

*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

## Melatonin

### Evidence Summary

Melatonin is a safe treatment in healthy adults, with some evidence that it can modestly regulate circadian rhythm and/or improve sleep, but it is not recommended for dementia patients.

**Neuroprotective Benefit:** Small clinical studies of melatonin treatment show mixed results on cognitive function in healthy adults. In dementia patients, melatonin does not significantly improve cognitive function and its risks may outweigh the benefits.

**Aging and related health concerns:** There is little direct evidence to suggest that melatonin supplementation can slow aging or delay death although, theoretically, the benefits on circadian rhythm may yield long-term anti-aging benefits. Some benefits are suggested for cancer and cardiovascular disease while potential harms are suggested for diabetes.

**Safety:** Melatonin is considered safe for most healthy adults but a few contraindications are known and long-term use has not been extensively studied. Recommendations against the use of melatonin have been made for elderly patients with dementia due to increased risks of falls and other adverse events.

## What is it?

In humans and other animals, melatonin is a hormone produced by the pineal gland located in the brain. It acts in various ways throughout the body and regulates sleep-wake cycles, also known as circadian rhythms. As we age, we make less melatonin, a process thought to account for disrupted and disordered sleep in older adults. As a result, melatonin is commonly used to treat sleep deprivation and sleep disorders in adults. Several drugs are available to act on melatonin receptors as well (described in the sources & dosing section).

**Neuroprotective Benefit:** Small clinical studies of melatonin treatment show mixed results on cognitive function in healthy adults. In dementia patients, melatonin does not significantly improve cognitive functions and its risks may outweigh the benefits.

### Types of evidence:

- No randomized controlled trials on the direct benefits of melatonin to dementia prevention
- 4 meta-analyses of melatonin treatment in dementia patients with sleep deprivation, with mixed conclusions
- 2 reviews/guidelines from the US Department of Health & Human Services and the American Academy of Sleep Medicine
- Numerous preclinical studies on possible mechanisms of action

Prevention of dementia/cognitive aging (human research): Although evidence from preclinical animal experiments suggests melatonin supplementation may prevent Alzheimer's disease and dementia, currently there is no human evidence to support this.

Although no studies have examined whether melatonin can prevent dementia, some studies report beneficial effects of melatonin on cognitive functions. In a double-blind randomized controlled trial enrolling 26 healthy older adults, 1 mg of melatonin daily for 4 weeks improved feelings of restedness and verbal fluency scores [[Peck et al., 2004](#)]. A single-blind placebo-controlled trial of 50 healthy young men showed that a single oral dose of 3 mg melatonin enhanced recognition memory of objects encoded under stress, but not of objects encoded in the absence of stress [[Rimmele et al., 2009](#)]. In another randomized controlled trial of 10 healthy volunteers, application of melatonin cream did not result in significant effects on cognitive parameters [[Scheuer et al., 2016](#)].



*Treatment of dementia or mild cognitive impairment (human research):*

Clinical trials do not report that melatonin can slow disease progression or improve cognitive function in patients with dementia or [MCI](#). 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.

A meta-analysis of 7 studies including 520 patients with dementia concluded that melatonin therapy improved sleep efficacy and extended total sleep time. Yet there was no evidence that these improvements impacted cognitive function [[Xu, 2015](#)]. 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) also concluded that melatonin did not improve cognitive scores (MMSE and ADAS-Cog) or the majority of measures of sleep [[Trotti and Karroum, 2016](#)]. A 2014 Cochrane meta-analysis of 2 RCTs including 209 mild-to-severe Alzheimer’s participants concluded that there was no evidence that melatonin supplementation improved any sleep disturbances [[McCleery, 2014](#)]. In sleep disorder summaries and guidelines from the [US Department of Health & Human Services](#) and the [American Academy of Sleep Medicine](#), melatonin treatment was not found to be effective in managing sleep disorders. They cite publication bias and insufficient data as reasons for not recommending melatonin to manage sleep disorders.

The [Agency for HealthCare Research & Quality](#) concluded that melatonin is not effective in managing sleep disorders. Also 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 [[Schutte-Rodin, 2008](#)]. In 2015, The American Academy of Sleep Medicine also recommended 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 [[Auger et al., 2015](#)].

Delirium is a state of confusion 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 two clinical trials, melatonin treatment significantly lowered the risk of delirium in elderly adults admitted to the hospital for emergency care [[Al-Aama, 2011](#); [Hatta, 2014](#)]. However in a clinical trial of 452 patients with hip fractures, treatment with melatonin after surgery did not reduce the incidence of delirium [[de Jonghe, 2014](#)]. According to a [2015 American Geriatrics Society](#) clinical guideline, melatonin has insufficient evidence to consider its use for delirium.



*Mechanisms of action for neuroprotection:* Results from multiple studies suggest that melatonin can reduce neurodegenerative processes and improve cognitive function through various mechanisms.

*Neurogenesis:* Neurogenesis is the growth and proliferation of new neurons in the hippocampus, an area of the brain responsible for learning and memory. Neurogenesis decreases with age and is reduced in disorders like 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 [[Ramirez-Rodriguez, 2012](#)].

*Mitochondria function:* [Mitochondria](#) are organelles that are essential for generating energy in a cell. In Alzheimer's disease, mitochondrial dysfunction is an early event and triggers cell degradation and death. In pre-clinical animal studies, it is suggested that melatonin helps in cell energy production by improving signaling in the [mitochondria](#) [[Acuna-Castroviejo, 2001](#); [Dragicevic, 2012](#)].

*Oxidative Stress:* Free radicals are produced as a natural by-product of energy metabolism, and oxidative stress is an imbalance between [free radical](#) production and detoxification. Preclinical studies suggest that the accumulation of [oxidative](#) damage may contribute to numerous diseases, including [dementia](#) and cancer. It may also be one of the driving forces of aging, although the benefits of antioxidants have been questioned in recent years. Melatonin is an antioxidant with the ability to scavenge "[free radicals](#)" and prevent DNA and protein damage. In animal studies, melatonin treatment inhibited neuronal damage and counteracted neurodegenerative conditions like oxidative stress [[Feng, 2006](#)].

*Amyloid- $\beta$ :* 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 [[Poeggeler, 2001](#); [Wang, 2005](#)].

*Circadian rhythm and sleep:* 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 [[Gehrman, 2005](#)]. Melatonin is a hormone that is directly involved in the regulation of circadian rhythm that has been shown to decrease with age. Animal studies suggest that melatonin may significantly improve circadian rhythm dysfunction and sleep impairment. In small

clinical trials, some modest benefits of melatonin in sleep and circadian rhythm have been reported, but overall, the evidence is limited [[Auger et al., 2015](#)].

***APOE4 interactions:*** In a test tube experiment, melatonin treatment in the presence of ApoE4 resulted in the inhibition of amyloid- $\beta$  fibril formation, a component of Alzheimer's pathology. In addition, melatonin prevented the neurotoxicity mediated by amyloid- $\beta$  and ApoE4 [[Poeggeler, 2001](#)]. However, no other studies have confirmed this initial finding and no clinical studies 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](#).

**Aging and related health concerns:** There is little direct evidence to suggest that melatonin supplementation can slow aging or delay death although, theoretically, melatonin's effect on circadian rhythm may yield long-term anti-aging benefits. Some benefits are suggested for cancer and cardiovascular disease while potential harms are suggested for diabetes.

**Longevity:** Some evidence from test tube experiments suggests that melatonin may influence the activity of telomerase, an enzyme responsible for regulating cellular aging [[Leon-Blanco, 2003](#); [Rastmanesh, 2011](#)]. However, the impact of this influence on life span in humans still needs to be researched. Researchers are also exploring whether melatonin and/or light entrainment of circadian rhythm [[Cajochen, 2003](#)] can improve outcomes in critically ill patients [[Madrid-Navarro, 2015](#)] and reduce the need for sedation [[Mistralletti, 2015](#)].

**Sleep deprivation:** Sleep is critically important for long-term health and overall mortality [[Hublin, 2007](#)]. Melatonin may improve sleep efficacy and/or circadian rhythm in some people but the effects are modest. Stronger melatonin agonists are available with better clinical efficacy. Evidence from clinical trials on melatonin's effect in humans varies and the absolute effect size is small compared to other pharmacological treatments for insomnia [[Ferracioli-Oda et al., 2013](#); [Wilt et al., 2016](#)].

**Cardiac disease:** Some evidence from animal studies suggests that melatonin may have cardioprotective effects due to its antioxidant profile, especially in limiting drug-induced heart damage, ischemic injury and heart hypertrophy [[Qiao, 2015](#); [Pechanova, 2014](#)]. In a small RCT, melatonin treatment reduced creatine kinase-MB levels in patients with myocardial infarction, suggesting that it may decrease the incidence of cardiovascular events [[Ghaeli et al., 2015](#)]. However, evidence on melatonin effects on the cardiovascular system is limited [[Laudon et al., 2014](#)].

**Cancer:** Melatonin has been investigated for cancer treatment and prevention. For example, the use of melatonin as an addition to standard cancer treatments was reported in a meta-analysis to reduce the risk of mortality by 40% (RR 0.60, 95% CI 0.54-0.73) [[Mills, 2005](#)]. In a more recent meta-analysis, melatonin improved complete and partial remission and the one-year survival rate in patients with solid tumor cancers, while concurrently alleviating radio/chemotherapy-related side effects [[Wang et al., 2012](#)]. For more information on melatonin and its effects in cancer therapy please refer to [WebMD](#).

**Diabetes:** Melatonin may increase blood sugar, and therefore decrease the effectiveness of medications to lower blood sugar in people with diabetes [[WebMD](#)]. Over 100 genetic variants are associated with type 2 diabetes, including a common variant of the melatonin receptor 1B gene (*MTNR1B*). Melatonin inhibits insulin secretion, and this effect is more pronounced in people with a specific variant (GG) of the *MTNR1B* gene [[Tuomi et al., 2016](#)]. Thus, people with this GG variant can have lower insulin and higher glucose levels in response to melatonin treatment.

**Safety:** Melatonin is considered safe for most healthy adults but a few contraindications are known and long-term use has not been extensively studied. Recommendations against the use of melatonin have been made for elderly patients with dementia due to increased risks of falls and other adverse events.

Types of evidence:

- 3 meta-analyses
- Some reviews, guidelines and observational studies
- Several preclinical studies

Side Effects and Warnings:

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 2 years) [[McCleery, 2014](#); [Xu, 2015](#); [Schutte-Rodin, 2008](#)]. 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 falls and other adverse events [[Auger et al., 2015](#)]. Although many healthy people have used it for periods longer than 2 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 [[Altun, 2007](#)].



Reports of serious adverse effects of melatonin supplementation are rare but include nausea, drowsiness, decreased blood-flow and lower body temperature (hypothermia) [[Buscemi, 2006](#)]. Melatonin may worsen symptoms of “orthostatic hypotension”, a blood-pressure condition common in older adults [[Ray, 2003](#)]. Melatonin may also be unsafe in people with the following conditions: bleeding disorders, diabetes, depression, autoimmune diseases, seizure disorders, and transplant recipients [[WebMD](#)]. In elderly patients with dementia, melatonin treatment has also been shown to worsen caregiver ratings of patient mood [[Riemersma-van der Lek et al., 2008](#)].

Drug interactions: Melatonin may reduce the effects of nifedipine and increase the effects of sedatives (clonazepam, lorazepam, phenobarbital, zolpidem) and warfarin [[Drugs.com](#), [WebMD](#)]. Caffeine and fluvoxamine may increase the effects of melatonin. On the other hand, melatonin may alleviate the sleep disruption caused by drugs like beta-blockers and benzodiazepines that alter melatonin production [[Wright, 2015](#); [Stoschitzky, 1999](#); [Scheer, 2012](#)].

### **Sources and Dosing:**

Melatonin is found in small concentrations in foods, such as meats, grains, fruits and vegetables. Since melatonin regulates sleep cycles in humans it is most commonly marketed as a sleep aid dietary supplement. It is available over-the-counter in the US and Canada as a liquid, tablet, pill, and transdermal patch.

Melatonin was once derived from bovine pineal glands, which carried the risk of it being contaminated with viruses [[Altun, 2007](#)]. Currently, melatonin supplements are made synthetically so they do not carry the risk of being contaminated with infectious material. However, over-the-counter melatonin is not regulated by the FDA so 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](#).

As a sleep-aid, melatonin is often taken orally in doses of 1-5 milligrams (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 9 months (for trouble falling asleep) [[WebMD](#)].

Bioavailability of melatonin can vary depending on whether it is ingested orally or sublingually. With oral tablets, it is estimated that about 33% is absorbed through the gastrointestinal tract, though bioavailability varies widely across people [[Di et al., 1997](#)]. Melatonin taken sublingually may have

higher bioavailability (50% or higher) and faster effects compared to oral tablets, though it is unlikely to follow natural physiological trajectories of melatonin levels in the body. There have not been any studies that directly compared the effectiveness of melatonin delivered orally versus sublingually.

### Other formulations/drugs:

#### Circadin® and other prolonged-release forms of melatonin

Prolonged-release melatonin is designed to mimic the pharmacokinetics of endogenously produced melatonin. Daily Circadin® (2 mg) consistently improved sleep quality, sleep latency (- 9 min), and next-morning alertness in middle aged people with insomnia [[Luthringer et al., 2009](#); [Lemoine et al., 2012](#); [Hajak et al., 2015](#)], middle-aged healthy people [[Otmani et al., 2008](#)], middle aged and elderly insomniacs with hypertension [[Lemoine et al., 2012](#)], and in perimenopausal women with insomnia [[Dolev, 2011](#)]. In mild to moderate AD patients taking AChE inhibitors and/or memantine, prolonged-release melatonin (2 mg) improved cognitive performance (IADL and MMSE) in addition to sleep quality [[Wade et al., 2014](#)]. Some of these clinical trials also showed improvement in quality of life with Circadin® [[Dolev, 2011](#); [Lemoine et al., 2012](#)]. According to some studies, prolonged-release melatonin does not cause negative effects on daytime psychomotor, driving, or memory performance [[Otmani et al., 2008](#); [Luthringer et al., 2009](#)] and is well-tolerated with no withdrawals or “rebound insomnia” upon discontinuation of the drug [[Lemoine et al., 2007, 2012](#); [Luthringer et al., 2009](#); [Wade et al., 2011, 2014](#)]. Side effects with Circadin® are not common but include irritability, nervousness, restlessness, and others. Circadin® should not be taken if you have diabetes, depression, bleeding/clotting disorders, high/low blood pressure, or epilepsy/seizure disorders. Drugs that may interact with melatonin include antibiotics, aspirin/acetoaminophen, birth control pills, insulin (and other diabetes medicine), narcotics, antacids (Prevacid, Prilosec, Zofran), ADHD medication, heart medicine (mexiletine, propranolol, verapamil), anticoagulant/antiplatelet drugs (Plavix, warfarin), NSAIDs, and steroids (prednisone, etc.). Other safety information can be found at [drugs.com](#).

#### Piromelatine® (Neu-P11)

Piromelatine® is a melatonin receptor (MT<sub>1/2/3</sub>) and serotonin receptor (5HT-1A/D) agonist. Neurim Pharmaceuticals Ltd has shown positive phase II randomized controlled trial results for the treatment of primary and comorbid insomnia [[link](#)]. Piromelatine® 20/50 mg treatment for 4 weeks resulted in significant and clinically meaningful improvements in polysomnographic parameters (Wake After Sleep Onset; WASO), sleep efficiency, total sleep time, time in NREM sleep, as well as subjective sleep duration/quality. Piromelatine® is generally safe and well-tolerated, with no negative effects on next-





day psychomotor performance. Neurim is currently sponsoring a phase II clinical trial testing the safety and efficacy of piromelatine (5, 20, and 50 mg) in mild Alzheimer's disease patients, and they have just started recruiting participants [[NCT02615002](#)].

### **Ramelteon (Rozerem®)**

Ramelteon, marketed as Rozerem® by Takeda Pharmaceuticals, is a synthetic drug that acts on melatonin receptors (MT<sub>1/2</sub>) and is approved for insomnia related to difficulty of sleep onset. Meta-analyses have shown that Ramelteon is associated with reduced sleep latency (-4.3 min), shorter latency to persistent sleep (-9.36 min), improved sleep quality and efficiency, and longer total sleep time (+7.26 min) [[Liu and Wang, 2012](#); [Kuriyama et al., 2014](#)]. However, no improvement in the percentage of REM sleep has been observed. Subjective sleep latency is reduced with 4 and 8 mg doses, sleep quality is increased with the 8 mg dose, and latency to persistent sleep is reduced in all doses studied (4, 8, 16, 32 mg). Side effects include diarrhea, dizziness, drowsiness, fatigue, and tiredness. The occurrence of somnolence, but not other adverse events reported, was significantly higher in people taking Ramelteon than placebo [[Kuriyama et al., 2014](#)]. Next-day residual effects were not significantly different between Ramelteon and placebo groups [[Liu and Wang, 2012](#)]. Ramelteon should not be taken if you have severe liver problems, sleep apnea, COPD, or mental or mood problems. Ramelteon interacts with azole antifungals, donepezil, doxepin, and fluvoxamine. Other safety information can be found [here](#).

Ramelteon has also been shown to reduce the incidence of delirium. In a randomized controlled trial with 67 intensive care unit elderly patients (65-89 years old), Ramelteon (8 mg/d for 7 d) lowered the risk of delirium with an odds ratio of 0.07 (95%CI 0.008-0.54) [[Hatta et al., 2014](#)]. In a small open-label study enrolling 10 elderly patients with delirium, Ramelteon (8 mg/d for 7d) treatment improved delirium symptoms in 6 out of 10 patients, with no marked adverse effects [[Tsuda et al., 2014](#)]. Larger randomized controlled studies are necessary to confirm the therapeutic benefits of Ramelteon in patients with delirium.

### **Tasimelteon (Hetlioz®)**

Tasimelteon is a selective agonist for the melatonin receptors MT<sub>1</sub> and MT<sub>2</sub> and is used for circadian rhythm sleep disorders [[Laudon, 2014](#)]. Tasimelteon was originally tested for treatment of non-24-hour-sleep-wake disorder in blind people, but is also approved for sighted people. Once-daily Tasimelteon (20 mg) effectively entrained totally blind people with non-24-hour sleep-wake disorder [[Lockley et al., 2015](#)]. A meta-analysis of safety profiles across 6 trials (4 in blind patients, 2 in sighted insomnia patients) showed that adverse events attributable to Tasimelteon included headache,

diarrhea, dry mouth, increased alanine aminotransferase, somnolence, dizziness, and nightmares [Leger et al., 2015]. No clinically significant differences were seen with Tasimelteon (1, 10, 20, 50 mg) compared to placebo in ECGs, vital signs, withdrawal, endocrine function, or suicide potential. When significantly higher doses than the recommended human dose (20 mg/d) are administered to rodents (up to 250 mg/kg/d, 75 times higher dose after accounting for body surface area), incidences of tumors in the liver, uterus, and cervix were increased, but lower doses (~10 times the recommended human dose) showed no increase in tumors [Rxlist]. Tasimelteon also disrupted the estrus cycle and decreased fertility in female rats at higher doses, but not at 5 mg/kg/d, which is approximately twice the recommended human dose. Additional safety and dosage information can be found [here](#).

### **Agomelatine (Valdoxan®, Melitor®, Thymanax®)**

Agomelatine has a high affinity to MT<sub>1</sub> and MT<sub>2</sub> receptors and also acts as a serotonin receptor (5-HT<sub>2C</sub>) antagonist. Because of its actions on serotonin receptors, leading to secondary effects on frontotemporal dopaminergic and adrenergic stimulation [Millan et al., 2003], Agomelatine has antidepressive actions and is marketed for the treatment of major depressive disorder. Many clinical trials have examined the effects of Agomelatine on major depressive disorder, obsessive-compulsive disorder, schizophrenia, and seasonal affective disorder. Recommended dosage is 25- 50 mg/d. While Agomelatine is one of the few antidepressants with a low likelihood of sleep-related side effects (e.g., insomnia) [Alberti et al., 2015], experts believe that the antidepressive effects of Agomelatine do not reach the strength of most classic antidepressants and may be unsuitable for treating severe depression [Hardeland, 2016]. One cause for concern with Agomelatine is its association with higher rates of liver injury and a positive relationship between Agomelatine dose and liver injury [Freiesleben and Fruczyk, 2015].

### **TIK-301 (LY-156735)**

TIK-301 is an agonist for the melatonin receptors MT<sub>1</sub> and MT<sub>2</sub> and an antagonist for 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptors [Hardeland, 2016]. It was originally developed by Eli Lilly as LY-156735, then was acquired by Phase 2 Discovery, then later transferred to Tikvah Therapeutics in 2007 and renamed TIK-301. TIK-301 received an orphan drug designation status for circadian rhythm sleep disorders. In a randomized crossover study enrolling 40 subjects with primary insomnia, TIK-301 (20, 50, 100 mg) treatment resulted in a significant improvement in sleep latency (-7 min) and subjective latency to fall asleep (-5 min) [Zemlan et al., 2005]. Due to its antagonistic actions on 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptors, TIK-301 may have antidepressant properties similar to Agomelatine, though these effects have not been tested in clinical trials [Hardeland, 2016]. Adverse events did not differ in frequency from controls. No clinical trials on TIK-301 are currently underway.

**Research underway:**

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](#). Neurim Pharmaceuticals Ltd is currently sponsoring a phase II clinical trial testing the safety and efficacy of piromelatine® (Neu-P11; 5, 20, and 50 mg) in mild Alzheimer's disease patients, and they have just started recruiting participants ([NCT02615002](#)). There is an on-going Rozerem™ trial that is examining Ramelteon in people with traumatic brain injury ([NCT01207050](#)), as well as multiple trials examining melatonin treatment and delirium ([NCT02324153](#), [NCT02588742](#), [NCT02536417](#), [NCT02597231](#), [NCT02282241](#), [NCT02615340](#), [NCT02654314](#)). More information about these and other clinical trials, including many that are evaluating melatonin for [insomnia](#), can be found at [clinicaltrials.gov](#).

**Search terms:**

PubMed, Google, Clinicaltrials.gov:

- Melatonin, Ramelteon, TAK-375, Rozerem, TIK-301, Tasimelteon, Agomelatine, Piromelatine, MEL, MLT, Pineal, hormone, Circadin, prolonged-release melatonin, PRM, plus the following terms in separate searches: amyloid, blood pressure, cancer, hypertension, dementia, Alzheimer's, aging, mortality, cognitive function, telomere, gait, lifespan, ApoE4, sleep deprivation, delirium, and USP certified supplements.

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