



Melatonin

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Melatonin is a hormone produced by a specialized gland called the pineal, which is located close to the brain. It acts throughout the body and the brain and regulates our sleep-wake cycles, also called circadian rhythms. Melatonin is commonly used to treat insomnia in adults. As we age, we make less melatonin, a process thought to account for disrupted and disordered sleep in older adults. Melatonin production is particularly impaired in Alzheimer's disease and other causes of dementia. Melatonin is available as a supplement as is generally considered a safe treatment in healthy adults with some evidence that it can modestly regulate circadian rhythm and/or improve sleep, which might theoretically lead to long-term protection against aging and Alzheimer's. However, other treatments for insomnia may be more effective [1] and clinical experts have recommended against the use of melatonin for elderly people with dementia [2].

EVIDENCE AND POTENTIAL BENEFIT FOR BRAIN HEALTH

Rated 2/4 based on 2/4 evidence

Preclinical studies suggest melatonin may inhibit neurodegenerative processes, but small clinical trials have shown mixed results on cognitive function in healthy adults.

Randomized controlled trials: Some studies in humans have shown beneficial effects of melatonin on cognitive functions, while others have not. In a double-blind randomized controlled trial enrolling only 26 healthy older adults, 1 mg of melatonin taken daily for 4 weeks improved sleep latency, feelings of restedness, and verbal memory (i.e., California Verbal Learning Test scores), with slight non-significant improvements in other cognitive tests [3]. A single-blind placebo-controlled trial enrolling 50 healthy young men showed that a single oral dose of 3 mg melatonin enhanced recognition memory acquisition under stress, but not after stress [4]. In another randomized controlled trial of 10 healthy volunteers, application of 12.5% melatonin cream on 80% of body surface did not result in significant effects on cognitive parameters after 36 hours [5].

Delirium is a confused state in elderly adults that includes changes in perception, mood, attention and sleep. It is not only a risk factor for dementia but also for mortality. Melatonin treatment for delirium has both positive and negative results in humans. For instance, in a few clinical trials in elderly adults, melatonin treatment significantly lowered the risk of delirium [6; 7]. However in a clinical trial of 452 patients with hip fractures, treatment with melatonin after surgery did not reduce the incidence of delirium [8]. According to a [2015 American Geriatrics Society](#) clinical guideline, melatonin has insufficient evidence to consider its use for delirium.



Biology: Results from multiple preclinical studies suggest that melatonin can reduce neurodegenerative processes and improve cognitive function through various mechanisms. Neurogenesis is the growth and proliferation of nervous tissue in the hippocampus, an area of the brain most responsible for learning and memory. Neurogenesis decreases with age and is reduced in disorders such as depression and Alzheimer's disease. In animal studies, melatonin supplementation stimulated the creation of new neurons and promoted cell survival in the hippocampus of aged mice. However, after 12 months of melatonin treatment, there was no effect in cell proliferation or survival, indicating that melatonin may delay, but not stop the decline of neurogenesis [9].

Circadian rhythms regulate human sleep-wake patterns through hormonal release and other bodily functions. Disturbances in sleep-wake cycles have been associated with an increased risk of dementia [10]. Melatonin is a hormone that is directly involved in the regulation of circadian rhythm but has been shown to decrease in sufficiency with age. In animal studies, it is recognized as a possible treatment that may significantly improve circadian rhythm dysfunction and sleep impairment. In small clinical trials, some modest benefits to sleep and circadian rhythm have been reported but, overall, the evidence is not convincing. In sleep disorder summaries and guidelines from the [US Department of Health & Human Services](#), the [American Academy of Sleep Medicine](#), and the [Agency for HealthCare Research & Quality](#), melatonin treatment was not found to be effective in managing sleep disorders due to publication bias and insufficient data. A 2008 clinical guideline for chronic insomnia in adults argued that melatonin should be discouraged as a treatment of insomnia because other, more effective and well-studied drugs, may be available [1].

Experiments in animal models of Alzheimer's disease suggest that melatonin may prevent or significantly reduce the production and accumulation of [Amyloid- \$\beta\$](#) plaques and tangles in the hippocampus and frontal cortex [11; 12], two of the hallmarks of Alzheimer's disease. Also, in preclinical animal studies, it has been suggested that melatonin helps to promote cell energy production [13; 14] and inhibits damage and degeneration from oxidative stress [15]. None of these effects have yet been proven to occur in humans.

APOE4 carriers: In an in vitro experiment, melatonin treatment in the presence of APOE4 resulted in the inhibition of amyloid- β fibril formation, a component of Alzheimer's pathology. In addition, melatonin prevented the neurotoxicity mediated by amyloid- β and APOE4 [11]. However, no other studies have confirmed this initial finding and no clinical studies of any kind in humans have reported that melatonin may have different effects in APOE4 carriers versus non-carriers. For more information on what the APOE4 gene allele means for your health, read our [APOE4 information page](#).



For Dementia Patients

In a 2015 American Academy of Sleep Medicine Clinical Practice Guideline, recommendations were made against the use of melatonin and discrete sleep-promoting medications for elderly people with dementia due to increased risks of falls and other adverse events [2].

Randomized Controlled Trials: Clinical trials do not report that melatonin can slow disease progression or improve cognitive function in patients with dementia or mild cognitive impairment. There may be some slight benefits to patients through melatonin treatment of sleep deprivation and “sun-downing”, which involves late-afternoon restlessness, agitation, and mood fluctuations. However in human trials, there is conflicting evidence on its effectiveness. For instance, a 2014 Cochrane meta-analysis of 2 randomized controlled trials including 209 mild-to-severe Alzheimer’s participants concluded that there was no evidence that melatonin supplementation improved any sleep disturbances [16]. A meta-analysis of 7 studies including 520 patients with dementia, however, concluded that melatonin therapy improved sleep efficacy and extended total sleep time. Yet there was no evidence if these improvements impacted cognitive function [17]. A more recent but smaller meta-analysis of patients with Alzheimer’s and other dementias (including 176–279 patients, depending on the outcome measure of interest) concluded that there are no significant benefits of melatonin on cognitive scores (e.g., MMSE and ADAS-Cog) or on the majority of actigraphic and subjective measures of sleep [18]. Some studies on melatonin have been criticized for bias so the discrepant conclusions might be due to the strict quality standards enforced by Cochrane meta-analyses.

SAFETY

Rated 3/4

Evidence reviews by the [AHRQ \(Agency for Healthcare Research and Quality\)](#), the [American Academy of Sleep Medicine](#) and numerous clinical trials suggests that melatonin supplementation is safe for most healthy people for short-term use (up to two years) [1; 16; 17]. The American Academy of Sleep Medicine, however, recommends against the use of melatonin and discrete sleep-promoting medications for demented elderly patients due to increased risks of adverse events [2]. Although many healthy people have used it for periods longer than two years, the risks or benefits from long-term use have not been well studied. Melatonin derived from animal pineal glands should be avoided as it may be contaminated with viruses [19].

Reports of serious adverse effects of melatonin supplementation are rare but include nausea, drowsiness, decreased blood flow, and lower body temperature (i.e., hypothermia) [20]. Melatonin may worsen symptoms of orthostatic hypotension, a blood-pressure condition common in older adults [21]. Melatonin may also be unsafe in people with the following conditions: bleeding disorders, diabetes, depression, autoimmune diseases,



seizure disorders, and transplant recipients. In elderly patients with dementia, melatonin treatment has also been shown to worsen caregiver ratings of patient mood [22].

Melatonin may reduce the effects of nifedipine and increase the effects of warfarin. Caffeine and fluvoxamine may increase the effects of melatonin [[Drugs.com](https://www.drugs.com)]. Melatonin may also alleviate the sleep disruption caused by drugs such as beta-blockers and benzodiazepines that alter melatonin production [23; 24; 25].

HOW TO USE

Melatonin is most commonly marketed as a sleep aid dietary supplement. It is available over-the-counter in the U.S. and Canada as a liquid, tablet, pill, and transdermal patch. As a sleep-aid, melatonin is often taken orally in doses of 0.3 to 5 mg per day before bed; the most effective dose will vary from person to person and should only be taken as advised by a physician. Length of treatment is also variable depending on the condition it is used to treat, but can range from a few days (for jet lag) to nine months (for trouble falling asleep).

Melatonin was once derived from bovine pineal glands, which carried the risk of it being contaminated with viruses [19]. Currently, melatonin supplements are made synthetically and do not have the contamination risk.

As with most supplements, there can be uncertainty of quality of the content. Several organizations offer independent testing of supplement quality to earn “seals-of-approval.” Quality testing and important facts about supplements are offered by the [NIH Office of Dietary Supplements](https://www.nih.gov/od/food-supplements/).

Some prescription drugs act on melatonin receptors but should have greater efficacy than melatonin itself. Ramelteon is a synthetic drug that acts on melatonin receptors and is approved for insomnia related to difficulty of sleep onset. Circadin is a prolonged-release form of melatonin designed to mimic the pharmacokinetics of endogenously produced melatonin. It has been reported to improve morning alertness as well as quality-of-sleep, quality-of-life, and sleep latency in patients with primary insomnia. Two other melatonin receptor agonists are available: agomelatone can modestly help treat depression and tasimelteon is used for circadian rhythm sleep disorders [26].

WHAT'S THE FUTURE?

There is a great need for improving epidemiology and large-scale randomized trials to evaluate the safety of long-term melatonin use and its potential ability to prevent cognitive decline and dementia, but few trials or studies appear to be underway. Numerous studies are underway, however, to examine melatonin for delirium. There is also an on-going Rozerem™ trial that is examining the synthetic drug, Ramelteon, in people with traumatic



brain injury. More information about these and other clinical trials, including many that are evaluating melatonin for insomnia, can be found at clinicaltrials.gov.

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