Review Article

Circadian Rhythms, Melatonin, and Suicide Risk: Exploring the Role of the Pineal Gland in Mental Health

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Abstract

Background: Suicidal behaviour is a significant global public health issue, with over 800,000 deaths per year attributed to suicide. Emerging research highlights the complex relationship between mental health disorders, sleep disturbances, and self-harm, indicating that multiple factors biological, psychological, and social—are involved. The pineal gland (PG), often referred to as the "third eye," has garnered increasing attention due to its crucial role in regulating circadian rhythms through the production of melatonin. **Material and Methods:** A narrative literature review was conducted using PubMed, Google Scholar, Scopus, and Science Direct to identify studies up to July 2025 examining the relationships between circadian rhythms, melatonin, the pineal gland, and suicidal behaviour. Studies other than English language and unpublished data were excluded. **Results:** Alterations in melatonin production, along with physical changes in the pineal gland, such as calcification, have been associated with abnormal sleep patterns frequently observed in psychiatric conditions. These disturbances are also associated with increase risk of suicide. Melatonin secretion is regulated by environmental light-dark cycles, which may help explain seasonal variations in suicide rates. Moreover, studies have demonstrated a connection between the use of sleep medications and suicidal behaviour, underscoring the importance of managing sleep to prevent suicide. This narrative review synthesizes current research on the relationship between the pineal gland, melatonin, and suicidal behaviour. Its aim is to elucidate how disruptions in pineal function and the body's internal clock may contribute to increased suicide risk. A deeper understanding of these mechanisms may lead to innovative diagnostic and therapeutic strategies, offering new avenues for prevention in at-risk populations with sleep and mood disorders. **Conclusion:** Disruption of pineal function and circadian rhythm regulation, particularly altered melatonin secretion, is closely associated with sleep disturbances and psychiatric conditions linked to increased suicide risk. Circadian misalignment may represent a modifiable biological factor, highlighting the potential role of chronotherapeutic interventions in suicide prevention.

Keywords: Pineal Gland, Melatonin, Circadian Rhythm, Sleep Problems, Psychiatric Disorders, And Suicide.

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Introduction

Self-harming behaviour, such as suicide, is a significant contemporary global social issue.[1] Every year, suicide claims the lives of about 800,000 people worldwide, making it a serious public health concern.[2] According to world health organization more than 7,20,000 individuals die by suicide every year. Numerous studies have been carried out in an effort to shed light on the etiopathogenesis of suicide and facilitate the prevention of this complex behaviour involving social, psychological, and biological aspects.[1]

Suicide is associated with mental health conditions.[3] Sleep-disorders are frequently associated with mental health issues and have been linked to suicidal thoughts and behaviour. Correlation between hypnotic medicines, such as benzodiazepines and nonbenzodiazepines, and suicide rates are proven through research.[4,5] Since suicide and suicide attempt rates have been shown to fluctuate based on circadian rhythms and suicidal behaviour is known to peak in the spring and autumn, variations in melatonin levels secreted by the pineal gland could likely influence the suicidal behaviour.[6]

The pineal gland (PG) has been known for centuries as the "third eye," "ajna chakra," "pineal eye," and "seat of the soul."[7] However its effects on mammalian physiology, particularly its mechanism that controls the sleep cycle and wakefulness, were not realised until the late 19th century.[8,9] The primary function of the PG is to produce and release the hormone melatonin by receiving and transmitting light-dark stimuli from the environment,[10] that maintains physiological circadian rhythms and has a role in immunological control, reproductive physiology,[11] sleep regulation and several neuroendocrine regulatory functions.[12] Fluorescence methods enabled the

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identification of melatonin and serotonin in the pineal gland as well as the quantitative variability dependent on day-night cycles.[13] Melatonin is prescribed for the treatment of circadian rhythm disruptions; it can also be used to treat homeostatic sleep issues, both of which are commonly disrupted in patients with mental disorders.[14]

The purpose of this narrative review is to integrate current research on the association between pineal gland and suicidal behaviour and how changes in pineal anatomy, calcification, and melatonin release contribute to the pathophysiology of suicide.

Material and Methods

This narrative review aimed to investigate the link between circadian rhythms, melatonin, the pineal gland, and suicidal behaviour. A complete literature search was carried out using databases such as PubMed, Google Scholar, Scopus, and ScienceDirect. Relevant papers published till July 2025 were identified using keywords. Original research papers, review articles, postmortem investigations, neurobiological studies, and clinical trials on pineal anatomy, melatonin physiology, circadian regulation, and suicidal behaviour were included. Studies other than English language, unpublished and incomplete data were excluded. The reference lists of selected publications were manually searched to find more relevant studies. Because this is a narrative review, no formal quality assessment or meta-analysis was conducted, and findings were synthesised descriptively to present an integrated summary of current evidence.

Review

Pineal gland: Anatomy and physiology

In humans, the pineal gland is a tiny interhemispheric brain region that sits proximally on the diencephalon's posterior aspect. It develops from the upper part of the third ventricle (prosencephalon) and is connected to the roof of the ventricle via the pedicle.[1] Human adults typically have pineal gland dimensions of 5-9 mm in length, 1-5 mm in width, and 3-5 mm in height, weighing between 100 and 180 mg based on age and gender.[11] It is an essential small neuroendocrine organ which secretes the neurohormone melatonin, which controls sleep and the circadian rhythm.[15] Melatonin is secreted in all physiological fluids after it is synthesised and not retained in the pineal gland.[1]

Melatonin secretion is highest during darkness, and there is strong evidence that depressed patients have lower nighttime melatonin secretion peaks.[16] Beta-adrenoceptors are a key component of the post-synaptic response to sympathetic nerve activation, and are impacted by environmental brightness. They influence melatonin synthesis, and reduced melatonin levels found in suicide victims' pineal glands may be a sign of beta-adrenoceptor subsensitivity.[17]

The hypothalamic suprachiasmatic nucleus contains an endogenous circadian timing system that regulates melatonin secretion in the pineal gland. This system is inhibited by light, causing a high blood melatonin level at night and a low level during the day.[10] Studies investigating neurobiological factors have showed a connection between suicidal behaviour and the serotonergic, dopaminergic, and noradrenergic systems. For example, it has been noted that suicide victims had lower levels of serotonin (5-HT) and its metabolites in the brain.[18] In the synthesis of melatonin, serotonin serves as the precursor and noradrenaline as the positive regulator.[1]

When impulses, particularly those associated with darkness, reach the pineal gland, they attach to the noradrenaline pinealocyte membrane's adrenergic receptors and initiate a sequence of events that activate the enzymes necessary for the synthesis of melatonin. Aralkylamine n-acetyltransferase (AANAT) and acetylserotonin O-methyltransferase (ASMT), also referred to as hydroxyindole-O-methyltransferase, catalyse the serotonin N-acetylation which produces melatonin [Figure 1].[19] Thus, the levels of plasma melatonin and pineal gland melatonin are strongly correlated.[10] Melatonin synthesis increases during the night in response to increased aralkylamine N-acetyltransferase activity. ASMT activity doesn't significantly change during the course of the 24-hour period.[20] In colocalization studies, ASMT is a marker specifically used to assess pinealocyte immunoreactivity.[20] In addition to research showing that suicide victims have lower melatonin levels, there are also studies that report increase in melatonin.[17,21]

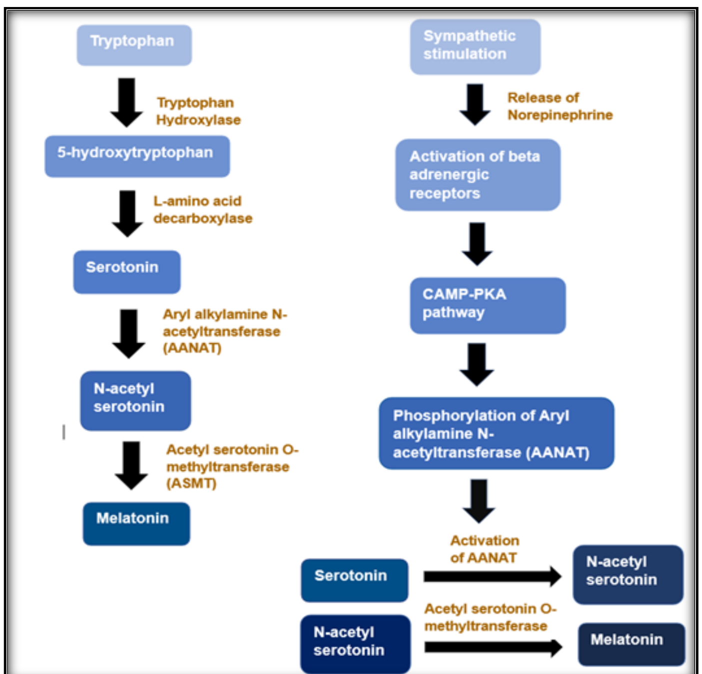

Figure 1: Biochemical pathway depicting synthesis of melatonin

Effects of melatonin on neurodevelopment and circadian rhythm: Melatonin production has been associated with the quality of the oocytes and the course of parturition since the start of a typical pregnancy. The concentrations at night begin to rise after 24 weeks of pregnancy and reach noticeably higher levels by 32 weeks. From the very beginning, melatonin receptors are widely distributed in the embryo and foetus. This neurohormone plays a part in foetal neuroprotection. Development of the foetal sleep patterns in late pregnancy is regulated by melatonin, and regular sleep patterns are essential for human neurodevelopment.[22] The levels of melatonin in the maternal blood gradually rise throughout pregnancy, reaching their maximum levels at term. Melatonin has also been detected in amniotic fluid.[23]

In animal models of foetal growth restriction in newborn lambs showed that melatonin administered to the mother improved neurodevelopment, lowered oxidative stress and brain damage, and decreased foetal hypoxia.[24] These findings imply that melatonin's impact on human foetus development seems to extend beyond circadian rhythmicity.[22] Natural maternal melatonin is an antioxidant and strong free radical scavenger that protects the foetus and infant within the maternal-placental-fetal unit.[25] Stress and trauma during pregnancy might reduce maternal melatonin synthesis, affecting the fetus's internal rhythms and physical and neurobehavioral development of the child. Melatonin rhythms established at about 3 months of age help explain why newborns have more consistent sleep-wake cycles and night-time sleep lasting 6 to 8 hours.[26] Extra-pineal melatonin, functions similarly to neurotrophic molecules in the brain and can alter cell survival, proliferation, and differentiation through signalling pathways that can be activated in response to stimulation of intracellular and membrane receptors.[27] Melatonin promotes the growth and survival of the brain through neurotrophic factors, which are essential for brain neuroplasticity and neurodevelopment.[28] Approximately 25% to 85% of children with developmental disorders experience sleep issues.[29] In addition to schizophrenia or bipolar disorder that manifest later in life, Neurodevelopmental disorders also include intellectual disability, autism spectrum disorder (ASD), or neurogenetic disorders that are associated with ASD. A significant number of people with these neurological disorders were found to have disrupted circadian rhythms.[30]

Pineal calcification and structural abnormalities

In humans, pineal calcification (also known as corpora arenacea, acervuli, brain sand, psammoma bodies, and pineal concretions) was first noted in 1653.[31] Computer tomography revealed calcified concretions in 2% of 0-3-year-old patients, 32% of 10-18-year-olds, 53% of 20-29-year-olds, and 83% of patients over 30 years old.[32] In a study carried out by Gheban et al., peak incidence of calcification is seen in the age group between 46-65 years.[33] In a study conducted by Arunkumar et al., Calcification was evident in all age groups. Pineal calcification increases with age throughout life.[34] The age at which it first appeared was in Four-year-old boy.[34]

Zimmermann and Bilaniuk found a considerable rise in the number of concretions during puberty.[35] Pineal melatonin is an anti-aging hormone, and the menopause is associated with a significant decrease in melatonin release and a higher rate of pineal calcification. The decrease in melatonin plasma levels during the initial stages of menopause may be a major contributing factor in the development of postmenopausal osteoporosis.[36]

Pineal concernments vary in different populations. Differences in calcification might be due to nutritional or environmental factors.[37] According to Mugondi and Poltera, Ugandans have the greatest rate of pineal calcification, which may be attributed to the high seasonal light intensity near the equator.[38]

The calcified concretions in the pineal gland range from few microns to several millimetres in diameter. Many theories exist regarding how brain sand is formed. The majority of them claim that the acervuli's core is made of calcifying biological material, such as cells or fibres.[37] Ueck and associates discovered calcium ATPase activity in pinealocytes.[39] An enzyme Ca2+ ATPase pumps calcium out of cells by hydrolysing ATP (adenosine triphosphate). Acervuli may develop when free intercellular calcium precipitates on structures. Concrements can also appear intracellularly.[39] Calbindin and Calretinin were identified in the pineal glands of both mammals and humans.[40] These proteins bind and transport calcium, regulating its intracellular levels. Research suggests that hyperparathyroidism and osteoporosis can affect pineal calcification and can cause epileptic seizures, brain atrophy, multiple sclerosis, and schizophrenia.[37] Pineal teratoma has a low rate of calcification, while pineal germinoma has a high incidence.[41] Patients who died from renal disease associated with hypertension, had the highest pineal calcium level in their pineal glands.[42] The relationship between pineal gland calcification and neurodegenerative diseases and ageing is still controversial in the literature.[43] Alzheimers disease patients had higher levels of pineal gland calcification compared to controls and individuals with other dementias.[44] In contrast, Fokin et al. found fewer concrements in pineal gland in patients with alzheimers disease.[45] Inconsistencies in literature may be due to individual variability in the pineal organ and varying levels of calcification between nations and time zones.[39]

Postmortem studies of the pineal gland in suicide victims

Suicides had lower melatonin concentrations in the pineal gland compared to controls who died during 2200-0600h, the peak melatonin-production time.[46] Beck-Friis found that suicidal inpatients have higher levels of melatonin compared to nonsuicidal depressed patients.[47] Depressed individuals who are associated with high risk of suicide may have low melatonin levels, slower nocturnal melatonin rise, and higher sensitivity to light's inhibitory effects at night.[46] However, melatonin levels were found to be higher in a study carried out by Pacchierotti et al., along with lobular disposition in pinealocytes, arborisation in connective tissues and glia, a decrease in cell nucleus volumes, and non-specific variations like irregular astrocyte distribution and "acervulina" formations.[21] These morphological changes may be indicators of pineal gland functional activation during the presuicidal phase.[21]

Suicide victims' postmortem pineal glands showed acetylserotonin O-methyltransferase (ASMT) immunoreactivity, and the suicide group's immunopositive pinealocyte count was found to be lower than that of the non-suicide group. Melke et al. found that melatonin levels and ASMT enzyme activity were positively correlated with the ASMT polymorphism (rs4446909).[48] Galecki et al. reported that the ASMT-gene polymorphism impacts the enzyme's expression and depressed patients had lower levels of ASMT mRNA expression. This gene might be the sensitivity gene for recurrent depressive illnesses. 49 Pineal glands from suicide victims have less 3H-serotonin binding sites.[46] Individuals with depression who commit suicide had more pineal beta-adrenergic binding, which reflects lower noradrenergic input.[50] When comparing suicide victims with major depression to matched controls, no significant differences in pineal beta-adrenergic receptors were found.[50]

Psychiatric disorders, pineal gland and suicide

Suicide is the primary cause of premature death in schizophrenic patients, which accounts for 12% of the excess mortality rate.[51] Sleep difficulties are frequently associated with psychotic symptoms. Insomnia is a typical prodromal symptom before a psychotic episode, which can worsen during the acute phase or remain as a residual symptom in clinically stable patients.[52] In both clinical and general populations, recent evidence also indicates a connection between sleeplessness and a psychotic experience, most notably paranoia.[53]

The percentage of individuals with schizophrenia who reported having nightmares was 16.7%, greater than the rate for healthy controls (4.9%).[54] Patients experiencing schizophrenia spectrum disorders are at a higher risk of attempting suicide when they lack sleep. Specifically, frequent insomnia was linked to a four-fold increased risk of suicide attempt. 40% to 80% of community-based individuals may experience chronic sleep disorders, like insomnia, during the period of three to five years of follow-up.[55]

Evidence suggests that sleep disorders may be associated with specific psychotic episodes, including command hallucinations and paranoia, which might increase the risk of suicide.[53] There are a number of possible pathways, but the exact mechanism between sleep disturbance with suicidal thoughts and actions in individuals with schizophrenia and other psychotic diseases has not been investigated.[56]

With an estimated lifetime suicide rate of 4.9%, schizophrenia is linked to an increased risk of suicide.[57] Sleep problems make people more prone to suicide thoughts and actions by exacerbating mood symptoms and psychotic episodes and by impairing executive and cognitive functioning, thereby resulting in deficiencies in problem-solving skills and susceptibility to impulsive actions.[53] One of the biggest challenges facing physicians is the timely identification of persons who are at risk of suicide.[56]

Cognitive behavioural therapy for insomnia (CBT-I) and imagery rehearsal therapy (IRT) for nightmares are two examples of sleep-focused psychological treatments whose clinical effectiveness has been well-established across a range of clinical groups and contexts.[58] Effective CBT-I treatment decreased suicide thoughts even after controlling the impact of concurrent improvements in the intensity of depressive symptoms. Despite the paucity of information about CBT-I's effectiveness in treating psychotic disorders, several promising results have been noted.[53]

For patients with schizophrenia, sleep problems may be a side effect of medication even after receiving the best possible drug treatment. The use of sedative antipsychotics or the addition of short-term adjunctive drugs, like benzodiazepines or hypnotic agents, to a nonsedating antipsychotic agent are two pharmacological strategies that have been proposed to treat residual sleep disturbances in schizophrenia. The evidence supporting these methods of treatment is, however, limited and there remains the concern that prescribing sedatives and hypnotics to vulnerable individuals can increase their risk of suicide.[56]

Melatonin is available for purchase over the counter in several countries, including India. The dearth of knowledge is problematic considering the high prescription rate for melatonin, especially among children and adolescents.59 According to Besag et al., melatonin treatment had little to no side effects; however, more thorough analysis is recommended.[60] The widespread use of melatonin and its variety of applications (such as treating sleep disorders or supporting mental health through dietary supplements) highlight the need of determining whether melatonin is associated with an elevated risk of suicidal behaviour. Individuals on melatonin who experience depression might represent a subgroup with an elevated risk of suicidal behavior.3 In a study carried out by Besag et al., melatonin-treated person are at greater risk of suicidal behaviour, though this may be partially due to underlying conditions like mental or sleep disorders.[60]

Potential Diagnostic and Therapeutic Implications

For the treatment of mental health conditions, sleep and circadian rhythm disturbances are essential therapeutic goals. Psychoactive drugs are not always effective in addressing circadian rhythm issues and may even worsen them.[61] Melatonin and melatonergic substances are promising supplementary therapies for managing sleep and circadian rhythm issues. However, there are limited well-designed trials to support melatonin supplementation as an effective treatment for sleep and rhythm disruption in psychiatric disorders. To maximise melatonin efficacy, ensure optimal dosage and timing based on sleep and circadian rhythm disturbances. A recent meta-analysis suggests that low-dose melatonin ($\leq$ 1 mg) may be more effective at promoting sleep and can effectively advance sleep phase and circadian rhythms as a chronobiotic agent.[62] High-dose melatonin has been shown to improve sleep efficiency and duration.[14]

A therapeutic technique called Bright Light Therapy (BLT) employs intense light exposure to control circadian rhythm entrainment., particularly for individuals with sleep disorders and neurodegenerative diseases.[14] BLT works by synchronising the Suprachiasmatic Nucleus (SCN) with the cycle of light and dark outside. Melatonin release, which encourages sleep and preserves circadian rhythms, is one of the physiological processes that the SCN controls.[63] BLT has been shown to lessen symptoms like agitation, anxiety, and behavioral issues during the day. It can help treat mental disorders by increasing melatonin release and suppressing neurotransmitters that cause wakefulness at night. The internal chronobiological clock can be synchronized with the natural light-dark cycle and advanced sleep phases can be treated with more light exposure (about 10,000 lux). However, factors like the duration, timing, and intensity of light exposure affect how BLT works. Individuals receiving treatment may benefit most from morning light exposure, especially in the early hours of the day.[63]

Numerous cutting-edge therapeutic strategies targeted at helping the aging population's circadian rhythms and those with neurodegenerative diseases have been developed as a result of increased study of the biological clock's molecular mechanisms that control the sleep-wake cycle.[64] In order to restore rhythmicity brought on by ageing and neurodegenerative diseases, these interventions focus on clock gene activity and downstream effectors within disturbed signalling pathways. The orexin antagonist is a significant pharmacological drug that inhibits the effects of orexin neuropeptides, which raise alertness and arousal. It is a crucial neuropeptide that controls cycles of wakefulness and sleep. Antagonising orexin helps initiate and maintain sleep while minimising disruption to the circadian rhythm. Elderly people who use Suvorexant (Belsomra), the first Dual Orexin Receptor Antagonist (DORA) licensed by the FDA, report longer sleep duration overall and reduced sleep start latency.[63]

In addition to light-based and pharmacological interventions to strengthen circadian rhythms, behavioural and lifestyle changes are crucial, particularly for ageing adults and patients with neurodegenerative diseases. Circadian alignment and improved health outcomes can be achieved with consistent mealtimes, planned physical activity, and frequent exposure to natural light.[64] Frequent exposure to daylight aids in circadian clock synchronization. especially the SCN. Natural light is very important in regulating melatonin release and hormonal cycles. Daily physical activity, in addition to light exposure, can improve peripheral clock synchronisation, which is essential for maintaining metabolic and physiological processes.[65] Dietary interventions like Time-Restricted Feeding can improve metabolic efficiency by synchronising calorie intake with circadian rhythms. Research suggests that consuming the majority of calories earlier in the day, when metabolic processes are more active, may lower the risk of circadian misalignment and related metabolic problems. Avoiding caffeine and artificial blue light in the evening can improve circadian health. These measures reduce disturbances in sleep and hormonal rhythms.[63]

Conclusion

This narrative review highlights the importance of the pineal gland and circadian rhythm regulation in the complicated neurobiology of suicidal behaviour. Melatonin secretion disruptions, pineal gland structural abnormalities, and disrupted circadian signalling are all linked to sleep difficulties and psychiatric diseases that increase the risk of suicide. Evidence from research suggests that circadian imbalances may actively contribute to suicide risk compared to merely an occurrence of a neurological disease. Recognising circadian rhythm disruptions as potentially modifiable risk factors opens up new possibilities for prevention using chronotherapeutic techniques such as melatonin-based treatments, light therapy, and sleep-focused behavioural interventions. Future research should concentrate on longitudinal studies and focused clinical trials to integrate circadian neuroscience into effective suicide risk assessment and preventive measures.

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Conflicts of interest

There are no conflicts of interest.

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