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Disturbances of Sleep and Circadian Rhythm: Adverse Effects on Health

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Abstract: Sleep is rigorously controlled by circadian rhythms, and any discrepancy between these rhythms and the external environment might result in circadian rhythm sleep disorders. Circadian rhythm sleep disturbances (CRSDs) are linked to detrimental health outcomes, including cancer and psychiatric illnesses. This systematic literature review explores the significance of disturbances of sleep and circadian rhythm. A systematic literature survey was conducted using PubMed, Scopus, Web of Science, Embase, and Cochrane Library databases. We used the following search terms: "Circadian clock," "sleep," " Circadian rhythm," *sleep disorders," "drugs to cure sleep and circadian rhythm,"* and "CRSD." for articles published between 2018 and 2023. This comprehensive review presents evidence from human research to assess the concept that sleep and circadian rhythms have direct effects on physiological processes in the human body and are significant underlying factors contributing to major health concerns. The first part of this review focussed on sleep and circadian rhythm, circadian clock and effects of altered metabolism." The second part discussed recent evidence that the circadian clock system plays a fundamental rolein health risk, adverse effects on health, and their connection with disturbances of sleep and circadian rhythm. These research lines are still in their early stages, but they have nonetheless established a conceptual framework that could be highly significant for comprehending metabolic health and illness

Keywords: Circadian rhythm, sleep, human health, sleep disorders, drugs

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INTRODUCTION

Sleep is a typical, reversible, recurring physiological state characterized by sophisticated and predictable physiological changes that diminish responsiveness to external stimuli. In addition to movements of the musculature and hormone fluctuations, these modifications involve coordinated, spontaneous, and internally generated cerebral activity. It is undeniable that sleep is necessary for general physical and mental well-being, and it cannot be substituted with any other processes (Kornowski and Sassone, 2021). Living organisms' sleep-wake cycle is regulated by a natural, intrinsic process known as circadian rhythm. It comprises a 24-hour period and is synchronized with the day-night cycle as part of the body's internal rhythm. A major aspect of virtually all behavioural and physiological processes is daily variation mediated by the circadian timing system. Diurnal rhythms are generated by an internal biological clock that is synchronized to the 24-h day by environmental cues, primarily the light:dark cycle. When external timing signals are absent, the 24-h rhythms "free run" with a period close to 24 h and are called "circadian" rhythms (about a day) (Chen et al., 2023), The rhythm of the circadian clock, the regulation of most behaviors and physiological activities depend on whether the organism is asleep or awake (Kurien et al., 2019; Lin et al., 2023). The evolution of a circadian system suggests that the ability of an organism to coordinate itself with the environment (external synchronization) and to maintain temporal organization of endogenous processes (internal synchronization) confers optimal health and survival potential. As we begin to unravel the many links between sleep, circadian rhythms, and metabolism, the survival benefits of temporal organization begin to emerge (Russell et al., 2023).

Circadian rhythms are endogenous biological mechanisms that allow all organisms to forecast and adapt to day-night shifts and regulate physiological functions and behaviours (Abott et al., 2018). Circadian rhythms control sleep which is influenced by work, family, social duties, and the light-dark cycle. Shift employment, jet lag, nocturnal light exposure, or

genetic anomalies might cause chronic circadian rhythm sleep disorder (CRSD). These variables impede (Talamanca et al., 2020) circadian regulation (Khosravipour et al., 2021).

The suprachiasmatic nuclei of the hypothalamus contain the master clock, whereas peripheral molecular clocks in organs make up the circadian rhythm (Wang et al., 2022). This system helps organise biological and physiological processes including body temperature, blood pressure, hormone production, gene expression, and immunological activities into daily cycles. Work, travel, and social engagements may disrupt sleep/wake and eating routines for the biological clock (Geng et al., 2023). Misalignment may disturb physiological and psychological factors, increasing the risk of chronic illnesses such cancer, cardiovascular disease, and metabolic disorders (Lane et al., 2023). Understanding sleep circadian cycles may reveal behavioural strategies that reduce the incidence of various illnesses (Martel et al., 2023). Evidence supports a rise in obesity, cancer, metabolic syndrome, cardiovascular illnesses, metal disorders, and CRSD's risk of physical and mental dysfunction (Manfredini et al., 2023)

In this systemic literature review, we will discuss that sleep and circadian rhythms have direct impacts on sleep wake cycle clock. Sleep and circadian rhythms represent important mechanisms includes the external and internal synchronisation that has occurred in the developed countries, that is now becoming recognized in many developing countries as well. The first part of this systemic literature review will focus on sleep and circadian rhythm, circadian clock and circadian clock genes. The second part will discuss adverse effects of circadian system and on human health, sleep disorders and drugs to cure them. It should be noted that sleep and the circadian clock are involved in energy metabolism. Therefore, that provides a framework for exciting future research and discussion, and one with potentially great importance for understanding the adverse effect of circadian cycle and sleep disorder on metabolic health and disease.

Method of Collection of data:

We conducted a systematic literature review using “PubMed, Scopus, Web of Science, Embase, and Cochrane Library databases”. We used the following search terms: *"Circadian clock," "sleep," "Circadian rhythm," "sleep disorders," "drugs to cure sleep and circadian rhythm,"* and *"CRSD."* for articles published between 2018 and 2023. Articles were included if they reported prevalence rates, adverse effects, or significance. We excluded studies that did not report sleep and circadian rhythm or those without primary outcomes related to drugs.

2.1 Study Selection

- All identified studies' titles and abstracts were examined by two independent reviewers to determine their eligibility. Studies were considered if they satisfied the following requirements:
- 209 studies total were found through database searches, and additional data came from various sources. Reviewers separated the articles based on the titles, and the abstracts were looked at to determine eligibility. Studies were taken into consideration if they met the following criteria:
- Duplicate data papers were removed during the initial screening phase, and additional analysis was performed on papers.
- Inclusion standards: The study supplied enough information about sleep and circadian rhythms
- Studies that focus on the adverse effects on sleep and circadian cycle were also considered
- Papers with Preventive measures were also included in the study.
- Approximately 60 publications were eliminated from the study after the first screening because they lacked the data necessary for analysis.
- A further 100 articles and other studies that dealt with data were also reviewed and 71 papers were excluded.
- Twenty-nine papers based on the inclusion criteria were included and reviewed (Figure 1).
- Those twenty- nine papers were included, and the eligibility of each study was assessed by two independent reviewers in accordance with the inclusion criteria for each study.
- Disagreements were resolved by communication or contact with a third reviewer.

2.2 Data Extraction and Quality Assessment

- Using a standardized data extraction form, two impartial reviewers extracted data from the included studies. From each study, the following information was taken out:
- Sleep and circadian rhythm, circadian clock and circadian clock genes, prevalence, adverse effects, sleep disorders, sleep and circadian rhythm effects on human health and significance of the sleep and circadian cycle and drugs to the disturbances in sleep and circadian rhythms were the metrics considered.

- Discussion or contact with a third reviewer was used to settle any disagreements in the data extraction or quality assessment.

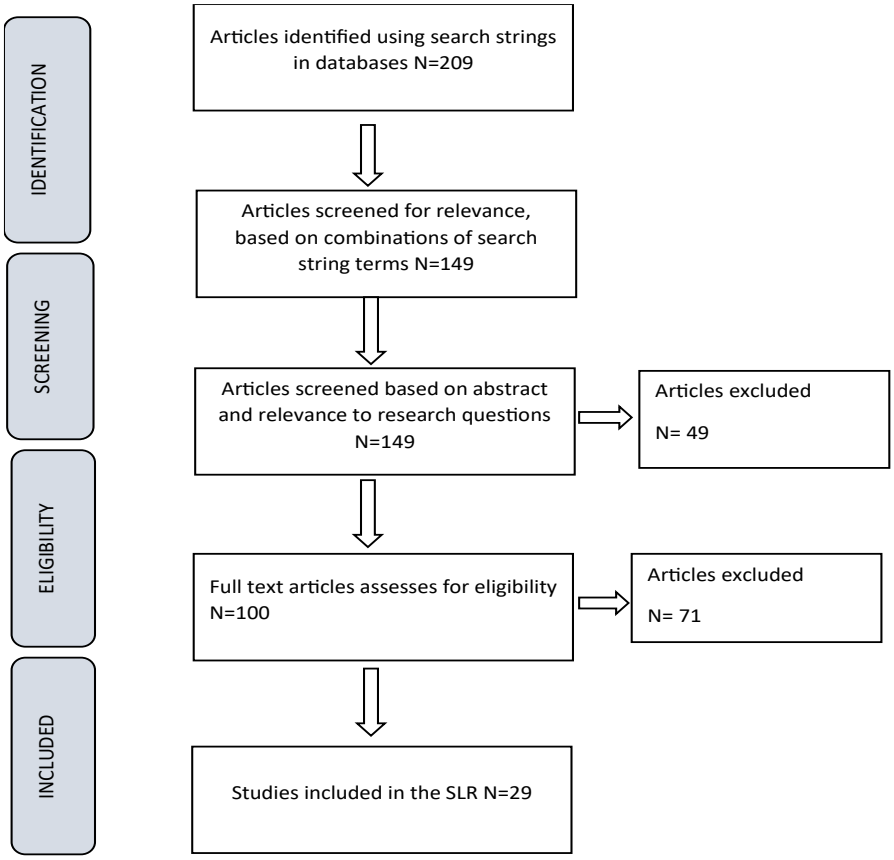

Figure 1: Literature Search process of selection of articles for inclusion in the SLR (based on the PRISMA flow diagram).

RESULTS:

1. Results and Discussion

In addition to sleep–circadian rhythm, "numerous oscillations in neurological, metabolic, endocrine, cardiovascular, and immune functions" are less apparent. Endogenous genetically encoded molecular clocks produce circadian rhythmicity; these clocks require the cooperation of their constituent elements to generate cyclic variations in their abundance and activity, with a periodicity of approximately one day (Patke et al., 2020). By modulating germane downstream programs, these molecular clocks impart temporal control to the operation of organs and tissues throughout the body (Baidoo and Knutson, 2023). Aspects of the circadian rhythm are examined including the components of these molecular oscillators, the mechanisms of action and function of central and peripheral clocks, their synchronization, and their significance in relation to human health, sleep need to be discussed.

3.1 Sleep and circadian rhythms

Mammalian sleep can be categorized into two primary phases: rapid eye movement sleep (REM sleep) and non-rapid eye movement sleep (NREM sleep). These states are characterized by distinct modifications in brain activity, resulting in physiological and behavioral changes (Mentzelou et al., 2023). NREM sleep is characterized by the presence of a synchronized electroencephalogram (EEG) with high-voltage slow waves exhibiting a prominent delta rhythm (0.5–4 Hz) and a reduction in muscle tone. Human NREM sleep is categorized into four states (N1-4) according to EEG features. However, "stages 3 and 4 have recently been merged and are now referred to as stage 3 (N3) or slow-wave sleep (SWS) (Liu et al., 2022).

Sleep remains one of the biggest scientific mysteries while being consistently important to human health. In the two-process paradigm, the sleep homeostat (process S) and circadian clock (process C) regulate sleep time, length, and depth (Rutters and Nefs, 2022). The circadian rhythm schedules sleep at an ecologically appropriate period (Cable et al., 2021). The hypothalamus' suprachiasmatic nucleus (SCN) controls mammalian circadian rhythms. SCN lesion eliminates the circadian

rhythm in the sleep-wake cycle, although ultradian rhythms with a 2–4-hour period persists. Direct retinal input from the retinohypothalamic tract (RHT) enables the SCN to synchronise with external light/dark signals. In the two-process paradigm, the interplay between processes C and S determines the timing of awake and sleep (Możdżyńska et al., 2022; Chellappa et al., 2021).

3.2 Circadian clock and circadian clock genes

The identification of the molecular mechanisms underlying the circadian clock, specifically the circadian clock genes, and the creation of animal models (both genetic and non-genetic) to study disruptions in the circadian system, have been instrumental in comprehending the extensive array of rhythms regulated by the circadian system. Furthermore, these advancements have shed light on additional significant functions of the circadian system that go beyond its primary role as a time regulator (Jackson and Drummond, 2023). A new and thrilling finding is the presence of circadian clock genes not only in the brain but also in several peripheral tissues throughout the body (Shen et al., 2023; Moore et al., 2023). The circadian system regulates various physiological and molecular processes. The circadian clock may be a contributing component in disorders like obesity, metabolic syndrome, and cardiovascular disease (Chaput et al., 2023). The next part will present a comprehensive examination of the circadian clock system and will analyze new discoveries that indicate the significant involvement of the circadian clock in both external and internal synchronization.

3.3 The circadian clock: external and internal synchronization

One of the primary purposes of the circadian clock is to externally synchronize the light-dark cycle. The circadian clock is crucial for the internal coordination of various behaviors, physiological systems, and biochemical pathways, such as the sleep-wake cycle, hormone rhythms, and gene transcription. During prolonged fasting sleep, the combination of slow wave sleep, heightened growth hormone (GH) levels, and elevated blood glucose concentration ensures the maintenance of glucose levels (Franzago et al., 2023). Growth hormone (GH) stimulates the production of glucose in the liver and decreases the release of insulin from pancreatic beta cells.

3.4 Health risks

Furthermore, the misalignment between the sleep/wake cycle and the endogenous circadian clock not only raises safety concerns but also gives rise to various hormonal and metabolic disruptions that have the potential to adversely impact both physical and mental well-being (Sletten et al., 2023).

The amount of sleep decreases as individuals age, gain body weight, develop diabetes, and experience cardiovascular illness. Additionally, there is evidence of structural changes in the brain's circadian pacemaker neurons and alterations in the expression of circadian genes in the paraventricular nucleus (PVN), a hypothalamic region that integrates metabolic signals and outputs the autonomic nervous system. It is generally established that hypertension, gastritis, congestive heart failure, type 2 diabetes, arrhythmias, various form of cancer and myocardial infarction are more prevalent at particular times of day (AlAbri et al., 2023).

3.5 Classification of Circadian rhythm sleep disorders

Circadian rhythm sleep disorders (CRSDs) are medical conditions characterized by a misalignment between the internal circadian rhythms and the external environment. There are four main classifications of Circadian Rhythm Sleep Disorders (CRSDs): Advanced Sleep Phase Disorder (ASPD), Delayed Sleep Phase Disorder (DSPD), Irregular Sleep-Wake Rhythm, and Non-24-Hour Sleep-Wake Disorder (Martel et al., 2023).

3.5.1 Advanced Sleep Phase Disorder

People with advanced sleep phase disorder commonly suffer from excessive sleepiness and have a tendency to go to bed early in the evening, usually between 6 and 9 pm. In addition, they have a tendency to wake up unusually early in the morning, usually between the hours of 2 and 5 am. Individuals with atypical patterns experience a phase advance of 3-4 hours in their sleep, temperature, and melatonin rhythms compared to those with usual patterns. However, when individuals are allowed to sleep at their desired times, their sleep quality and duration correspond to those of the whole population (Shen et al., 2023).

3.5.2 Delayed Sleep Phase Disorder

Delayed sleep phase disorder (DSPD) is a condition where there is a consistent and difficult-to-change delay in the time a person falls asleep and wakes up, compared to what is considered normal. This delay is typically more than 2 hours. Individuals with Delayed Sleep Phase Disorder (DSPD) experience difficulty in initiating sleep and awakening at socially conventional times, leading to heightened levels of daytime somnolence (Chaput et al., 2023).

1.6

1.7 The adverse consequences of circadian rhythm sleep disorders

Sleep and circadian rhythm disruptions are connected to several diseases, including cancer, mental illness, and metabolic problems (Atan et al., 2023). Circadian misalignment affects mental, cardiovascular, sleep, inflammation, glucose metabolism, and cell cycles, as well as cancer and metabolic health (Russell et al., 2023). NREM and REM sleep quality and quantity alter with age (Russell et al., 2023). Sleep behaviour can influence neurodegenerative and mental illnesses. Neuropsychiatric illnesses such as Alzheimer's disease, Parkinson's disease, and major depressive disorder may be preceded by these alterations. Whatever the source, inadequate sleep has serious cardio-metabolic, emotional, and cognitive impacts (Vethe, 2023). This review will concentrate on cognitive alterations and their neurological foundation related with poor sleep-in normal ageing. CRSDs occur when internal circadian rhythms are misaligned with the external environment (Chen et al., 2023). Four main CRSDs include advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), irregular sleep-wake rhythm, and non-24-hour sleep and wake disorder.

3.7 The importance of the clock for human health

Disruptions in the circadian clock have also been linked to the abnormal metabolism of cancer cells. Research has demonstrated that in humans, a disrupted circadian rhythm caused by shift work and sleep disturbances can result in metabolic disorders (Chen et al., 2023; Vedhe, 2023). Due to the vast amount of data on humans currently available, it has been feasible to determine that there are frequent changes in the activity of circadian genes in both healthy and ill individuals. Furthermore, the implementation of pharmacological interventions to manipulate the circadian rhythm has been proposed as a strategy to combat cancer. Due to the abundant availability of data, there has been an increasing identification of linkages between the circadian clock and malignant growths in recent years. In summary, our present comprehension indicates that the absence of a functional circadian clock contributes to erratic and dispersed food consumption and metabolic problems, potentially resulting in elevated cancer rates and a reduced lifespan. Conversely, numerous factors contribute to the deterioration of the circadian rhythm. Some of these factors are related to lifestyle choices, such as disturbances in sleep patterns, working in shifts, and not observing 12-hour fasting periods. Others are associated with health conditions, such as the natural process of aging, chronic diseases that affect metabolism, and the presence of cancer.

3.8 Drugs in sleep and circadian rhythm

There are numerous medications that can be prescribed to treat circadian rhythm and sleep disturbances. Patients with sleep and circadian disturbances may benefit from the use of exogenous melatonin and other melatonin receptor agonists to adjust circadian timing and enhance sleep (Gumz et al., 2023). Antidepressant effects on sleep are contingent upon the kind of antidepressant medication, dosage, timing of drug delivery, and length of therapy. As a result, all antidepressants ought to make sleep normal. However, many antidepressants with so-called activating effects (fluoxetine, venlafaxine, etc.) may interfere with sleep, at least during the short term of treatment. Conversely, sedative antidepressants (doxepin, mirtazapine, trazodone, etc.) rapidly improve sleep but may cause issues during long-term treatment due to oversedation (Chen et al., 2023). Nevertheless, the safety concerns and circadian resetting and sleep-inducing effects of each medication differ. It is critical to seek medical advice prior to initiating any medication regimen.

Treatment for circadian rhythm and sleep disorders is conditional on the disorder's nature and degree of severity. Common treatments consist of melatonin, brilliant light therapy, and healthy lifestyle modifications (Sletten et al., 2023). Naturally generated by the body, melatonin is a hormone that controls the sleep-wake cycle. It is accessible as a non-prescription dietary supplement and is indicated for the treatment of circadian rhythm sleep-wake disorders (Chen et al., 2023). The safety concerns and circadian resetting and sleep-inducing properties of each medication vary. It is imperative to emphasize that medication utilization should only occur under the supervision of a healthcare professional.

2. Conclusion

Ultimately, Circadian rhythm sleep disturbances have significant socioeconomic implications as they contribute to a heightened susceptibility to various medical ailments, as well as an elevated likelihood of errors and accidents in the professional environment. Individuals' tolerance to shifting work varies significantly and is influenced by factors such as disruptions in the circadian rhythm cycle, misalignment of the circadian rhythm, and individual and household predisposing factors.

Circadian rhythm sleep disturbances (CRSDs) are linked to detrimental health outcomes, including cancer and mental disorders. Circadian misalignment has detrimental effects on metabolic health, cancer risk, cardiovascular health, and mental health. This is mostly due to the induction of sleep deficit, hormonal imbalance, inflammation, poor glucose metabolism, and dysregulated cell cycles.

The systematic review has provided evidence suggesting that prolonged partial sleep deprivation, disruption of the body's internal clock, and/or changes in the functioning of genes responsible for regulating sleep patterns can result in notable disruptions in energy balance and cardiovascular health. The identification of circadian clock genes as active participants in the molecular mechanisms governing lipid and glucose homeostasis, inflammatory responses, and sleep-wake regulation has presented a novel perspective for investigating the involvement of the circadian clock system in many disease processes. Antidepressant medications can provide temporary relief for sleep problems and disruptions in the circadian rhythm. The fields of sleep research and circadian biology have the potential to significantly contribute to our understanding of the behavioral, physiological, and molecular factors underlying epidemic disorders, such as obesity, diabetes, and metabolic syndrome.

5. Future directions

The bidirectional link between circadian rhythm disruptions, sleep problems, and critical diseases disease should be discussed in future. It emphasises sleep length, timing, fragmentation, patient perception, and circadian rhythms, including alignment and amplitude. Alzheimer's disease and sleep disturbance treatments are both pharmaceutical and non-pharmacological. Another future perspective discusses circadian processes and eating disorder and stresses the necessity of measuring circadian profiles in eating disorder patients. Research should address how circadian rhythms affect daily meals, sleep-wake cycles, neuroendocrine hormone release, and homeostatic and metabolic processes.

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