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Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: A pilot study

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Abstract

Objectives—Sleep, which comprises of rapid eye movement (REM) and non-REM stages 1–3 (N1–N3), is a natural occurring state of decreased arousal that is crucial for normal cardiovascular, immune and cognitive function. The principal sedative drugs produce electroencephalogram beta oscillations, which have been associated with neurocognitive dysfunction. Pharmacological induction of altered arousal states that neurophysiologically approximate natural sleep, termed biomimetic sleep, may eliminate drug-induced neurocognitive dysfunction.

Methods—We performed a prospective, single-site, three-arm, randomized-controlled, crossover polysomnography pilot study (n = 10) comparing natural, intravenous dexmedetomidine- (1-μg/kg over 10 minutes [n = 7] or 0.5-μg/kg over 10 minutes [n = 3]), and zolpidem-induced sleep in healthy volunteers. Sleep quality and psychomotor performance were assessed with

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Conflict of interest statement

O.A. and E.N.B have a provisional patent application describing the use of alpha-2 agonists for promoting N3 sleep. M.T.B has a patent pending on a home sleep monitoring device, has consulting and research agreements with MC10, Insomnisolv, International Flavors and Fragrances, and McKesson Health, he serves as a Medical Monitor for Pfizer, and has provided expert testimony in sleep medicine. E.N.B. has a consulting agreement with Masimo Corporation.

polysomnography and the psychomotor vigilance test, respectively. Sleep quality questionnaires were also administered.

Results—We found that dexmedetomidine promoted N3 sleep in a dose dependent manner, and did not impair performance on the psychomotor vigilance test. In contrast, zolpidem extended release was associated with decreased theta (~5–8 Hz; N2 and N3) and increased beta oscillations (~13–25 Hz; N2 and REM). Zolpidem extended release was also associated with increased lapses on the psychomotor vigilance test. No serious adverse events occurred.

Conclusions—Pharmacological induction of biomimetic N3 sleep with psychomotor sparing benefits is feasible.

Keywords

Dexmedetomidine; N3 sleep; biomimetic sleep; zolpidem; sedation

Introduction

Sleep is a natural occurring state of decreased arousal that is crucial for normal cardiovascular, immune and cognitive function (Rosenberg-Adamsen et al., 1996, Saper et al., 2010). However, the principal sedative drugs, most of which modulate the γ amino butyric acid A ($GABA_A$) receptor, do not produce the neurophysiological oscillations of sleep (Akeju et al., 2017). Rather, they produce neurophysiological oscillations that reflect cortical circuit disruptions, which manifest as electroencephalogram frontal beta oscillations, frontal alpha oscillations, burst suppression and isoelectricity (Patat et al., 1994, Feinberg et al., 2000, van Lier et al., 2004, Purdon et al., 2013, Akeju et al., 2014a, Akeju et al., 2014b, Akeju et al., 2017). These neurophysiological dynamics likely reflect disruption in sensory, memory encoding, and cognitive processing circuits that may in part explain why these medications are associated with neurocognitive dysfunction (Wafford et al., 2008, Maldonado, 2013, Soehle et al., 2015, Winkelman, 2015, Fritz et al., 2016, Akeju et al., 2017).

Pharmacological induction of biomimetic sleep may significantly reduce drug-induced neurocognitive dysfunction (Akeju et al., 2017). We define biomimetic sleep as the induction and maintenance of rapid eye movement (REM) and non-REM stages 1–3 (N1–N3) brain states that neurophysiologically approximate natural sleep. At the molecular level, we suggest that biomimetic sleep states reflect minimal unintended drug action in cortical circuits. Over the past decade, substantial advances in circuit mapping have furthered our understanding of brainstem arousal nuclei that generate sleep (Brown et al., 2012, Weber et al., 2016). Insights from these advances suggest that α2a adrenergic receptor agonist medications may closely pattern the activity of arousal nuclei similar to non-REM sleep (Weber et al., 2016).

α2a adrenergic receptor agonist medications are expected to reduce the firing rate of locus coeruleus neurons (Correa-Sales et al., 1992, Nacif-Coelho et al., 1994). Reduced activity of locus ceruleus neurons plays a key role in the initiation and maintenance of sleep by decreasing arousal promoting adrenergic inputs to the cortex, basal forebrain, thalamus, and

preoptic area of the hypothalamus (Saper et al., 2010, Szabadi, 2013, Weber et al., 2016). Decreased adrenergic signaling in the preoptic area results in the activation of sleep active neurons (Saper et al., 2010, Szabadi, 2013, Weber et al., 2016). These sleep active neurons inhibit brainstem arousal nuclei through GABA- and galanin- mediated mechanisms (Saper et al., 2010, Szabadi, 2013, Weber et al., 2016). α2a adrenergic receptor agonist medications may also directly modulate non-adrenergic neurons in the thalamus and basal forebrain to promote sleep (Buzsaki et al., 1991, Manns et al., 2003). Thus, α2a adrenergic receptor agonists alter cortical dynamics primarily by decreasing ascending noradrenergic inputs to the cortex, without significant direct drug action in cortical circuits.

Consistent with this mechanistic framework of non-REM sleep generation, our research group and others have demonstrated that a continuous infusion of dexmedetomidine, an α2a adrenergic receptor agonist, is associated with slow-delta (0.1–4 Hz) and spindle oscillations (12–16 Hz) with a transient-time domain morphology that is similar to N2 sleep spindles (Huupponen et al., 2008, Oto et al., 2012, Akeju et al., 2014a, Alexopoulou et al., 2014, Akeju et al., 2016). N3 sleep is associated with improved cognition and synaptic plasticity (Huber et al., 2004, Marshall et al., 2004, Molle et al., 2004, Backhaus et al., 2006, Huber et al., 2006, Huber et al., 2007, Rasch et al., 2007, Wafford et al., 2008, Prehn-Kristensen et al., 2014), suggesting that biomimetic N3 sleep may confer cognitive benefits. However, it is unclear whether biomimetic N3 sleep is feasible in humans. Neurophysiologically, larger amplitude slow-delta oscillations, a result of cortical and thalamic hyperpolarization, dominate N3 sleep (Brown et al., 2012, Prerau et al., 2017). Although slow-delta oscillations are associated with medications that modulate $GABA_A$ receptors, GABA associated slow-delta oscillations are functionally distinct (i.e. larger in amplitude, coupled to frontal alpha oscillations, asynchronous)(Lewis et al., 2012, Purdon et al., 2013, Akeju et al., 2014a, Akeju et al., 2014b, Purdon et al., 2015) from N3 sleep slow-delta oscillations.

Therefore, the aim of this study was to investigate whether dexmedetomidine may be administered to induce biomimetic N3 sleep in humans. Our negative and positive control study arms consisted of natural sleep and zolpidem (ER) sleep, respectively. Zolpidem extended release (ER) is a $GABA_A$ receptor agonist and commonly administered sleep aid with oscillatory dynamics that can be related to cortical circuit disruptions (Patat et al., 1994, McCarthy et al., 2008, Nutt et al., 2015, Struyk et al., 2016). We hypothesized that dexmedetomidine would promote biomimetic N2 and N3 sleep, and preserve psychomotor performance due to more precise targeting of brainstem arousal nuclei.

Materials and Methods

Ethics Statement

The Partners Human Research Committee approved this human research study that was conducted at the Massachusetts General Hospital, Boston, MA.

Subject Selection

Subjects were recruited for this study between April 2015 and December 2015 (NCT01485393). One hundred and fifty five potential study participants contacted a clinical

research coordinator who administered a questionnaire to confirm that the study inclusion and exclusion criteria were met. The following information was also confirmed by self-report: regular sleep-wake cycles, not routinely taking naps or consuming alcoholic or caffeinated beverages before sleep, and drug-free, non-smoking status. Prior to potential enrollment, subjects underwent a complete medical history, as well as standard pre-anesthesia assessments. Other procedures included toxicology screen to rule out prohibited drug use, a pregnancy test for females, and an electrocardiogram to rule out cardiac conduction deficits. None of the subjects had any known history of sleep disorders or any physical or psychiatric illness. Written informed consent was obtained from a total of 12 subjects during the screening visit. Two subjects withdrew from participating before any experimental study visits due to scheduling conflicts. The remaining 10 subjects (5 males) with ages ranging 21–29 years (mean: 23.9, std: 2.5) completed all study visits.

Experimental protocol and recording

Study subjects were instructed to arrive at the sleep laboratory at approximately 20:00 hours to prepare for polysomnography recording. The Massachusetts General Hospital sleep lab uses the GRASS recording system (0.3Hz low filter, 35.0Hz high filter Notch 60Hz) and follows American Academy of Sleep Medicine practice standards. A urine toxicology screen was performed at each of the four study visits to rule out the use of prohibited substances. Additionally, a urine pregnancy test was also performed to rule out pregnancy in all female study subjects. Four nights were spent in the sleep laboratory, with the first night serving to acclimate subjects to the new sleep environment and polysomnography recording equipment. Using a crossover unblinded study design, subjects were randomly assigned to receive only one of three treatments on each experimental study visit: intravenous dexmedetomidine (1.0 μg/kg bolus over 10 minutes or 0.5 μg/kg bolus over 10 minutes), oral zolpidem (ER) (Ambien CR [12.5 mg]), or natural sleep defined as no pharmacological intervention. Experimental study visits were separated by at least a 48-hour washout period to ensure that there were no residual effects or interactions with the drugs being studied. Polysomnography data were recorded and scored by a certified sleep laboratory technician. Lights out and/or drug administration occurred at 22:00 hours. On the dexmedetomidine infusion nights, once the infusion was complete, the subject was monitored by the study anesthesiologist for at least one-hour post infusion, and for the remainder of the night by the sleep technician. Subjects were instructed to stay in bed and try to sleep as they normally would, and they were awoken approximately 8 hours later. Morning-after sleep questionnaires that are routinely administered for all clinical polysomnography studies at the Massachusetts General Hospital were administered (Castillo et al., 2014). Nighttime and morning-after psychomotor vigilance tests were also administered. Briefly, the psychomotor vigilance test is a computerized timed reaction task that measures the speed with which subjects respond to visual stimuli presented at random every few seconds for 5 minutes.

Spectral analysis

Multitaper spectral estimates were computed as implemented in the Chronux toolbox. The parameters for the multitaper spectral analysis were: window length T = 6 seconds with no overlap, time-bandwidth product TW = 6, number of tapers K = 11. To capture drug induced oscillatory dynamics, we derived F3–F4 bipolar electrodes and analysed 2-minute

electroencephalogram (EEG) epochs corresponding to the midpoint of N2, N3, and REM sleep stages.

Statistical Power Analysis

An a priori sample size calculation was not performed.

Statistical Analysis

The three 0.5 μg/kg of dexmedetomidine study nights were only analyzed to make dose dependent inferences on N3 and REM sleep duration. A Tukey honest significant difference test was used to assess group differences in all other analyses. Thus, inferences (sleep metrics, PVT, EEG) for dexmedetomidine were based on the seven subjects that received 1.0 μg/kg. We constructed a model using a random intercept by subject with a fixed effect for drug to analyze the psychomotor vigilance test data. No variables outside of psychomotor vigilance test data, and group specification were included in the model. Thus, psychomotor vigilance test inferences were based on only the subjects who had complete paired data. All tests were two-sided with alpha = 0.05. Analyses were performed using JMP®, Pro 12 (SAS Institute Inc., Cary, NC, 1989–2007) and R Studio statistical software (R. RStudio, Inc., Boston, MA, 2015).

To assess statistical significance for the difference in spectra at each frequency, we computed the 99% confidence interval of the median difference between groups by using an empirical bootstrap approach. We resampled spectral estimates for each non-overlapping window to obtain replicates of the estimates for each volunteer, and took the median value across volunteers for each group. We took the difference between two median estimates, repeated this 5,000 times and calculated the 99% confidence interval of the median difference at each frequency. The null hypothesis was rejected only if the confidence interval of the median difference at each frequency exceeded the significance threshold over a contiguous frequency range ≥ 2W.

Results

No serious adverse events were reported during this study. One subject woke up during the dexmedetomidine (1.0 μg/kg) night because of severe discomfort at the intravenous line insertion site. This discomfort necessitated a clinician to discontinue the intravenous line prior to the subject retuning to sleep. Thus, we treated the polysomnography data for this subject after the clinician intervention as missing data.

Dexmedetomidine biased the sleep architecture towards N3 sleep

Total sleep times during the entire experiment were similar between the groups (Fig. 1A). However, dexmedetomidine significantly increased total non-REM sleep by 33.2 [4.6, 61.7] minutes compared to natural sleep (Fig. 1A; p = 0.021). This increase in non-REM sleep was compensated for by a significant decrease in REM sleep of 35 [9.8, 60.3] minutes (Fig. 1A; p = 0.006). Total N1 and N2 sleep were similar between the groups (Fig. 1B). However, dexmedetomidine significantly increased N3 sleep by 35.8 [2.7, 68.9] minutes compared to natural sleep (Fig. 1B; p = 0.032).

We analyzed the sleep stages during the first and second halves of the nights to more clearly characterize the putative effects of intravenous dexmedetomidine on sleep. Dexmedetomidine-induced sleep was associated with significantly increased N3 sleep of 53.7 [26.7, 80.8] minutes compared to natural sleep (Figure 1C, p = 0.0001). This increase in N3 sleep was compensated for by decrease in all sleep stages (Figure 1C). However, only the decrease in REM sleep of 15.7 [3, 28.4] was significant (Fig 1C, p = 0.013). Zolpidem (ER)-induced sleep was also associated with significantly increased N3 sleep of 26.8 [2.2, 51.3] minutes compared to natural sleep (Figure 1C, p = 0.031). The only significant difference during the second half of the night was an increase in N2 sleep of 25.8 [0.9, 50.8] minutes during dexmedetomidine-induced sleep compared to natural sleep (Figure 1D, p = 0.042).

While the correlation was not significant relative to the standard alpha level of 0.05, the association between dexmedetomidine and increased total N3 sleep during the first half of the night appeared to be dose dependent such that higher doses of dexmedetomidine resulted in increased total N3 sleep (Fig. 1E; Spearman $\rho = 0.58$, p = 0.08). Also, there appeared to be a dose dependent association between dexmedetomidine and decreased REM sleep during the first half of the night such that higher doses of dexmedetomidine resulted in decreased REM sleep (Fig. 1F; Spearman $\rho = -0.44$, p = 0.2).

Objective and subjective assessments of zolpidem (ER)-induced sleep quality were discordant

Objective assessments of sleep quality, such as sleep maintenance, sleep efficiency, and total wake time were similar and not significantly different between the groups (Table 1A). However, the subjective assessment (obtained from a questionnaire) of zolpidem (ER)-induced sleep quality was rated 1.2 [0.5, 2.0] and 1.2 [0.3, 2.0] points higher on an ordinal scale ranging from 1 to 5 than natural sleep (Table 1B; p = 0.001) and dexmedetomidine-induced sleep (Table 1B; p = 0.006), respectively. Analogous to the objective polysomnography total sleep time (Fig. 2A), the subjective total sleep times were similar between the groups (Table 1B). However, unlike the polysomnography total awake times, which were similar between groups (Table 1A), 42.7 [2.4 83.1] minutes of significantly more time awake was subjectively reported with dexmedetomidine compared to zolpidem (Table 1B; p = 0.037).

Next-day psychomotor vigilance is preserved after dexmedetomidine-induced sleep and worse after zolpidem (ER)-induced sleep

Lapse 400, defined as responses on the psychomotor vigilance test greater than 400 milliseconds, were 26 out of 293 responses for zolpidem (ER)-induced sleep night compared to 12 out of 291 responses for natural sleep and 14 out of 291 responses for dexmedetomidine-induced sleep. To make inferences on group differences between this and other psychomotor vigilance test metrics, we constructed a random effects model for nighttime (Supplementary Table S1) and morning-after psychomotor vigilance test metrics (Table 2). Expectedly, none of the nighttime psychomotor vigilance test metrics were significantly different between the groups (Supplementary Table S1). However, the morning-after psychomotor vigilance test lapse 400 was significantly increased after zolpidem (ER)-

induced sleep compared to the natural sleep and dexmedetomidine-induced sleep nights (Table 2).

Electroencephalogram dynamics confirm that early (dexmedetomidine-induced) and late (dexmedetomidine-associated) N2 sleep stages were biomimetic

We found that the first dexmedetomidine-induced N2 sleep epoch neurophysiologically approximated natural sleep (Fig. 2A), while zolpidem (ER)-induced N2 sleep was associated with decreased theta oscillation power (Fig. 2B; 5.3 – 9.8 Hz). The midpoints of the first N2 epochs occurred at 28.2 (21.6), 15 (8.4), 33.5 (25.7) minutes from sleep onset for natural sleep, dexmedetomidine-, and zolpidem (ER)-induced sleep, respectively. We also analyzed the last N2 period to study potentially late occurring drug-induced changes, and found that dexmedetomidine-induced N2 sleep remained neurophysiologically approximated natural sleep (Fig. 2C). However, zolpidem (ER)-induced N2 sleep became associated with increased beta oscillation power (Fig. 2D; 15.5 – 24.9 Hz). The midpoints of the last N2 epochs occurred at 422.9 (50.3), 436.8 (37.2), 435.9 (40.5) minutes from sleep onset for natural sleep, dexmedetomidine-, and zolpidem (ER)-induced sleep, respectively.

Electroencephalogram dynamics confirm that early (dexmedetomidine-induced) and late (dexmedetomidine-associated) N3 sleep stages were biomimetic

We found that the first dexmedetomidine-induced N3 sleep epoch neurophysiologically approximated natural sleep (Fig. 3A), while zolpidem (ER)-induced N3 sleep was associated with decreased theta/alpha oscillation power (Fig. 3B; 6.8 – 9.8 Hz). The midpoints of the first N3 epochs occurred at 47.8 (24.6), 42.9 (17.1), 60.8 (25.3) minutes from sleep onset for natural sleep, dexmedetomidine-, and zolpidem (ER)-induced sleep, respectively. We also analyzed the last N3 period to study potentially late occurring drug-induced changes, and found that dexmedetomidine-induced N3 sleep neurophysiologically approximated natural sleep (Fig. 3C). However, zolpidem (ER)-induced N3 sleep remained predominantly associated with decreased theta oscillation power (Fig. 3D; 2.5 – 8.9 Hz). The midpoints of the last N3 epochs occurred at 356.9 (105.4), 255.4 (87.2), 326.8 (95.4) minutes from sleep onset for natural sleep, dexmedetomidine-, and zolpidem (ER)-induced sleep, respectively.

Electroencephalogram dynamics confirm that dexmedetomidine-associated REM sleep was biomimetic

We found that REM sleep during the dexmedetomidine-induced sleep night also neurophysiologically approximated natural sleep (Fig. 4A). In contrast to dexmedetomidine-induced sleep, and similar to Zolpidem (ER) EEG dynamics during the last N2 sleep stage, Zolpidem (ER) REM sleep was associated with increased beta oscillation power (Fig. 4B; 12.1 – 22.3 Hz, 23.1 – 25 Hz). The midpoints of the REM epochs occurred at 176.5 (76.1), 289.1 (65.8), 178.6 (56.4) minutes from sleep onset for natural sleep, dexmedetomidine-, and zolpidem (ER)-induced sleep, respectively.

Discussion

Biomimetic sleep states may benefit patients by eliminating drug-induced neurocognitive dysfunction that result from unintended drug action in sensory, memory encoding, and

cognitive processing circuits (Akeju et al., 2017). This state may also be targeted to harness cardiovascular, immune or cognitive benefits of sleep (Rosenberg-Adamsen et al., 1996, Saper et al., 2010, Akeju et al., 2017). By comparing dexmedetomidine-induced sleep to natural sleep in a pilot-study, we found that dexmedetomidine induces biomimetic sleep, promotes non-rapid eye movement stage N3 sleep, and does not impair performance on the psychomotor vigilance test. We also found that zolpidem (ER), a commonly administered sleep medication that modulates $GABA_A$ receptors, is associated with non-neurophysiological oscillations (Patat et al., 1994, Nutt et al., 2015, Struyk et al., 2016) or non-biomimetic sleep, and increased lapses on the psychomotor vigilance test.

Neurophysiological sleep quality (biomimetic sleep versus non-biomimetic) may explain drug-induced neurocognitive dysfunction

We found that the total duration N3 sleep was increased during the dexmedetomidine sleep night compared to the normal sleep night. Because dexmedetomidine-induced N3 sleep closely approximated natural N3 sleep (compared to Zolpidem N3 sleep), we suggest that it may be associated with neurocognitive benefits (Huber et al., 2004, Marshall et al., 2004, Molle et al., 2004, Backhaus et al., 2006, Huber et al., 2006, Huber et al., 2007, Rasch et al., 2007, Wafford et al., 2008, Prehn-Kristensen et al., 2014). Although, zolpidem (ER) was associated with increased N3 sleep during the first half of the night, the presence of non-physiological oscillations during zolpidem (ER) sleep, including N3, explains why zolpidem may not confer the known neurocognitive benefits of N3 sleep (Huber et al., 2004, Marshall et al., 2004, Molle et al., 2004, Backhaus et al., 2006, Huber et al., 2006, Huber et al., 2007, Rasch et al., 2007, Wafford et al., 2008, Prehn-Kristensen et al., 2014, Akeju et al., 2017). Consistent with our findings, Hall-porter et al. also found that zolpidem (ER) was associated with increased N3 sleep during the first half of the night (Hall-Porter et al., 2014). Despite an increase in N3 sleep, which is associated with improved cognition and synaptic plasticity (Huber et al., 2004, Marshall et al., 2004, Molle et al., 2004, Backhaus et al., 2006, Huber et al., 2006, Huber et al., 2007, Rasch et al., 2007, Wafford et al., 2008, Prehn-Kristensen et al., 2014), zolpidem (ER) N3 sleep was negatively correlated with sleep dependent memory consolidation (Hall-Porter et al., 2014). This finding, which is inconsistent with the role of N3 sleep in sleep dependent memory consolidation (Marshall et al., 2004, Molle et al., 2004, Prehn-Kristensen et al., 2014), confirms our hypothesis that zolpidem (ER) N3 sleep does not provide the same benefit as natural N3 sleep (Hall-Porter et al., 2014).

Functional characteristics of the electroencephalogram, which may not be readily ascertained by visual PSG scoring of the raw EEG signals (Prerau et al., 2017), may explain why zolpidem (ER) sleep is associated with impaired sleep dependent memory consolidation. By using spectral analysis methods, we demonstrate that although the ultradian sleep cycle appeared preserved after the administration of zolpidem (ER), the scored sleep stages were neurophysiologically distinct from sleep. Increased beta oscillation power was prominent during the later part of the night for both N2 and REM sleep (Figs. 2D, 4B). During N3 sleep, which reflects the most profound cortical state of inactivation during sleep (i.e. largest slow-delta oscillation power), decreased theta oscillation power was prominent during both the early and later parts of the night (Fig. 3). These neurophysiological dynamics make clear that zolpidem (ER) sleep is not biomimetic. They

also suggest that zolpidem (ER)-induced changes to the normal brain neurophysiological dynamics persist from sleep onset until at least approximately 7 hours after drug administration (the latest time-point studied), and perhaps longer.

The zolpidem (ER)-induced EEG dynamics we describe is explained by a model that was constructed to study propofol, an intravenous anesthetic drug that also modulates the $GABA_A$ receptor. Consistent with our finding of increased beta oscillation power during the latter periods of N2 (Fig. 2D) and REM (Fig. 4B), the model suggests that enhanced inhibitory postsynaptic currents through $GABA_A$ receptor modulation causes antisynchrony of low threshold spiking (LTS) cells in cortical circuits (McCarthy et al., 2008). This antisynchrony manifests in the EEG as beta oscillations (McCarthy et al., 2008). Further, our results suggest that zolpidem (ER)-induced beta oscillations are not a characteristic feature of N3 sleep. Rather, decreased theta oscillations persisted during this sleep stage at a time point between REM and N2 sleep epochs that were associated with beta oscillations. Thus, it is likely that the hyperpolarization state of neuron during N3 sleep is not consistent with GABA-initiated rebound spiking. Mechanisms to explain the zolpidem (ER)-induced decrease in theta oscillation power are not clear. However, we suggest that decreased theta and increased beta oscillation power reflects undesired direct drug action in cortical circuits to explain why zolpidem (ER) is associated with impaired sleep dependent memory consolidation, amnesia, and complex sleep related disorders (Winkelman, 2015).

Biomimetic sleep states may be a preemptive delirium prevention strategy

Delirium is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder (American Psychiatric Association. et al., 2013). It remains a leading cause of preventable morbidity and mortality in hospitalized elderly patients (Maldonado, 2013). Despite its impact, there are no definitive pharmacological preventative strategies for delirium. Sleep deprivation, which is associated with increased pro-inflammatory cytokine levels including interleukin-6 (Shearer et al., 2001, Vgontzas et al., 2004, Haack et al., 2007), has been found to precede the onset of delirium in patients (Johns et al., 1974, Mundigler et al., 2002). A recent investigation showing a link between brain activity of microglia, astrocytes, interleukin-6 and delirium in humans (Munster et al., 2011), suggests that an underlying mechanism associated with sleep deprivation and brain inflammation may precipitate delirium. There is no preemptive therapeutic sleep strategy for the prevention of delirium, and sedative drugs that modulate $GABA_A$ receptors increase the risk for developing of delirium.

The administration of a continuous infusion of dexmedetomidine, which results in an N2 sleep stage arrest (i.e. absence of N1, N3 and REM sleep), (Oto et al., 2012, Akeju et al., 2014a, Alexopoulou et al., 2014) has been associated with a reduced incidence on delirium in critically ill and mechanically ventilated patients (Pandharipande et al., 2007, Maldonado et al., 2009, Riker et al., 2009, Reade et al., 2016). The present finding that a single nighttime dose of dexmedetomidine preserves normal sleep cycling, and promotes non-REM stage N3 sleep, is consistent with the notion that dexmedetomidine targets brainstem arousal nuclei involved in non-REM sleep generation to promote N3 sleep. Thus, orally available

alpha2a adrenergic agonists may represent a new class of sleep enhancing medications with neurocognitive sparing benefits.

Rapid Eye Movement sleep and dexmedetomidine

Because dexmedetomidine increased the duration of N3 sleep, and our study lasted approximately 8-hours (i.e. 2200 to 0600 hours), a compensatory decrease in the duration of REM sleep duration was expected. We note that even though dexmedetomidine was associated with a reduced duration of REM sleep, dexmedetomidine-induced REM sleep was biomimetic. However, zolpidem (ER)-induced REM sleep was associated with non-biomimetic beta oscillations. The clinical significance of dexmedetomidine-induced reduction in REM sleep duration is unknown. Also unknown is whether a minimum or critical REM sleep duration threshold was met during the dexmedetomidine-induced sleep night. We conjecture that in spite of the decreased duration of REM sleep, pharmacological induction or maintenance of biomimetic sleep stages is more beneficial compared to the non-biomimetic status quo. Confirming this conjecture, we note that performance on the psychomotor vigilance test was worse after zolpidem (ER)-induced sleep compared to natural sleep.

Subjective and objective measures of sleep quality post zolpidem (ER) were discordant

While results from subjective measures obtained from unblinded studies such as ours may be confounded by bias (i.e. recall), we note that our objective and subjective measures of zolpidem (ER) sleep quality were discordant. For example, lapses on the psychomotor vigilance test were significantly higher after zolpidem (ER)-induced sleep compared to normal and dexmedetomidine-induced sleep, even though sleep maintenance and efficiency were similar between the groups. This finding of increased morning-after lapses after zolpidem (ER)-induced sleep is in line with reports that the sedative effects of zolpidem (ER), which are associated with dangerously impaired next-day performance, persist long after drug administration (Farkas et al., 2013). This sedative effect, is reflected in the EEG as increased beta oscillations that persisted throughout the night. Even though lapses on the psychomotor vigilance test performance was worse after zolpidem (ER)-induced sleep, we found it concerning that subjective sleep quality was rated highest after zolpidem (ER)-induced sleep compared to natural and dexmedetomidine-induced sleep. Misperception of total sleep time resulting from the amnestic effects of GABA receptor modulation may account for patients to falsely perceive their sleep to be better after taking zolpidem (ER) (Bonin et al., 2008). Thus, we caution that after the administration of $GABA_A$ receptor modulating drugs, self-perception of sleep quality should not be considered as a definitive gauge of objective sleep quality or morning-after impairment.

Limitations

Limitations of our crossover study are the sample size, unblinded randomized treatment assignments, and psychomotor vigilance test learning effects. Thus, it is conceivable that unmeasured confounders may have contributed to our results (i.e. our subjective data may have been heavily influenced by the unblinded nature of this study). However, the dose dependent N3 promoting effects demonstrated in this study argues for biological plausibility. Further, because volunteers routinely complained of overnight irritation at the intravenous

site, we speculate that the sleep promoting effects of dexmedetomidine may have been underestimated in this study. Future studies to determine the generalizability of our findings to patients (i.e. elderly, critically ill) are necessary

Conclusion

Sleep medications that modulate the $GABA_A$ receptor are associated with non-biomimetic oscillatory dynamics that reflect cortical circuit dysfunction. We conclude that dexmedetomidine mediated induction of biomimetic sleep with psychomotor sparing benefits is feasible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance

These results suggest that alpha2a adrenergic agonists may be developed as a new class of sleep enhancing medications with neurocognitive sparing benefits.

Highlights

1. Dexmedetomidine approximated natural sleep neurophysiology and promoted non-REM 3 sleep.
2. Zolpidem did not closely approximate natural sleep neurophysiology.
3. Lapses on the psychomotor vigilance test were worse with zolpidem.

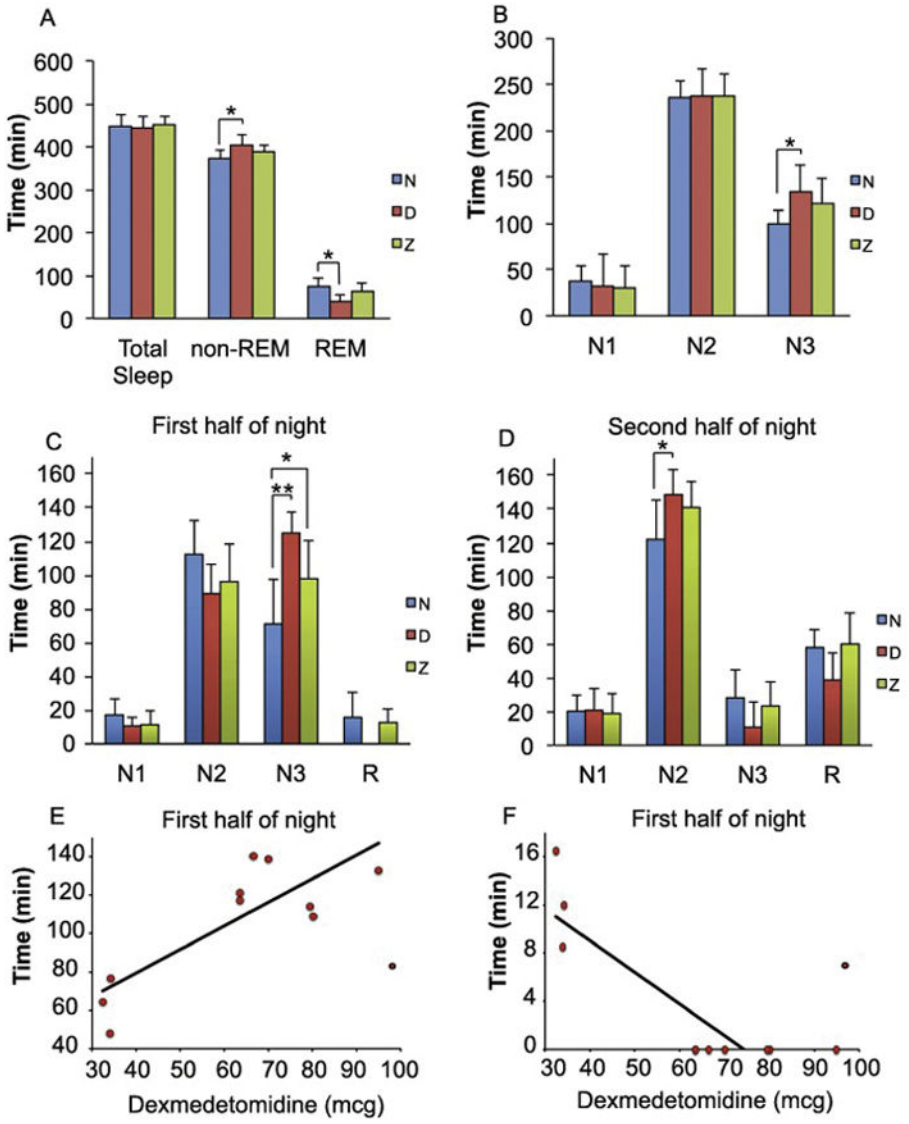

Fig. 1. Dexmedetomidine increases N3 sleep in a dose dependent fashion

A) Total sleep time was not significantly different between the sleep groups. However, dexmedetomidine significantly increased the total time spent in non-REM sleep compared to natural sleep ($p = 0.021$). This increase was compensated for by a significantly decreased time spent in REM sleep compared to natural sleep ($p = 0.006$). B) N1 and N2 sleep were not significantly different between the groups. However, dexmedetomidine significantly increased the total time spent in N3 sleep compared to natural sleep ($p = 0.032$). C) The effect of dexmedetomidine on N3 sleep increase was most prominent during the first half of the night. Dexmedetomidine significantly increased the total time spent in N3 sleep compared to natural sleep during the first half of the night ($p = 0.0001$). Zolpidem also significantly increased the total time spent in N3 sleep compared to natural sleep during the first half of the night ($p = 0.031$). D) Dexmedetomidine significantly increased the total time spent in N2 sleep compared to natural sleep during the second half of the night ($p = 0.042$). E) There was a dose dependent association between dexmedetomidine and total N3 sleep

with higher doses of dexmedetomidine resulting in increased total N3 sleep (Spearman's ρ = 0.58, p = 0.08). F) There was also a dose dependent association between dexmedetomidine and total REM sleep with higher doses of dexmedetomidine resulting in decreased total REM sleep (Spearman's ρ = −0.44, p = 0.2). REM, rapid eye movement; *, p <0.05; **, p <0.05. Error bars represent standard deviation.

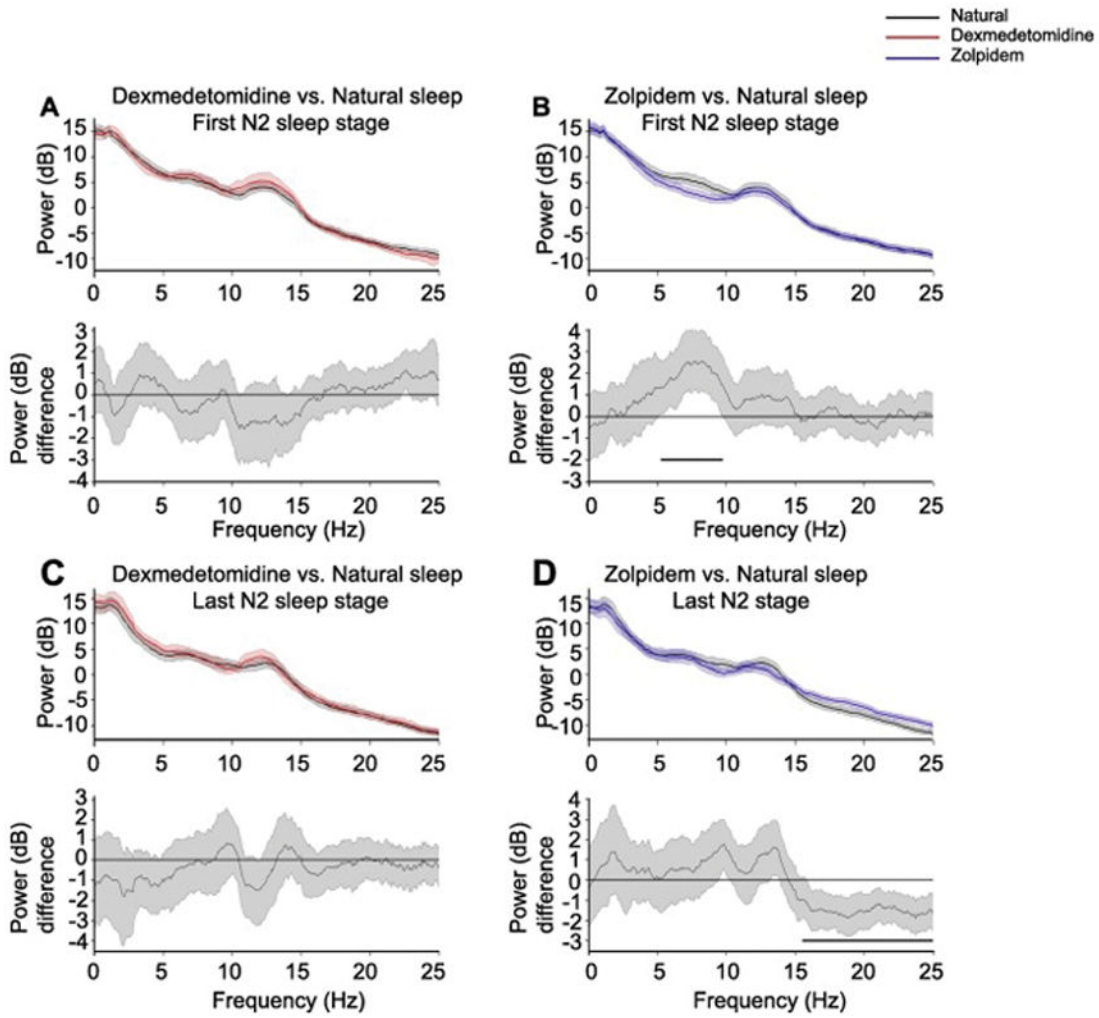

Fig. 2. Spectral comparison of EEG power during non-rapid eye movement stage N2 sleep

(A) Top panel; Overlay of median first natural sleep N2 spectrum (black), and median first dexmedetomidine N2 spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We did not find differences between the two spectra. (B) Top panel; Overlay of median first natural sleep N2 spectrum (black), and median first zolpidem N2 spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We found differences in power between the first natural N2 spectrum and the first zolpidem N2 spectrum (zolpidem < natural sleep: 5.3 – 9.8 Hz). (C) Top panel; Overlay of median last natural sleep N2 spectrum (black), and median last dexmedetomidine N2 spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with

shaded regions representing the 99% confidence of the difference. We did not find differences between the two spectra. (D) Top panel; Overlay of median last natural sleep N2 spectrum (black), and median last zolpidem N2 spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We found differences in power between the last natural N2 spectrum and the last zolpidem N2 spectrum (zolpidem > natural sleep: 15.5 – 24.9 Hz). Black lines in bottom panel represent regions that me our threshold for significance.

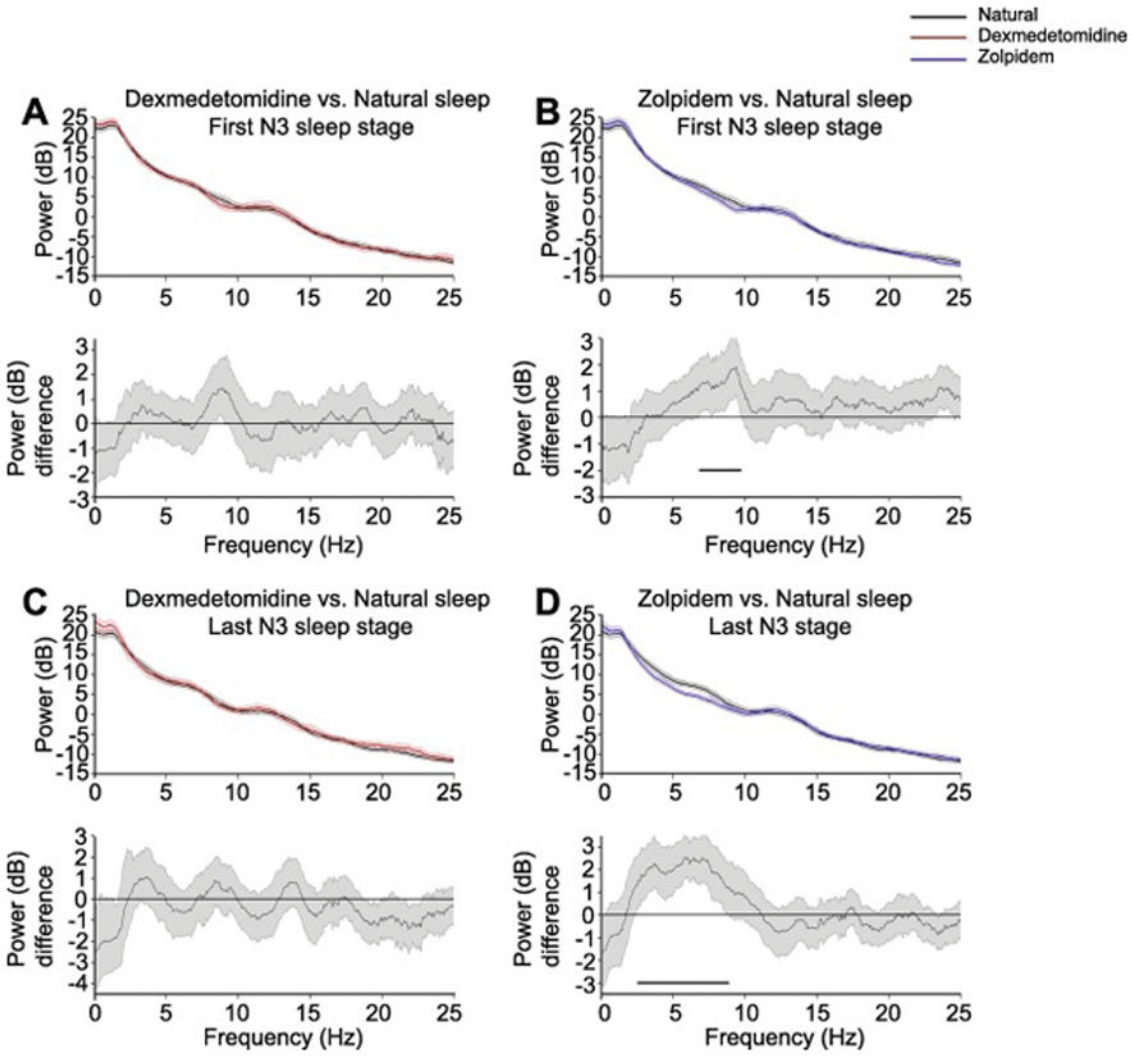

Fig. 3. Spectral comparison of EEG power during non-rapid eye movement stage N3 sleep

(A) Top panel; Overlay of median first natural N3 spectrum (black), and median first dexmedetomidine N3 spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We did not find differences between the two spectra. (B) Top panel; Overlay of median first natural sleep N3 spectrum (black), and median first zolpidem N3 spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We found differences in power between the first natural sleep N3 spectrum and the first zolpidem N3 spectrum (zolpidem < natural sleep: 6.8 – 9.8 Hz). (C) Top panel; Overlay of median last natural sleep N3 spectrum (black), and median last dexmedetomidine N3 spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the

uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We did not find differences between the two spectra. (D) Top panel; Overlay of median last natural sleep N3 spectrum (black), and median last zolpidem N3 spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We found differences in power between the last natural sleep N3 spectrum and the last zolpidem N3 spectrum (zolpidem > natural sleep: 2.5 – 8.9 Hz). Black lines in bottom panel represent regions that me our threshold for significance.

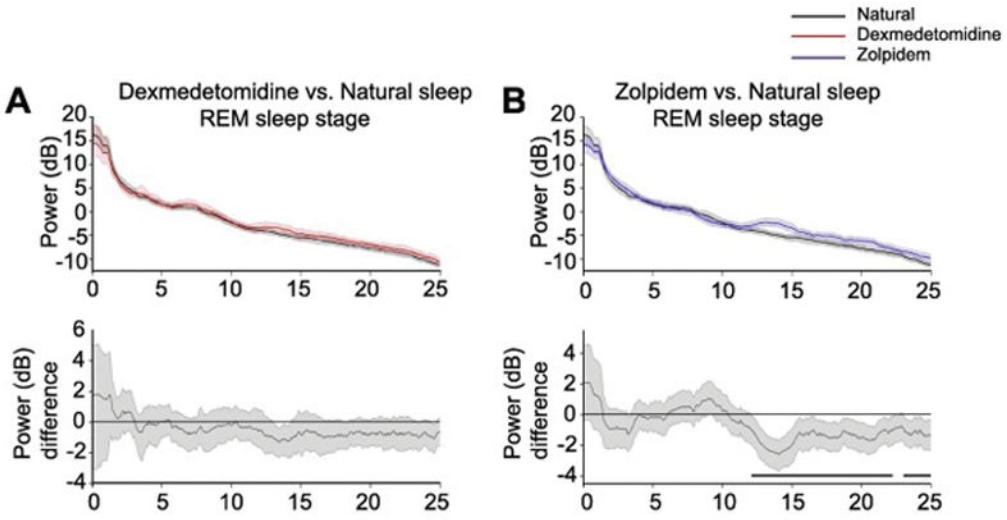

Fig. 4. Spectral comparison of EEG power during non-rapid eye movement stage N3 sleep

(A) Top panel; Overlay of median natural REM sleep spectrum (black), and median dexmedetomidine REM sleep spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We did not find differences between the two spectra. (B) Top panel; Overlay of median natural REM sleep spectrum (black), and median last zolpidem REM sleep spectrum (red). Bootstrapped median spectra are presented, and the shaded regions represent the 99% confidence interval for the uncertainty around each median spectrum. Bottom panel: Median bootstrap difference in spectra with shaded regions representing the 99% confidence of the difference. We found differences in power between the last natural sleep N3 spectrum and the first zolpidem (zolpidem < natural sleep: 12.1 – 22.3 Hz, 23.1 – 24.9 Hz).

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Table 1

Sleep quality measures. Mins, minutes; N, Natural (n = 10); D, dexmedetomidine (n = 6); Z, zolpidem (ER) (n = 10).

Table 1A. Objective Sleep Quality Metrics

	Normal (Mean)	Dexmedetomidine (Mean)	Zolpidem (ER) (Mean)	Contrast	Effect Size	95% CI	P-Value
Sleep Efficiency (%)	93.6	92.6	94.4	D-N	−1.0	−8.3, 6.2	0.938
				Z-N	0.8	−5.4, 7.1	0.942
				Z-D	1.8	−5.4, 9.1	0.807
Sleep Maintenance (%)	94.1	94.1	97.4	D-N	−2.0	−7.3, 3.3	0.609
				Z-N	1.3	−3.3, 5.9	0.775
				Z-D	3.3	−2.0, 8.6	0.286
Total Wake Time (mins)	31.6	36.4	26.4	D-N	4.9	−31.4, 41.2	0.940
				Z-N	−5.2	−36.6, 26.3	0.911
				Z-D	−10.0	−46.3, 26.3	0.771

Table 1B. Subjective Sleep Quality Metrics

	Normal (Mean)	Dexmedetomidine (Mean)	Zolpidem (ER) (Mean)	Contrast	Effect Size	95% CI	P-Value
Total Sleep Time (mins)	413.0	440.3	463.5	D-N	27.3	−21.9, 21.0	0.167
				Z-N	50.5	−16.7, 117.2	0.657
				Z-D	23.2	−54.4,100.8	0.738
Sleep Quality	2.3	2.3	3.5	D-N	0.03	−0.81, 0.88	0.995
				Z-N	1.2	0.5, 2.0	0.001
				Z-D	1.2	0.3, 2.0	0.006
Total Wake Time (mins)	31.0	52.0	9.0	D-N	20.3	−20.1, 60.6	0.431
				Z-N	−22.4	−54.3,12.5	0.264
				Z-D	−42.7	−2.4, 83.1	0.037

Table 2

Morning-after PVT results. Ms, milliseconds; PVT, psychomotor vigilance; RRT, reciprocal response time. N, Natural (n = 7); D, dexmedetomidine (n = 7); Z, zolpidem (ER) (n = 7).

	Normal (Mean)	Dexmedetomidine (Mean)	Zolpidem (ER) (Mean)	Contrast	Effect Size	95% CI	P-Value
PVT Score (ms)	287.0	285.0	292.0	D-N	−2.1	−20.8, 16.6	0.956
				D-Z	−7.7	−26.4, 13.0	0.553
				N-Z	−5.6	−24.3, 13.0	0.726
RRT	3.6	3.6	3.6	D-N	0.0	−0.2, 0.2	0.933
				D-Z	0.0	−0.1, 0.3	0.720
				N-Z	0.1	−0.2, 0.3	0.906
Lapse Time (ms)	45.4	53.7	65.4	D-N	8.4	−21.4, 38.1	0.736
				D-Z	−20.0	−40.4, 17.1	0.553
				N-Z	−11.6	−47.2, 7.2	0.167
Lapse 400 (lapse/trial)	0.1	0.0	0.1	D-N	0.0	−0.1, 0.0	0.059
				D-Z	0.1	−0.1, 0.0	0.004
				N-Z	0.0	−0.1, 0.0	0.009
Slow 10% (ms)	408.0	406.0	437.0	D-N	−1.2	−35.2, 31.6	0.989
				D-Z	−30.8	−62.4, 0.8	0.056
				N-Z	−29.0	−60.6, 2.6	0.074
Fast 10% (ms)	219.0	218.0	214.0	D-N	−1.2	−7.3, 4.9	0.867
				D-Z	4.2	−1.4, 9.8	0.146
				N-Z	5.4	−0.6, 11.3	0.076