Seminars in Medical Writing and Education. 2025; 4:461
doi: 10.56294/mw2025461

ORIGINAL

The Role of Melatonin in Insomnia and Neurodegenerative Conditions: A Critical Study

El papel de la melatonina en el insomnio y las enfermedades neurodegenerativas: Un estudio crítico

Komal Parashar[1], Ashutosh Niranjan[2], Naresh Kaushik[3], Suvendu Narayan Mishra[4], Lokesh Ravilla[5], Madhur Grover[6]

[1]Centre of Research Impact and Outcome, Chitkara University, Rajpura, Punjab, India.
[2]Noida International University, Department of General Surgery, Greater Noida, Uttar Pradesh, India.
[3]ATLAS SkillTech University, Department of uGDX, Mumbai, Maharashtra, India.
[4]IMS and SUM Hospital, Siksha 'O' Anusandhan (Deemed to be University), Department of Psychiatry, Bhubaneswar, Odisha, India.
[5]Centre for Multidisciplinary Research, Anurag University, Hyderabad, Telangana, India.
[6]Chitkara Centre for Research and Development, Chitkara University, Himachal Pradesh India.

Cite as: Parashar K, Niranjan A, Kaushik N, Narayan Mishra S, Ravilla L, Madhur Grover M. The Role of Melatonin in Insomnia and Neurodegenerative Conditions: A Critical Study. Seminars in Medical Writing and Education. 2025; 4:461. https://doi.org/10.56294/mw2025461

Submitted: 13-02-2024 **Revised:** 01-08-2024 **Accepted:** 12-02-2025 **Published:** 13-02-2025

Editor: PhD. Prof. Estela Morales Peralta

ABSTRACT

The subsequent leading cause of mortality, neurodegenerative diseases (ND), gradually reduces the capacity of the central or peripheral nervous system to function properly and think coherently. In contemporary culture, the primary goal of public health is ND prevention. Numerous physiological functions in the brain are regulated by the hormone Melatonin (MLT), It was generated in the Pineal Gland (PG). Circadian rhythms (CR), biomolecular oxidation, eliminating free radicals, and preventing neuroinflammation are some of these mechanisms. MLT has been proven to have a multitude of neuroprotective effects through altering signaling pathways and pathophysiological processes. Neurological disorders may cause lower MLT levels. MLT regulates itself, interacts with molecules, and affects biological processes in ND. We also discuss the therapeutic use of MLT in the management of neurodegenerative illnesses. This knowledge might lead to the development of cutting-edge therapeutic approaches for the treatment of different ND and further our understanding of how MLT controls the brain's Circadian Rhythm (CR).

Keywords: Neurodegenerative Disease (ND); Melatonin (MLT); Pineal Gland (PG); Circadian Rhythms (CR).

RESUMEN

La principal causa de mortalidad posterior, las enfermedades neurodegenerativas (EN), reducen gradualmente la capacidad del sistema nervioso central o periférico para funcionar correctamente y pensar con coherencia. En la cultura contemporánea, el principal objetivo de la salud pública es la prevención de las EN. Numerosas funciones fisiológicas del cerebro están reguladas por la hormona Melatonina (MLT), generada en la Glándula Pineal (PG). Los ritmos circadianos (RC), la oxidación biomolecular, la eliminación de radicales libres y la prevención de la neuroinflamación son algunos de estos mecanismos. Se ha demostrado que la MLT tiene multitud de efectos neuroprotectores mediante la alteración de las vías de señalización y los procesos fisiopatológicos. Los trastornos neurológicos pueden causar niveles más bajos de MLT. La MLT se regula a sí misma, interactúa con moléculas y afecta a los procesos biológicos en las EN. También se analiza el uso terapéutico de la MLT en el tratamiento de las enfermedades neurodegenerativas. Este conocimiento podría conducir al desarrollo de enfoques terapéuticos de vanguardia para el tratamiento de diferentes EN y a una mayor comprensión de cómo la MLT controla el Ritmo Circadiano (RC) del cerebro.

Palabras clave: Enfermedad Neurodegenerativa (EN); Melatonina (MLT); Glándula Pineal (PG); Ritmo Circadiano (RC).

INTRODUCTION

Severe sleep and wakefulness turbulence is widespread within the populace with ND. Along with the loss of neuronal populations in the brain stem as well as the hypothalamus, the circadian, homeostatic, ultradian, along with autonomic/respiratory systems may all be affected. Patients with ND are more likely to have clinical sleep disorders such as all forms of insomnia, hypersomnia, abnormal circadian rhythms, breathing issues while sleeping, Sleep-Related Movement Disorders (SMD), along with parasomnias, notably "Sleep Behavior Disorder (SBD)and Paradoxical sleep.[1] In both diurnal and nocturnal species, melatonin (MLT), a neurohormone derived from serotonin (5-HT), has a distinctive circadian rhythm with the acrophase occurring in the dark phase and the nadir in the light phase. The human pineal gland is the primary source of melatonin production. A healthy adult normally has blood MLT values of 10 pg/ml during an day and 60 pg/ml at night. The suprachiasmatic nucleus (SCN) controls its production, which peaks at night and falls during day.[2] Aron B. Lerner developed MLT, a tryptophan derivative, in 1958. Parenchymatous cells in the PG primarily generate light when it arrives through retinohypothalamic circuits. More light is directed toward the SCN, which contains the circadian clock. Consequently, the circadian clock's phases and the cycle of light and dark may overlap. The SCN communicates time information to the PG through the superior cervical ganglion.[3] The control of insomnia continues to be a well-known benefit of Neurohormone. Hormone was previously demonstrated in clinical studies to significantly improve the significance and depth of sleep in patients with schizophrenia, insomnia and traumatic brain injury, who also have other comorbid conditions like Obesity, Diabetic condition, Tumor, Cardiovascular disorders, and Dementia of the Alzheimer's type.[4] Numerous sleep disorders, including parasomnias like REM and SBD and hypersomnia (diurnal drowsiness), may co-occur in individuals with neurological issues. Patients with neurological diseases who have insomnia may do so as a direct result of their illness or as a result of variables related to it, such as medication, discomfort, or despair. It may be challenging to fall asleep, stay asleep, or avoid getting up early due to the widespread sleep disorder known as insomnia.[5] For all the investigated species, MLT synthesis peaks at night and declines throughout the day. Despite not being able to store MLT, the PG can still produce it as shown by the hormone's plasma levels. Early non-mammalian vertebrates have a PG that is directly light-responsive, but later vertebrates lose this sensitivity. MLT may readily cross the blood-brain barrier and reach most cell membranes because of its high lipid- and water-soluble nature.[6] The length and distribution of REM and NREM sleep, as well as the other sleep phases, may be regulated, according to studies. "Adipose tissue, coronary arteries, alpha- and beta-pancreatic cells, myometrium, and testis" have all been shown to have MLT receptors.[7] The change of "REM sleep behavior (iRBD)" is a well-known prodromal symptom of synucleinopathies like PD and "Dementia with Lewy Bodies (DLB)". Figure 1 shows that the Benefits of Melatonin. According to a new study, changes in the circadian rhythm's regulation may be a precursor to the development of clinically evident synucleinopathies brought on by iRBD. Therefore, it could be essential to use disease-modifying medications to encourage circadian rhythm in those with iRBD.[8]

Figure 1. Therapeutic Benefits of Melatonin

https://doi.org/10.56294/mw2025461

MLT therapy has been shown to have clinically significant effects in human placebo-controlled studies, particularly in conditions where MLT rhythms are disrupted or out of sync, such as CR-related sleep disorders, shift work and jet lag, insomnia in children with Neuro-Developmental Disorders (NDD), poor sleep quality, non-dipping nocturnal blood pressure, and AD.[9]

The present article examined hypothalamic dysfunction in Alzheimer's disease AD, linking neurodegeneration, metabolic instability, and insomnia.[10] It investigated the role of the circulation hormone in regulating insomnia and facilitating beta- amyloid elimination. Finding in the initial phases of AD, the circulation hormone improves rest, reduces Aß accumulation, and enhances its glymphatic clearance. However, in more severe cases its neural benefits remain minimal.

MLT, a singular, phylogenetic conserved chemical initiate to oxygen-dependent microbes, merits more research since avoiding ND is now one of society's top goals.[11] One of the country's newest public medical concerns is the prevention of neurodegenerative diseases.[12] In the brain, the intrinsic hormonal circadian hormone performs a number of physiological tasks, including as controlling biological rhythms, eliminating radical species, preventing cellular oxidation, and reducing neuroinflammation. As a result of melatonin suppresses neuroinflammation, reduces oxidative damage, and regulates physiological rhythms, providing significant neuroprotective benefits. Patients with cognitive impairments tend to have lower levels of melatonin.

Examine reviewed the most current research on MLT's regulation, molecular processes, and biological effects in ND such as "Multiple Sclerosis (MLS), Amyotrophic Lateral Sclerosis (ALS), Huntington's disease (HD), vascular dementia (VD), Parkinson's disease (PD), and Alzheimer's Disease (AD)".[13] Another area of interest is the use of MLT in the treatment of ND. Due to its cytoprotective properties (CP), which may be helpful future in support of the AD-related disorder, MLT, a pineal product, is relevant in this respect.[14]

This evaluation highlights the role of microRNA in regulating these mechanisms as it explores the connection between insomnia, neurodegenerative diseases, and circadian rhythm impairment. It examined existing knowledge on post-transcriptional mechanisms and translational feedback loops.[15] The outcome suggests that neurodegeneration is driven by circadian distortion, and isolated neurodegenerative diseases are largely caused by microRNA malfunction and the deregulation of virulent genes. For the purpose to examine innate variations in unconscious and circadian characteristics, the current work used painless piezoelectric assessment of Rest-activity cycles in young individuals, Midsection adulthood, and elderly cost-benefit analysis creatures, a Stress competent of neurohormone production.[16] The findings show that Young rodents Insomnia than mature adult or geriatric mice, particularly at night, and that older mice exhibit delayed activity initiation and activity peak duration.

MLT has been shown in therapeutic potential in the treatment of HD, PD, ALS, AD, stroke, and brain injury because it is efficient in reducing Oxidative Damage (OD) in Cultured Neuronal Cells (CNC) or the Brains of Animals (B of A) given various Neurotoxic Agents (NA).[17] The information on MLT's helpful function in virus-induced neuropathogenesis is compiled and covered.[18] With ADHD, autism, and other neurodevelopmental diseases where sleep disturbance is often seen, MLT has been used effectively to treat insomnia in children.[19]

In addition, melatonin was believed to regulate the Body Mass Index (BMI), regulate the digestive tract, and be crucial for body temperature control, generation, and cardioprotective effect. Melatonin's effectiveness in treating a variety of pain disorders has been documented in a number of recent examination.[20] Their concluded by talking about latest findings that revealed new melatonin transmitters that were successful in managing Neurogenic pain.

A number of important topics about the usage of melatonin during pregnant and breastfeed and the fitness and illness of the offspring.[21] Targeting melatonin's functions during pregnancy and infant feeding will help avoid a number of chronic adult disorders later in life, particularly neurobiological and circulatory system diseases.

Investigate presented the most current research on the clinical impact of illnesses including diabetes, cancer, gastrointestinal issues, and brain disorders that are linked to mitochondrial malfunction.[22] Study discussed the physiological characteristics of MLT and how it could be advantageous for numerous therapeutic uses in pain treatment, critical care, and perioperative management.[23] MLT receptors have been found in several lymphoid organs including lymphocytes, which points to several potential methods of action. Study demonstrated that MLT has potent antioxidant properties as well as direct and indirect anticancer effects, the latter of which is mediated through its impact on hormones related to reproduction.[24] All three of the N1-acetyl-N2-formyl-5-methoxykinuramine, cyclic 3-hydroxy MLT, and MLT oxidation products are strong antioxidants. MLT's capacity to scavenge free radicals is principally responsible for its advantageous neuroprotective qualities.

Sleep and circadian rhythm are regulated by the pineal gland bioactive compound melatonin. Its oxidative stress reducer properties and possible influence on the progression of Neurodegenerative disorder were shown by recent neuroscience and molecular biology investigations.[25] The neurodegenerative and depressive qualities of melatonin point to possible medication development. This examines outlines novel roles and suggests a therapeutic target for the mechanism that operates of melatonin.

https://doi.org/10.56294/mw2025461

Examine elucidated the impact of stress on the hippocampus, which is associated with memory processes.[26] Research anticipated to describe the biochemical changes brought on by brain aging and how MLT-mediated circadian restoration of neuronal hemodynamics may increase healthy lifespan in age-related ND.[27] Author examined the potential benefits of herbal remedies, such as MLT, in the preclusion and/or treatment of ND, including AD and post-ischemic brain disorders.[28] The most recent research on agomelatine highlights its benefits for treating psychologic sleep disorders (PSD) and CR abnormalities, as shown in human clinical trials and animal studies.[29]

METHOD

Tryptophan is dynamically taken up, by the PG to start the production of melatonin. Serotonin (5-hydroxytryptamine, 5-HT) is created by the subsequent hydroxylation and decarboxylation of tryptophan.

Melatonin's role

In addition to influencing CR and serving as an antioxidant, MLT also has anti-inflammatory and anti-apoptotic characteristics. MLT is an important factor in the CR of the majority of animals. MLT secretion and synthesis are inhibited by light, but they are induced when it is not present. MLT has been demonstrated to influence clock genes in vivo by lessening circadian disturbance. The decarboxylation process requires vitamin B6. By way of the rate-limiting enzyme serotonin N-acetyl transferase, serotonin is transformed into N-AS. The rate-limiting step requires Protein Kinase A (PKA), which also activates serotonin N-AT. The enzyme hydroxy indole O-methyl transferase turns N-acetylserotonin into MLT together with folate. MLT activates the SCN, which causes the SCN to produce norepinephrine. More calcium (Ca2+) builds up in the cytosol when norepinephrine interacts with pinealocytes' endoplasmic reticulum and activates their -1/adrenoceptors. Adenylyl cyclase which is membrane-bound is also activating to manufacture intracellular cAMP, which binds to Protein Kinase A along with increased Protein Kinase A activity. The crucial decarboxylation process requires vitamin B6 to function. The rate-limiting enzyme serotonin N-AT transforms serotonin into N-acetylserotonin. A rate-limiting mechanism needs serotonin N-AT, which PKA makes accessible. In the presence of folate, the enzyme hydroxy indole O-methyl transferase transforms N-AS into MLT. Norepinephrine is produced when the SCN is activated by MLT, which activates the SCN. When norepinephrine interacts with pinealocytes' endoplasmic reticulum and activates their -1/adrenoceptors, more calcium (Ca2+) accumulates in the cytosol.

Melatonin biosynthesis

The primary MLT makers are pinealocytes, which are located in the PG, retina, skin, bone marrow, and Gastro-Intestinal Tract (GIT). The hydroxylation, decarboxylation, acetylation, and methylation stages in the production of MLT. First, tryptophan hydroxylase converts L-tryptophan into 5-hydroxytryptophan in response to the stimulus of darkness. Second, the enzyme 5-hydroxytryptophan decarboxylase converts 5-hydroxytryptophan into 5-hydroxytryptamine (serotonin), Decarboxylation requires vitamin B6, which is necessary. The rate-limiting enzyme serotonin "N-acetyl transferase (N-AT) converts serotonin into N-Acetylserotonin (N-AS)". The rate-limiting step requires Protein Kinase A (PKA), which activates serotonin N-AT. The hydroxy indole O-methyl transferase enzyme works with folate to convert N-acetylseroton (N-AS) into MLT. The SCN is stimulated by MLT, which results in the production of norepinephrine. More calcium (Ca2+) builds up in the cytosol when norepinephrine interacts with pinealocytes' endoplasmic reticulum and activates their -1/adrenoceptors. Additionally, intracellular cAMP is produced by membrane-bound adenylyl cyclase, which binds to PKA and increases PKA activity.

Mlt's mode of operation

Membrane receptors in the body that are primarily found in the central nervous system (CNS), are necessary for MLT. These receptors, which come in the MT1, MT2, and MT3, MLT receptor subtypes, are extensively dispersed. In a variety of situations, including sleep difficulties, pain, anxiety, depression, and ND, activation of MT1 and MT2 G-protein coupled receptors exerts physiological or pathological effects on MLT. Although quinone reductase has been identified as the enzyme, its roles in connection to MLT are yet unknown. MLT could affect the nuclear transcriptional regulator RZR/ROR, also known as the retinoid-related orphan receptor-alpha. The control of antioxidant enzymes and the regulation of the immune system by ROR depend on this link.

Melatonin's impact and the molecular causes of nd

According to growing evidence, MLT may be able to both cure and prevent a variety of ND. They have been linked to several pathophysiological characteristics of neurodegenerative disorders, including "mitochondrial dysfunction, autophagic insufficiency, increased oxidative stress, neuro inflammation, neuronal loss, and circadian rhythm instability".

https://doi.org/10.56294/mw2025461

Melatonin has been extensively studied for its potential neuroprotective effects across various neurodegenerative disorders, including Vascular Dementia (VD), Amyotrophic Lateral Sclerosis (ALS), Huntington's Disease (HD), Multiple Sclerosis (MS), Parkinson's Disease (PD), and Alzheimer's Disease (AD). In AD, melatonin has been shown to improve cognition and regulate circadian rhythms while reducing beta-amyloid aggregation and synaptic dysfunction. For PD, melatonin's neuroprotective properties help mitigate motor symptoms and cognitive decline. In HD, melatonin may reduce oxidative stress and neuroinflammation, offering therapeutic benefits for motor and cognitive symptoms. MS, a chronic inflammatory disease, could see improvements in symptom management with melatonin's anti-inflammatory effects. In ALS, melatonin helps reduce motor neuron damage and potentially delays disease progression. Finally, for VD, melatonin may protect the brain by alleviating oxidative stress and neuroinflammation, thereby improving cognitive function and reducing disease progression.

Therapeutic use of melatonin in nd

MLT's positive effects on a variety of experimental cell and animal models have prompted research into its potential impact on the clinical indicators of neurodegenerative disorders. The use of MLT in AD patients is included in case studies and clinical research. The first case study, which included a set of twins with AD, sundown syndrome, behavioral difficulties, cognitive impairment, and sleep quality were all improved. A common symptom of AD patients is sundowning, a neuropsychiatric disease also known as sundown syndrome that often shows up in the evening. In a second case study, MLT treatment dosages of two milligrams at eight p.m. for a week and overall 4 milligrams at three in the afternoon for the following week improved the patient's sleep and behavior. The patient had the typical sundown syndrome. The frequency of REM sleep, a kind of sleep activity, is likewise decreased by MLT. More research has shown that not all AD patients would get symptom relief with MLT. The effects of MLT on a patient's mood, daytime drowsiness, and circadian rhythm have been shown. The second patient received no further benefits from MLT; its sole advantage was a reduction in cognitive agitation.

In Parkinson's Disease (PD) patients, melatonin treatment has shown significant benefits in reducing daytime drowsiness, improving sleep quality, and alleviating cognitive dysfunction. Various assessment methods, such as PSG, PDSS, ESS, MMSE, and cognitive tests like the five-word test,Hamilton scale, and the digit span, have been used to measure the impact of melatonin. Additionally, actigraphy, sleep diaries, and scales like ESS, SSS, and GSDS are employed to assess the effects of melatonin on nocturnal sleep. Treatment typically involves administering melatonin at bedtime for varying durations and dosages, depending on the specific therapeutic goal.

Recent research found that in those with early- or late-stage PD, MLT considerably improved sleep quality and reduced anxiety. The use of MLT supplements did not, however, result in any appreciable modifications in the autonomic disorder, cognitive dysfunction, motor impairment, or depressive mood. The necessity for appropriate guidelines for treatment dosage, duration, and procedures for assessing motor function, cognitive function, and sleep quality is highlighted by these unfavorable outcomes.

In two studies investigating the effects of medication on Parkinson's Disease (PD) patients, significant improvements were observed in sleep quality and cognitive function. The first study involved 38 PD patients (mean age: 67,3 years) who were treated with 3 mg of the medication 30 minutes before bedtime for 6 weeks. Assessments included polysomnography (PSG), Parkinson's Disease Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS), and cognitive tests such as the Mini-Mental State Examination (MMSE) and Hamilton Scale. Results indicated a significant reduction in daytime drowsiness, poor sleep quality, and cognitive dysfunction. In the second study, 40 PD patients (aged 40–80 years) were treated with doses ranging from 5 to 50 mg at bedtime for 2 weeks. Actigraphy, sleep diaries, and other sleep assessments such as ESS, St. Louis Sleep Scale (SSS), and Glasgow Sleep Disorder Scale (GSDS) were used. The results showed objective improvements in nocturnal sleep, with the 50 mg dosage yielding the most significant benefit in sleep quality.

The effectiveness of MLT in treating neurodegenerative illnesses like ALS and MS, among others, has not been thoroughly investigated in clinical investigations. The first MLT therapy for ALS was administered to three patients, and it included taking slow-release MLT orally every night for 13 months. Testing on two more individuals demonstrated less deterioration after MLT was found to have halted the most severe case of ALS from developing.

Neurodegenerative disease prevalence

PD and AD are the two most common neurological illnesses, and as individuals age, their likelihood of having them increases. AD often affects older people. It is uncertain whether the existence of aberrant protein aggregates such as hyperphosphorylated tau (p-tau), amyloid-(A), and -synuclein corresponds with the level of cognitive decline in aged people's brain tissue, even though these aggregates have been discovered in these individuals. AD affects 50 % of those 95 years and older (figures 3,4,5). This research contains prospective

treatment approaches and summarizes the most recent scientific discoveries on the molecular mechanisms behind normal brain aging and neurodegeneration. The main subjects of discussion are AD and PD, but other neurodegenerative disorders with important links to signs and symptoms of aging are also discussed.[30]

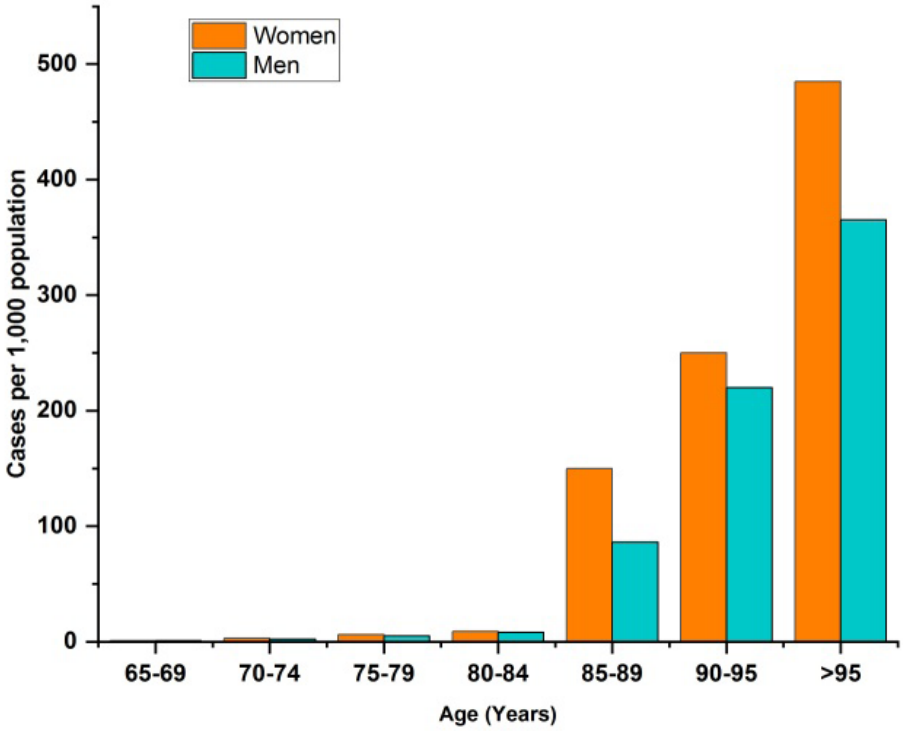

Figure 3. The Frequency of Neurodegenerative Illnesses. The Incidence of Alzheimer's Disease Per 1 000 Men and Women, Broken Down by Age 3, 8, And 9

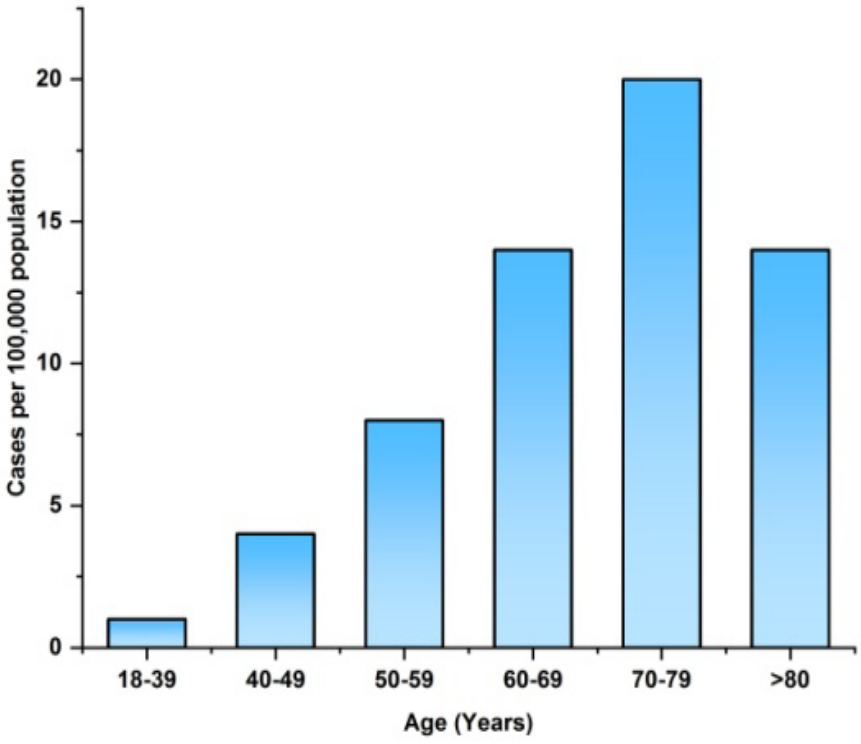

Figure 4. PD prevalence per 100 000 men and women worldwide, broken down by age 8, 10

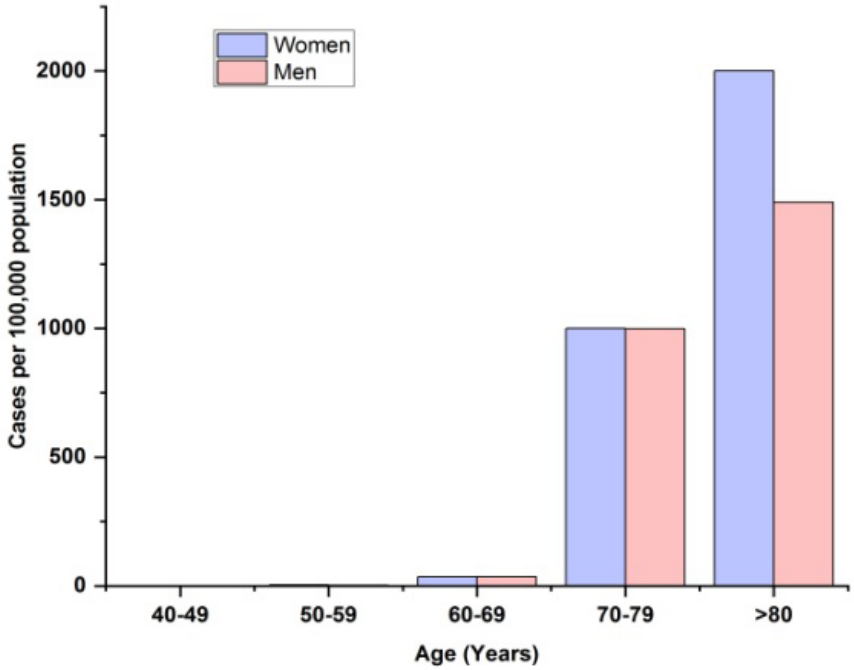

Figure 5. The number of cases of ALS per 100 000 people in 201

CONCLUSIONS

MLT is crucial for reducing circadian rhythms, oxidative stress, inflammation, neuronal death, and clinical symptoms within a range of ND, including HD, ALS, VD, MS, AD, and PD. Research indicates that MLT is a very effective therapeutic option for neurodegenerative diseases. The majority of research has been on preventing cognitive impairments and sundown syndrome as well as the advantages of getting more sleep. Clinical research on PD, HD, ALS, VD, and MS is still not widely available. Formulations, dosages, and durations of MLT administration, as well as various research design techniques and behavioral assessment techniques, all have an impact on clinical trials. We urgently need a thorough, multicenter clinical study that is well-designed to assess the effectiveness and value of MLT for the clinical symptoms of individuals with ND. Clinical trial outcomes have been variable because of MLT's short half-life (less than 30 minutes), which necessitates continuous release production. MLT supplements with controlled release might be the answer. The use of MLT in the treatment of neurodegenerative illnesses has a bright future since MLT's precise and efficient roles in clinical dysfunctions are being researched in several different substances.

REFERENCES

1. Wongprayoon P, Govitrapong P. Melatonin receptor as a drug target for neuroprotection. Current Molecular Pharmacology. 2021 Apr 1;14(2):150-64. https://doi.org/10.2174/1874467213666200421160835

2. Loh D, Reiter RJ. Melatonin: regulation of biomolecular condensates in neurodegenerative disorders. Antioxidants. 2021 Sep 17;10(9):1483. https://doi.org/10.3390/antiox10091483

3. Kafle OP, Cheng S, Ma M, Li P, Cheng B, Zhang L, Wen Y, Liang C, Qi X, Zhang F. Identifying insomnia-related chemicals through integrative analysis of genome-wide association studies and chemical–genes interaction information. Sleep. 2020 Sep 1;43(9):zsaa042. https://doi.org/10.1093/sleep/zsaa042

4. Cardinali DP. Melatonin: clinical perspectives in neurodegeneration. Frontiers in endocrinology. 2019 Jul 16;10:480. https://doi.org/10.3389/fendo.2019.00480

5. Wongchitrat P, Shukla M, Sharma R, Govitrapong P, Reiter RJ. Role of melatonin on virus-induced neuropathogenesis—a concomitant therapeutic strategy to understand SARS-CoV-2 infection. Antioxidants. 2021 Jan 2;10(1):47. https://doi.org/10.3390/antiox10010047

6. Polyakova VO, Kvetnoy IM, Anderson G, Rosati J, Mazzoccoli G, Linkova NS. Reciprocal interactions of mitochondria and the neuroimmunoendocrine system in neurodegenerative disorders: An important role for melatonin regulation. Frontiers in physiology. 2018 Mar 12;9:199. https://doi.org/10.3389/fphys.2018.00199

7. Spinedi E, Cardinali DP. Neuroendocrine-metabolic dysfunction and sleep disturbances in neurodegenerative disorders: focus on Alzheimer's disease and melatonin. Neuroendocrinology. 2019 Jun 12;108(4):354-64. https://doi.org/10.1159/000494889

8. Yousaf T, Pagano G, Wilson H, Politis M. Neuroimaging of sleep disturbances in movement disorders. Frontiers in Neurology. 2018 Sep 11;9:767. https://doi.org/10.3389/fneur.2018.00767

9. Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. British journal of pharmacology. 2018 Aug;175(16):3190-9. https://doi.org/10.1111/bph.14116

10. Vecchierini MF, Kilic-Huck U, Quera-Salva MA. Melatonin (MEL) and its use in neurological diseases and insomnia: Recommendations of the French Medical and Research Sleep Society (SFRMS). Revue Neurologique. 2021 Mar 1;177(3):245-59. https://doi.org/10.1016/j.neurol.2020.06.009

11. Cahan JG, Abbott SM. Use of light therapy for insomnia in the elderly: role of circadian rhythm disorders. Current Sleep Medicine Reports. 2020 Sep;6:176-83. https://doi.org/10.1007/s40675-020-00181-z

12. Ferlazzo N, Andolina G, Cannata A, Costanzo MG, Rizzo V, Currò M, Ientile R, Caccamo D. Is melatonin the cornucopia of the 21st century?. Antioxidants. 2020 Nov;9(11):1088. https://doi.org/10.3390/antiox9111088

13. Kopustinskiene DM, Bernatoniene J. Molecular mechanisms of melatonin-mediated cell protection and signaling in health and disease. Pharmaceutics. 2021 Jan 20;13(2):129. https://doi.org/10.3390/pharmaceutics13020129

14. Palagini L, Manni R, Aguglia E, Amore M, Brugnoli R, Bioulac S, Bourgin P, Micoulaud Franchi JA, Girardi P, Grassi L, Lopez R. International expert opinions and recommendations on the use of melatonin in the treatment of insomnia and circadian sleep disturbances in adult neuropsychiatric disorders. Frontiers in psychiatry. 2021 Jun 10;12:688890. https://doi.org/10.3389/fpsyt.2021.688890

15. Kinoshita C, Okamoto Y, Aoyama K, Nakaki T. MicroRNA: a key player for the interplay of circadian rhythm abnormalities, sleep disorders and neurodegenerative diseases. Clocks & sleep. 2020 Jul 23;2(3):282-307. https://doi.org/10.3390/clockssleep2030022

16. Paulose JK, Wang C, O'Hara BF, Cassone VM. The effects of aging on sleep parameters in a healthy, melatonin-competent mouse model. Nature and Science of Sleep. 2019 Aug 12:113-21. https://doi.org/10.2147/NSS.S214423

17. Ferini-Strambi L, Galbiati A, Casoni F, Salsone M. Therapy for insomnia and circadian rhythm disorder in Alzheimer disease. Current treatment options in neurology. 2020 Feb;22:1-8. https://doi.org/10.1007/s11940-020-0612-z

18. Wongchitrat P, Shukla M, Sharma R, Govitrapong P, Reiter RJ. Role of melatonin on virus-induced neuropathogenesis—a concomitant therapeutic strategy to understand SARS-CoV-2 infection. Antioxidants. 2021 Jan 2;10(1):47. https://doi.org/10.3390/antiox10010047

19. Yang S, Wang J, Wang D, Guo L, Yu D. Melatonin receptor agonist ramelteon suppresses lps-induced neuroinflammation in astrocytes. ACS Chemical Neuroscience. 2021 Apr 20;12(9):1498-505. https://doi.org/10.1021/acschemneuro.0c00743

20. Kuthati Y, Lin SH, Chen J, Wong CS. Melatonin and their analogs as a potential use in the management of Neuropathic pain. Journal of the Formosan Medical Association. 2019 Aug 1;118(8):1177-86. https://doi.org/10.1016/j.jfma.2018.09.017

21. Hsu CN, Huang LT, Tain YL. Perinatal use of melatonin for offspring health: Focus on cardiovascular and neurological diseases. International journal of molecular sciences. 2019 Nov 13;20(22):5681. https://doi.org/10.3390/ijms20225681

22. Biggio G, Biggio F, Talani G, Mostallino MC, Aguglia A, Aguglia E, Palagini L. Melatonin: from neurobiology to treatment. Brain Sciences. 2021 Aug 25;11(9):1121. https://doi.org/10.3390/brainsci11091121

23. Li T, Jiang S, Lu C, Yang W, Yang Z, Hu W, Xin Z, Yang Y. Melatonin: another avenue for treating osteoporosis?. Journal of pineal research. 2019 Mar;66(2):e12548. https://doi.org/10.1111/jpi.12548

24. Zhang F, Niu L, Liu X, Liu Y, Li S, Yu H, Le W. Rapid eye movement sleep behavior disorder and neurodegenerative diseases: an update. Aging and disease. 2020 Mar 9;11(2):315. https://doi.org/10.14336/AD.2019.0324

25. Lee JG, Woo YS, Park SW, Seog DH, Seo MK, Bahk WM. The neuroprotective effects of melatonin: Possible role in the pathophysiology of neuropsychiatric disease. Brain sciences. 2019 Oct 21;9(10):285. https://doi.org/10.3390/brainsci9100285

26. Bah TM, Goodman J, Iliff JJ. Sleep as a therapeutic target in the aging brain. Neurotherapeutics. 2019 Jul 15;16:554-68. https://doi.org/10.1007/s13311-019-00769-6

27. Manni R, Cremascoli R, Perretti C, De Icco R, Picascia M, Ghezzi C, Cerri S, Sinforiani E, Terzaghi M. Evening melatonin timing secretion in real life conditions in patients with Alzheimer disease of mild to moderate severity. Sleep Medicine. 2019 Nov 1;63:122-6. https://doi.org/10.1016/j.sleep.2019.04.018

28. Madari S, Golebiowski R, Mansukhani MP, Kolla BP. Pharmacological management of insomnia. Neurotherapeutics. 2021 Jan 1;18(1):44-52. https://doi.org/10.1007/s13311-021-01010-z

29. Stefano GB, Pilonis N, Ptacek R, Raboch J, Vnukova M, Kream RM. Gut, microbiome, and brain regulatory axis: relevance to neurodegenerative and psychiatric disorders. Cellular and molecular neurobiology. 2018 Aug;38(6):1197-206. https://doi.org/10.1007/s10571-018-0589-2

30. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, Bohr VA. Ageing as a risk factor for neurodegenerative disease. Nature reviews neurology. 2019 Oct;15(10):565-81. https://doi.org/10.1007/s10571-018-0589-2

FINANCING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

Conceptualization: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Data curation: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Formal analysis: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Research: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Methodology: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Project management: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Resources: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Software: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Supervision: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Validation: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Visualization: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

Writing – original draft: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh

Ravilla, Madhur Grover.

Writing – review and editing: Komal Parashar, Ashutosh Niranjan, Naresh Kaushik, Suvendu Narayan Mishra, Lokesh Ravilla, Madhur Grover.

https://doi.org/10.56294/mw2025461