MAYO CLINIC

THE UNIT THAT NEVER SLEEPS

PHARMACOLOGIC SLEEP AGENTS FOR CRITICALLY ILL PATIENTS



Nikitha Yagnala, PharmD

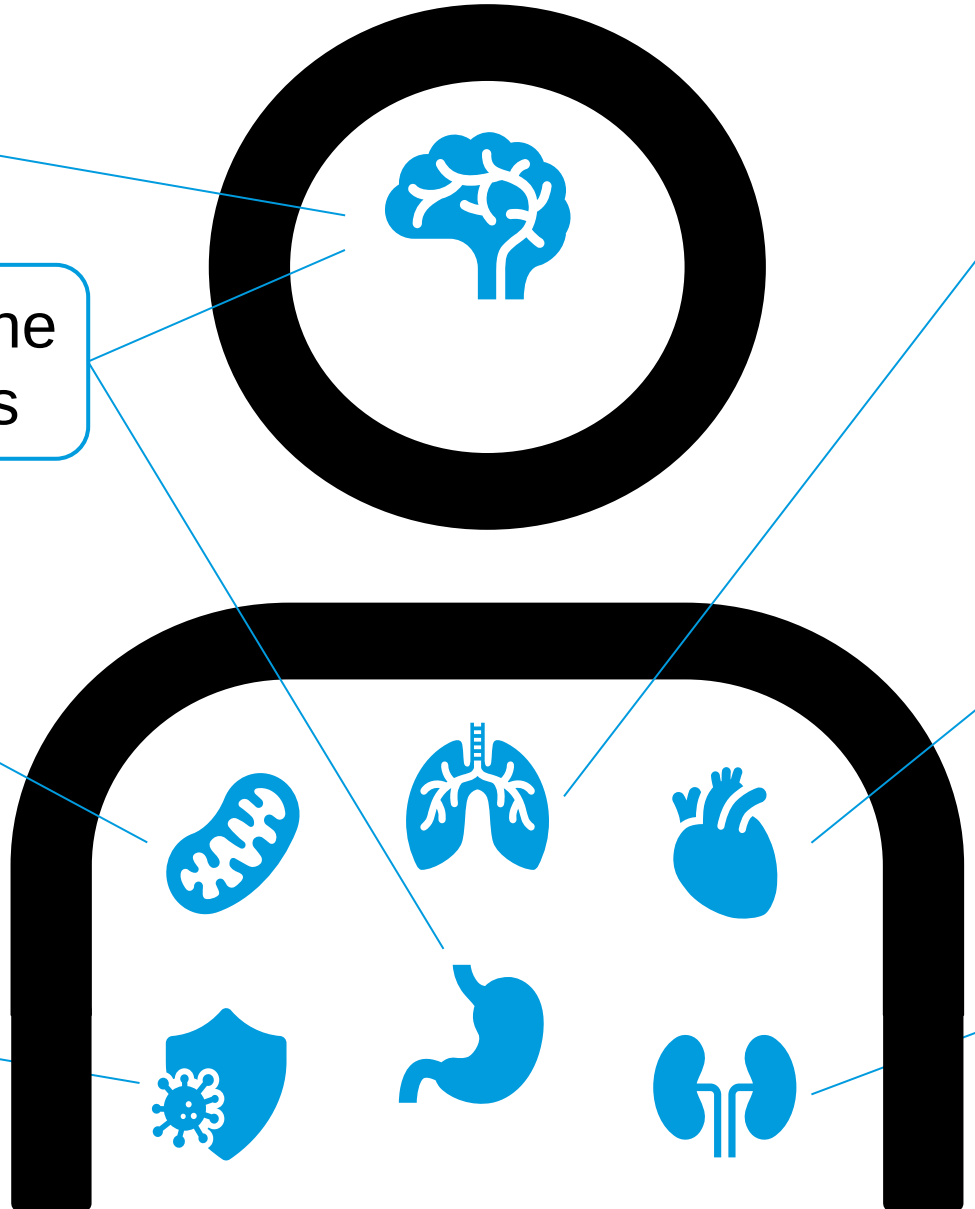
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OBJECTIVES

- Recognize the physiologic consequences of sleep disturbances in critically ill patients
- Discuss the mechanisms of sleep promotion for pharmacologic sleep agents
- Outline appropriate utilization of pharmacologic sleep agents in critically ill patients

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SIGNIFICANCE OF SLEEP DISTURBANCES



Neurocognitive slowing

Neuroendocrine abnormalities

Oxidative stress

Immunity attenuation

Ventilatory disturbances

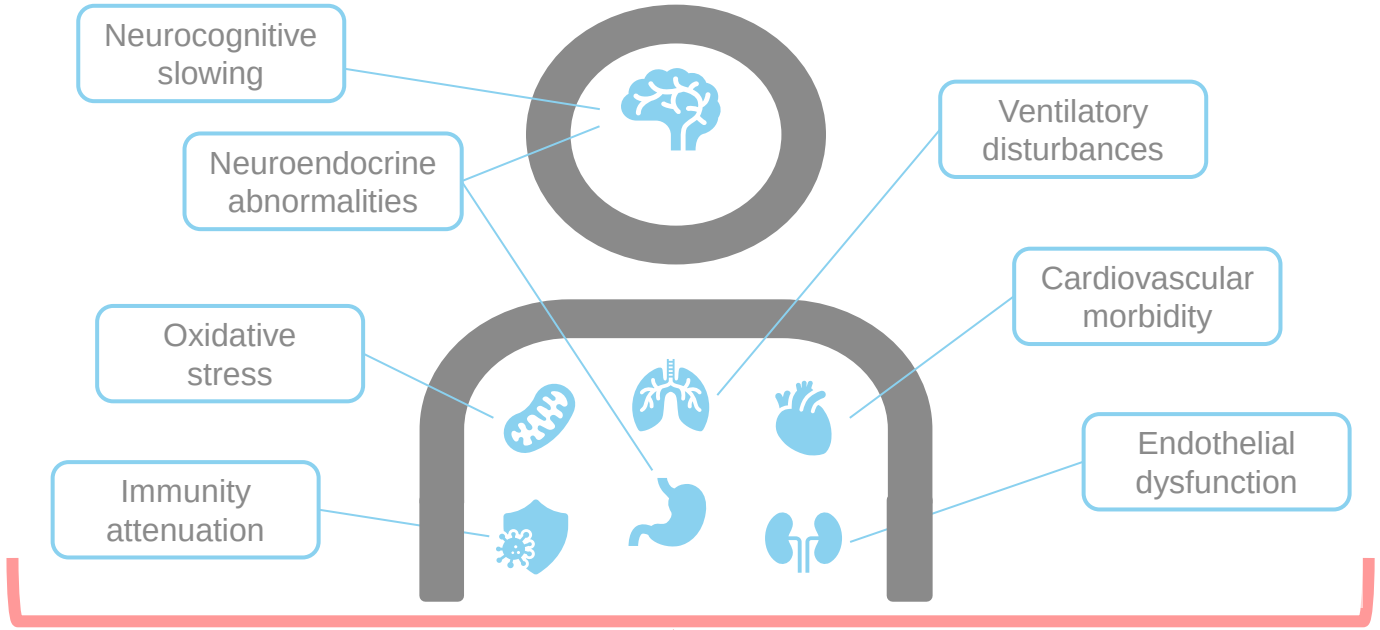
Cardiovascular morbidity

Endothelial dysfunction

J Intensive Care Med. 2012;27(2):97-111.

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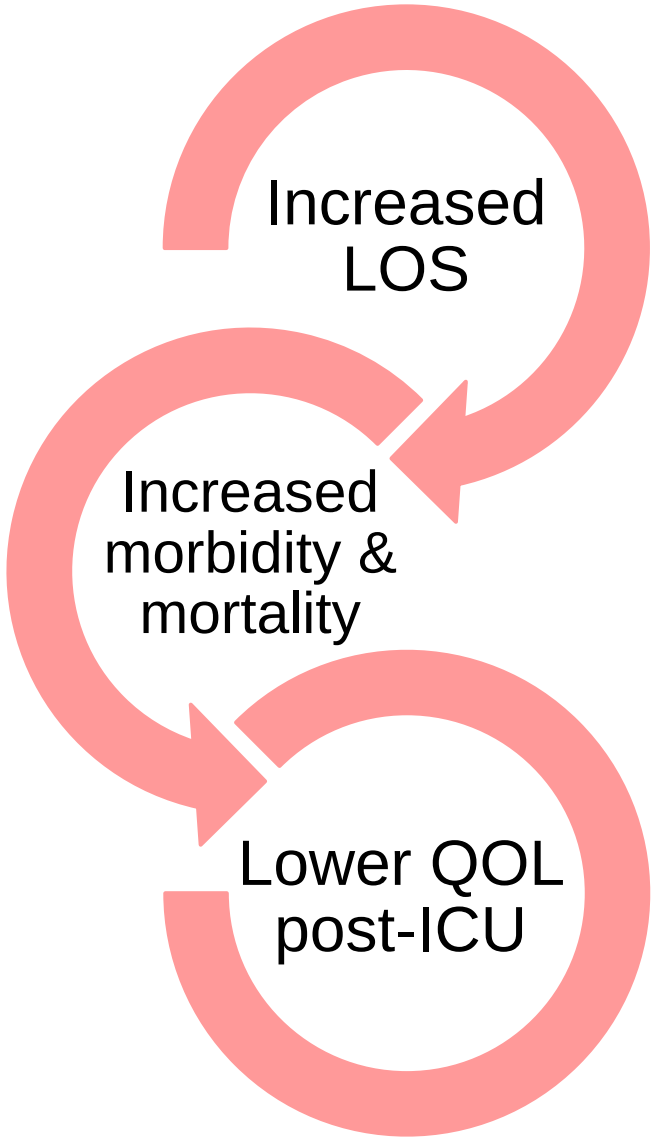
CONSEQUENCES & CLINICAL IMPLICATIONS



Difficulty with extubation

Delirium

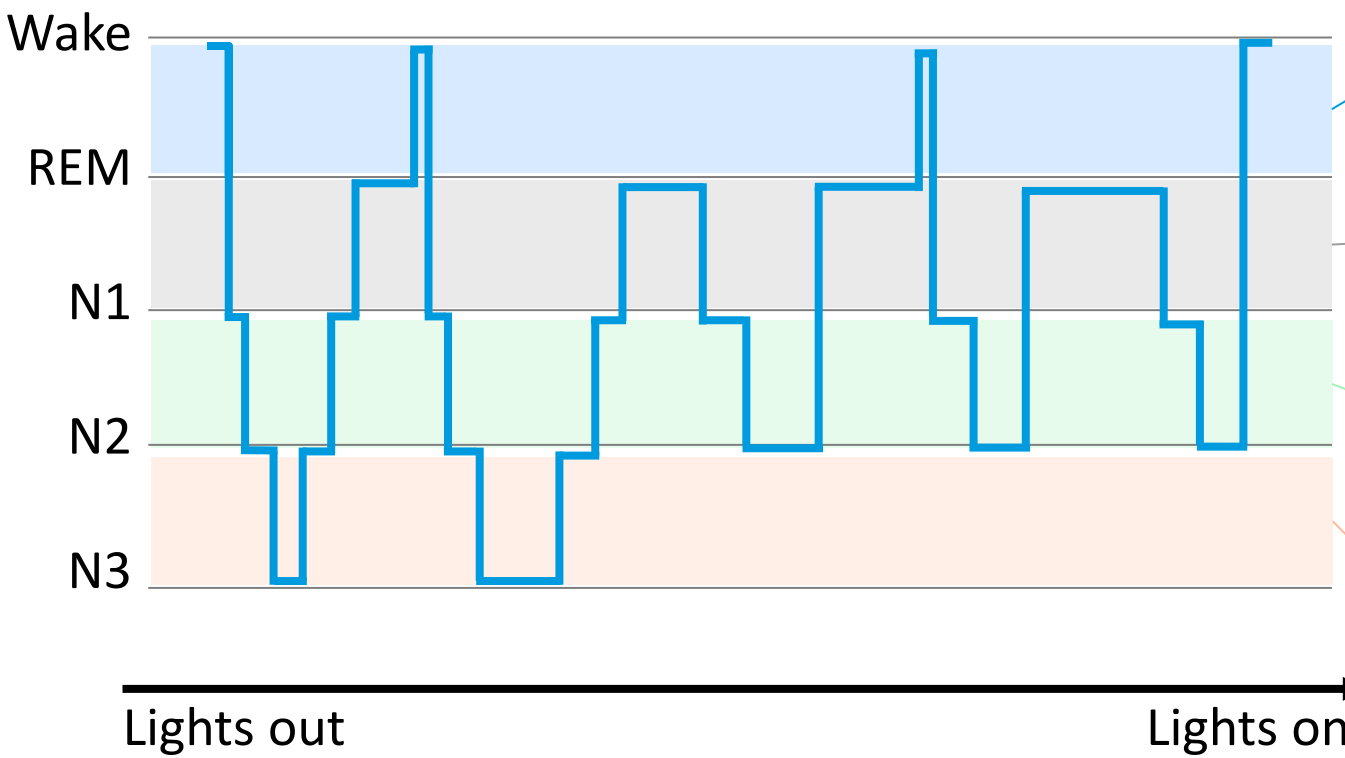
Neurocognitive impairment



LOS: Length of stay
QOL: Quality of life

J Intensive Care Med. 2012;27(2):97-111.
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NORMAL SLEEP ARCHITECTURE



REM: 20-25%
"restful sleep", rapid eye movements, dreaming

N1: 2-5%
"light sleep", transition between wakefulness → sleep

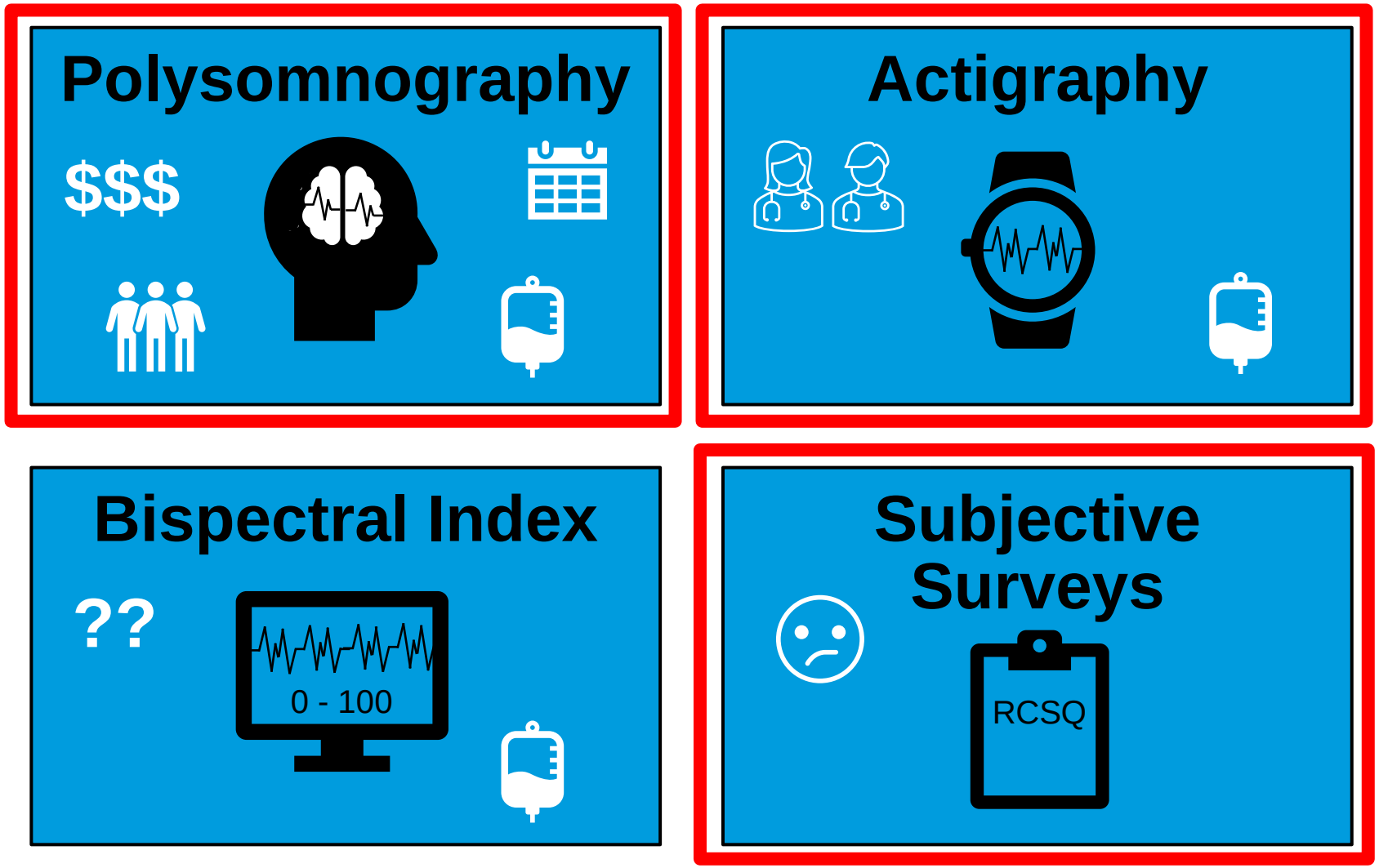
N2: 25-55%
"moderate sleep", memory consolidation

N3: 15-20%
"deep sleep", muscle relaxation, restorative

REM: Rapid eye movement

J Intensive Care Med. 2012;27(2):97-111.
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MEASURING SLEEP



RCSQ: Richard Campbell Sleep Questionnaire

J Intensive Care Med. 2012;27(2):97-111.
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SLEEP CHARACTERISTICS

Total sleep time (TST)

- Amount of time spent sleeping in a given recording period (7-24h)

Sleep efficiency index (SEI)

- Ratio of total sleep time (TST) to time in bed

Wake after sleep onset (WASO)

- Amount of time spent awake after initial sleep onset

Sleep latency (SL)

- Amount of time it takes from being fully awake to sleeping

Time in each sleep stage – N1, N2, N3, REM ★

Slow wave sleep (SWS) ★

- Time in deep sleep

?important in assessing restorative sleep function

Telias. *Crit Care* 23, 82 (2019).
J Intensive Care Med. 2012;27(2):97-111.

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SLEEP-WAKE CYCLE IN HEALTHY ADULTS

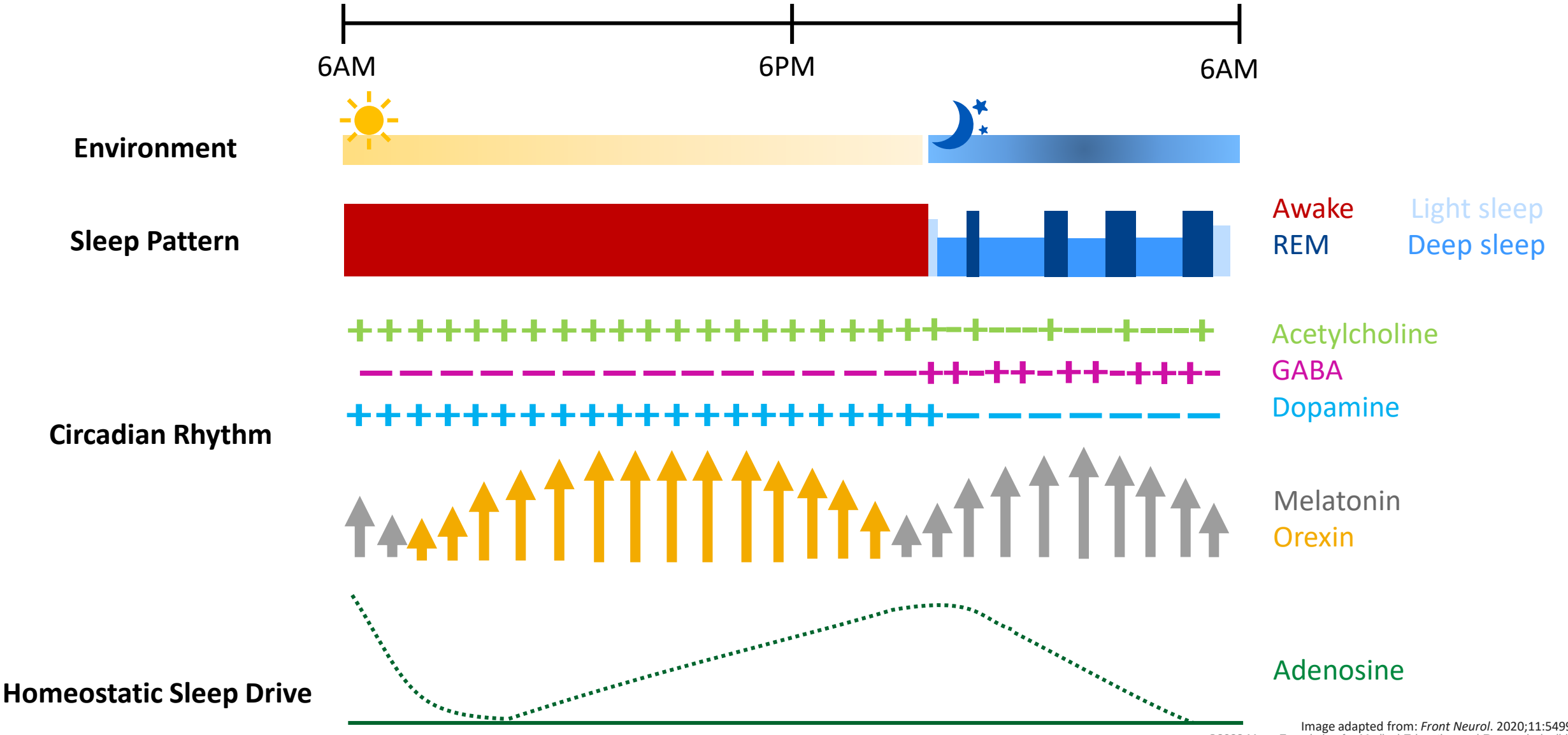


Image adapted from: *Front Neurol*. 2020;11:549908.

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SLEEP-WAKE CYCLE IN CRITICALLY ILL ADULTS

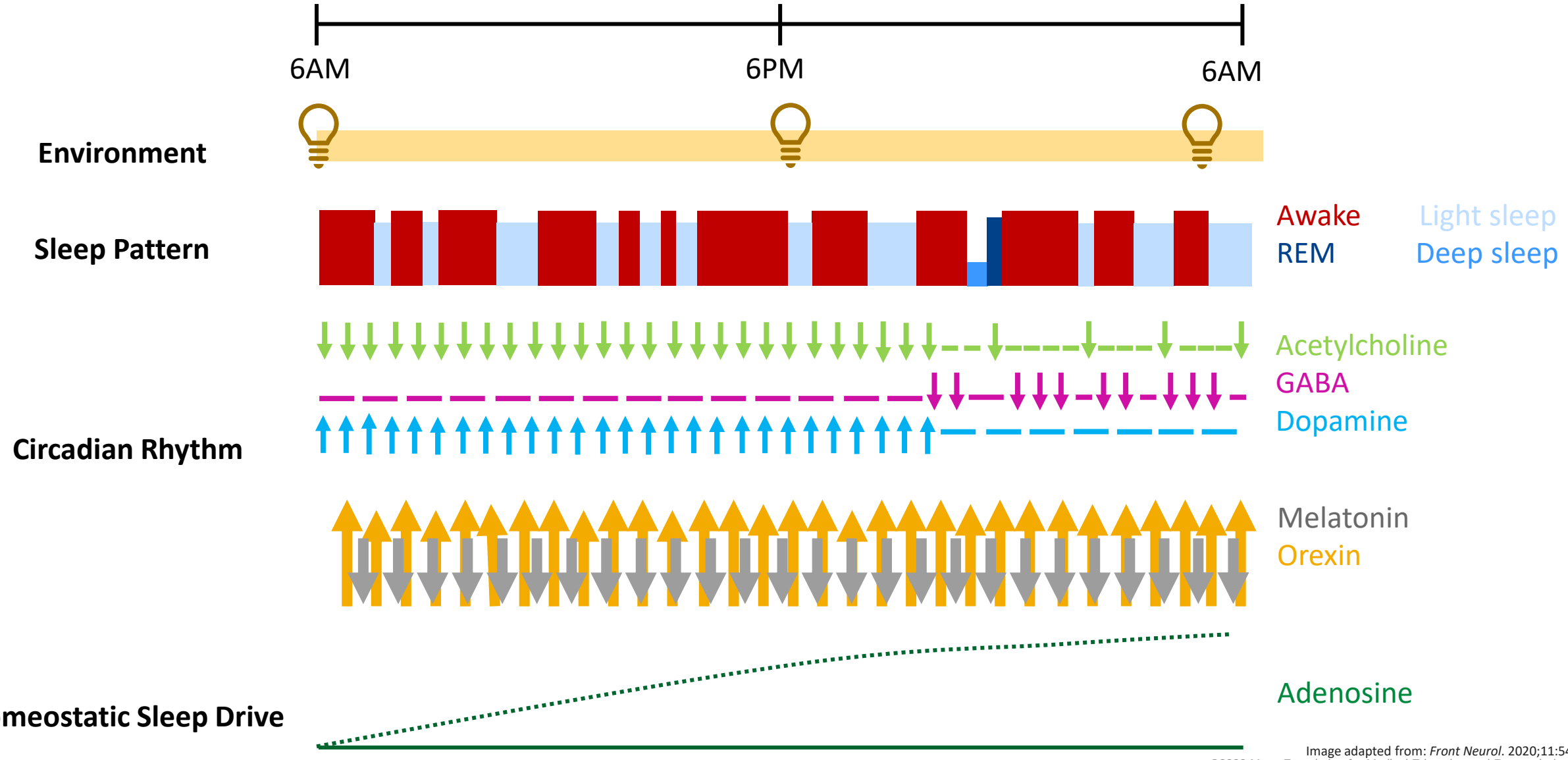
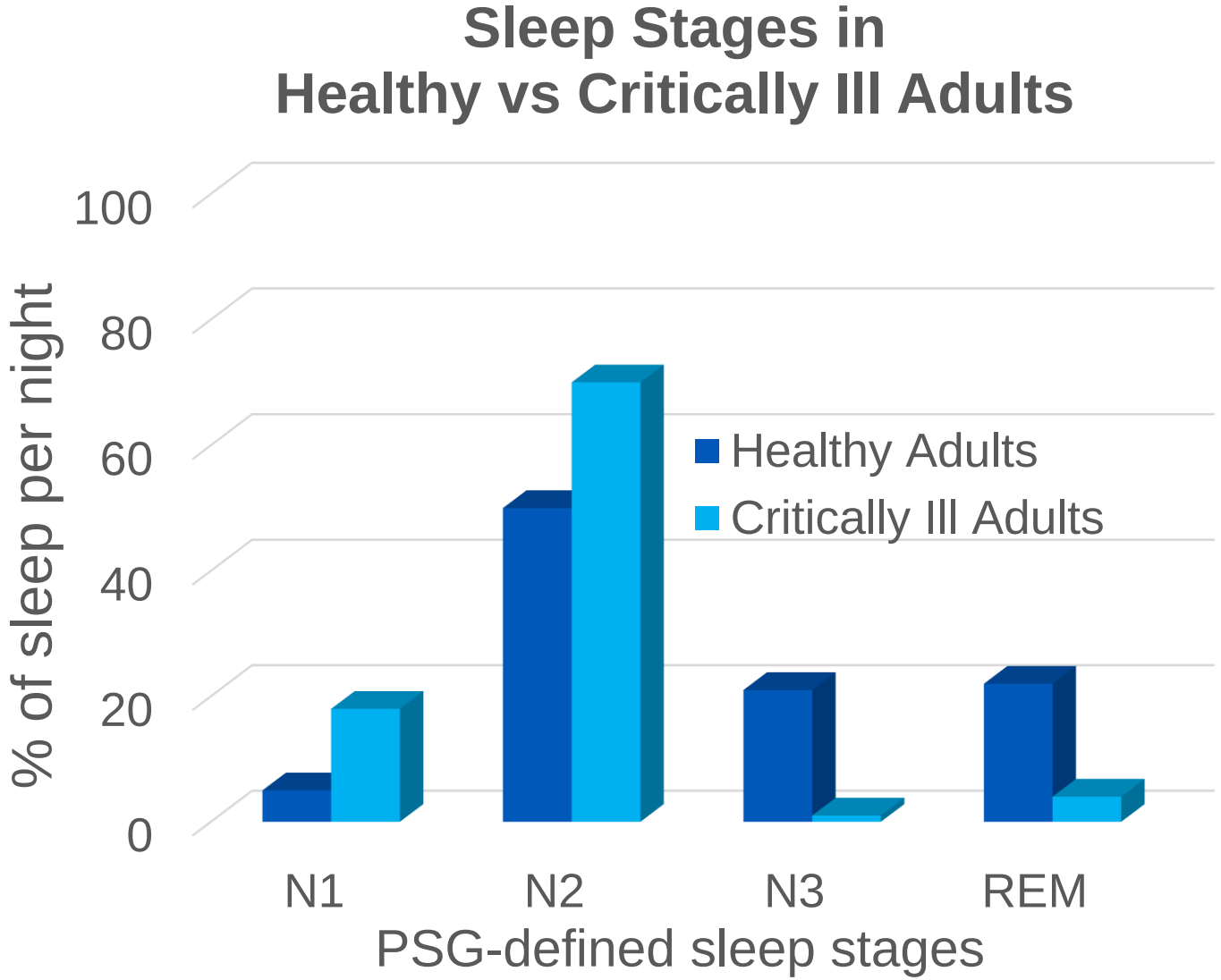


Image adapted from: *Front Neurol*. 2020;11:549908.

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DISRUPTED SLEEP ARCHITECTURE IN ICU PATIENTS



- Sleep fragmentation
- Lighter depth of sleep
- "Atypical" sleep
- 50% of total sleep at night

PSG: Polysomnography

Semin Respir Crit Care Med. 2019;40(5):614-628.
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RISK FACTORS FOR SLEEP DISRUPTION

	Total Sleep Time (TST)	N3	REM	Wakefulness
Steroids	↓	↓	↓	↑
Vasopressors	↓	↓	↓	↑
Opioids	↓	↓	↓	↓
BZDs, Propofol	↑	↓	↓	↓

REM: Rapid eye movement
N3: “Deep sleep”
BZDs: Benzodiazepines

J Intensive Care Med. 2012;27(2):97-111.
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ASSESSMENT QUESTION #1

Which of the following describes the disrupted sleep architecture in critically ill patients compared to healthy adults?

A. Mean total sleep time is lower in critically ill patients
B. Time in N3 and REM sleep is longer in critically ill patients
C. Roughly 50% of sleep occurs during daytime hours in critically ill patients
D. Time in N1 and N2 sleep is shorter in critically ill patients

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2018 SCCM PADIS GUIDELINES ON SLEEP PROMOTION

Non-Pharmacologic Measures

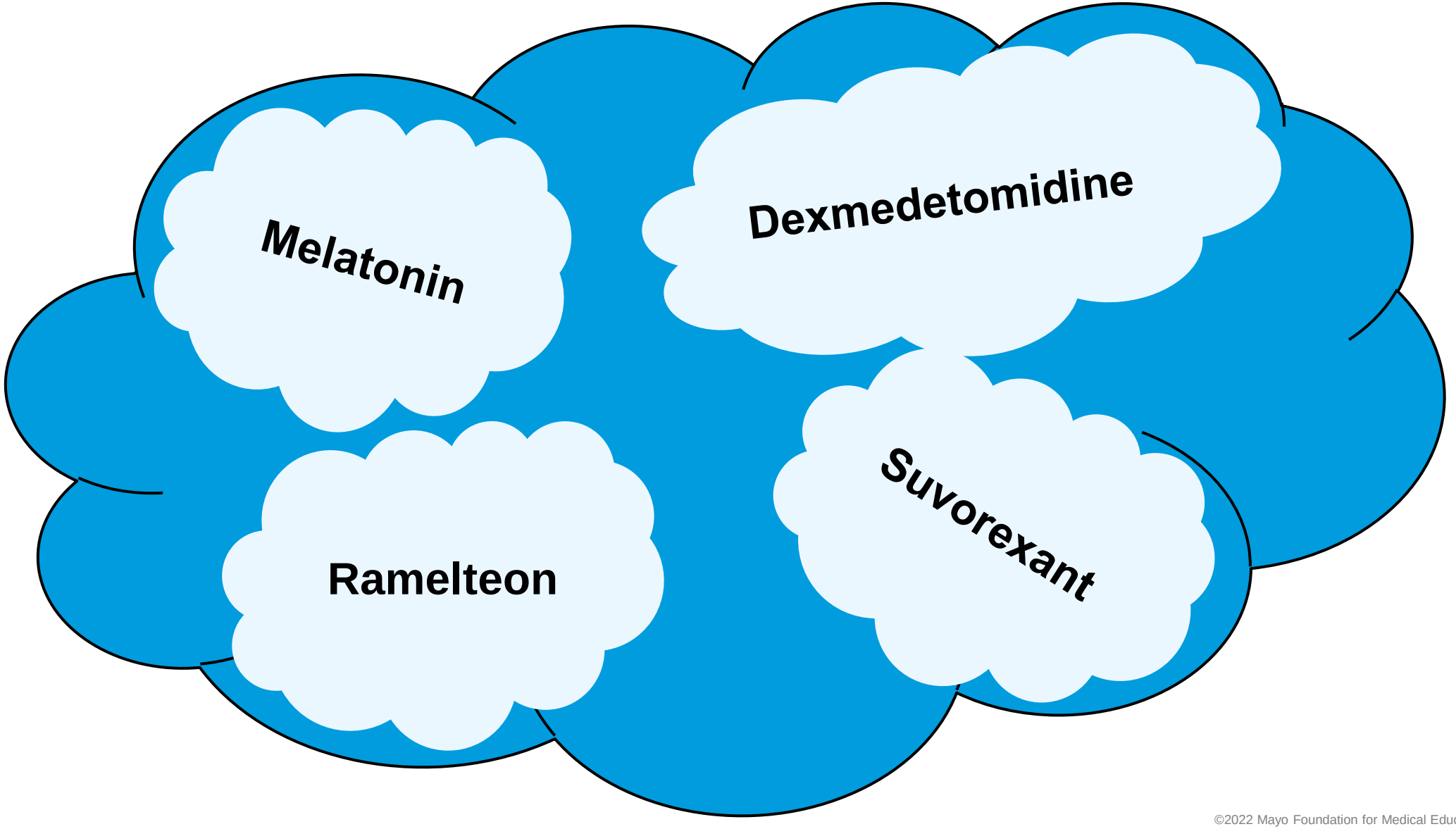
- Assist control ventilation at night
- Noise and light reduction strategies

Pharmacologic Measures

- No recommendation regarding melatonin to improve sleep
- No recommendation regarding dexmedetomidine to improve sleep
- Suggest NOT using propofol

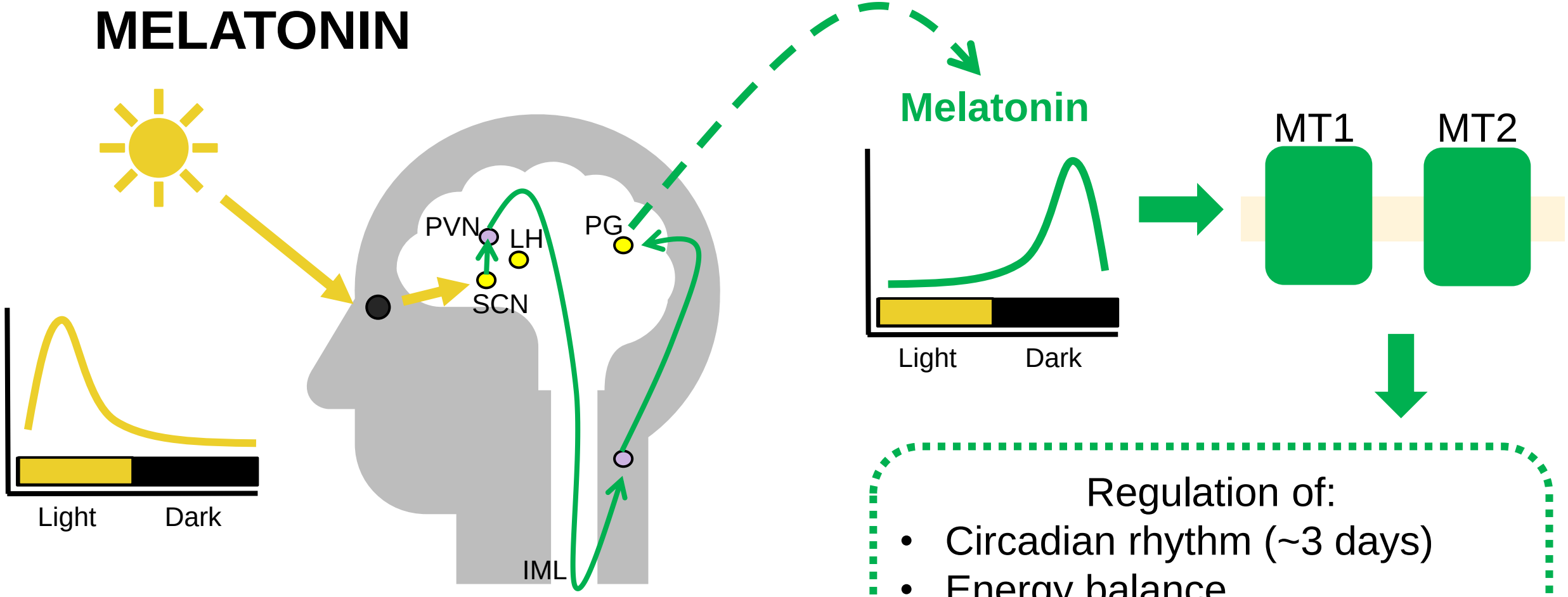
Devlin JW. Crit Care Med. 2018;46(9):e825-e873.
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SLEEP AGENTS AVAILABLE “ON THE CLOUD”



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MELATONIN



Regulation of:

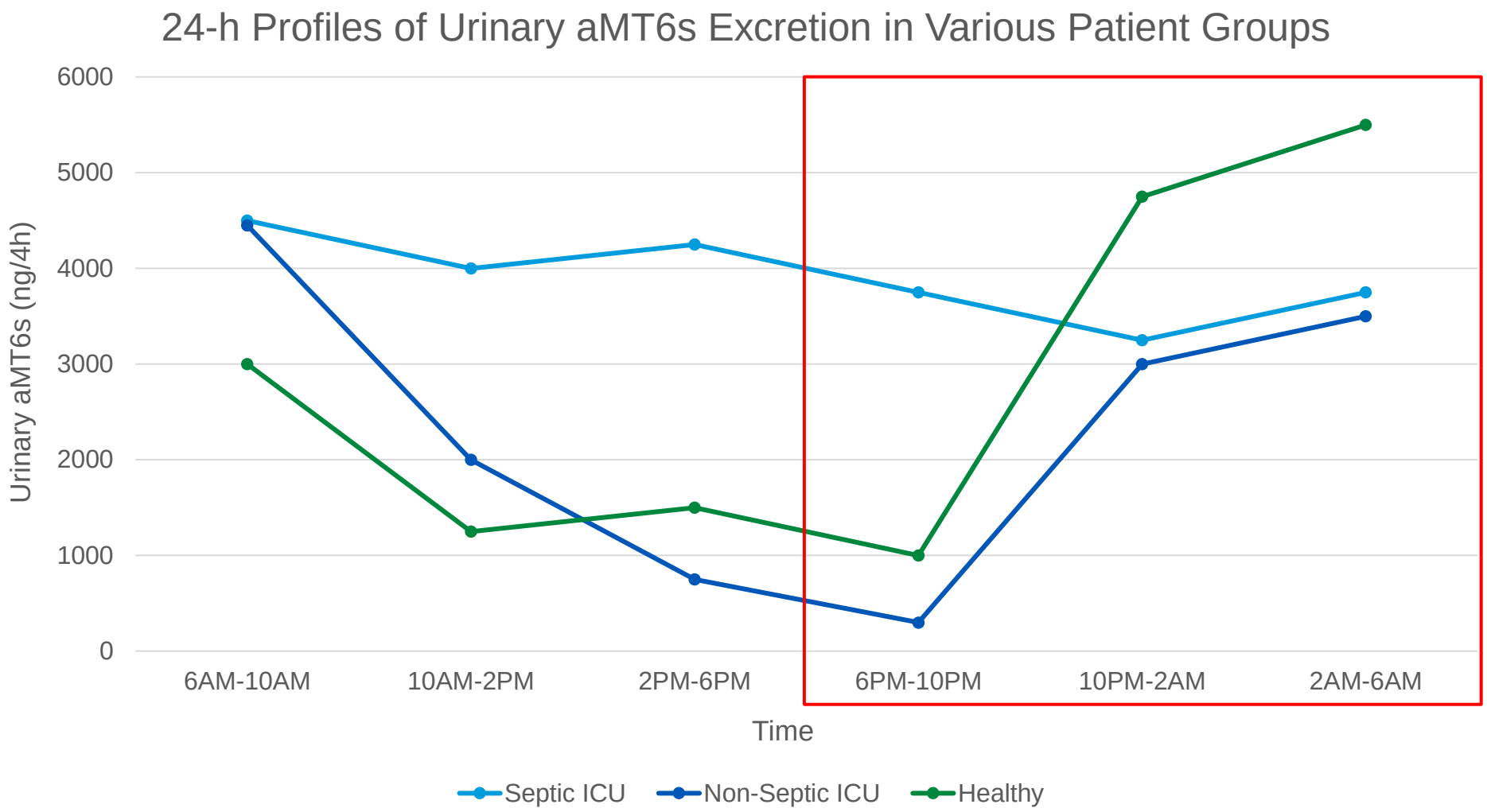
- Circadian rhythm (~3 days)
- Energy balance
- Insulin secretion
- Inflammation

PVN: Paraventricular hypothalamic nucleus
SCN: Suprachiasmatic nucleus
LH: Lateral hypothalamic (area)
IML: Intermediolateral nucleus
PG: Pineal gland

Imaged adapted from Tsuneki H. *Trends Endocrinol Metab*. 2016;27(9):633-642.

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MELATONIN EXCRETION IN CRITICALLY ILL PATIENTS



Mundigler G. Crit Care Med 2002;30(3):536-540.

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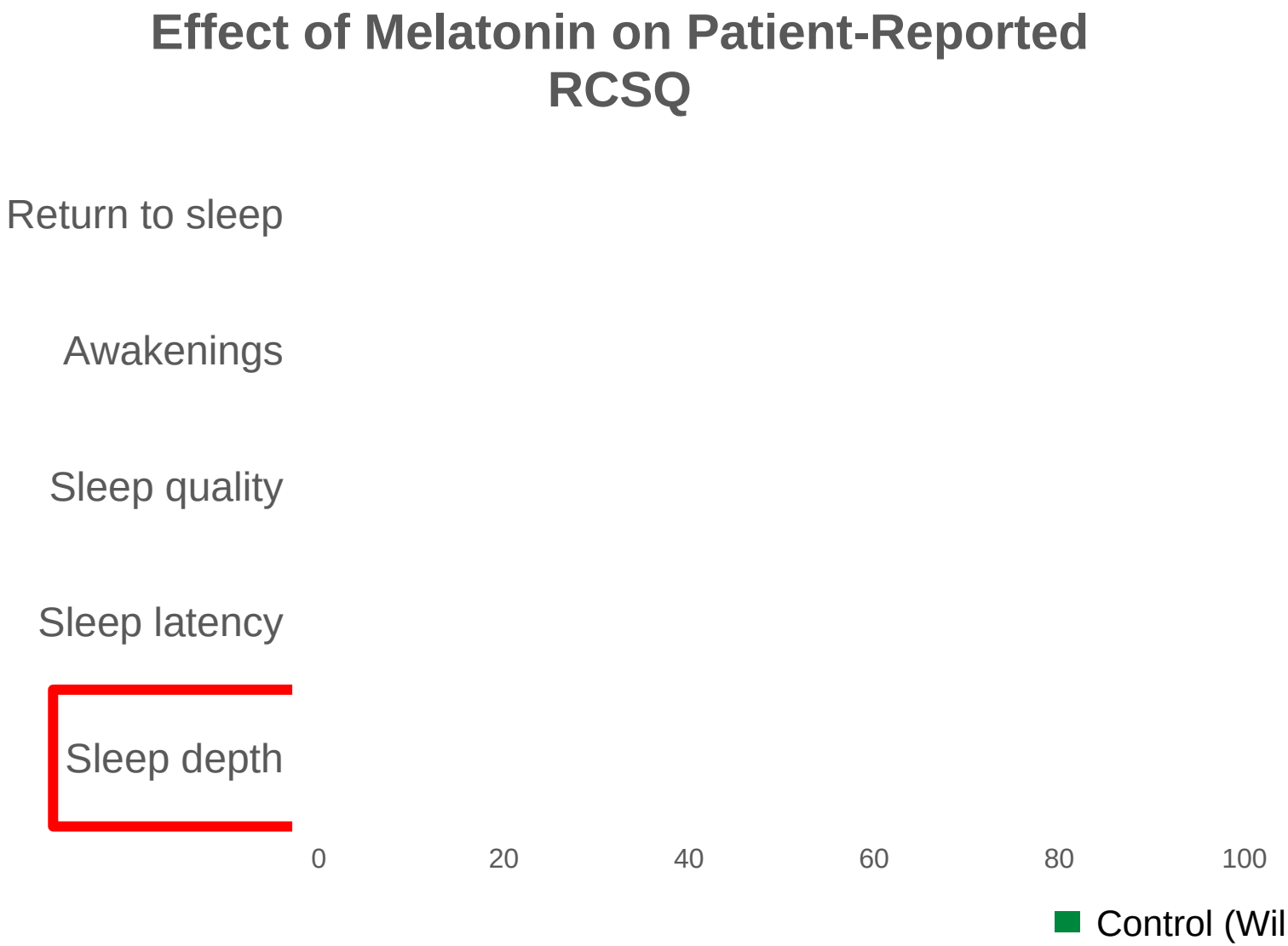
MELATONIN AND SLEEP QUANTITY

Author, Year	Type	Population (N) MV	Sleep Measurement	Intervention	Cont Infusion Sedation?	LOS (d)	Result
Shilo, 2000	before/ after	Medical ICU (N=8) Mixed MV	actinography	melatonin 3mg	No	3	↑ sleep duration
Ibrahim, 2006	RCT	Medical ICU (N=32) Tracheostomized	nursing assessment	melatonin 3mg vs placebo	No	3	~ total sleep time
Bourne, 2008	RCT	Medical ICU (N=24) All MV	BSI, actigraphy, RCSQ	melatonin 10mg vs placebo	No	16.5	~ sleep efficiency
Foreman, 2015	RCT	Neuro ICU (N=12) Mixed MV	PSG	melatonin 3mg vs SOC	Yes (propofol)	7	~ total sleep time

MV: Mechanical ventilation
BSI: Bispectral index
RCSQ: Richard Campbell sleep questionnaire
PSG: Polysomnography
SOC: Standard of care

Shilo L. *Chronobiol Int*. 2000;17(1):71-76.
Ibrahim MG. *Crit Care Resusc*. 2006;8(3):187-191.
Bourne RS. *Crit Care*. 2008;12(2):R52.
Foreman B. *J Clin Neurophysiol*. 2015;32(1):66-74.
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MELATONIN AND SLEEP QUALITY (RCSQ)



Gandolfi, 2020 (N=203)

- ✓ 50% surgical ICU patients
- ✓ 100% able to answer RCSQ
- ✓ 50% on analgesics
- ✓ Melatonin 10mg x7d

Wilbrow, 2022 (N=847)

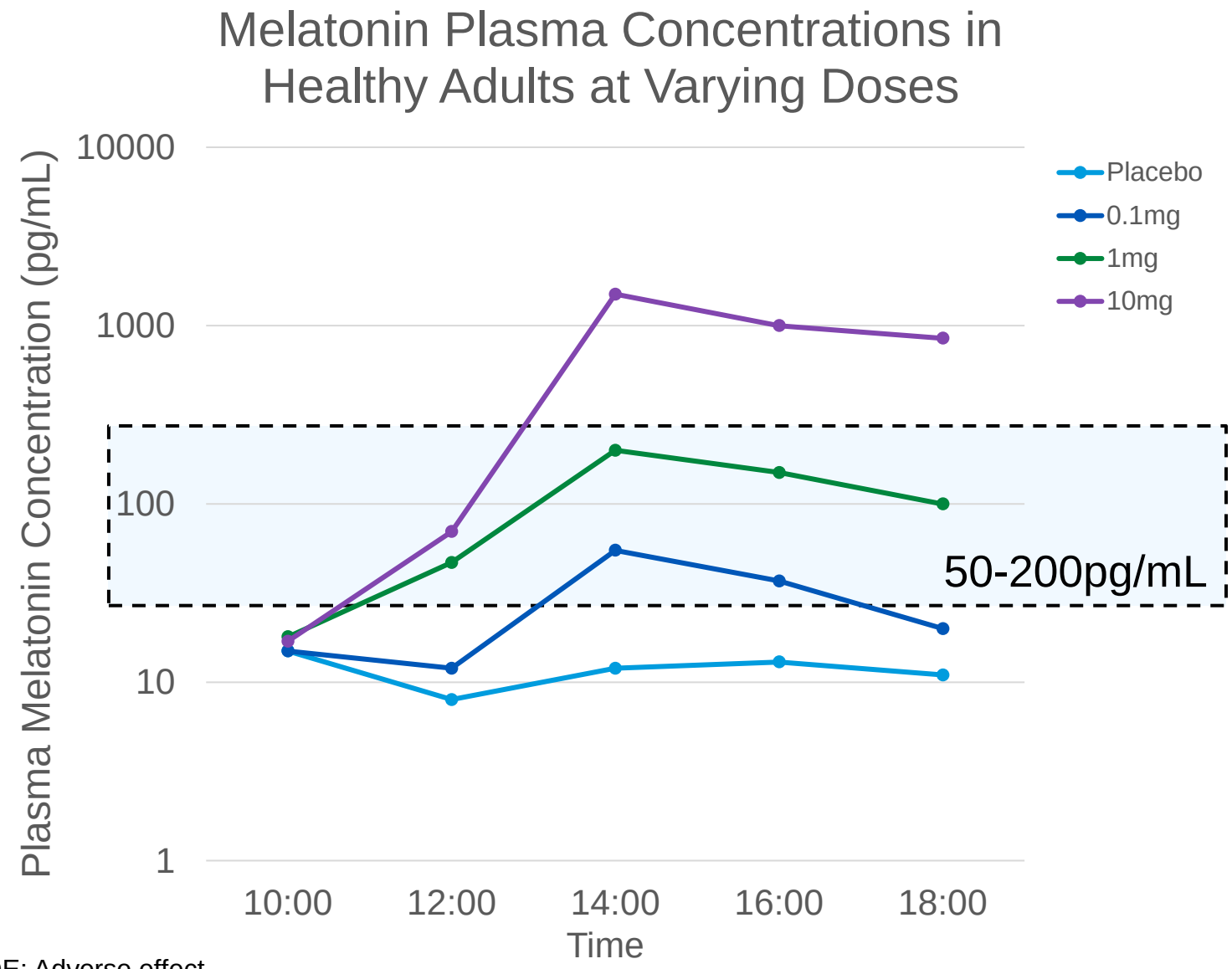
- ✓ 20% surgical ICU patients
- ✓ 20% able to answer RCSQ
- ✓ 50% on analgesics + propofol
- ✓ Melatonin 4mg x14d

RCSQ: Richard campbell sleep questionnaire

Gandolfi JV. *Crit Care Med*. 2020;48(12):e1286-e1293. Wibrow B. *Intensive Care Med*. 2022;48(4):414-425.

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MELATONIN DOSING & SAFETY



- ADE profile benign (0.1mg – 200mg)
  - Headache
  - Fatigue
  - Nightmares

- Overdosing does not facilitate sleep-promoting effects & may desensitize MT1 receptors

Melatonin 3mg-6mg

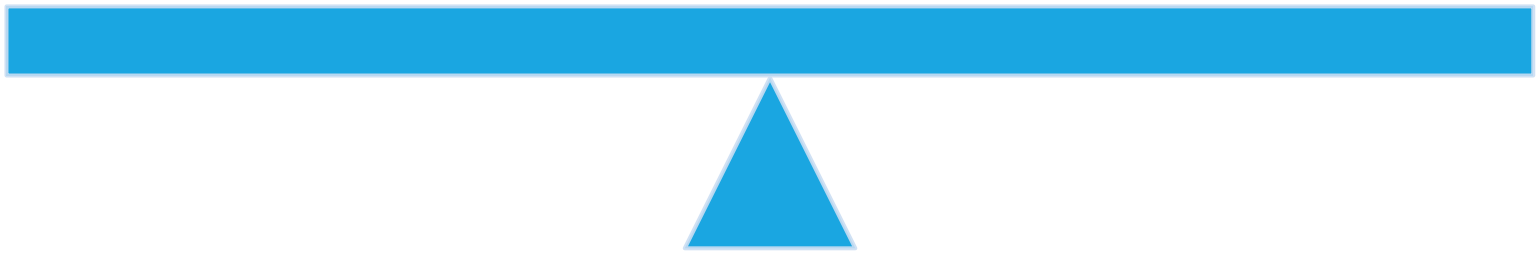
ADE: Adverse effect

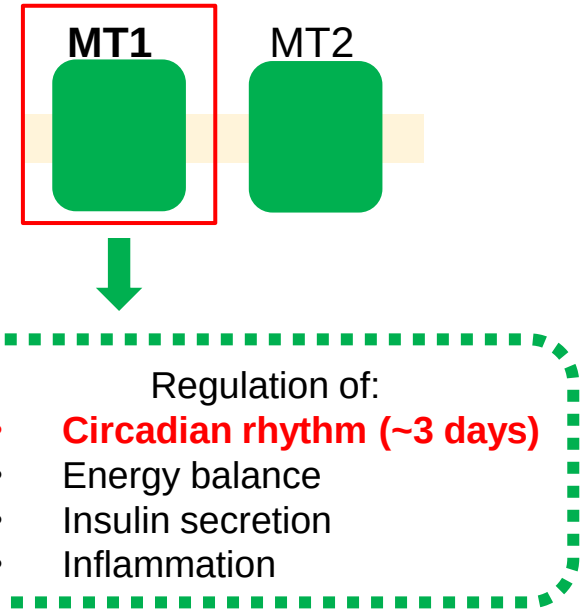
Zhdanova IV. *Sleep Med Rev*. 2005;9(1):51-65.

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RAMELTEON – A MELATONIN RECEPTOR AGONIST

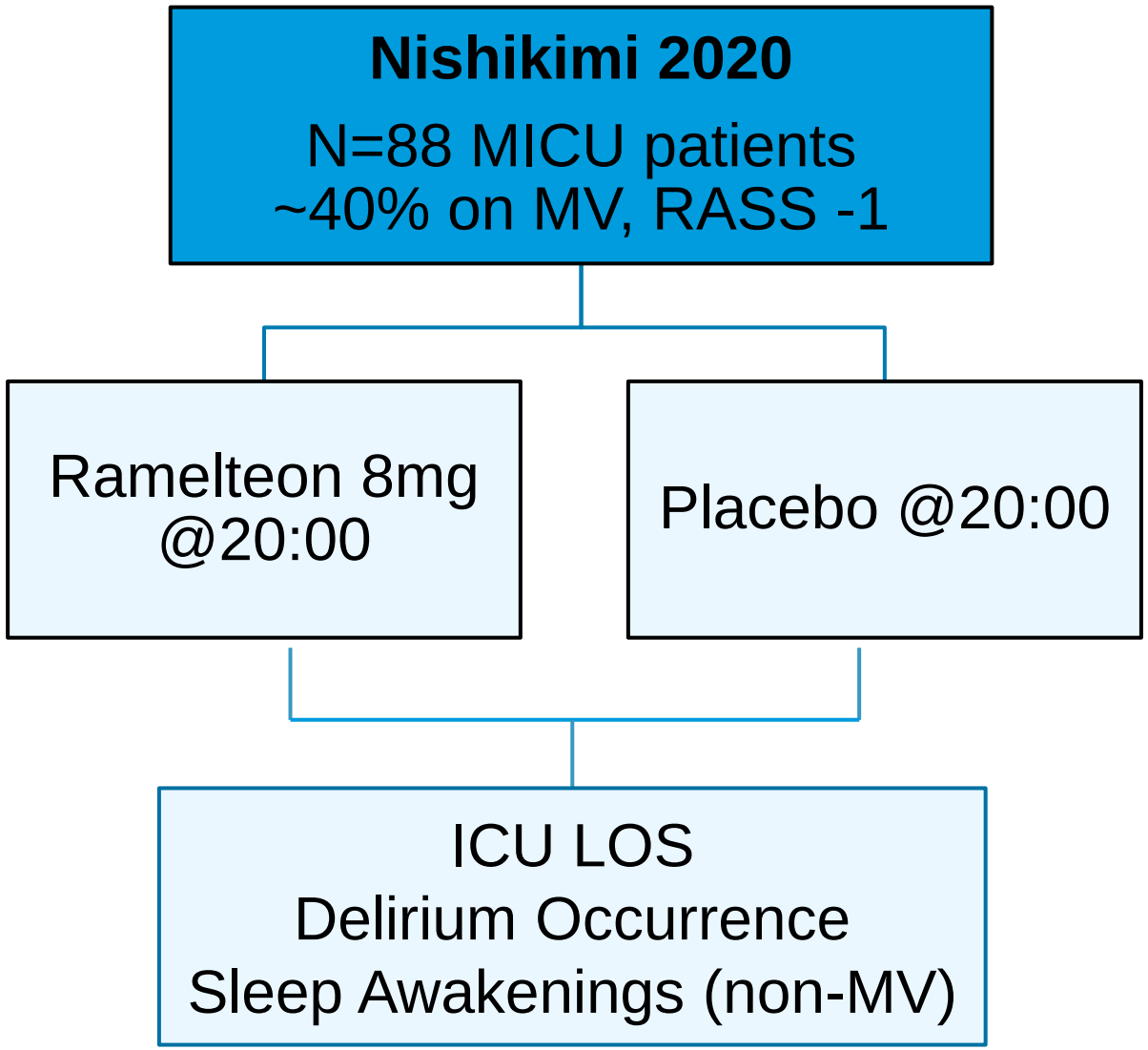
Melatonin	Ramelteon
Dietary supplement	FDA approved for sleep onset insomnia (2005)
MT1, MT2, MT3 receptors	MT1 > MT2 receptor selectivity
$0.26 USD per 3mg tab	$14.78 USD per 8mg tab
Dosing range: 0.5mg -10mg	Dosing range: 8mg





Erland LA2. *J Clin Sleep Med*. 2017;13(2):275-281.
Romero N. *Ann Pharmacother*. 2021;55(11):1347-1354.
Lexi-Comp Inc., 2022. Melatonin; [updated 5/2022].
Lexi-Comp Inc., 2022. Ramelteon; [updated 7/2022].
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RAMELTEON EVIDENCE



MV: Mechanical ventilation
LOS: Length of stay

Results

Variables	Ramelteon (N=45)	Placebo (N=43)	P-value*
ICU LOS, d	4.6	5.9	0.028
Delirium occurrence, n (%)	11 (24.4%)	20 (46.5%)	0.044
No. awakenings per night (SD)	0.80 (0.87)	1.31 (0.87)	0.036

*after adjustment from multivariate analysis

Conclusions

- Highly underpowered
- Retrospective chart review to assess sleep outcomes = poor methodology
- Ramelteon is safe, efficacy unclear

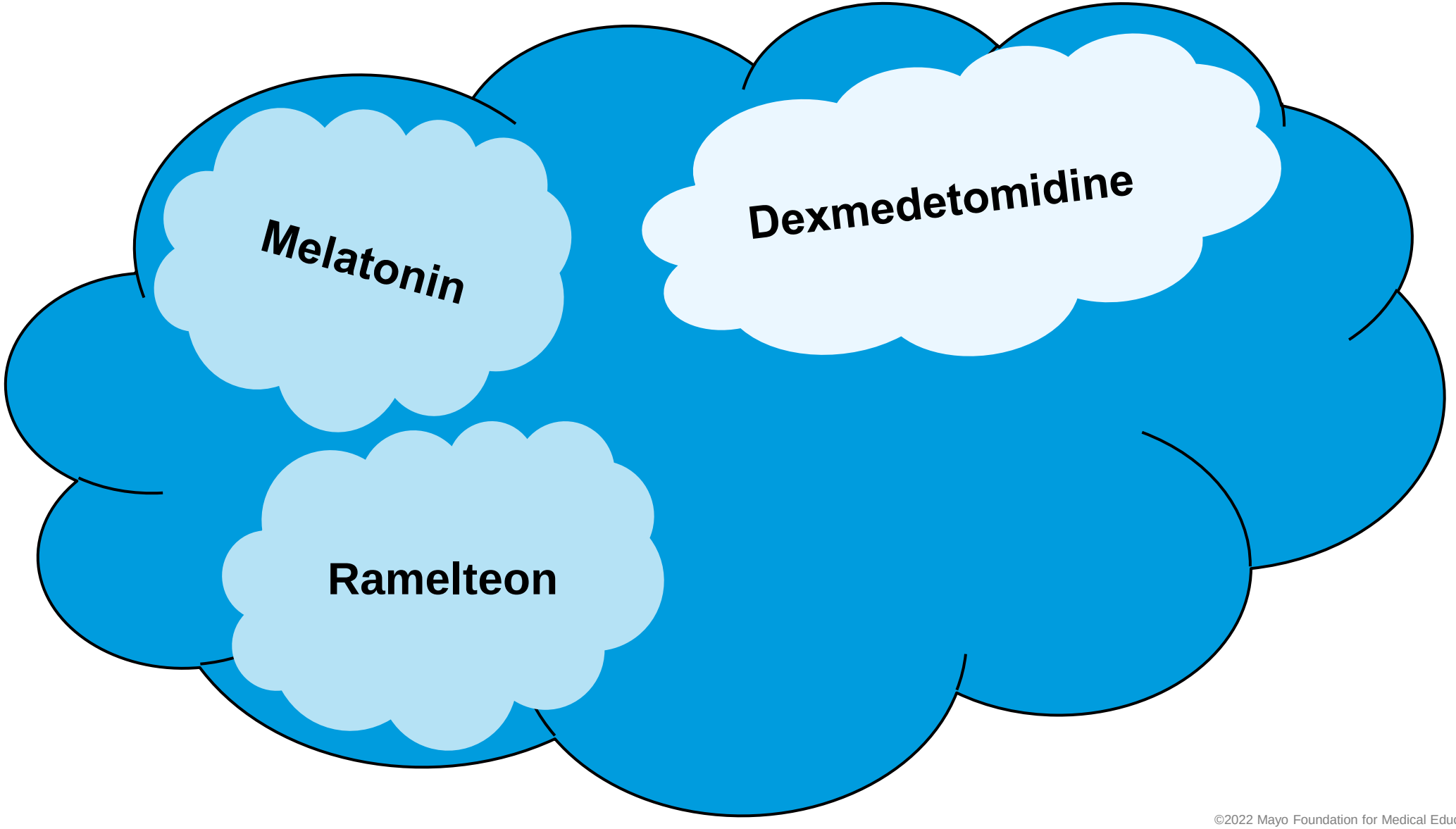
Nishikimi M. *Crit Care Med*. 2018;46(7):1099-1105.
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MELATONIN RECEPTOR AGONISTS SUMMARY

- Melatonin levels in ICU are abnormal and unpredictable
- Melatonin and ramelteon are safe options that target the circadian rhythm pathway
- Studies with melatonin and ramelteon are highly variable, underpowered, and have significant limitations
- Melatonin may be a preferred agent in non-MV patients, though comparative data is needed between both agents

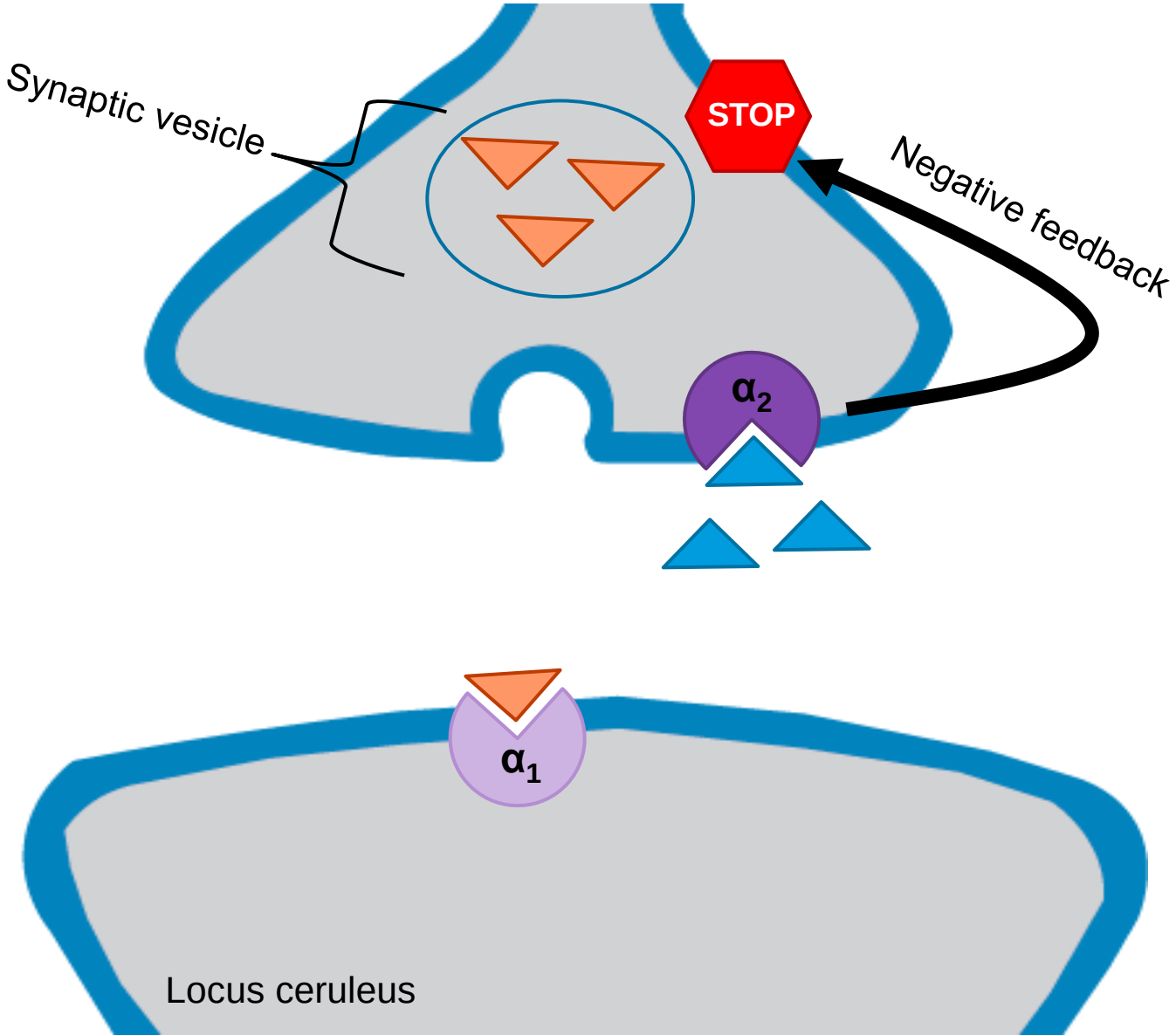
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SLEEP AGENTS AVAILABLE “ON THE CLOUD”



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DEXMEDETOMIDINE



Effects:

Inhibition of sympathetic activity

Analgesia

Anxiolytic

ADEs:

Bradycardia

Hypotension

Potential for withdrawal

Key:

Norepinephrine

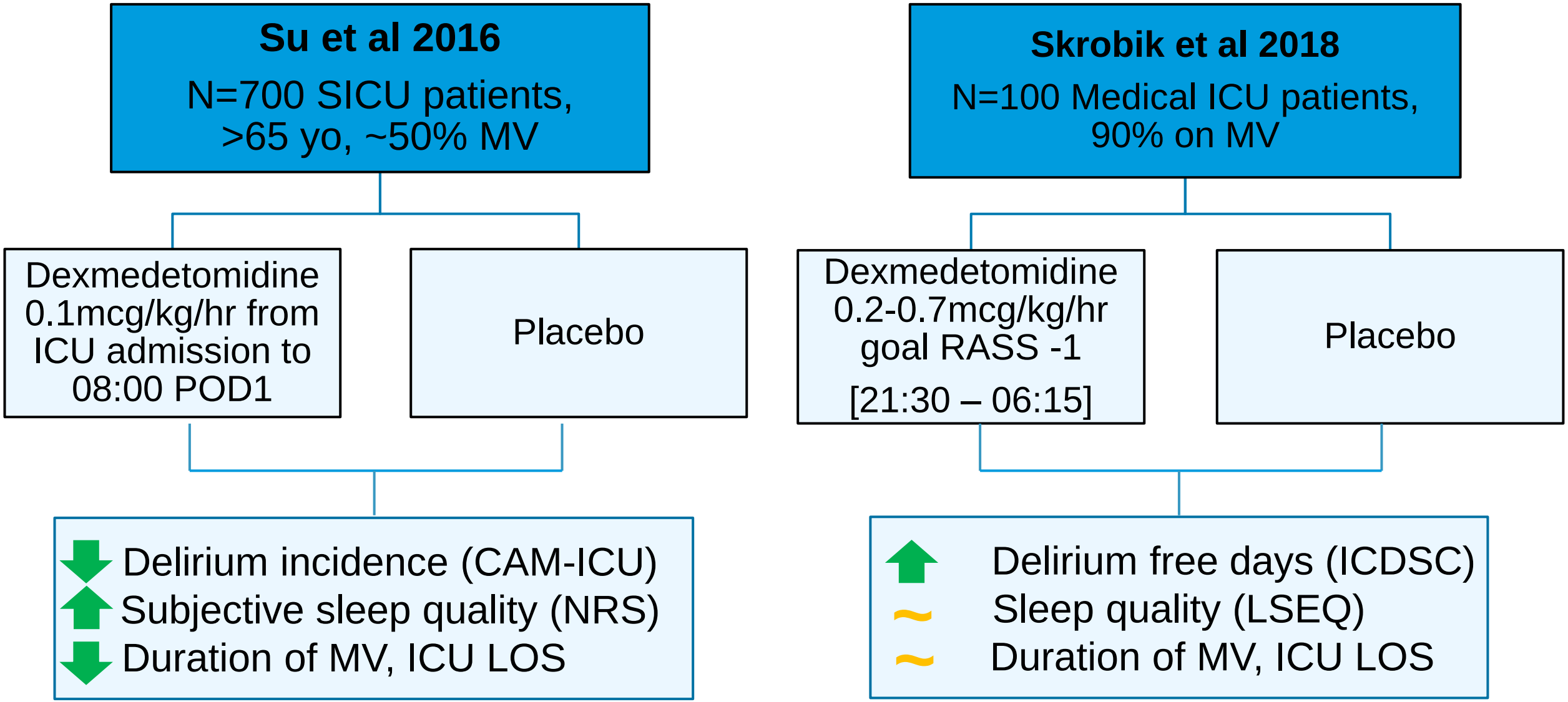
Dexmedetomidine

Devlin et al. Crit Care Med. 2018;46(9):e825-873.

Receptor courtesy of Julia Osborne & Hannah Brokmeier

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DEXMEDETOMIDINE - DECREASES DELIRIUM INCIDENCE ✓



NRS: Number rating scale
LSEQ: Leeds sleep evaluation questionnaire

CAM-ICU: Confusion assessment method for ICU
ICDSC: Intensive care delirium screening checklist

Skrobik Y. *Am J Respir Crit Care Med*. 2018;197(9):1147-1156.
Su X. *Lancet*. 2016;388(10054):1893-1902.
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DEXMEDETOMIDINE – IMPACT ON SLEEP ARCHITECTURE ?

Oto, 2012

Descriptive

Adult ICU patients on MV (N=10)
- MDZ or propofol +/- PRN fentanyl

Dexmedetomidine 0.2-0.7mcg/kg/hr
Goal RASS -1 to -4

PSG – Predominantly stage N2 sleep
No stage N3 or REM sleep

78% TST occurred at night

MDZ: Midazolam
PSG: Polysomnography
REM: Rapid eye movement
TST: Total sleep time
MV: Mechanical ventilation

Alexopoulou C. *Anesthesiology*. 2014;121(4):801-807.
Oto J. *Intensive Care Med*. 2012;38(12):1982-1989.
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DEXMEDETOMIDINE – ENHANCES SLEEP ARCHITECTURE ✓

Wu, 2016

N=61 SICU patients
>65 yo, non-MV, +/- morphine

Dexmedetomidine 0.1mcg/kg/hr overnight [RASS 0]

Placebo

PSG – sleep stages
TST, sleep efficiency
subjective sleep quality

Variables	Dex (N=31)	Placebo (N=30)	P-value
% stage N1 sleep, median (IRQ)	56.4 (13.-83.4)	84.2 (28.2-96.7)	0.038
% stage N2 sleep, median (IRQ)	43.5 (16.6-80.2)	15.8 (1.3-62.8)	0.048
TST [min], median (IRQ)	213 (124-324)	130 (72-220)	0.028
% sleep efficiency, median (IRQ)	22.4 (14.2-37.1)	15 (7.9-26.3)	0.033

Dexmedetomidine Conclusions:

- ✓ Deeper sleep
- ✓ Higher sleep efficiency & TST
- ✓ Improved subjective sleep quality

PSG: Polysomnography
TST: Total sleep time

Wu XH. *Anesthesiology*. 2016;125(5):979-991.
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DEXMEDETOMIDINE SUMMARY

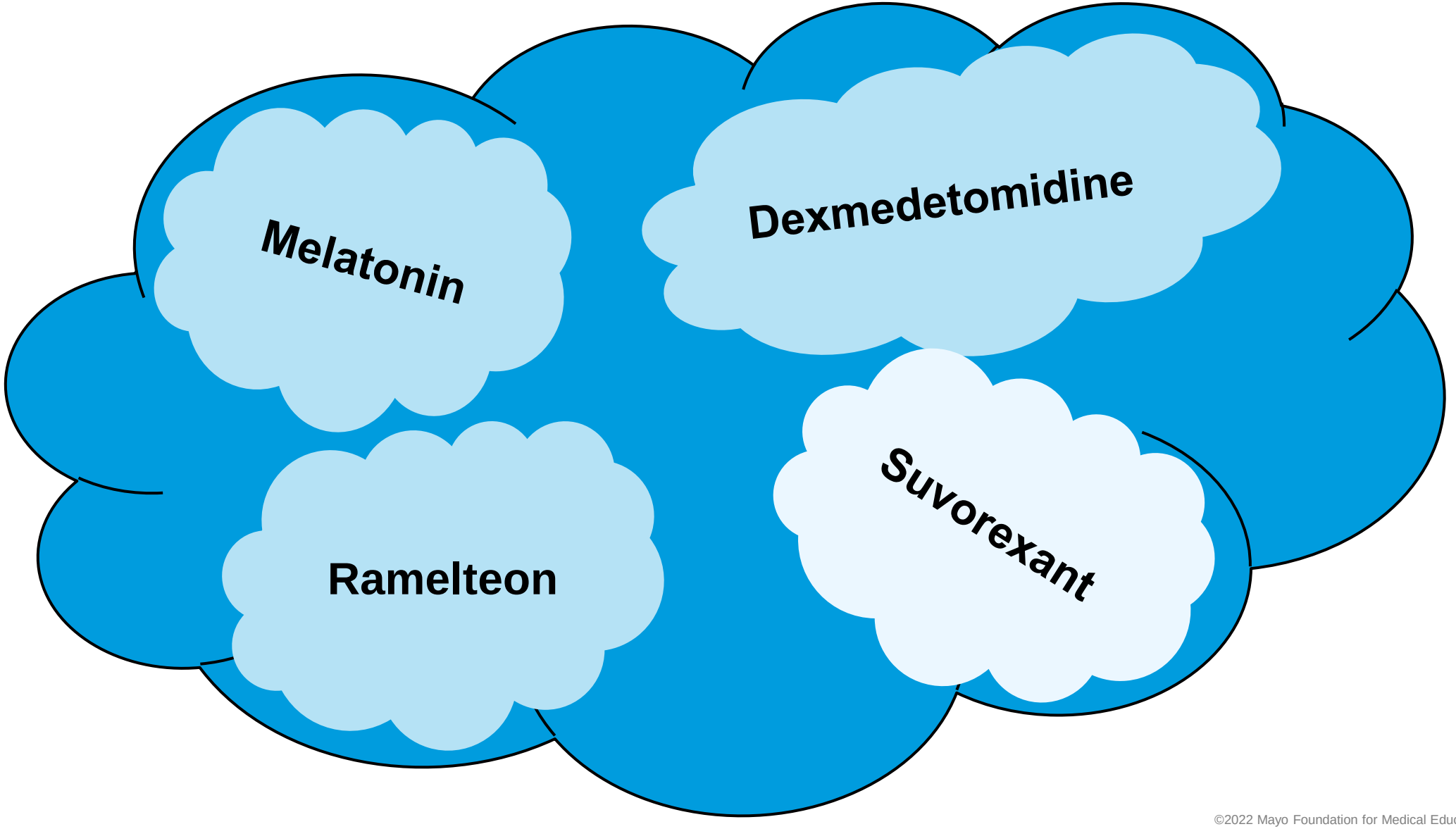
Overnight dexmedetomidine infusion has the potential to improve day-night sleep cycle and reduce incidence of delirium

Dexmedetomidine has been shown to improve subjective sleep quality and sleep architecture (N2 sleep > N1 sleep)

Dexmedetomidine may be a preferred option in hemodynamically stable MV medical-surgical ICU patients requiring sedation overnight

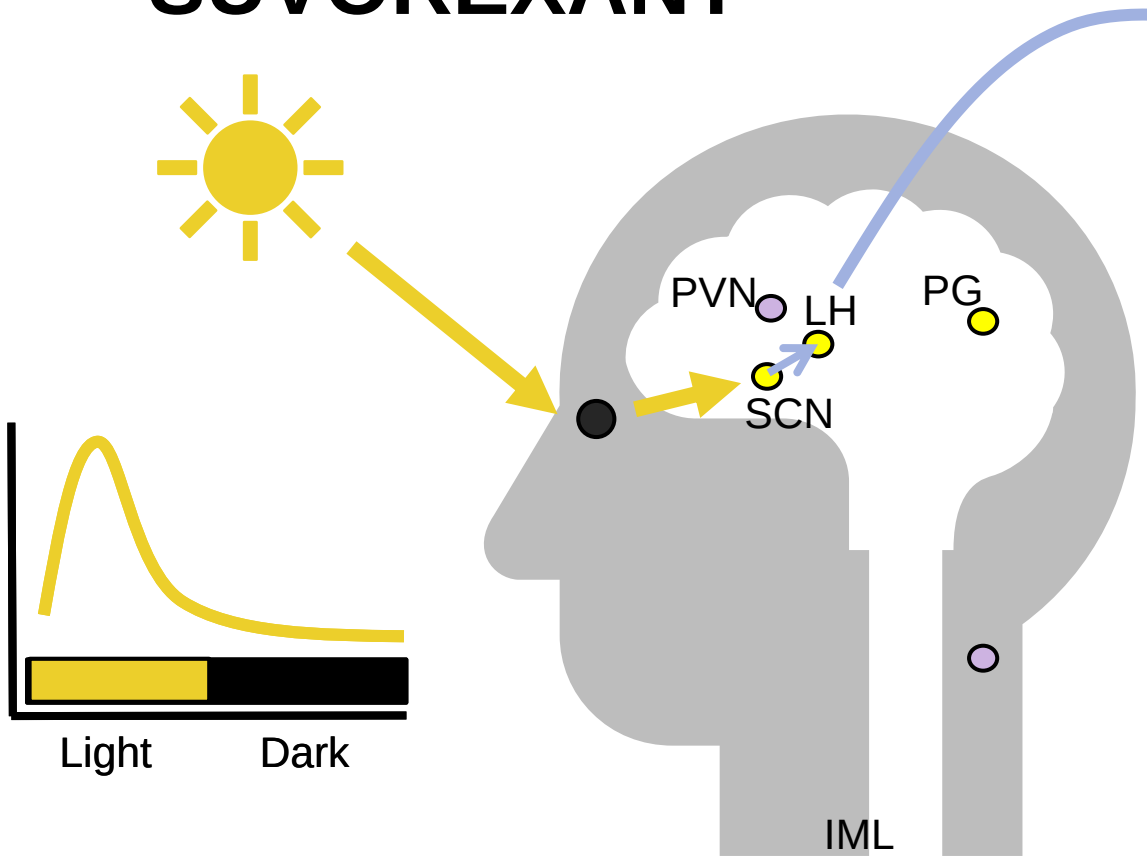
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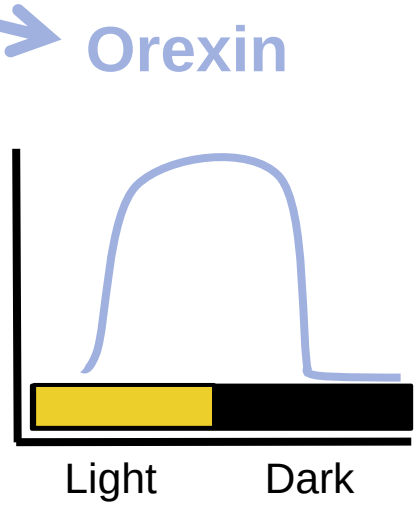
SLEEP AGENTS AVAILABLE “ON THE CLOUD”

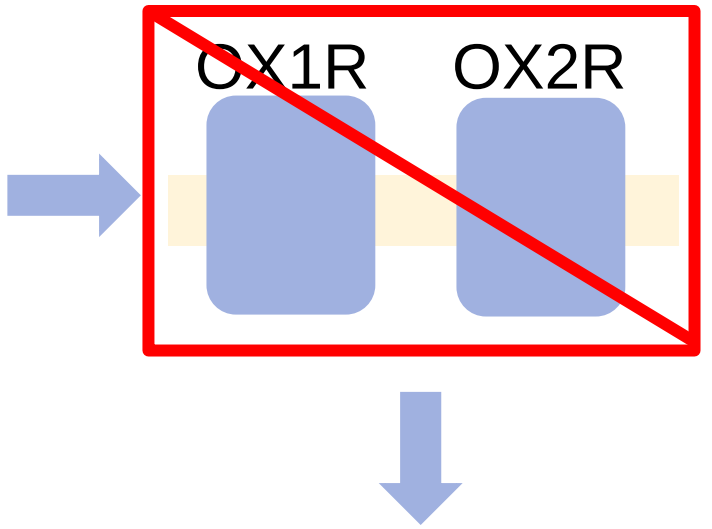


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SUVOREXANT







Regulation of:

- Wakefulness
- Food intake
- Energy
- Glucose metabolism

PVN: Paraventricular hypothalamic nucleus
SCN: Suprachiasmatic nucleus
LH: Lateral hypothalamic (area)
IML: Intermediolateral nucleus
PG: Pineal gland

Imaged adapted from Tsuneki H. *Trends Endocrinol Metab*. 2016;27(9):633-642.
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SUVOREXANT EVIDENCE – DELIRIUM ⟷ SLEEP ?

Author, Year	Type	Population (N)	Intervention	Control	Results
Hatta 2017	RCT	ICU or acute care (N=72)	Suvorexant 15mg	placebo	Delirium ↓ Sleep parameters ~
Tamura 2019	Retrospective observational	SICU + ward (N=88)	Suvorexant 20mg	No suvorexant	Delirium ↓
Hatta 2019	Prospective observational	Acute care or elective surgery (N=526)	Ramelteon 8mg +/- Suvorexant 15mg	placebo	Delirium ↓ Sleep quality ↑

BZDs: Benzodiazepines

Masuyama T. *Psychogeriatrics*. 2018;18(3):209-215.
Azuma K. *Acute Med Surg*. 2018;5(4):362-368.
Kawada K. *J Stroke Cerebrovasc Dis*. 2019;28(1):142-148.
Tamura K. *Ann Thorac Cardiovasc Surg*. 2019;25(1):26-31.
Hatta K. *J Clin Psychiatry*. 2017;78(8):e970-e979.
Hatta K. *J Clin Psychiatry*. 2019;81(1):19m12865.
Booka E. *Esophagus*. 2017;14(3):229-234.

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SUVOREXANT SUMMARY

Elevated plasma orexin-A levels may be associated with development of delirium

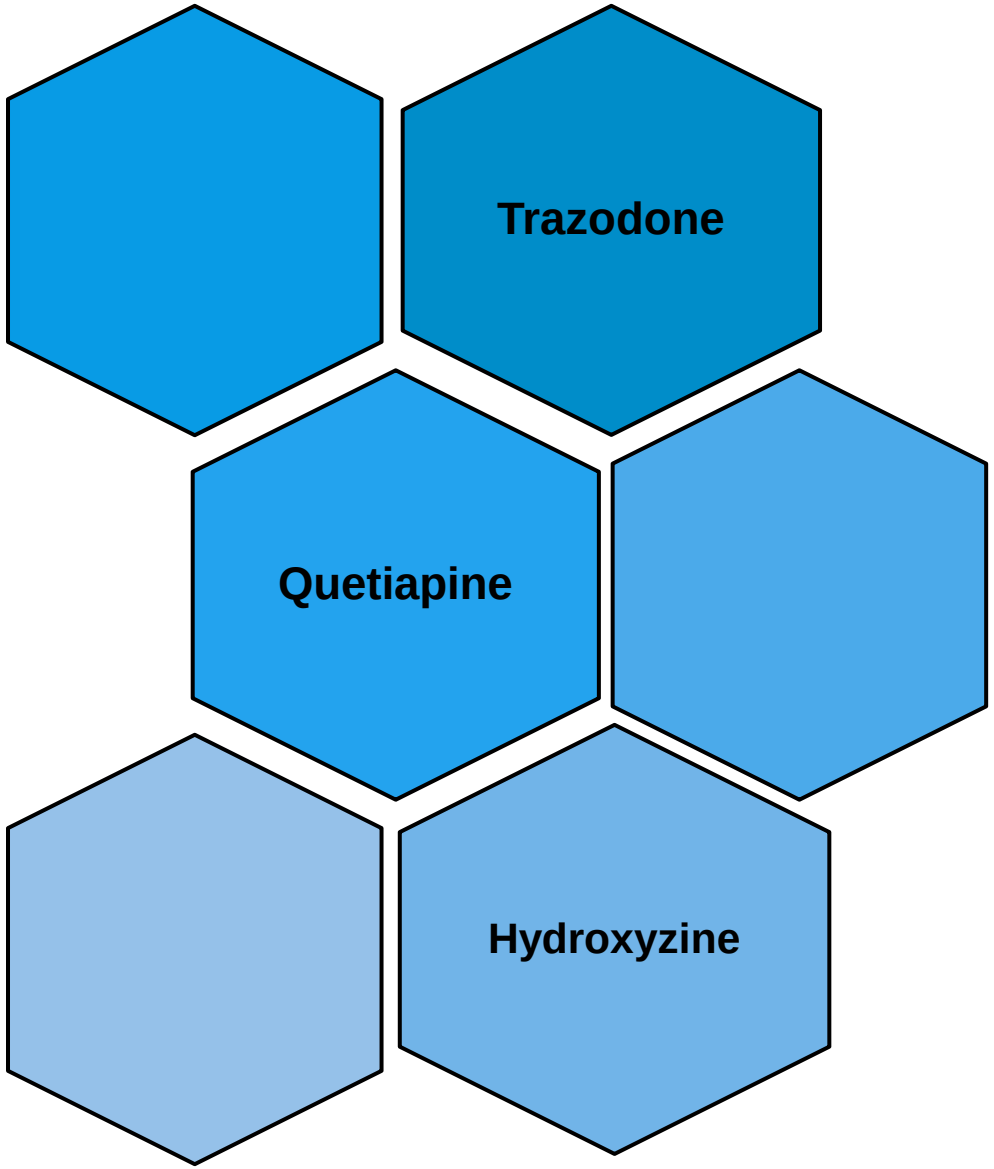
Suvorexant may help regulate the sleep-wake cycle in combination with melatonin receptor agonist

Current studies are flawed, underpowered and retrospective in nature

Further prospective RCTs with specific populations, standardized control groups and objective sleep endpoints are warranted

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OTHER COMMONLY USED AGENTS FOR SLEEP



Risks

- Not studied for sleep in ICU patients
- Short + long term adverse effects
- Do not enhance sleep architecture
- Continuing use through hospitalization & discharge

Benefits

- Promotes sedation & sleep onset

Kram BL. *J Crit Care*. 2015;30(4):814-818.
Lambert J. *J Crit Care*. 2021;61:162-167.
J Intensive Care Med. 2012;27(2):97-111.
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ASSESSMENT QUESTION #2

Based on the evidence presented, which of the following statements is correct regarding the proposed mechanisms and efficacy of sleep agents?

A. Ramelteon is superior to melatonin in promoting sleep onset and depth
B. Melatonin doses should be maximized at 10mg nightly to optimize efficacy
C. Dexmedetomidine has been shown to improve sleep architecture
D. Suvorexant alone promotes sleep onset & prevents delirium compared to placebo

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SUMMARY OF SLEEP AGENTS ‘ON THE CLOUD’

Melatonin & Melatonin Receptor Agonists

- Potential to promote sleep without significant adverse effect on normal sleep architecture
- Efficacy seen with subjective sleep depth improvement in non-MV ICU patients

Dexmedetomidine

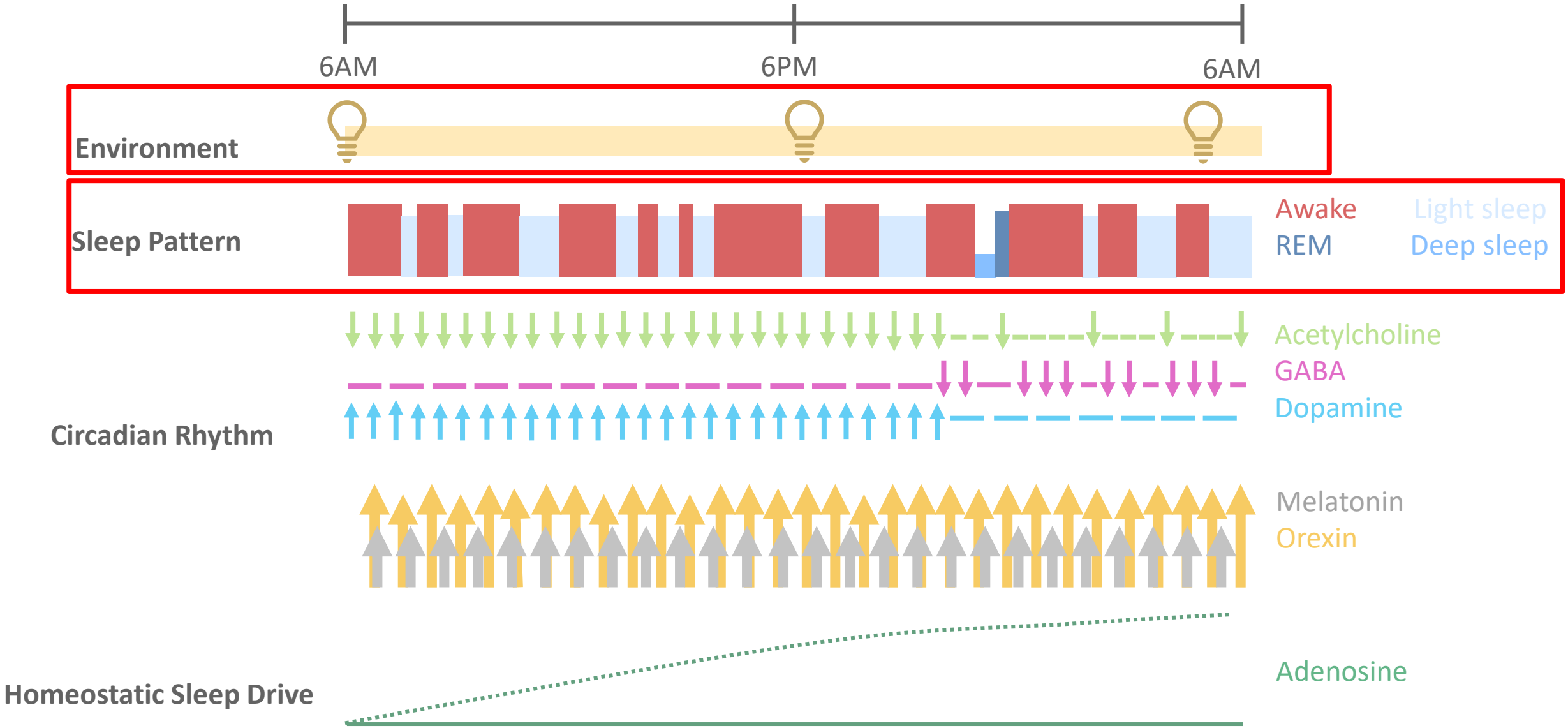
- Promotes sleep onset & maintenance through enhancement of sleep architecture
- Efficacy seen in both MV & non-MV ICU patients
- Additional delirium-sparing, analgesic effects

Suvorexant

- Targets an alternative pathway to promote sleep onset in healthy adults
- Studies in ICU patients are poorly designed to confirm true benefit at this time

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OPTIMIZING THE SLEEP WAKE CYCLE IN ICU PATIENTS



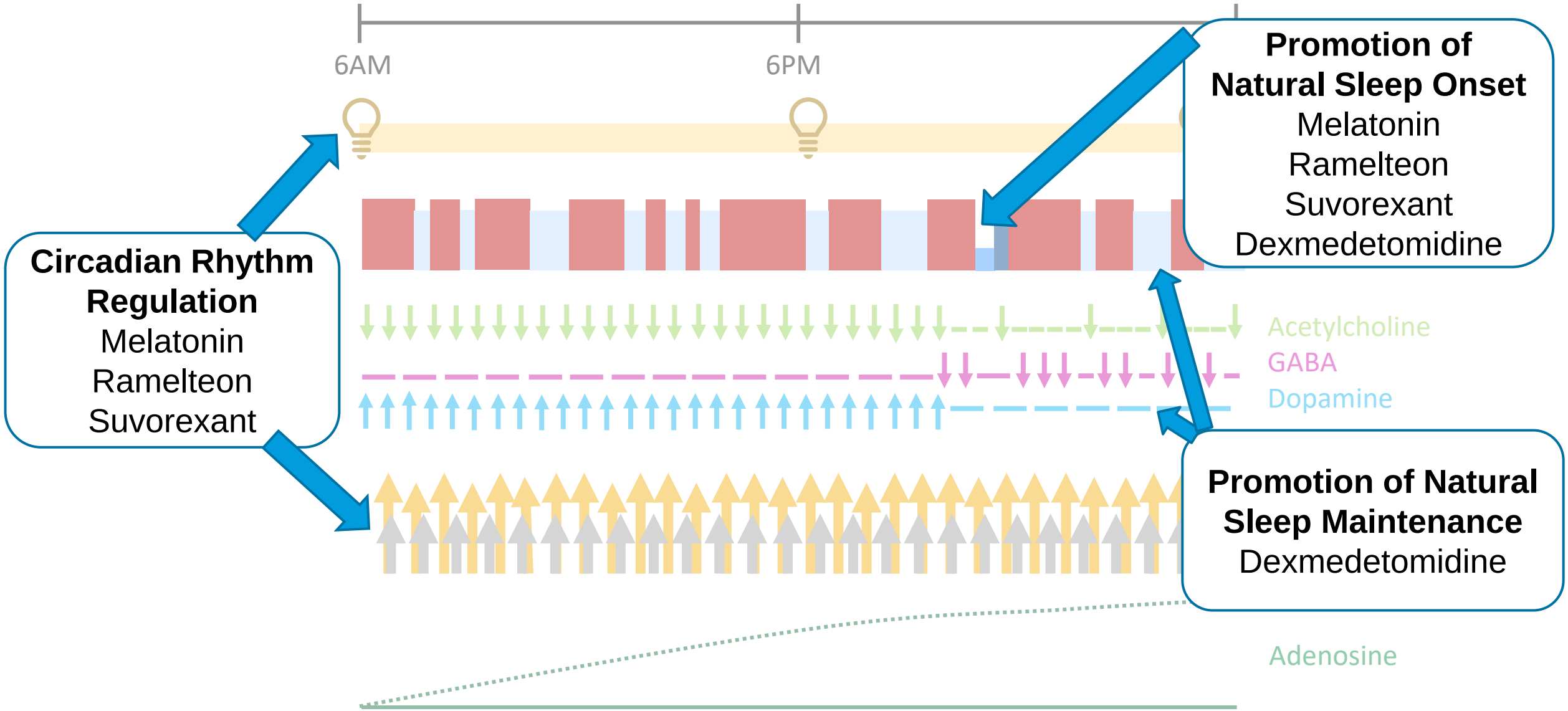
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PRIORITIZING NON-PHARMACOLOGIC MEASURES

- ❑ Ear plugs
- ❑ Eye masks
- ❑ Retime overnight medications [Q4H vs QID]
- ❑ Minimize overnight lab draws
- ❑ Obtain history of sleep strategies at home
- ❑ Minimize duration of ‘activating’ medications
- ❑ Music & aromatherapy
- ❑ Optimize family & social support

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PHARMACOLOGIC AGENTS ON SLEEP WAKE CYCLE



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IDEAL PHARMACOLOGIC SLEEP AGENT

Property	Melatonin	Ramelteon	Dexmedetomidine	Suvorexant
Rapid time to effect			✓	
Ease of administration	✓	✓		✓
Titratable	✓		✓	✓
Minimal residual sedation	✓	✓	✓	✓
Low adverse drug reactions	✓	✓		✓
Low potential for withdrawal	✓	✓		✓
Minimal drug interactions	✓	✓		
Low cost	✓			

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COST CONSIDERATIONS

Agent	Average Wholesale Cost	
Melatonin	$0.26 per tab	
Ramelteon	$14.78 per tab	$
Dexmedetomidine	$1.02 per mL (400mcg/mL)	$$$
Suvorexant	$16.13 per tab	$

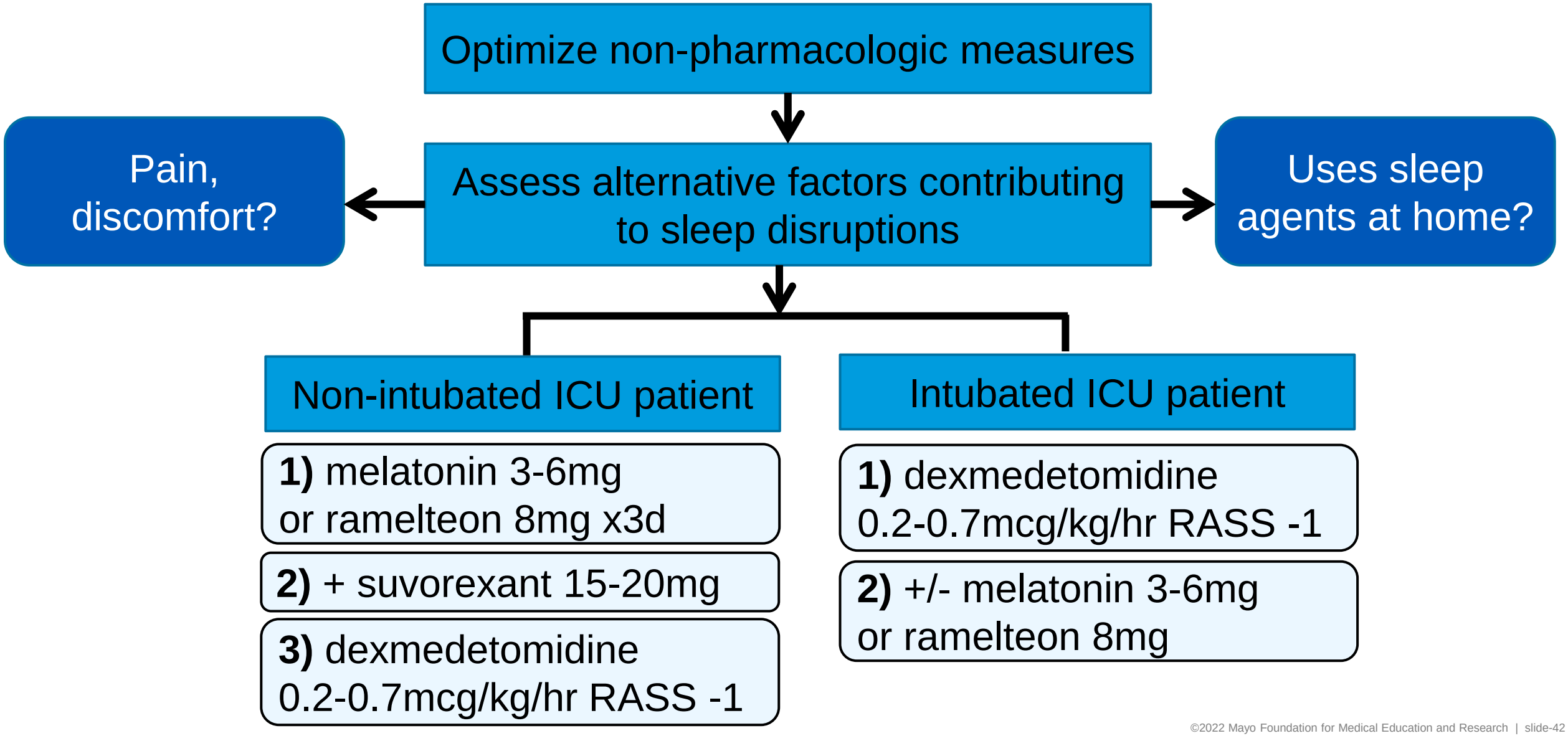
Lexi-Comp Inc., 2022. Melatonin; [updated 5/2022].
Lexi-Comp Inc., 2022. Ramelteon; [updated 7/2022].
Lexi-Comp Inc., 2022. Dexmedetomidine; [updated 7/2022].
Lexi-Comp Inc., 2022. Suvorexant; [updated 7/2022].
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PATIENT SPECIFIC CONSIDERATIONS

Factors	Melatonin	Ramelteon	Dexmedetomidine	Suvorexant
Melatonin depleted (sepsis)	✓	✓		
Mechanically ventilated, agitated patients			✓	
Surgical patients	✓	✓	✓	✓
Elderly, high delirium risk	✓	✓	✓	✓
Hemodynamically unstable	✓	✓		✓

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SELECTING A PHARMACOLOGIC SLEEP AGENT



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PATIENT CASE

AB is a 65 yo F with PMH depression and chronic pain admitted to MICU for management of AMS and septic shock due to CAP

Hospital Day 1

- Intubated on propofol
- Resuscitated & started on pressors
- Ceftriaxone + azithromycin
- Holding home trazodone & oxycodone ER due to AMS

Hospital Day 4

- Off pressors
- Extubated, on room air
- IV antibiotics → oral
- Plan to transfer tomorrow

Overnight**:** Agitated (RASS +2), unable to sleep, resident starts dexmedetomidine

Hospital Day 5-6

- Ongoing overnight agitation requiring dexmedetomidine
- Completed antibiotics
- ~3h TST at night per nursing
- Started Seroquel 50mg QHS

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ASSESSMENT QUESTION #3

What recommendations do you have to optimize AB's sleep?

A) Start melatonin 3mg QHS
B) Start ramelteon 8mg QHS
C) Resume home trazodone
D) Assess pain and resume home oxycodone ER
E) Start suvorexant 15mg QHS
F) Increase quetiapine to 100mg QHS
G) Stop quetiapine

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SUMMARY

- Disrupted sleep architecture in critically ill patients leads to both physiologic & clinical consequences
- The optimal measurements for sleep quantity and quality in critically ill patients remains unknown
- Data supporting the efficacy of oral sleep agents (melatonin, suvorexant) is limited, though safety is well established
- Consider optimizing non-pharmacologic measures and taking patient & medication factors into account prior to starting pharmacologic sleep agents

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