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Melatonin receptor agonists in neurodegenerative diseases and psychiatric disorders

Nicola Dyrek
Hospital of the Order of Brothers Hospitallers of St. John of God in Cracow
Ul. Trynitarska 11, 31-061 Kraków
https://orcid.org/0009-0004-8615-2327
nicola.dyrek@gmail.com

Magdalena Balwierz
Upper Silesian Medical Centre of Professor Leszek Giec in Katowice
Ziołowa 45/47, 40-635 Katowice, Poland
https://orcid.org/0009-0007-8254-5440
magbalwierz@gmail.com

Marcin Łata
Hospital of the Order of Brothers Hospitallers of St. John of God in Katowice,
ul. Markiefki 87, 40-211 Katowice, Poland
https://orcid.org/0009-0005-9725-2785
marcinlataa@gmail.com

Agnieszka Kosińska
District Hospital in Chrzanów,
Ul. Topolowa 16, 32-500 Chrzanów, Poland
https://orcid.org/0009-0008-3041-274X
agnieszka0kosinska@gmail.com

Abstract:
Neurodegenerative and psychiatric diseases remain a therapeutic challenge. Mental illnesses such as depression and bipolar affective disorder lead to disruption of the diurnal rhythm of melatonin secretion and disruption of the sleep-wake axis. The use of new melatonergic drugs has received special attention in recent years. Selective melatoninergic M1 and M2 receptor agonists (tasimelteon, ramelteon) show a more favorable metabolic profile, better regulation of circadian rhythms, and effects on total sleep time and sleep quality compared to the already well-studied melatonin. In addition, these drugs show no addictive potential. Agomelatine, through its action on M1 and M2 receptors, as well as serotonergic 5-HT2C and 5-HT2B receptors, exhibits antidepressant, normothymic, and neuroprotective effects, providing primary therapy or adjunctive treatment.

Keywords: melatonergic receptors agonists, melatonin, agomelatine, ramelteon, tasimelteon

Introduction

We classify neurodegeneration as a major pathophysiological change in most disorders related to brain function. Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and psychiatric disorders such as depression, anxiety disorders, bipolar affective disorder, among others, are conditions that have a significant impact on patients' health-related quality of life and satisfaction with medical care. The prevalence of these conditions varies significantly by age and background [1]

Depression is a common disease worldwide, with an estimated 3.8% of the population affected, including 5.0% among adults and 5.7% among those older than 60. About 280 million people worldwide suffer from depression. Patients who suffer from depression experience anhedonia, fatigue, sleep disturbances, loss of libido and self-destructive behavior. Depression can be caused by a variety of factors, such as monoamine deficiency, neuroinflammation, neuroplastic changes, and hypothalamic-pituitary-adrenal (HPA) axis overactivity [2]. Patients with low nocturnal melatonin levels have “low melatonin syndrome” , as well as an abnormal setting of the biological clock in relation to bedtime [3].

Anxiety disorders are a very heterogeneous set of conditions that have a serious and sometimes very negative impact on quality of life. The most common type is generalized anxiety disorder (GAD), which is unfortunately becoming increasingly common. They are usually characterized by pervasive anxiety and nervousness, disproportionate worrying and overgeneralization of true anxiety to neutral or ambivalent stimuli, sometimes based on previous adverse experiences [4]. GAD is associated with disorders such as fatigue, irritability, poor concentration, physical disturbances, and sleep problems.

In addition, GAD often co-occurs with other anxiety conditions, such as social phobia and also dysthymia or frank depression [5]. Excessive 5-HT receptor activity, as well as impaired MT receptor activity, has been found to play a large role in the pathomechanism of anxiety disorders [6].

Bipolar disorder (BPAD), on the other hand, is a chronic and recurrent disorder that affects >1% of the world's population.[x]. It is understood that BPAD affects about 48.8 million people worldwide [7]. The following varieties of the disorder exist, i.e. BPAD Type I (episodes of depression and mania, BPAD I), BPAD Type II (episodes of depression and hypomania, BPAD II) and cyclothymic disorder (episodes of mania and depression punctuated by periods of mood stabilization, referred to as a milder form of BPAD).Unfortunately, the pathophysiology of bipolar disorder remains unclear. Factors cited as most common include genetic susceptibility, neurotransmission abnormalities and environmental factors [8]. The neuroanatomical studies show a reduced density of neurons and glial cells in the prefrontal cortex, which appears to be more extensive than in unipolar depression. Neurotransmitter systems likely involved in the pathophysiology of bipolar disorder include serotonergic pathways, as well as the hypothalamic-pituitary-thyroid-adrenal systems [9].

The emergence of the COVID-19 pandemic created an environment in which many determinants of poor mental health were exacerbated[x]. The COVID-19 pandemic highlighted the importance of loneliness as a modifiable risk factor for the development of depression and anxiety disorders [10].

The unifying feature of the above disorders is the role melatonin plays in their occurrence. Therefore, melatonergic drugs as well as agomelatine have found use in their treatment. This represents a step towards improving the quality of life of patients suffering from these disorders.

In this post, we'll take a closer look at what applications the new melatonergic drugs are finding in the treatment of mental disorders such as depression, anxiety and BPAD.

New melatonergic drugs

In recent years, significant progress has been made in the field of pharmacology. This has led to the discovery of an increasing number of substances that exhibit agonistic effects on melatonin receptors. These include both drugs currently approved in clinical practice, such as ramelteon, agomelatine, tasimelteon, and those substances whose effects are being further evaluated in studies: TIK-301, LY-156, UCM765, IIK7, UCM793, UCM924, Neu-P11 [11].

Ramelteon

It is the first selective melatonin(MT1/MT2) receptor agonist to be approved by the FDA in the US in 2005 for the treatment of insomnia. Studies have shown that ramelteon acts more potently on MT1 and MT2 receptors than melatonin, and more selectively on MT1 receptors than MT2 receptors, allowing the conclusion that it has a stronger effect on sleep than with melatonin alone [12].Ramelteon is more easily absorbed from the gastrointestinal tract than melatonin and reaches higher concentrations in target tissues due to its increased lipophilicity. The time required for ramelteon to reach maximum concentration is 45 minutes. Ramelteon also has its active metabolite, M-II.

The half-life for the starting compound is 1-2.6 hours and 2-5 hours for the active metabolite M-II [13], this is significantly longer than for melatonin, which has a half-life of 20-30 min [12]. In patients with primary chronic insomnia, ramelteon causes a significant reduction in sleep latency, an increase in total sleep time, and has a beneficial effect on disrupted daily rhythms [3].Side effects reported during treatment are mild and the incidence is low. There is also a lack of addictive potential and withdrawal effect which positions ramelteon higher than the benzodiazepine receptor agonists often prescribed for the treatment of insomnia. In conclusion, ramelteon, through its clinical efficacy together with its good safety profile, is a drug worth being considered in people dealing with insomnia [14].

Tasimelteon

It is a selective MT1 and MT2 receptor agonist. In in vitro studies, it shows higher binding affinity for the MT2 receptor than MT1[15]. Tasimelteon is used to treat Non-24-Hour Sleep-Wake Disorder/Non-24. Non-24 syndrome is a condition that occurs most commonly in blind people, but can also occur in sighted people with little exposure to light. It is caused by the failure of the biological clock to adjust to the day-night cycle.[3]. The research shows that tasimelteon prolongs sleep at night and reduces daytime naps, with high safety and tolerability [16]. Another disorder where the effects from tasimelteon are promising is Jet lag disorder [17].

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is the main hormone secreted by the pineal gland. Other, non-pineal sources of melatonin include the retina, bone marrow cells, platelets, skin, lymphocytes, Harder's gland, cerebellum, and especially in the gastrointestinal tract of vertebrates [18]. It is in the gastrointestinal tract that its concentration is recorded up to 400 times higher than in the blood [19].

Melatonin is mainly synthesized by pinealocytes from tryptophan, which is hydroxylated (by tryptophan 5-hydroxylase) into 5-hydroxytryptophan. It is further decarboxylated (by 5-hydroxytryptophan decarboxylase) into serotonin. Two enzymes, located mainly in the pineal gland, convert serotonin into melatonin [20]. Serotonin is first acetylated to N-acetylserotonin by serotonin N-acetyltransferase (AA-NAT; it is the rate-limiting enzyme in melatonin synthesis), and then N-acetylserotonin is methylated by 5-Hydroxyindole-O-methyltransferase (ASMT) to form melatonin.

Melatonin synthesis and secretion are increased by darkness and inhibited by light-it is controlled by an endogenous mechanism called the biological clock. Light information is transmitted from the retina to the pineal gland via the suprachiasmatic nucleus (SCN) of the hypothalamus. In humans, its secretion begins shortly after sunset, peaks in the middle of the night (between 2 and 4 am) and gradually decreases in the second half of the night. Most melatonin is synthesized at night, and its serum concentration ranges from 80 to 120 pg/ml [21].

Mechanism of action

The main purpose of melatonin is its role in the sleep process. Melatonin is released from the pineal gland into the third ventricle and from there into the circulation. Its interactions with the suprachiasmatic nucleus of the hypothalamus and retina, promoting sleep and inhibiting wakefulness-promoting signals through interactions with MT1 and MT2 receptors [22]. MT1 receptor is found in the anterior lobe area of the pituitary and SCN of the hypothalamus, as well as in the cortex, thalamus, black matter, paraventricular nucleus, amygdala, hippocampus, cerebellum, cornea and retina. MT2 expression was shown mainly in the retina and in the hippocampus, cortex, paraventricular nucleus and cerebellum. The melatonin signaling pathway targets a decrease in intracellular cAMP. In addition, melatonin can inhibit guanylate cyclase with a subsequent decrease in guanosine 3',5'-cyclic monophosphate (cGMP) and stimulate phospholipase C (PLC, or phospholipase C) responsible for inositoltriphosphate (IP3) production and an increase in intracellular Ca^{2+} ion concentration. The PKC signaling pathway is considered an important element in the circadian action of melatonin. Melatonin can also activate Kir3 potassium channels directly stimulated by G proteins. Opening of Kir3 channels leads to intracellular K^+ influx and depolarization of the cell membrane [23].

Depression

Melatonin production is controlled by the endogenous circadian rhythm system and peaks at night, around 2 o'clock, while it is then gradually suppressed by daylight. Its rhythm is often used as an indicator of phase shift, i.e. the difference between daylight and the endogenous circadian rhythm. It has been observed that people suffering from various mood spectrum disorders, such as major depressive disorder or seasonal affective disorder, often have a dysregulation of it and also a disruption of the sleep-wake cycle [11]. The diurnal rhythm disturbances accompanying depressive disorders were first described in 1979. At that time, several independent studies observed lower nocturnal melatonin levels in patients with mood disorders. This abnormality was described for both depression and bipolar and seasonal affective disorder. This phenomenon has been linked to reduced serotonin and norepinephrine levels in the brain correlating with melatonin levels. Another study demonstrated the effect of antidepressants and normothymics on the rhythmic secretion of melatonin, which controls the endogenous biological clock, and showed a link between the severity of unipolar depression and dysfunction of the diurnal rhythm. A so-called phase shift in the form of a delay in circadian rhythm relative to bedtime was observed in people with depressive disorders
[3,11]. However, it turned out that lower nocturnal melatonin levels were not present in all depressed patients studied, but only in those patients with a false-positive dexamethasone inhibition test. This phenomenon was given the name ‘low melatonin syndrome’ [3]. These findings suggest that altered circadian rhythms may be biological markers of mood spectrum disorders having a strong link to melatonin levels, which is considered to be a chronobiotic factor, i.e. able to regulate biological functions dependent on the time of day , such as body temperature or internal secretion rhythms [11].
Looking at the results of clinical trials on patients with mood disorders comparing melatonin with placebo, it was concluded that there was no significant evidence for its antidepressant effect.

However, the conclusions were not conclusive and warranted further research in this direction [24]. However, a significant increase in melatonin secretion was observed in the study subjects approximately 2-3 weeks after starting antidepressants. In addition, increased urinary excretion of 6-methoxymelatonin, the primary metabolite of the hormone, was noted in these patients [3,24]. This may indicate a potential impact of melatonin on the pathophysiology of depressive disorders due to its influence on biological rhythms and other processes in which it is involved. Its effect on the treatment of patients can be understood not as an antidepressant, but as multifactorial and more complex [25].

Anxiety

Anxiety disorders are the most common mental illnesses. Both the anxiety itself and the accompanying symptoms can significantly reduce a patient's quality of life, interfering with social life, work life, and other areas of functioning. In addition, anxiety disorders show a strong association with cardiovascular and other somatic diseases mutually stimulating or reinforcing each other. The pathophysiology of these disorders itself is complex and involves changes in stress hormone production, free radical production, and neurotransmitter pathways. The side-effects of available treatments for anxiety disorders, their impact on the patient and the complex etiology of the disease mean that new therapies for these conditions are constantly being sought [26]. Both in clinical settings and in animal experiments, melatonin has been shown to have anti-anxiety effects. This hormone, produced in the pineal gland and released into the blood during the night, induces a number of physiological processes through binding to specific melatonin receptors, or through pleiotropic effects independent of them. Underlying the pathomechanism of melatonin's anxiolytic effects may be, among other things, its inhibitory effect on the sympathetic nervous system, its ability to modulate the hypothalamic-pituitary-adrenal axis and the renin-angiotensin-aldosterone system, and its antioxidant nature and ability to scavenge free radicals [26, 27]. Melatonin concentration is significantly higher in the cerebrospinal fluid than in the blood. Thus, ensuring sufficient production of this hormone by limiting excessive nocturnal lighting and maintaining a regular sleep pattern may support the endogenous anxiolytic system [26]. Premedication melatonin probably reduces preoperative anxiety in adult patients. Its effect on postoperative anxiety, compared to placebo, was also evident, but significantly less. It has been shown that melatonin may have a similar effect to benzodiazepines in reducing anxiety both before and after surgery, which is potentially clinically relevant [28]. Due to its effects, melatonin can be successfully used to reduce the body's stress reactions. Due to its easy availability and limited side effects, it can often be considered as an additional or alternative treatment for patients with various anxiety-related conditions [26].

Bipolar affective disorder and Seasonal affective disorder

Bipolar affective disorder is characterized by recurrent episodes of depression and mania alternating with periods of well-being. The neurobiological cause of BPAD is still unknown, although there is evidence pointing to a malfunction of the melatonin-regulated diurnal rhythm. Studies of patients with BPAD have shown that changes in its levels were related to changes in the course of the disease.

Melatonin has also been shown to regulate the gut microflora, which some studies suggest plays an important role in neuropsychiatric disorders, including BPAD [29]. Sleep disturbances occurring in BPAD patients are associated with a worse disease course, increased symptom severity and reduced quality of life. During the transition from depressive to mania phases, patients experience a significant reduction in sleep during the preceding night. In addition, it is common for the patient to completely miss one night's sleep between two nights during which there are no sleep problems. This phenomenon is referred to as 'internal desynchronisation'[3]. Although melatonin levels appear to be a reliable indicator of diurnal rhythm, studies focusing on this topic have shown conflicting results. Some of them reported no differences in melatonin levels in different phases of BPAD [30], while in other cases these were significant [31,32]. Patients in the study had significantly lower nocturnal peak melatonin concentrations compared to healthy controls, as well as people diagnosed with unipolar depression [30,33]. In addition, patients showed hypersensitivity of the pineal gland to light exposure in each during both disease exacerbations and euthymia [34]. Some studies have also reported a decrease in melatonin secretion during the depression phase, an increase during the mania phase and normalization during the remission phase of the disease [31,32]. A difference in phase position was also described in patients where the nocturnal peak melatonin concentration was shifted by one hour during the mania phase, demonstrating that it is not just the amplitude of melatonin that changes in bipolar disorder. [3] However, it is not possible to determine whether the results of the above studies are due to a primary dysfunction of the diurnal rhythm or whether they occurred secondary to the sleep disturbances characteristic of BPAD [11]. The administration of exogenous melatonin to BPAD patients mostly resulted in an increase in sleep duration, as well as an alleviation of insomnia and the severity of manic episode symptoms [35].
In some cases, however, the administration of melatonin did not have a beneficial effect on the subject [36] or the differences between the study sample and the control sample were very small and consequently not conclusive for the study [24]. There is also evidence that administration of exogenous melatonin may have had a suppressive effect on endogenous melatonin secretion [11,36].
Seasonal affective disorder is a seasonally recurrent depressive disorder, usually beginning in autumn and lasting into the winter months. The subsyndromal type of seasonal affective disorder , commonly known as the 'winter blues', causes depression in spring or early summer. Symptoms include lack of energy, slowing down, decreased motivation to do things, as well as increased appetite and weight gain. Young women living far from the equator with a family history of mood disorders are particularly at risk. Standard treatment includes antidepressants, phototherapy, vitamin D supplementation and psychotherapy [37]. In seasonal affective disorder, as in BPAD, not only the level but also the timing of melatonin secretion is altered. Patients with seasonal affective disorder have been reported to have higher daily melatonin levels during the winter months, as well as a phase delay in circadian rhythms, which is most likely due to a later dawn, resulting in a disruption of the sleep-wake cycle [3,38]. Although phototherapy is an effective treatment for the condition as it bridges the gap between the endogenous biological clock and the sleep-wake rhythm, the beneficial effect of this treatment does not appear to be due to changes in melatonin levels. Studies testing the efficacy of melatonin administration to these patients have shown conflicting results.

In some of them, despite significant improvements in mood in the subjects after melatonin administration [39], no significant differences were found compared to placebo [40]. Despite this, the ability to accelerate or delay the phase depending on the time of intake of exogenous melatonin confirms its efficacy in the treatment of seasonal depression [3,11].

Agomelatine

Agomelatine, as a synthetic analog of melatonin, is widely used in the treatment of psychiatric disorders and the regulation of circadian rhythms. It is a selective agonist of melatoninergic receptors (MT1, MT2) and an antagonist of the serotonergic receptor 5-HT2C and 5-HT2B. [6, 41,42,43] Compared to melatonin, due to its more lipophilic structure, it shows better penetration into the brain. [44] Agomelatine was registered for the treatment of episodes of major depression in adults by the European Medicines Agency (EMA) in 2009. [43]

Unlike other drugs used for anxiety and depressive disorders, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine inhibitors (SNRIs), agomelatine has a low risk of side effects, such as those related to the gastrointestinal tract, weight changes, sexual dysfunction, and sleep-wake cycle disturbances and sedation. Termination of treatment has no risk of withdrawal syndrome. [43, 45]

Its safe profile of action is also associated with a lack of affinity for adrenergic, GABA-ergic, histamine, muscarinic, benzodiazepine, glutamatergic, dopaminergic receptors. [42, 46] Its antagonism to 5-HT2C receptors implies a number of biological processes: an increase in noradrenergic and dopaminergic conduction in the prefrontal cortex, a decrease in glutaminergic transmission, and, together with its action on melatonergic receptors, also an increase in brain-derived neurotrophic factor- (BDNF) production in the hippocampus and prefrontal cortex. [47, 48, 49]

Clinical effects of melatoninergic receptor activation include: increased total sleep time, decreased frequency of waking after falling asleep, improved sleep quality and mood upon awakening. [46, 50, 51, 52] All of these effects appear to be related to effective antidepressant, normothymic and neuroprotective effects. [6, 53]

The drug is rapidly absorbed. It reaches maximum plasma concentration after about 1-2 hours, with a half-life of 140 min. Hepatic metabolism (the cytochrome P450 system CYP1A2 isoenzymes, as well as CYP2C9 and CYP2C19) creates the possibility that the blood concentration of agomelatine may be altered by other substances (increased by some SSRI drugs; decreased by caffeine, nicotine, among others). [43, 54]

Use of agomelatine in the treatment of depression

Circadian rhythm disturbances are an important part of the clinical picture of depression. Patients present difficulties with falling asleep, maintaining uninterrupted sleep and early morning awakenings. [55] This fact is explained, among other things, by the phase shift hypothesis. It suggests that in depression there is a delay or acceleration of the phase of the central pacemaker of circadian rhythms, which are responsible for regulating cortisol and melatonin levels, body temperature and the duration of the REM phase of sleep relative to other circadian rhythms.

The phase shift hypothesis is supported by changes in melatonin levels, morning awakenings, and earlier occurrence of REM phase during sleep in depressed patients compared to healthy subjects. [56, 57] The use of melatoninergic receptor agonists makes it possible to resynchronize disturbed circadian processes.

The efficacy of agomelatine in depression is based on its simultaneous agonist action against melatonergic receptors MT1, MT2 and antagonist action against serotonergic receptors 5HT-2C. These receptors are located in areas associated with the pathogenesis of depression (suprachiasmatic nucleus and cerebral cortex, hippocampus, amygdala and thalamus) and are activated by the influence of light, circadian variables. [44]

The action of agomelatine on melatoninergic receptors results in an improvement in the quality of sleep and daytime wakefulness through resynchronization of circadian processes. By inhibiting serotonergic 5HT-2C receptors, which are located on GABAergic neurons in the brainstem, there is a reduction in their inhibitory effect on the release of norepinephrine and dopamine in the prefrontal cortex, which is a therapeutic target in the treatment of depression and the point of action of classic antidepressants. [44, 45]

It has also been shown that the pre-mRNA of 5HT-2C receptors undergoes modifications to form isoforms that are regionally specific to the cerebral cortex. Neurotransmission and receptor function are then impaired. Particular intensification of this phenomenon occurs mainly in the prefrontal cortex, responsible for regulating emotions. Intensification of this process occurs especially in patients exhibiting suicidal behavior. [45, 58]

Studies show greater efficacy of agomelatine over placebo and SSRI and SNRI drugs in treating depression. [59, 60] A large meta-analysis involving 116,477 patients showed greater efficacy of antidepressants over placebo and of agomelatine, escitalopram, vortioxetine, amitriptyline, venlafaxine and paroxetine over other antidepressants. [61] Agomelatine also had lower dropout and adverse reaction rates than paroxetine and venlafaxine. [62, 63] It may be most effective in depressive episodes combined with circadian rhythm disturbances and anxiety. [64]

Use of agomelatine in the treatment of bipolar affective disorder

In addition to genetic and environmental factors, neurotransmitter dysfunction also plays a key role in the pathogenesis of bipolar disorder. It has been postulated that depression is associated with decreased levels of norepinephrine and dopamine, while mania is associated with increased levels of these. Both phases were also explained by decreased synaptic levels of serotonin. However, an association has now been shown with increased sensitivity of their postsynaptic receptors rather than synaptic concentrations. These disorders also affect the abnormal activity of other neurotransmitters, such as GABA and substance P, which is directly linked to the symptoms of bipolar disorder. Serotonin and dopamine concentrations play the most important role, as it has not been proven whether abnormal norepinephrine transmission is a cause or effect of the other disorders. In addition, as a result of stress contributing to the development of bipolar disorder, BDNF secretion is reduced, which impairs neuroplasticity and neurogenesis of the central nervous system. [65, 66]

The pathomechanisms of bipolar affective disorder outlined above seem to justify the search for agomelatine's use in pharmacotherapy due to its mode of action, points of action and neurobiological effects.

A small study involving the evaluation of the efficacy of agomelatine in the treatment of bipolar I disorder in 21 patients showed a good response rate (81%) and a high rate of remission of depression (38%) after a 6-week follow-up period. The tool used to measure treatment effects was the Hamilton Rating Scale for Depression (HRDS). [67]

Another study evaluated improvements in sleep quality in patients with bipolar I (as an adjunct to initial treatment with lamotrigine or valproate) and bipolar II (as monotherapy) compared to a group of patients with recurrent depressive disorder. After 8 weeks of use, a response rate of 91% and a remission rate of 65% was achieved in the affective disorder group. [68]

However, the only large randomized trial involving 344 patients evaluated the efficacy of agomelatine 25-50 mg/d versus placebo after 8 and 52 weeks in patients who were not on lithium or valproate therapy using the Montgomery - Åsberg Depression Rating Scale (MADRS). Agomelatine was not shown to be superior to placebo. [69]

Currently, agomelatine is not registered for the treatment of bipolar affective disorder, and more studies are required to confirm or rule out its efficacy in this disease entity.

Use of agomelatine in the treatment of seasonal affective disorder

Seasonal affective disorder (SAD) is more common in geographic areas with reduced daily sunlight. Several mechanisms have been postulated in the pathogenesis: disorders of the hypothalamic-pituitary-adrenal axis, abnormal melatonin and serotonin levels. Patients have a higher expression of SERT protein, which is responsible for serotonin reuptake at the synaptic gap, than healthy subjects. [37]

Meta-analyses show that the studies conducted did not conclusively prove the efficacy or validity of agomelatine in seasonal affective disorder. They also highlighted possible bias and confounding factors in the studies. [70, 71] Currently, the mainstay of SAD treatment is SSRIs, SNRIs, NDRIs and phototherapy.[37]

Use of agomelatine in the treatment of anxiety disorders

The action of agomelatine in anxiety disorders is based on the inhibition of the anxiety-induced increased activity of serotonin 5HT-2C receptors in the amygdala, nucleus accumbens of the striatum and hippocampus, as well as the activation of melatonergic MT receptors in the low thalamic nucleus, hippocampus and reticular nucleus of the thalamus, which enhances its anxiolytic effect. [6] Modulation of glutamatergic transmission, as well as anti-inflammatory and antioxidant effects, are not negligible. [72, 73]

Compared to placebo, agomelatine showed greater short-term efficacy (over a 12-week period) in studies using the Hamilton Anxiety Rating Scale (HAM-A) and the Sheehan Disability Scale for assessment. Relief of anxiety symptoms and improvements in patients' functioning have been demonstrated. [74, 75] Agomelatine showed similar efficacy to escitalopram (SSRI), and in a longer follow-up period (6 months), its effectiveness in preventing anxiety disorder relapse was also observed. [76, 77]

Summary

Neurodegenerative disorders like Alzheimer's and Parkinson's, along with psychiatric conditions such as depression, anxiety, and bipolar disorder (BPAD), significantly affect quality of life. Depression, impacting 280 million people globally, involves symptoms like anhedonia and sleep disturbances, potentially linked to monoamine deficiency and neuroinflammation. Anxiety disorders, especially generalized anxiety disorder (GAD), often co-occur with other mental health conditions. BPAD, affecting over 1% of the population, involves complex neurotransmission and genetic factors [5].

The COVID-19 pandemic worsened mental health issues, with loneliness as a key risk factor. A common link among these disorders is melatonin, a hormone regulating sleep and circadian rhythms [10]. New melatonergic drugs like ramelteon and tasimelteon, targeting melatonin receptors, show promise [6]. Ramelteon treats insomnia by selectively acting on MT1 and MT2 receptors, while tasimelteon is effective for Non-24-Hour Sleep-Wake Disorder and jet lag.

Melatonin's role in mood regulation is intricate. Although evidence linking melatonin levels to mood disorders like depression and BPAD is mixed, melatonin and its agonists may improve sleep and alleviate symptoms, particularly in seasonal affective disorder and BPAD [9].

Disclosure:

Authors'contribution:

Conceptualization: Nicola Dyrek, Magdalena Balwierz, Agnieszka Kosińska, Marcin Łata
Methodology: Nicola Dyrek, Magdalena Balwierz, Agnieszka Kosińska, Marcin Łata
Software: Magdalena Balwierz, Agnieszka Kosińska
Check: Nicola Dyrek, Magdalena Balwierz
Formal Analysis: Nicola Dyrek, Magdalena Balwierz
Investigation: Nicola Dyrek, Magdalena Balwierz, Agnieszka Kosińska, Marcin Łata
Resources: Agnieszka Kosińska, Marcin Łata
Data curation: Nicola Dyrek, Marcin Łata
Writing-Rough Preparation: Nicola Dyrek, Magdalena Balwierz, Agnieszka Kosińska, Marcin Łata
Writing-Review and Editing: Nicola Dyrek, Magdalena Balwierz,
Visualization: Magdalena Balwierz, Agnieszka Kosińska,
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Project Administration: Nicola Dyrek, Magdalena Balwierz

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