Sleep and Postoperative Delirium- New Avenues

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the ANESTHESIOLOGY annual meeting

American Society of Anesthesiologists

Disclosures

- NIH R01 funding as PI (NIGMS, NIA)
- Mallinckrodt (Investigator initiated research, Consultant)
- Edward Life Sciences (Investigator initiated research, Consultant)

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Postoperative Delirium

- Current Postoperative Delirium Burden
- Sleep and Delirium- What is the connection
- Enhancing Natural Sleep- Current work

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Topic Outline

- Current Postoperative Delirium Burden
- Sleep and Delirium- What is the connection
- Enhancing Natural Sleep- Current work

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Association of any Adverse Hospital Outcomes by Complication and Delirium Status[a]

Table 5. Association of any Adverse Hospital Outcomes by Complication and Delirium Status[a]

	Any Adverse Outcome		
Status	Patients, No. (%)	Adjusted RR (95% CI)[b]	PAR, % (95% CI)[c]
No complications or delirium (n = 404)	252 (62.4)	1 [Reference]	1 [Reference]
Complications only (n = 27)	22 (81.5)	1.2 (1.0-1.6)	0.8 (0.0-1.5)
Delirium only (n = 115)	105 (91.3)	1.4 (1.3-1.5)	5.8 (4.7-6.8)
Complications and delirium (n = 20)	20 (100)	1.6 (1.4-1.8)	1.3 (1.0-1.6)

Abbreviations: PAR, population attributable risk; RR, relative risk.

[a] Adjusted for age, sex, race, Charlson Comorbidity Index score, surgery type (orthopedic vs all others), and anesthesia type (general vs spinal).

[b] Relative risks were calculated with a generalized linear model, Poisson error term, log-link, and robust error variance.

[c] Population attributable risk percentage is the product of a function of the RR of the outcome associated with the exposure and the prevalence of adverse outcome. It is the difference in rate of a condition between an exposed population and an unexposed population.

– **Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults.** JAMA Surg. 2015;150(12):1134-1140.

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

Crit Care Med. 2018 Sep;46(9):e825-e873.

Answer Options	Rating Average
Non-pharmacologic prevention: Early mobility	4.50
Non-pharmacologic prevention: Environment (e.g., noise, light)	4.50
Non-pharmacologic prevention: Sleep protocols	4.50
Non-pharmacologic prevention: Music therapy	4.50
Predictors for ICU delirium (i.e., modifiable vs. non-modifiable)	4.33
Pharmacologic prevention: choice of sedative	4.33
Pharmacologic prevention: haloperidol	4.17
Pharmacologic prevention: atypical antipsychotics	4.17
Pharmacologic treatment: dexmedetomidine	4.17
Non-Pharmacologic treatment: early mobility	4.00
Non-Pharmacologic treatment: environment (e.g. noise, light etc)	4.00
Non-Pharmacologic treatment: sleep protocols	4.00
Non-Pharmacologic treatment: music therapy	4.00
Pharmacologic treatment: haloperidol	4.00

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Complete consensus for delirium treatment

We suggest using a multicomponent, non-pharmacological intervention* that is focused (but not limited to) reducing modifiable risk factors for delirium, improving cognition, and optimizing sleep, mobility, hearing/vision in critically ill adults. (Conditional recommendation, Low quality of evidence) *These multicomponent interventions include (but are not limited to) strategies to improve cognition (e.g., re-orientation, cognitive stimulation, music, use of clocks), improve sleep (e.g., minimizing light and noise), improve wakefulness (i.e., reduced sedation), reduce immobility (e.g., early mobilization), and reduce hearing and/or visual impairment (e.g. use of hearing aids, glasses).

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Intervenable causes

- Sleep, Pain and Cognition

Conclusions and Relevance—Major postoperative complications and delirium are separately associated with adverse events and demonstrate a strong combined effect. Delirium occurs more frequently, and has greater impact at the population level than other major complications.

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery
The DEXACET Randomized Clinical Trial

Balachundhar Subramaniam, MD, MPH; Puja Shankar, MD; Shahzad Shaefi, MD, MPH; Ariel Mueller, MA; Brian O'Gara, MD; Valerie Banner-Goodspeed, MPH; Jackie Gallagher, MS; Doris Gasangwa, BS; Melissa Patxot, BS; Senthil Packiasabapathy, MBBS; Pooja Mathur, BS; Matthias Eikermann, MD, PhD; Daniel Talmor, MD, MPH; Edward R. Marcantonio, MD, SM

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TABLE 2. List of Factors That Patients Report as Disruptive to Sleep

Environmental	Physiologic and Pathophysiologic
Noise (447, 453, 454, 480, 483–488, 490, 491)	Pain (454, 483–486, 488, 490, 491)
Light (241, 453, 454, 480, 482–484, 486–488)	Discomfort (454, 483, 486, 488, 490)
Comfort of bed (483, 486–488)	Feeling too hot or too cold (484, 486, 488)
Activities at other bedsides (483, 486, 487)	Breathing difficulty (484, 491)
Visitors (clinician or family) (483)	Coughing (484, 491)
Room ventilation system (483)	Thirst (484, 486) and hunger (486, 488)
Hand washing by clinicians (483)	Nausea (484, 488)
Bad odor (486, 488)	Needing to use bedpan/urinal (486, 488)
Care Related	**Psychologic**
Nursing care (447, 453, 480, 482–484, 486, 488, 491)	Anxiety/worry/stress (483, 484, 486, 489–491)
Patient procedures (447, 453, 480, 482, 483, 487, 488)	Fear (485, 486, 489)
Vital sign measurement (442, 448, 475, 477, 481, 483)	Unfamiliar environment (485, 488, 491)
Diagnostic tests (447, 453, 480, 483)	Disorientation to time (454, 486)
Medication administration (447, 453, 480, 482)	Loneliness (488, 491)
Restricted mobility from lines/catheters (454, 486, 488)	Lack of privacy (485, 488)
Monitoring equipment (454, 486, 488)	Hospital attire (486, 488)
Oxygen mask (486, 488)	Missing bedtime routine (483)
Endotracheal tube (491)	Not knowing nurses' names (486)
Urinary catheters (486)	Not understanding medical terms (486)

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Abnormal Sleep patterns in ICU

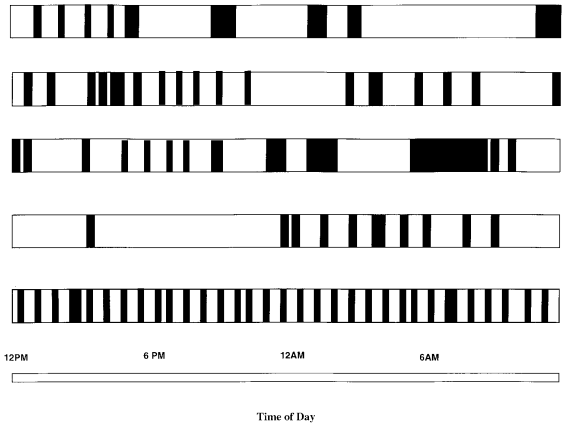

Figure 2. Schematic representation of the redistribution of sleep and wake in five subjects over the 24-h period. *Black* areas represent episodes of sleep and *white* areas represent wakefulness.

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ICU Sleep- Key features

- Total sleep time (TST) and sleep efficiency are often normal
- Sleep fragmentation, the proportion of time spent in light sleep (stages N1 + N2), and time spent sleeping during the day (vs. night) are higher
- The proportion of time spent in deep sleep (stage N3 sleep and REM) is lower
- Subjective sleep quality is reduced
- NO CAUSE AND EFFECT between sleep and delirium
- Sleep measurements in ICU is challenging
- Is sleep different in critically ill adults if delirium is present?
  - Greater disruption of circadian rhythm; REM sleep is lower

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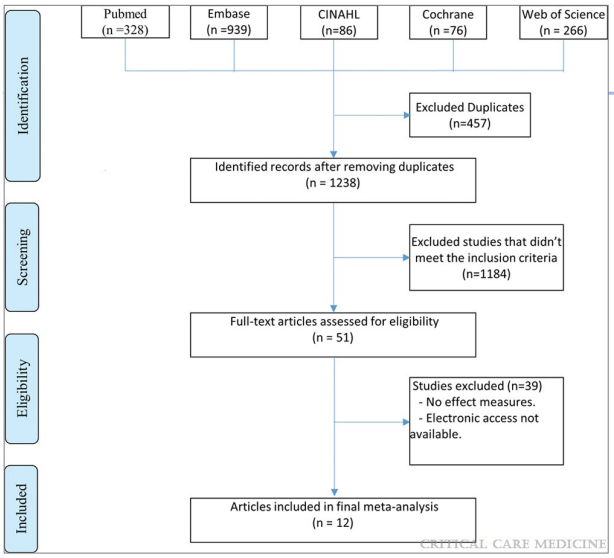
A Systematic Review and Meta-Analysis Examining the Impact of Sleep Disturbance on Postoperative Delirium



Fadayomi, Ayòtúndé B.; Ibala, Reine; Bilotta, Federico; Westover, Michael B.; Akeju, Oluwaseun Critical Care Medicine46(12):e1204-e1212, December 2018.

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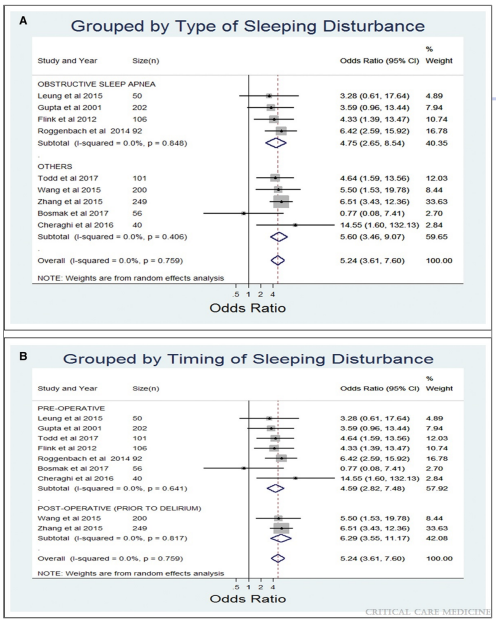
A Systematic Review and Meta-Analysis Examining the Impact of Sleep Disturbance on Postoperative Delirium



Fadayomi, Ayòtúndé B.; Ibala, Reine; Bilotta, Federico; Westover, Michael B.; Akeju, Oluwaseun. Critical Care Medicine46(12):e1204-e1212, December 2018.

Forest plot for all studies and subgroup analyses by study characteristics. A, Forest plot showing pooled analysis of studies categorized into obstructive sleep apnea and unspecified types of sleep disturbance. B, Forest plot showing pooled analysis of studies categorized into preoperative sleep disturbance and postoperative sleep prospective.

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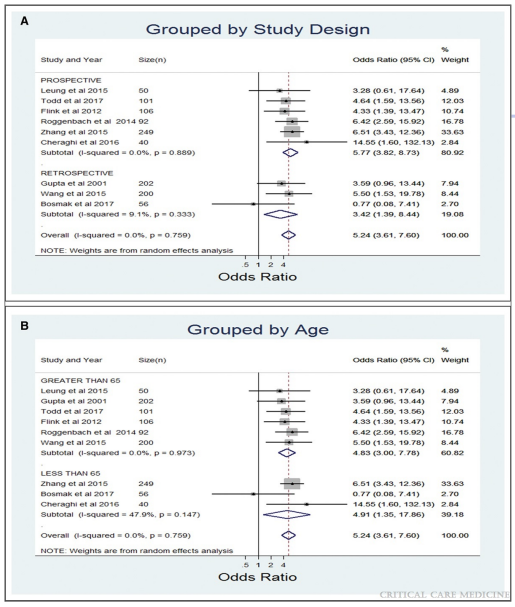
A Systematic Review and Meta-Analysis Examining the Impact of Sleep Disturbance on Postoperative Delirium



Fadayomi, Ayòtúndé B.; Ibala, Reine; Bilotta, Federico; Westover, Michael B.; Akeju, Oluwaseun

Critical Care Medicine46(12):e1204-e1212, December 2018.

Forest plot for all studies and subgroup analyses by study characteristics. A, Forest plot showing pooled analysis of studies categorized into prospective and retrospective study design. B, Forest plot showing pooled analysis of studies categorized into studies with median/mean age less than 65 yr and greater than or equal to 65 yr.

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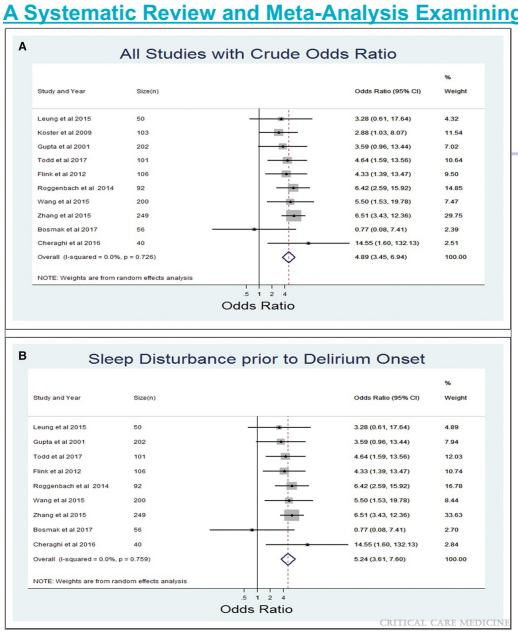
A Systematic Review and Meta-Analysis Examining the Impact of Sleep Disturbance on Postoperative Delirium



Fadayomi, Ayòtúndé B.; Ibala, Reine; Bilotta, Federico; Westover, Michael B.; Akeju, Oluwaseun

Critical Care Medicine46(12):e1204-e1212, December 2018.

Forest plot for all studies and subgroup analyses by study characteristics. A, Forest plot showing pooled analysis of studies with crude odds ratio. B, Forest plot showing pooled analysis after restricting to those with sleep disturbance before onset of delirium.

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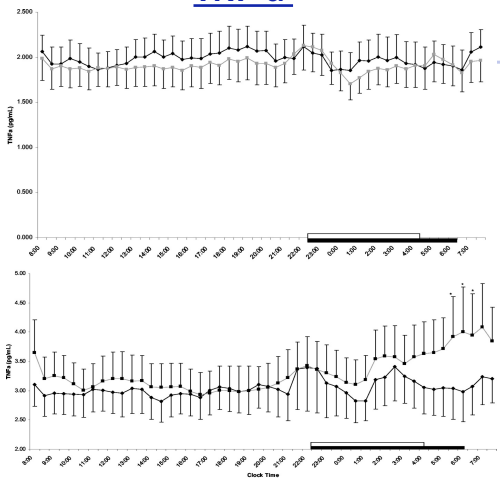
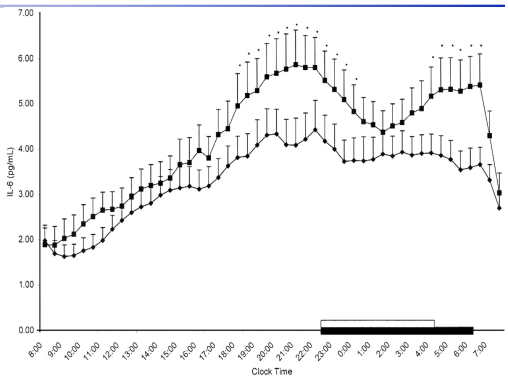
Sleep Restriction on Circadian secretory pattern

TNF α



IL-6



The Journal of Clinical Endocrinology & Metabolism, Volume 89, Issue 5, 1 May 2004, Pages 2119–2126,

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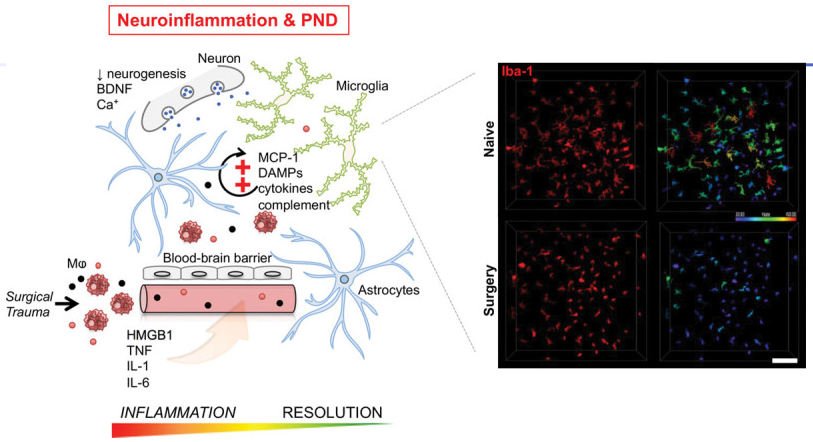
Neuroinflammation and Perioperative NeuroCognitive Disorders



Subramaniyan S, Terrando N. Neuroinflammation and Perioperative Neurocognitive Disorders. *Anesth Analg*. 2019;128(4):781–788.

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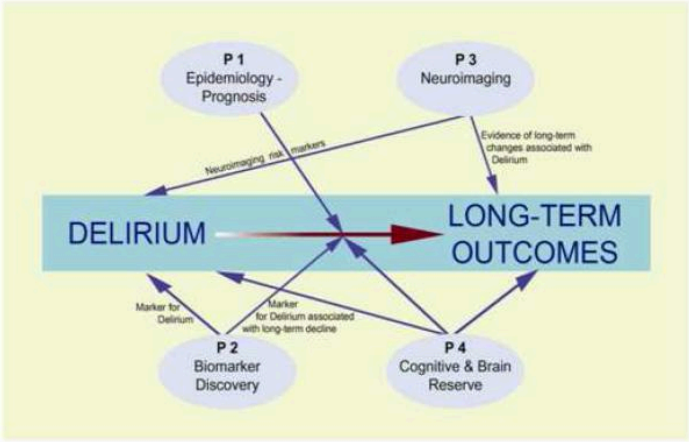
Novel risk markers and long-term outcomes of delirium: The Successful Aging after Elective Surgery (SAGES) Study Design and Methods

Schmitt EM,, et al. Novel risk markers and long-term outcomes of delirium: the successful aging after elective surgery (SAGES) study design and methods. *J Am Med Dir Assoc*. 2012;13(9):818.



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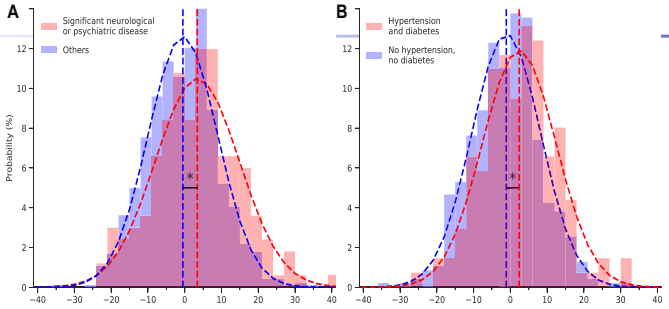
Brain age from the electroencephalogram of sleep

Haoqi Sun [a], Luis Paixao [a], Jefferson T. Oliva [a,b], Balaji Goparaju [a], Diego Z. Carvalho [a],

H. Sun et al. / Neurobiology of Aging 74 (2019) 112–120



apart shows an average of 5.4 years increase in BA. Participants with significant neurological or psychiatric disease exhibit a mean excess BA, or "brain age index" (BAI = BA-CA) of 4 years relative to healthy controls. Participants with hypertension and diabetes have a mean excess BA of 3.5 years. The findings raise the prospect of using the sleep EEG as a potential biomarker for healthy brain aging.

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Meditation and Sleep

- ↓GABA and inflammatory markers- Streeter CC. J Altern Complement Med, 2010
- Higher Melatonin levels
- Mimic Natural Sleep
- ↑ sleep quality, efficiency Khalsa S. Appl Psychophysiol Biofeedback, 2004 (Yoga)
- Cancer patients (Mindfulness)
  - Reduce total wake time
  - Improve Sleep Quality
- ↑Sleep Quality in old (Tai Chi)
- Cognitive Based Therapy-Insomnia

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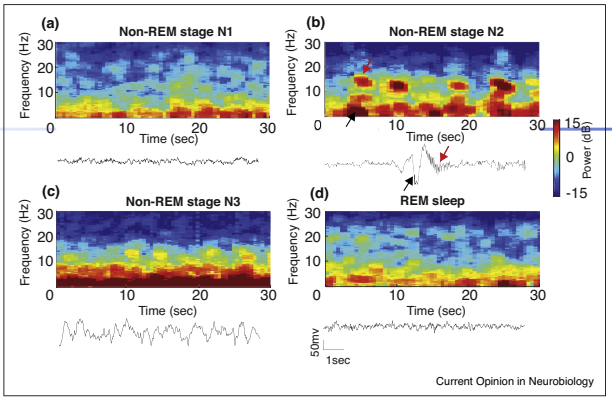

Sleep stages have distinct EEG signatures that result from differences in the neural circuits that are involved in their generation and maintenance. The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. These signatures are also visible in the raw EEG signal (black traces represent first 10 s of data shown in spectrogram). **(a)** EEG slowing and the loss of the awake state alpha oscillations are distinguishing features of N1 sleep. **(b)** Slow-delta (0.1–4 Hz) oscillations, K-complexes (black arrow on spectrogram and raw EEG), and spindle oscillations (12–16 Hz, red arrow on spectrogram and raw EEG) are distinguishing features of N2 sleep. **(c)** The predominance of slow-delta oscillations is a distinguishing feature of N3 sleep. **(d)** Activated 'saw-tooth' EEG without the awake-state alpha oscillations are distinguishing features of REM sleep.
dB, decibels; EEG, electroencephalogram; Hz, Hertz; N1, non-rapid eye movement stage 1 sleep; N2, non-rapid eye movement stage 3 sleep; N3, non-rapid eye movement stage 3 sleep; REM, rapid eye movement.

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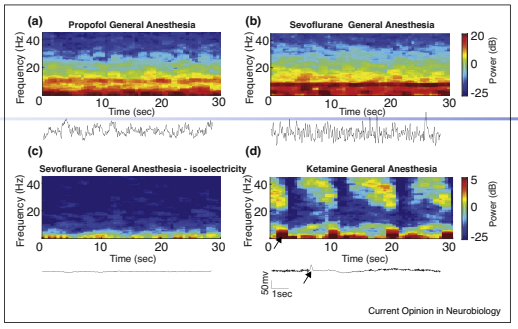
Figure 2



General anesthesia. Each anesthetic drug has a different EEG signature that results from differences in the neural circuits that are involved in state generation and maintenance. The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. These signatures are also visible in the raw EEG signal (black traces represent first 10 s of data shown in spectrogram). **(a)** Slow-delta (0.1–4 Hz) and alpha (8–12 Hz) oscillations are the predominant EEG signatures of propofol-general anesthesia. This finding is consistent with the EEG signatures of other intravenous $GABA_A$ receptor targeting anesthetics (*i.e.*, benzodiazepines, etomidate) during general anesthesia. **(b)** Slow-delta oscillations, theta (4–8 Hz), and alpha oscillations are the predominant EEG signatures of sevoflurane-general anesthesia. This finding is consistent with the EEG signatures of other modern day derivatives of ether during general anesthesia (desflurane, isoflurane). The close similarities between the EEG signatures of propofol and modern day derivatives ether anesthesia has been suggested to result from enhancement of $GABA_A$ receptor IPSCs. **(c)** Isoelectricity is observed when high doses of anesthetics such as sevoflurane and propofol are administered. Significantly enhancement of IPSCs in cortical circuits is a mechanism to explain isoelectricity. **(d)** Gamma oscillations (~30–45 Hz) that are interspersed with slow-delta (black arrow on spectrogram and raw EEG) oscillations are the predominant EEG signatures of general anesthesia maintained with the NMDA receptor antagonist ketamine.
dB, decibels; EEG, electroencephalogram; $GABA_A$, gamma amino butyric acid A; Hz, Hertz; IPSCs, inhibitory post synaptic currents; NMDA, *N*-methyl-*D*-aspartate.

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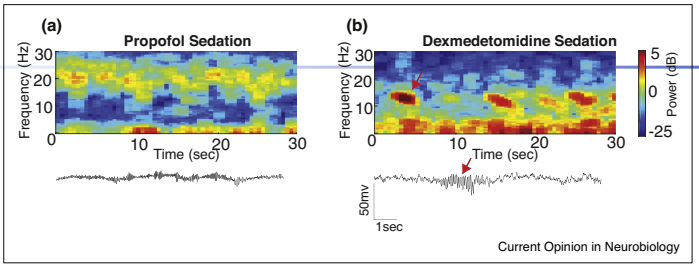
Figure 3



Sedation states. Each anesthetic drug has a different EEG signature that results from differences in the neural circuits that are involved in state generation and maintenance. The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. These signatures are also visible in the raw EEG signal (black traces represent first 10 s of data shown in spectrogram). **(a)** Beta (~13–30 Hz) oscillations are the predominant EEG signature of sedation maintained by propofol and other medications that enhance $GABA_A$ receptor IPSCs (*i.e.*, ether anesthetics, benzodiazepines, zolpidem). **(b)** Slow-delta and spindle (12–16 Hz; red arrow on spectrogram and raw EEG) oscillations are the predominant EEG signatures of dexmedetomidine-sedation. These dexmedetomidine-induced EEG signatures very closely approximate the EEG signatures of N2 sleep (Figure 1b).
dB, decibels; EEG, electroencephalogram; $GABA_A$, gamma amino butyric acid A; Hz, Hertz; IPSCs, inhibitory post synaptic currents.

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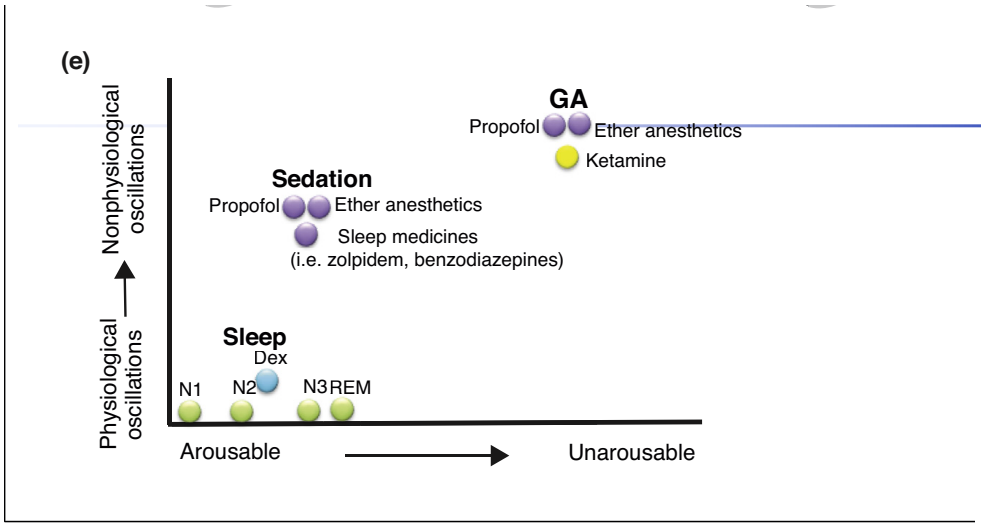

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Low-dose nocturnal dexmedetomidine prevents ICU delirium. A Randomized, Placebo-controlled Trial. Am J Respir Crit Care Med 2018

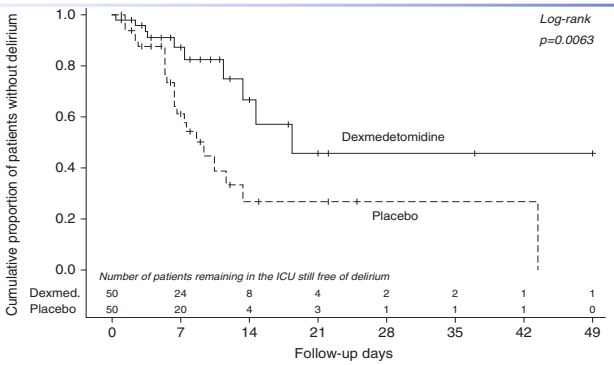

Figure 2. Kaplan-Meier curve for the time to the first occurrence of delirium between dexmedetomidine (dexmed.) and placebo groups during the ICU stay for those patients still at risk for developing delirium each day for the first time (log rank *P* value = 0.006). Patients with persistent coma on any given day were deemed not to have delirium.

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Wong *et al. BMC Anesthesiology* (2018) 18:1
DOI 10.1186/s12871-017-0465-5

BMC Anesthesiology

STUDY PROTOCOL

The prevention of delirium in elderly wit
obstructive sleep apnea (PODESA) study:
protocol for a multi-centre prospective
randomized, controlled trial

Jean Wong[1*], David Lam[1], Stephen Choi[2], Mandeep Singh[1,3], Naveed Siddiqui[4], Sanjeev Sockalingam[2] and Frances Chung[1]

Sleep/Wake Protocol Implementation to Improve Sleep Quality in the ICU (NCT03313115)
1.Contributors: Joseph Tonna
Date created: 2018-08-21 03:01 PM | Last Updated: 2019-05-11 04:47 PM

Suvorexant and Sleep/Delirium in ICU Patients
Eikermann M et al.
Orexin receptor antagonist -blocks awake state

Anaesthesia 2017, 72, 729–736 doi:10.1111/anae.13833

Original Article

A randomised trial of peri-operative positive airway pressure for postoperative delirium in patients at risk for obstructive sleep apnoea after regional anaesthesia with sedation or general anaesthesia for joint arthroplasty*

J. W. Nadler,[1] J. L. Evans,[2] E. Fang,[3] X. A. Preud'Homme,[4] R. L. Daughtry,[5] J. B. Chapman,[6] M. P. Bolognesi,[7] D. E. Attarian,[8] S. S. Wellman[9] and A. D. Krystal[10,11]
1 Assistant Professor of Anaesthesiology, University of Rochester, Rochester, NY, USA

...dm, we did not find that providing a short-course of auto-titrating CPAP affected its likelihood or severity. Voluntary adherence to CPAP is particularly poor during the initiation of therapy.

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CLINICAL RESEARCH STUDY

Not effective

THE AMERICAN JOURNAL of MEDICINE®

Melatonin and Sleep in Preventing Hospitalized Delirium: A Randomized Clinical Trial

Stuti J. Jaiswal, MD, PhD,[a,b] Thomas J. McCarthy, MD,[b] Nathan E. Wineinger, PhD,[a] Dae Y. Kang, PhD,[c] Janet Song,[a] Solana Garcia,[a] Christoffel J. van Niekerk, MD,[b] Cathy Y. Lu,[a] Melissa Loeks, MPH,[d] Robert L. Owens, MD[c]

[a]*The Scripps Research Institute, La Jolla, Calif;* [b]*Department of Internal Medicine, Scripps Clinic/Scripps Green Hospital, La Jolla, Calif;* [c]*Division of Pulmonary, Critical Care & Sleep Medicine, University of California San Diego School of Medicine, La Jolla, Calif;* [d]*Respironics, Inc., a Philips Healthcare Company, Murrysville, Pa.*

The Journal of Arthroplasty 30 (2015) 2370–2375

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Impact of Melatonin on Sleep and Pain After Total Knee Arthroplasty Under Regional Anesthesia With Sedation: A Double-Blind, Randomized, Placebo-Controlled Pilot Study

Meghan A. Kirksey, MD, PhD [a,1,2,3], Daniel Yoo, MB [a,4,5,6], Thomas Danninger, MD [a,b,7,8,9], Ottokar Stundner, MD [a,b,10,11], Yan Ma, PhD [c,12,13,14], Stavros G. Memtsoudis, MD, PhD [a,15,16,17]

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Step count on Postoperative Delirium Following Cardiac Surgery

Enrolling… from Clinicaltrials.gov

Thank you

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