BMJ Open Study protocol for a randomised controlled trial evaluating the effects of the orexin receptor antagonist suvorexant on sleep architecture and delirium in the intensive care unit

Omid Azimaraghi,¹ Maximilian Hammer,¹ Peter Santer ,¹ Katharina Platzbecker,¹ Friederike C Althoff,¹ Maria Patrocinio,¹ Stephanie D Grabitz,¹ Karuna Wongtangman,² Sandra Rummyantsev,³ Xinling Xu,¹ Maximilian S Schaefer,¹ Patrick M Fuller,⁴ Balachundhar Subramaniam,¹ Matthias Eikermann ¹

To cite: Azimaraghi O, Hammer M, Santer P, *et al.* Study protocol for a randomised controlled trial evaluating the effects of the orexin receptor antagonist suvorexant on sleep architecture and delirium in the intensive care unit. *BMJ Open* 2020;**10**:e038474. doi:10.1136/bmjopen-2020-038474

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-038474>).

Received 11 March 2020
Revised 14 May 2020
Accepted 29 May 2020

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Matthias Eikermann;
meikerma@bidmc.harvard.edu

ABSTRACT

Introduction Insomnia frequently occurs in patients admitted to an intensive care unit (ICU). Sleep-promoting agents may reduce rapid eye movement sleep and have deliriogenic effects. Suvorexant (Belsomra) is an orexin receptor antagonist with Food and Drug Administration (FDA) approval for the treatment of adult insomnia, which improves sleep onset and maintenance as well as subjective measures of quality of sleep. This trial will evaluate the efficacy of postoperative oral suvorexant treatment on night-time wakefulness after persistent sleep onset as well as the incidence and duration of delirium among adult cardiac surgical patients.

Methods and analysis In this single-centre, randomised, double-blind, placebo-controlled trial, we will enrol 120 patients, aged 60 years or older, undergoing elective cardiac surgery with planned postoperative admission to the ICU. Participants will be randomised to receive oral suvorexant (20 mg) or placebo one time a day starting the night after extubation. The primary outcome will be wakefulness after persistent sleep onset. The secondary outcome will be total sleep time. Exploratory outcomes will include time to sleep onset, incidence of postoperative in-hospital delirium, number of delirium-free days and subjective sleep quality.

Ethics and dissemination Ethics approval was obtained through the 'Committee on Clinical Investigations' at Beth Israel Deaconess Medical Center (protocol number 2019P000759). The findings will be published in peer-reviewed journals.

Trial registration number This trial has been registered at clinicaltrials.gov on 17 September 2019 (NCT04092894).

INTRODUCTION

Insomnia occurs frequently in patients admitted to an intensive care unit (ICU).^{1 2} Polysomnographic (PSG) studies have shown that prolonged sleep latency, sleep fragmentation, frequent arousals, decreased or absent

Strengths and limitations of this study

- This is a randomised, double-blind, placebo-controlled pharmacophysiological randomised controlled trial to examine sleep and delirium after cardiac surgery.
- We will study the effects of suvorexant, a dual orexin receptor antagonist approved for the treatment of insomnia, on sleep architecture in patients recovering from cardiac surgery.
- Sleep will be quantified objectively using electroencephalography and accelerometry.
- Electroencephalography (EEG) recordings will be performed during the first night after surgery; sleep questionnaires will be used during the rest of the hospital stay to prevent interference with clinical care and mobilisation of the patients.
- Sleep staging in the intensive care unit setting will require expertise due to possible interference with other devices and altered sleep architecture.

stage 3 sleep and decreased or absent rapid eye movement (REM) sleep are features of the disorganised sleep observed in ICU patients.^{3–5}

The aetiology of sleep disturbances in ICU patients is multifactorial (figure 1). Sleep is the result of a dynamic balance of various complex neurochemical interactions. Alterations in any of the neuromodulators involved in this equilibrium may affect sleep regulation in ICU patients in the postoperative period. For example, an increase in norepinephrine and serotonin levels is associated with inhibition of REM sleep, while loss of a normal melatonin secretion pattern is associated with severe lack of sleep in ICU patients.^{6–10}

Figure 1 Pathophysiology of insomnia and delirium after cardiac surgery. ICU, intensive care unit; REM, rapid eye movement; TST, total sleep time; GABA, gamma-aminobutyric acid

Furthermore, inflammatory factors involved in acute illness, such as interleukin (IL)-1, IL-6 and tumour necrosis factor- α , contribute to sleep regulation and promote slow-wave sleep.^{11–13}

Next to the causes directly related to surgical trauma, additional factors related to ICU care play a key role in the pathophysiology of insomnia. Medications adversely affect normal sleep physiology: opioids and benzodiazepines are used to manage pain and insomnia in the ICU and can alter sleep architecture by suppressing slow-wave sleep and REM.^{14–19}

Many patients in the ICU are administered continuous intravenous infusions of catecholamines, which may pass the blood-brain barrier in sedated critically ill patients and decrease slow-wave and REM sleep.^{1 10 20} Beta-blockers, antibiotics, β adrenoceptor agonists and corticosteroids can also affect sleep architecture negatively.^{10 20–24} Furthermore, the environment in an ICU is not favourable in promoting sleep: procedural pain, anxiety and fear impair patients' ability to sleep.^{25 26} Not only are multiple sources of noise and lighting present in the ICU setting, but routine interventions such as nursing procedures, blood draws, vital sign measurements and imaging also interrupt patients' rest. Multiple studies have demonstrated sleep disruption by constant exposure to ambient sound levels in surgical ICUs, which are consistently above levels recommended by the WHO and Environmental Protection Agency.^{20 27–29}

Sleep deprivation in the ICU is a mechanism underlying the aetiology of delirium, a frequent complication during acute illness that develops in up to 80% of patients requiring mechanical ventilation.³⁰ Key elements in the diagnosis of delirium, such as attention and memory impairment as well as characteristic changes in the EEG power spectrum, have been linked to sleep deprivation.^{31–33} Delirium is associated with prolonged hospital and ICU stays, and increased 1-year mortality.^{34 35} The

opportunity to possibly improve patient outcomes by reducing the risk of postoperative delirium as a consequence of improved sleep quality is of great importance.

Various pharmacological and non-pharmacological strategies have been used to promote night-time sleep in the ICU. Many physicians use benzodiazepines, melatonin receptor agonists and sedating antidepressants for the treatment of insomnia, but these drugs may not be effective enough or may increase the vulnerability to delirium in the ICU.^{36–38}

Natural sleep and drug-induced sedation share the same phenotype of arousability through arousal pathways involving orexin receptors or the locus coeruleus.³⁹ Suvorexant (Merck & Co.) is a sleep-promoting orexin receptor antagonist with FDA approval for the treatment of adult insomnia. In phase 3 clinical trials, suvorexant proved superiority over placebo in promoting sleep onset and sleep maintenance measured by PSG. Suvorexant also improved subjective measures of total sleep time (TST) and sleep onset latency.⁴⁰ Additionally, no withdrawal symptoms have been observed after the long-term use of suvorexant, suggesting a low potential for physical dependence.⁴¹ Somnolence, fatigue and dry mouth are common side effects and suvorexant is also associated with abnormal dreams.⁴²

The gold standard of objective sleep measurement is polysomnography. In a previous pharmacophysiological interaction study, we used out-of-office PSG in the ICU to study early sleep apnoea after extubation in ICU patients.⁴³ However, use of full scale PSG may further increase the vulnerability to insomnia. We therefore will monitor sleep in the ICU using a portable EEG monitor (SedLine), which requires minimal setup time and expertise, resulting in potentially less interference of clinical care. The monitor uses frontal electrode placements that approximate those recommended by the American Academy of Sleep Medicine (AASM).⁴⁴ Simultaneous

PSG and SedLine monitoring has previously demonstrated similarities between PSG and SedLine recordings, and sleep monitoring in an ICU setting using the SedLine monitor has been shown to be feasible and well tolerated.⁴⁵

In this study, we will evaluate the effects of suvorexant on sleep and delirium in the cardiovascular ICU. We hypothesise that suvorexant compared with placebo decreases wakefulness after persistent sleep onset (WASO) during the first night after extubation in the cardiac ICU as measured by a portable EEG monitor. Our secondary hypothesis is that suvorexant compared with placebo increases TST during the night of the sleep trial in the cardiac ICU. We will test the exploratory hypothesis that suvorexant compared with the placebo decreases the incidence of postoperative in-hospital delirium, increases delirium free days and decreases time to sleep onset.

METHODS AND ANALYSIS

Study design and setting

This single-centre, randomised, double-blind, placebo-controlled trial will be conducted at Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA. The 'Committee on Clinical Investigations' at Beth Israel Deaconess Medical Center has reviewed and approved this study (protocol number 2019P000759). The study started enrolling participants on 28 February 2020 and the estimated study completion date is July 2022. Any modifications to the protocol, which may have an impact on the conduct of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects, will be sent for approval to the ethics committee/institutional review board (IRB) prior to implementation and notified to the health authorities in accordance with local regulations.

Study population

A total of 120 patients will be enrolled to reach the enrolment goal of 100 patients accounting for drop-outs. Participants aged ≥ 60 years and undergoing coronary artery bypass graft surgery with or without aortic and/or mitral valve replacement will be included. Participants meeting any of the following criteria will be excluded: preoperative left ventricular ejection fraction $<30\%$, renal failure (creatinine >2 mg/dL or dialysis dependence), liver failure (Child-Pugh score >6), coma (Richmond Agitation Sedation Scale (RASS) <-1), signs and symptoms of delirium and agitation at time of enrolment (confusion assessment method (CAM)-ICU positive), Montreal Cognitive Assessment (MoCA) <23 at time of consent, psychiatric or neurological diseases (including chronic benzodiazepine use, bipolar disorder, psychotic disorder, post-traumatic stress disorder, the requirement of prophylactic psychiatric medication, evidence of acute depression on screening visit, pre-existing cognitive impairment, Alzheimer disease, Parkinson's

disease, medications for cognitive decline, history of recent seizures (within 1 year prior to visit), alcoholism or documented history of alcohol abuse, and narcolepsy), severe sleep apnoea requiring home continuous positive airway pressure (CPAP) treatment, morbid obesity (body mass index (BMI) >40), known or suspected pregnancy, patients with known hypersensitivity to study medications, English language limitations, or enrolment in other interventional studies which could confound the primary endpoint.

The following secondary exclusion criteria will be assessed after surgery and before randomisation: time between discontinuation of sedation and start of sleep trial <4 hours, discharge from ICU before sleep trial, coma, evidence of delirium, loss of enteral access, massive intraoperative haemorrhage or postoperative respiratory failure.

Potentially eligible patients will be identified on medical and surgical floors, at preadmission testing clinic appointments, or in the cardiac catheterisation lab. Potential study participants will be approached preoperatively by trained study staff and informed written consent will be obtained. Figure 2 outlines the flow of the study.

Intervention

Patients will receive the study medication (suvorexant 20 mg or placebo) orally on the night of the sleep trial, if extubated before 19:00. If a patient is extubated after 19:00, the study medication will be administered the night after extubation if the patient is still in the cardiac ICU. The study medication will be administered at the same time every day (between 21:00 and 22:00) for all the patients. We allowed for a 1-hour window of study drug administration to provide some degree of flexibility to nursing staff administering the study drug. Prior to every drug administration, the RASS will be assessed. In case of a RASS value less than -1 , the study drug will not be administered.

The study drug will be discontinued

1. after seven consecutive doses following extubation; or
2. at hospital discharge (if less than 7 days after extubation); or
3. at ICU discharge if signs of airway obstruction were observed during sleep in the ICU; or
4. at ICU discharge or after three consecutive doses, whichever occurs sooner, if inhibitors of CYP3A (eg, ciprofloxacin, verapamil, diltiazem, erythromycin, digoxin) are coadministered; or
5. in the event of early termination (ie, subject withdrawal of consent, investigator withdrawal for toxicity or other reasons).

Dexmedetomidine will not be administered to subjects enrolled in the study after extubation due to possible preventive effects on postoperative sleep or delirium. To decrease the possible effects of sleep promoting agents on the study outcome, first choice rescue medication will be low-dose melatonin (2 mg to be administered no earlier than 3 hours after study drug administration). If

Figure 2 Study flow and eligibility criteria. BMI, body mass index; CABG, coronary artery bypass graft ICU, intensive care unit; RASS, Richmond Agitation Sedation Scale.

this is insufficient and sleeplessness persists, a low-dose benzodiazepine may be added (no earlier than 2 hours after melatonin administration). Haloperidol may be given for agitation, and oxycodone (or dilaudid as second line choice) may be given for pain control, as deemed necessary by the primary care team. Study subjects will receive care as per standard practice.

Assessment of study endpoints

Sleep and wakefulness will be measured by EEG using a SedLine Brain Function Monitor during the night of the sleep trial. A frontal bilateral array of sensors will be placed similar to AASM recommendations before study medications are administered. Bifrontal electrodes measure four channels of raw EEG with separate recording of locomotor electromyography (EMG) artefacts. This provides a less invasive, but effective, way to quantify sleep. EEG data will be analysed using dedicated computer software and visual inspection in accordance

with AASM guidelines to differentiate sleep (REM stage or non-REM stages N1–N3) and wakefulness (stage W).

Additionally, EEG band power analysis will be performed by analysing the EEG data using customised routines in MatLab in order to assist visual inspection. This provides means to rapidly characterise sleep architecture defined as structured temporal order of different sleep stages throughout the night.⁴⁶ An illustration of how inspection might be supported by power spectrum density is shown in figure 3. A wrist actigraph will be used to detect movements during sleep to help trace motion-related EEG artefacts more precisely.

Primary outcome

The primary outcome will be WASO in minutes, which will be defined as the duration of wakefulness after the onset of sleep in the observation period between 22:00 (lights off) and 06:00 (lights on). The onset of sleep will be defined on the EEG as the first 30 seconds epoch of sleep (REM or

Figure 3 Data derived from a portable EEG monitor with six 6 electrodes, including four 4 active channels (R1, R2, L1, L2), one reference channel (CT), and one ground channel (CB). The acquisition montage mimics electrodes placed according to the International 10–20 System – Fp1, Fp2, F7, and F8, each referenced to FpZ. The raw 250 Hz EEG is converted to European Data Format and filtered at low and high frequency (LFF 0.3Hz– HFF 35 Hz). Similarly, EMG is approximated from changes in forehead muscle tone in channels Fp1–F8 and Fp2–F7. These channels will be filtered as EMGs (LFF 10 Hz, HFF 70 Hz). Absence of muscle tone from these leads will assist in scoring REM sleep. (A) EEG waveform, (B) corresponding multitaper spectrogram and its characteristics at different vigilance states (C) during a full night sleep (7.5 hours). While the raw whole night EEG (A) does not allow immediate interpretation, sleep architecture is distinguishable in the corresponding multitaper spectrogram (B). Spectrograms will be used to assist and accelerate sleep staging by trained sleep physicians. *C-1-Awake*: active wakefulness presents with strong alpha activity (8–13 Hz) in both, the raw EEG and the power spectrum. *C-2-NREM Sleep*: absence of spindles and predominance of slow delta waves (0.5–2 Hz) in sleep stage 3 are observed. The multitaper spectrogram is dominated by strong delta power. *C-3-REM*: alpha and theta waves present during rapid eye movement (REM) sleep in the absence of K-complexes or spindles is observed in the EEG which corresponds with REM sleep, accordingly the spectrogram is dominated by theta and alpha power.

non-REM stages 1, 2, 3) after lights off. Wakefulness will be defined as an awake period of 30s or longer.

Secondary outcome

Secondary outcomes will include TST (REM or non-REM stages 1, 2, 3) measured during the night of the sleep trial by using EEG, in analogy to the primary outcome.

Exploratory outcomes

Subjective sleep quality will be assessed using the Richards-Campbell Sleep Questionnaire (RCSQ). Patients will be asked to complete a sleep questionnaire for at least one night before surgery or, if possible, daily, starting 3 days before surgery and for as long as the study medication is administered. The RCSQ is a validated survey instrument for assessing sleep quality in critically ill patients based on a five-item, Visual Analogue Scale (each ranging from 0 (worst value) to 100 (best value)).^{47 48} The questionnaire evaluates perceptions of depth of sleep, sleep onset latency, number of awakenings, time spent awake and overall sleep quality.

Delirium

After the patient consents to be enrolled in the study, a trained study team member will proceed with a baseline cognitive and delirium assessment. This will include the assessment of cognitive function using the MoCA, which will then be used to complete the CAM.⁴⁹ This standardised assessment tool focuses on the four main features of delirium: acute onset and fluctuating course, inattention, disorganised thinking and altered level of consciousness.

These assessments and scorings will be repeated daily between 10:00 and 12:00 by trained study team members blinded to the treatment allocation until the patient is discharged from the hospital. Nurses additionally assess and document the CAM-ICU score once per shift.

Furthermore, cognitive assessments will be performed at a participant's convenience to ensure ability to finish the evaluations. Treating clinicians will assess and treat delirium following standard of care guidelines, including assessment and correction of reversible causes. Delirium assessments performed for research purposes will not be provided to the treating clinicians. Use of intravenous haloperidol for agitation, if needed, will be documented in the study records. Non-verbal (intubated) patients will be administered the CAM-ICU, which includes both brief cognitive testing and the CAM algorithm to determine the presence or absence of delirium. CAM/CAM-ICU is valid only if a patient is not oversedated. Therefore, the RASS is recorded before every delirium assessment, and the CAM/CAM-ICU assessment is administered only if RASS > –3. In participants with a positive CAM result, a research team member blinded to the study group will perform the Delirium Symptom Interview, a standardised cognitive assessment evaluating attention, orientation and memory of patients.

Blinding and randomisation

After postoperative extubation, eligible patients will be randomly allocated in a 1:1 ratio to receive either suvorexant 20 mg or placebo. Variable block size randomisation will be stratified by duration of perioperative anaesthesia and sedation, using a cut-off value of 420 min of perioperative sedation based on observations in previous studies.⁴⁹ An independent statistician not involved in data

analysis will provide the allocation sequence directly to the research pharmacy. All other study personnel will be unaware of a participants' treatment allocation. Randomisation number-specific codebreakers, prepared by the research pharmacy, will contain information about a participant's treatment allocation in a sealed envelope and will be kept in the patient's medical record. If unblinding procedures are necessary for clinical reasons, the codebreaker envelope will only be opened with principal investigator (PI) approval, as instructed on the envelope. The PI will immediately inform the research pharmacy and study team of any unblinding procedures. Study team members will physically deliver the first dose of the study medication. Subsequently, the research pharmacy will be responsible for delivering the study medication during the upcoming nights. Any unused drug will be returned to the research pharmacy for disposal.

Data collection

We will obtain baseline descriptive data, including age, sex, ethnicity, BMI, admission diagnosis, acute physiology and chronic health evaluation (APACHE-II) score, type and severity of chronic lung disease, American Society of Anesthesiologists (ASA) physical status, history of obstructive sleep apnoea, sleeping history prior to surgery, smoking history, history of hypertension, coronary artery disease, heart failure, cerebrovascular accident or neurological dysfunction, chronic kidney disease, diabetes mellitus, Charlson Comorbidity Index, Procedural Severity Score and laboratory values. In order to differentiate effects of other variables on sleep from the effects of the study drug, we will further record data throughout the perioperative period, including vital signs, medications administered, length and type of surgery, time of surgery, duration of mechanical ventilation, duration of bypass time, total blood loss, blood transfusions, vasopressor requirement, total opioid requirement, postoperative complications and ICU length of stay prior to drug administration.

We will also record nursing-patient interactions (eg, intravenous line placement, intravenous flushing, blood sampling, turning/positioning of patients, wound care, breathing treatments, medication administrations, vital sign checks, neurological checks, point-of-care glucose measurements and patient-initiated contacts). We will measure ambient light exposure, using an actigraph wristwatch with an integrated RGB light sensor. This device will also measure movements (ie, accelerations and linear displacements) during the EEG defined epochs.

Adverse events and safety

Adverse events will be recorded daily. Nursing charts, physicians' notes and online medical records will be used to identify potential adverse events. Adverse events are defined as any undesirable experience associated with the use of a medical product in a patient. The PI will rate the adverse events by the likelihood of association (not related, unlikely related, possibly related, probably related, definitely related) and severity of the event

(mild, moderate or severe). All events will be logged by study staff and, if necessary, will be reported to the ethics committee/IRB. The most common side effects of suvorexant in clinical trials were somnolence, diarrhoea, dry mouth, headaches, dizziness and coughing. Abnormal dreams, hallucinations, tachycardia and sleep paralysis are less common side effects of suvorexant.^{41 42} Standard-of-care monitoring in the ICU, such as continuous blood pressure, heart rate, and respiratory measurements and regular blood sampling, will be in place. In this setting, any side effects related to suvorexant can be quickly diagnosed and treated, if necessary.

Data management

Data will be uploaded, stored and maintained on the secure Research Electronic Data Capture. The research database will not be unblinded until the medical/scientific review has been completed, protocol violations have been identified and data collection has been declared as complete. The study team will be responsible for all data entry and quality control activities.

Statistical analysis

Our primary analysis will be by modified intention to treat. As such, all randomised participants receiving at least one dose of study medication will be included in the analysis. We will consider a 30 min difference in WASO, with a SD of 45 min, as clinically meaningful.^{40 45} Accordingly, we expect a sample size of 50 subjects per group to provide >90% power to detect a difference between treatment groups, using a two-sided t-test with $\alpha=0.05$.

For the exploratory outcome, we may see a difference of 3 delirium-free days between groups, with a SD of 5 days. This assumption is based on previous findings observed in a similar cohort studying early mobilisation.^{50 51} The given sample size of 100 patients will yield a power of 84.4% to detect a difference in the exploratory outcome. To account for participant drop-outs, we plan to enrol up to 120 patients to achieve the desired sample size of 100 dosed subjects.

All analyses will be conducted by blinded research staff and supervised by a statistician. The primary and secondary analyses will be by modified intention to treat and will compare WASO and TST between patients receiving suvorexant or placebo.

To determine differences between groups regarding continuous outcomes, we will analyse the data using Student's t-test or Mann-Whitney U test, as appropriate based on the distribution of the data. Binary outcomes will be compared between the two groups using a χ^2 test.

A p value of <0.05 will be considered statistically significant. There will be no adjustment for multiple testing. Results of secondary outcomes and post hoc analyses will therefore be considered exploratory.

While our primary analysis will be intention to treat, we will add sensitivity analyses, to control for the possible effects of low-dose benzodiazepines (lorazepam equivalent doses) on postoperative insomnia.

To determine whether there is an association between each of the previously described confounders and TST during the night of the sleep trial, we will use multivariable logistic regression models. Subsequently, we will evaluate potential interactions between any statistically significant predictors of TST and suvorexant treatment on TST.

Patient and public involvement

No patients or the public were involved in the design or conduct of this study. Patients or the public were not invited to contribute to the writing or editing of this document for readability or accuracy.

Ethics and dissemination

Ethics approval was obtained through the 'Committee on Clinical Investigations' at Beth Israel Deaconess Medical Center (protocol number 2019P000759). Results arising from this study will be published in a peer-reviewed medical journal, as well as presented at both national and international conferences.

Author affiliations

¹Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

²Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

³Pharmacy, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

⁴Department of Neurology, Program in Neuroscience and Division of Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Twitter Balachundhar Subramaniam @Balachundhar and Matthias Eikermann @MatthiasEikerm1

Contributors ME, BS and PMF conceived the study and initiated the study design. ME is the principal investigator and grant holder. XX and SDG provided statistical expertise in clinical trial design. OA, MH and ME wrote the first manuscript draft. PS, KP, FCA, MP, SDG, MSS, KW, SR, PMF, BS and ME wrote the first grant proposal. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Funding This work is supported by Merck Sharpe & Dohme Corp., a subsidiary of Merck & Co., Kenilworth, New Jersey, USA.

Competing interests ME also received compensation for serving on the advisory board for Suvorexant in 2018.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Peter Santer <http://orcid.org/0000-0002-1735-0774>

Matthias Eikermann <http://orcid.org/0000-0002-7893-0596>

REFERENCES

1 Weinhouse GL, Schwab RJ. Sleep in the critically ill patient. *Sleep* 2006;29:707–16.

- 2 Tembo AC, Parker V, Higgins I. The experience of sleep deprivation in intensive care patients: findings from a larger hermeneutic phenomenological study. *Intensive Crit Care Nurs* 2013;29:310–6.
- 3 Friese RS, Diaz-Arastia R, McBride D, et al. Quantity and quality of sleep in the surgical intensive care unit: are our patients sleeping? *J Trauma* 2007;63:1210–4.
- 4 Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. *Intensive Care Med* 2004;30:197–206.
- 5 Elliott R, McKinley S, Cistulli P, et al. Characterisation of sleep in intensive care using 24-hour polysomnography: an observational study. *Crit Care* 2013;17:R46.
- 6 Luppi P-H, Clément O, Peyron C, et al. Neurobiology of REM sleep. In: *Oxford textbook of sleep disorders*. 15, 2017.
- 7 Drucker-Colin R, Merchant-Nancy H. *Evolution of concepts of mechanisms of sleep. The pharmacology of sleep*. Springer, 1995: 1–28.
- 8 Sack RL, Hughes RJ, Edgar DM, et al. Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? *Sleep* 1997;20:908–15.
- 9 Shilo L, Dagan Y, Smorjick Y, et al. Patients in the intensive care unit suffer from severe lack of sleep associated with loss of normal melatonin secretion pattern. *Am J Med Sci* 1999;317:278–81.
- 10 Bourne RS, Mills GH. Sleep disruption in critically ill patients--pharmacological considerations. *Anaesthesia* 2004;59:374–84.
- 11 Frenette E, Lui A, Cao M. Neurohormones and sleep. *Vitam Horm* 2012;89:1–17.
- 12 Krueger JM, Majde JA, Rector DM. Cytokines in immune function and sleep regulation. *Handb Clin Neurol* 2011;98:229–40.
- 13 Späth-Schwalbe E, Hansen K, Schmidt F, et al. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *J Clin Endocrinol Metab* 1998;83:1573–9.
- 14 Dimsdale JE, Norman D, DeJardin D, et al. The effect of opioids on sleep architecture. *J Clin Sleep Med* 2007;3:33–6.
- 15 Wang D, Teichtahl H, Opioids TH. Opioids, sleep architecture and sleep-disordered breathing. *Sleep Med Rev* 2007;11:35–46.
- 16 Shaw IR, Lavigne G, Mayer P, et al. Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study. *Sleep* 2005;28:677–82.
- 17 Bastien CH, LeBlanc M, Carrier J, et al. Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. *Sleep* 2003;26:313–7.
- 18 Aeschbach D, Dijk D-J, Trachsel L, et al. Dynamics of slow-wave activity and spindle frequency activity in the human sleep EEG: effect of midazolam and zopiclone. *Neuropsychopharmacology* 1994;11:237–44.
- 19 Borbély AA, Mattmann P, Loepe M, et al. Effect of benzodiazepine hypnotics on all-night sleep EEG spectra. *Hum Neurobiol* 1985;4:189–94.
- 20 Pisani MA, Friese RS, Gehlbach BK, et al. Sleep in the intensive care unit. *Am J Respir Crit Care Med* 2015;191:731–8.
- 21 McAtosh J, Cruickshank JM. Beta-Blockers and central nervous system side effects. *Pharmacol Ther* 1990;46:163–97.
- 22 Pulak LM, Jensen L. Sleep in the intensive care unit: a review. *J Intensive Care Med* 2016;31:14–23.
- 23 Unseld E, Ziegler G, Gemeinhardt A, et al. Possible interaction of fluorquinolones with the benzodiazepine-GABA_A-receptor complex. *Br J Clin Pharmacol* 1990;30:63–70.
- 24 Turner R, Elson E, disorders S. Steroids cause sleep disturbance. *BMJ* 1993;306:1477.
- 25 Lautenbacher S, Kundermann B, Krieg J-C. Sleep deprivation and pain perception. *Sleep Med Rev* 2006;10:357–69.
- 26 Nelson JE, Meier DE, Oei EJ, et al. Self-reported symptom experience of critically ill cancer patients receiving intensive care. *Crit Care Med* 2001;29:277–82.
- 27 Tainter CR, Levine AR, Quraishi SA, et al. Noise levels in surgical ICUs are consistently above recommended standards. *Crit Care Med* 2016;44:147–52.
- 28 Meyer TJ, Eveloff SE, Bauer MS, et al. Adverse environmental conditions in the respiratory and medical ICU settings. *Chest* 1994;105:1211–6.
- 29 Knauer M, Jeon S, Murphy TE, et al. Comparing average levels and peak occurrence of overnight sound in the medical intensive care unit on A-weighted and C-weighted decibel scales. *J Crit Care* 2016;36:1–7.
- 30 Pun BT, Ely EW. The importance of diagnosing and managing ICU delirium. *Chest* 2007;132:624–36.
- 31 Mograss MA, Guillem F, Brazzini-Poisson V, et al. The effects of total sleep deprivation on recognition memory processes: a study of event-related potential. *Neurobiol Learn Mem* 2009;91:343–52.
- 32 Fisher S. The microstructure of Dual-task interaction. 4. Sleep deprivation and the control of attention. *Perception* 1980;9:327–37.

- 33 Drouot X, Roche-Campo F, Thille AW, *et al.* A new classification for sleep analysis in critically ill patients. *Sleep Med* 2012;13:7–14.
- 34 Weinhouse GL, Schwab RJ, Watson PL, *et al.* Bench-to-bedside review: delirium in ICU patients - importance of sleep deprivation. *Crit Care* 2009;13:234.
- 35 Ely EW, Shintani A, Truman B, *et al.* Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753–62.
- 36 Brito RA, do Nascimento Rebouças Viana SM, Beltrão BA, *et al.* Pharmacological and non-pharmacological interventions to promote sleep in intensive care units: a critical review. *Sleep Breath* 2020;24:25–35.
- 37 Morin CM, Drake CL, Harvey AG, *et al.* Insomnia disorder. *Nat Rev Dis Primers* 2015;1:15026.
- 38 Lewis SR, Pritchard MW, Schofield-Robinson OJ, *et al.* Melatonin for the promotion of sleep in adults in the intensive care unit. *Cochrane Database Syst Rev* 2018;5:CD012455.
- 39 Eikermann M, Akeju O, Chamberlin NL. Sleep and anesthesia: the shared circuit hypothesis has been put to bed. *Curr Biol* 2020;30:R219–21.
- 40 Herring WJ, Connor KM, Snyder E, *et al.* Effects of suvorexant on the insomnia severity index in patients with insomnia: analysis of pooled phase 3 data. *Sleep Med* 2019;56:219–23.
- 41 Merck Sharp & Dohme Corp. Belsomra (suvorexant) package insert, 2014. Available: http://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_pi.pdf [Accessed 26 Jun 2018].
- 42 Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: a systematic review and meta-analysis. *Sleep Med Rev* 2017;35:1–7.
- 43 Timm FP, Zaremba S, Grabitz SD, *et al.* Effects of opioids given to facilitate mechanical ventilation on sleep apnea after extubation in the intensive care unit. *Sleep* 2018;41:zsx191.
- 44 Berry RB, Brooks R, Gamaldo C, *et al.* AASM scoring manual updates for 2017 (version 2.4). *J Clin Sleep Med* 2017;13:665–6.
- 45 Vacas S, McInrue E, Gropper MA, *et al.* The feasibility and utility of continuous sleep monitoring in critically ill patients using a portable electroencephalography monitor. *Anesth Analg* 2016;123:206–12.
- 46 Eikermann M, Zaremba S. Sleep medicine. In: Gropper MA, Miller RD, Eriksson LI, *et al.*, eds. *Miller's anesthesia*. Philadelphia, PA: Elsevier Health Sciences, 2019: 267–93.
- 47 Bourne RS, Minelli C, Mills GH, *et al.* Clinical review: sleep measurement in critical care patients: research and clinical implications. *Crit Care* 2007;11:226.
- 48 Kamdar BB, Shah PA, King LM, *et al.* Patient-nurse interrater reliability and agreement of the Richards-Campbell sleep questionnaire. *Am J Crit Care* 2012;21:261–9.
- 49 Subramaniam B, Shankar P, Shaefi S, *et al.* 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. *JAMA* 2019;321:686–96.
- 50 Schaller SJ, Anstey M, Blobner M, *et al.* Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet* 2016;388:1377–88.
- 51 Hammer M, Grabitz SD, Teja B, *et al.* Functional mobility recovery predicts readmission to the surgical intensive care unit. *Intensive Care Med* 2020;46:1054–6.