slow-wave sleep and REM
  - ↓fragmentation

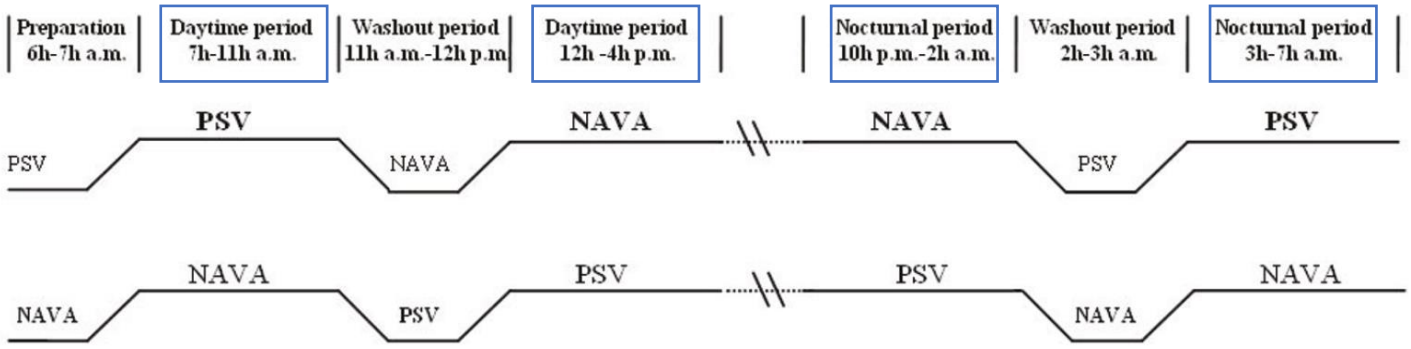


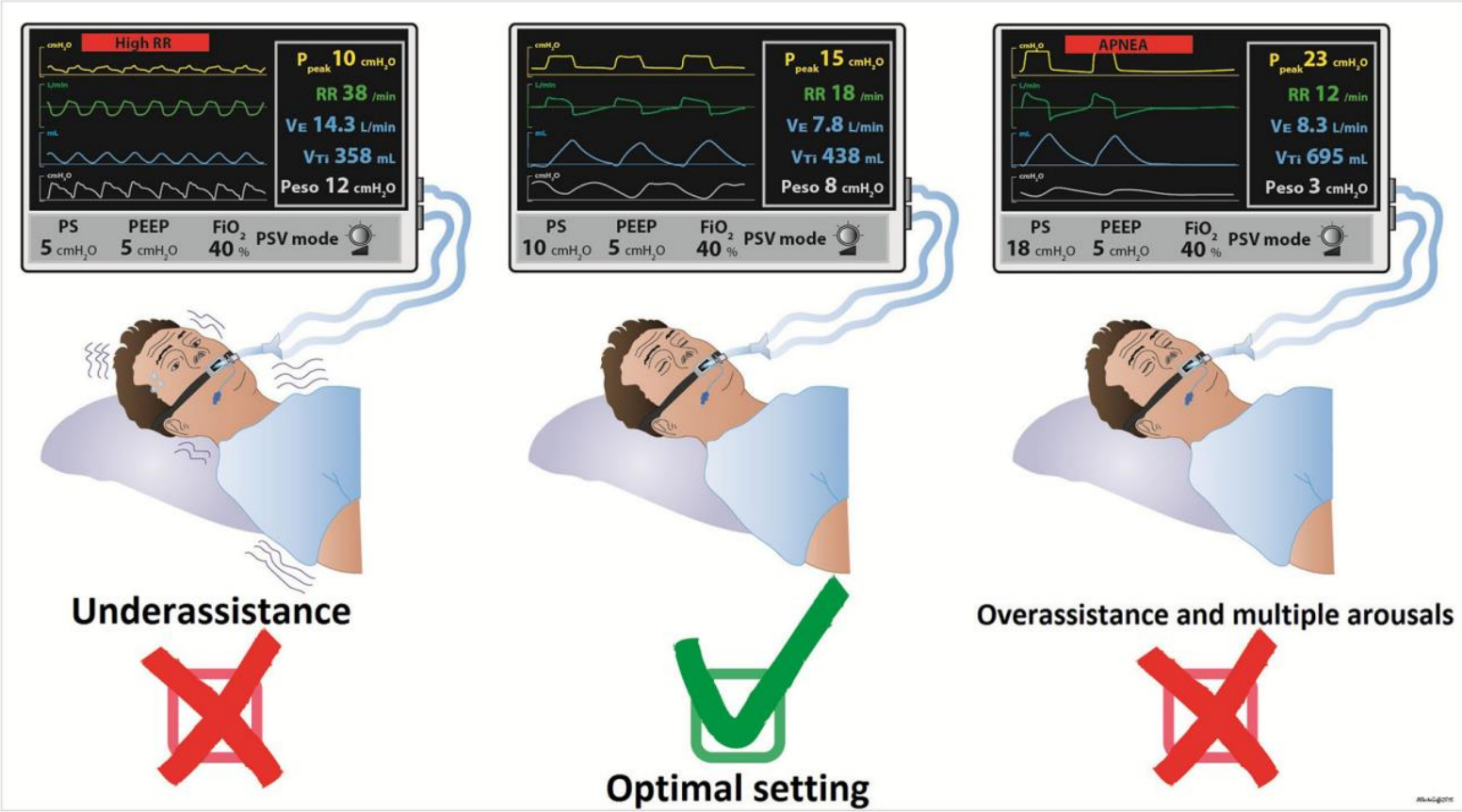
Table 3 Comparison of sleep quality between the ventilatory modes

	PSV	NAVA	*p*
Stage 1, %	7.5 [4-15]	4 [3-5]	0.006*
Stage 2, %	68 [66-75]	55 [52-58]	0.001*
Stage 3 and 4, %	16.5 [17-20]	20.5 [16-25]	0.001*
REM, %	4.5 [3-11]	16.5 [13-29]	0.001*
Fragmentation index, (n/h)	33.5 [25-54]	17.5 [8-21.5]	0.001*
Sleep efficacy, %	44 [29-73.5]	73.5 [52.5-77]	0.001*

Ann Intensive Care. 2011 Sep 28;1(1):42.

MV on sleep in the ICU

- Effect of PSV on sleep in the ICU
- Level of pressure support should be set according to the patient's demand
  - Underassistance → increase patient effort
  - hyperventilation→ central apnea



Intensive Care Med. 2016 Apr;42(4):531-541.

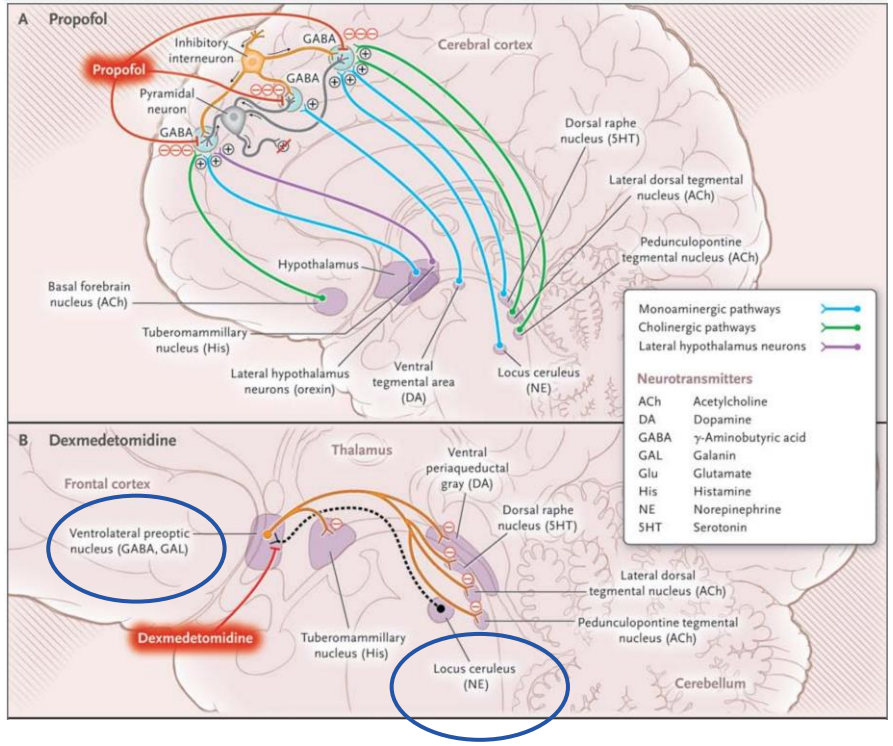
Sedatives

Agent[a]	Time to onset (min)	Time to offset	Analgesic Effect	Provides deep sedation[b]	Reduces respiratory drive	Risk for delirium	Risk for withdrawal	Dosing	Comments[c]
Sedatives									
Dexmedetomidine	15–20	60–90 min	+	N	N	–	++	0.2–1.5 mcg/kg/h	Dose > 1.5 mcg/kg/hr increases cardiac toxicity; unlikely to add clinical benefit
Midazolam	2–5	1–72 hr[d]	–	Y	Y	+++	++	1–10 mg/h	Consider PRN or scheduled IVP before initiating a continuous infusion
Propofol	0.5–1	5–10 min	–	Y	Y	+	–	10–250 mg/h	Time to offset ↑ in older adults/ infusions > 72-h. Avoid if triglycerides > 800 mg/dL. Monitor for PRIS

1. Bradycardia
2. Hypotension

1. Hypotension
2. Hypertriglyceridemia
3. Propofol-related infusion syndrome (PRIS)

✓ Anticonvulsant effects



Dexmedetomidine

- selective α2-agonist
- inhibits NE release (NE: causing GABA output)
- regulates arousal by inhibiting cholinergic neurotransmission

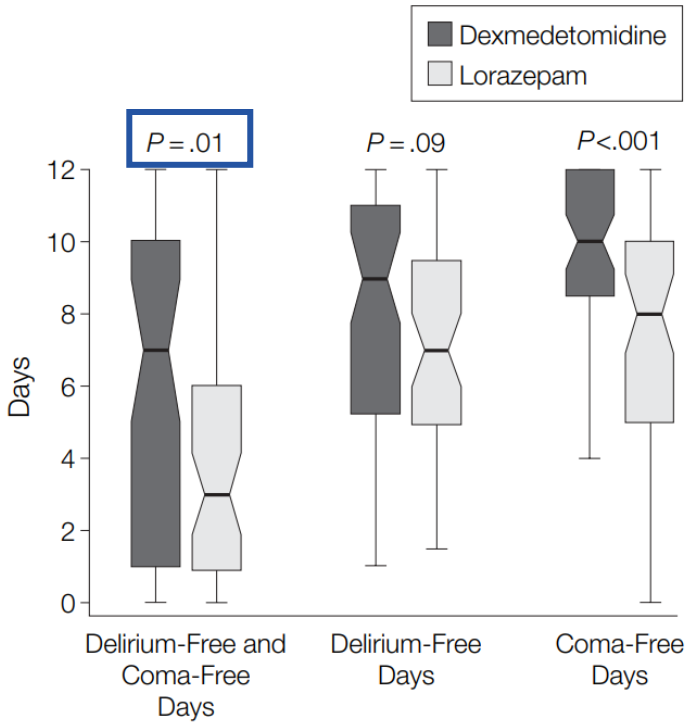
N Engl J Med. 2010 Dec 30;363(27):2638-50.

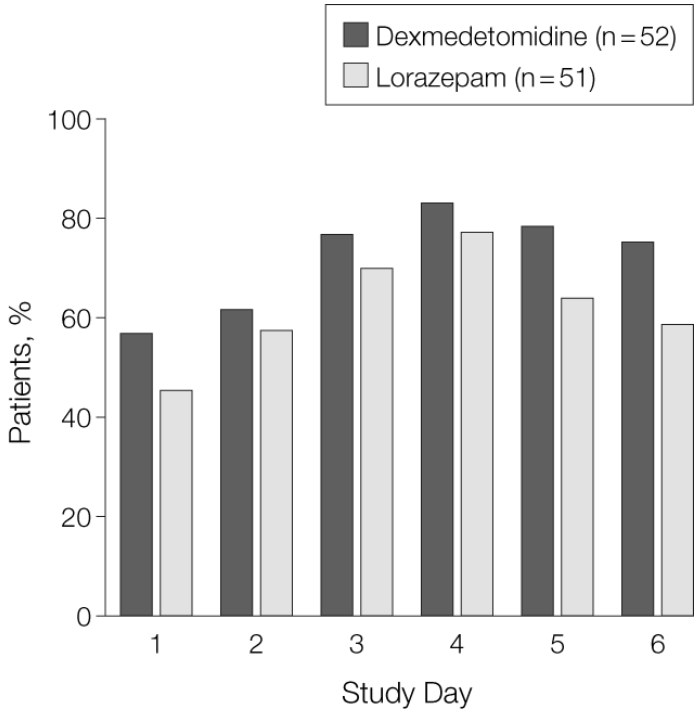
Dexmedetomidine vs BZD for delirium

MENDS trial

- **Dexmedetomidine** ± fentanyl (n=52) vs. **Lorazepam** ± fentanyl (n=51): ~extubation or ~120 hours

➢ Dexmedetomidine: **delirium-free and coma-free days ↓,** being at the target RASS score ↑





Percentage of patients within 1 point of the RASS

JAMA. 2007 Dec 12;298(22):2644-53.

Dexmedetomidine vs BZD for delirium

SEDCOM trial

- **Dexmedetomidine** (n=244) vs. **Midazolam** (n=122)
- MV patients (target RASS score −2 to +1)

➢ No difference in time at targeted sedation level , **delirium↓, time to extubation↓, bradycardia↑**

Outcome	No. (%) Dexmedetomidine (n = 244)	Midazolam (n = 122)	*P* Value
Time in target sedation range (RASS score −2 to +1), mean, %[a]	77.3	75.1	.18
Patients completing all daily arousal assessments	225 (92)	103 (84.3)	.09
Patients requiring study drug interruption to maintain RASS score −2 to +1	222 (91)	112 (91.8)	.85
Duration of study drug treatment, median (IQR), d	3.5 (2.0-5.2)	4.1 (2.8-6.1)	.01
Time to extubation, median (95% CI), d[b]	3.7 (3.1-4.0)	5.6 (4.6-5.9)	.01
ICU length of stay, median (95% CI), d[b]	5.9 (5.7-7.0)	7.6 (6.7-8.6)	.24
Delirium			
Prevalence	132 (54)	93 (76.6)	<.001
Mean delirium-free days[c]	2.5	1.7	.002
Open-label midazolam use			
No. treated	153 (63)	60 (49)	.02
Dose, median (IQR), mg/kg[d]	0.09 (0.03-0.23)	0.11 (0.03-0.28)	.65
Fentanyl use			
No. treated	180 (73.8)	97 (79.5)	.25
Dose, median (IQR), µg/kg[d]	6.4 (1.8-26.3)	9.6 (2.9-28.6)	.27

Outcome[a]	No. (%) Dexmedetomidine (n = 244)	Midazolam (n = 122)	*P* Value
Cardiovascular			
Bradycardia	103 (42.2)	23 (18.9)	<.001
Bradycardia with intervention	12 (4.9)	1 (0.8)	.07
Tachycardia	62 (25.4)	54 (44.3)	<.001
Tachycardia with intervention	24 (9.8)	12 (9.8)	>.99
Hypotension	137 (56.1)	68 (55.7)	>.99
Hypotension with intervention	69 (28.3)	33 (27)	.90
Hypertension	106 (43.4)	54 (44.3)	.91
Hypertension with intervention	46 (18.9)	36 (29.5)	.02
Metabolic (hyperglycemia)	138 (56.6)	52 (42.6)	.02
Infections	25 (10.2)	24 (19.7)	.02
30-d mortality[b]	55 (22.5)	31 (25.4)	.60

JAMA 2009;301:489-99

Dexmedetomidine vs usual care for delirium

SPICE III trial

- MV patients (target RASS score: −2 to +1)
- **Dexmedetomidine** vs. **Usual Care** (propofol, midazolam, or other)

➢ No difference in 90-day mortality

➢ DEX: **higher number of days free from coma or delirium**, and ventilator-free days

Table 2. Clinical Outcomes.*

Outcome	Dexmedetomidine (N=1948)	Usual Care (N=1956)	Odds Ratio (95% CI)	Adjusted Risk Difference (95% CI)†
Death from any cause at 90 days: primary outcome — no. (%)	566 (29.1)	569 (29.1)	1.00 (0.87 to 1.15)	0.0 (−2.9 to 2.8)
Secondary outcomes				
Death at 180 days — no./total no. (%)	609/1935 (31.5)	610/1946 (31.3)	1.01 (0.88 to 1.16)	0.1 (−2.8 to 3.1)
Institutional dependency at 180 days — no./total no. (%)	89/1323 (6.7)	94/1337 (7.0)	0.96 (0.73 to 1.27)	−0.3 (−2.1 to 1.5)
Mean score on Short IQCODE at 180 days (95% CI)‡	3.14 (3.11 to 3.17)	3.08 (3.05 to 3.11)		0.06 (0.02 to 0.11)
Mean score on the EQ-5D-3L questionnaire (95% CI)§	69.8 (68.5 to 71.1)	70.2 (69.0 to 71.5)		−0.4 (−2.2 to 1.3)
Median no. of days free from coma or delirium (IQR)¶	24.0 (11.0 to 26.0)	23.0 (10.0 to 26.0)		1.0 (0.5 to 1.5)
Median no. of ventilator-free days (IQR)¶	23.0 (0.0 to 26.0)	22.0 (0.0 to 25.0)		1.0 (0.4 to 1.6)

Table S9 –Reported Adverse and Serious Adverse Events¥

	DEX (N=1954)	Usual care (N=1964)	P value
One or more AE during study	188 (9.6%)	35 (1.8%)	< 0.0001
One or more SAE during study	52 (2.7%)	7 (0.4%)	< 0.0001
Adverse Events:			
Bradycardia	99 (5.1%)	9 (0.5%)	< 0.0001
Hypotension	52 (2.7%)	10 (0.5%)	< 0.0001
Other AE	44 (2.3%)	16 (0.8%)	< 0.0001
Serious Adverse Events:			
Bradycardia	13 (0.70%)	1 (0.05%)	0.001
Hypotension	10 (0.50%)	1 (0.05%)	0.006
Prolonged sinus pause (Asystole)	14 (0.70%)	2 (0.10%)	0.003
Other SAE	16 (0.82%)	3 (0.15%)	0.003
Uncontrolled agitation during study	44 (2.3%)	77 (3.9%)	0.003
Protocol deviation during study	360(18.4%)	214 (10.9%)	< 0.0001

N Engl J Med. 2019 Jun 27;380(26):2506-2517.

Dexmedetomidine vs propofol for delirium

MENDS2 trial

- MV patients with sepsis (target RASS score −2 to 0)
- **Dexmedetomidine** vs. **Propofol: No differences**

Table 3. Primary and Secondary Efficacy End Points.*

End Point	Dexmedetomidine (N = 214)	Propofol (N = 208)
Primary end point		
Days alive without delirium or coma at 14 days		
Unadjusted no. of days — median (IQR)	8.0 (1.0–12.8)	7.5 (1.8–11.2)
Adjusted no. of days — median (95% CI)	10.7 (8.5–12.5)	10.8 (8.7–12.6)
Adjusted odds ratio (95% CI)	0.96 (0.74–1.26)	Reference
Secondary end points		
Ventilator-free days at 28 days		
Unadjusted no. of days — median (IQR)	20.9 (0.0–26.1)	19.9 (4.2–24.9)
Adjusted no. days — median (95% CI)	23.7 (20.5–25.4)	24.0 (20.9–25.4)
Adjusted odds ratio (95% CI)	0.98 (0.63–1.51)	Reference
Death at 90 days		
Unadjusted no. of patients (%)	81 (38)	82 (39)
Adjusted hazard ratio (95% CI)	1.06 (0.74–1.52)	Reference
TICS-T score at 6 mo†		
Unadjusted score — median (IQR)	39 (28–48)	38 (30–46)
Adjusted score — median (95% CI)	40.9 (33.6–47.1)	41.4 (34.0–47.3)
Adjusted odds ratio (95% CI)	0.94 (0.66–1.33)	Reference

Telephone Interview for Cognitive Status questionnaire (TICS-T) range from 0 to 100, lower scores: worse cognition

➢ Similar safety end points

Table S7. Safety end points during 14-day study period by treatment group

End point	Dexmedetomidine N=214	Propofol N=208
Hypotension (SBP<80 mm Hg)—no. (%)	119 (56%)	115 (55%)
Median CV SOFA score [IQR]	0.91 [0.43-1.98]	1.00 [0.50-1.44]
Proportion of days CV SOFA≥2—(%)	25%	21%
Bradycardia (HR<60 bpm)—no. (%)	65 (30%)	39 (19%)
Tachycardia (HR>100 bpm)—no. (%)	163 (76%)	165 (79%)
Severe lactic acidosis (>5 mmol/L)—no. (%)	31 (14%)	30 (14%)
ARDS—no. (%)	111 (52%)	135 (65%)
Signs of trial drug withdrawal—no. (%)*	22 (10%)	36 (17%)
Self extubation		
Ever occurred while on trial drug— no. (%)	13 (6%)	5 (2%)
Required re-intubation on same day— no. (%)	5 (39%)	1 (20%)
Triglycerides		
Median level day 7 [IQR]	140 [98-202]	166 [112-254]
Level >500 mg/dL on day 7†	3/159	6/164
Median level day 14 [IQR]	132 [101-198]	151 [109-216]
Level >500 mg/dL on day 14†	1/71	6/96
Cortisol		
Median level day 7 [IQR]	13.0 [7.8-17.9]	13.2 [9.0-18.6]
Level <20 mcg/dL on day 7†	132/159	126/161
Median level day 14 [IQR]	11.7 [8.0-16.6]	13.6 [9.0-18.7]
Level <20 mcg/dL on day 14†	64/71	72/94

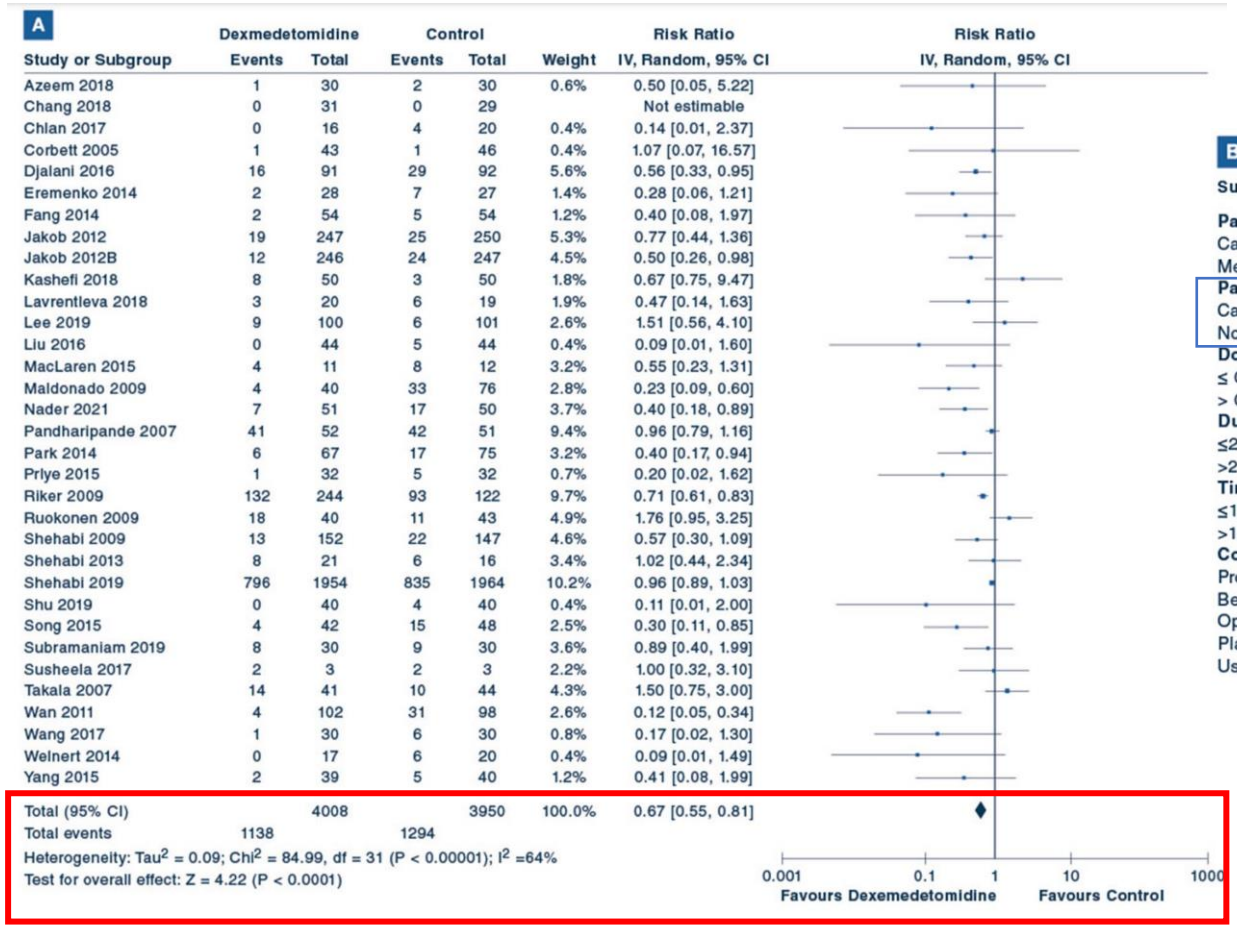
N Engl J Med. 2021 Apr 15;384(15):1424-1436.

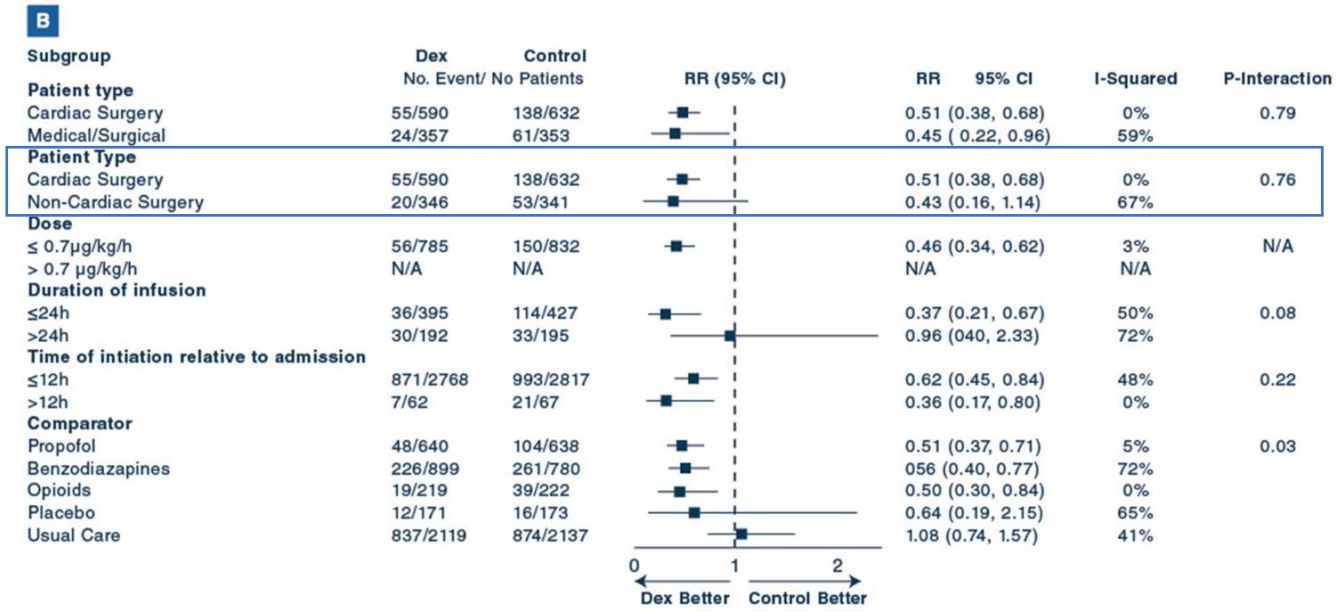
Dexmedetomidine

- Systematic review and meta-analysis of 77 RCTs (n=11,997)
- **Dexmedetomidine** vs **other sedatives**

Dexmedetomidine

- **Delirium, RR 0.67 (0.55 to 0.81)**
- **MV duration: MD -1.8 h (-2.89 to -0.71)**
- **ICU LOS: MD -0.32 days (-0.42 to -0.22)**
- **Bradycardia: RR 2.39 (1.82 to 3.13)**
- **Hypotension: RR 1.32 (1.07 to 1.63)**





Intensive Care Med. 2022 Jul;48(7):811-840.

Pharmacologic interventions to promote sleep

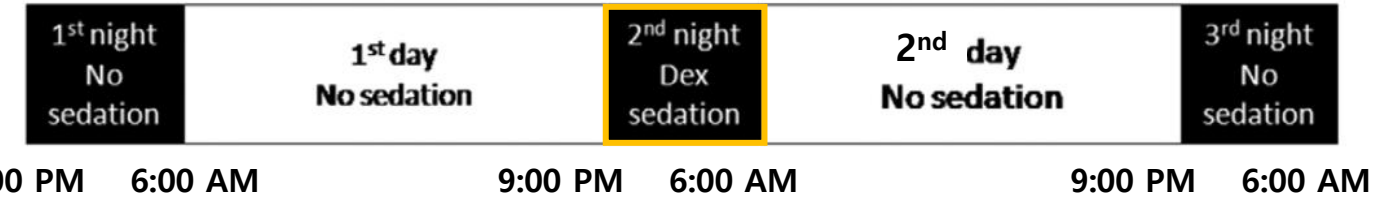
Medication	Mechanism of action	Side effects	Sleep effects
Dexmedetomidine	a2-agonist	Bradycardia, hypotension	↑N2 with sleep spindles, **?↑N3/SWS**, ↓REM, **↑SE**, **↓SL**
Propofol	GABA receptor agonist	Bradycardia, hypotension, propofol infusion syndrome, respiratory depression	↓REM, ↓SL, ↑TST, ↓W
Benzodiazepines	GABA receptor agonist	Dependency, delirium-inducing, dizziness, hypotension, withdrawal	↓N3, ↓REM, ↓SL, ↑TST, ↓W
Melatonin and melatonin R agonists	Melatonin 1 and 2 receptor agonist	Dizziness, hallucinations, nausea, vivid dreams	↑SE, **↓SL**, ↑TST

SE, sleep efficiency; SL, sleep latency; TST, total sleep time; W, wake

Semin Respir Crit Care Med 2019;40:614–628.

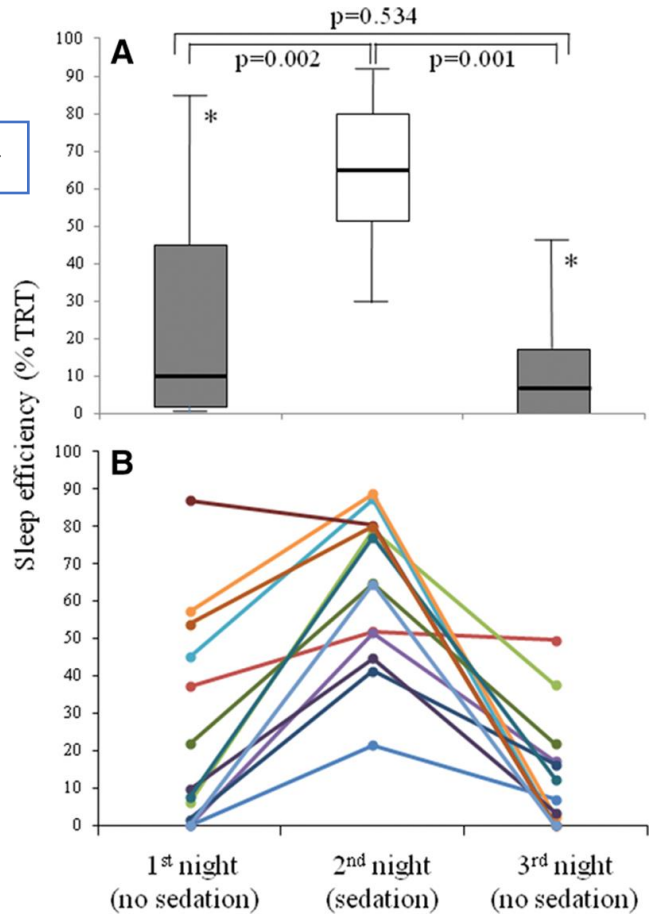
Dexmedetomidine and sleep quality

- Dexmedetomidine on sleep quality in MV patients (n=13)
- RASS −1 to −2

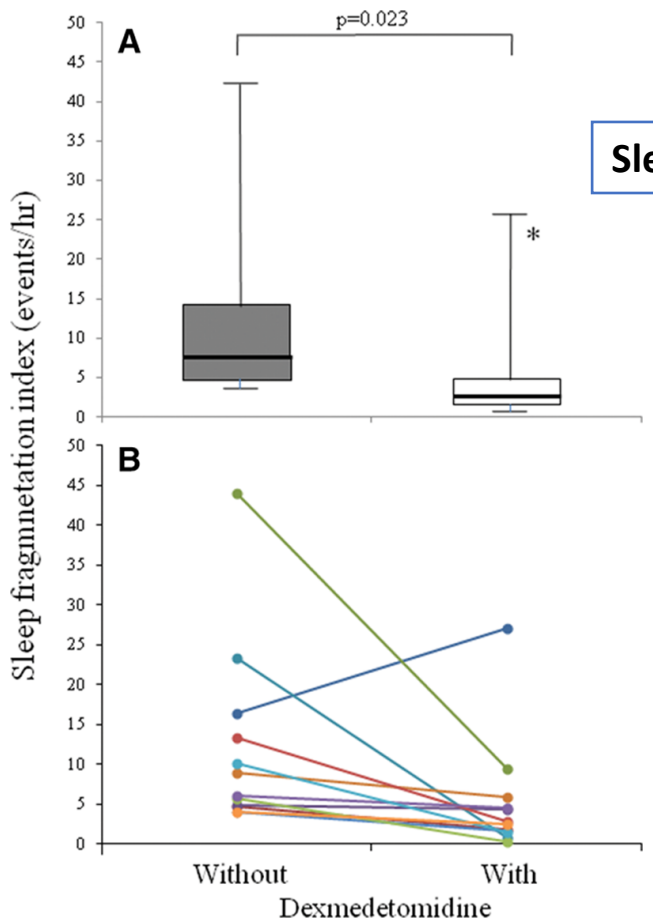


Sleep efficiency↑

$$\frac{Total\ sleep\ time}{Total\ recording\ time}$$



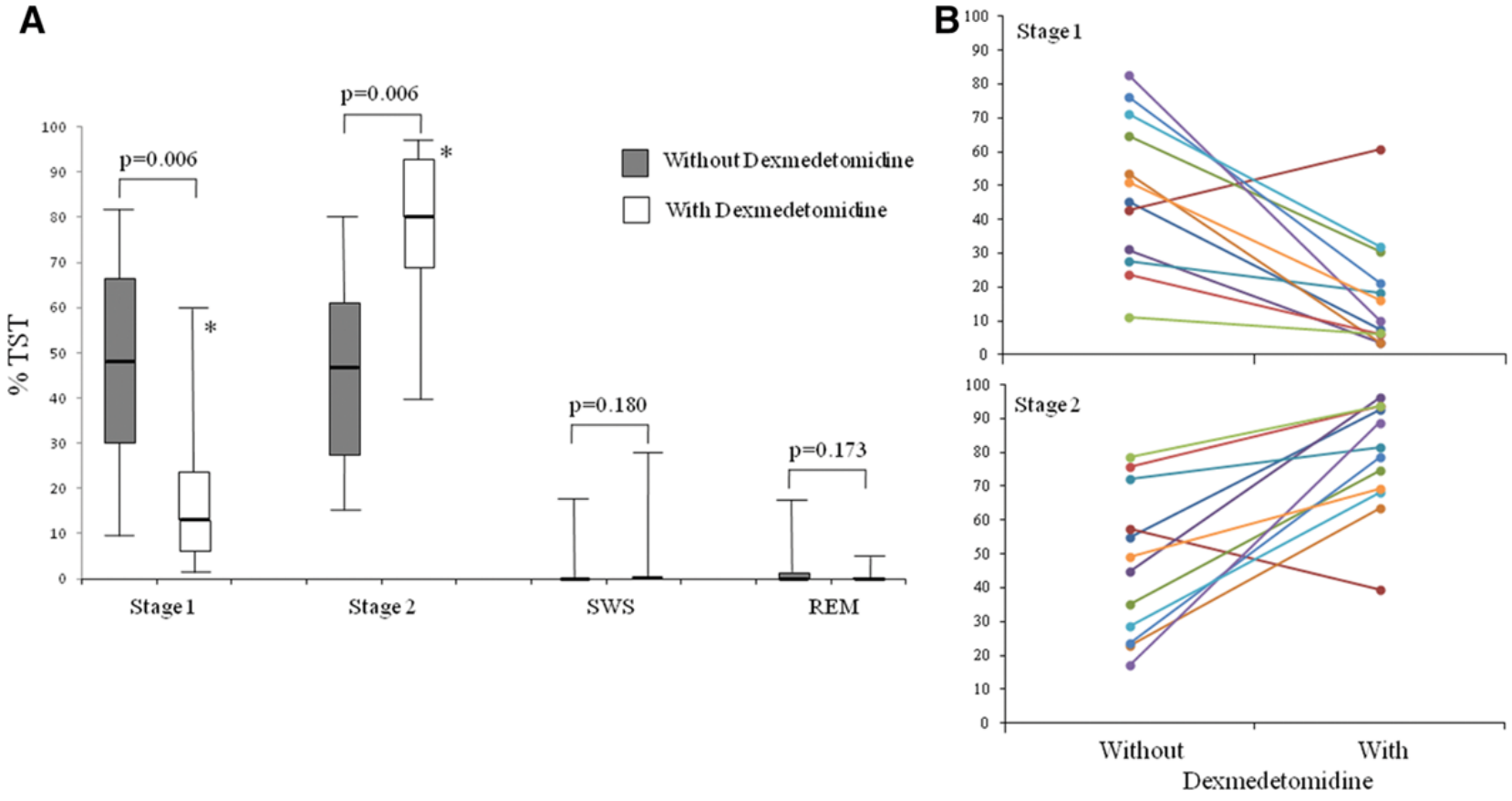
Sleep fragmentation index ↓



Anesthesiology. 2014 Oct;121(4):801-7.

Dexmedetomidine and sleep quality

- Dexmedetomidine during the night
  - sleep efficiency and stage 2↑
  - shifting sleep mainly to the night
  - no positive effect on restorative and REM sleep



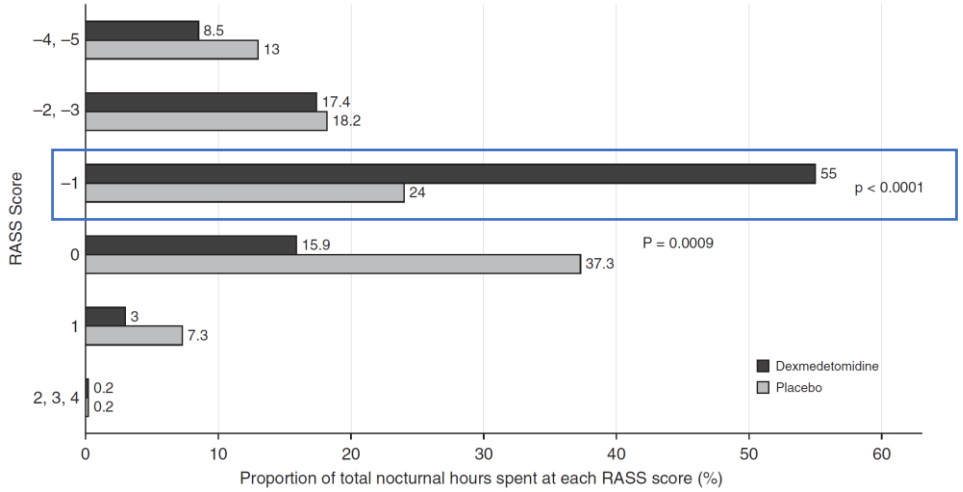
Anesthesiology. 2014 Oct;121(4):801-7.

Dexmedetomidine and sleep quality

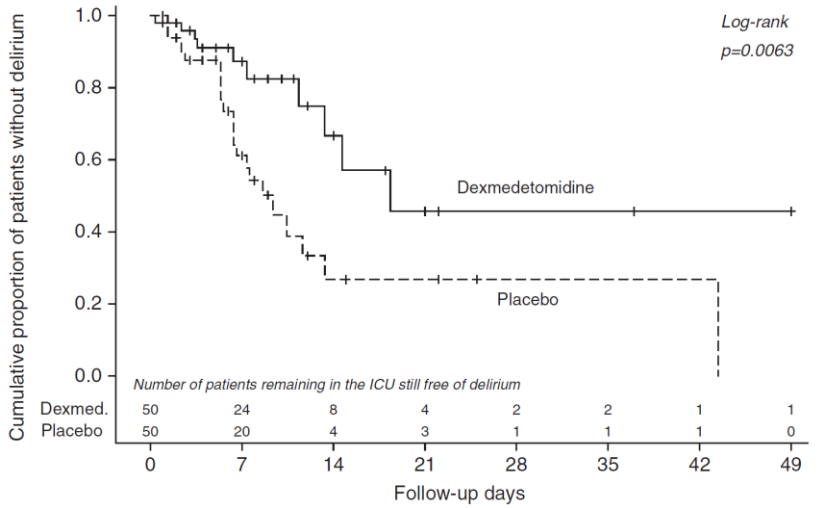
- Phase II, double-blind RCT, 2013 ~ 2016
- nocturnal dexmedetomidine vs. placebo (D5W)
- Patients (n=100): currents sedatives (midazolam, lorazepam, or propofol)
- 9:30 PM: dexmedetomidine at 0.2~0.7 mg/kg/h (Targeted RASS of -1)
- 6:00 AM: d/c dexmedetomidine → adjusted nonstudy sedatives

Nocturnal low-dose dexmedetomidine
- delirium↓
- sleep quality: unchanged

Dexmedetomidine group: greater proportion of nights at an RASS = -1



Time to the first occurrence of delirium during ICU stay

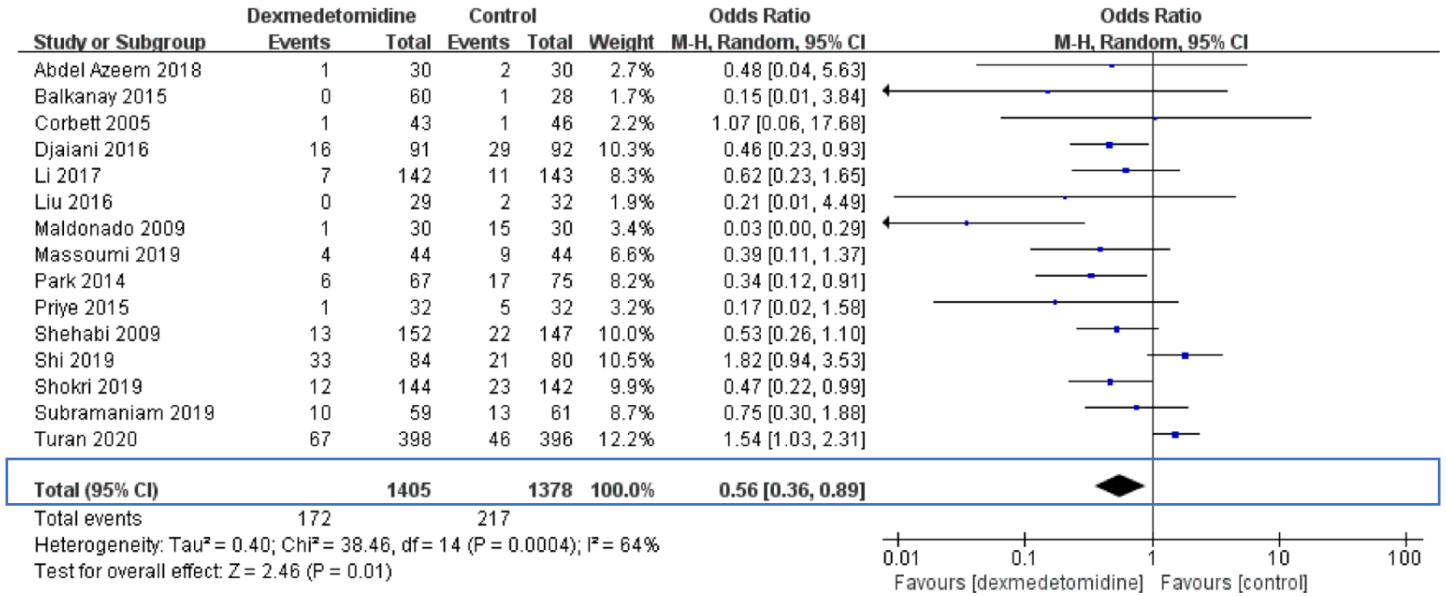


Am J Respir Crit Care Med. 2018 May 1;197(9):1147-1156.

Dexmedetomidine and postoperative delirium

- Meta-analysis of 15 RCTs, ~ August 27,2020
- Patients: after cardiac surgery (n=2813)
- Primary endpoint: incidence of postoperative delirium after cardiac surgery during hospital stay

- Dexmedetomidine
  - ↓ postoperative delirium compared to other sedatives and opioids after cardiac surgery



Study or Subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdel Azeem 2018	1	30	2	30	2.7%	0.48 [0.04, 5.63]
Balkanay 2015	0	60	1	28	1.7%	0.15 [0.01, 3.84]
Corbett 2005	1	43	1	46	2.2%	1.07 [0.06, 17.68]
Djaiani 2016	16	91	29	92	10.3%	0.46 [0.23, 0.93]
Li 2017	7	142	11	143	8.3%	0.62 [0.23, 1.65]
Liu 2016	0	29	2	32	1.9%	0.21 [0.01, 4.49]
Maldonado 2009	1	30	15	30	3.4%	0.03 [0.00, 0.29]
Massoumi 2019	4	44	9	44	6.6%	0.39 [0.11, 1.37]
Park 2014	6	67	17	75	8.2%	0.34 [0.12, 0.91]
Priye 2015	1	32	5	32	3.2%	0.17 [0.02, 1.58]
Shehabi 2009	13	152	22	147	10.0%	0.53 [0.26, 1.10]
Shi 2019	33	84	21	80	10.5%	1.82 [0.94, 3.53]
Shokri 2019	12	144	23	142	9.9%	0.47 [0.22, 0.99]
Subramaniam 2019	10	59	13	61	8.7%	0.75 [0.30, 1.88]
Turan 2020	67	398	46	396	12.2%	1.54 [1.03, 2.31]
Total (95% CI)		**1405**		**1378**	**100.0%**	**0.56 [0.36, 0.89]**
Total events	172		217			

Heterogeneity: Tau² = 0.40; Chi² = 38.46, df = 14 (P = 0.0004); I² = 64%
Test for overall effect: Z = 2.46 (P = 0.01)

BMC Anesthesiol. 2021 May 18;21(1):153.

Dexmedetomidine and postoperative delirium

- Double-blind RCT (n=331)
- January 2019 to July 2021
- Patients: elective cardiac surgery (≥ 65 years)
- Dexmedetomidine after surgery: 8 pm to 8 am, in ICU or ~ 7 days
- Primary outcome
  - occurrence of PoD within the 7 days after surgery
- **Incidence of PoD : 12.6% vs. 12.4% (p=0.97)**

- Overnight dexmedetomidine after elective cardiac surgery
  - did not decrease postoperative delirium
  - Better sleep quality
  - **More hypotensive events**

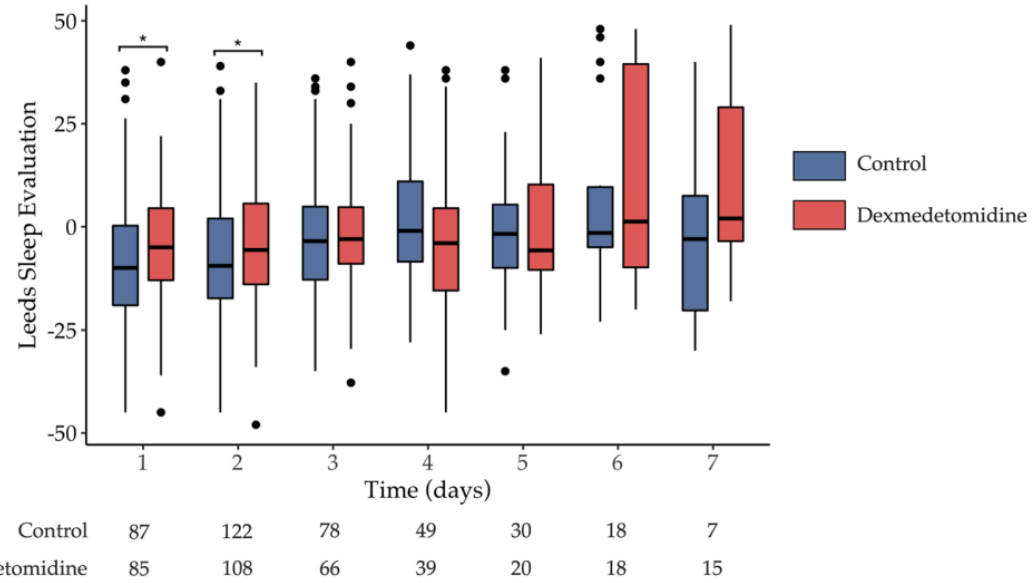


Table 3 Safety outcomes and arrythmia within the 7 days in patients assigned to dexmedetomidine and placebo group

	Total ($n=331$)	Dexmedetomidine group ($n=165$)	Placebo group ($n=166$)	*P*
Hypotension				
Yes	13 (3.9)	12 (7.3)	1 (0.6)	<0.01
No	318 (96.1)	153 (92.7)	165 (99.4)	
Bradycardia				
Yes	7 (2.1)	6 (3.6)	1 (0.6)	0.07
No	324 (97.9)	159 (96.4)	165 (99.4)	
Ventricular arrythmia				
Yes	21 (6.3)	8 (4.8)	13 (7.8)	0.27
No	310 (93.7	157 (95.2	153 (92.2)	
Supra ventricular arrythmia				
Yes	139 (42)	74 (44.8)	65 (39.2)	0.29
No	192 (58)	91 (55.2)	101 (60.8)	

Data are expressed as number (percentage)

Crit Care. 2024 Feb 29;28(1):64.

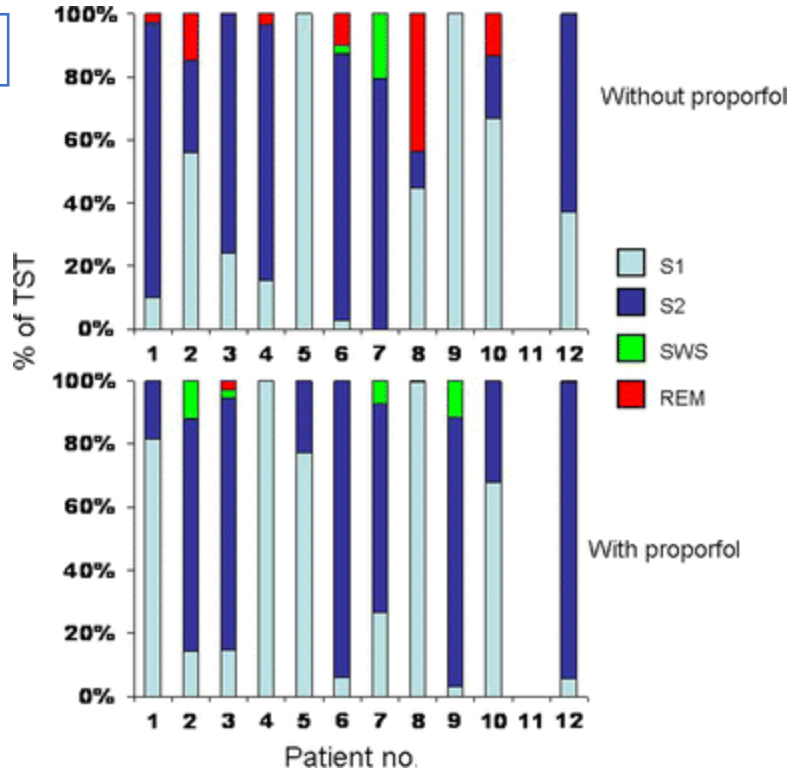
Propofol and sleep quality

- Randomized crossover physiological study
- 2009 ~ 2011
- MV, hemodynamically stable (n=13)
- 2 consecutive nights (10:00 p.m. ~ 7:00 a.m.)
  - propofol infusion target Ramsay scale 3

Table 2 Sleep architecture without and with propofol

	Without propofol	With propofol	*p* value
TST (min)	214 (40–285)	260 (113–417)	0.37
Sleep efficiency (% TST)	62.6 (13.1–85.9)	76.3 (28.4–96.9)	0.37
Stage 1 (% TST)	30.7 (4.6–66.7)	20.8 (5.6–80.6)	1.00
Stage 2 (% TST)	46.1 (3.0–80.4)	48.9 (4.8–84.0)	0.66
SWS (% TST)	0 (0–0)	0 (0–5.8)	0.75
REM (% TST)	1.4 (0–13.0)	0 (0–0)	0.04
TSFI (events/h)	8.1 (2.9–16.2)	4.8 (1.3–14.6)	0.33
Stage shifts	21 (7–48)	22 (11–28)	0.69
Intersleep awake (% TST)	11.4 (3.1–42.9)	6.8 (1.2–43.5)	0.79

Sleep architecture



- Sleep efficiency: not different
- Propofol: abolished the REM sleep (p = 0.04)

- **Propofol decreased REM**, compared with patients who did not receive propofol

Intensive Care Med. 2012 Oct;38(10):1640-6.

Melatonin and sleep quality

Darkness stimulates the pineal gland → melatonin → sleep initiation & maintenance ↑

- Double-blind RCT (n=203)
- Oral melatonin (10mg) or placebo, ~ 7 nights
- Sleep quality: RCSQ
- Melatonin serum peak levels at 2 am

Time	Melatonin	Placebo	p
2:00	150 (125–2,125)	32.5 (18.8–35)	< 0.001
6:00	40 (33–100)	25 (12.5–35)	0.021
12:00	35 (30–50)	15 (5–35)	0.024
18:00	40 (32.5–75)	30 (10–40)	0.087

TABLE 3. Classification of the Richards Campbell Sleep Questionary in Groups–Sleep in the ICU and Sleep in the ICU and Ward

RCSQ Sleep in the ICU	Melatonin (*n* = 96) (%)	Placebo (*n* = 96) (%)	RR (95% CI)
Very poor sleep (0–25 mm)	3 (3.1)	14 (14.6)	0.21 (0.06–0.72)
Poor sleep (26–50 mm)	17 (17.7)	15 (15.6)	1.13 (0.60–2.14)
Good sleep (51–75 mm)	32 (33.3)	34 (35.4)	0.94 (0.64–1.39)
Very good sleep (76–100 mm)	44 (45.8)	33 (34.4)	1.33 (0.94–1.89)

Melatonin: better sleep quality in the ICU

TABLE 2. Richards Campbell Sleep Questionary

Richards Campbell Sleep Questionary	Melatonin (*n* = 96)	Placebo (*n* = 96)	*p*
Sleep depth (general)	69.6 ± 26.0	58.0 ± 27.4	0.008
Sleep depth (ICU)	70.9 ± 33.2	57.7 ± 28.6	0.004
Sleep depth (ward)	64.9 ± 29.0	63.5 ± 29.4	0.764
Sleep latency (general)	68.3 ± 26.2	60.6 ± 31.6	0.182
Sleep latency (ICU)	68.3 ± 25.4	60.6 ± 29.5	0.116
Sleep latency (ward)	67.5 ± 30.2	61.5 ± 30.9	0.367
Awakenings (general)	64.9 ± 28.0	60.8 ± 32.9	0.526
Awakenings (ICU)	64.6 ± 28.5	57.7 ± 35.3	0.305
Awakenings (ward)	63.7 ± 31.2	63.2 ± 33.2	0.909
Returning to sleep (general)	68 ± 30.9	64.3 ± 32.1	0.355
Returning to sleep (ICU)	74.0 ± 27.0	63.5 ± 34.2	0.053
Returning to sleep (ward)	65.9 ± 34.6	69.5 ± 28.9	0.997
Sleep quality (general)	71.0 ± 27.0	65.5 ± 29.0	0.185
Sleep quality (ICU)	71.0 ± 26.0	64.0 ± 29.7	0.116
Sleep quality (ward)	70.2 ± 30.2	67.2 ± 27.1	0.413
Total score (general)	69.7 ± 21.2	60.7 ± 26.3	0.029
Total score (ICU)	69.7 ± 21.4	60.7 ± 26.3	0.027
Total score (ward)	66.4 ± 27.2	65.0 ± 26.6	0.746

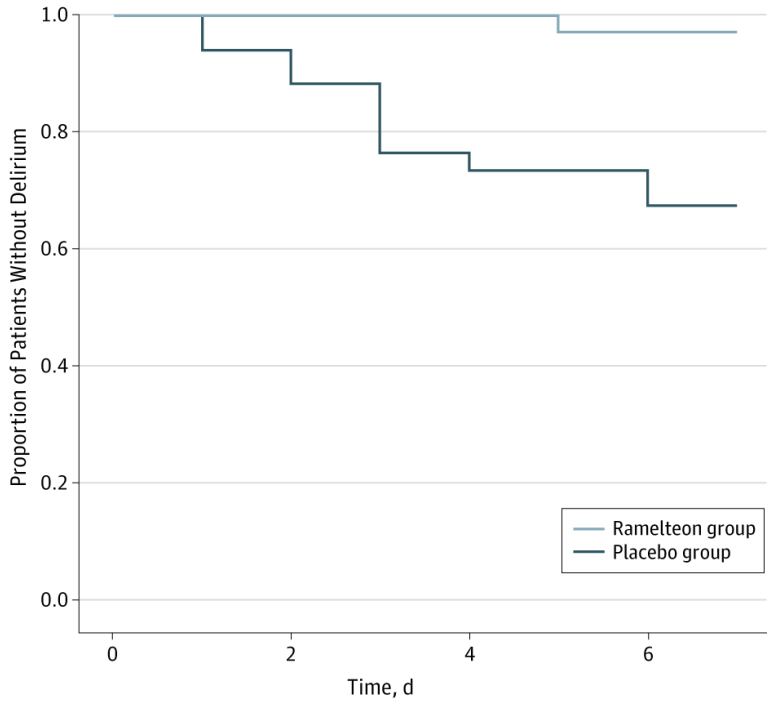
Data are presented as mean and SD.

Crit Care Med. 2020 Dec;48(12):e1286-e1293.

Melatonin agonists and delirium

- Multicenter RCT (n=67)
- September 1, 2011 ~ October 31, 2012
- Patients: 65 ~ 89 years, admitted to ICU
- Oral ramelteon vs placebo for 7 days
- Primary outcome: incidence of delirium

- Ramelteon: lower risk of delirium (3% vs 32%; P = 0.003)



Time to development of delirium

- Ramelteon: 6.94 (95% CI, 6.82-7.06) days
- Placebo 5.74 (5.05-6.42) days

JAMA Psychiatry. 2014 Apr;71(4):397-403.

Melatonin agonists and delirium

- Single-center RCT
- Patients: admitted to EICU or MICU (n=88)
- May 2015 ~ April 2017
- Ramelteon vs placebo, ~ ICU discharge
- Primary endpoint: duration of ICU stay

TABLE 2. Mulitivariate Analysis to Compare a Primary Endpoint

Variables	β Coefficient (SE)	*t* Statistic	*p*
Ramelteon or placebo	−0.379 (0.169)	−2.24	0.028
Age ≥ 60 (vs < 60)	−0.110 (0.189)	−0.59	0.560
Acute Physiology and Chronic Health Evaluation II score < 30 (vs ≥ 30)	−0.184 (0.204)	−0.90	0.371
Mechanical ventilation	0.720 (0.246)	2.93	0.004
Dementia	0.442 (0.324)	1.27	0.176
Mean of Richmond Agitation-Sedation Scale during the ICU stay	−0.248 (0.103)	−2.42	0.018

- Ramelteon decreases in the occurrence rate of delirium in patients admitted to the ICU

TABLE 3. Analysis of Secondary Endpoints

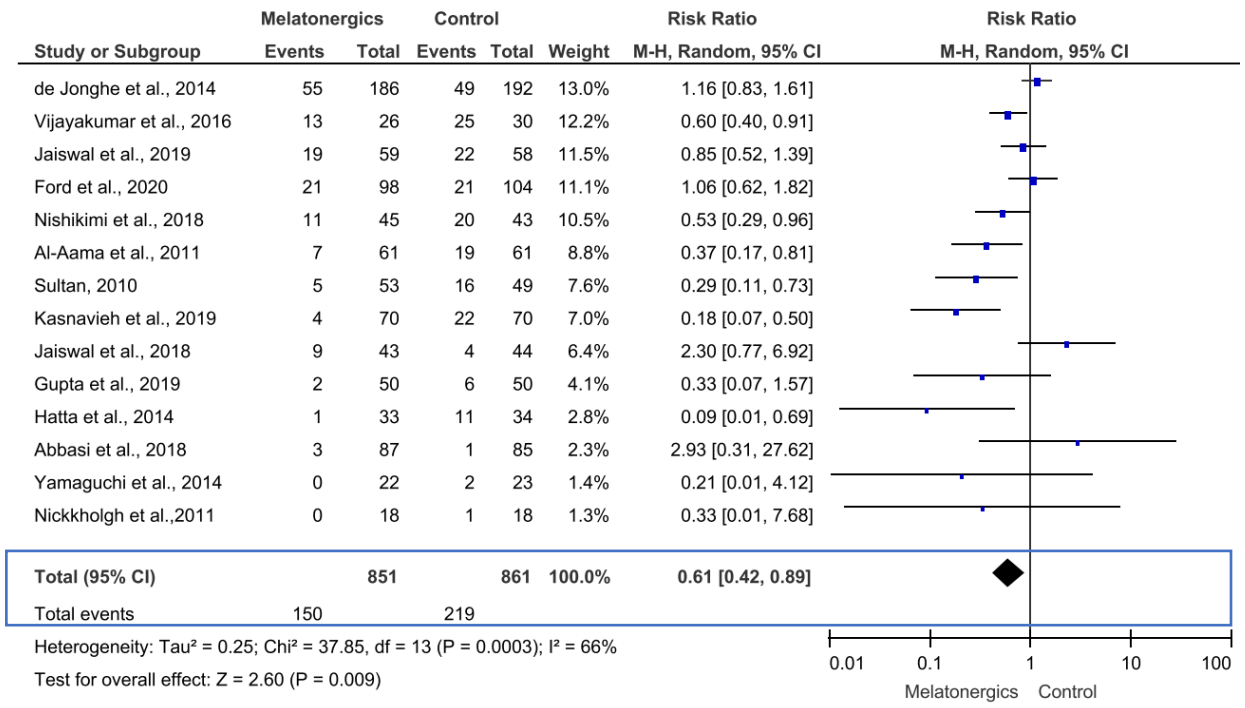
Variables	Ramelteon Group (*n* = 45)	Control Group (*n* = 43)	OR (95% CI)	*p*
The occurrence of delirium, *n* (%)	11 (24.4)	20 (46.5)	2.69 (1.09–6.65)	0.044
The length of delirium, mean (SD), d	0.78 (1.81)	1.40 (2.30)		0.048
Mortality at their discharge, *n* (%)	3 (6.7)	3 (7.5)		> 0.999

Crit Care Med. 2018 Jul;46(7):1099-1105.

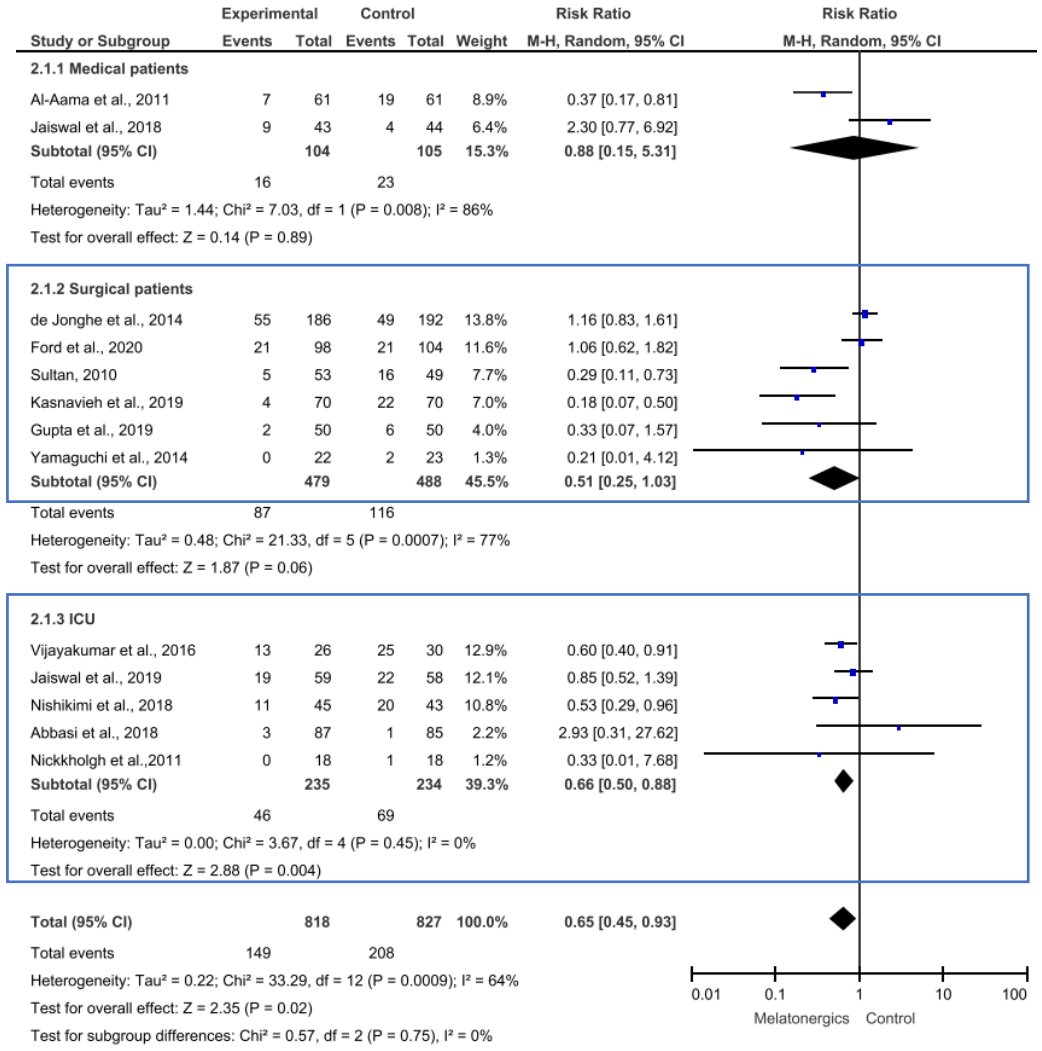
Melatonin for delirium prevention

- Systematic review and meta-analysis, ~May 7, 2020
- 14 RCTs of melatonin/ramelteon (n=1712)
- Primary outcome: delirium incidence

Reduction in delirium in hospitalized patients



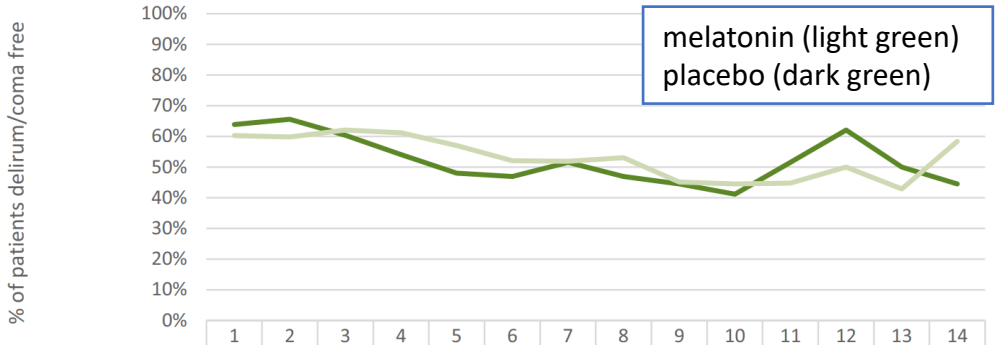
this effect seems confined to surgical and ICU patients



J Psychiatr Res. 2021 Jan;133:181-190.

Melatonin agonists

- Double-blind, RCT
- Patients: requiring ICU admission (n=841)
- ~14 nights or ICU discharge
- 4 mg melatonin or placebo at 21:00
- Primary outcome: proportion of delirium-free assessments (marker of delirium prevalence)
- No significant difference
  - average proportion of delirium-free assessments per patient
  - quantity or quality of sleep



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Placebo	64%	66%	60%	54%	48%	47%	52%	47%	44%	41%	52%	62%	50%	44%
Placebo patient no.	404	322	237	172	125	98	66	49	45	34	33	29	18	9
Melatonin	60%	60%	62%	61%	57%	52%	52%	53%	45%	44%	45%	50%	43%	58%
Melatonin patient no.	397	356	253	188	142	96	81	66	51	45	38	28	21	12

Sleep quality and quantity experience in ICU

	Melatonin	Control	P-value
RCSQ questionnaire (daily in ICU)[1]			
Number of patient with data	373	366	
- Sleep latency	5.4 ± 2.5	5.2 ± 2.5	0.250
- Awakenings	5.6 ± 2.6	5.7 ± 2.5	0.903
- Return to sleep	5.6 ± 2.6	5.6 ± 2.4	0.993
- Sleep quality	5.9 ± 2.6	5.8 ± 2.6	0.803
- Sleep depth	5.6 ± 2.7	5.5 ± 2.5	0.432
- Sleep hours	5.5 ± 2.4	5.3 ± 2.2	0.218
Little's Questionnaire[2]			
Quality of sleep in ICU			
- Very poor	76 (19.5%)	71 (18.4%)	0.805
- Poor	91 (23.4%)	87 (22.5%)	-
- Good	66 (17.0%)	71 (18.4%)	-
- Very good	21 (5.4%)	17 (4.4%)	-
- Excellent	9 (2.3%)	9 (2.3%)	-
- Don't remember	55 (14.1%)	53 (13.7%)	
- Missing	71 (18.3%)	78 (20.2%)	
Quantity of sleep in ICU			
- Very poor	71 (18.3%)	74 (19.2%)	0.498
- Poor	91 (23.4%)	91 (23.6%)	-
- Good	68 (17.5%)	66 (17.1%)	-
- Very good	20 (5.1%)	14 (3.6%)	-
- Excellent	8 (2.1%)	8 (2.1%)	-
- Don't remember	59 (15.2%)	54 (14.0%)	
- Missing	72 (18.5%)	79 (20.5%)	
Est. hours of sleep in ICU, mean ± sd[2]	3.8 ± 2.9	3.9 ± 3.4	0.975

Intensive Care Med. 2022 Apr;48(4):414-425.

Take home message

- Sleep deprivation is associated with delirium and agitation
- Sleep measurement in the ICU: Challenging, No widely accepted gold standard
- Critically ill ICU patients
  - Sleep efficiency↓, fragmentation (disruption) ↑
  - Light sleep ↑, deep NREM, REM sleep ↓
- Bundled intervention for sleep promotion: pharmacologic and non-pharmacologic
- Ventilators and Sleep
  - optimizing ventilator settings is crucial
  - Ventilators modes at night: PCV or ACV > PSV
- Effect of dexmedetomidine and melatonin agonist on the risk of delirium: controversial