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.

Piromelatine

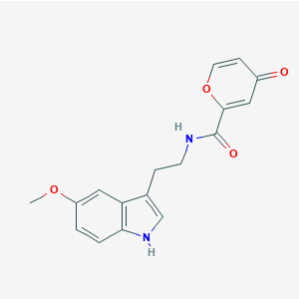
Evidence Summary

Piromelatine improved sleep parameters in people with insomnia and improved neuropathic pain and metabolic dysfunctions in rodent models. Long-term safety has not been established.

Neuroprotective Benefit: Preclinical models of pathology/injury suggest that piromelatine improves cognitive functions and promotes neuronal survival. No human data on neuroprotection is available yet, but a clinical trial in Alzheimer's is underway.

Aging and related health concerns: A phase 2 study reported that piromelatine improves sleep parameters in people with insomnia. Preclinical studies suggest it may also alleviate neuropathic pain, improve insulin sensitivity, and decrease cholesterol levels.

Safety: Based on two short-term clinical studies, piromelatine was generally safe with no negative effects on next-day psychomotor performance. The most frequently reported adverse event was mild headache. Long-term safety is unknown.

Availability: In clinical trials. Also known as Neu-P11.	**Dose:** A phase 2 study for primary and comorbid insomnia has shown positive results at doses of 20 and 50 mg/day (Neurim press release).	**Chemical formula:** $C_{17}H_{16}N_2O_4$ **MW:** 312.32  Source: PubChem
Half life: 1.2-2.9 hours	**BBB:** Not documented but likely penetrant due to its effects on sleep.	
Clinical trials: The largest completed clinical trial to date included 120 patients with insomnia.	**Observational studies:** None.	

What is it? Piromelatine® (also known as Neu-P11) is a melatonin receptor (MT1, MT2, and MT3) and serotonin receptor (5-HT_{1A} and 5-HT_{1D}) agonist. It is also reported to be a low-affinity antagonist of 5-HT_{2B}, P2X3, and TRPV1 receptors (Abad and Guilleminault, 2018). Piromelatine® is under development by Neurim Pharmaceuticals Ltd for indications including insomnia and Alzheimer's disease. A phase 2 study for primary and comorbid insomnia has shown positive results (Neurim press release). A phase 2 clinical trial testing the safety and efficacy of piromelatine in mild Alzheimer's disease patients was scheduled to be completed in November 2019 (NCT02615002).

Neuroprotective Benefit: Preclinical models of pathology/injury suggest that piromelatine improves cognitive functions and promotes neuronal survival. No human data on neuroprotection is available yet, but a clinical trial in Alzheimer's is underway.

Types of evidence:

- 0 clinical trials (1 ongoing for Alzheimer's disease)
- 0 observational studies
- 3 laboratory studies
- 1 review

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

None.

Human research to suggest benefits to patients with dementia:

In Alzheimer's patients, there is decreased melatonin 1 and 2 receptors (MT1 and MT2) in the cortex, pineal gland, and the suprachiasmatic nucleus, the brain region that controls circadian rhythm (Hardeland, 2016). Decreased MT1 expression is also seen in the suprachiasmatic nucleus of healthy older people.

There is an ongoing randomized placebo-controlled phase 2 clinical trial testing the safety and efficacy of piromelatine in mild Alzheimer's disease patients (NCT02615002). Estimated study completion date was November 30, 2019. As of 2/10/2020, the study is "Active, not recruiting".

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

Melatonin levels decline with aging and this decline is more pronounced in age-related diseases including Alzheimer's disease (Hardeland, 2016). Dysregulation of the circadian system also occurs during aging and can be profound in severe neurodegenerative diseases, changes that contribute to, or are causally linked to, melatonin deficits.

In a rat model of Alzheimer's disease (intrahippocampal injection of Aβ42), piromelatine treatment (50 mg/kg, i.p.), but not melatonin treatment (50 mg/kg, i.p.), attenuated hippocampal cellular loss and cognitive impairment as measured by the novel object recognition task and the Y-maze task (He et al., 2013). The Aβ42 injection resulted in a ~40% cell number loss in the CA1 region of the hippocampus, but piromelatine restored the cell number close to that of controls. A single morning or afternoon administration of piromelatine enhanced object recognition memory measured at 4 or 24 hours after training.

In a rat model of stress-induced memory deficits (exposed to chronic mild stressors for 7 weeks), some rats exhibit anhedonia (inability to feel pleasure) while others are resistant. Piromelatine treatment (50 mg/kg) for the last 2 weeks of chronic mild stress exposure ameliorated memory deficits and depressive-like behavior in rats that exhibited anhedonia (Fu et al., 2016). Piromelatine treatment increased BDNF, CREB, and pCREB in non-stressed control, stressed-anhedonic, and stressed-resistant rats, but increased neurogenesis only in stressed-anhedonic rats.

In a mouse model of brain ischemia, piromelatine treatment (1 mg/kg, i.p.) administered 5 minutes after thrombotic stroke significantly reduced infarct volume (Buendia et al., 2015). Piromelatine's protective

benefits were abolished by a melatonin receptor antagonist (luzindole), a JAK2 inhibitor (AG490), a PI3/AKT inhibitor (LY294002), and a MEK/ERK1/2 inhibitor (PD98059), suggesting that the neuroprotective effects may be mediated in part by activation of melatonin receptors, JAK/STAT, PI3K/Akt, and MEK/ERK1/2 pro-survival signaling pathways.

APOE4 interactions: Unknown.

Aging and related health concerns: A phase 2 study reported that piromelatine improves sleep parameters in people with insomnia. Preclinical studies suggest it may also alleviate neuropathic pain, improve insulin sensitivity, and decrease cholesterol levels.

Types of evidence:

- 1 clinical trial for insomnia
- 9 laboratory studies
- 2 reviews

Insomnia: BENEFIT.
In a phase 2 double-blind randomized controlled trial of 120 people with primary and comorbid insomnia, piromelatine treatment (20 or 50 mg/day) for 4 weeks resulted in statistically significant and clinically meaningful improvements in sleep parameters relative to placebo (Neurim press release). Improvements were found in key polysomnographic parameters including Wake After Sleep Onset (p=0.02 for both doses) and in particular for the first 6 hours of sleep (WASO-6h) (p=0.0008 and p=0.04 for the 50 mg and 20 mg groups, respectively). Piromelatine 50 mg also improved Sleep Efficiency (p=0.02), Total Sleep Time (p=0.02), Total Time Awake (p=0.01), and time in NREM sleep (p=0.028) indicating beneficial effects on sleep maintenance. Subjective improvements relative to placebo in quality of sleep and total sleep time measured by the Pittsburg Sleep Quality Questionnaire were also observed in line with the polysomnographic findings. Piromelatine enhanced NREM sleep EEG delta power and significantly reduced beta power ($p<0.05$). The decrease in EEG beta activity, a marker of cortical arousal, is a physiological surrogate marker of the efficacy of piromelatine in sleep maintenance.

Neuropathy: POTENTIAL BENEFIT BASED ON A STUDY IN MICE.
In a mouse model of neuropathic pain (partial sciatic nerve ligation), a single piromelatine treatment (25, 50, or 100 mg/kg, i.p., 1 hour before assessment) significantly prolonged thermal and mechanical latencies and increased NREM sleep (Liu et al., 2014). Piromelatine at 50 and 100 mg/kg doses had

thermal latency and mechanical threshold comparable to sham controls and melatonin-treated (100 mg/kg) mice. Piromelatine did not impair motor coordination of mice with neuropathy based on the comparable performance on rotarod staying time. The antinociceptive effect of piromelatine was prevented by a melatonin receptor antagonist (luzindole), opioid receptor antagonist (naloxone), and 5-HT_{1A} receptor antagonist (WAY-100635). The hypnotic effect of piromelatine was blocked by luzindole but not by naloxone or WAY-100635. Thus, the antinociceptive effect of piromelatine may be mediated by melatonin, opioid, and 5-HT_{1A} receptors; and the hypnotic effect of piromelatine appears to be mediated by melatonin receptors.

Metabolic problems: POTENTIAL BENEFIT BASED ON PRECLINICAL STUDIES.
In a rat model of type 2 diabetes (high fat diet combined with streptozotocin treatment), piromelatine treatment (5, 10, or 20 mg/kg, intragastric) for 4 weeks restored changes in food intake, water consumption, hyperglycemia, glucose intolerance, and insulin resistance (Zhou et al., 2017). Piromelatine treatment increased glucocorticoid receptor expression and suppressed 11β-hydroxysteroid dehydrogenase 1 activity in the hippocampus by enhancing glucocorticoid sensitivity and hypothalamus-pituitary-adrenal (HPA) feedback, leading to decreased glucocorticoid levels. Transcript levels of the glucose metabolism-related genes (PPAR-γ, glucose transporter type-4, and adiponectin) in adipose tissue were significantly increased after piromelatine treatment, while leptin mRNA was significantly decreased. Melatonin receptor (MT1 and MT2) protein levels were also increased by piromelatine. Together, piromelatine may regulate metabolic profiles and insulin sensitivity by normalizing the hyperactivated HPA axis, which in turn, attenuates insulin resistance and glucose homeostasis. Piromelatine did not significantly impact blood lipid levels in these rats.

In chronically stressed rats with insulin resistance (induced by a high fat diet), piromelatine treatment (10 or 20 mg/kg, oral gavage) for 4 weeks normalized hyperglycemia and insulin resistance (HOMA-IR)(Zhou et al., 2018). Piromelatine also prevented diet/stress-induced dysregulation of genes involved in glucose and lipid metabolism including proinflammatory cytokines in adipose tissue. Piromelatine also attenuated diet/stress-induced excess free corticosterone release, increased glucocorticoid receptor expression, and decreased 11β-hydroxysteroid dehydrogenase-1 expression, suggesting that piromelatine might ameliorate impaired glucose metabolism and prevent insulin resistance by normalizing HPA-axis functions.

In rats with insulin resistance induced by chronic sleep restriction (4 hours of sleep per day), piromelatine treatment (20 mg/kg, i.p.) for 8 days restored levels of plasma glucose, triglycerides, and total cholesterol, and improved glucose tolerance and antioxidative potency compared to the vehicle-

treated group (She et al., 2014). Levels of plasma glucose, triglycerides, total cholesterol, HDL cholesterol, plasma insulin, and HOMA-IR in the piromelatine groups were comparable to controls that were not sleep restricted. Chronic sleep deprivation can induce metabolic dysfunction, oxidative stress, and insulin resistance, but in this rodent model, these symptoms were improved by treatment with piromelatine. Piromelatine increased glucose tolerance and decreased the fasting plasma insulin levels and the HOMA index by 35.1% and 50% respectively.

In obese rats with insulin resistance (fed a high fat high sucrose diet), piromelatine treatment (10 mg/kg, i.p.) for 8 weeks inhibited both body weight gain and deposit of abdominal fat with no influence on food intake (She et al., 2009). The impaired insulin sensitivity and antioxidative potency were improved and the levels of plasma glucose, total cholesterol, and triglycerides decreased while HDL increased. The effects of piromelatine were similar to those of melatonin treatment (4 mg/kg, i.p.).

In a cell culture model of insulin resistance (3T3-L1 adipocytes preincubated in high glucose and high insulin conditions), piromelatine treatment inhibited the increase in triglyceride levels possibly by increasing levels of the adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) (Wang et al., 2013).

Hypertension: POTENTIAL BENEFIT BASED ON RODENT STUDIES.
In a rat model of hypertension (spontaneously hypertensive rats), piromelatine treatment (5, 15, and 50 mg/kg) reduced blood pressure (Huang et al., 2013). Piromelatine, but not melatonin (10 mg/kg), also reduced these rats' body weight.

Ischemia: POTENTIAL BENEFIT BASED ON IN VITRO STUDIES.
In a cell culture model of ischemia (hypoxia/reoxygenation model of H9c2 myocardial cells), piromelatine treatment significantly reduced apoptosis (17.94% versus 39.66%) and decreased levels of creatinine kinase (muscle damage biomarker), lactic dehydrogenase (tissue damage biomarker), and malondialdehyde (lipid peroxidation marker)(Yu et al., 2014).

Safety: Based on two short-term clinical studies, piromelatine was generally safe with no negative effects on next-day psychomotor performance. The most frequently reported adverse event was mild headache. Long-term safety is unknown.

Types of evidence:

- 2 clinical trials for insomnia

A phase 1 single ascending dose study completed in June 2010 demonstrated the safety tolerability, pharmacokinetics and pharmacodynamics of piromelatine in 32 healthy male volunteers (Neurim press release). Ascending single piromelatine doses of 5mg, 20mg, 50mg, and 200mg were found to be safe and well tolerated. The most frequently reported adverse event was headache of mild intensity and short duration. The multiple ascending dose study was a double-blind placebo-controlled cross-over study of piromelatine tolerability, pharmacokinetics, and pharmacodynamics in 25 insomnia patients aged 18-80. Patients were treated by ascending doses of 2mg, 5mg, 20mg and 50mg piromelatine and placebo nightly for 6 days with a 1-month washout between treatments. The study confirmed that piromelatine is generally safe and well tolerated with a pharmacokinetic profile typical of a short acting hypnotic drug (half-life of 1.2-2.9 hours) with no evidence of accumulation. Piromelatine had no detrimental effects on memory consolidation or sleep structure.

The phase 2 double-blind randomized controlled trial in 120 patients with primary and comorbid insomnia reported that piromelatine treatment (20 or 50 mg/day) for 4 weeks was generally safe and well-tolerated (Neurim press release). Piromelatine had no detrimental effects on next-day psychomotor performance (as assessed by the Digit Symbol Substitution Test) for any dose group and no deleterious effects on sleep structure and architecture.

Drug interactions: Unknown. Based on the mechanism of action, piromelatine may interact with melatonin supplements, melatonin agonists, and serotonin receptor agonists.

Contraindications: Unknown. One study has suggested that high melatonin levels are detrimental in Parkinson's disease (Willis, 2008), suggesting that activation of melatonin receptors by piromelatine may be harmful.

Sources and dosing: Piromelatine® is under development by Neurim Pharmaceuticals Ltd for indications including insomnia and Alzheimer's disease. A phase 2 study for primary and comorbid insomnia has shown positive results at doses of 20 and 50 mg/day (Neurim press release). Neurim is also sponsoring a phase 2 clinical trial testing the safety and efficacy of piromelatine in mild Alzheimer's disease patients at doses of 5, 20, and 50 mg/day (NCT02615002).

Research underway: There is an ongoing randomized placebo-controlled phase 2 clinical trial testing the safety and efficacy of piromelatine in mild Alzheimer's disease patients (NCT02615002). This trial is recruiting 500 participants and they are randomized to 5 mg, 20 mg, or 50 mg/day of piromelatine or placebo for 26 weeks. The primary outcome is change from baseline in Computerized

Neuropsychological Test Battery. Secondary outcome measures include change from baseline in Global Impression of Change, ADCS-MCI-ADL (activities of daily living scale for mild cognitive impairment), ADAS-cog14, safety, and tolerability. Estimated study completion date was November 30, 2019. As of 2/10/2020, the study is "Active, not recruiting".

Search terms:
Pubmed, Google: Piromelatine and Neu-P11

Websites visited for piromelatine:

- Clinicaltrials.gov (1)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Cafepharma (0)
- Pharmapro.com (0)