

SURPRISING DIFFERENCES FOUND IN HOW SLEEP MEDICATIONS INCREASE DEMENTIA RISK FOR SOME, PROTECT OTHERS

Plus, Two Treatment Trials Tackle Sleep Problems in People with Dementia

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Other studies reported at AAIC 2019 looked at the use of sleep medicines in mid-life in diverse groups and found surprising differences in their impact on later-life risk of dementia.

Sleep disturbances are common among people with Alzheimer's and other dementias, including changes in sleep schedule and restlessness/wandering during the night. It has been reported that up to 45% of people with dementia may have sleep problems. Many people with Alzheimer's wake up more often and stay awake longer during the night. Those who cannot sleep may wander, be unable to lie still, or yell or call out, disrupting the sleep of their caregivers. Experts estimate that in late stages of Alzheimer's, individuals spend about 40% of their time in bed at night awake and a significant part of their daytime sleeping.

Disruption in the body's sleep-wake cycle can lead to more behavioral problems, though [effective coping strategies](#) exist. At the same time, research suggests that poor sleep habits in mid- and late- life may increase the risk for developing dementia.



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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2019

SURPRISING DIFFERENCES FOUND IN HOW SLEEP MEDICATIONS INCREASE DEMENTIA RISK FOR SOME, PROTECT OTHERS

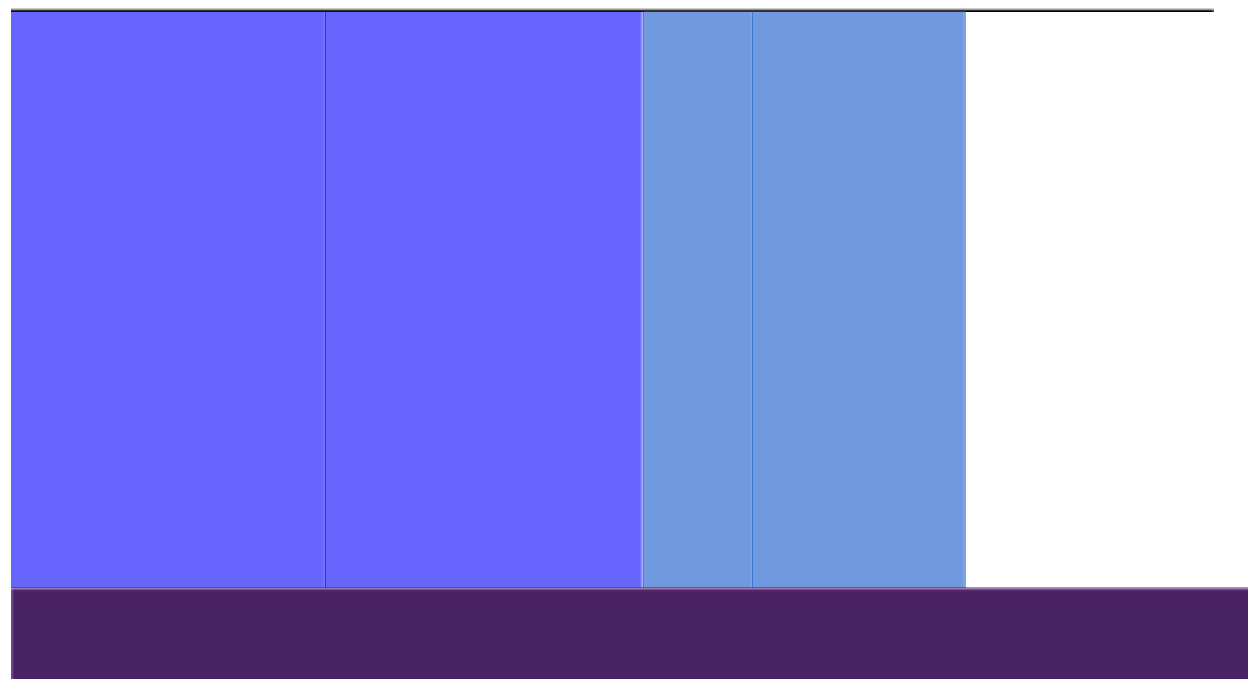
Plus, Two Treatment Trials Tackle Sleep Problems in People with Dementia

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New sleep-related research findings reported at AAIC 2019 include:

- • More frequent use of sleep medications may be associated with higher risk of dementia, especially in older white adults compared to older black adults who experienced reduced risk.

Whether the change in risk is due to the medications or sleep problems is not yet known.
- • Men over 65 years of age who used sleep medications were at increased risk of developing Alzheimer's dementia, as were some women. However, women who used sleep medications but did not have interrupted sleep had a reduced risk.
- • A Phase 2 pilot study found evidence that the experimental drug lemborexant (Eisai) improved total sleep time and reduced sleep fragmentation for some persons living with mild to moderate Alzheimer's disease dementia.
- • A personalized program to reset an individual's optimal bedtime and wake time, combined with physical activity, improved sleep quality in older adults with mild cognitive impairment.

“Research has shown us that not getting enough sleep because of insomnia or sleep apnea may result in problems with memory and thinking, and increase the risk for Alzheimer's-related brain changes,” said Maria C. Carrillo, PhD, Alzheimer's Association chief science officer. “The new findings reported at AAIC 2019 are important because disrupted sleep patterns not only put the overall health of people with dementia at further risk, they may also worsen their memory loss and disrupted thinking.”

Frequent Use of Sleep Medications May Increase Dementia Risk, But Differently by Race

Researchers at the University of California, San Francisco, overseen by Kristine Yaffe, MD, professor of psychiatry, neurology and epidemiology, evaluated data of 3,068 black and white (45% of women and 33% of men, African American) community-dwelling older adults age 70–79 at baseline without dementia who were enrolled in the Health, Aging and Body Composition study. The study participants were followed to see if they

would develop dementia over 15 years using an algorithm that incorporates medical records, information on medication use and assessment of cognition.

A total of 147 (4.8%) participants reported taking sleep medications “sometimes”; 172 (5.6%) reported “often” or “almost always.” Thirty-four (34, 2.7%) blacks and 138 (7.7%) whites reported taking sleep medications “often” or “almost always.”

The researchers found that study participants who reported taking sleep medications “often” or “almost always” were 43% more likely to develop dementia compared to those who reported “never or rarely” taking sleep medications. Increased risk for dementia among frequent sleeping medication users was only observed among white adults in the study.

No increased risk was found for people taking sleep medications “sometimes.” There was no difference reported in men versus women.

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“Based on our findings, we recommend that clinicians make more effort to be aware of their patients’ sleep problems including use of sleep aids,” said lead study author Yue Leng, PhD, University of California, San Francisco. “In particular, clinicians may need to be more cautious about prescribing sleep medications to older adults who are at high risk for dementia. There are non-pharmacological sleep treatment options that should be considered.”

Sleep Medications May Impact Dementia in Women and Men Differently

An observational study of 3,656 adults 65 and older (57.8% female) from the Cache County Study on Memory and Aging (CCSMA) evaluated if use of sleep medications was associated with an increased risk of developing Alzheimer’s, and whether risk differed between men and women.

The study found that men who reported use of sleep medication had a 3.6 times increased risk of developing Alzheimer’s disease compared to those who did not use sleep medications. In women, the risk varied by whether or not they experienced sleep disturbances. Women who used sleep medications but did not report sleep disturbances were at nearly four times greater risk for developing Alzheimer’s. Women who said they had sleep disturbances and used sleep medications were at a 35.2% reduced risk of developing Alzheimer’s.

“More research is needed to determine and understand the mechanisms underlying the differences between men and women, and the cognitive impact of using sleep medications,” said Elizabeth Vernon, MS, Utah State University, who presented the data at AAIC 2019.

Phase 2 Study Shows Potential Drug May Help Circadian Rhythms

In a four-week randomized controlled trial, lemborexant (LEM) appeared to benefit individuals with mild to moderate Alzheimer’s dementia who experience irregular sleep-wake rhythm

disorder (ISWRD), a circadian rhythm sleep disorder where an individual takes numerous naps in a 24-hour period and is not able to sustain a consolidated sleep at night. LEM is currently under review with the U.S. Food and Drug Administration (FDA) as a potential drug for treatment of insomnia for adults who have difficulty falling asleep and staying asleep.

In this small Phase 2 study, 62 participants age 60 to 90 with ISWRD and mild to moderate Alzheimer's were randomized to receive various doses of LEM (2.5 mg, 5 mg, 10 mg, 15 mg) or placebo. The study participants wore a device to track their sleep and awake times. These data were supplemented by a sleep diary completed daily by caregivers. Researchers analyzed the strength of circadian signals — the internal biological clock that regulates a person's sleepiness and alertness, as well as daytime and nighttime activity levels, and sleep time.

The study found lower nighttime activity levels ($p < 0.05$) for individuals in the LEM 5 mg ($n=13$) and LEM 15 mg ($n=12$) groups versus placebo ($n=12$). There were statistical trends toward less sleep fragmentation and higher total sleep time. No serious adverse events were reported, and cognitive function did not appear to worsen.

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“We know that sleep disturbances are a significant problem for persons with Alzheimer's disease and their caregivers,” said Margaret Moline, PhD, Eisai Inc., Woodcliff Lake, NJ. “This pilot study provides preliminary evidence that lemborexant may help improve circadian rhythms to improve sleep patterns. This may be a promising treatment for sleep problems in individuals with Alzheimer's.”

Resetting the Biological Clock to Improve Sleep Quality

Researchers at the University of British Columbia, Vancouver, Canada conducted a 24-week randomized controlled clinical trial to examine whether improving circadian regulation by resetting the biological clock (“chronotherapy”) in older adults with mild cognitive impairment can help improve sleep quality and cognitive function.

The 96 study participants (average age 71; 57% female; $n=48$ per group) were randomized to either the chronotherapy intervention group or the waitlist plus education control group. The intervention included:

- ● four once-weekly general sleep hygiene education classes, followed by
- ● 20 weeks of individually-timed bright light therapy, and
- ● bi-weekly, individually-tailored physical activity counseling phone calls, plus
- ● a consumer-available physical activity tracking device.

Primary outcomes were sleep quality measured objectively using an activity monitor and subjectively with a sleep quality index (Pittsburgh Sleep Quality Index). Sleep quality was observed at baseline, 12 weeks and 24 weeks.

Participants in the intervention group significantly improved objectively measured sleep efficiency (p=0.03), sleep fragmentation (p=0.02), wake after sleep onset (p=0.04) and subjective sleep quality (p=0.03). The improvements in the intervention group were seen at 12 weeks for the objectively measured outcomes and at 24 weeks for the subjectively measured outcomes compared to the control group.

“Our results provide new evidence that a personalized behavioral medicine approach may help realign the biological clock to improve sleep quality in adults with mild cognitive impairment,” said Ryan Falck, MSc, University of British Columbia, Vancouver. “Our hope is that, by improving sleep quality, we can contribute to preventing further cognitive decline in older adults with mild cognitive impairment. More research is needed to test this possibility.”

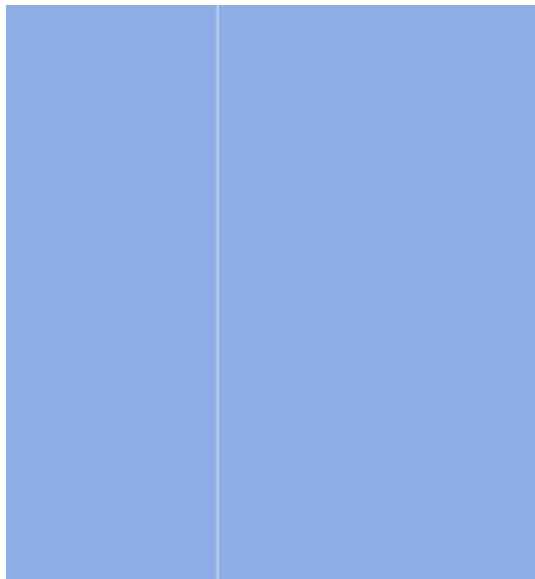
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About AAIC

The Alzheimer’s Association International Conference (AAIC) is the world’s largest gathering of researchers from around the world focused on Alzheimer’s and other dementias. As a part of the Alzheimer’s Association’s research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

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The Alzheimer’s Association is the leading voluntary health organization in Alzheimer’s care, support and research. Our mission is to eliminate Alzheimer’s disease through the advancement of research, to

provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call 800.272.3900.

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- • Yue Leng, PhD, et al. Sleep Medication Use and Risk of Dementia in a Biracial Cohort of Older Adults. (Funder(s): U.S. National Institute on Aging; Global Brain Health Institute; Global Brain Health Institute; Alzheimer's Association; Alzheimer's Society)
- • Elizabeth Vernon, MS, et al. Sex Differences in the Association between Sleep Medications and Risk of Alzheimer's Disease: The Cache County Study. (Funder(s): U.S. National Institute on Aging)
- • Margaret Moline, PhD, et al. Response to Treatment with Lemborexant: Subjects with Irregular Sleep-Wake Rhythm Disorder and Alzheimer's Disease Dementia. (Funder(s): Eisai Inc., Purdue Pharma)
- • Ryan Falck, MSc, et al. Improving Sleep Quality in Mild Cognitive Impairment through Chronotherapy and Physical Activity: A Randomized Controlled Trial. (Funder(s): Alzheimer Society of Canada; Vancouver Coastal Health Research Institute)

*** AAIC 2019 news releases may contain updated data that does not match what is reported in the following abstracts.

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Sleep Medication Use and Risk of Dementia in a Biracial Cohort of Older Adults [Monday Featured Research Session, July 15, 2:40 p.m. PT, F2-05-03]

Background: The use of sleep medications is common among older adults. However, little is known about the association between sleep medication use and subsequent risk of dementia, whether this is independent of sleep quality, and if there are differences by race.

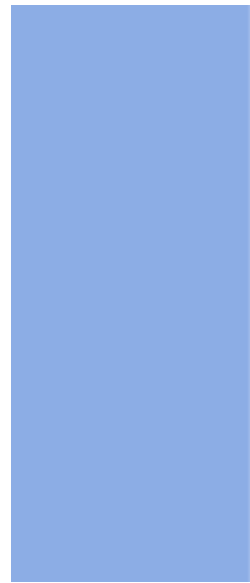
Method: We studied 3068 black and white community-dwelling older adults without dementia (aged 70-79 years) enrolled in the Health, Aging, and Body Composition study. At baseline, the use of sleep medications was evaluated based on participants' responses to the following question: "Do you take sleeping pills or other medication to help you sleep" with the following responses: "Never (0)", "Rarely (1/month or less)", "Sometimes (2-4/month)", "Often (5-15/month)" or "Almost Always (16-30/month)". Participants were followed for incident dementia over 15 years based on dementia medication use, hospitalization records, or a ≥ 1.5 SD decline in race-specific global cognition score. We examined the association between sleep medication use and dementia risk using Cox proportional hazards models, and stratified the analysis by race and sex.

Result: A total of 147 (4.8%) participants reported taking sleep medications "sometimes", and 172 (5.6%) reported "often" or "almost always". 34 (2.7%) blacks and 138 (7.7%) whites reported taking sleep medications "often" or "almost always". After adjustment for demographics, socio-demographic status, smoking, alcohol use, body mass index, depressive symptoms, physical activity, comorbidities and APOE4 genotype, those who reported taking sleep medications often or more were 43% [hazard ratio (HR) = 1.43, 95%CI 1.01-2.02] more likely to develop dementia, compared to those who reported never or rarely taking sleep medications. We did not find an increased dementia risk among those who reported taking sleep medications sometimes. The association remained after further adjustment for nocturnal sleep duration and disturbances. The increased dementia risk among the frequent users was only observed among the whites [HR= 1.79, 95% CI:1.21-2.66; for blacks, HR= 0.84 (0.38-1.83); p for interaction=0.048]. The association did not differ by sex.

Conclusion: Frequent use of sleep medications was associated with increased long-term risk of dementia, particularly among older white adults. Further studies are needed to examine the cognitive effects of different types of sleep medications and to understand potential mechanisms.

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Sex Differences in the Association between Sleep Medications and Risk of Alzheimer's Disease: The Cache County Study [Monday poster, July 15, P2-557]

Background: Sleep medications such as benzodiazepines, tetra- or tri-cyclics, antihistamines, and certain antidepressants are commonly prescribed to older adults. Adverse events have been reported with use of some of these medications such as memory problems and increased risk of falls. Several classes of sleep medication are known to disrupt the sleep-wake cycle and result in decreases in slow-wave sleep and Rapid Eye Movement (REM) sleep, which are important for memory consolidation. We examined the association between use of sleep medications and risk of Alzheimer's Disease (AD) in a community sample of older adults in Cache County, Utah and if this association varied by sex.

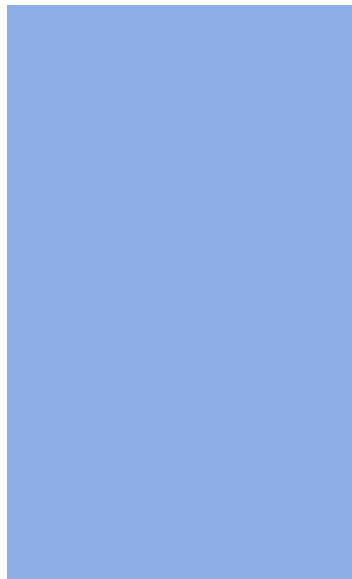
Method: 3,656 participants without dementia at baseline (57.8% female) participated in a longitudinal study that assessed risk factors for AD and cognitive decline. Dementia screenings and assessments were conducted in four triennial waves spanning 12 years to determine dementia and non-case (screened or evaluated negative for cognitive impairment). Dementia was determined based on a clinical assessment and diagnosis of AD was made using DSM-III-R and NINCDS-ADRDA criteria. Medication history was obtained via interview and visual inspection of all medications. Use of any sleep medication (time-varying) and time to dementia or right censoring was modeled using Cox proportional hazards regression in separate models for males and females. Covariates tested were sleep disturbance, depression status, age, presence of APOE E4 allele, and educational attainment.

Result: In men, use of sleep medication was associated with 3.6 times increased risk of developing AD (HR=3.604, $p = 0.0001$) compared to those who did not use sleep medications. In women, risk of AD varied by endorsement of a sleep disturbance: women who did not endorse a sleep disturbance but used sleep medications were nearly 4 times at greater risk for developing AD (3.916; $p = .0001$) whereas those without sleep disturbance and who used sleep medications were at a 35.2% reduced risk of developing AD.

Conclusion: Caution is warranted in prescribing sleep medications for older adults, though effects in AD risk vary by sex and endorsement of sleep disturbance. Further research is needed to determine the mechanisms underlying the observed sex differences.

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Response to Treatment with Lemborexant: Subjects with Irregular Sleep-Wake Rhythm Disorder and Alzheimer's Disease Dementia [Monday poster, July 15, P2-617]

Background: Irregular Sleep-Wake Rhythm Disorder (ISWRD) is a circadian rhythm sleep disorder characterized by the irregular distribution of sleep bouts across the 24-hour period rather than consolidated sleep at night. ISWRD symptoms are common in patients with Alzheimer's disease dementia (AD). Here we describe results from a Phase 2 proof-of-concept study for the dual orexin receptor antagonist lemborexant (LEM) in subjects with ISWRD and AD.

Methods: The study (NCT03001557) was a randomized, double-blind, multicenter, global, placebo (PBO)- controlled parallel group trial. Subjects (aged 60-90y) met DSM-5 criteria for ISWRD and mild-moderate AD (MMSE 10-26). Subjects wore an actigraph (MotionWatch 8, CamNtech) continuously on the non-dominant wrist for ~14 days to qualify and for 28 days during PBO or LEM (2.5mg [LEM2.5], 5mg [LEM5], 10mg [LEM10], or 15mg [LEM15]) treatment. Actigraph data were collected in 30sec epochs and scored using an algorithm as sleep or wake. Actigraph data were supplemented by a sleep

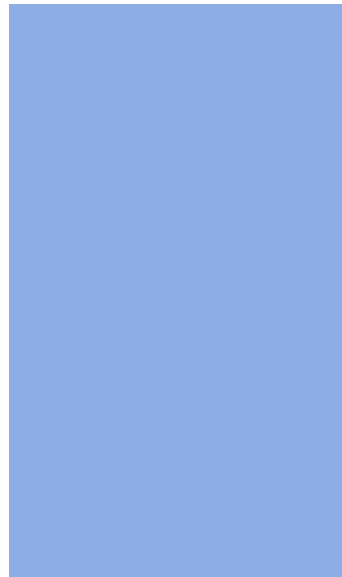
diary completed daily by caregivers. Analyses of circadian parameters included Relative Amplitude (RA), reflecting the strength of the circadian signal and differentiation between daytime and nighttime activity levels, and least active 5 hours of the day (L5; higher values indicate restlessness). Sleep-related endpoints included Sleep Fragmentation Index (SFI) and Total Sleep Time (TST). The MMSE and ADAS-cog were administered prior to and at the end of treatment to assess for change in cognitive function.

Results: 62 subjects were randomized and provided data for circadian, nighttime, and daytime parameters. Compared with baseline values, LEM5 (n=13) and LEM15 (n=12) led to a significantly higher RA and lower nocturnal activity levels (counts in the L5) versus PBO (P<0.05) during the four weeks of treatment. Additionally, these doses were associated with numerically lower SFIs and higher TST. LEM was well tolerated; adverse events (AEs) were similar to those in the insomnia program. No subjects discontinued treatment. There were no treatment-emergent serious AEs or worsening of cognitive function.

Conclusions: This pilot study provides preliminary evidence that LEM improves both circadian rhythm variables and nocturnal sleep variables in subjects with ISWRD and AD. Further analyses will determine characteristics of treatment responders. Support: Eisai Inc., Purdue.

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Improving Sleep Quality in Mild Cognitive Impairment through Chronotherapy and Physical Activity: A Randomized Controlled Trial [Monday poster, July 15, P2-619]

Background: Poor sleep quality is common among older adults with Mild Cognitive Impairment (MCI) and may contribute to their increased risk for dementia. Chronotherapy is a set of intervention strategies which can improve sleep quality by strengthening the entrainment of the biological clock to the solar light-dark cycle, and includes strategies such as: 1) bright light therapy (BLT); 2) physical activity (PA);

and 3) good sleep hygiene. We therefore aimed to examine the efficacy of a multimodal, personalized chronotherapy intervention to improve sleep quality among older adults with MCI.

Method: This study was a 24-week randomized controlled trial (RCT; NCT02926157) wherein 96 older adults (65+ years) with MCI were randomized to either: 1) a multimodal personalized chronotherapy group (INT); or 2) a waitlist plus education control group (CON). Participants allocated to the INT (Figure 1) received four once-weekly, general sleep hygiene education classes, followed by 20 weeks of 1) individually-timed BLT; and 2) bi-weekly, individually-tailored PA counselling phone calls in conjunction with receiving a consumer-available PA tracker—the Fitbit® Flex™. Our primary outcomes were objectively measured sleep quality (i.e., sleep efficiency, sleep duration, sleep fragmentation, and sleep latency) using the MotionWatch8®, and subjectively measured sleep quality using the Pittsburgh Sleep Quality Index (PSQI). Sleep quality was observed at baseline, 12 weeks, and 24 weeks.

Result: Table 1 characterizes the 96 participants (mean age of 71 years; 57% female; n= 48 per group) included in the trial and our intention-to-treat analyses. We found a significant group x time interaction for objectively measured sleep fragmentation ($F[2,139.31]= 5.01$; $p< 0.01$) and also for PSQI score ($F[2,126.56]= 3.76$; $p= 0.03$) (Table 2). Post-hoc analyses indicate that the INT: 1) maintained sleep fragmentation while CON worsened at 12 weeks (estimated mean difference: -3.16 ± 1.04 ; $p< 0.01$); and 2) had improved PSQI score compared to CON at both 12 weeks (estimated mean difference: -1.46 ± 0.47 ; $p< 0.01$) and 24 weeks (estimated mean difference: -1.58 ± 0.74 ; $p= 0.04$).

Conclusion: Our results provide novel evidence that a multimodal personalized chronotherapy approach may promote both objective and subjective aspects of sleep quality in older adults with MCI.

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