**Agomelatine: a potential novel approach for the treatment of memory disorder in neurodegenerative disease**

Qiang Su1,2,3,4, Tian Li1,2,8, Guo-Wei Liu4, Yan-Li Zhang5,6, Jun-Hong Guo5,7, Zhao-Jun Wang1,2, Mei-Na Wu1,2, Jin-Shun Qi1,2,8

https://doi.org/10.4103/1673-5374.353479

Date of submission: February 11, 2022
Date of decision: April 20, 2022
Date of acceptance: June 18, 2022
Date of web publication: September 16, 2022

From the Contents

Introduction 727
Search Strategy and Selection Criteria 728
Agomelatine and Mood Disorders 728
Agomelatine and Sleep Disorders 729
Limitations of Agomelatine 730
Conclusions 730

**Abstract**

Agomelatine is a selective agonist of melatonin receptor 1A/melatonin receptor 1B (MT1/MT2) and antagonist of 5-hydroxytryptamine 2C receptors. It is used clinically to treat major depressive episodes in adults. The pro-chronobiological activity of agomelatine reconstitutes sleep-wake rhythms and normalizes circadian disturbances via its agonistic effect of melatonin receptor 1A/melatonin receptor 1B, which work simultaneously to counteract depression and anxiety disorder. Moreover, by antagonizing neocortical postsynaptic 5-hydroxytryptamine 2C receptors, agomelatine enhances the release of dopamine and noradrenaline in the prefrontal cortex, increases the activity of dopamine and noradrenaline, and thereby reduces depression and anxiety disorder. The combination of these two effects means that agomelatine exhibits a unique pharmacological role in the treatment of depression, anxiety, and disturbance of the circadian rhythm. Emotion and sleep are closely related to memory and cognitive function. Memory disorder is defined as any forms of memory abnormality, which is typically evident in a broad range of neurodegenerative diseases, including Alzheimer’s disease. Memory impairment and cognitive impairment are common symptoms of neurodegenerative and psychiatric diseases. Therefore, whether agomelatine can improve memory and cognitive behaviors if used for alleviating depression and circadian-rhythm sleep disorders has become a research “hotspot”. This review presents the latest findings on the effects of agomelatine in the treatment of psychologic and circadian-rhythm sleep disorders in clinical trials and animal experiments. Our review evaluates recent studies on treatment of memory impairment and cognitive impairment in neurodegenerative and psychiatric diseases.

**Key Words:** agomelatine; antidepressant; anxiety; apathy; circadian-rhythm sleep disorder; cognitive impairment; depression; melatonergic; memory disorder; mood disorder; neurodegenerative disease

---

**Introduction**

Agomelatine (AGO) is N-(2-[7-methoxy-1-naphthalenyl]ethyl) acetamide (S20098). It was discovered and developed by the European Pharmaceutical Company Servier Laboratories Limited in 1992 (Yous et al., 1992; Armstrong et al., 1993). As the first melatonergic antidepressant, AGO was approved by the European Medicines Agency in the European Union in 2009 and Therapeutic Goods Administration in Australia in 2010 for the treatment of major depression. AGO alleviates circadian-rhythm sleep disorders in patients suffering from depression with synergistic agonism at melatonin receptor 1A/melatonin receptor 1B (MT1/MT2) and antagonism at 5-hydroxytryptamine 2C (5-HT2C) receptors. AGO provides a useful alternative pharmacological strategy to existing antidepressant drugs (Norman and Olver, 2019).

Commonly used drugs for depression are selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs), which ameliorate depression by increasing the 5-hydroxytryptamine (5-HT) level. However, SSRIs and SNRIs produce adverse effects, such as withdrawal syndrome, sexual dysfunction, difficulties in sleeping, and agitation (Erdögan et al., 2020). Compared with SSRIs and SNRIs, AGO exerts an antidepressant effect by binding directly to 5-HT2C receptors in postsynaptic membranes without affecting 5-HT concentrations in synaptic clefts. Furthermore, compared with natural endogenous melatonin, the replacement of an indole ring with a naphthalene ring in AGO (Table 1) enhances the metabolic stability of AGO and prolongs its biological half-life, which leads to more effective correction of circadian-rhythm disorders and alleviation of sleep disorders by activating MT1 and MT2. With synergistic agonism at MT1/MT2, and antagonism at 5-HT2C receptors, AGO has obvious positive effects on the sleep-wake cycle and depression while lacking serious side effects (including sexual side effects) (Kennedy et al., 2008).

**Table 1 | Comparison of drug characteristics between agomelatine and melatonin**

| Drug name | Agomelatine | Melatonin |
|-----------|-------------|-----------|
| Source    | Chemical synthesis | Endogenous hormone |
| Weight (kDa) | 243 | 232 |
| Half-life | < 2 h | 35–50 min |
| Chemical formula | C17H17NO2 | C17H17NO2 |
| Chemical structure | ![Chemical Structure](image) | ![Chemical Structure](image) |
| Pharmacological properties | Antagonist of 5-HT2C receptors, agonist of MT1 and MT2 | Agonist of MT1 and MT2 |

5-HT2C: 5-Hydroxytryptamine 2C; MT: melatonin receptor 1A; MT1: melatonin receptor 2C.

Neurodegenerative disease refers to the principal pathology associated with disorders such as Alzheimer’s disease, Huntington’s disease and Parkinson’s disease. The patients with these diseases exhibit diverse patterns of sleep disturbance, memory disorder and cognitive impairment. Many researchers have reported a strong association among sleep disturbance, mood changes, memory complaints, and reduced cognitive performance (Tempesta et al., 2018; Guan et al., 2020; Gutierrez et al., 2021; Xie et al., 2021; Hernandez and Shukla, 2022). Sleep disorders, emotional abnormalities, and cognitive decline are usually present in the same individual and influence each other. An improvement in sleep and mood disorders often alleviates memory deficit and cognitive decline. Therefore, based on the peculiar characteristic of AGO

---

1Key Laboratory of Cellular Physiology, Ministry of Education, Taiyuan, Shanxi Province, China; 2Department of Physiology, Shanxi Medical University, Taiyuan, Shanxi Province, China; 3Department of Neurology, First Hospital of Shanxi Medical University, Taiyuan, Shanxi Province, China; 4Department of Laboratory Medicine, Fenyang College of Shanxi Medical University, Fenyang, Shanxi Province, China; 5Department of Neurology, Sixth Hospital of Shanxi Medical University (General Hospital of Tisco), Taiyuan, Shanxi Province, China; 6Department of Neurology, Sixth Hospital of Shanxi Medical University (General Hospital of Tisco), Taiyuan, Shanxi Province, China; 7Department of Laboratory Medicine, Fenyang College of Shanxi Medical University, Fenyang, Shanxi Province, China; 8Department of Neurology, Sixth Hospital of Shanxi Medical University (General Hospital of Tisco), Taiyuan, Shanxi Province, China

*Correspondence to: Jin-Shun Qi, PhD, jinshunj2009@163.com. https://orcid.org/0000-0001-9223-8806 (Jin-Shun Qi)

**Funding:** The work was supported by Shanxi “1331 Project” Key Subjects Construction, No. 1331KSC (to JSQ); Science Research Start-up Fund for Doctors of Shanxi Province, No. S20098 (to TL); and Science Research Start-Up Fund for Doctors of Shanxi Medical University, No. XD2017 (to TL).

**How to cite this article:** Su Q, Li T, Liu GW, Zhang YL, Guo JM, Wang ZJ, Wu MN, Qi JS (2023) Agomelatine: a potential novel approach for the treatment of memory disorder in neurodegenerative disease. Neur Regen Res 18(4):727-733.
integrating melatonergic agonism and 5-HT antagonism and the efficacy of AGO in improving sleep and mood, it is intriguing and meaningful to ascertain if AGO can also ameliorate the deficits in memory and cognitive behaviors while attenuating depression and sleep-rhythm disorders.

Here, we summarize the latest research progress of AGO in the treatment of depressive, sleep disorders, and cognitive impairments. We aim to provide new insights into the pharmacological action and mechanisms of AGO in the clinical setting.

**Search Strategy and Selection Criteria**

The studies cited in this narrative review were published from 2001 to 2021. They were searched by QS and TL on 31 December 2021 using the PubMed database and met the inclusion criteria, search terms include at least one of the following the keywords “agomelatine” and “S20098”, and at least one of the following the keywords: “mood disorder”, “depression”, “anxiety”, “apathy”, “anhedonia”, “sleep-rhythm disorder”, “memory”, “cognition”, “dementia”, and “neurodegenerative disorder”.

**Agomelatine and Mood Disorders**

Mood disorders are a group of mental or psychiatric disorders, such as depression, anxiety, and apathy, and are characterized by abnormalities of emotional state (Marshall, 2020). These emotional disorders have a negative impact on the physical and mental health of patients, and also impose a heavy burden on their families and society. According to Chisholm et al. (2016), depression and anxiety disorders cost the global economy USD1.15 trillion each year. AGO, a novel 5-HT receptor antagonist, has been shown to treat depression, anxiety, and other mood disorders, especially major depressive disorder (MDD).

**Depression**

Depression (also known as depressive disorder) is one of the most common mood disorders, and is characterized by a persistent low mood state. The accompanying symptoms of depression include inactivity, loss of concentration, social withdrawal, sleep disturbances, and cognitive impairments, such as memory deficit (LeMoult and Gotlib, 2019; Price and Duman, 2020).

AGO is used mainly for the treatment of depression, especially MDD. Heun et al. (2013) undertook a study on 222 older patients with MDD. They found that AGO treatment for 8 weeks relieved depressive symptoms efficiently and was well tolerated in older patients suffering from depression (Heun et al., 2013). Similarly, Robillard et al. (2018) reported that AGO reduced depressive symptoms significantly in 24 young adults with depression. Moreover, they found that the timing of dim light melatonin onset (DLOM) was shifted 3.6-hour earlier after treatment with AGO, which indicated a strong correlation between the improvement of depression and the phase shift of DLOM (Robillard et al., 2018). In a network meta-analysis, Cipriani et al. (2018) reported that AGO was more efficacious and acceptable in adult patients with major depressive disorder (MDD) than those elicited by SSRIs or SNRIs (Buoli et al., 2017). AGO alleviated social isolation-induced anxiety in rats effectively and reversed increased plasma levels of vasopressin, AT1 receptor, and corticosterone in depressed rats (Lu et al., 2018). Similarly, the pathogenesis of anxiety disorder is complex, and the anxiolytic mechanism of AGO is incompletely understood. Several studies have suggested that the anxiolytic effects of AGO are associated mainly with its antagonism of 5-HT1A receptors (Sant’Ana et al., 2019; Demireva et al., 2020). The modulation of glutamate neurotransmission, anti-inflammatory action, antioxidant action, and correction of melanin rhythms are also involved in the anxiolytic-like effects of AGO (Tchekalarova et al., 2018; Santos et al., 2019). Moreover, anxiety disorder and depression are commonly accompanied by another, and a similar pathogenesis may exist between them. Therefore, AGO may relieve anxiety disorder by improving depression, and vice versa.

**Other emotional disorders**

Apart from its antidepressant and anxiolytic properties, it has been suggested that AGO may exhibit special curative effects on particular neuropsychiatric symptoms, such as apathy, anhedonia, and abulia. Apathy is one of the most prevalent behavioral and psychological symptoms of dementia. Apathy is characterized by an insidious decline in motivation and goal-directed actions, which leads to reduced interest in social, recreational, occupational, and creative pursuits. Callegari and colleagues showed that AGO (but not metoclopramide) improved apathy in patients with frontotemporal dementia and was well-tolerated (Callegari et al., 2016). Moreover, an analysis of the literature showed that AGO had an obviously positive effect on the treatment of apathy in people suffering from dementia (Harrison et al., 2016). De Bernardo et al. (2017) showed that AGO reversed social isolation-induced anhedonia markedly in a patient with MDD. Whether used alone or in combination with acetyl-L-carnitine, AGO can alleviate apathy in older patients with mild or moderate depression (Gavrilova et al., 2015). Clinical studies suggest that AGO has potential for the treatment of apathy, but how it improves apathy merits further exploration.

Another prominent symptom of many neuropsychiatric disorders is anhedonia (loss of interest and pleasurable feelings in response to previously rewarding stimuli) (Husain and Roiser, 2018). Anhedonia is most notable in MDD and schizophrenia. A pooled analysis of an open clinical trial showed that AGO improved anhedonia and anhedonia-like deficits in patients suffering from depression (di Giannantonia et al., 2019). AGO has been shown to reverse anhedonia-like deficits in rats exposed to chronic constant light (Tchekalarova et al., 2018). How AGO improves anhedonia is not well understood, but it has been reported that treatment with AGO or an antagonist of 5-HT2C receptors, SB242084, reversed the anhedonia-like state in mice with knockout of glutamate ionotropic receptor NMDA type subunit 2D (Yamamoto et al., 2017). Hence, antagonizing 5-HT2C receptors may be a potential strategy for treating apathy which has been linked to dysfunctions in the dopamine system, which plays a part in reward prediction, motivational arousal, and responsiveness to conditioned incentive stimuli (Tye et al., 2013). Chenu and collaborators (Chenu et al., 2019) showed that chronic administration of AGO in rats increased the number of spontaneously active dopamine neurons, the "burst" activity of dopamine neurons, the firing rate of 5-HT neurons in the dorsal-raphé nucleus, and tonic activation of postsynaptic 5-HT2C receptors located in the hippocampus. Those findings suggest that AGO may be involved in the modulation of dopamine release in anhedonia. Nevertheless, the therapeutic mechanism of action of AGO in apathy and anhedonia must be elucidated.
Agomelatine and Sleep Disorders

Sleep disorders are a group of conditions in which the normal sleep pattern or the ability to have meaningful sleep is disturbed. Primary sleep disorders include insomnia, hypersomnia, early waking, circadian-rhythm disorders, parasomnias, sleep-related movement disorders, and sleep-related breathing disorders (Pavlova and Latreille, 2019). Sleep disorders bring heavy economic burdens to patients and their families. Annual indirect and direct medical costs estimated to be US$150–175 billion worldwide in 2016 (Reynolds and Ebben, 2017). Patients with psychiatric disorders and dementia have more severe sleep disorders which, in turn, contribute to earlier onset and more rapid progression of neurodegenerative disorders (Bensa et al., 1992; Shi et al., 2018). Frobose et al. (2012) showed that a young patient with fatal familial insomnia had improved sleep efficiency, enhanced slow-wave sleep, and fewer awakenings during periods after AGO treatment for 6 months decreased the Depressive Scale score significantly, and improved limb movements, sleep, and awakening significantly in patients suffering from depression and Parkinson’s disease (Avila et al., 2015). Querra-Salazar et al. (2010) demonstrated that AGO administered all aspects of sleep abnormalities in patients with depression (particularly falling sleep and the quality of sleep) with an improvement in daytime alertness. The effects of AGO on sleep architecture in MDD have been measured using polysomnography: significant improvements in sleep efficiency, slow-wave sleep, and the distribution of delta activity throughout the night have been documented, but with no change in the amount or latency of rapid eye movement (REM) sleep. Moreover, after AGO treatment, the depressive symptoms of patients suffering from depression were reduced significantly and, on average, the timing of DLMO shifted 3.6-hour earlier, sleep onset was phase-shifted 28-minute earlier, and total sleep time increased by 24 minutes (Robillard et al., 2018).

In adults with autism spectrum disorder with intellectual disability, AGO treatment was associated with circadian-rhythm disorders and sleep disorders. Descamps and colleagues showed that AGO could attenuate impairments of wake-sleep architecture, reverse the beta-1 electroencephalogram power band, and improve stress-related rebound of REM sleep (Descamps et al., 2017). Dethmers-Mc�er et al. (2020) demonstrated that AGO could adjust circadian homeostasis of motor activity and the sleep-wake cycle in a rat model of chronic constant light, including enhancing the latency of REM sleep and non-REM sleep and upregulating expression of MT$_1$ and BDNF protein. The researchers previously demonstrated AGO to be effective in restoring impaired circadian patterns and plasma melatonin levels as well as improving depression and anxiety-like behavior in rats exposed to chronic constant light (Tchekalarova et al., 2018).

In mammals, melatonin is a neuroendocrine hormone. It is synthesized and secreted principally by the pineal gland at night (Lerner et al., 1960). Its primary function is to entrain the daily cycle of light and darkness to body structures, to regulate circadian rhythms, and to synchronize rhythms. Usually, the rhythmic secretion of melatonin is driven by the circadian clock in the suprachiasmatic nucleus of the hypothalamus. Light can entrain melatonin production according to the light schedule, suggesting that melatonin secretion from the pineal gland is closely related to the duration of darkness (Kastin et al., 2010). Plasma melatonin receptors distributed widely in various tissues to respond to periodic changes of light, such as the sleep-wake cycle. Exposure to light activates the suprachiasmatic nucleus and suppresses melatonin production, which then transmits the light information from the circadian clock and induces awakening in daytime. At night, the synthesis and secretion of melatonin remain high, which promotes sleep (Zisapel, 2018). Therefore, if the rhythmic secretion of melatonin is disrupted, then circadian rhythms are also disrupted (e.g., poor sleep quality and circadian-rhythm sleep-wake disorders). 5-HT and its receptors have been reported to be involved in sleep and wakefulness, as well as cognition and mood. Antagonism of 5-HT$_1$A receptor prolongs the duration of slow wave sleep (SWS) and low-frequency (LF) activity in the electroencephalogram (Landolt and Wehrle, 2009). Moreover, antagonism of 5-HT$_2$C receptors stimulates dopaminergic and adrenergic pathways and exerts antidepressant and anxiolytic actions in behavioral paradigms, which favors sleep (Millet, 2005). AGO activates MT$_1$ receptor, and antagonizes 5-HT$_1$ receptors synchronously, so it has a unique role in regulating the sleep-wake cycle and correcting sleep structure.

Agomelatine and Impairment of Cognition and Memory

A series of studies demonstrated that emotional disorders and sleep disorders can impact the function of memory and cognition negatively (McHutchison et al., 2020; Xu et al., 2020). Neurodegenerative diseases characterized by cognitive impairment (e.g., Alzheimer’s disease, and mild cognitive impairment) are characterized by abnormal emotional performance and sleep performance. About 50 million people worldwide have dementia (mainly Alzheimer’s disease), and the number is expected to increase to 152 million by 2050 (Alzheimer’s Disease International and Patterson, 2018). The estimated total global societal cost of dementia is $1.3 trillion, which is expected to surpass $2.8 trillion by 2050 (World Health Organization, 2021). However, efficacious disease-modifying therapeutics for dementia management are lacking. Interestingly, AGO has been reported to be efficacious in the treatment of depression (Tseng et al., 2015) and also in improving emotional memory (Bogolepova et al., 2011; Altnayan and Kiyligolu, 2016; Callegari et al., 2016).

Additional Table 1 summarizes the effects of AGO on memory impairment and cognitive impairment in clinical trials. Most AGO studies have focused on the treatment of patients with emotional disorders, but some studies have also shown that AGO improves cognitive function in patients with Alzheimer’s disease (Altnayan and Kiyligolu, 2016; Callegari et al., 2016), stroke, schizophrenia, or severe depression. Through evaluation of cognitive ability, English et al. (2018) and Bruno et al. (2014) found that AGO treatment could improve memory impairment/probability of “perseverative errors” in the Wisconsin Card Sorting Test in patients with schizophrenia (Additional Table 1). Moreover, studies have indicated that patients suffering from depression with cognitive impairments (especially those with major depression) had different degrees of improvements in cognitive ability after AGO treatment (Gavrilova et al., 2014; Gorwood et al., 2014, 2015; Kalyn et al., 2015; Cleary-Melin and Gorwood, 2017; Medvedev et al., 2018).

Safarova et al. (2018) and Gavrilova et al. (2015) showed that a combination of AGO and paroxetine improved the cognitive function in patients and pronounced therapeutic effect for cognitive dysfunction in older patients with mild or moderate depression. In a trial involving 20 older patients with mild or moderate depression, AGO reduced anxiety disorder and depression symptoms and improved sleep and cognitive ability as well as improved quality of life in patient significantly, with a slight increase in the Mini-Mental State Examination score and without pronounced or serious adverse events (Gavrilova et al., 2014). In another trial of 15 patients with primary fibromyalgia, treatment with AGO improved depression, anxiety disorder, and pain significantly in patients; the authors reported a trend towards the improvement of performances in executive/cognitive symptoms (Bruno et al., 2013). Through a double-blind parallel-group design in healthy volunteers, Harmer et al. (2011) observed that AGO increased the subjective rating of sadness, reduced recognition of sad facial expressions, improved affective memory, and reduced the emotion-potentiated startle response, whereas AGO alone produced no change in stress-related startle response without affecting other types of emotional processing. The researchers indicated that AGO is also beneficial for memory improvement in healthy cohorts. Nevertheless, how AGO improves the cognitive dysfunction accompanied by these diseases is not known.

Additional Table 2 summarizes the characteristics of AGO on memory and cognition in healthy animals and pathological animal models. Chronic AGO treatment reduced the error percentage of streptozotocin-treated rats in the eight-arm radial arm maze test, thereby suggesting that AGO could improve the spatial working memory of rats with Alzheimer’s disease (Bergamini et al., 2013; Gavrilova et al., 2013). Furthermore, Armstrong et al. (1993) demonstrated that AGO advanced sleep onset in rats with delayed sleep-phase syndrome, which lays the foundation for further studies of AGO on circadian-rhythm disorders and sleep disorders. Descamps and colleagues showed that AGO could attenuate impairments of sleep-wake architecture, reverse the beta-1 electroencephalogram power band, and improve stress-related rebound of REM sleep. Descamps et al. (2017) and Dethmers-McElroy et al. (2020) demonstrated that AGO could adjust circadian homeostasis of motor activity and the sleep-wake cycle in a rat model of chronic constant light, including enhancing the latency of REM sleep and non-REM sleep and upregulating expression of MT$_1$ and BDNF protein. The researchers previously demonstrated AGO to be effective in restoring impaired circadian patterns and plasma melatonin levels as well as improving depression and anxiety-like behavior in rats exposed to chronic constant light (Tchekalarova et al., 2018).

In mammals, melatonin is a neuroendocrine hormone. It is synthesized and secreted principally by the pineal gland at night (Lerner et al., 1960). Its primary function is to entrain the daily cycle of light and darkness to body structures, to regulate circadian rhythms, and to synchronize rhythms. Usually, the rhythmic secretion of melatonin is driven by the circadian clock in the suprachiasmatic nucleus of the hypothalamus. Light can entrain melatonin production according to the light schedule, suggesting that melatonin secretion from the pineal gland is closely related to the duration of darkness (Kastin et al., 2010). Plasma melatonin receptors distributed widely in various tissues to respond to periodic changes of light, such as the sleep-wake cycle. Exposure to light activates the suprachiasmatic nucleus and suppresses melatonin production, which then transmits the light information from the circadian clock and induces awakening in daytime. At night, the synthesis and secretion of melatonin remain high, which promotes sleep (Zisapel, 2018). Therefore, if the rhythmic secretion of melatonin is disrupted, then circadian rhythms are also disrupted (e.g., poor sleep quality and circadian-rhythm sleep-wake disorders). 5-HT and its receptors have been reported to be involved in sleep and wakefulness, as well as cognition and mood. Antagonism of 5-HT$_1$A receptor prolongs the duration of slow wave sleep (SWS) and low-frequency (LF) activity in the electroencephalogram (Landolt and Wehrle, 2009). Moreover, antagonism of 5-HT$_2$C receptors stimulates dopaminergic and adrenergic pathways and exerts antidepressant and anxiolytic actions in behavioral paradigms, which favors sleep (Millet, 2005). AGO activates MT$_1$ receptor, and antagonizes 5-HT$_1$ receptors synchronously, so it has a unique role in regulating the sleep-wake cycle and correcting sleep structure.
It has been demonstrated that AGO reduced amyloid β-42 (Aβ-42) accumulation in the frontostriatal and hippocampus of male rats with streptozotocin-induced Alzheimer’s disease (Ilieva et al., 2019), activated mitogen-activated protein kinase (MAPK) and prevented tau phosphorylation by activation of GSK3β and oxidative damage in PC12 cells (Yao et al., 2019). Furthermore, chronic administration of AGO completely prevented the stress-induced increase in glutamate release in the prefrontal/frontal cortex of rats by reducing glutamate transporters (Tardito et al., 2010). Recently, Ilieva et al. (2021) suggested that chronic treatment with AGO alleviated anxiety disorder and depressive-like behavior and decreased the Aβ level in the hippocampus by enhancing α-secretase and suppressing BACE1 in a rat model of Alzheimer’s disease (Tarkara et al. 2021) showed that AGO attenuated cisplatin-induced neurotoxicity in a mouse hippocampal neuronal cell line (HT22), and improved cisplatin-induced deficits in memory and recognition. In addition, in rat models with cognitive impairments, AGO also reversed neuronal loss in the hippocampus (Esvald et al., 2020; Ilieva et al., 2021) and caused significant enhancement in the volume of hippocampal CA1–3 subfields and the total number of pyramidal neurons in this region (Demir Özkan et al., 2015), thereby implying that AGO had neuroprotective effects.

BDNF is a neurotrophin distributed widely in the mammalian brain. BDNF has prominent functions in plastic regulation, including control of neuronal and glial development, neuroprotection, and modulation of short- and long-lasting synaptic interactions, which are critical for cognition and memory (Veitch et al., 2015; Unald and Halbach and von Bohnen Und Halbach, 2018). It has been reported that AGO alleviates depressive symptoms effectively in patients suffering from depression, with restoration of the plasma level of BDNF (Martinotti et al., 2016). AGO also increases the hippocampal BDNF level and improved the number of BDNF-positive neurons in rats with chronic unintentional mild stress by mild stress (Lu et al., 2018). Notably, Ladurelle et al. (2012) demonstrated that chronic administration of AGO increased the level of mature BDNF in the hippocampus significantly, and promoted rapid, sustained, enhanced cognitive plasticity in normal rats.

Cyclic adenosine monophosphate-responsive element binding protein (CREB) is a transcription factor. CREB regulates expression of several genes involved in the control of neuroplasticity, circadian rhythms, cell survival, and cognition (Carlezon et al., 2005). Moreover, CREB is a pivotal component of the "memory-switch" that converts short-term memory to long-term memory (Lisman et al., 2018). Furthermore, the CREB family is a major regulator of BDNF expression after tropomysin receptor kinase B (TrkB; a BDNF receptor) signaling (Esvald et al., 2020). Recent evidence suggests that chronic administration of AGO leads to improvements in memory determined by the upregulation of hippocampal expression of CREB and BDNF in mice exposed to unpredictable chronic, mild stress (Gumusu et al., 2014). It has been revealed that activation of MT1 and MT2 receptors activates ERK-90 kDa ribosomal S6 kinase (R6S6K) and BDNF signaling (Sun et al., 2018) and BDNF-TrkB signaling in hippocampal neurons (Li et al., 2018). Moreover, mice with deletion of the MT1 receptor show increased levels of the mature form of BDNF in the hippocampus (Patrício et al., 2015). In naive rats, Wada et al. (2014) found that chronic administration of AGO—contrary to traditional antidepressants—did not increase CREB phosphorylation, but instead modulated the mitogen-activated protein kinase (MAPK)-ERK1/2 and AKT-GSK3β pathways. ERK1/2 is one of the best-characterized members of the MAPK family. ERKs are involved in the proliferation, differentiation, apoptosis, inflammation, and synaptogenesis of cells (Albert-Gascó et al., 2020).

In neurons, an important function of ERK-MAPK signaling is regulation of synaptic plasticity, which relates to learning and memory processes (Alkadhi and Doo, 2019). Several studies have indicated that phosphatidylinositol 3-kinase (Akt) can activate AKT in brain cells and, by activation of this protein, GSK3β, which inhibits tau hyperphosphorylation (Chen et al., 2004; Endo et al., 2006). AKT shows high expression in some brain areas that are known to regulate cognition and neuroprotection, thereby having a key role in synaptic plasticity and neuroprotection in the neural plasticity of the brain. It supports the growth and survival of neurons (Beauilieu et al., 2009; Kitagishi et al., 2012). Studies have reported that activation of melatonin receptors (MT1 and MT2) can activate MAPK-ERK1/2 and AKT-GSK3β signaling pathways (Werry et al., 2005; Had Ayed Tka et al., 2015; Chagraoui et al., 2016; Li et al., 2020). Therefore, AGO may protect hippocampal neurons and improve memory and cognition by regulation of MAPK-ERK and AKT-GSK3β signaling pathways, but not by the classical CREB pathway induction.

It has been shown that 5-HT2C receptors mediate Ca2+ release from endoplasmic reticula via the phospholipase C-inositol 1,4,5-trisphosphate-Ca2+ and the mitochondrial Ca2+-transporting ATPase (Watan et al., 1995; Wada et al., 2006). 5-HT2C receptors show high expression and are upregulated in the brains of mice with acute infusion of AB (Bonn et al., 2013) and in rats with pilocarpine-induced epilepsy with memory impairment (Krishna Kumar et al., 2015). These studies indicated that intracellular Ca2+ dysregulation might (at least in part) result from 5-HT2C overexpression. Ca2+ dysregulation leads to neuronal apoptosis and cell death resulting in memory impairment and cognitive impairment (Kumar, 2020). Scholars have applied various sequencing methods and databases and analyzed “omics” data to discover new uses for existing drugs. Such studies have demonstrated AGO to also be involved in regulation of axon development, glutamatergic activity, netrin signaling, synaptic long-term potentiation, and Rho-GTPase-related pathways (an important regulator of morphological neuroplasticity) in hippocampal neurons (Patricio et al., 2015), as well as a neurotransphin signaling pathway and insulin signaling pathway in patients suffering from depression (Dmitrzak-Weglarz et al., 2021), which are closely related to memory and cognitive function.

Although the findings mentioned above are not entirely consistent (possibly caused by differences among different animal models and treatment regimens), it shows that AGO improves memory and cognitive function by activating multiple signal-transduction pathways (Figure 1). Clinical and basic-science studies investigating the effect of AGO on memory and cognition suggest that AGO might be a potential treatment strategy for the treatment of memory impairment and cognitive impairment. With the increase in age of populations worldwide, the dementia observed in degenerative diseases has become a growing public-health problem. However, prevention of the memory impairment and cognitive impairment in patients with dementia is not possible, and few drugs can be used for treatment. With its unique pharmacological effects, AGO provides a new idea for the treatment of dementia.

**Figure 1** Pathways involving the neuroprotective effects of AGO (schematic).

Through MT1/MT2, AGO can activate PI3K-AKT-GSK3β and MAPK-ERK1/2-RSK90-CREB cascades, which control cell transcription or protein modification. Activation of GSK3β inhibits tau phosphorylation. CREB can control BDNF transcription. By inhibiting the 5-HT2C receptor (5-HT2C), AGO can also inhibit IP3 from releasing Ca2+ from the endoplasmic reticulum, and promote expression of BDNF, which combined with TrkB and activates the MAPK-ERK1/2-RSK90-CREB signaling pathway. 5-HT2C-5-Hydroxytryptamine: 2C; AGO: agomelatine; AKT: protein kinase B; BDNF: brain-derived neurotrophic factor; CREB: cyclic adenosine monophosphate-response element binding protein; ERK: extracellular signal-related kinase; GSK3β: glycogen synthase kinase 3β; IP3: inositol 1,4,5-trisphosphate; MAPK: mitogen-activated protein kinase; MT1: melatonin receptor 1A; MT2: melatonin receptor 1B; PI3K: phosphatidylinositol-3-kinase; RSK90: 90 kDa ribosomal S6 kinase; TrkB: tropomyosin-related kinase B.

**Limitations of Agomelatine**

Although AGO possesses some distinct advantages, it also has some disadvantages. The commonly reported adverse events associated with using AGO are headache, nausea and fatigue, which are of mild-to-moderate severity (Stein et al., 2018). Moreover, due to its propensity to increase the level of liver enzymes, AGO is contraindicated in patients with impaired liver function (Stuhec, 2013; Friedrich et al., 2016). Hence, monitoring of liver function is recommended before AGO initiation and periodically during treatment. Nevertheless, developing AGO analogs with low toxicity and fewer effects for the treatment of chronic neurodegenerative diseases is important.

**Conclusions**

The most remarkable feature of AGO is its synergistic action between its agonism at MT1/MT2, and antagonism at 5-HT2C receptors. Given its innovative mechanism of action and favorable side-effects profile, AGO is beneficial for the treatment of mood disorders and sleep disorders, and most reviews have focused on these aspects. Unlike those reviews, in light of the neuroprotective effects of AGO, we have summarized research progress regarding the improvement of memory and cognitive function using AGO. However, few studies undertaken so far on the clinical treatment of cognition and dementia by AGO (particularly on the specific treatment of neurodegenerative diseases) need to be bolstered with additional studies. Nevertheless, clinical studies and animal experiments suggest that AGO should have a promising treatment option for improving memory, sleep, and mental activity simultaneously.
the manuscript.

Conflicts of interest: The authors declare no conflicts of interest.

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer reviewers: Melinda Barkhuizen, Philip Morris International, Netherlands; Nemil N. Bhatt, The University of Texas, USA.

Additional files: Additional Table 1: Characteristics of AGO for the treatment of memory and cognitive impairments in clinical studies. Additional Table 2: Characteristics of AGO for the treatment of memory and cognitive impairments in animal studies.

References
Albert-Gasch H, Ros-Bernal F, Castillo-Gómez E, Olucha-Bordonau FE (2020) MAP/ERK signaling in developing cognitive and emotional function and its effect on pathological and neurodegenerative processes. J Int J Mol Sci 21:4471.

Alex KD, Pehek EA (2007) Pharmacologic mechanisms of serotoninergic regulation of dopamine neurotransmission. Pharmacol Ther 113:296-320.

Alkadhi KA, Dao AT (2019) Effect of exercise and AJ protein infusion on long-term memory-related signaling molecules in hippocampal areas. Mol Neurobiol 56:4980-4987.

Altnyazir V, Kiyiğilu N (2016) Insomnia and dementia: is agomelatine treatment helpful? Case report and review of the literature. Ther Adv Psychopharmacol 6:263-266.

Alzheimer’s Disease International, Patterson C (2018) World Alzheimer Report 2018: The state of the art of dementia research: New frontiers. London: Alzheimer’s Disease International (ADI).

Antonen EG, Nikitina MV, Kruchek MM (2015) Clinical experience of the use of agomelatine in the treatment of patients with depression and chronic brain ischemia. Zh Nevrol Psikhiatr Im S S Korsakova 115:79-85.

Armstrong SM, McNulty OM, Guardiola-Lemaître B, Redman JR (1993) Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS). Pharmacol Biochem Behav 46:45-49.

Avila A, Cardona X, Martín-Baranera M, Leon L, Caballol N, Millet F, Bello J (2015) Agomelatine for depression in Parkinson’s disease: additional effect on sleep and motor dysfunction. J Clin Psychopharmacol 35:719-723.

Azim MS, Agarwal NB, Vohora D (2017) Effects of agomelatine on pentylentetrazole-induced kindling, kindling-associated oxidative stress, and behavioral despair in mice and modulation of its actions by luzindole and 1-(m-chlorophenyl)piperazine. Epilepsy Behav 72:140-144.

Ballester P, Martínez-M, Inda MD, Javaloyes A, Richdale AL, Muriel J, Belda C, Toral N, Azim MS, Agarwal NB, Vohora D (2017) Effects of agomelatine on pentylenetetrazole-kindled seizures in rats: a novel open-label, uncontrolled preliminary study. J Clin Psychopharmacol 33:507-511.

Budzi M, Grassi S, Serati M, Altamura AC (2017) Agomelatine for the treatment of generalized anxiety disorder. Expert Opin Pharmacother 18:1373-1379.

Calabrese F, Molteni R, Gabriel C, Mocaré E, Ragni G, Riva MA (2011) Modulation of neuroplastic molecules in selected brain regions after chronic administration of the novel antidepressant agomelatine. Psychopharmacology (Berl) 215:267-275.

Calabrese JR, Guelfi JD, Perdrizet-Chavellier C (2007) Agomelatine adjuvant therapy for acute bipolar depression: preliminary open data. Bipolar Disord 9:628-635.

Callegeri I, Matti C, Benassi F, Krueger S, Graftan J, Yaldizli O, Sossos D, Masuzzo D, Scialò C, Nobili F, Serrati C, Amore M, Cocito L, Embìt Giailloreti L, Paridini M (2016) Agomelatine improves apathy in frontotemporal dementia. Neurodegener Dis 16:352-356.

Can D Ö, Üçel U, Demir Özky ˚ u, Ulupinar E (2018) The effect of agomelatine treatment on diabetes-induced cognitive impairments in rats: concomitant alterations in the hippocampal neuron numbers. Int J Mol Sci 21:2461.

Cankara FN, Günaydın C, Çelik ZB, Sahin Y, Erzurumlu Y, Gülle K (2021) Agomelatine confers neuroprotection against cisplatin-induced hippocampal neurodegeneration. Aging 13:291-301.

Carleón WA Jr., Duran RS, Nestler EJ (2005) The many faces of CREB. Trends Neurosci 28:434-445.

Chagraoui A, Thibaut F, Skiba M, Thuillez C, Bourin M (2016) 5-HT2C receptors in psychiatric disorders: a review. Prog Neuropsychopharmacol Biol Psychiatry 66:120-135.

Chen G, Bower KA, Ma C, Fang S, Thiele CI, Luo J (2004) Glycogen synthase kinase β3eta (GSKβ3eta) mediates 6-hydroxydopamine-induced neuronal death. J Neurochem 88:1162-1164.

Chenu S, El Mansari M, Blot P (2013) Electrophysiological effects of repeated administration of agomelatine on the dopamine, norepinephrine, and serotonin systems in the rat brain. Neuropsychopharmacology 38:275-284.

Chisholm D, Sweeney K, Sheehan P, Rasmussen B, Smit F, Cuijpers P, Saenx S (2016) Scaling-up treatment of depression and anxiety: a global return on investment analysis. Lancet Psychiatry 3:415-424.

Cipriani A, Furukawa TA, Salanti G, Chaiman A, Atkinson L, Ogawa Y, Leucht S, Ruhe HG, Turner DR, Higgins JPT, Egger M, Takeda N, Hayakawa Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 391:1357-1366.

Clety-Melin ML, Gorwood P (2017) A simple attention test in the acute phase of a major depressive episode is predictive of later functional remission. Depression Anxiety 34:159-170.

Corboy I, Tanrikut C, Zoladz PR, Campbell AM, Park CR, Gabriel C, Mocaré E, Sandi C, Diamond DM (2009) The antidepressant agomelatine blocks the adverse effects of stress on memory and enables spatial learning to rapidly increase neural cell adhesion molecule (NCAM) expression in the hippocampus of rats. Int J Neuropsychopharmacol 12:329-341.

Dagyte G, Luiten PG, De Jager T, Gabriel C, Mocaré E, Den Boer JA, Van der Zee EA (2011) Chronic stress and antidepressant agomelatine induce region-specific changes in synapsin I expression in the rat brain. J Neurosci Res 89:1646-1657.

De Berardis D, Valcher A, Fornaro S, Nmarini S, Marinelli S, Moschetta FS, Martignetti G, Di Giannantonio M (2013) Agomelatine reversal of escitalopram-induced apathy: a case report. Psychiatr Clin Neurosci 67:190-191.

Demir Özky ˚ u, ˚ Zotutar E, Can D Ö, Üçel U, ˚ Oztrük Y, Ulupinar E (2015) Effects of long-acting antidepressant treatment on cognitive performance and hippocampal plasticity of adult rats. Behav Pharmacol 26:469-480.

Demireva EV, Suri D, Morelli E, Mahadevia D, Chuhma N, Teixeira CM, Ziolkowski A, Hersh M, Fifer J, Bagchi S, Chemiakine A, Moore H, Gingrich JA, Balsam P, Rayport S, Anserge MS (2020) 5-HT2C receptor blockade reverses SRI-associated basal ganglia dysfunction and potentiates therapeutic efficacy. Mol Psychiatry 25:3304-3321.

Descamps A, Roussel C, Dugua H, Deligreb B, Delargenè re P, Csepregi R (2014) Agomelatine restores a physiological response to stress in the aged rat. Neurosci Lett 566:257-262.

Di Giannantonio M, Montemirto C, Segpede G, Brunetti M, Baroni G, Corbo M, Anders M, Vandèr R, Martignetti G, Manozoli L (2019) Agomelatine effectiveness, tolerability, and impact on anhedonia in major depression: a pooled analysis. J Clin Psychopharmacol 39:288-290.

Dimitrak-Weglarz M, Banach E, Bilska K, Narozna B, Szczepankiewicz A, Reszka E, Jabolonska E, Kapelski P, Skobinska P, Pawlak J (2021) Molecular regulation of the melatonin biosynthesis pathway in unpolar and bipolar depression. Front Pharmacol 12:668541.

Drozd R, Rychlik M, Fijalkowska A, Rygula R (2019) Effects of cognitive judgement bias and acute antidepressant treatment on sensitivity to feedback and cognitive flexibility in the rat version of the probabilistic reversal-learning test. Behav Brain Res 359:619-629.

Duda P, Hajda D, Wójcicka O, Rakus D, Giza ˚ k A (2020) GSK3β: a master player in depressive disorder pathogenesis and treatment responsiveness. Cells 9:727.
Endo H, Nito C, Kamada H, Yu F, Chan PH (2006) Agt/GSKbeta survival signaling is involved in acute brain injury after subarachnoid hemorrhage in rats. Stroke 37:2140-2146.

Englisch S, Jung HS, Eisenacher S, Lewien A, Becker A, Nowak U, Braun H, Thiem J, Meyer-Lindenberg A, Zink M (2018) Neurocognitive effects of agomelatine treatment in schizophrenia patients suffering from comorbid depression: results from the AGOPOSCH study. Neuropsychopharmacology 38:357-361.

Erdogan C, Ozdemir Rezaki P, Kocaoglu OM, Buturak S V (2020) Comparison of the effects of antidepressants with different mechanisms of action on efficacy, cognitive functions and side effects. Turk Psikiyatri Derg 31:90-98.

EsvaRD EE, Tuivksene J, Sirp A, Patil S, Bramham CR, Timmusk T (2020) CREB family transcription factors are major mediators of BDNF transcriptional autoregulation in cortical neurons. J Neurosci 40:1405-1426.

Fornaro M, Mccarthy A, Berardis D, De Pasquale C, Tabaton M, Martino M, Collicchio S, Cattaneo CI, D Angelino E, Fornaro P (2013) Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: a preliminary open label study. Neuropsychiatr Dis Treat 9:243-251.

Friedrich ME, Akimova E, Huf W, Konstantinidis A, Papageorgiou K, Winkler D, Toto S, Grell W, Grothmann R, Kasper S (2016) Drug-induced liver injury during antidepressant treatment: results of aVISP, a drug surveillance program. Int J Neuropsychopharmacol 19:26-26.

Froboese T, Slawik H, Schreiner R, Vesely Z, Wengand M, Bäuml J, Forst H (2012) Agomelatine improves sleep in a patient with familial insomnia. Pharmacopsychiatry 45:34-36.

Gavriloova SI, Kolykhov IV, Ponomareva EV, Seleznева ND (2014) Clinical experience with agomelatine for the treatment of depression in elderly patients in outpatient practice. Zh Nevrol Psikiatr Im S S Korsakov 114:43-48.

Gavrilova SI, Kalyn YaB, Safarova TP, Yakovleva OB, Sheshenin VS, Korotkov VV, Shipilov VS, Shipilova ES (2015) Optimization of the efficacy and safety of antidepressant therapy in patients of a geriatric psychiatric unit. Zh Nevrol Psikiatr Im S S Korsakov 115:24-32.

Gorwood P, Richard-Devantoy S, Baylé F, Cléry-Melin ML (2014) Psychomotor retardation is a scar of past depressive episodes, revealed by simple cognitive tests. Eur Neuropsychopharmacol 24:1630-1640.

Gorwood P, Vaiva G, Corrubie E, Llorca PM, Baylé FJ, Courert P (2015) The ability of early changes in motivation to predict later antidepressant treatment response. Neuropsychiatr Dis Treat 11:2875-2882.

Gorwood P, Benichou J, Moore N, Wattiez M, Secouraud MC, Desobry X, Picarel-Blanchot F, de Bodinat C (2020) Agomelatine in standard medical practice in depressed patients: results of a 1-year multicentre observational study in France. Clin Drug Investig 40:1009-1020.

Grunze H, Vieta E, Goodwin GM, Bowden CJ, Goodwin GM (2011) Agomelatine facilitates positive versus negative affective processing in healthy volunteer models. J Psychopharmacol 25:1159-1167.

Gupta S, Sharma B (2014) Pharmacological benefits of agomelatine and vanillin in Alzheimer's disease. Neural Regen Res 17:1190-1198.

Hadj Ayed Tka K, Mahfoudh Boussaid A, Zaouali MA, Kammoun R, Bejaoui M, Ghoul Gutierrez MEZ, Savall ASP, da Luz Abreu E, Nakama KA, Dos Santos RB, Guedes MCM, Gupta S, Singh P, Sharma BM, Sharma B (2015) Neuroprotective effects of agomelatine in a rat model of Alzheimer’s disease. Physiol Behav 239:113525.

Il'yaeva F, Yuze M, Aign AE, Güzell, Baki H, Uşar F, Babadagüz, Z Müldecı M, Mutlu E (2015) The combination of agomelatine and riltnesin exerts a synergistic interaction in passive avoidance task. Hum Exp Toxicol 34:787-795.

Kalym YaB, Safarova TP, Yakovleva OB, Sheshenin VS, Korotkov VV, Shipilov VS, Gavrilova SI (2015) Experience of the antidepressive therapy with valdoxan (agomelatine) in a psychiatriatic unit of the psychiatric hospital. Zh Nevrol Psikiatr Im S S Korsakov 115:55-62.

Kannaway DI (2019) A critical review of melatonin assays: Past and present. J Pineal Res 67:e12577.

Kennedy SH, Rizvi S, Fulton K, Rassmussen J (2008) A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. J Clin Psychopharmacol 28:239-333.

Kitagahi Y, Kobayashi M, Kituka K, Matsuda S (2012) Roles of PI3K/AKT/GSK3β/MTOR pathway in cell signaling of mental illnesses. Depress Res Treat 2012:752563.

Krishnakumar A, Nandhu MS, Paulose CS (2009) Uproregulation of 5-HT2C receptors in hippocampus of pilocarpine-induced epileptic rats: antagonism by Bacopa monnieri. Epilepsy Behav 16:225-230.

Kumar A (2020) Calcium signaling during brain aging and its influence on the hippocampal synaptic plasticity. Adv Exp Med Biol 1131:985-1012.

Lauderrille N, Gabriel C, Viggiano A, Mocaer E, Baulieu EE, Bichu M (2012) Agomelatine (S29098) modulates the expression of cytoskeletal microtubular proteins, synaptic markers and BDNF in the rat hippocampus, amygdala and PFC. Psychopharmacology (Berl) 221:493-509.

Landolt HP, Welheir R (2009) Antagonism of serotoninergic 5-HT2A/2C receptors: mutual improvement of sleep, cognition and mood? Eur J Neurosci 29:1795-1809.

Lapmanee S, Chaorenphandhu J, Teerapornpuntak J, Krishnamna N, Chaorenphandhu N (2017) Agomelatine, venlafaxine, and running exercise effectively prevent anxiety- and depression-like behaviors and memory impairment in restraint stressed rats. PLoS One 12:e0187671.

LeMouël J, Gotlib IH (2019) Depression: a cognitive perspective. Clin Psychol Rev 69:51-66.

Lerner AB, Case JD, Takahashi Y (1960) Isolation of melatonin and 5-methoxyindole-3-acetic acid from bovine pineal glands. J Biol Chem 235:1992-1997.

Li K, Shen S, Ji Y, Li X, Yang LS, Wang XD (2018) Melatonin augments the effects of fluoxetine on depression-like behavior and hippocampal BDNF-TrkB signaling. Neurosci Bull 34:303-311.

Li P, Hu C, Yao X, Luo L, Tu Q (2020) Melatonin receptor protects cardiomyocyte against oxidative stress-induced apoptosis through the MAPK-ERK signaling pathway. J Recept Signal Transduct Res 40:117-125.

Lisman J, Cooper K, Sehgal M, Silva AJ (2018) Memory formation depends on both synapse-specific modifications of synaptic strength and cell-specific increases in excitability. Nat Neurosci 21:309-314.

Lu Y, Ho CS, McIntyre RS, Wang W, Ho RC (2018) Agomelatine-induced modulation of brain-derived neurotrophic factor (BDNF) in the rat hippocampus. Life Sci 210:177-184.

Marocco J, Reynaert ML, Gatta E, Nicoletti F, Maccari S, Morley-Fletcher S, Mairesse J (2014) The effects of antidepressant treatment in prenatally stressed rats support the glutamatergic hypothesis of stress-related disorders. J Neurosci 34:2015-2024.

Marshall P (2020) The hidden links between mental disorders. Nature 581:19-21.

Martin V, Allali N, Evrard M, Marday M, Riffaud A, Franc B, Mocaer E, Gabriel C, Fossati F, Lehericy S, Lamurency L (2017) Effect of agomelatine on memory defects and hippocampal gene expression induced by chronic social defeat stress in mice. Sci Rep 8:45907.

Marseille P, Pettorossi M, de Berardis D, Varasano PA, Lucidi Pressanti G, De Remigis V, Valcheria A, Ricci V, Di Nicola M, Jani L, Biggio G, Di Giannantonio M (2016) Agomelatine increases BDNF serum levels in depressed patients in correlation with the improvement of depressive symptoms. Int J Neuropsychopharmacol 19:pyw003.

Mchutchison CA, Leighton DJ, McIntosh A, Cleary E, Warner J, Porteous M, Chandran S, Pal S, Abrahams S (2020) Relationship between neuropsychiatric disorders and cognitive and behavioural change in MND. J Neurol Neurosurg Psychiatry 91:245-253.
Medvedev VE, Ter-Isaakyan AV, Frolova VI, Korovaychuk VA, Gushanskaia EV (2018) Treatment of depression with cognitive impairment. Zh Nevrol Psikiatr Im S S Korsakov 118:77-80.

Millan MJ (2005) Serotonin 5-HT2C receptors as a target for the treatment of depressive and anxious states: focus on novel therapeutic strategies. Therapie 60:441-460.

Millan MJ, Gobert A, Lejeune F, Deyame A, Newman-Tancredi A, Pasteau P, Viet JM, Cussac D (2003) The novel melatonin agonist agonist (S)-20989 is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. J Pharmacol Exp Ther 306:954-964.

Musazzi L, Seguini M, Maleri A, Trecarni G, Pelizzari M, Tornese P, Racagni G, Tardito D (2014) Time-dependent activation of MAPK/Erk1/2 and Akt/GSK3 cascades: modulation by agonist. BMC Neurosci 15:119.

Norman TR, Oliver JS (2019) Agomelatine for depression: expanding the horizons? Expert Opin Pharmacother 20:657-665.

O’Neill B, Gardani M, Findlay G, Whyte T, Cullen T (2014) Challenging sleep and sleep cycle brain injury: a preliminary response to agomelatine treatment. Brain Inj 28:378-381.

Patricio P, Mateus-Pinho A, Imler M, Alves ND, Machado-Santos AR, Morais M, Correia O’Neill B, Gardani M, Findlay G, Whyte T, Cullen T (2014) Challenging sleep and sleep cycle brain injury: a preliminary response to agomelatine treatment. Brain Inj 28:378-381.

Price RB, Duman R (2020) Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. Mol Psychiatry 25:530-543.

Quera-Salva MA, Lemoine P, Guilleminault C (2010) Impact of the novel antidepressant of antidepressants’ action in the hippocampal dentate gyrus. Neurropsychopharmacology 40:338-349.

Pavlova MK, Latreille V (2019) Sleep disorders. Am J Med 132:292-299.

Patrício P, Mateus-Pinheiro A, Irmler M, Alves ND, Machado-Santos AR, Morais M, Correia O’Neill B, Gardani M, Findlay G, Whyte T, Cullen T (2014) Challenging sleep and sleep cycle brain injury: a preliminary response to agomelatine treatment. Brain Inj 28:378-381.

Norman TR, Olver JS (2019) Agomelatine for depression: expanding the horizons? Expert Opin Pharmacother 20:657-665.

O’Neill B, Gardani M, Findlay G, Whyte T, Cullen T (2014) Challenging sleep and sleep cycle brain injury: a preliminary response to agomelatine treatment. Brain Inj 28:378-381.

Reynolds SA, Ebben MR (2017) The cost of insomnia and the benefit of increased access to evidence-based treatment: cognitive behavioral therapy for insomnia. Sleep Med Clin 12:39-46.

Robillard R, Carpenter JS, Feilds KL, Hermens DF, White D, Naismith SL, Bartlett D, Quera-Salva MA, Lemoine P, Guilleminault C (2010) Impact of the novel antidepressant a 5-HT2C receptor agonist in non-depressed out-patients with generalized anxiety disorder. Eur Neuropsychopharmacol 28:970-979.

Sung YJ, Bae JH, Lee JH, Kim YN, Kim DK (2018) The melatonin signaling pathway in a long-term memory in vitro study. Molecules 23:737.

Tardito D, Milanesi M, Bonifacio T, Musazzi L, Grilli M, Mallei A, Mocaer E, Gabriel-Gracia C, Racagni G, Popoli M, Bonanno G (2010) Blockade of stress-induced increase of glutamate release in the rat prefrontal/frontal cortex by agonist melatonin involves synergy between melatoninergic and 5-HT2C receptor-dependent pathways. BMC Neurosci 11:68.

Tchekalarova J, Stoyanova T, Ilieva K, Mitreva R, Atanasova M (2018) Agomelatine treatment corrects symptoms of depression and anxiety by restoring the disrupted melatonin circadian rhythms of rats exposed to chronic constant light. Pharmacol Biochem Behav 171:1-9.

Tchekalarova J, Kortenska L, Ivanova N, Atanasova M, Marinov P (2020) Agomelatine treatment corrects impaired sleep-wake cycle and sleep architecture and increases sensitivity of 5-HT2C receptor as well as BDNF expression in the hippocampus during the subjective light phase of rats exposed to chronic constant light. Psychopharmacology (Berl) 237:503-518.

Tchekalarova J, Atanasova D, Nenchovska Z, Atanasova M, Kortenska L, Gesheva R, Lazarov N (2017) Agomelatine protects against neuronal damage without preventing epileptogenesis in the kindling model of temporal lobe epilepsy. Neurobis 140:1-14.

Tendesa P, Soci V, De Gennaro L, Ferrara M (2018) Sleep and emotional processing. Sleep Med Rev 20:183-195.

Toledo L, Vázquez GH, Ballestinari RI (2017) Depression and mania in bipolar disorder. Curr Neuropharmacol 15:353-358.

Tsuno N, Besset A, Ritchie K (2005) Sleep and depression. J Clin Psychiatry 66:1254-1269.

Tye KM, Mirzabekov JJ, Warden MR, Ferenci EA, Tsai HK, Finkelstein J, Kim SY, Adrihaki A, Thompson KR, Andalman AS, Gunaydin LA, Witten IB, Deisseroth K (2013) Dopamine neurons modulate neural encoding and expression of depression-related behaviour. Nature 493:537-541.

von Bohlen Und Halbach O, von Bohlen Und Halbach V (2018) BDNF effects on dendrit spine morphology and hippocampal function. Cell Tissue Res 373:729-741.

Wada K, Hu L, Mores N, Navarro CE, Fuda H, Krsmannovic LZ, Catt KJ (2006) Serotonin 5-HT receptor subtypes mediate specific modes of 5-HT-induced signaling and regulation of neurosecretion in gonadotropin-releasing hormone. Mol Endocrinol 20:125-135.

Watson JA, Elliott AC, Brown PD (1995) Serotonin elevates intracellular Ca2+ in rat choroid plexus epithelial cells by acting on 5-HT2C receptors. Cell Calcium 17:120-128.

Weissmann D, van der Laan S, Underwood MD, Salvetat N, Cavares L, Vincent L, Molina F, Mann J, Angano V, Piujol JF (2016) Region-specific alterations of A-to-I RNA editing on serotonin 2C receptor in the cortex of suicides with major depression. Transl Psychiatry 6:878.

Werry TD, Gregory KJ, Sexton PM, Christopoulos A (2005) Characterization of serotonin 5-HT2C receptor signaling to extracellular signal-regulated kinases 1 and 2. J Neurochem 93:1603-1615.

Werry TD, Laioacono R, Sexton PM, Christopoulos A (2008) RNA editing of the serotonin 5HT2C receptor and its effects on cell signalling, pharmacology and brain function. Pharmacol Ther 119:7-23.

World Health Organization (2021) Dementia: Key Facts. https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed November 8, 2021.

Wu X, Xi J, Zhou QY, Li Y, Gao XP (2011) Role of microglia-mediated neuronal injury in neurodegenerative diseases. Zhongguo Zhihu Gengcheng Yanyu 25:1109-1115.

Xu W, Tan CC, Zou JH, Ren YJ, Liu YJ, Gu XP (2021) Role of microglia-mediated neuronal injury in neurodegenerative diseases. Zhongguo Zhihu Gengcheng Yanyu 25:1109-1115.

Yous S, Andrieux J, Howell HE, Morgan PJ, Renard P, Pfeiffer B, Lesieur D, Guardiola-Guilleminault P, Lemoine P, Guilleminault C (2018) Serotonin 5-HT2C receptor signaling to extracellular signal-regulated kinases 1 and 2. J Neurochem 93:1603-1615.

Yoon S, Andrieux J, Howell HE, Morgan PJ, Renard P, Pfeiffer B, Lesieur D, Guardiola-Guilleminault P, Lemoine P, Guilleminault C (2018) Serotonin 5-HT2C receptor signaling to extracellular signal-regulated kinases 1 and 2. J Neurochem 93:1603-1615.

Zou HB (2019) Melatonin receptor stimulation by agomelatine prevents light phase of rats exposed to chronic constant light. Psychopharmacology (Berl) 237:503-518.

Zsizser SG, Bhatt NN; C-Editor: Zhao M; S-Editors: Yu J, Li CH; L-Editors: Yu J, Song LP; T-Editor: Jia Y

Review

www.nrronline.org

NEURAL REGENERATION RESEARCH

Vol 18 | No. 4 | April 2023 | 733
### Additional Table 1 Characteristics of AGO for the treatment of memory impairment and cognitive impairment in clinical studies

| Study design                  | Patients                                | Agent and dose (route)                                                                 | Primary measure and results                                                                 | Conclusions                                                                 | Study                                      |
|-------------------------------|-----------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------|
| 1 month, case report          | 1 AD patient                            | AGO (25 mg/d, p.o.)                                                                 | MMSE; MMSE score: 19 (before AGO treatment) vs. 23 (after 1-month AGO treatment)          | Significant improvement in cognitive function                              | Altinyazar and Kiylioglu, 2016            |
| 10 wk, double-blind           | 24 FTD patients                         | AGO (50 mg/d, p.o.) or melatonin (10 mg/d, p.o.)                                    | AES-C; 50.6 ± 2.4 (AGO) vs. 42.7 ± 2.4 (melatonin), *P* = 0.006                           | Significant reduction of apathy and improvement in cognitive function by AGO, but not melatonin | Callegari et al., 2016                    |
| 6–8 wk, randomized            | 2048 MDD patients                       | AGO (25 or 50 mg/d, p.o.)                                                           | TMT-A, TMT-B, d2 test; 67.68% of patients were responders and 43.31% were in remission   | Significant improvement in cognitive function                              | Gorwood et al., 2014                     |
| 8 wk, single-blind            | 42 patients with mild-to-moderate depression | Antidepressant monotherapy (fluvoxamine, venlafaxine or AGO, 25 mg/d) or use the same antidepressant in combination with actovegin (p.o.) | MMSE; 26.23 ± 2.32 (day 0) vs. 28.44 ± 1.49 (day 56), *P* < 0.01 | Significant improvement in cognitive function, with faster improvement in cognitive function by the antidepressant in combination with actovegin | Safárova et al., 2018                    |
| 7 d, double-blind             | 48 healthy volunteers                   | AGO (25–50 mg/d, p.o.)                                                              | Facial expression recognition task; AGO (25 mg) vs. placebo (group × emotion F(6, 174) = 2.6, *P* = 0.018), AGO (50 mg) vs. placebo (group × emotion F(6, 180) = 0.8, *P* = 0.6) | Significantly reduced subjective ratings of sadness, reduced recognition of sad facial expressions, improved positive affective memory and reduced emotion-potentiated startle response with 25 mg of AGO, but not 50 mg of AGO | Harmer et al., 2011                      |
| 12 wk, proof-of-concept study | 27 patients with schizophrenia and comorbid depression | Antipsychotic drugs in combination with AGO (p.o.)                                  | MCCB; composite score (baseline vs. after treatment, *P* = 0.001), reasoning/problem-solving subscore (baseline vs. after treatment, *P* = 0.001) | Significant improvement in the MCCB composite score and the reasoning/problem-solving subscore | Englischt et al., 2018                   |
| Duration          | Sample Size                        | Intervention                | Endpoints                                    | Results                                                                 | Reference                              |
|-------------------|------------------------------------|-----------------------------|----------------------------------------------|-------------------------------------------------------------------------|----------------------------------------|
| 6 wk, randomized  | 35 patients with depression and marked cognitive impairment | AGO (25 mg/d, p.o.)        | MMSE, Rey test for auditory-speech learning, RAVLT; 74.3% of patients were responders and 51.4% were in remission | Significant improvement in cognitive function | Medvedev et al., 2018                  |
| 16 wk, open-label uncontrolled trial | 20 patients with schizophrenia | AGO (50 mg/d, p.o.)        | Wisconsin Card Sorting Test; perseverative errors: 14.75 ± 10.05 (baseline) vs. 11.25 ± 10.46 (week 16), P = 0.033, Cohen’s d = 0.3 | Improvement in performances of the Stroop task and “perseverative errors” in the Wisconsin Card Sorting Test | Bruno et al., 2014                     |
| 12 wk, open-label, preliminary study | 15 FMS patients                  | AGO (25 mg/d, p.o.)        | Wisconsin Card Sorting Test; perseverative errors: 26.87 ± 30.963 (baseline) vs. 25.13 ± 30.223 (week 16), P = 0.1 | Improvement in cognitive function | Bruno et al., 2013                     |
| 6–8 wk, multicenter study | 2048 outpatients with depression | AGO (25 mg/d, p.o.)        | TMT-A, TMT-B, d2 test; TMT-A (time) and TMT-B (time): P < 0.0001, TMT-A (mistakes): P = 0.0004, TMT-B (mistakes): P < 0.0001, F1 (number of omission mistakes): P < 0.05 | Significant improvement in d2, TMT-A, and TMT-B tests | Cléry-Melin and Gorwood, 2017           |
| 42 d, randomized study | 18 patients with depression         | AGO (25–50 mg/d, p.o.)    | MMSE; 26.76 ± 3.30 (day 0) vs. 28.17 ± 2.0 (day 42) | Improvement in cognitive function | Kalyn et al., 2015                    |
| 6 wk, multicenter, observational, phase-IV study | 1565 patients with depression | AGO (25–50 mg/d, p.o.)    | MAThyS; 4.05 ± 1.11 (baseline) vs. 4.87 ± 1.16 (week 6), P < 0.001 | Significant improvement in cognitive function | Gorwood et al., 2015                  |
| 8 wk, randomized study | 40 patients with mild-to-moderate depression | Antidepressant monotherapy (fluvoxamine, venlafaxine) AGO (25–50 mg/d, p.o.) | MMSE; 26.90 ± 2.10 (day 0) vs. 28.15 ± 1.53 (day 56), P < 0.05 | Significant improvement in cognitive function, but faster improvement using the antidepressant in combination with carnitine | Gavrilova et al., 2015                 |
or AGO, 25–50 mg/d) or use the same antidepressant in combination with carnitine (p.o.)

| Study Duration         | Participants                                | Treatment                  | Outcome Measures                                      | Results                                                                 |
|------------------------|---------------------------------------------|----------------------------|-------------------------------------------------------|------------------------------------------------------------------------|
| 3 months, randomized   | 40 patients with post-stroke depression      | AGO (25 mg/d, p.o.)       | MMSE; 25.2 ± 1.1 (0 day) vs. 27.2 ± 0.6 (month 3)    | Improvement in cognitive function                                       |
| 6 wk, randomized       | 20 older patients with mild-to-moderate depression | AGO (25–50 mg/d, p.o.)   | MMSE; median MMSE score before treatment = 28.5 and at study termination = 29.5 ($P > 0.05$) | AGO had no effect on cognitive function and did not elicit pronounced or serious adverse events, but the cognition of patients showed an increase |

AD: Alzheimer’s disease; AES-C: apathy evaluation scale-clinician version; AGO: agomelatine; CBI: chronic brain ischemia; FMS: fibromyalgia syndrome; FTD: frontotemporal dementia; MAThyS: multidimensional assessment of thymic states; MCCB: measurement and treatment research to improve cognition in schizophrenia consensus cognitive battery; MDD: major depressive disorder; MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; p.o.: per os; RAVLT: Rey auditory verbal learning test; TMT-A: trail-making test-A; TMT-B: trail-making test-B.
### Additional Table 2 Characteristics of AGO for the treatment of memory impairment and cognitive impairment in animal studies

| Study model                                | Animal    | Agent and dose (route) | Main results and conclusion                                                                                                                                                                                                 | Study                      |
|--------------------------------------------|-----------|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| CCH                                         | Mouse     | AGO (2–4 mg/kg per day, i.p.), 24 d | In the Morris water maze test, AGO treatment decreased escape latency time in CCH-induced mice ($P < 0.05$). AGO improved long-term memory.                                                                                                         | Gupta et al., 2015          |
| Renovascular hypertension inducedvascular dementia | Rat       | AGO (2–4 mg/kg per day, i.p.), 24 d | In the Morris water maze test, the escape latency time was reduced significantly on day 4 (40.1 ± 2.6 (2-mg AGO) and 39.8 ± 2.59 (4-mg AGO), $P < 0.001$). AGO improved long-term memory. | Singh et al., 2015          |
| 3-Nitropropionic acid-induced Huntington’s disease | Rat       | AGO (2–4 mg/kg per day, p.o.), 28 d | In the Morris water maze test, AGO treatment reduced the escape latency time significantly on day 4 ($P < 0.001$) as compared with that in the 3-3-nitropropionic acid-treated group. AGO improved long-term memory. | Gupta and Sharma, 2014      |
| Streptozotocin-induced model of AD          | Rat       | AGO (40 mg/kg per day, i.p.), 30 d | In the radial arm maze test, AGO treatment decreased working memory error ($P < 0.01$). AGO improved working memory.                                                                                                                                                      | Ilieva et al., 2019         |
| PRS                                         | Rat       | AGO (40 mg/kg per day, i.p.), 21 d | In the social memory test, PRS rats treated with AGO displayed a reduction in sniffing behavior compared with vehicle-treated PRS rats ($P < 0.05$). AGO improved social memory performance.                                               | Marrocco et al., 2014       |
| Restraint-induced stress                   | Rat       | AGO (10 mg/kg per day, i.p.), 4 wk | In the Morris water maze test, AGO-treated stressed rats exhibited a reduction in escape latency on days 1 ($P < 0.01$), 2 ($P < 0.001$), and 3 ($P < 0.001$) and correct quadrant time ($P < 0.001$) compared with vehicle-treated stressed rats. AGO improved long-term memory. | Lapmane et al., 2017        |
| Chronic social defeat stress               | Mouse     | AGO (10 mg/kg per day, i.p.), 3 wk | In the novel object recognition test, stressed-AGO mice displayed a significantly increase in the recognition index compared with stressed (hydroxyethylcellulose-treated) mice ($P < 0.05$). AGO improved recognition memory. | Martin et al., 2017         |
| Memory deficit induced by scopolamine      | Mouse     | AGO (1, 10, or 30 mg/kg per day, i.p.), 30 min before testing | In the passive avoidance task, AGO (30 mg/kg) significantly increased the retention time as compared with scopolamine ($P < 0.05$). AGO alleviated episodic memory deficit.                                                      | Ilkaya et al., 2015         |
| Pentylenetetrazol-induced kindling         | Mouse     | AGO (10 mg/kg per day, p.o.), 3 wk | In the Y maze test, AGO treatment significantly enhanced percentage alternation and the number of arm entries ($P < 0.001$) following PTZ                                                                 | Azim et al., 2017           |
| Status                        | Species | AGO Dose and Administration | Treatment Duration | Behavioral Test | Outcome Description                                                                                                                                                                                                 | Reference |
|-------------------------------|---------|------------------------------|--------------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Chronic mild stress-induced  | Mouse   | AGO (10 mg/kg per day, i.p.), 5 wk | Kindling-induced seizures. AGO improved working memory. In the Morris water maze test, AGO shortened the escape latency significantly in the familiarization session ($P < 0.001$) and increased the time spent in the escape platform quadrant ($P < 0.01$). AGO improved long-term memory. In the novel object recognition test, AGO increased the ratio index significantly compared with stress-exposed control mice ($P < 0.001$). AGO improved recognition memory. | Gumuslu et al., 2014 |
| cognitive deterioration       |         |                              |                    |                 |                                                                                                                                                                                                                         |           |
| Normal                        | Rat     | Single intraperitoneal administration of AGO (10–40 mg/kg) in the evening or AGO (2.5, 10, or 40 mg/kg) in the morning | In the novel object recognition test, AGO (10 and 40 mg/kg) increased the recognition index significantly ($P < 0.01$). AGO improved recognition memory in the morning or evening. | Bertaina-Anglade et al., 2011 |
| Stress                        | Rat     | AGO (10 mg/kg per day, i.p.), 22 d | In the radial-arm water maze test, AGO treatment reduced arm-entry errors significantly in non-stressed and stressed rats ($P < 0.001$). AGO blocked the predator stress-induced impairment of spatial memory and improved spatial memory. | Conboy et al., 2009 |
| Normal                        | Rat     | AGO (40 mg/kg per day, i.p.), 20 wk | In the Morris water maze test, AGO-treated rats located the hidden platform significantly faster than did control rats on days 2 ($P < 0.01$), 3 ($P < 0.001$), and 4 ($P < 0.01$). During the probe trial, AGO-treated rats spent significantly more time ($P < 0.001$) in the target quadrant compared with that of control rats. AGO enhanced spatial memory. | Demir Özkay et al., 2015 |
| Normal                        | Rat     | AGO (40 mg/kg per day, i.p.), 22 d | In the novel object recognition test, AGO increased the D2 index (ability to discriminate between a familiar object and novel object) ($P < 0.05$). AGO improved recognition memory. | Ladurelle et al., 2012 |
| KA status epilepticus         | Rat     | AGO (40 mg/kg per day, i.p.), 10 wk | In the radial arm maze test, KA-vehicle and KA-AGO groups exhibited more working memory errors compared with naive rats treated with vehicle after the | Tchekalarova et al., 2017 |
| Model                                                                 | Species | Treatment                        | Results                                                                                                                                                                                                 | Reference                          |
|----------------------------------------------------------------------|---------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Streptozotocin-induced model of type-2 diabetes mellitus              | Rat     | AGO (40–80 mg/kg per day, i.p.), 2 wk | AGO had no effect on kainate acid-induced memory impairment. Administration of AGO at 40 (P < 0.05) or 80 mg/kg (P < 0.01) induced a significant increase in the target quadrant time of diabetic rats. AGO treatment reversed the impaired long-term learning and memory performance of diabetic rats effectively. In the passive avoidance task, treating diabetic rats with 40 (P < 0.05) or 80 mg/kg (P < 0.001) of AGO prolonged the entrance latency to the dark compartment. AGO improved episodic memory deficit. | Can Ö et al., 2018                |
| Chronic psychosocial stress                                          | Mouse   | AGO (10–25 mg/kg per day, p.o.), acute treatment or 12 d | Although there was no stress × drug interaction or main effect of drug in the simple reversal learning test, mice completed more reversals after AGO (25 mg/kg) (P < 0.05) treatment relative to vehicle-treated naive mice in the complex reversal learning test. AGO reversed cognitive deficits partially. | Bergamini et al., 2016            |
| “Pessimistic” and “optimistic” traits                                | Rat     | AGO (5, 10, or 40 mg/kg per day, p.o.), acute treatment | Following acute treatment with AGO, the proportion of lose-shift behavior in the probabilistic reversal-learning test was reduced significantly in pessimistic rats compared with optimistic rats (P < 0.05). | Drozd et al., 2019                 |
| Intracerebroventricular Aβ1-42 model of AD                           | Rat     | AGO (40 mg/kg per day, i.p.), 30 d | AGO treatment did not improve spatial memory of the Aβ group in the radial arm maze test, but AGO enhanced the α-secretase concentration (P < 0.05) and decreased the γ-secretase concentration (P < 0.05 or P < 0.01) in the hippocampus, with decreased Aβ1-42 levels in the frontal cortex and hippocampus (P < 0.01 or P < 0.001). | Ilieva et al., 2021               |
| Cisplatin-induced model                                               | Rat     | AGO (20–40 mg/kg, p.o.), 7 d | In the passive avoidance test, AGO (20 and 40 mg/kg) improved the cisplatin-induced decrease in the step-through latency significantly (P < 0.001). In the novel object recognition test, AGO (20 and 40 mg/kg) attenuated the cisplatin-induced decrease in the discrimination index significantly (P < 0.05). AGO improved memory retention and recognition. | Cankara et al., 2021              |

AD: Alzheimer’s disease; AGO: agomelatine; Aβ: amyloid β; CCH: chronic cerebral hypoperfusion; i.p.: intraperitoneal; KA: kainate acid; p.o.: per os; PRS: prenatal restraint stress.