Sleeping pill found to reduce levels of Alzheimer's proteins

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Sleep disturbances can be an early sign of Alzheimer's disease. Many people eventually diagnosed with Alzheimer's start experiencing difficulty falling and staying asleep years before cognitive problems such

as memory loss and confusion emerge. It's a vicious cycle: Alzheimer's disease involves changes to the brain that disrupt sleep, and poor sleep accelerates harmful changes to the brain.

Researchers at Washington University School of Medicine in St. Louis have identified a possible way to help break that cycle. A small, two-night study has shown that people who took a sleeping pill before bed experienced a drop in the levels of key Alzheimer's proteins—a good sign, since higher levels of such proteins tracks with worsening disease.

The study, which involved a sleeping aid known as suvorexant that is already approved by the Food and Drug Administration (FDA) for insomnia, hints at the potential of sleep medications to slow or stop the progression of Alzheimer's disease, although much more work is needed to confirm the viability of such an approach. The study is published on April 20 in *Annals of Neurology*.

"This is a small, proof-of-concept study. It would be premature for people who are worried about developing Alzheimer's to interpret it as a reason to start taking suvorexant every night," said senior author Brendan Lucey, MD, an associate professor of neurology and director of Washington University's Sleep Medicine Center. "We don't yet know whether long-term use is effective in staving off cognitive decline, and if it is, at what dose and for whom. Still, these results are very encouraging. This drug is already available and proven safe, and now we have evidence that it affects the levels of proteins that are critical for driving Alzheimer's disease."

Suvorexant belongs to a class of insomnia medications known as dual orexin receptor antagonists. Orexin is a natural biomolecule that promotes wakefulness. When orexin is blocked, people fall asleep. Three orexin inhibitors have been approved by the FDA, and more are in the pipeline.

Alzheimer's disease begins when plaques of the protein amyloid beta start building up in the brain. After years of amyloid accumulation, a second brain protein, tau, begins to form tangles that are toxic to neurons. People with Alzheimer's disease start experiencing cognitive symptoms such as memory loss around the time tau tangles become detectable.

Lucey and colleagues were among the first to show in people that poor sleep is linked to higher levels of both amyloid and tau in the brain. The question remains as to whether good sleep has the opposite effect—a reduction in amyloid and tau levels, and a halt in or reversal of the progress of Alzheimer's disease—but mouse studies with orexin inhibitors have been promising.

As a first step to assess the effect of orexin inhibitors on people, Lucey and colleagues recruited 38 participants ages 45 to 65 and with no cognitive impairments to undergo a two-night sleep study. The participants were given a lower dose (10 mg) of suvorexant (13 people), a higher dose (20 mg) of suvorexant (12 people) or a placebo (13 people) at 9 p.m. and then went to sleep in a clinical research unit at Washington University. Researchers withdrew a small amount of cerebrospinal fluid via spinal tap every two hours for 36 hours, starting one hour before the sleeping aid or placebo was administered, to measure how amyloid and tau levels changed over the next day and a half.

Amyloid levels dropped 10% to 20% in the cerebrospinal fluid of people who had received the high dose of suvorexant compared to people who had received placebo, and the levels of a key form of tau known as hyperphosphorylated tau dropped 10% to 15%, compared to people who had received placebo. Both differences are statistically significant. There was not a significant difference between the people who received a low dose of suvorexant and those who received the placebo.

By 24 hours after the first dose, hyperphosphorylated tau levels in the high-dose group had risen, while amyloid levels remained low compared to the placebo group. A second dose of suvorexant, administered on the second night, sent the levels of both proteins down again for people in the high-dose group.

"If we can lower amyloid every day, we think the accumulation of amyloid plaques in the brain will decrease over time," Lucey said. "And hyperphosphorylated tau is very important in the development of Alzheimer's disease, because it's associated with forming tau tangles that kill neurons. If you can reduce tau phosphorylation, potentially there would be less tangle formation and less neuronal death."

The study is preliminary, since it only looked at the effect of two doses of the drug in a small group of participants. Lucey has studies underway to assess the longer-term effects of orexin inhibitors in people at higher risk of dementia.

"Future studies need to have people taking these drugs for months, at least, and measuring the effect on amyloid and tau over time," Lucey said. "We're also going to be studying participants who are older and may still be cognitively healthy, but who already have some amyloid plaques in their brains. This study involved healthy middle-aged participants; the results may be different in an older population.

"I'm hopeful that we will eventually develop drugs that take advantage of the link between sleep and Alzheimer's to prevent cognitive decline," he continued. "We're not quite there yet. At this point, the best advice I can give is to get a good night's sleep if you can, and if you can't, to see a sleep specialist and get your sleep problems treated."

More information: Brendan P. Lucey et al, Suvorexant acutely decreases tau phosphorylation and Aβ in the human CNS, *Annals of*

Neurology (2023). DOI: 10.1002/ana.26641