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Melatonin deficiency and sleep fragmentation in frequent travelers: A modern circadian health crisis

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Abstract

Background: Frequent travel disrupts the circadian rhythm, often leading to disturbed melatonin production. This disruption contributes to sleep fragmentation, reduces sleep quality, and cumulative fatigue that many travelers experience as more than just temporary jet lag. Despite the growing spread of global travel, the long-term consequences of melatonin deficiency and chronic circadian misalignment remain underrecognized and insufficiently addressed.
Aim: To review the available literature on how frequent travel leads to melatonin deficiency and sleep fragmentation and to highlight the need for better strategies to address this growing circadian health issue.
Methods: A narrative review was conducted using 35 peer-reviewed articles identified through PubMed, Scopus, and Google Scholar. The studies were organized into six thematic categories: biological mechanisms of melatonin production, circadian rhythm disturbances and frequent long-distance travel (jet lag), sleep fragmentation – mechanisms and consequences, correlation

between melatonin deficiency and sleep fragmentation, long-term health issues and current intervention strategies.
Results: Melatonin deficiency and sleep fragmentation in frequent travelers, by disrupting the central circadian rhythm, are associated with a number of serious long-term health consequences, such as neurodegeneration and cognitive impairment, metabolic disorders and cardiovascular diseases, diabetes, obesity, mental health issues and increased risk of cancer. Further research is needed to develop better strategies for managing circadian rhythm disruption and reducing its long-term effects.
Conclusions: The circadian rhythm dysfunction is closely connected to many future health problems. Addressing this growing issue requires greater awareness and more effective, evidence-based strategies to support circadian stability in those who travel regularly.

Keywords: melatonin deficiency, sleep fragmentation, jet lag, frequent travelers, obesity, diabetes, mental health issues, neurodegeneration, circadian rhythm, metabolic disorders

1. Introduction

Melatonin (MEL; N-acety-5-methoxytryptamine) is a hormone synthesized mainly by the pineal gland and secreted with a distinct circadian rhythm. [1] Due to its secretion pattern, which peaks during the dark phase of the cycle (around 3:00-4:00 a.m.), melatonin has been defined as the "darkness hormone" [1][2]
Its primary function is to convey information about the photoperiod (such as the time and length of the day). [1] Melatonin acts as the main synchronizer for the circadian organization of many internal processes in the body [1], and its rhythm regulates sleep propensity [2][3]. Melatonin levels are suppressed by exposure to bright light [1][4], which is the mechanism for synchronising the central circadian clock (located in the Suprachiasmatic Nucleus)[3].

Sleep fragmentation is a condition closely linked to poor sleep quality [3] and irregular sleep/wake patterns, leading to an irregular rhythm [4]. Sleep disorders are destructive to behavioral and emotional well-being [5]. Sleep fragmentation is the result of brief awakenings (microarousals, MAs) that disrupt sleep continuity [5]. It has been shown that stressful events induce micro-awakenings, which consequently lead to fragmentation of NREM sleep [5]. Sleep fragmentation and circadian rhythm disorders are associated with an increased risk of dementia and cognitive decline in older adults [6][7].

Although sources do not precisely define a "frequent traveler", the problem affects people exposed to rapid time zone changes (transmeridian travel), leading to let lag syndrome (JLS). This syndrome is characterized by circadian misalignment [3], as well as temporary symptoms such as poor sleep, problems with daytime alertness, and reduced performance. A similar desynchronization also affects night shift workers [8][9].

Circadian rhythm dysregulation and melatonin deficiency are the central driving forces behind sleep and circadian rhythm disorders [10]. These disorders are common in modern society [9]. Exposure to artificial bright light (ALAN) in the evening suppresses endogenous melatonin production [3][4], contributing to further desynchronization.
Chronic circadian desynchronization (caused, among other things, by shift work) and its consequences - melatonin deficiency and poor sleep quality (including fragmentation) - are associated with a number of serious long-term problems, such as neurodegeneration and

cognitive impairment [11][12], metabolic and cardiovascular diseases [13] or mental disorders [12].

The aim of this study is to determine the relationship between melatonin deficiency and sleep fragmentation in individuals experiencing chronic circadian desynchronization (frequent travelers/shift workers), as well as to identify the health consequences of this condition (especially in the neurodegenerative and metabolic context) and possible chronotherapeutic interventions, including the potential use of exogenous forms of melatonin and bright light therapy (BLT) to restore synchronization [3][10].

2. Methodology

This narrative review synthesizes recent research on melatonin deficiency and sleep fragmentation and their contributions to future health problems. A structure search was conducted in PubMed, Google Scholar and Scopus for studies published between 2009 and 2025. Key search terms included: melatonin deficiency, sleep fragmentation, jet lag, frequent travelers, obesity, diabetes, mental health issues, neurodegeneration, circadian rhythm and metabolic disorders. Studies were included if they were peer-reviewed, published in English, focused on human subjects and examined the impact of sleep disorders and melatonin deficiency on health problems and their subjective feelings. Exclusion criteria encompassed non-full-text publications, and non-primary data sources.

A total of 35 relevant articles were selected and studied. Articles were thematically categorized into six domains: biological mechanisms of melatonin production, circadian rhythm disturbances and frequent long-distance travel (jet lag), sleep fragmentation – mechanisms and consequences, correlation between melatonin deficiency and sleep fragmentation, long-term health issues and current intervention strategies. This structure guided both selection and synthesis of findings. As a narrative review, this study does not include formal quality scoring or meta-analysis. However, methodological diversity and relevance were considered when interpreting results.

2.1 AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3.1 Biological Mechanisms of Melatonin Production

The production and regulation of melatonin (MEL) is closely synchronized with the light-dark cycle and is a key element in the regulation of the circadian rhythm. This process is controlled by the main biological clock located in the brain.

Melatonin, defined as the “darkness hormone”, is a neurohormone primarily synthesized and

secreted by the pineal gland [1-2][12][14]. Melatonin synthesis exhibits a distinct circadian rhythm [1][15]. Physiologically, its concentration reaches its maximum peak during the dark phase of the cycle (around 3:00-4:00 a.m.) [1]. Although melatonin is synthesized in many tissues (extra-pineal melatonin), only that produced by the pineal gland is released into the bloodstream with a circadian rhythm and contributes to the global regulation of biological rhythms [1].

3.1.1 The Role of the Suprachiasmatic Nucleus (SCN)

The suprachiasmatic nucleus (SCN) in the hypothalamus acts as a central oscillator that controls the rhythmic production of melatonin and coordinates the circadian system [1]. The SCN circadian rhythm is generated at the cellular level by feedback loops of clock genes, including CLOCK, BMAL1, PER and CRY [1][16]. The rhythmic secretion of melatonin is the output of the SCN and reflects the state of the clock in terms of phase and amplitude [1][14]. Melatonin is seen as the "hand" of the biological clock [14]. Melatonin provides feedback to the SCN, acting as a chronobiotic - a substance that adjusts the timing of internal biological rhythms [11][14]. The action of melatonin in the SCN is mediated by MT1 and MT2 receptors [4][17][18]. Activation of MT2 receptors in the SCN leads to phase advance of the circadian clock [16-18]. One of the actions of melatonin is to inhibit spontaneous firing of SCN neurons (SCN neuronal firing), which is associated with MT1 receptor activation [1][17].

3.1.2 Influence of Environmental Factors (Light, Time of Day)

The environmental light-dark cycle is the most important synchronizing factor (zeitgeber) [11]. Light synchronizes the circadian rhythm generated in the SCN [11]. Exposure to bright light suppresses melatonin secretion, which is why it is referred to as the "darkness hormone" [14]. Light information is transmitted to the SCN, and melatonin suppression is extremely sensitive to light and is primarily driven by melanopsin [19]. Melatonin serves as a chemical code for the duration of the night and is crucial in transmitting light information to the neuroendocrine system [14].

Preclinical studies have shown that neuroplastic changes in the adult brain are subject to circadian rhythms and are influenced by the light/dark cycle [16]. For example, neuroplastic rhythms often have maximum amplitude during the dark phase, coinciding with peak melatonin secretion, regardless of the activity pattern of the species [16]. The timing of the signal (whether light or exogenous melatonin) relative to the circadian phase determines the direction of the rhythm shift:

- Administration of melatonin in the evening induces an advance in endogenous circadian rhythms (e.g., Dim-Ligth Meleatonin Onset rhythms, body temperature) [1]
- Administration of melatonin in the morning causes a delay in endogenous circadian rhythms [1].

Internal biological time can be determined by the onset of melatonin secretion in dim light (DLMO), which is measured in dim light conditions after 5:00-6:00 p.m. to avoid the masking effect of the natural photoperiod [1].

3.2 Circadian Rhythm Disorders and Frequent Intercontinental Travel (Jet Lag)

Circadian rhythm disorders associated with frequent interzone travel, known as jet lag syndrome (JLS), result from a temporary misalignment of the internal biological clock with the external time at the destination [20][21]. This misalignment is the main cause of symptoms such as poor sleep, daytime sleepiness and reduced performance [20].

Jet lag is an episodic phenomenon that occurs after rapid travel [22] across 3 or more time zones (transmeridian travel, i.e., east-west or west-east) [21][22]. The greater the number of time zones crossed, the greater the desynchronization and severity of symptoms [21].
Adaptation to a new time zone is not symmetrical and depends on the direction of travel, which directly affects the required phase shift of the endogenous clock (Suprachiasmatic Nucleus) [21][23]:

3.2.1 Traveling West (Phase Delay)
Requires the circadian clock to delay, to shift backward to an earlier time of day [22][23]. The human circadian clock naturally has a period slightly longer than 24 hours [14], which makes it easier to delay the phase [21]. Adaptation (resynchronization - re-entrainment) is faster and takes about 0,5 days for each time zone crossed (which translates to about two hours of adjustment per day) [21].

3.2.2. Traveling East (Phase Advance)
Requires the circadian clock to speed up, to move forward to a later time of day [22][23]. Traveling east is more challenging than traveling west because it is more difficult to advance the clock than to delay it [21]. Adaptation takes longer, approximately one day for each time zone crossed, approximately one hour of adjustment per day [21].
For example, traveling east across 7 time zones requires the internal clock to shift to an earlier bedtime, which is difficult if the internal rhythm is still on departure time [23].

3.2.3 Adaptation and Short Stops
For short stays (short stops) in the destination zone, it is recommended not to try to adapt to the circadian rhythm, but to focus on maintaining sleep and alertness as much as possible [20].

3.2.4 Impact on Endogenous Melatonin Production
The endogenous melatonin rhythm is a critical indicator of circadian status and is directly disrupted by jet lag [20][22]. Melatonin is a darkness hormone [22], and its rhythm secretion at night serves as a marker of internal circadian time (phase) [20]. Melatonin has chronobiotic properties, meaning it can shift the phase of the central pacemaker (SCN) both *in vitro* and *in vivo* [20].

During jet lag, the body is in a state of desynchronization, in which the melatonin rhythm (controlled by the Suprachiasmatic Nucleus) is out of synchronization with the light/dark cycle in the new time zone [20]. As a result, melatonin may be secreted during what is daytime at the destination, or its secretion may be suppressed during what should be nighttime.
Exposure to light is the primary factor controlling the circadian system and must be considered with any intervention [20]. Bright light suppressed melatonin secretion [22], which is used in therapies, but incorrect light exposure in a new time zone (e.g. bright light in the morning after traveling west) can hinder resynchronization [3][24].
Returning to synchronization requires gradual adaptation of the melatonin rhythm [23]. Studies have shown that the plasma melatonin rhythm can be resynchronized after eastward flights (e.g. 9-hour or 11-hour flights) [22][23]. The use of exogenous melatonin or its agonists is dictated by its ability to shift the phase rhythm in the Suprachiasmatic Nucleus, which aims to accelerate adaptation to the new time [20].
In summary, jet lag is a state of desynchronization in which the number and direction of time

zones crossed dictate how much phase shift (delay vs. advance) is required and how quickly resynchronization will occur. The melatonin rhythm is a key but slow-to-adapt biological signal that becomes mis-timed and must be reset to alleviate the symptoms of Jet Lag Syndrome [20]

3.3 Sleep Fragmentation - Mechanisms and Consequences

Sleep fragmentation is one of the key symptoms of stress-related sleep disorders, such as insomnia or post-traumatic stress disorder (PTSD), and has a serious impact on behavioral and emotional well-being [5].

Sleep fragmentation involves interruptions in sleep continuity [5]. Its physiological basis is short awakenings, known as micro-awakenings (MAs), which last less than 20 seconds and occur during NREM (non-rapid eye movement) sleep [5]. Micro-awakenings are characterized by EEG desynchronization and EMG activation [5].

Glutamatergic neurons in the preoptic area (POA) of the hypothalamus play a key role in the regulation of micro-awakenings. VGLUT2 glutamatergic neurons in the POA region are activated in sync with the infraslow rhythm (in the spindle band of the EEG) during NREM sleep and undergo transient activation during MAs [5]. Activation of these POA glutamatergic neurons promotes micro-awakenings and wakefulness [5]. Brief stimulation of these neurons can immediately induce arousal [5]. Inhibiting the activity of POA VGLUT2 neurons reduces the number of MAs and consequently consolidates NREM sleep [5].

Sleep fragmentation, caused by an increased number of MAs, is harmful and leads to many health problems. Sleep fragmentation impairs memory and learning [5]. Impairment of sleep and circadian rhythms threatens the integrity of the brain, e.g., the hippocampus [25], Poor sleep quality is strictly linked to worse cognitive functions and, possibly, increased risk of dementia [26]. Sleep fragmentation induced anxiety [5].

3.3.1 Sleep Disorders Related to Time Changes (Jet Lag)

Sleep disorders accompanying rapid travel across time zones (jet lag, JLS) result from the desynchronization (mismatch) of the endogenous oscillator (SCN) to external time [20].

Jet lag is characterized by poor sleep and problems with alertness during the day [20]. Desynchronization of circadian rhythms and sleep regulation leads to insufficient sleep duration [27][28]. For example, night shifts workers have been observed to sleep significantly less on workdays compared to day shift workers [8].

Social jet lag is a widely occurring phenomenon, which involves a mismatch between biological and social time. For example, the evening chronotype, the type with tendencies to fall asleep later, is associated with the phenomenon of social jet lag [29].

3.3.2 The Role of Stressors (Peripheral Mechanisms)

Stress is a key factor contributing to sleep fragmentation. Stress activates POA VGLUT2 glutamatergic neurons in the lateral hypothalamus (LH) [5]. This activation is likely caused by presynaptic inputs from stress-regulating areas. The stimulation promotes wakefulness and MAs [5]. That suggests a mechanism in which stress enhances the activity of excitatory inputs from the LH to the POA, causing sleep disturbances [5]. The activity of POA VGLUT2 neurons is similarly dynamic to that of noradrenergic neurons in the locus coeruleus (LC-NE) which are also activated during MAs [5].

3.3.3 The Role of Environmental Factors (Light)

The environmental cycle of light and darkness strongly influences the circadian rhythm, and its disruption leads to sleep dysfunction. Natural and artificial light strongly influence circadian rhythms by synchronizing endogenous oscillators [10]. Evening use of light-emitting devices (e.g. eReaders) negatively affects sleep and circadian timing [30]. Although sleep fragmentation is closely related to circadian rhythms and their disruption, there is no direct mechanism linking nighttime light exposure (LAN) to the induction of micro-awakenings (MAs) in the POA fragmentation model, it is known that LAN inhibits melatonin synthesis [16] and contributes to overall rhythm dysregulation [16].

3.4 Correlation Between Melatonin and Sleep Fragmentation

Chronic exposure to irregular light-dark cycles, typical of frequent transmeridian travel, known as jet lag, and shift work, results in chronodisruption and is closely linked to disturbances in the sleep-wake cycle [8] [13] [29]. This misalignment fundamentally impacts the central hormone regulating nocturnal physiology, melatonin [3] [12].

3.4.1 Melatonin as the Central Timing Signal

Melatonin, synthetized predominantly by the pineal gland during darkness, functions as a time cue and conveys the message of darkness to the master circadian clock located in Suprachiasmatic Nucleus (SCN) of the hypothalamus [3] [14] [15]. This signal is crucial for establishing the internal temporal order and including night-state physiological functions, including the sleep/wake cycle [3] [15].

The acute suppression of nocturnal melatonin secretion, which occurs upon exposure to light (Artificial Light at Night, ALAN) [8] [13] [32], is a core pathological mechanism underlying the negative health effects of chronodisruption. A resulting melatonin deficiency - either due to diminished production (commonly observed with age or certain diseases like Alzheimer's disease) [8] [12] [32] or misalignment of its timing - is consistently associated with general sleep difficulties [32].

3.4.2 Correlation Between Irregularity and Melatonin Phase Delay

Fragmented and irregular sleep patterns are quantitatively linked to significant delays in the endogenous melatonin rhythm, reflecting the desynchronization of the circadian clock.

Delayed Dim-Light Melatonin Onset (DLMO: Irregular sleep schedules lead to a significant circadian phase delay in the timing of the endogenous melatonin rhythm [13]. In a study comparing college students with the most irregular versus regular sleep schedules, the irregular group exhibited a significantly later Dim-Light Melatonin Onset (00:08 ± 1;54) compared to the regular group (21:32 ± 1:48; $p<0,003$) [13]. This phase delay is considerable equating to a person traveling two to three time zones westward [13].

Quantitative Correlation: A strong negative correlation ($r=-0,66$; $p<0,001$) was demonstrated between the Sleep Regularity Index (SRI) - a metric quantifying day-to-day irregularity/fragmentation - and Dim-Light Melatonin Onset timing [13]. This indicates that less regular sleep patterns are directly associated with later melatonin secretion [13].

Mechanism via Light Exposure: This observed difference in circadian timing (delayed Dim-Light Melatonin Onset) between irregular and regular sleepers is primarily attributed to their different patterns of light exposure [13]. Exposure to light during the early biological night

causes a phase delay in the circadian clock. Mathematical modeling confirms that differences in light exposure patterns between the irregular and regular groups can predict the average delay in Dim-Light Melatonin Onset timing [13].

3.4.3 Sleep Fragmentation and Melatonin Dysfunction

Melatonin deficiency or misalignment exacerbates sleep fragmentation through dysregulation of key sleep components:

- Impaired Sleep Initiation: Melatonin as an important physiological sleep regulator in diurnal species like humans [8]. It promotes sleep initiation via MT1 receptor-dependent actions at the Suprachiasmatic Nucleus, which are subsequently mediated to the hypothalamic sleep switch [26] [32]. The sharp increase in sleep propensity usually occurs approximately 2 hours after the onset of endogenous melatonin production [8] [14]. Thus, a delayed melatonin signal directly delays the onset sleep propensity [13].
- Loss of Restorative Sleep: While melatonin does not influence Slow Wave Sleep (SWS), which is dependent on homeostatic sleep pressure, it contributes to sleep quality, often termed the "restorative value of sleep" [8]. Poor sleep quality/fragmentation is a feature of primary sleep disorders and is frequently observed in neurodegenerative disorders such as Alzheimer's Disease [8] [12]. In AD, sleep fragmentation (increased awakenings) is associated with an increased risk of cognitive decline [8].
- Neurodegenerative Link: The chronic nature of sleep fragmentation and circadian disruption (including diminished melatonin) is seen as both a consequence and a driver of neurodegeneration, impairing processes critical for restorative sleep, such as the clearance of harmful metabolites like Amyloid-β in the brain [12].

3.5 Long-term Health Consequences of Melatonin Deficiency and Sleep Fragmentation

Chronic circadian rhythm disruption, such as that experienced during fixed night-shift work or frequently crossing time zones (jet lag), leads to the prolonged impairment of physiological, behavioral and biochemical rhythms, resulting in a loss of internal rhythmicity [8]. Evidence suggests that circadian desynchronization, sleep deprivation and suppression of nocturnal melatonin secretion by light exposure are primary pathological mechanisms underlying the harmful health effects observed in shift workers. This long-term process can result in accelerated aging and an increased risk of disease. Melatonin is a highly pleiotropic signaling molecule and a key endogenous synchronizer of central and peripheral tissues; therefore, its deficiency or dysfunction impacts numerous regulatory systems [8] [32].

3.5.1 Metabolic Diseases (Obesity, Metabolic Syndrome, Type 2 Diabetes)

Disruption of the circadian timing system leads to hormonal imbalance, including dysregulation of circulating leptin and ghrelin [12] [15] [32]. Furthermore, irregular eating patterns severely impact the phase resetting of circadian rhythms in various metabolites (including lipids and hepatic proteins), potentially leading to a desynchronization between central and peripheral biological clocks [15] [34].

Reduced melatonin levels are observed in various diseases, including type 2 diabetes. Melatonin signaling dysfunction is linked to insulin resistance; specific polymorphisms in the MTNR1B receptor are associated with elevated risk of type 2 diabetes. Preclinical studies indicate that

melatonin supports glycogen synthesis in hepatic cells, which consequently reduces blood concentration [32].

3.5.2 Cardiovascular and Vascular Diseases (CVD)

Shift work, a common model of chronic chronodisruption analogous to frequent jet lag, is implicated in higher rates of cardiovascular diseases, including an increased risk of coronary heart disease [12] [13].

Circadian rhythm abnormalities, specifically in the amplitude of blood pressure (BP) and heart rate (HR), are associated with increased risk of cardiovascular disease (CVD), sometimes greater than the risk associated with elevated blood pressure alone [14]. Patients with hypertension and the "non-dripping" pattern (lack of nocturnal BP drop) often show impaired nocturnal melatonin secretion [3]. Melatonin improves sleep in hypertensive patients with sleep disorders, its supplementation in the evening can lower nocturnal blood pressure [12].

Melatonin demonstrates protective effects on the neurovascular system, potentially by decreasing neurovascular oxidative damage and protecting against early increases in blood-brain barrier (BBB) permeability following transient focal cerebral ischemia in mice. Melatonin receptor activation (MT1/MT2) upregulates tight junction proteins, enhancing the structural integrity of the blood-brain barrier [12].

3.5.3 Cancer

Chronodisruption is linked to increased cancer risk, primarily mediated by the loss of melatonin's protective effect.

The suppression of nocturnal melatonin release by light exposure at night is a key pathological mechanism contributing to harmful outcomes [8] [32]. It possesses documented oncostatic, anti-apoptotic and immunomodulatory effects [8]. Melatonin deficiency or dysfunction is associated with various forms of cancer [32].

Rotational night shift work, a classic model of chronodisruption relevant to frequent travelers, is associated with increased risk of breast cancer [13] [29]. Lowered nocturnal melatonin levels have been observed in patients with endometrial cancer [32] and non-small-cell lung cancer (NSCLC) [32]. Chronic jet lag in mice models has shown the increased rate of tumor growth [13] [29].

3.5.4 Immunological Inflammatory Diseases

Melatonin is a powerful antioxidant, anti-inflammatory agent and free radical scavenger [18]. It helps reduce oxidative stress by acting as a direct radical scavenger at high concentrations or by regulating redox-relevant enzymes at lower concentrations. It acts as a suppressor or prooxidant excitatory and inflammatory processes [32].

Melatonin functions as a mitochondrial modulator [32] and has been claimed to be present in mitochondria to protect against oxidative stress [34].

3.5.5 Psychiatric and Neurodegenerative Diseases

Melatonin deficiency and circadian rhythm dysregulation are closely linked to neurological and psychological conditions [12] Sleep fragmentation and poor sleep efficiency are associated with poorer executive function and an increased risk of dementia [26]. Melatonin deficiency and circadian disruption are prominent in the molecular neurodegenerative disorders [12]. Sleep is crucial for the activation of the glymphatic system, responsible for brain metabolite clearance [3]. Sleep fragmentation or deprivation can disrupt this system [26]. Melatonin is involved in

regulating glymphatic function, which clears interstitial waste, including Amyloid-β *(Aβ)*. Melatonin enhances this function by improving AQP4 polarization and promoting deeper sleep, which is required for effective clearance [12]. Aβ accumulation plays a key role in the pathogenesis of Alzheimer's Disease [12].
Melatonin is implicated in affective disorders, including depression and seasonal affective disorders (SAD) [29] [32] [35]. Circadian malfunction is often the underlying issue [29] [32]. For instance, the synthetic melatonin analog, agomelatine, acts as a MT1/MT2 agonist (chronobiotic) and an antidepressant through 5-HT2C receptor antagonism [12]. Melatonin treatment can effectively readjust rhythms in bipolar and SAD cases where circadian malfunctioning is involved [32].
Individuals with highly irregular sleep/wake patterns (high "social jet lag") show delayed circadian rhythms (later Dim-Light Melatonin Onset (DLMO)), equivalent to a 2 to 3-hour westward travel, and this irregularity is correlated with poorer academic performance [13].

3.6 Current Methods of Intervention in Jet Lag

The core challenge in managing jet lag is mitigating temporary symptoms, such as poor sleep and reduced daytime alertness, which result from the slow adaptation of the central circadian pacemaker (SCN) and sleep deprivation during long-haul flights [20]. Intervention strategies aim either to hasten the re-synchronization of internal rhythms (chronobiotics) or simply to manage immediate symptoms. For travelers on short stopovers, preserving sleep and alertness without full circadian modification is often recommended [20].

3.6.1 Melatonin supplementation

Melatonin acts as a potent chronobiotic with hypnotic (sleep-inducing) properties therefore it is theoretically ideal for jet lag management [20].
The successful use is dependent on precise timing relative to the traveler's internal biological clock. To achieve phase advances (for eastward travelers) melatonin should be taken during the biological dusk. On the other hand for westward travel, to achieve phase delays, it should be used at the biological dawn. Incorrect timing can negate the effect or lead to detrimental phase shifts [20].
Melatonin is relatively safe, non-habit forming and has a low potential for addiction. The American Academy of Sleep Medicine (AASM) recommends it for jet lag.
Tasimelteon, a newer agonist, is also promising in simulated jet lag studies.

3.6.2 Circadian rhythm management

Light exposure must be timed to ensure phase shifts occur in the direction of adaptation. Exposure to light during the biological evening delays the system, while exposure during the late biological night advances it. The most effective is light of shorter wavelength like blue-green (480-540 nm). Unfortunately the mistiming of light exposure reverses the intended effect [20].

3.6.3 Combined strategies

Optimized resynchronization often involves integrating timed light/dark exposure, melatonin supplementation and gradually shifted sleep schedules initiated before the flight. Following local meal times is also recommended in jet lag treatment [20].

3.6.4 Symptom management

Pharmacological adjuncts can address immediate symptoms, sleepiness or wakefulness but typically do not fix the underlying circadian desynchrony [20].
Hypnotics, mostly short-acting, such as benzodiazepines or so called Z-drugs (e.g. zolpidem) are used to promote or conserve sleep, especially during short stopovers where adaptation is not necessary [20].
Stimulants, caffeine is widely used to maintain daytime alertness and performance. It also has demonstrated chronobiotic potential, capable of delaying the circadian system. Modafinil and armodafinil were primarily used for daytime sleeplessness caused by narcolepsy or obstructive sleep apnoea, however, are also effective in managing jet lag or shift-work related sleep disorder. In those causes prescribed off-label [20].

3.7 Methodological limitations and research gaps

3.7.1 Methodological Constraints:
Study design and statistical power: Numerous investigations are characterized by cross-sectional designs, which fundamentally preclude the establishment of casual relationships [8]. Furthermore, studies frequently suffer from small sample sizes, potentially leading to non-significant results and limiting the external validity and generalizability of findings [8] [31].
Measurement bias and data quality: Reliance on self-reported questionnaires for crucial sleep parameters introduces measurement bias and reduces accuracy compared to objective data. Similarly, the limited number of biological samples collected (e.g. saliva for hormone levels) may fail to capture the high degree of inter-individual variability and physiological fluctuations [8].
Actigraphy standardization: Methodological heterogeneity in actigraphy use (e.g. variations in technical features, scoring algorithms and sensitivity thresholds) necessitates that future studies uniformly publish detailed technical and scoring procedures to ensure replicability and validity. Notably, actigraphy remains an inadequate measure for definitive diagnosis of certain conditions, such as Periodic Limb Movement Disorder (PMLD) [31].

3.7.2 Mechanistic and translational deficiencies
Supra-physiological dosing: Much of the compelling preclinical evidence relies on supra-physiological concentrations of melatonin, raising critical questions regarding the specifics of action (i.e., whether effects are receptor-mediated or non-specific) [15].
Lack of mechanistic rigor: A common deficiency is the absence of appropriate experimental conditions to establish conclusive concentration-response curves or definitely identify the molecular targets and precise mechanisms responsible for the observed effects [15].
Pharmacokinetic ambiguity: The exact process underlying the efficacy build-up observed with prolonged-release melatonin (PRM), whether it involves MT1 receptor up-regulation or the synchronization of the internal temporal order, remains unelucidated [29].
Chronobiological disregard: Failure to adhere to fundamental chronobiological principles, specifically the Phase Responsive Curve (PRC), when determining the timing of melatonin administration, can lead to inaccurate conclusions regarding therapeutic efficacy [32].

3.7.3 Research gaps

Efficacy comparison and clinical trials: Melatonin has not been widely investigated in large-scale randomized controlled trials [10] [32]. Consequently, insufficient data exist to compare its efficacy against established first-line pharmacotherapies [32]
Unregulated supplementation risks: Melatonin's status as a widely available dietary supplement carries risks associated with inaccurate dosing (under- or over-dosing) and potential exposure to active contaminants [33].
Biomarker translation: The successful translation of chronobiologically guided strategies into routine clinical practice is hampered by the persistent lack of robust and clinically applicable circadian biomarkers. Validation of markers like peripheral clock gene expression and salivary melatonin profiles is a future imperative [15].

4. Summary

4.1 The Link Between Melatonin Deficiency and Sleep Fragmentation in Frequent Travelers

Frequent transmeridian travel leads to a disruption of the body's central circadian rhythm, manifesting as Jet Lag Syndrome (JLS). This syndrome is characterized by circadian misalignment. Melatonin is the hormone called the "darkness hormone" and acts as the main synchronizer for the internal clock. Its production is suppressed by bright light exposure.
Under jet lag conditions, the melatonin rhythm, which serves as a critical indicator of internal circadian time, becomes desynchronized (mistimed) relative to the light/dark cycle at the destination, or its production may be suppressed.
Sleep fragmentation, a condition linked to poor sleep quality, involves interruptions in sleep continuity caused by brief awakenings known as microarousals (MAs). The deficiency of melatonin and the resulting circadian dysregulation directly contribute to the sleep fragmentation, which is a key symptom experienced by travelers.

4.2 The Impact of Circadian Rhythm Disruption on Health

Chronic circadian desynchronization, such as that experienced by frequent travelers or shift workers, is associated with a range of serious, long-term health consequences, like:

- Metabolic Diseases: Disruption of the circadian system leads to hormonal imbalances including leptin and ghrelin then to the unbalanced center of appetite and hunger. Moreover melatonin signaling dysfunction is associated with insulin resistance and elevated risk of Type 2 Diabetes.
- Cardiovascular Diseases (CVD): Changes in the circadian rhythm cause the lack of the physiological drop of blood pressure during the night, which leads to increased Cardiovascular Diseases risk.
- Neurodegeneration and Cognitive Impairment: Poor sleep quality and fragmentation are linked with worse executive function and an increased risk of dementia. Melatonin is also included in regulating glymphatic function, cleaning brain metabolites, such as Amyloid-β, its plaques accumulate and can lead to Alzheimer's Disease.
- Increased Cancer Risk: Chronodisruption is associated with an increased risk of certain cancers e.g. breast or lung cancer. The suppression of nocturnal melatonin, which has documented oncostatic and immunomodulatory effects, is considered a one of the pathological mechanisms of carcinogenesis.
- Mental Health Issues: Circadian malfunction is often implicated in affective disorders, including depression and Seasonal Affective Disorder (SAD).

4.3 The Importance of Research into Prevention and Early Intervention Strategies

Effective management of jet lag requires strategies that mitigate temporary symptoms and, more importantly, accelerate the re-synchronization of internal rhythms. Exogenous melatonin is viewed as a potent chronobiotic (phase-shifting) with hypnotic properties, making it theoretically ideal for Jet Lag Syndrome management.

However, successful intervention depends on precise timing relative to the traveler's internal biological clock. Melatonin administration in the biological evening induces a phase advance (necessary for eastward travel), while supplementation in the morning causes a phase delay (for westward travel). Other effective strategies include carefully timed bright light exposure and combined chronotherapeutic approaches.

Individual variability in circadian rhythm sensitivity means that the effectiveness of jet-lag interventions can differ markedly between travelers, highlighting the importance of personalized approaches. Moreover, growing interest in circadian science has prompted research into behavioral and environmental modifiers that may further enhance adaptation to new time zones. As understanding of these mechanisms deepens, it may become possible to develop even more refined and reliable strategies for minimizing travel-related circadian disruption.

4.4 Methodological Limitations and Research Gaps

There are some significant methodological limitations and research gaps, such as:

- There is insufficient data from large-scale Randomized Controlled Trials to definitely compare melatonin's efficacy against established first-line pharmacotherapies.
- Much compelling preclinical evidence utilizes supra-physiological concentrations of melatonin, raising questions about the specificity of its action.
- The successful clinical translation of chronobiologically guided strategies is hampered by the lack of robust and clinically applicable circadian biomarkers, e.g. validated salivary melatonin profiles, necessary to accurately determine a traveler's circadian phase.

4.5 The Necessity of Raising Awareness in the Population of Global Travelers

Despite the increasing globalization of travel, the long-term health consequences associated with chronic melatonin deficiency and circadian misalignment remain underrecognized and insufficiently addressed.

Addressing this escalating public health concern requires greater awareness and the promotion of effective, evidence-based strategies designed to support circadian stability. This necessity extends not only to frequent travelers but also shift workers, who face analogous long-term health risks. Awareness must also be developed concerning the impact of factors like evening exposure to artificial light, which suppresses endogenous melatonin and contributes to general rhythm dysregulation.

More comprehensive public health initiatives could help integrate circadian-friendly practices into everyday routines, emphasizing their role in maintaining long-term physiological resilience. Furthermore, expanding research on environmental and behavioral determinants of circadian health may support the development of more targeted interventions for vulnerable populations.

5. Conclusions

The findings strongly support the conclusion that circadian rhythm dysfunction is closely connected to many future health problems. Melatonin deficiency and subsequent sleep fragmentation in frequent travelers constitute a chronic circadian desynchronization state that poses a severe, systemic threat to overall health, encompassing metabolic, cardiovascular, neurological and oncological risks.

Effectively managing this emerging health crisis requires two-pronged approach:

1. Increased Awareness: There is a critical need to enhance societal and professional awareness regarding the profound long-term health implications of chronic circadian desynchronization in populations exposed to rapid time-zone changes or shift work.
2. Research Intensification: Further research is imperative to overcome current methodological constraints. Future work must focus on large-scale clinical trials (RCTs) to validate the efficacy of chronotherapeutic interventions (such as appropriately timed melatonin and light therapy) and to establish robust, clinically relevant circadian biomarkers (e.g. salivary melatonin profiles) to guide personalized treatment strategies. The disruption of the biological clock, much like the loss of synchronization in a complex industrial system, does not merely lead to temporary performance errors (jet lag) but ultimately results in long-term systemic failure and accelerated disease risk.

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