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.

Ramelteon

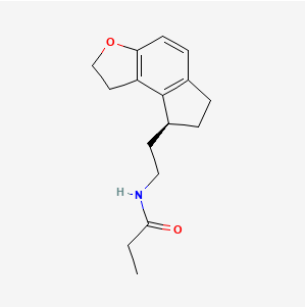
Evidence Summary

Ramelteon modestly improves sleep in people with insomnia. It may also prevent postoperative delirium by up to 50%. While generally safe, it should not be used in people with hepatic insufficiency.

Neuroprotective Benefit: Ramelteon improves sleep parameters in people with insomnia, which in turn may benefit brain health. It did not significantly improve sleep outcomes in people with Alzheimer's disease, based on a small phase 2 clinical trial.

Aging and related health concerns: Ramelteon modestly improves total sleep time and sleep onset latency. Meta-analyses of clinical trials suggest that ramelteon treatment may prevent postoperative delirium by up to 50%, though evidence is mixed.

Safety: Ramelteon is generally well-tolerated, with common side effects including drowsiness, dizziness, and nausea. Ramelteon should not be used in people with severe liver disease. It should not be used with CYP1A2 or CYP2C9 inhibitors.

Availability: Rx	**Dose**: The dose used in adults for insomnia is 8 mg orally within 30 minutes of going to bed.	**Chemical formula:** $C_{16}H_{21}NO_2$ **MW**: 259.34  Source: PubChem
Half-life: 1.0-2.6 hours	**BBB**: penetrant	
Clinical trials: Meta-analyses have included thousands of people with insomnia treated with ramelteon.	**Observational studies**: not available	

What is it?

Ramelteon, marketed as Rozerem® by Takeda Pharmaceuticals, is a synthetic drug that acts on melatonin receptors 1 and 2 (MT1 and MT2) in the suprachiasmatic nucleus, a brain region known as the body's "master clock", regulating the sleep-wake cycle (DrugBank.com). Ramelteon is highly selective for MT1 receptors, which are critically involved in the regulation of the sleep cycle. In 2005, ramelteon was approved for the treatment of insomnia related to difficulty of sleep onset.

Insomnia disorder is characterized by at least 3 months of difficulty in initiating and maintaining sleep, frequent awakenings, or problems returning to sleep after awakenings. Insomnia disorder affects up to 20% of the general population. Consequences of insomnia can include reduced productivity, higher health care costs, increased accident risk, and risks of diabetes, obesity, hypertension, coronary heart disease, and depression (CDC.gov/sleep).

Ramelteon has also been investigated as a potential treatment or preventative intervention for postoperative delirium (Beaucage-Charron et al., 2023; Yu et al., 2023).

Neuroprotective Benefit: Ramelteon improves sleep parameters in people with insomnia, which in turn may benefit brain health. It did not significantly improve sleep outcomes in people with Alzheimer's disease, based on a small phase 2 clinical trial.

Types of evidence:

- 3 meta-analyses or systematic reviews
- 1 case study
- A few laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested ramelteon for the prevention of dementia or age-related cognitive decline.

Human research to suggest benefits to patients with dementia:

In a 2020 Cochrane meta-analysis of 9 randomized controlled trials testing pharmacotherapies for sleep disturbances in Alzheimer's dementia, 5 studies of melatonin, 2 studies of orexin antagonists, 1 study of ramelteon, and 1 study of trazodone were included (McCleery and Sharpley, 2020). Overall, the evidence was moderate or low quality, and further research is needed. Results from the phase 2 trial investigating ramelteon were only reported in summary form on the sponsor's website, with no peer-reviewed publications. NCT00325728 was a multi-centered, parallel-group, randomized controlled trial testing ramelteon treatment (8 mg per night) for 8 weeks in 74 mild-to-moderate Alzheimer's patients. Sleep outcomes were measured by actigraphy, and the primary outcome was total nocturnal sleep time at one week. There were no significant differences between ramelteon and placebo groups for the total nocturnal sleep time outcome or other measures such as percentage of subjects whose night-time sleep increased by 30+ minutes, time awake after sleep onset, sleep efficiency, or number of daytime naps. The daytime total sleep time was significantly higher in the ramelteon group at 1 week (mean difference, 43.1; p=0.010), though this difference was not seen at later time points. The ramelteon group also had a significantly higher ratio of daytime to night-time sleep at weeks 1 (p=0.014), 4 (p=0.019), and 8 (p=0.029), or early termination. No other sleep outcomes differed significantly between groups at week eight. Overall, the evidence related to ramelteon was of low certainty as it was from a single trial with no peer-reviewed publications. The risk of bias was unclear due to incomplete reporting (McCleery and Sharpley, 2016).

A case study reported potential benefits of ramelteon in a 79-year-old Alzheimer's disease patient with refractory behavioral and psychological symptoms and sleep disturbances (Asano et al., 2013). The patient was admitted to a hospital for worsening violent behavior, wandering, screaming, and circadian rhythm disturbances. He had slowly developed memory impairment and executive system dysfunction, along with disturbances in the sleep-wake cycle approximately 2 years prior. On admission, his MMSE score was 5 out of 30. Laboratory results (complete blood count, renal and liver functions, inflammation markers) were all within the normal range. No abnormalities were detected in serologic screening for toxic, infectious, paraneoplastic, and metabolic etiologies. Brain MRI imaging showed global and hippocampal atrophy. He scored 56 on the Japanese version of the Neuropsychiatric Inventory (NPI). Various medications such as donepezil, Yi-Gan-San (traditional herbal medicine), memantine, risperidone, and quetiapine were administered but were discontinued, because of increased irritability, oversedation, inadequate improvement of BPSD, extrapyramidal symptoms, and oversedation, respectively. Ramelteon monotherapy (8 mg) was administered orally once daily at 9pm. One week after starting ramelteon treatment, the behavioral and psychological symptoms improved dramatically along with improvement in sleep. Nighttime awakenings decreased, and he became able to sleep regularly at night for approximately 7 hours per day. The patient became able to accept nursing care without violent behavior. Then, he started to participate in group occupational therapy. The NPI score decreased to 20, with remarkable improvements in subcategories of agitation/aggression and irritability. The MMSE score was 6 out of 30 when he was discharged. These effects continued for at least 3 months (at follow-up).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease is associated with severe sleep-wake disturbances and insomnia, and these are associated with cognitive decline and memory impairment (Srinivasan et al., 2010). People with Alzheimer's disease and other dementias often experience "sundowning", which refers to increased confusion occurring from dusk through the night, with symptoms including disorganized thinking, reduced attention to external stimuli, agitation, and emotional disturbances.

Several studies have shown that melatonin levels in the cerebral spinal fluid are lower in Alzheimer's patients compared to age-matched control subjects, and an impairment in melatonin production at night correlates with cognitive impairment (Liu et al., 1999; Magri et al., 1997). Although, theoretically, interventions to correct the circadian rhythm and deficits in melatonin production, such as administration of melatonin or melatonin agonists before bedtime, could be helpful, the American Academy of Sleep Medicine recommends against the use of melatonin and sleep-promoting medications

for elderly people with dementia due to increased risks of falls and other adverse events (Auger et al., 2015).

In a mouse model of Alzheimer's disease [B6C3-Tg(APPswe,PSEN1dE9)85Dbo/J mice], ramelteon treatment (3 mg/kg/day) for 6 months starting at the age of 3 months did not produce an improvement in cognitive performance, as measured by the Morris water maze (McKenna et al., 2012). In contrast to wild-type control mice, these mice did not learn the location of the escape platform. Ramelteon treatment did not alter neuropathological markers, such as amyloid plaques and apoptosis (PARP-positive cells).

APOE4 interactions:

No studies have evaluated whether ramelteon treatment would have differential effects based on APOE4 carrier status.

Aging and related health concerns: Ramelteon modestly improves total sleep time and sleep onset latency. Meta-analyses of clinical trials suggest that ramelteon treatment may prevent postoperative delirium by up to 50%, though evidence is mixed.

Types of evidence:

- 3 meta-analyses or systematic reviews on insomnia
- 5 meta-analyses or systematic review on delirium
- Several reviews

Insomnia: IMPROVES TOTAL SLEEP TIME AND SLEEP ONSET

The first-generation drugs for insomnia were barbiturates, including pentobarbital and phenobarbital, which have a high abuse potential and significant risks of overdose and respiratory suppression (reviewed in Miyamoto et al., 2009). The second-generation insomnia drugs were benzodiazepines, such as lorazepam, triazolam, and estazolam. While benzodiazepines have a lower potential for abuse and risk of overdose, they are associated with side effects including cognitive impairment, psychomotor impairment, dependence, tolerance, rebound insomnia, and others. Third-generation drugs were benzodiazepine receptor agonists with non-benzodiazepine chemical structures: zolpidem, zopiclone, zaleplon, and others. These benzodiazepine receptor agonists were aimed to induce sleep while

reducing the cognitive and motor side effects. However, these agonists still have abuse and dependence potential. It is worth noting that sleep induced by benzodiazepines and benzodiazepine receptor agonists is electrophysiologically distinct from naturally occurring sleep (Borbely et al., 1985; Brunner et al., 1991). For example, these drugs decrease REM sleep and increase stage 2 sleep.

More recently, direct administration of exogenous melatonin and/or melatonin receptor agonists has garnered interest and attention. Melatonin itself has a short half-life, though there are formulations that have prolonged release (e.g., Circadin and others). Ramelteon has a much longer half-life (up to 2.6 hours), exhibits a 6-fold higher affinity for the MT1 receptor compared to melatonin, and unlike the earlier generation drugs for insomnia, is not associated with residual effects, rebound insomnia, or withdrawal effects. In addition, sleep induced by ramelteon is indistinguishable from natural sleep using FFT analysis in monkeys (Miyamoto et al., 2009).

In a 2023 meta-analysis of 22 randomized controlled trials (total of 4,875 participants) testing melatonin or ramelteon in acute and long-term management of insomnia disorder in adults, ramelteon treatment (4, 8, or 16 mg every night) showed efficacy with a large effect size at 4 weeks on objective total sleep time (weighted difference, 17.9 min; p=0.010), subjective total sleep time (weighted difference=11.7 min; p = 0.007), subjective sleep onset latency (weighted difference = -8.74 min; p = 0.009), and objective sleep onset latency (weighted difference = -14 min; p = 0.017)(Maruani et al., 2023). Regarding long-term efficacy, ramelteon treatment had a large effect size on objective total sleep time (weighted difference=2.02 min; p<0.001) and subjective total sleep time (weighted difference=14.5 min; p < 0.001). Four clinical trials assessed objective sleep efficiency and the results showed a trend toward increased objective sleep efficiency in the ramelteon group compared with placebo (mean difference=2.83; p=0.067; weighted difference=3.91%).

In a 2022 meta-analysis of 17 randomized controlled trials in older adults (mean age over 55 years old) with insomnia disorder, melatonin (0.3 to 5.4 mg nightly) and/or ramelteon treatment (4 or 8 mg nightly) for a range of time (7 days to up to a year) modestly improved objective total sleep time (by 21 minutes), objective and subjective sleep latency (by 13.8 minutes), and sleep quality, but not sleep efficiency, when compared to placebo (Marupuru et al., 2022). This meta-analysis combined data from melatonin and ramelteon studies, as there were not enough studies of ramelteon, so effects of ramelteon alone were not investigated.

In a 2022 network meta-analysis of 170 trials testing 30 interventions for insomnia disorder in a total of 44,089 adults, benzodiazepines, eszopiclone, zolpidem, and zopiclone were more efficacious than

ramelteon, melatonin, and zaleplon with regards to acute treatment (De Crescenzo et al., 2022). However, benzodiazepines are associated with poor tolerability, risk of cognitive impairment, delirium, falls, and motor accidents, and therefore, are not ideal for long-term use (American Geriatrics Society 2015 Beers Criteria update). Other benzodiazepine receptor agonists have also been associated with emergency department visits. For long-term treatment, eszopiclone was more effective than ramelteon and zolpidem (De Crescenzo et al., 2022). When considering all outcomes at different time points, lemborexant and eszopiclone had the best profile in terms of efficacy, acceptability, and tolerability. Overall, melatonergic interventions had poor efficacy compared to other classes of insomnia medications.

Post-operative delirium: MAY REDUCE POST-OPERATIVE DELIRIUM RISK

Delirium is characterized by disturbance in attention, awareness, and cognition. Delirium is a common complication in hospitalized patients, especially in older patients, and it is associated with a longer hospital stay, increased risk of functional and cognitive decline, increased dementia risk, and increased mortality risk (Pereira et al., 2021; Inouye et al., 2023). Other predisposing factors of delirium include medical comorbidities, medication use, and circadian rhythm disturbance. Sleep deprivation and delirium share behavioral and biological similarities, including disturbances in the sleep-wake cycle and abnormal melatonin secretion (Weinhouse et al., 2009; Yoshitaka et al., 2013). Observational studies have reported lower plasma melatonin levels in people with delirium compared to those without delirium (Yoshitaka et al., 2013). While the causes of delirium are not clearly defined and likely vary across people, several potential causes are modulated by melatonin, including diurnal sleep disturbance, melatonin dysregulation, neuroinflammation, oxidative stress, and neurotransmitter dysregulation (Maldonado, 2013).

In a 2023 meta-analysis of 8 randomized controlled trials including a total of 587 hospitalized patients, ramelteon treatment (3-8 mg nightly, or 0.1 mg/kg) lowered the odds of delirium occurrence compared to placebo (OR=0.50; 95% CI, 0.29 to 0.86), without significant heterogeneity (Yu et al., 2023). Based on a trial sequential analysis (a statistical method to control for type I and II errors in systematic reviews and meta-analyses and assess the reliability of the existing body of evidence), the available evidence is sufficient to suggest that ramelteon reduces the relative risk of delirium by 50% in hospitalized patients compared to placebo. In a subgroup analysis of elderly people, ramelteon treatment lowered the odds of delirium occurrence (OR=0.28; 95% CI, 0.09 to 0.85). In a subgroup analysis of people receiving more than 2 doses of ramelteon, the odds ratio for delirium was decreased (OR=0.34; 95% CI, 0.14 to 0.82). Ramelteon treatment did not significantly lower delirium incidence in non-elderly people and in people

who received a single or double dose of ramelteon. Postoperative delirium typically occurs on days 2 to 5. Thus ramelteon treatment once or twice before or after surgery may not be sufficient. Ramelteon treatment also did not significantly affect all-cause mortality or all-cause discontinuation compared to placebo.

In a 2023 meta-analysis of delirium prevention in ICU patients, 9 randomized controlled trials were included, but only 1 randomized controlled trial tested ramelteon (8 mg nightly, total of 78 patients)(Aiello et al., 2023). Treatment with melatonin/ramelteon did not significantly reduce delirium incidence (RR=0.76; 95% CI, 0.54 to 1.07; p=0.12), based on 6 randomized controlled trials and including a total of 1,625 patients. However a sensitivity analysis that added 4 studies (2 retrospective studies and 2 randomized controlled trials) showed that melatonin/ramelteon reduced delirium risk (RR=0.67; 95% CI, 0.48 to 0.92; p=0.01). Of secondary outcomes, there was a trend towards a reduction in the duration of mechanical ventilation (mean difference, -2.80; p=0.09), but no significant effects in the ICU length of stay (mean difference, -0.26; p=0.42) or mortality (RR=0.85; p=0.30). The authors noted that the overall risk of bias ranged from low to high risk. In contrast to the 2023 meta-analysis by Yu et al. discussed above, the trial sequential analysis showed that the sample size required was far from sufficient, with only 1,625 patients enrolled in the included randomized controlled trials versus the 13,699 patients needed (Aiello et al., 2023). The authors concluded that the results are not yet robust, and more studies are needed to validate these findings.

In another 2023 meta-analysis of 5 randomized controlled trials including a total of 443 patients randomized to ramelteon or placebo, ramelteon treatment (8 mg at night) did not result in a reduction in the risk of incident delirium (OR=0.49; 95% CI, 0.13 to 1.85)(Dang et al., 2023). Of the 5 clinical trials, 2 studies showed a statistically significant reduction in delirium incidence, 1 study showed a non-significant reduction in delirium incidence, and 2 studies showed no differences between ramelteon and placebo. The overall quality of the included studies was good with low risk of bias. The meta-analysis found substantial heterogeneity (over 50%) among the included studies. It is also worth noting that the timing and duration of ramelteon treatment varied greatly, from only 2 doses before surgery to up to 7 days of treatment. The authors noted the possibility that ramelteon may be effective for delirium prevention in specific patient populations (e.g., those with preexisting circadian rhythm disturbance).

In a 2023 meta-analysis of delirium treatments, melatonin treatment reduced the duration of delirium (-1.72 days, 95% CI, -2.66 to -0.77; p=0.0004) based on 2 randomized controlled trials (Beaucage-Charron et al., 2023). The authors noted that the current data is limited for ramelteon. The risk of bias of

included studies was moderate to high due to limited information available of study methods. Neither melatonin nor ramelteon improved the hospital length of stay or duration of mechanical ventilation.

In a double-blind randomized controlled trial of 42 Asian elderly people undergoing surgery, preoperative low-dose ramelteon treatment (4 mg) started at least 2 weeks before surgery significantly reduced the incidence of postoperative delirium (4.3%, or 1 out of 23 people receiving ramelteon, versus 21.1%, or 4 out of 19 people receiving placebo)(Tanifuji et al., 2022). The risk ratio was 0.21 (95% CI, 0.03 to 1.70). The incidence of postoperative delirium in the placebo group increased gradually over time. In the same study, a meta-analysis was performed including 3 randomized controlled studies from Asia. The meta-analysis showed that ramelteon treatment significantly reduced postoperative delirium compared to the control (RR=0.27; 95% CI, 0.08 to 0.84; p=0.02). However, funnel plots indicated publication bias.

Prior meta-analyses have found that dexmedetomidine, a selective α2-adrenergic receptor agonist, is effective in reducing the incidence of delirium by about 50%. A 2020 review that explored different preventive interventions for delirium noted that ramelteon and dexmedetomidine appear to have the best supporting evidence thus far (Fontaine et al., 2020). There is a lack of studies comparing melatonergic agents with dexmedetomidine and other agents thought to prevent delirium. Dexmedetomidine is associated with a high dropout rate and adverse events such as bradycardia and hypotension. It is also worth noting that the route of administration for dexmedetomidine (continuous intravenous infusion) precludes at-home use of dexmedetomidine.

Prevention and management of delirium involve many non-pharmacological interventions, such as overnight eye masks, ear plugs, early mobilization, limiting the use of sedative drugs, and strategies to improve the quality of sleep. With regards to the addition of ramelteon, current literature supports early utilization, prior to the development of delirium, at a dose of 8 mg nightly, 30 minutes before bedtime, continued throughout the hospital stay, or for 6 to 30 days (Fontaine et al., 2020).

Safety: Ramelteon is generally well-tolerated, with common side effects including drowsiness, dizziness, and nausea. Ramelteon should not be used in people with severe liver disease. It should not be used with CYP1A2 or CYP2C9 inhibitors.

Types of evidence:

- 6 meta-analyses or systematic reviews
- 1 comparative study using regulatory database and patient reviews
- 3 reviews

General safety:

Ramelteon should only be taken before going to bed and you have at least 7 to 8 hours to dedicate to sleeping (Drugs.com). Ramelteon has generally been well-tolerated across numerous clinical trials (Miyamoto et al., 2009; Fontaine et al., 2020). Common side effects of ramelteon include drowsiness, dizziness, nausea, or worsening sleep problems. Some people using ramelteon have engaged in activity (walking, driving, eating, etc.) while not fully awake and later had no memory of it. Other side effects of ramelteon include unusual thoughts or behavior, hallucinations, worsening depression, and thoughts of hurting yourself. Ramelteon may affect the levels of testosterone or prolactin; this may cause missed menstrual period, nipple discharge, and loss of interest in sex. You should not breastfeed within 25 hours after using ramelteon (if a breast pump is used, throw out the milk collected within this time frame).

Ramelteon should not be used if you have severe liver disease or if you also take fluvoxamine (Drugs.com). Ramelteon is metabolized mainly in the liver; CYP1A2 and CYP2C9 are the hepatic enzymes involved in ramelteon metabolism (Srinivasan et al., 2010). Therefore, ramelteon should not be used in combination with inhibitors of CYP1A2 (e.g., ciprofloxacin) or CYP2C9 (e.g., fluconazole). People with hepatic insufficiency should practice caution when using ramelteon (Aiello et al., 2023). In the presence of a CYP inducer such as rifampicin, the plasma level of ramelteon may be significantly reduced. Ramelteon clearance is significantly reduced in elderly people and its half-life is significantly increased.

Ramelteon should not be taken with alcohol. Until you know how ramelteon affects you, driving should be avoided.

The safety profile for ramelteon (and melatonin) is more attractive than other classes of insomnia medications, including benzodiazepines and benzodiazepine receptor agonists, which are classified as

schedule IV controlled substances and have the potential for abuse (reviewed in Miyamoto et al., 2009). In contrast, ramelteon has shown no effects on measures of abuse.

People with insomnia:

In a 2023 meta-analysis of 22 randomized controlled trials (total of 4,875 participants) testing melatonin or ramelteon in acute and long-term management of insomnia disorder in adults, ramelteon treatment (4, 8, or 16 mg every night) had a good safety profile, with no diurnal residual effects, no rebound effect after withdrawal, and no misuse or addiction (Maruani et al., 2023).

In a 2022 network meta-analysis of 170 trials testing/comparing 30 interventions for insomnia disorder in a total of 44,089 adults, ramelteon treatment had higher discontinuations due to any cause than intermediate-acting benzodiazepines, long-acting benzodiazepines, and eszopiclone, with acute treatment (De Crescenzo et al., 2022). With long-term treatment, eszopiclone and zolpidem caused fewer discontinuations than ramelteon. With regards to adverse events, ramelteon was associated with increased fatigue. A large group of drugs, including benzodiazepines, doxylamine, eszopiclone, lemborexant, ramelteon, suvorexant, trazodone, zolpidem, and zopiclone, had a higher risk of sedation and somnolence than placebo or other active treatments.

In a comparative study of adverse events across different insomnia drugs, databases and online patient reviews of ramelteon, eszopiclone, suvorexant, zaleplon, and zolpidem were examined (Brochert et al., 2019). Based on the Medical Dictionary for Regulatory Activities, the most common adverse event reported by all 5 drugs was "drug ineffective" (23.1% for ramelteon; 14.1% for eszopiclone, 28.0% for suvorexant, 27% for zaleplon, 3.4% for zolpidem). Based on the Food and Drug Administration Adverse Event Reporting System (FAERS), "drug ineffective" also emerged as the most common events (14.4% with ramelteon, 17.0% with eszopiclone, 18.0% with suvorexant, 23% with zaleplon, and 14.5% with zolpidem). With regards to online reviews on Drugs.com, a high percentage of reviewers assigned ramelteon and suvorexant as the lowest possible score of "1" (41.5% for ramelteon, 53.1% for suvorexant). The average rating (10-point) was 7.30 for zolpidem, 6.20 for eszopiclone, 5.69 for zaleplon, 4.63 for ramelteon, and 3.65 for suvorexant. Adverse events that were particular to specific drugs included nightmare with suvorexant, dysgeusia (foul taste in the mouth) and product substitution issue with eszopiclone, and dizziness with ramelteon.

People with or at risk of delirium:

In a 2023 meta-analysis of 5 randomized controlled trials including a total of 443 patients randomized to ramelteon or placebo, ramelteon treatment (8 mg at night) did not result in a significant difference in the number of adverse events compared to placebo (OR=1.03; 95% CI, 0.31 to 2.47)(Dang et al., 2023). Common adverse events included nausea, hypotension, and dizziness. There were 3 severe adverse events in patients receiving ramelteon: ventricular bigeminy, hypotension, and fall.

In a different 2023 meta-analysis of clinical trials and observational studies examining delirium treatments, ramelteon use did not cause adverse events such as falls, nausea, rash, neurologic deterioration, or oversedation (Beaucage-Charron et al., 2023).

Dementia patients:

In a 2020 Cochrane meta-analysis of 9 randomized controlled trials testing pharmacotherapies for sleep disturbances in Alzheimer's dementia, adverse events that were considered possibly related to the study drug occurred at a similar rate as placebo (McCleery and Sharpley, 2020). Four patients in the placebo group experienced at least one serious adverse event, while no such events occurred in the ramelteon group.

Preclinical data:

General safety of ramelteon has also been demonstrated in animal models. In the conditioned place preference test for rewarding property, ramelteon treatment (3-30 mg/kg, orally) in rats showed no preference in the drug-associated compartment, indicating a low potential for reinforcing/rewarding behavior or abuse (Hirai et al., 2005). In cats and monkeys, ramelteon did not cause any significant adverse effects such as cognitive impairment, motor coordination deficits, or drug abuse potential (Miyamoto et al., 2009).

Drug interactions:

There are 385 drugs known to interact with ramelteon (of which 29 are major interactions), along with 5 disease interactions (depression, severe renal impairment, sleep apnea, glaucoma, and liver disease)(Drugs.com). Alcohol must not be used with ramelteon. Ramelteon should be avoided if you are allergic to it, you have severe liver disease, or if you also take fluvoxamine. You should not breastfeed within 25 hours after using ramelteon. Ramelteon may affect the levels of testosterone or prolactin, which may affect menstrual periods in women, sexual desire in men, or fertility in men or women.

Sources and dosing:

Ramelteon is marketed as Rozerem® by Takeda Pharmaceuticals for the treatment of insomnia related to difficulty of sleep onset (DrugBank.com). The dose used in adults for insomnia is 8 mg orally within 30 minutes of going to bed.

Research underway:

There is currently one ongoing phase 4 clinical trial testing whether ramelteon (8 mg daily, orally at night) might treat and/or prevent delirium in the ICU (NCT05069428). This is a randomized double-blind placebo-controlled study with an estimated enrollment of 506 participants. This study is scheduled to be completed in 2025.

Search terms:

Pubmed, Google: ramelteon

- + meta-analysis, , + clinical trial, + Alzheimer, + dementia, + APOE

Websites visited for ramelteon:

- Clinicaltrials.gov
- NIH RePORTER
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com (0)
- PubChem
- DrugBank.ca

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.