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Melatonin's impact on sleep, cognition and its potential role as an adjuvant in neurocognitive enhancement

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Abstract:
Melatonin, produced by the pineal gland, regulates sleep and circadian rhythms, with deficiency linked to sleep issues and cognitive impairment. It manages NREM and REM sleep cycles, enhancing sleep quality and memory through synaptic reinforcement. Beyond sleep, melatonin offers antioxidant, anti-aging, immune-modulating, anti-cancer benefits and influences fertility and sexual function. Melatonin supplements effectively treat sleep disorders like insomnia and jet lag and may protect against Alzheimer's disease. Thus, melatonin could be an adjuvant therapy in neurocognitive disorders due to its effects on sleep and cognition.

Keywords: Melatonin, REM sleep, neurocognitive disorder, memory, sundowning, adjuvant drug

Background:
Melatonin, a neurohormone secreted mainly by the pineal gland, regulates circadian rhythms and sleep **[1]**. Recent studies highlight its pleiotropic effects, including antioxidant, anti-inflammatory and neuroprotective properties, sparking interest in its cognitive impact and therapeutic potential in neurocognitive disorders **[2]**. Sleep disturbances and cognitive impairment often coexist in neurodegenerative diseases like Alzheimer's and Parkinson's, with melatonin secretion disturbances reported in these conditions **[3]**. This suggests melatonin supplementation as a potential adjuvant therapy. Animal and human studies indicate melatonin enhances memory consolidation, reduces oxidative stress and mediates neuroinflammation, all linked to cognition and neurodegeneration **[1]**. By analysing mechanistic studies and clinical data, this paper seeks to provide a comprehensive view of melatonin's therapeutic use in neurology and geriatrics **[4]**. Therefore, it is of interest to integrate the current knowledge on melatonin's effects on sleep and cognition and assess its value as an adjuvant in neurocognitive disorders.

Physiology and mechanism of action of melatonin:
Melatonin is crucial for regulating sleep and circadian rhythms. While neurotransmitters like GABA, Acetylcholine and dopamine regulate wakefulness and sleep, melatonin is particularly important **[5]**. It is a natural hormone produced mainly by the pineal gland, as well as the retina and skin. Melatonin's chemical name is N-acetyl-5-methoxytryptamine. Melatonin production and secretion depend on the time of day, increasing in darkness. Long-term serum melatonin concentration also depends on age, decreasing with age. Light and dark cues from the retina are transmitted to the Suprachiasmatic nucleus in the hypothalamus, stimulating norepinephrine secretion, which prompts the pineal gland to release melatonin **[6]**. Dopamine, another neurotransmitter related to sleep-wake rhythms, decreases during the day, while melatonin levels rise, inducing sleep. Night time exposure to light from devices like computers and smartphones disrupts sleep and causes insomnia by mimicking daylight and reducing melatonin secretion **[2]**. Melatonin levels in humans are low before three months, increase with growth and peak before puberty and then decrease with age due to pineal gland changes **[7]**. **Figure 1** depicts the synthesis of melatonin in response to external stimuli**.** Melatonin offers benefits like anti-cancer, anti-aging, improved sexual desire and fertility, immune support and antioxidant effects **[3]**. Melatonin is crucial for circadian rhythm regulation, especially in disrupted sleep-wake cycles and can improve sleep quality in Alzheimer's patients. They spend less time in deep NREM sleep, leading to more awakenings and reduced total sleep time **[8]**. Different neurons are active in each state: GABAergic during sleep, monoamine and orexin during wakefulness and acetylcholine follows monoamine patterns. Melatonin affects sleep by acting on the suprachiasmatic nucleus, reducing wake impulses and improving sleep quality. Its secretion starts around 22:00-23:00, peaking at 03:00-04:00 and it increases total sleep time and reduces latency **[5]**. Melatonin influences REM sleep, with significant changes in REM latency and prolonged first REM episode, especially in those with reduced REM sleep. Pharmacotherapy can alter sleep by activating or inhibiting neurons, highlighting melatonin's role in sleep induction **[4]**.

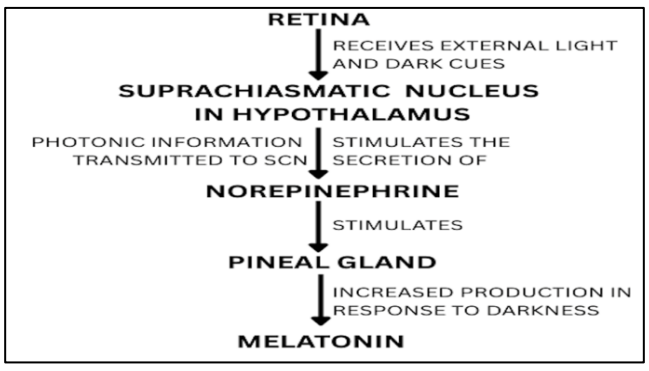

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Figure 1: Representation of the synthesis of melatonin in response to external stimuli

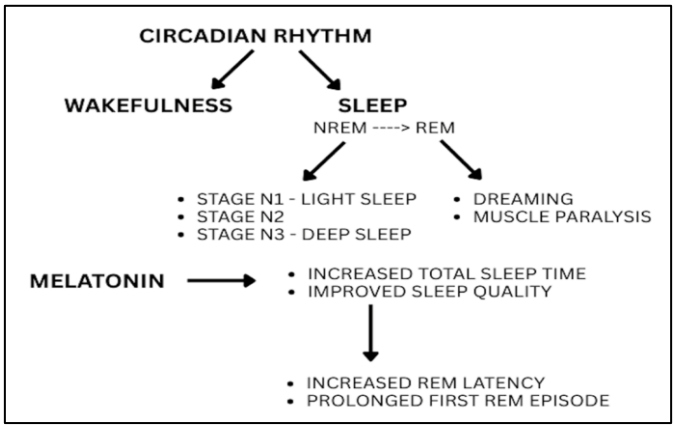

Figure 2: Representation of sleep cycle and effect of melatonin on it

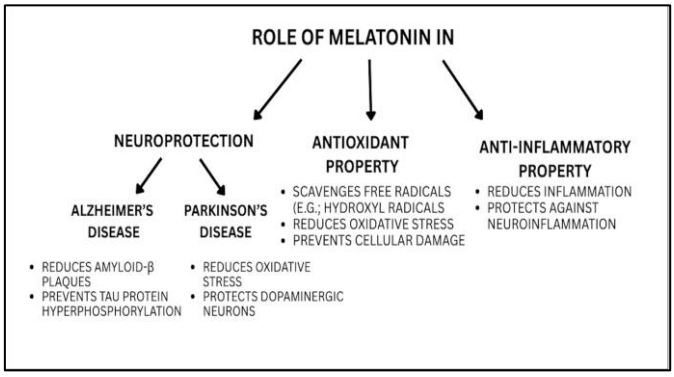

Figure 3: Melatonin's role in neuroprotection and anti-inflammatory effects.

Association of sleep with memory and cognition:

Figure 2 shows the effect of melatonin on sleep cycle. Memory is reorganised into efficient forms during sleep, consolidating daily experiences **[6]**. Neurophysiological processes, including neuroplasticity, synaptic potentiation and the conversion of transient memories to long-term storage, are key in this process **[9]**. Neuroplasticity enables the brain to adapt, strengthening existing connections and forming new synapses for memory storage. While awake, transient information is easily lost, but sleep secures it in long-term memory **[7]**. REM sleep, first described in 1953, is autonomically regulated and linked to creativity and associative thinking. Memory consolidation involves both the hippocampus and neocortex, with semantic memories stored in the neocortex and episodic ones in the hippocampus. Functional MRI shows NREM activates the hippocampus, while REM mainly engages the neocortex for semantic memory. NREM sleep replays low-level sensory representations, while REM fuses memories into dreams for evaluation. Feedforward pathways act as discriminators and feedback pathways as generators **[10]**. REM involves the Papez circuit, supporting spatial and contextual memory **[9]**. Research emphasizes REM's role in implicit memory and emotional processing, while explicit memory consolidates in NREM. Implicit memory aids problem-solving without conscious recall. Acetylcholine and norepinephrine regulate sleep stages and memory consolidation, with acetylcholine enhancing REM and spatial memory **[10]**. Norepinephrine reuptake inhibition improves declarative memory in adults. Optogenetic suppression of medial septum activity in REM disrupts contextual memory, highlighting theta rhythm importance **[8]**. Adult-born neurons in the hippocampal dentate gyrus contribute to memory processing **[11]**. Altering these neurons during REM impairs contextual memory consolidation. REM inhibition weakens synapses of newborn neurons, aligning with its role in selective dendritic spine reinforcement. Even minimal adult-born neuron activity during REM is essential; both activation and inhibition can cause memory deficits **[12]**. Theta oscillations may synchronize pre- and post-synaptic activity in REM to induce Hebbian long-term potentiation. Learning-activated ABNs selectively strengthen, while non-integrated neurons undergo synaptic depression. REM also enhances motor cortex spines related to learned tasks and prunes irrelevant ones **[13]**. REM sleep after new learning upregulates mRNAs, phosphoproteins and proteins in hippocampal and cortical neurons. Theta waves support the hippocampal replay of place cell sequences, aligning with learning plasticity. Highly regulated theta activity maintains hippocampal network plasticity and memory consolidation **[14]**.

Associated sleep abnormalities in neurocognitive disorders:

Neurodegenerative diseases with REM involvement indicate its role in memory. Alzheimer's patients show fewer K complexes, reduced SWS and altered REM patterns contributing to cognitive decline. Reduced REM hinders glymphatic clearance of amyloid-β and tau proteins **[14]**. Glymphatic activity is suppressed during wakefulness due to noradrenaline bursts. Hyperphosphorylated tangles in the locus coeruleus may drive noradrenergic axonal degeneration in AD. Parkinson's studies show poor sleep, prolonged latency, reduced REM and fragmentation in 80% of patients. REM sleep disorder affects CA1 hippocampal muscarinic receptors, causing amnesia **[13]**. REMSD alters noradrenaline levels and impairs hippocampal plasticity. Melatonin regulates sleep and may indirectly enhance cognition. Qin *et al.* reported that restorative sleep improves memory and attention **[12]**. Its antioxidant and anti-inflammatory properties offer neuroprotection **[15]**. Patients with circadian rhythm disruptions may benefit from melatonin therapy. Melatonin's neuroprotection in rat brain injury models **[16]**. Other animal studies showed cognitive improvements with melatonin. Human trials are needed. **Figure 3** shows the role of melatonin as an anti-inflammatory agent and for neuro protection. Its anti-oxidant and anti-inflammatory properties play a key role in neuro protection **[17].**

Melatonin in neurocognitive disorders and sundowning:

Melatonin may help manage sundowning, where evening agitation worsens in dementia **[14]**. In neurocognitive disorders,

melatonin secretion is impaired, delaying sleep and disturbing mood. Sundowning is linked to Alzheimer's, Parkinson's and vascular risks like hypertension and CKD. ApoE4 allele carriers with AD are more prone to sundowning. Symptoms include agitation, confusion, restlessness and hallucinations. ICU settings often worsen delirium due to disrupted melatonin cycles. Melatonin aids sleep initiation and reduces agitation, though it does not reverse neurocognitive decline. Music therapy, exercise and melatonin-rich foods like cherries and pistachios can boost natural melatonin **[18]**. Recent meta-analytic evidence lends further weight to this translational argument. Pooling data from eight randomized trials in 518 participants with cognitive impairment, melatonin supplementation was found to produce a significant improvement in global cognition on the MMSE, though its effect on disease-specific measures such as the ADAS-Cog fell short of significance **[19].** This pattern suggests that melatonin's cognitive benefits may be easier to detect through broad screening tools than through more granular, disease-specific instruments, and that outcomes likely depend on factors such as dosing, treatment duration and baseline severity. Rather than weakening the case for melatonin as an adjuvant therapy, this finding sharpens it, pointing to the need for the standardized, multi-dimensional outcome measures called for above before its role in clinical practice can be fully defined.

Conclusion:

Melatonin regulates sleep and circadian rhythm, improving cognition indirectly. It shows neuroprotective and adjuvant potential in managing neurocognitive disorders and sundowning. Thus, clinical use requires careful monitoring due to drug interactions and variable responses. Further studies must define its optimal dosage and mechanisms.

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