Randomized controlled trial of pharmacological replacement of melatonin for sleep disruption in individuals with tetraplegia

Jamie M. Zeitzer^{1,2}, Ban Ku², Doug Ota^{3,4}, B. Jenny Kiratli^{3,4}

¹Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA, ²Psychiatry Service, VA Palo Alto Health Care System, Palo Alto, CA, USA, ³Spinal Cord Injury Service, VA Palo Alto Health Care System, Palo Alto, CA, USA, ⁴Physical Medicine and Rehabilitation Division, Department of Orthopaedic Surgery, Stanford University, Palo Alto, CA, USA

Objective: To determine the effectiveness of a melatonin agonist for treating sleep disturbances in individuals with tetraplegia.

Design: Placebo-controlled, double-blind, crossover, randomized control trial.

Setting: At home.

Participants: Eight individuals with tetraplegia, having an absence of endogenous melatonin production and the presence of a sleep disorder.

Interventions: Three weeks of 8 mg of ramelteon (melatonin agonist) and 3 weeks of placebo (crossover, randomized order) with 2 weeks of baseline prior to and 2 weeks of washout between active conditions.

Outcome: Change in objective and subjective sleep.

Measures: Wrist actigraphy, post-sleep questionnaire, Stanford sleepiness scale, SF-36.

Results: We observed no consistent changes in either subjective or objective measures of sleep, including subjective sleep latency ($P=0.55$, Friedman test), number of awakenings ($P=0.17$, Friedman test), subjective total sleep time ($P=0.45$, Friedman test), subjective morning alertness ($P=0.35$, Friedman test), objective wake after sleep onset ($P=0.70$, Friedman test), or objective sleep efficiency ($P=0.78$, Friedman test). There were significant increases in both objective total sleep time ($P<0.05$, Friedman test), subjective time in bed ($P<0.05$, Friedman test), and subjective sleep quality ($P<0.05$, Friedman test), although these occurred in both arms. There were no significant changes in any of the nine SF-36 subscale scores (Friedman test, P s > Bonferroni adjusted α of 0.005).

Conclusion: In this pilot study, we were unable to show effectiveness of pharmacological replacement of melatonin for the treatment of self-reported sleep problems in individuals with tetraplegia.

Trial Registration: ClinicalTrials.gov # NCT00507546.

Keywords: Spinal cord injuries, Melatonin, Tetraplegia, Randomized control trial, Sleep, Sleep initiation and maintenance disorders

Introduction

Chronic sleep disruption is a very common problem in individuals with tetraplegia.^{1–4} Such chronic disruption of sleep leads to increased physical and psychological morbidities and contributes to a poorer quality of life in these individuals.^{5–7} Two main categories of sleep problems occur in individuals with tetraplegia. The first is sleep-disordered breathing, during which

breathing temporarily ceases or is reduced during sleep, causing a decrease in blood oxygen saturation that induces an awakening that results in the resumption of normal breathing. Sleep apnea may be common in individuals with tetraplegia because of additional factors conducive to airway collapse (e.g. lack of innervation of intercostal and abdominal muscles – although upper airway muscles are still innervated by intact cranial nerves – and, in C4 and above, lack of or reduced innervation of the diaphragm),⁸ increased neck circumference,⁹ and use of spasmolytics that

Correspondence to: Jamie Zeitzer, Department of Psychiatry and Behavioral Sciences, Stanford University, 3801 Miranda Avenue (151Y), Palo Alto, CA 94304, USA. Email: jzeitzer@stanford.edu

depress nocturnal breathing and promote airway collapse through selective reduction of upper airway dilator muscle activity.⁸ Although 5–10% of the able-bodied population has sleep apnea,¹⁰ the percentages are much higher in those with tetraplegia, ranging from 27.5 to 48% in the literature.^{8,9} Although sleep disruption and daytime sleepiness are concomitants of sleep apnea, there may be non-apnea-related causes of these problems in individuals with spinal cord injury (SCI). In one Australian study, approximately half of the 40 individuals with SCI had complaints of excessive daytime sleepiness.⁸ This daytime sleepiness was significantly correlated with disrupted sleep, but not with the sleep disruptions caused by apneic events. In another study of sleep apnea, 22 individuals with SCI had increased amounts of wakefulness after sleep onset and a decrease in slow wave sleep, neither of which appeared to be associated with the breathing-related disruptions in sleep.¹¹ In a further study of sleep apnea after SCI, a group of seven individuals with SCI had an increase in wakefulness after sleep onset, a decrease in stage 2 of non-rapid eye movement (non-REM) sleep, and a decrease in REM sleep, although there was more sleep disruption evident than could be accounted for by the oxygen desaturation observed during sleep.¹² Thus, while sleep-disordered breathing is a concern for individuals with tetraplegia, there is greater disruption of sleep and greater amounts of daytime sleepiness than can be explained based on apneic events alone.

Insomnia is another sleep problem that is highly prevalent in those with tetraplegia. Insomnia is typically treated symptomatically, often with antidepressants or benzodiazepine agonists, but these treatments have significant side effects and unwanted drug–drug interactions. In fact, a recent report by the National Institutes of Health indicates that there are currently no adequately tested treatments for the chronic sleep disruption common in individuals with tetraplegia.¹³ An alternative approach might be based on the supposition that difficulties in sleeping may be a direct result of the damage to the spinal cord. That is, individuals with neurologically complete damage to their cervical spinal cord (tetraplegia) produce no melatonin,¹⁴ a hormone that has been shown to be involved in sleep physiology.¹⁵ Almost all melatonin in mammals is produced by the pineal gland. In mammals, including humans, denervation or decentralization of the pineal gland results in the absence of melatonin production.^{14,16} Even though the pineal is located deep within the skull, it is outside of the blood–brain barrier and requires innervation from spinal nerves, primarily those arising from the sympathetic branch of the nervous system (superior cervical

ganglion). In humans, there are two main specific melatonin receptors, MT₁ and MT₂. Activation of MT₁ in the suprachiasmatic nuclei (SCN), the site of the central circadian clock in humans, reduces neuronal firing in the SCN.¹⁷ Normally, the SCN provide a strong drive for wakefulness during the late evening.^{18,19} This drive for wake abates about the same time as habitual bedtime. Melatonin concentrations begin to rise in an hour or two before habitual bedtime.²⁰ Given the electrophysiological properties of melatonin on the SCN and the relative timing of melatonin and sleep onset, it has been hypothesized that melatonin acts to suppress or quiet the wake signal from the SCN, which creates a neural environment more conducive to sleep initiation. One of the key physiological phenomena associated with the initiation of sleep is a drop in core temperature caused by an active release of heat in the periphery.²¹ Melatonin has been hypothesized to enhance this phenomenon in two different locales. One is the preoptic area (POA), which has both temperature sensitive neurons and sleep-active neurons.²² Melatonin might act directly on POA neurons to enhance their sleep-promoting activity, or it might act on POA neurons to change their temperature sensitivity, which could lead to changes in thermoregulation and indirectly lead to enhanced sleep onset mechanisms.²³ Melatonin may also act indirectly on temperature regulation through its activity in the peripheral vasculature.²⁴ It has been proposed that melatonin may work against peripheral vasoconstriction caused by release of noradrenaline, thus promoting a more dilated state in arteries. This increase in dilation would lead to greater heat loss in the periphery. Thus, although the physiological substrate for the sleep-inducing mechanism of melatonin is not definitely known, it is likely to act both directly and indirectly (via changes in thermoregulation) to enhance the mechanisms of sleep onset – which is supported by physiology research on both endogenous and exogenous melatonin.^{15,25}

Given the purported role of endogenous melatonin in sleep physiology, the absence of endogenous melatonin in those with neurologically complete damage to their cervical spinal cord, and the high prevalence of sleep disruption in these individuals, we initiated a study to examine the effects of replacing melatonin signaling on sleep. Using a randomized controlled crossover trial design, we tested the hypothesis that a melatonin dual agonist (acting on both MT₁ and MT₂), as compared with placebo, would significantly improve subjective and objective sleep complaints, as well as overall quality of life, in individuals with tetraplegia who lacked endogenous melatonin production. We chose to

use a pharmacological melatonin dual agonist rather than the native melatonin compound since over-the-counter melatonin is not regulated by the United States Food and Drug Administration and contaminants similar to those which caused the L-tryptophan-associated outbreak of eosinophilia-myalgia syndrome have been detected in commercially available over-the-counter melatonin supplements.²⁶

Methods

We recruited participants who met the following inclusion criteria: 18 years or older, either sex, neurologically complete damage (American Spinal Injury Association (ASIA) Impairment Scale (AIS)²⁷ to the lower (C4–C8) cervical spinal cord or assessed absence of melatonin production, time since SCI greater than 6 months, and a subjective sleep complaint. Exclusion criteria included current use of drugs (fluvoxamine, rifampin, fluconazole) that induce pharmacokinetic changes secondary to interactions with liver enzyme metabolism of ramelteon, hepatic dysfunction, concomitant use of over-the-counter melatonin, pregnancy or breast feeding, a history of drug or alcohol abuse, or a score >19 on the Alcohol Use Disorders Identification Test²⁸ that was administered during screening, acute or unstable illness, and travel across three or more time zones during or up to 3 weeks before entering the protocol. In

individuals with neurologically incomplete damage to the spinal cord, determination of a lack of melatonin production was assessed through collection of an overnight urine sample. Although we expected all individuals who had neurologically complete damage (no motor function below the neurological level) to lack melatonin production, we also collected an overnight urine sample from these participants to verify an absence of melatonin production. As the majority of melatonin is produced during the night and is rapidly metabolized, such an overnight collection is a method that can be used to confirm an absence of endogenous melatonin production in individuals normally entrained to the 24-hour light:dark cycle. While the complete cycle of melatonin production is not captured with this method, due to suppression of melatonin production by room light,²⁹ it is sufficient to determine the binary presence/absence outcome of melatonin production. Two of the 12 participants who had an overnight urine collection were excluded due to the presence of significant levels of 6-sulfatoxymelatonin,³⁰ the major urinary metabolite of melatonin (assays performed by Pharmasan, Osceola, WI, USA). Both participants were clinically rated as having incomplete SCI (AIS C). Three individuals declined to participate due to a conflict between the rigors of the study and their personal life and two individuals completed screening, but were never randomized due to the completion of study funding (Fig. 1).

Figure 1 CONSORT flow diagram⁴⁵ describing the number of participants at each stage of the protocol.

At screening, participants provided demographic information and completed the following questionnaires: Pittsburgh Sleep Quality Index (overall sleep satisfaction),³¹ Morningness-Eveningness Questionnaire (chronotype),³² Beck Depression Inventory,³³ State-Trait Anxiety Index (state form only),³⁴ Caffeine Consumption Questionnaire,³⁵ and Brief Pain Inventory.³⁶ Individuals were recruited via poster advertisements, newsletters, and word-of-mouth at the VA Palo Alto Health Care System (VAPAHCS) SCI Center and the surrounding environs of the bay area. All advertising materials and all study procedures were reviewed and approved by the Stanford University Institutional Review Board. The study was listed on www.clinicaltrials.gov (NCT00507546) and was open for enrollment from July 2007 until June 2010. All procedures performed in this study conform to the principles outlined in the Declaration of Helsinki.

Eight participants were randomized to the 10-week randomized controlled trial with crossover design. All study procedures were performed in the individual's home. Participants spent weeks 1–2 in baseline, weeks 3–5 in arm 1, weeks 6–7 in washout, and weeks 8–10 in arm 2. During the 2-week baseline, there were no restrictions on a participant's sleep pattern. At-home sleep was monitored using participant-completed sleep logs and wrist actigraphy (Actiwatch-L, Minimitter, Bend, OR, USA), a useful proxy for monitoring sleep–wake patterns in individuals who do not have damage to their spinal cord,³⁷ as well as in those with lower cervical SCI.^{38,39} The sleep log was completed every morning and consisted of questions regarding the prior night of sleep. It also included a question regarding subjective sleep quality (rated on a scale of 1–9 with 9 being best) and current subjective alertness (Stanford Sleepiness Scale,⁴⁰ Likert-like scale of 1–7 with descriptors indicating 1 being most alert). During weeks 3–10, participants received a pill every night (i.e. 56 consecutive nights) 1 hour before a target bedtime. Participants in randomization group 1 received placebo during arm 1, placebo during washout, and 8 mg of ramelteon in arm 2. Participants in randomization group 2 received 8 mg of ramelteon in arm 1, placebo during washout, and placebo during arm 2. We selected the 8 mg dose and the timing of treatment as these are the clinically recommended parameters for the use of ramelteon to treat insomnia in individuals without SCI. Participants were not aware of the arm 1 – washout – arm 2 design; rather, they were informed that on any given night they would receive either placebo or drug. Ramelteon and placebo tablets were provided by Takeda Pharmaceuticals (Deerfield, IL)

and prepared by the VAPAHCS research pharmacist who determined and held the study blind. The pharmacist provided the research assistant with 3-week supplies of drug or placebo, as appropriate, for each participant. Neither the research assistants nor the principal investigator was aware of participant allocation until after all data were processed. A locked, timed pill dispenser provided a tablet 1 hour prior to the target bedtime on each night. A research assistant ensured that the pill dispenser was loaded with the correct pill (i.e. drug or placebo) and that no pills remained when the dispenser was returned. Participants were asked to report failure to take a pill. As during baseline, sleep was monitored continuously during weeks 3–10 using wrist actigraphy and sleep logs. Participants also completed quality-of-life questionnaires (RAND SF-36)^{41,42} during screening and at the end of baseline, end of arm 1, and end of arm 2.

The primary outcome measures were change in subjective (sleep log) and objective (wrist actigraphy) sleep. A secondary outcome measure was the change in quality of life (SF-36). Effects of treatment were analyzed with a Friedman test (www.vassarstats.net/). Within participant changes were analyzed with analysis of variance with *post hoc* paired *t*-tests (OriginPro8, OriginLab, Northampton, MA, USA). Within participant differences in variance were analyzed with *F*-tests. Between subject summary data are presented as median (range) whereas within subject summary data are presented as mean $\pm$ (SD).

Results

We present general characteristics of the randomized participants in Table 1. Sleep complaints in these participants ranged from self-reported difficulty in initiating or maintaining sleep, unsatisfactory sleep, and daytime sleepiness. This was corroborated with elevated scores on the Pittsburgh Sleep Quality Index (Table 1), in which scores greater than five are associated with insomnia.³¹ Sleep efficiency, as determined by actigraphy during the *ad libitum* baseline, was moderate and consistent with the subjective sleep complaints (Table 1). Seven of the eight participants had AIS A rated SCI (neurologically complete damage to the spinal cord) while one had AIS C rated SCI (neurologically incomplete). In this individual, despite the clinical rating of AIS C, the pineal was sufficiently decentralized such that there was an absence of melatonin production as assessed by an overnight urine collection.

Of the eight participants who were randomized, half were scheduled to receive the drug in arm 1 and the other half were scheduled to receive the drug in arm 2 (Fig. 1). One of the participants in the former group

Table 1 Baseline subject characteristics

Sex	7 male, 1 female
Age	55 years (37–76 years)
Race	All Caucasian
AIS	7 AIS A, 1 AIS C
Time since injury	16.5 years (0.66–38 years)
Pittsburgh Sleep Quality Index	10 (5–19)*
Morningness-Eveningness Questionnaire	21 (17–25) [†]
Beck Depression Inventory	12 (2–29) [‡]
State-Trait Anxiety Index (trait)	37 (20–69) [§]
AUDIT	2.0 (0–7) [¶]
Brief Pain Inventory – severity	3.1 (0–6)**
Brief Pain Inventory – interference	2.1 (0–5.9)**
Self-reported time in bed	8.38 hours (3–10 hours)
Self-reported typical bed time	22:52 (21:30–01:00)
Self-reported typical wake time	7:08 (4:00–8:30)
Actigraphy – two week <i>ad lib</i> baseline	
Sleep efficiency	87.0% (80.0–97.1%)
Time in bed	7.7 hours (6.1–8.4 hours)
Wake after sleep onset	56.6 minutes (13.6–101 minutes)

Continuous data are presented as median (range).

*All subjects had scores that are associated with insomnia (>5).

[†]All subjects rated as “neither” or “moderate morning types”.

[‡]Two subjects had clinically relevant levels of depressive symptomatology.

[§]Three subjects had elevated (>75% of normative data³⁴) trait anxiety.

[¶]All subjects had scores indicating non-harmful alcohol use.

**Neither pain severity or interference were elevated in any subject however, two subjects had scores >5 (out of 10) on the question referring to interference of sleep by pain.

AIS, American Spinal Injury Association (ASIA) Impairment Scale; AUDIT, Alcohol Use Disorders Identification Test.

discontinued the study in week 7 due to an unrelated hospitalization. One of the participants in the latter group was dispaneled by study personnel due to non-compliance. Another participant in the latter group discontinued for unspecified reasons in week 8. Therefore, five participants completed all aspects of the protocol. Of the five participants who completed the protocol, all study-related medications appeared to be consumed accurately.

We examined changes in both subjective and objective measures of sleep. Subjective quantification of sleep did not reveal any treatment-specific changes except for a possible effect on subjective sleep quality, wake time, and time in bed (Table 2). Follow-up *post hoc* Wilcoxon signed rank tests, however, did not indicate any difference between any two of the three groups. Individual participants had sporadic treatment-specific changes (e.g. 2000M had improved sleep quality on drug), but none of these changes were consistent among participants (Table 2). In addition to comparing the changes in mean bed time, wake time, and time in bed, we also examined the changes in the variance in these three measures, but also found no significant difference among the three conditions (Table 2).

While there was an increase in the overall amount of objectively determined sleep per night (Table 3) of 36.4

(12.8–55.1) minutes (drug) and 53.2 (36.8–64.2) minutes (placebo), these were not significant after *post hoc* analysis ($P = 0.125$, Wilcoxon signed rank tests). This also was not accompanied by a change in sleep efficiency (Table 3). Thus, there was an increase in time in bed with a consistent fractional increase in total sleep time, but this effect did not differ between the placebo and drug conditions.

We observed no significant change in any of the nine SF-36 subscale scores between baseline and the end of either arm (Friedman test, Bonferroni adjusted $\alpha = 0.005$).

Discussion

We examined the effectiveness of nightly administration of a melatonin agonist (ramelteon) in alleviating sleep problems in individuals who had neurologically complete damage to their cervical spinal cord such that they no longer had significant endogenous melatonin production. Despite the nightly use of the melatonin agonist for 3 weeks, we observed no significant change in either subjective or objective measures of sleep quality. Participants did spend a longer amount of time in bed with a sleep efficiency similar to baseline, but this occurred in both arms (placebo and drug) and was likely secondary to the demands of the protocol.

Table 2 Subjective measures of sleep during the 3-week baseline, drug, or placebo sections of the protocol

Participant code		2000M	2001M	2002M	2009M	2011M	Friedman test
Sleep latency (minutes)	Baseline	96.4 ± 61.1	18.6 ± 15.9	115 ± 49.8	35.5 ± 39.8	42.5 ± 29.3	<i>P</i> = 0.55
	Drug	59.5 ± 34.7	29.0 ± 58.0	65.0 ± 39.5*	108 ± 62.2	33.3 ± 15.1	
	Placebo	82.1 ± 55.6	22.9 ± 20.9	71.4 ± 7.4*	m.d.	34.0 ± 20.5	
Number of awakenings	Baseline	4.1 ± 2.0	1.9 ± 0.7	2.0 ± 0.7	2.5 ± 0.9	3.8 ± 1.0	<i>P</i> = 0.17
	Drug	2.4 ± 0.9*	2.6 ± 1.1*, [†]	1.0 ± 1.1*	1.6 ± 2.1	4.0 ± 1.2 [†]	
	Placebo	3.0 ± 1.2	1.7 ± 0.7	0.9 ± 1.0*	1.8 ± 1.5	3.2 ± 0.5	
Total sleep time (minutes)	Baseline	370 ± 93.3	437 ± 52.6	276 ± 90.5	473 ± 52.9	255 ± 51.0	<i>P</i> = 0.45
	Drug	366 ± 64.8	434 ± 124	397 ± 96.7*	514 ± 162	280 ± 48.7 [†]	
	Placebo	339 ± 90.1	452 ± 44.1	295 ± 218	567 ± 124	314 ± 30.0*	
Sleep quality (1–9; 9 = best)	Baseline	3.6 ± 2.1	6.6 ± 0.9	5.2 ± 1.4	5.9 ± 1.3	5.6 ± 1.5	<i>P</i> < 0.05
	Drug	6.0 ± 1.6*, [†]	6.8 ± 1.7	6.2 ± 1.7	5.0 ± 2.1	7.6 ± 1.6*	
	Placebo	4.7 ± 1.5	7.0 ± 0.8	6.6 ± 1.7	6.8 ± 0.9	8.5 ± 1.7*	
Alertness (1–7; 1 = most alert)	Baseline	3.4 ± 1.7	3.2 ± 0.7	3.6 ± 0.8	3.5 ± 0.7	2.3 ± 2.0	<i>P</i> = 0.35
	Drug	2.6 ± 1.0	2.9 ± 0.8	3.6 ± 1.3	5.7 ± 1.7*	2.0 ± 1.5 [†]	
	Placebo	3.3 ± 0.9	2.8 ± 0.6	3.1 ± 1.0	5.8 ± 1.7*	1.2 ± 0.4*	
Bed time (HH:MM)	Baseline	00:23 ± 00:55	22:25 ± 01:00	00:20 ± 00:52	21:47 ± 00:22	23:31 ± 00:20	<i>P</i> = 0.82 (avg) <i>P</i> = 0.09 (SD)
	Drug	23:53 ± 00:11*, [§]	22:30 ± 00:35 [†]	00:09 ± 00:38 [§]	21:54 ± 00:27 [†]	23:27 ± 00:05 [†]	
	Placebo	23:47 ± 00:21*, [†]	22:09 ± 00:36 [†]	23:59 ± 01:00	22:37 ± 00:54*, [†]	23:31 ± 00:06	
Wake time (HH:MM)	Baseline	06:41 ± 01:15	06:41 ± 00:31	08:01 ± 00:47	07:05 ± 01:26	05:24 ± 01:11	<i>P</i> < 0.05 (avg) <i>P</i> = 0.95 (SD)
	Drug	07:44 ± 00:27*, ^{†,§}	07:10 ± 00:32	08:41 ± 01:03	08:28 ± 01:27	06:11 ± 00:43*	
	Placebo	07:20 ± 00:48	06:56 ± 00:36	08:30 ± 01:18	09:47 ± 01:26*	06:01 ± 00:36	
Time in bed (hours)	Baseline	6.30 ± 2.00	7.78 ± 1.82	7.68 ± 1.15	8.97 ± 1.80	5.88 ± 1.32	<i>P</i> < 0.05 (avg) <i>P</i> = 0.25 (SD)
	Drug*	7.83 ± 0.500*, ^{†,§}	8.58 ± 0.800 [†]	8.43 ± 1.37	10.6 ± 1.55	6.72 ± 0.733*, [†]	
	Placebo*	7.55 ± 0.900*, [†]	8.78 ± 0.850 [†]	8.52 ± 1.67	11.2 ± 1.90*	6.48 ± 0.583 [†]	

Data are presented as mean ± SD. Statistics for changes within individual subjects are given in the subject columns and statistics for group changes are given in the far right column.

**P* < 0.05 vs. baseline, *post hoc t*-test.

[†]*P* < 0.05 vs. placebo, *post hoc t*-test.

[‡]*P* < 0.05 vs. baseline, *post hoc F*-test.

[§]*P* < 0.05 vs. placebo, *post hoc F*-test.

m.d.: missing data.

Table 3 Objective measures of sleep derived from analysis of wrist actigraphy data collected during the 3-week baseline, drug, or placebo sections of the protocol

Participant code		2000M	2001M	2002M	2011M	Friedman test
Wake after sleep onset (minutes)	Baseline	49.1 ± 28.6	101 ± 36.9	64.1 ± 46.1	20.7 ± 12.4	$P = 0.70$
	Drug	81.3 ± 0.8*	63.3 ± 27.6*	92.3 ± 54.4	24.0 ± 33.1	
	Placebo	80.1 ± 31.0*	72.8 ± 29.2*	117 ± 66.7*	20.7 ± 10.2	
Sleep efficiency (%)	Baseline	87.7 ± 6.07	80.0 ± 7.06	86.3 ± 8.57	94.4 ± 3.22	$P = 0.78$
	Drug	82.7 ± 6.18*	88.2 ± 5.20*	81.3 ± 10.1	91.5 ± 16.3	
	Placebo	82.9 ± 6.65*	86.3 ± 5.15*	79.0 ± 10.6	94.9 ± 2.41	
Total sleep time (minutes)	Baseline	329 ± 83.5	399 ± 41.3	383 ± 68.1	345 ± 42.6	$P < 0.05$
	Drug	384 ± 28.7*	473 ± 64.8*	396 ± 75.1	371 ± 102	
	Placebo	389 ± 41.5*	452 ± 36.9*	426 ± 75.0	382 ± 33.9	

Data are presented as mean ± SD. Statistics for changes within individual subjects are given in the subject columns and statistics for group changes are given in the far right column.

* $P < 0.05$ vs. baseline, *post hoc t*-test; note, due to failure of instrumentation, data are not available for subject 2009M.

Although a larger study of similar design would be necessary to conclude on the utility of melatonin replacement therapy for sleep disruption in individuals with tetraplegia, the effect sizes for the changes we observed were all relatively small (Cohen's $d < 0.3$, data not shown). This indicates that even if a larger sample was to indicate statistical significance, melatonin would likely provide only a small benefit to individuals with tetraplegia as a whole. Individual participants may have benefited from this pharmacotherapy, but the group results of this small, although tightly controlled study indicate that the use of nightly pharmacological stimulation of melatonin receptors is unlikely to be a successful strategy to treat sleep problems across individuals with neurologically complete cervical spinal cord damage.

There are several possible reasons for the lack of this agonist being effective at treating the sleep problems observed in those with cervical SCI. First, the use of exogenous melatonin in individuals with intact spinal cords and endogenous melatonin shows little if any hypnotic effect when administered at night, when endogenous melatonin is presumably being produced.²⁵ We had hypothesized that this was because of adding exogenous melatonin on top of endogenous melatonin would have little effectiveness. If the hypnotic effects of melatonin were mediated through its interaction with the SCN, it is possible that reduced sensitivity of the SCN to melatonin stimulation during the sleep period^{43,44} could negate the utility of nocturnal melatonin administration as a hypnotic. We did observe positive effects of the treatment in some of our participants, which could have been spurious or might indicate that exogenous melatonin could still be effective in a subset of individuals with cervical SCI. This might also indicate that the effects of the agonist are moderated by other

factors, such as anxiety, depression, pain, or sleep-disordered breathing (e.g. as presented in Table 1). Owing to an insufficient sample size, however, we were unable to examine this possibility. Another possibility is that the loss of endogenous melatonin production may have resulted in a decline in receptor sensitivity, leading to inadequate stimulation by the drug. Our sample size was too small to test the hypothesis that time since injury accounted for variability in response. A final possibility is that if the melatonin agonist acted through stabilization of nocturnal thermoregulation, then variability in endogenous and exogenous thermoregulation and its relationship to sleep may have affected individual responses to the drug. We have observed highly variable patterns of core body temperature regulation during sleep in individuals with SCIs (Zeitzer *et al.*, unpublished observations). It might be that only those individuals in whom core body temperature regulation during sleep is disrupted would benefit from melatonin replacement therapy. We neither examined nor controlled thermoregulatory processes in this study, although future studies should consider this as a mediator variable.

Conclusion

This randomized controlled trial indicated that pharmacological melatonin replacement therapy had little if any effect on sleep disruption in individuals with tetraplegia.

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