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UNRAVELLING THE MOLECULAR MECHANISMS OF SLEEP REGULATION: IMPLICATIONS FOR SLEEP DISORDER PATHOPHYSIOLOGY

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Abstract

Background: *This study evaluates organs involvement pattern, liver size or echotexture, splenomegaly, ascites, gall bladder abnormalities, cortical echogenicity and renal alterations in thalassemia patients.*

Objective: *To evaluate and compare abdominal sonographic findings in individuals with thalassemia and healthy individuals.*

Methodology: *This study employs a cross-sectional comparative design, conducted at the Ruqayya Medical Centre and Fatimid Foundation, Lahore, utilizing a Toshiba Nemio XG ultrasound machine, to assess the prevalence and characteristics of abdominal organs among thalassemia and healthy individuals. A total sample size of 150 participants. The sampling technique adopted was convenient sampling, ensuring the inclusion of eligible participants during the study period.*

Results: *The study considered various demographic, clinical, and different abdominal organs-related variables to assess the prevalence and severity of thalassemia. Gender distribution included 81 females (54.0%) and 69 males (46.0%), with age groups divided into <12 years (33.3%), 13-18 years (58.7%), and above 30 years (8.0%). Liver size included homogeneous (12.0%), Heterogenous (82.0%), and Coarse (6.0%), Splenomegaly was reported by (67.6%), Gall bladder wall thickness status showed moderate (3.3%), severe (48.0%) and (28.0%) exhibited Sludge and (8.7%) had Calculi, Ascites in (31.3%). while (30.0%) experienced Mildly increased cortical echogenicity. In right Kidney group (36.0%) reported small, (33.3%) exhibited large right kidney, while left kidney group (42.0%) reported small left kidney, (32.0%) exhibited large left kidney.*

Conclusions *This study emphasizes the importance of routine abdominal ultrasound in early detection and management of organ complication in thalassemia. Regular monitoring may help to control diseases progression and improve patient's outcomes.*

INTRODUCTION

Unquestionably essential for both mental and physical health, sleep is a particular behaviour that humans and other animals share that alternates cyclically with waking (Irwin, 2015; Umar et al., 2022). One of the most crucial factors taken into account for the subjective evaluation of overall health and quality of life is sleep quality. Sleep is a physiological aspect of human existence that is essential to maintaining health and wellbeing. It is a natural and reversible condition that is largely regulated by brain processes (Irwin, 2015; Krueger et al., 2016). Sleep causes a person to feel less aware of things happening around them and stops the body from moving around (Krueger et al., 2016; Umar et al., 2025).

Numerous factors, including nutrition, exercise, genetics, and the environment, affect how well people sleep (Dashti et al., 2019; Murawski et al., 2018). Sleep affects the body in many ways. It lowers how much energy the body uses and helps the brain store energy more efficiently. It also helps control the body's defense system, both the way it adapts to threats and its natural protections. Plus, sleep helps the brain solidify new information that has been learned (Hu et al., 2020; Irwin, 2015; Rakowska et al., 2021).

Sleep is very important for the health and happiness of children, teenagers, and grown-ups (Foster, 2020; Matricciani et al., 2019). Cognitive performance, mood, mental wellness, and the health of the heart, brain, and metabolism all depend on getting enough sleep. Getting enough sleep, both in terms of quantity and quality, also helps lower the risk of accidents and injuries brought on by exhaustion and drowsiness, such as car collisions and workplace mishaps (Czeisler et al., 2016).

Sleep physiology must be explained in order to comprehend the significance of sleeping temperature conditions and bedding systems as well as their potential impacts on human sleep. Despite substantial research, the intricate physiological and behavioural mechanisms involved in sleep remain poorly understood (Deboer, 2013). The circadian rhythm and homeostasis are two mechanisms that are frequently regarded as important in sleep physiology. The body's internal stability is preserved via homeostatic mechanisms. They control the propensity to sleep by making it stronger while awake for longer periods of time, decreasing it as sleep duration increases, and then rising again when awake (Fisher et al., 2013). In the subsequent sleep cycle, a person's inclination to sleep and/or the depth of their sleep are increased to make up for the loss of sleep. Our circadian rhythms, a 24-hour internal day-night clock cycle made up of patterns of arousal and drowsiness, also control how much sleep we get (Fisher et al., 2013).

Sleep is a ubiquitous natural phenomenon (Vyazovskiy, 2015), yet incredibly intricate, distinct, and highly variable both within and across individuals (Fang et al., 2021; Lemola et al., 2013). The innovative and profoundly revolutionary discipline of "personalised sleep medicine" addresses each person's unique sleep-related medical requirements. In order to maximise sleep quantity and quality and successfully treat sleep disorders, this innovative framework transcends conventional one-size-fits-all methods and acknowledges the unique physiological and psychological traits of every individual. This strategy is based on acknowledging and addressing the various factors that affect sleep, including genetic predispositions, behaviour and lifestyle choices (e.g., diet, exercise, and drug and stimulant use), environmental factors, and underlying medical conditions (Genderson et al., 2013; Sejbuk et al., 2022).

Personalised sleep medicine can provide more precise diagnoses, focused therapies, and proactive management techniques that better suit the requirements of each patient by taking these

factors into account. It is remarkable how quickly new technologies are being developed and incorporated into this industry. Innovative treatments for sleep-related problems are being offered by personalised sleep medicine, which is being driven to the forefront by the introduction of new tools, particularly digital ones, and a better knowledge of sleep patterns (Cheung et al., 2023). To collect comprehensive information on sleep patterns, amount, quality, and disruptions, wearable technology, smartphone health apps, and sophisticated diagnostic tools are being used more and more. Continuous monitoring and analysis are made possible by these technologies, which yield a multitude of data that may be efficiently utilised to customize interventions and treatments (De Zambotti et al., 2019; Vijayan et al., 2021).

Furthermore, the possibilities of personalized sleep medicine have been significantly expanded and improved with the introduction of advanced data analysis tools, including machine learning and artificial intelligence (AI) (Bragazzi et al., 2019). Large datasets may be more easily interpreted thanks to these technologies, which provide subtle insights on sleep patterns and possible diseases. They enable medical professionals to create highly individualized treatment programs that precisely match each patient's unique sleep profile. Furthermore, this subject is greatly benefiting from a greater comprehension of sleep science, which includes the study of circadian rhythms and sleep physiology (Foster, 2020).

These fields of study are revealing new facets of the intricate relationship between sleep and general health and wellbeing, offering important insights that can guide individualized treatment plans. All things considered, personalized sleep medicine is in the front of a revolution in healthcare that prioritizes individualised treatment and uses science and technology to enhance sleep quality (Ryba-White et al., 2021). Given that adequate sleep is essential for overall health and wellbeing, this strategy not only more successfully treats sleep problems but also improves quality of life in general (Ramar et al., 2021).

The current review's research goal is to better frame and conceptualise the nascent field of personalised sleep medicine. It envisions how this innovative approach to healthcare, which uses data analysis, new technologies, and a thorough understanding of sleep science to customise sleep-related treatments and interventions to each patient's needs, can enhance sleep health and general well-being.

Overview of sleep stages (NREM, REM)

Human sleep has two states: NREM and REM sleep (Fisher et al., 2013; Vyazovskiy & Delogu, 2014). When you sleep at night, your brain goes through different stages. It moves between quiet, slow brain activity called NREM and more active stages called REM. Each time it goes through these stages, the length of the REM part gets longer as the night goes on (Staunton et al., 2017).

Non-REM (Non-Rapid Eye Movement):

Non-Rapid Eye Movement: 70% of sleep is finished at this point. Five stages are essentially used to categories non-rapid eye movement.

NREM1- In this stage, sleep is light or the beginning of sleep, called somnolence or drowsy sleep, where a person can be easily awakened. The eyes close and open slowly, meaning the eye movements are gradually slowing down. The muscle movements also become slow and gradual. When someone wakes up from this stage, they might remember some faint images or pictures from a dream. The mind's activity changes from alpha waves, which are between 8 to 13 Hz, to theta waves, which are between 4 to 7 Hz. This stage makes up about 5 to 10% of the total sleep time for a person. The body loses some muscle control and has less awareness of the surroundings.

NREM2- In this stage, which starts after the NREM1 stage is finished, the eyes are completely closed and the brain waves slow down. Theta waves appear, and people who are sleeping in this stage find it harder to wake up. This stage makes up about 45 to 55% of the total sleep time for the human body. The sleep rhythm ranges from 12 to 14 Hz. Muscle activity is shown by a decrease in

EMG readings, and there is less awareness of the outside environment.

NREM3- Bbeginning with the finished stage and ending with the NREM2 stage. The brain slows down and stops moving the eyes.

NREM4- This stage begins with the NREM3 stage being finished. The mind fully constructs the delta wave. This stage is a wake-up call. The human body enters a state of profound slumber. The brain, muscles, and other human organs are in a relaxed and liberated state. 15–25% of the human body's total sleep occurs during this phase. This phase is referred to as the deep slumber stage. During these phases, delta waves—which are incredibly slow waves—begin to show up, followed by smaller and quicker waves.

NREM5- Certain human bodies will reach this stage, but not all of them will. Sleep will be interrupted, although the eye is closed. Humans listen to everyone who speaks. This syndrome is often encountered in the morning. The human body reaches this stage during 1% of total sleep.

REM (Rapid Eye Movement):
During this stage, breathing becomes fast, uneven, and deep, while the eyes move in different directions as if following instructions. The muscles in the limbs temporarily become paralyzed. Blood pressure and heart rate increase. This stage accounts for about 20 to 25% of total sleep time in the human body. Important body signals show that the mind is more active and uses more oxygen than when a person is awake. Quick muscle paralysis, which happens during REM sleep, might be important for protecting the body from harm, possibly by preventing people from acting out their dreams (Siddiqui et al., 2016).

Prevalence and impact of sleep disorders
Sleep disorders are conditions that affect a person's ability to sleep properly and stop them from getting good rest (Hombali et al., 2019). Insomnia, respiratory disorders linked to sleep, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, movement disorders related to sleep, and other sleep disorders are among the categories of sleep disorders according to the International Classification of Sleep Disorders (ICSD) (Sateia, 2014). Sleep efficiency, sleep latency, length, and wakefulness after sleep onset are the four characteristics that make up sleep quality, which is defined as an individual's pleasure with every facet of their sleep experience (Nelson et al., 2022). Poor sleep quality can result from sleep disorders (Khalladi et al., 2019). A person's productivity and physical and mental well-being can be significantly impacted by sleep disorders and poor sleep quality. Additionally, it may interfere with their positive social interactions (Wells & Vaughn, 2012). According to research, lack of sleep impairs immunological function, lowers pituitary, adrenal, and hypothalamic function, and raises blood pressure (Han et al., 2012). Additionally, the possible detrimental effects of sleep disorders and sleep quality on mental health have been emphasized by Petrov et al. (2014). Employees with sleep difficulties have been shown to miss work far more frequently, which raises expenses for both their company and society at large. It is said that these employees are less satisfied with their jobs and have less self-confidence (Afonso et al., 2022). Unsettlingly, studies on industrial jobs indicate that poor sleep quality and sleep disorders may raise the likelihood of accidents at work. One profession where employees work in shifts is firefighting (Orr & Bennett, 2017). Therefore, it should come as no surprise that it is among the professions with the highest documented prevalence of sleep disturbances. Within 37% and 70% of firefighters report having sleep difficulties, with many percentages falling within these two ranges (Abbasi et al., 2018; Khumtong & Taneepanichskul, 2019). Among addition to the previously stated shift work, musculoskeletal conditions, a higher body mass index, depression, stress, psychosomatic diseases, and post-traumatic stress disorder were also identified to be factors linked to sleep disturbances among firefighters (Khumtong & Taneepanichskul, 2019; Wolkow et al., 2019). Many studies have looked at how common sleep problems and bad sleep quality are among firefighters, but they have found different

results with no clear answers. Also, not much has been talked about regarding the reasons behind these sleep issues. Because of this, this study aimed to find out how common sleep disorders and poor sleep quality are worldwide, and what factors are linked to them among firefighters. The study also guessed that firefighters, especially those in low-income countries, are more likely to have sleep problems and poor sleep quality.

Molecular Basis of Sleep Regulation

Neurotransmitters involved (e.g., GABA, serotonin, dopamine)

The majority of animals, if not all of them, display two behavioural and physiological states: sleep and awake (Ungurean et al., 2020). These two states, sleep and wakefulness, show different ways of reacting to things happening around them. When animals are awake, they notice and react to important things in their environment easily. But when they are sleeping, they are less likely to react to outside influences. Sleep also brings a feeling of rest and helps the body keep things balanced. Scientists have studied these states in many animals, especially mammals and other backboned creatures. They have also looked at some invertebrates, like insects, snails, worms, flatworms, and even Hydra. In backboned animals, sleep and being awake are controlled by similar brain chemicals. Some chemicals, like acetylcholine, dopamine, glutamate, and histamine, help keep an animal awake. Other chemicals, such as adenosine, serotonin, and GABA, help bring about sleep (Stenberg, 2007). There is relatively little information on how neurotransmitters control wakefulness and sleep in invertebrates. Only a few species from these less well-studied groupings are known. Many of these neurotransmitters cause the same behavioural response in fruit flies (Drosophila melanogaster) as they do in vertebrates (Joiner, 2016). The behavioural reactions of cnidarians, the most primitive group of creatures with a neural system, are less comparable to those of vertebrates. The cnidarian, Hydra, is also induced to sleep by GABA, melatonin (a hormone that encourages sleep in diurnal animals), and pyrilamine (an H1 histamine receptor antagonist that promotes sleep). On the other hand, acetylcholine, glutamate, histamine, and serotonin do not affect Hydra behaviour. It's interesting to note that dopamine was discovered to promote sleep in Hydra as opposed to wakefulness, as was the case in every other taxonomic study. This suggests that at least some neurotransmitters are evolutionarily labile. The primary obstacle to comprehending how neurotransmitter systems have evolved during evolutionary time has been the relative paucity of comparative data on the behavioural response of invertebrates to neurotransmitters (Joiner, 2016). More information, especially about animal groups that haven't been studied much, is needed to figure out which parts of the sleep and wake control system are common across different species and which ones are unique. To help with this, we are looking at flatworms, a type of simple invertebrate. Flatworms do sleep, but we don't know how chemicals in the brain, called neurotransmitters, control when they sleep and when they are awake. Flatworms are simple creatures that don't have systems for moving blood, breathing, or producing hormones. This simplicity makes it easier to study how neurotransmitters work, especially since in some animals, these chemicals can affect parts of the body that aren't directly connected to the brain. Some research has been done on neurotransmitter systems in free-living and parasitic flatworms, but most of this work has focused on single cells or muscle fibers, and hasn't taken into account the daily rhythm of waking and sleeping (McVeigh & Maule, 2017). Whole animal behavioural tests are required to provide the most comprehensive view of the consequences on the individual, even though examining these effects at the cellular level may be useful (Lim, 2021). Here, we provide fresh information on how seven popular neurotransmitters and one pharmaceutical drug affect flatworms' sleep and alertness.

Neuromodulators and hormones (e.g., melatonin, orexin/hypocretin, adenosine)

Neuromodulators affect many synapses and the cells that surround them, which affects how messages are sent in different parts of the brain (Gill & Mizumori, 2006). They either intensify or weaken the nerve impulses that cause activity. It

involves a variety of neuroactive chemicals, including steroids and neuropeptides. As pituitary neurohormones, several hypothalamic neuromodulators really aid in connecting actions and environmental cues to neuronal and hormonal responses (Grosjean & Tsai, 2007). The hypothalamic neuropeptide oxytocin has dual roles as a hormone and a neurotransmitter. It enhances brain development, reduces stress reactions, and affects nursing experiences and affiliative bonding. As part of a feedback loop, some emotional events increase the creation of oxytocin (Dermietzel, 2006). For example, a baby's cry can make a mother's breast produce milk. Hormones made by glands move through the body more slowly, using liquids like blood. These hormones help different parts of the body, like other glands, organs, tissues, cells, and nerves, talk to each other. Hormones use less energy than nerve signals and stay in the body longer, so they affect parts of the body slowly. Because of this, it's harder to balance hormone levels. Women, whose bodies are more affected by hormones and stress, often feel this challenge more than men. Melatonin, also known as N-acetyl-5-methoxytryptamine, is an indole compound. For a long time, people thought it was only made by the pineal gland. But now we know that melatonin is also made in many other parts of the body, not just the endocrine system. These areas include the retina, harderian glands which are connected to the tear glands, bone marrow, skin, cells in the digestive tract that make serotonin, the cerebellum, and parts of the immune system (Acuña-Castroviejo et al., 2014).

So, melatonin isn't like a typical hormone because it's made in several parts of the body and doesn't just affect one specific organ. The production and release of melatonin is controlled by the suprachiasmatic nucleus, which is a part of the brain. Once melatonin is made, it helps regulate the suprachiasmatic nucleus and other clocks in the body, acting as a signal for the body's daily rhythm. To make melatonin, the cells in the pineal gland first change tryptophan from the blood into serotonin through a series of chemical reactions. Then, an enzyme called N-acetyltransferase turns serotonin into N-acetylserotonin, and another enzyme, hydroxylindole-O-methyltransferase, adds a methyl group to form melatonin (Poza et al., 2022). Melatonin helps you fall asleep mainly because it affects the SCN, which controls your body's internal clock. It also influences parts of the body that control body temperature and heart function. The SCN controls the daily rhythm, matching it with the day and night cycle, and melatonin helps keep other body rhythms in line. When the environment changes, melatonin helps the SCN reset the body's clock. High levels of melatonin in the blood tell the body it's nighttime, which helps keep things running smoothly. Melatonin can reset the body's daily rhythm and sleep patterns, and also control when animals have babies. In animals that have baby seasons, removing the pineal gland stops them from changing with the seasons. But if you give them melatonin, those seasonal changes come back (Poza et al., 2022).

Given how it functions and is produced in the nervous system, adenosine is typically thought of as a neuromodulator rather than a neurotransmitter. The intracellular depletion of the energy-rich molecule adenosine-triphosphate (ATP) is associated with alterations in the brain's adenosine synthesis that are activity-dependent (Klyuch et al., 2012). ATP is dephosphorylated to adenosine-diphosphate, adenosine-monophosphate (AMP), and adenosine in response to energy use. There are four distinct Gprotein-coupled adenosine receptors that extracellular adenosine can bind to. The most widely ingested psychostimulant in the world, caffeine, works by blocking certain adenosine receptors to increase alertness and decrease sleep. A number of variables influence changes in extracellular adenosine activity-dependent levels (Sebastião et al., 2012). Equilibrative nucleoside transporters (ENTs) can release adenosine straight from neurones when intracellular adenosine concentrations are high. Adenosine's primary metabolic processes are its irreversible breakdown to inosine by adenosine deaminase (ADA) and its phosphorylation to AMP by adenosine kinase (ADK). Ecto-nucleotidases may hydrolyse and dephosphorylate ATP to create adenosine directly in the extracellular space (Krueger et al., 2013).

Cellular activity causes γ-amino-butyric acid (GABA)ergic, glutamatergic, cholinergic, and monoaminergic neurones to release ATP. It may be important to remember that the striatum and olfactory bulb are where the last stage of AMP dephosphorylation in rats releases adenosine (Langer et al., 2008). It has recently been shown that the striatum, a key component of the basal ganglia (BG), plays significant functions in the regulation of sleep and wakefulness (Lazarus et al., 2012). Moreover, a newly discovered mechanism known as gliotransmission can release ATP and adenosine. Glial cells are a major source of extracellular adenosine in the brain, which is essential for sleep and other sleep-dependent brain activities, according to molecular genetic modifications in mice (Schmitt et al., 2012). The so-called non-concentrative nucleoside transporters primarily stop the neuromodulatory effects of adenosine through neuronal and astrocytic (re)-uptake. Conversely, ADA is thought to significantly alter receptor affinity for adenosine and is primarily expressed on the extracellular membrane and on cell surface-bound adenosine receptors (Schmitt et al., 2012). This enzyme might be very important for removing adenosine from the body when there is a lot of it, like after staying awake for a long time.

The orexin or hypocretin system in the brain helps control sleep and how the body uses energy.

Orexin helps keep a person alert and boosts energy use. If there's not enough orexin, it can lead to narcolepsy, a condition that causes sudden, uncontrollable sleepiness and often results in weight gain (Arrigoni et al., 2019; Dhafar & BaHammam, 2022). Orexin peptides come in two forms called orexin A and orexin B. There are also two types of receptors that respond to these peptides, known as G-protein-coupled receptors. The first type, called Ox1R, prefers orexin A much more than orexin B, about 100 times more. The second type, Ox2R, works with both orexin A and B. Some drugs that activate Ox2R are being tested to treat narcolepsy, and several drug companies are trying them out in clinical trials (Saitoh & Sakurai, 2023; Wang et al., 2024; Yin et al., 2022). Nevertheless, Ox2R's functional modes of action remain incompletely understood. The lateral hypothalamus contains neurones that produce orexin and melanin-concentrating hormone (MCH). These neurones have opposing roles in several brain activities and, amazingly, do not overlap in the production of these important neuropeptides as shown by immunohistochemistry labelling (Kukkonen, 2023). Unlike orexin neurones, MCH neurones decrease insulin sensitivity and energy expenditure while accelerating sleep phases by causing transitions from non-rapid eye movement sleep (NREMS) to REMS (Hausen et al., 2016). Glucose directly inhibits orexin neurones while directly activating MCH neurones, demonstrating intricate interdependent regulation processes that preserve the functional balance in sleep and metabolism. Orexin neurones also inhibit MCH neurones through GABAergic interneurons (González et al., 2016; Viskaitis et al., 2024).

Role of cytokines and immune signaling in sleep

Immunity and sleep are inversely correlated; immune system activity can influence sleep, and sleep can influence the immune system (Irwin et al., 2016; Irwin & Opp, 2017). At the end of the 1800s, some experiments on animals showed that not sleeping could cause deadly results after several or up to 15 days. One idea was that these animals died because of a serious infection in the blood, which was linked to not sleeping at all (Sateia, 2014). These observations showed that sleep plays a big role in the immune system, and this idea still needs to be proven in people.

Cytokines

Pro-inflammatory Cytokines (IL-1, IL-6, TNF-a)

Pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) have been shown in several studies to decrease during regular sleep, indicating that sleep has an anti-inflammatory effect. On the other hand, there is a rise in blood levels of pro-inflammatory cytokines when sleep is lacking (Poluektov, 2021). Adaptive immunity is mediated by the cytokine IL-2. Under typical conditions, no alterations are seen while you sleep. Nevertheless, a rise in IL-2 levels has been noted following immunisation, which is not the case when there is extended

wakefulness following vaccination (Poluektov, 2021).

Anti-inflammatory Cytokines (IL-4, IL-10)

On the other hand, it has been shown that sleep lowers levels of the anti-inflammatory cytokines IL-4 and IL-10 (Poluektov, 2021).

Ratio of Pro- and Anti-inflammatory Cytokines

Dimitrov et al. (2004) Discovered that the TNF-α/IL-4 ratio increased during the first half of sleep, indicating a pro-inflammatory activity, and then decreased during the second half of the night, indicating an anti-inflammatory activity. Consistent with these findings, Axelsson et al. (2013) found that extended sleep deprivation causes an increase in the IL-2/IL-4 ratio (pro-inflammatory activity). When considering cytokine levels, these results collectively point to a reduction in anti-inflammatory action when you sleep. Analysing the ratios of pro-inflammatory to anti-inflammatory cytokines enables one to detect pro-inflammatory activity early in the evening and confirm anti-inflammatory activity later in the evening.

Immune System and Sleep-wake Cycle

In daily living, we may witness how our immune system and sleep interact. Every time someone becomes ill or contracts a virus, they get more sleep to speed up their recovery. A person's strength and immunity can be significantly increased by getting enough sleep (Farhud & Aryan, 2018). The body's functions and behaviours are controlled by a natural daily cycle called the circadian rhythm. This rhythm is managed by a group of cells in the hypothalamus called the suprachiasmatic nuclei (SCN), which is also known as the 'hypothalamic pacemaker'. The circadian rhythm helps control when we sleep and wake up, and it is managed by certain genes that control sleep and the body's daily rhythm. It also affects other body processes like the immune system, heart health, mood, physical activity, and body temperature. When someone doesn't get enough sleep, it can change the levels of substances that cause inflammation and affect the body's stress hormone, cortisol (Tempesta et al., 2018). SCN regulates the daily behaviour of cortisol secretion, which may be changed by issues with circadian rhythm through the sleep-wake cycle and hypothalamic pituitary-adrenal (HPA) axis. Additionally, alterations in anti-inflammatory and pro-inflammatory proteins (TNF-α) were noted (Wright et al., 2012). Tumour necrosis factor (TNF)-α and interleukin (IL) are essential factors that produce variations in the NREM sleep phase and sleep-wake cycle. According to research findings, anti-TNF-based treatment has demonstrated beneficial effects on REM sleep improvement and enhanced sleep efficiency (Besedovsky et al., 2019).

Circadian Rhythms and Sleep-Wake Regulation

The suprachiasmatic nucleus (SCN) is the master clock

The circadian rhythm, one of the numerous rhythmic processes in our bodies, aids in our ability to anticipate and adapt to daily changes in our surroundings. Our lives are dominated by circadian rhythms, which last about a day. This is most evident in the sleep-wake cycle (Czeisler, 2016; Potter et al., 2016). Indeed, circadian regulation governs nearly every aspect of crucial physiology and metabolism. These rhythms, which are driven by cellular "clocks" dispersed throughout the body, let us adapt to the outside environment by getting the brain and other tissues ready to carry out radically different—and sometimes incompatible—tasks that are suited for the expected day or night (Dallmann et al., 2014). For instance, in diurnal species like humans, neural mechanisms that sustain attention and cognitive function are activated during the day, while pathways necessary for sleep-dependent memory consolidation (and reconsolidation) and synaptic scaling are activated during the night (De Vivo et al., 2017). Mice and other nocturnally active animals show equally strong daily variations, although they phase in opposing directions to light and dark. These rhythms are the result of properly phased daily programs of tissue-specific gene expression at the cellular level (Mure et al., 2018; Zhang et al., 2014). Sleep efficiency, cognitive function, and related processes like synaptogenesis and brain metabolite clearance are all negatively impacted when the brain's circadian schedule is

disturbed (Xie et al., 2013). Therefore, it should come as no surprise that several neurological, metabolic, and behavioural conditions have been linked to problems with circadian timekeeping (Panda, 2016). Thus, the nervous system should be viewed as a 24-hour machine. However, how is temporal organisation established? The suprachiasmatic nucleus (SCN) of the hypothalamus is the primary circadian pacemaker in mammals, although there are many cellular clocks throughout the body. Because the SCN is essential for circadian behaviour, daily rhythms are disturbed when it is compromised in animals by surgical ablation and in humans by pituitary tumours or vascular illness. Additionally, it is enough for circadian behaviour: Rest-activity rhythms are restored in SCN-ablated animals using transplants of neonatal SCN tissue (LeGates et al., 2014). Furthermore, whether isolated in vivo or ex vivo, the SCN may display circadian cycles of spontaneous action-potential firing, making it an independent timekeeper. Direct retinal innervation is necessary for it to be entrained to and hence predictive of solar time to function as a clock (LeGates et al., 2014). Lastly, the SCN serves as the body's primary pacemaker, coordinating the subordinate cellular clocks. By regulating behavioural, neuro-endocrine, and autonomic signals that synchronise cellular clocks in target tissues, it does this (Morf & Schibler, 2013). The local hypothalamus, as well as subcortical and brainstem regions, receive the projections from the SCN that orchestrate this coordination (Gizowski et al., 2016). The SCN makes sure that daily neuronal and metabolic routines are clearly defined and intricately linked through various pathways.

Clock genes (PER, CRY, CLOCK, BMAL1) and transcription-translation feedback loops

One important system that offers a means of adjusting to the daily changes in the environment is the circadian rhythm. Numerous physiological processes exhibit rhythmic oscillations throughout 24 hours (Gumz, 2016). The central clock necessary to preserve the circadian rhythm is the transcription-translation feedback loop (TTFL) (Hardin & Panda, 2013; Takahashi, 2018). Circadian Locomotor Output Cycles Kaput protein (CLOCK) and Brain and Muscle ARNT-Like 1 protein (BMAL1) combine to create a heterodimer (CLOCK-BMAL1) in the mammalian model of TTFL. CLOCK-BMAL1 stimulates the transcription of clock-controlled genes by binding to the E-box region in their promoters. Among these gene products, CLOCK-BMAL1 activity may be adversely regulated by Cryptochromes (CRY1/CRY2), Periods (PER1, PER2), and Nuclear Receptor Superfamily 1 Group D (NR1D1/NR1D2). CRY interacts with DNA's CLOCK-BMAL1 to cause transcriptional repression mediated by CLOCK-BMAL1 (Ye et al., 2014). PER eliminates the impact of CLOCK-BMAL1 by removing it from DNA in a CRY-dependent way (Chiou et al., 2016; Ye et al., 2014). NR1D attaches to the retinoic acid response element (RRE) in the Bmal1 and Cry1 genes, which stops them from being turned into proteins. This process lowers the levels of CLOCK-BMAL1 and CRY1. It's difficult to study the biochemical mechanisms of the circadian clock at the whole-body level. Changing these core clock genes can cause other issues besides problems related to the body's clock. For example, mice without the Bmal1 gene grow slowly, age faster, and have trouble having babies. Mice missing Nr1d1 also die after birth or can't have babies. Also, many different factors, from how organs talk to each other, affect the timing of mouse behaviours. This makes it hard to understand the exact causes behind these rhythms. For instance, the circadian clock in non-brain tissues can be influenced by the nervous system and hormones, which are constantly changing and carefully controlled (Solanas & Benitah, 2019). Purified protein in vitro investigations have revealed details regarding the structures, DNA binding, and protein-protein interactions of the proteins implicated in TTFL. However, there was no direct correlation between the transcriptional readouts and results from in vitro trials. Since synchronisation allows for the detection of circadian gene rhythmic expression, cell lines have been employed in the TTFL investigation (Solanas & Benitah, 2019). To investigate TTFL of the circadian clock, mouse embryonic fibroblast

(MEF) cells derived from animals deficient in certain TTFL components are an appropriate instrument. For instance, cells from cry1−/− cry2−/− double knockout mice have been used to clarify the distinction between CRY1 and CRY2 in the preservation of TTFL (Khan et al., 2012). However, the puzzle of how these core clock proteins interact still hasn't been completely solved. For example, when CRY levels change, it's hard to tell whether the change in genes controlled by CLOCK and BMAL1 is because CRY activity changed, or because PER activity changed, or because there was a change in how much CLOCK and BMAL1 are present, which is affected by NR1D. New methods like genome editing are helping scientists understand the circadian clock's timing system better. Researchers can now study how the timing loop works by using cell lines that lack several key clock proteins. For instance, using a type of mouse cell line that doesn't have CRY or PER, scientists have shown the different ways CRY and PER influence the work of CLOCK and BMAL1 (Ye et al., 2014). In a different study, the Per/Nr1d_KO MEF cell line was created to investigate PER-mediated transcriptional activation of CLOCK-BMAL1-regulated genes without altering CLOCK-BMAL1 levels as a result of PER's suppression of Nr1d1 and Nr1d2 (Chiou et al., 2016). In order to investigate TTFL, we created a cell line model devoid of CRY, PER, and NR1D in response to these successful examples. In a simplified environment, this cell line might help examine CLOCK-BMAL1 activity and individual clock proteins in the TTFL-negative limb.

Interaction between the circadian clock and sleep homeostasis

There is now a plethora of data to support the two primary regulatory systems proposed by sleep regulation models: the circadian and the homeostatic (Czeisler & Dijk, 2001). The hypothalamic suprachiasmatic nucleus (SCN), which is regarded as the primary circadian clock in mammals, produces a self-sustaining circadian oscillation. This clock's oscillating output guarantees that internal rhythms are properly synchronised with the daily light-dark cycle and provides temporal context for the majority of physiological processes and behaviours, including sleep. Therefore, the circadian clock has a significant influence on how sleep is distributed throughout the 24-hour day (Potter et al., 2016). The homeostatic process monitors the requirement for sleep. When awake, the urge for sleep and the tendency to start sleeping rise, and when asleep, they diminish. The homeostatic process also appears as a 24-hour oscillation due to the daily (circadian) sleep-wake alternation. The key difference is that the circadian rhythm is self-sustaining, whereas the oscillation is imposed or pushed by the sleep-wake distribution. To highlight this difference, the oscillation produced by the circadian process is often called a self-sustained oscillation, whereas the oscillation produced by the homeostatic process is sometimes called a "hour-glass" or relaxation oscillator. Although the two processes are produced separately, how they combine influences when, how long, and how well people sleep and wake up (Dijk & von Schantz, 2005). The "twoprocess" model's ideas were confirmed and expanded upon in research where participants' sleep-wake cycles were compelled to diverge from their natural circadian rhythms. This protocol makes it possible to thoroughly examine how the two processes interact (Dijk & von Schantz, 2005). These tests' primary finding is that the circadian clock produces a sleep-wake propensity cycle that is synchronised to counteract homeostatic shifts in sleep drive. This allows us to sleep at night, even while our need for sleep is decreasing, and to remain awake and attentive throughout the day (Czeisler et al., 2016; Dijk & von Schantz, 2005). The frequency and magnitude of slow oscillations in the nonrapid-eye-movement (NREM) sleep electroencephalogram (EEG), measured as delta power (i.e., EEG power in the 1–4 Hz range, also known as slow-wave activity), most consistently fluctuates as a function of time awake and asleep among the different homeostatically regulated aspects of sleep (Czeisler & Dijk, 2001). Changes in delta power in both people and mice are sufficiently regular that their time course can be precisely predicted mathematically using just the sleep-wake distribution, both before and after sleep restriction (Franken et al., 2006). The idea

that a sleep-wake-dependent homeostatic process accounts for the majority of an individual's variance in delta power is supported by the near approximation of anticipated and actual measures of delta power. Research on animals with arrhythmias caused by SCN lesions or changes in the light-dark cycle demonstrates that the homeostatic control of sleep—specifically, the rise in delta power brought on by sleep deprivation—is unaffected and does not rely on a functional circadian clock (Waddington Lamont et al., 2012). Additionally, the circadian contribution to the time course of delta power during sleep is extremely tiny, but not negligible, according to data from research conducted on people using the forced desynchrony methodology (Nakamura et al., 2015). These and other findings support the well-established theory that the production of circadian rhythms and sleep homeostasis are physically and functionally distinct processes.

Genetic and Epigenetic Mechanisms in Sleep

Key genes associated with sleep phenotypes

To find the genetic variations underlying the usual phenotypic diversity of human sleep, a number of potential investigations have been carried out. Most of these investigations concentrated on genes implicated in the mechanism of the mammalian molecular clock. For instance, it has been observed that self-perceived circadian phenotypes are linked to variations in the period homologues (PER1, PER2, PER3) and CLOCK (Von Schantz, 2008). Studying main sleep disorders such as narcolepsy, insomnia, and sleep apnoea provides further insight into the genetic basis of sleep (Sehgal & Mignot, 2011). Actigraphy and polysomnography (PSG), two additional objective sleep metrics, were used in just a small number of eligible research studies. ARNTL and NPAS2 single-nucleotide polymorphisms (SNPs) were linked to actigraphic sleep onset and wake onset times (Evans et al., 2013). Kripke et al. (2015) Discovered a correlation between ARNTL and polysomnographic sleep duration. Circadian activity rhythms are impacted by a PER1 SNP. Additionally, in individuals with HIV, actigraphic characteristics were linked to CLOCK and cytokine polymorphisms (Lee et al., 2015). Self-reported sleep duration, typical bedtime, and daytime tiredness were all examined in the first genome-wide association (GWA) research on sleep-related traits. The top hit showed how PDE4D affected daytime drowsiness. Additionally, SNP rs324981 in the neuropeptide S receptor gene was found to have a substantial yet suggestive relationship with regular bedtime (Spada et al., 2014). An association between sleep duration and SNP rs11046205 in ABCC9, a gene encoding a potassium channel subunit, was discovered and confirmed by a more recent GWA analysis (Allebrandt et al., 2013). The GWA of insomnia and sleeping patterns by Byrne et al. (2013) found substantial non-genome-wide correlations between CACNA1C and both sleep quality and latency. Three interesting genetic loci were reported in a recent GWA analysis; however, no genome-wide significant hits were associated with sleep duration (Ollila et al., 2014). Lastly, two extensive GWAs were carried out that connected variations in PAX8 and DRD2 to typical sleep length, respectively (Cade et al., 2016). The majority of the candidate gene studies and all of these GWA investigations relied on self-report evaluations. Self-reported information on sleep/wake patterns, however, may be skewed by emotional and cognitive factors. Actually, it has been demonstrated that self-report measures only weakly correlate with more objective measurements like actigraphy (Wang et al., 2011).

Epigenetic modifications (DNA methylation, histone acetylation)

One of the organs most affected by sleep—or lack thereof—is the brain. Sleep is necessary for synaptic plasticity and synapse strength maintenance, as well as cognitive functions, including memory and learning (Tudor et al., 2016), which are compromised with a lack of sleep. One hour after cognitive learning, even a little period of sleep deprivation can affect memory formation, and the hippocampus memory system seems to be particularly vulnerable to sleep deprivation (Havekes & Abel, 2017; Havekes et al., 2016). Sleep deprivation causes changes in the brain that can show up as a variety of phenotypes. These characteristics may include mood swings and the

exacerbation of specific mental illnesses (Lewis et al., 2017) and neurodegenerative conditions like Alzheimer's disease due to elevated amyloid-β buildup (Kang et al., 2009). Individual differences in the burden of sleep deprivation indicate that a variety of biological and environmental variables influence how sleep deprivation impacts a person. One twin research highlighted the crucial genetic component of sleep by demonstrating that behavioural performance after sleep restriction was substantially heritable. Additionally, significant alterations in gene expression have been seen after sleep loss, and certain patterns of gene expression can be linked to sensitivity levels to sleep deprivation (Arnardottir et al., 2014). Numerous processes, including epigenetic mechanisms, control gene expression. In general, modifications to the genome that do not change the underlying genetic sequence are referred to as epigenetics. In particular, epigenetic processes alter the chromatin structure and accessibility of the genome to regulate gene expression and, consequently, cell function (Espada & Esteller, 2013). Three main epigenetic processes are identified: Histone alterations, non-coding RNAs, and DNA methylation and hydroxymethylation (Espada & Esteller, 2013). The epigenome is made up of the DNA changes brought about by various epigenetic processes, and because epigenetic changes are dynamic and environment-sensitive, they differ between cells and generations. Both human and animal model systems have been used to study the effects of sleep deprivation on the epigenome; however, it is crucial to consider the limitations of both systems when interpreting the findings of these investigations. For rats, a number of sleep deprivation techniques have been developed that enable environmental control and the collection of particular brain tissue (Havekes & Abel, 2017). An inherent issue with this paradigm, though, is that outcomes observed in rats might not be comparable to those shown in people. Human sleep deprivation research helps with this problem, but it needs to be conducted using easily accessible materials, namely blood or saliva, and ambient influences may cause confusion.

Role of microRNAs in post-transcriptional regulation

Technically, the central dogma idea describes a transcription–translation feedback loop that generates periodic gene expression through a series of regulatory events that form the basis of the circadian clock system (Mohawk et al., 2012). Clock gene(s) control the circadian clock, and most of these genes exhibit diurnal oscillations in their expression. Indeed, the periodic regulation of gene expression allows circadian regulation to govern a wide range of physiological processes. Since lab animals lacking clock genes are healthy and fruitful, a circadian clock anomaly by itself usually does not immediately kill living things (Tsang et al., 2017). But it's becoming more and more obvious that animals with overexpressed clock genes or those without them are prone to several illnesses that can be deadly (Zhang & Sehgal, 2019).

In the early history of life, RNA or RNA-like compounds performed the majority of the metabolic changes and information processing required for biology to develop from chemistry, according to the RNA World idea (Robertson & Joyce, 2012). RNA serves as a structural element of ribosomes and ribozymes, a protein building block, a DNA "photocopier," and a regulator of biological functions. Thus, RNA may have been the starting point of life, and it may have developed with it. It would seem logical to infer that the circadian system and RNA regulation developed concurrently, and that there was some interaction between them, if we take into account this RNA World notion in addition to the thought that the circadian clock was established in the first living forms on Earth.

Long believed to be "junk," non-coding RNAs that do not convert into a protein product have lately been shown to be different (Re et al., 2017; Wright & Bruford, 2011). Non-coding RNAs are, in fact, a popular study area right now. Numerous non-coding RNAs play an important role in biological systems and use different strategies to make up for their incapacity to be translated into proteins. One type of non-coding RNA that acts as a post-transcriptional regulator is called a microRNA (miRNA). A number of variables that are critical

to the body's biological processes are regulated by miRNAs. Recent lines of evidence demonstrate that miRNAs control the circadian rhythm of gene expression and vice versa (Cheng et al., 2007).

Post-transcriptional and post-translational regulation, which are based on a well-structured transcription and translation feedback loop, accurately regulate the circadian clock's molecular mechanism. Nonetheless, a number of illnesses have been linked to the circadian clock system's malfunction. Neurological problems, such as sleep disorders and neurodegenerative diseases, may result from a malfunction in the central nervous system. Sleep disturbance may contribute to the onset and progression of neurodegenerative illnesses, as it can be an early indication of many conditions. Furthermore, individuals with sleep difficulties and those with neurodegenerative illnesses frequently have miRNAs that are aberrantly expressed in the blood, bodily fluids, and/or several tissues in common (Piletič & Kunej, 2016).

These findings suggest that miRNAs may serve as both useful treatments and indicators of disease aetiology due to their capacity to alter the expression of genes linked to or responsible for disorders.

Molecular Dysregulation in Sleep Disorders

Insomnia: altered HPA axis, neurotransmitter imbalance

Through use-dependent synaptic downscaling and strengthening, sleep facilitates continuous adaptability to a changing environment. A growing amount of research indicates that sleep is essential for coordinating neuroplasticity and significantly influencing fundamental learning and memory functions (Maier & Nissen, 2017; Nissen et al., 2021). Through active cortical plasticity refinement, sleep may restore performance by regulating sleep-specific brain activity (Maier & Nissen, 2017; Nissen et al., 2021). A good night's sleep is critical for mental health, and recent studies have shown that sleep plays a fundamental role in controlling emotions as well as the stress response and stress system. Sleep processes are crucial for mental health since psychopathology is primarily characterised by emotional and cognitive instability. Subjective and "objective" sleep disturbances are, in fact, very common in people with nearly all mental illnesses (Seow et al., 2018). According to recent studies, there may be a reciprocal association between mental disorder symptoms and sleep disturbances, with insomnia in particular serving as a risk factor for the de novo genesis of psychiatric illnesses (Hertenstein et al., 2019). There is strong evidence that a variety of mental problems often co-occur with insomnia, one of the sleep disturbances. Sleeplessness is regarded as a risk factor in and of itself, as well as an early indicator of many mental illnesses and a significant contributor to their recurrences and relapses. About 70% to 80% of patients have sleeplessness during the acute phase of a mental disease, making it a commonly occurring and clinically relevant aspect of many mental abnormalities. According to this theory, the severity of the disease, cognitive impairment, impulsive and violent behaviours, and an elevated risk of suicide can all be linked to insomnia (Palagini et al., 2019; Palagini et al., 2022). Specifically, it has been shown that, regardless of other psychopathologies and sociodemographic traits, complaints of sleeplessness may predict suicide attempts (Geoffroy et al., 2021). Although sleep is necessary for brain homeostasis, brain plasticity, and mental health, sleep disorders, particularly insomnia, may promote an allostatic overload state that compromises emotional, immunological, and endocrine pathways as well as brain plasticity, potentially leading to mental health issues (Hertenstein et al., 2019; Palagini et al., 2022). Current research views sleeplessness as a symptom that may be used to diagnose a variety of mental illnesses. Numerous new insights for both clinical treatment and mechanism research have been made possible by investigating insomnia from several viewpoints as a transdiagnostic phenotype (Riemann et al., 2020). The purpose of this effort was to connect the present understanding of the processes behind insomnia with the current understanding of the dysregulatory systems underlying mental health. The current effort will concentrate on mood disorders, anxiety disorders, and psychotic illnesses, which pose significant difficulties in treatment. Clinical, neurological, and therapeutic

implications for mental illnesses and insomnia were searched in the literature. Numerous word combinations were employed, including "insomnia," "unipolar depression," "bipolar depression," "psychosis," and "anxiety disorders."

Narcolepsy: orexin deficiency

A long-term neurological condition that impairs the regulation of sleep and wakefulness is called narcolepsy. Abnormal rapid eye movement (REM) sleep events, including sleep paralysis (being paralysed but awake at the same time), cataplexy (sudden episodes of muscle weakness triggered by emotions), and hypnagogic hallucinations (dream-like experiences that occur while still conscious at sleep onset), are its hallmarks (Mignot et al., 2021). Disturbed nocturnal sleep was not recognised as another hallmark symptom of narcolepsy until the late 1970s, when it was shown that gamma hydroxybutyric acid (sodium oxybate), a potent slow-wave sleep-enhancing drug, was an effective treatment for the majority of narcolepsy symptoms. Today, narcolepsy type 1 (NT1) is the term used to describe this characteristic appearance (Thorpy, 2017). It is often identified when a Multiple Sleep Latency Test (MSLT) is positive, showing fast transitions to REM sleep, and is closely linked to the immunological gene Human Leukocyte Antigen (HLA)-DQB1*06:02. The loss of cells that produce the neuropeptide hypocretin (orexin) due to an autoimmune reaction is the aetiology of NT1 (Sateia, 2014). Although instances without cataplexy (also known as narcolepsy type 2 or NT2) but with a positive MSLT were later included in the term "narcolepsy," the focus of this chapter is mostly on NT1 because patients with NT2 typically do not have hypocretin.

The Effect of Acute Hypocretin/Orexin Cell Loss in Human Narcolepsy

Children with NT1 are best suited to evaluate the acute effects of hypocretin/orexin cell loss since symptoms may appear within weeks and are quite sudden. Pizza et al. (2013) demonstrated that narcolepsy first manifests as a true hypersomnia, characterised by lengthy daytime naps (often lasting hours), increased total daily sleep time over the 24 hours, and the incidence of distressing awakenings and dreams. A worldwide floppy aspect, a generalised hypotonia with significant facial involvement (mouth opening and tongue protrusion), and a disruption in gait, where falls to the ground might happen without any apparent emotional connection, are also linked to it. This phenotype implies that the main effects of hypocretin are to regulate muscular tone, promote alertness, and limit the onset of REM sleep. Children usually experience weight gain suddenly, a phenotype that is probably complicated and at least partly caused by decreased activity and metabolism in response to increased or comparable hunger (Ponziani et al., 2016). Additionally, early puberty may result. After this, children usually progress to the most well-known phenotype of adult narcolepsy, which is typified by periods of muscular weakness brought on by intense emotions and short, rejuvenating sleep spells. Wake transitions cause ever greater disruptions to sleep. Sodium oxybate, a medication that restores the proportion of deeper phases of sleep at night and enhances the overall pattern, helps patients who frequently complain of restless sleep (Black et al., 2009). Although it is currently challenging to determine this due to the rise in the number of individuals receiving appropriate treatment, cataplexy may also lessen with age. The effects of orexin antagonists, which increase sleep but decrease REM sleep latency, are also consistent with this (Clark et al., 2020). A crucial topic in the area, as orexin agonists become accessible, is whether they would normalise disturbed nocturnal sleep in addition to increasing alertness and decreasing cataplexy, which is tentatively supported by pilot trials employing the orexin receptor 2 agonist TAK925 (Mignot et al., 2021).

Sleep apnea: inflammatory signaling and oxidative stress

The clinical disorder known as Obstructive Sleep Apnoea Syndrome (OSAS) is marked by recurrent bouts of upper airway blockage during sleep that last longer than 10 seconds and are accompanied by persistent thoracoabdominal motions (Kapur et al., 2017). During apnoea episodes, inadequate

nighttime alveolar ventilation often causes the arterial blood's oxygen saturation (SaO2) to drop and, in the event of protracted attempts, the blood pressure of carbon dioxide (PaCO2) to gradually rise (Paruthi et al., 2015). Micro awakenings, which are characterised as "arousal," an electroencephalographic change in the micro- and macrostructure of sleep, take place at the conclusion of apneic episodes. These nocturnal awakenings are linked to tachycardia, a brief rise in blood pressure, and autonomic alterations that activate the sympathetic nervous system (Cuspidi et al., 2019; Iannella et al., 2020). Between 2% and 4% of middle-aged women and men suffer from OSAS, a common and frequently underdiagnosed condition. However, according to certain clinical research, it can occur at a significantly greater rate in older adults (20–60%) if there is a substantial difference in the Apnea-Hypopnea Index (AHI) (Iannella et al., 2019; Vicini et al., 2018). Numerous authors have shown that OSAS is linked to a higher prevalence of cardiovascular conditions, including arrhythmias, ischaemic heart disease, excessive blood pressure, and cerebrovascular issues. Continuous Positive Airway Pressure (CPAP) therapy is still a basic strategy, although treatment with more creative approaches shows promise in lowering related comorbidities (Di Luca et al., 2020; Vanek et al., 2020). Patients with obstructive apnoea syndrome appear to have a persistent systemic inflammatory state, similar to those with dysmetabolic disorders. The upper airways collapse during the night, and the resulting chronic intermittent hypoxia causes recurrent cycles of hypoxia and reoxygenation, increases systemic oxidative stress, and produces biomarkers linked to systemic inflammation (Kheirandish-Gozal & Gozal, 2019). Even though the exact processes relating OSAS to cardiovascular diseases are yet unknown, endothelial dysfunction associated with intermittent hypoxaemia and the resulting production of pro-inflammatory and reactive oxygen species (ROS) may be a significant factor. According to several experts, oxidative stress is the underlying factor in OSAS patients that may contribute to ischaemic heart attacks and other cardiovascular harm. In the early stages of the disease, reactive oxygen species (ROS) in particular damage the vascular endothelium and promote the expression of leukocyte adhesion molecules (integrins, L-selectin) and associated endothelial adhesion molecules (E-selectin, P-selectin, ICAM-1, VECAM-1) (Wang et al., 2019). It would appear that endothelial lesions brought on by these biomolecular changes cause microvascular damage in OSAS patients (Wang et al., 2019). The inducible transcription factor of hypoxia-1 (HIF-1) and reactive oxygen species produced by intermittent hypoxia (ROS) form the pathway that causes harmful cardiovascular consequences, such as the development of aortic dissection (Liu et al., 2019). Numerous inflammatory indicators, chemicals produced by the oxidation of nucleic acids, proteins, and lipids, and the manifestation of multilayer cell damage may all be used to measure the ensuing imbalance between oxidative stress from elevated oxygen free radicals and an insufficient antioxidant capacity (Düger et al., 2021). Conversely, elevated ROS generation brought on by the hypoxia/reoxygenation cycles may raise the expression of cytokines and adhesion molecules associated with cardiovascular disease and endothelial dysfunction. Typically, the term "oxidative stress biomarkers" refers to a broad category of species that includes both the substances released as free oxygen radicals and plasma indicators of systemic inflammation (Lira & de Sousa Rodrigues, 2016).

Molecular Dysregulation, Causality, and Mechanistic Links in Sleep Disorders

Key disorder	Key molecular deregulation	Mechanistic insight	References
Narcolepsy	Loss of hypocretin-producing neurons in the lateral hypothalamus	Autoimmune-mediated destruction of hypocretin neurons causes severe instability of sleep-wake transitions,	**(14)**

		leading to cataplexy and daytime sleepiness	
Insomnia	Hyperactivity of the HPA axis	Chronic hyperarousal state disrupts the initiation and maintenance of sleep	**(15)**
Sleep apnea	Genetic polymorphisms in PHOX2B, serotonin transporter	Affect ventilatory control and upper airway tone, increasing OSA risk	**(16)**

Restless leg syndrome and periodic limb movement disorder

The need to move one or both legs (and occasionally the arms) when stationary is the hallmark of restless legs syndrome (RLS), a sleep-related movement condition that is most noticeable in the evening or at night and is frequently accompanied by dysesthesias in the afflicted limbs (Allen et al., 2014). The intensity of RLS varies from sporadic bouts over extended periods of sitting or inactivity to everyday, almost constant, pain and movement. The symptoms of RLS can be mimicked in children by growth pains, leg cramps, and behavioural problems, and in adults by neuropathy, akathisia, spasticity, positional discomfort, joint discomfort, and nocturnal leg cramps. Since there is no objective test to help with the diagnosis of RLS, a thorough clinical history is essential. 2–3% of adults and 0.5–1% of children have clinically significant RLS, which is defined as occurring at least twice a week and linked to at least moderate distress (Allen et al., 2014). Since children may have trouble articulating their symptoms, identifying RLS in them can be difficult. Adult females are around 50% more likely to experience RLS, which may be associated to pregnancy. People with northern European ancestry are also more likely to experience this condition. Insomnia is the main morbidity caused by RLS, which can make prolonged immobility at night practically impossible. Roughly 90% of RLS patients have trouble sleeping or staying asleep (Hening et al., 2004). People with RLS frequently have periodic limb movements during sleep (PLMS), which are short (0.5–10 seconds) repetitive flexion movements of the lower extremities that happen about every 15–30 seconds on polysomnography. In individuals with RLS, PLMS are most common in the first four hours of sleep and are very variable from night to night in both adults and children. These motions are always linked to increases in blood pressure and heart rate, but they can also be linked to electroencephalogram arousal (Pennestri et al., 2013). PLMD is identified when: (1) PLMS occurs frequently (> 15 events/h in adults and > 5 events/h in children); (2) a clinically significant sleep disturbance and/or daytime dysfunction coexists and cannot be better explained by another concurrent sleep, medical, neurological, or mental disorder; and (3) no sleep disorders, such as RLS, untreated obstructive sleep apnoea, rapid eye movement sleep behaviour disorder, or narcolepsy, are present and are linked to high rates of PLMS. The implication for PLMD is that PLMS directly contributes to the disorder's symptoms at night and/or during the day, and thus PLMS decreases will alleviate symptoms. Though brain iron deficiency and heredity most certainly play a contribution, the underlying pathophysiology of RLS and PLMD is only poorly known (Schormair et al., 2017). RLS is more common in people with illnesses linked to systemic iron insufficiency, such as pregnancy and end-stage renal disease [ESRD] (Trenkwalder et al., 2016). People with RLS had lower brain iron indices, according to magnetic resonance imaging, transcranial doppler, and cerebrospinal fluid studies (Rizzo & Plazzi, 2018). Additionally, RLS is highly heritable; around 50% of individuals with RLS have a first-degree relative who also has the disease. Genome-wide association studies have linked the condition to at least 164 genetic variations.

Environmental and lifestyle factors

A person must have enough time available for sleep at a suitable circadian phase and generally follow basic sleep hygiene guidelines, which include sleeping in a sleep-friendly setting, in order to have both enough and quality sleep. Studies of sleep and circadian rhythms indicate the role of regular sleep scheduling in favorable sleep outcomes (Sletten et al., 2015) and recent consensus findings on sleep requirements support the idea that people need 7 to 9 hours of sleep each night (Panel: et al., 2015). The scientific evidence for the suggestions of what makes an optimal sleep environment is scattered throughout several research, despite the fact that environmental sleep disruptors are acknowledged as a contributing factor to some sleep disorders.

Light

Light disrupts sleep for two reasons: first, it resets the circadian pacemaker, which causes the circadian phase timing to change in relation to the planned sleep episode. Second, light is an environmental stimulant that might wake people up at night and interfere with their sleep. Exposure to light through the eyes resets the circadian rhythm (Foster, 2020). Exposure to light at the wrong moment can prevent sleep from starting and cause changes in the circadian rhythm that can affect sleep on other nights. Compared to evening light exposure of 3 lux, evening light exposure as low as 65 lux can cause a 1-hour change in the circadian phase of melatonin (Burgess & Molina, 2014).

The wavelength of the light, in addition to its intensity, determines how powerful the light stimulation is on human circadian physiology. The 460–480 nm region of short wavelength light is the most sensitive to the human circadian pacemaker (van Marken Lichtenbelt et al., 2006). This reaction is a dosage response, with higher blue light irradiances producing stronger phase shifting and melatonin suppression effects (Brainard et al., 2001). Conversely, melatonin is not suppressed by exposure to low intensity red light (West et al., 2011). Although it can be challenging to separate the direct effects of evening or morning light exposure on sleep from the indirect effects of circadian phase shifts, some research indicates that light may have an impact on the architecture and quality of sleep.

Ambient temperature

When assessing how temperature affects sleep, it is important to consider the interplay between endogenous core body temperature, skin temperature, ambient temperature, airflow and humidity, clothing, and bedding insulation. Under typical circumstances, the core body temperature's circadian rhythm decreases just before the ideal time for sleep onset and keeps decreasing during the sleep period, naking around six hours after the start of sleep (Dijk & Lockley, 2002). The morning awakening during a circadian-entrained sleep period coincides with the rising phase of the core body temperature rhythm. The decrease in heat generation brought on by a slower metabolic rate and heat loss from inactivity are the causes of this shift in core temperature.

On the other hand, compared to active waking, both the proximal and distal skin temperatures increase during sleep. (van Marken Lichtenbelt et al., 2006). When people are in charge of their sleeping environment, the ideal temperature is usually self-selected by using clothes and bedding to create a microclimate inside the surrounding space. Numerous category 1A studies have found that temperature variations during a sleep episode can also affect the quality of sleep. Compared to a night with a constant temperature of 26 °C, sleep latency increases when the ambient temperature is altered from lower (25 °C) early in the night to hotter (28 °C) later in the night (Lan et al., 2016). On the other hand, it has been demonstrated that slow wave sleep is improved when the surrounding temperature is higher (29.5 °C) at the start of the night and gradually lowered to a lower temperature (27.5 °C). Similarly, compared to skin cooling (category 1A), it has been demonstrated that using a thermosuit that is warmed to about 34 °C without any further insulation can improve slow wave sleep, decrease night waking, and decrease sleep latency (Raymann et al., 2008). Notably, people self-report thermal comfort as being worse when temperatures are raised before they go to sleep, even though there have been

documented benefits in sleep quality linked to warmer temperatures. These results imply that, depending on the kind of manipulation, changes in the ambient or microclimate temperature inside the thermoneutral zone may either improve or impair sleep.

NOISE

Both the quantity and quality of sleep can be affected by noise exposure. The decibel level (dB), frequency and pitch, length (continuous, intermittent, or impulsive), and significance of the noise (e.g., a known voice) all affect how much noise disturbs sleep. According to a World Health Organisation working group study on noise, exposure to noise at night is causally linked to self-reported sleep disruptions, medication usage, self-reported health issues, and symptoms similar to insomnia (Tsuzuki et al., 2008).

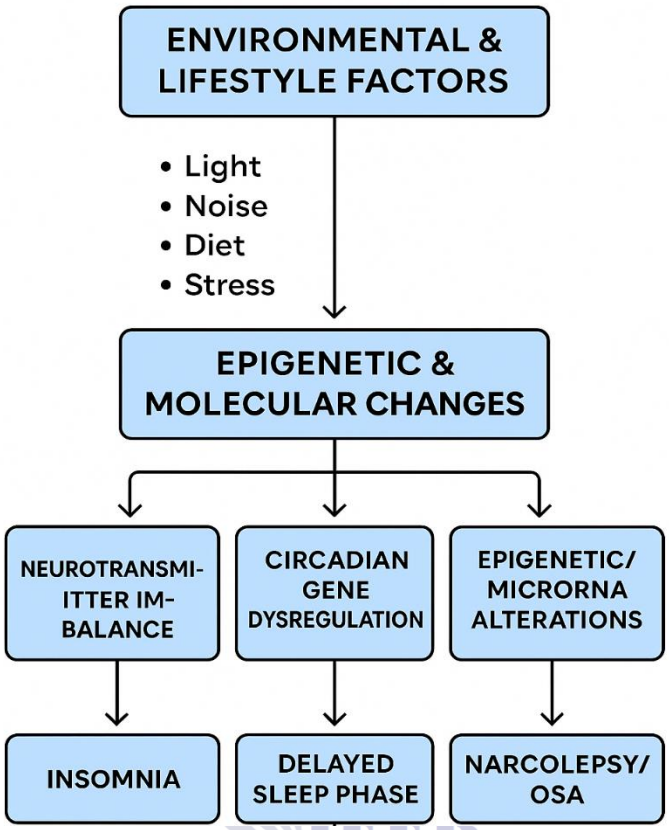
Because greater noise levels in the sleep environment alter the length of sleep cycles and increase sleep fragmentation, the same group released guidelines for noise exposure during sleep, establishing an average level limit of 30 to 40 dBA. Noise exposure levels below 50 dBA are more likely to wake people up in shallow sleep phases (i.e., stages 1 and 2), but louder noises or noises with low frequencies (about 500 Hz) are needed to wake people up in deeper sleep stages (i.e., stages 3 and 4). Notably, the impact of dreaming makes it difficult to estimate the arousal threshold in REM sleep (Muzet, 2007).

Both the volume and the frequency of the noise's recurrence seem to affect how completely a person wakes up, with more frequent pulses disrupting sleep more than others (Nakagawa, 1986). There are significant inter-individual variations in noise sensitivity, and repeated exposure to noise has also been demonstrated to alter the auditory arousal threshold (McGuire et al., 2016). Speaking a sleeper's name, hearing human voices, and seeing movement about the house can all trigger awakenings since sleeping people are aware of their environment (Sasazawa et al., 2006).

Lifestyle factors

A growing number of studies have connected "lifestyle factors," which include healthy habits like exercise, nutrition, smoking, and sleep, to the development and symptoms of several mental illnesses (Lianov & Johnson, 2010). For example, a wealth of cross-sectional data indicates that, in comparison to healthy controls, a variety of mental illnesses (such as schizophrenia, bipolar disorder, depression, and anxiety and stress-related disorders) are linked to unhealthy behaviours, such as poorer sleeping and eating habits, low levels of physical activity, and higher rates of tobacco use. Furthermore, new results from population-scale research show that many of these lifestyle risk factors continue to be associated with mental illness in low- and middle-income nations (Firth et al., 2019; Stubbs et al., 2018).

This large volume of cross-sectional research is helpful, but it does not prove that the observed relationships are causative. Consequently, there is presently very little evidence to support the idea that lifestyle variables should be taken into consideration when trying to either prevent the onset of mental illness or lessen symptoms in people who already have it. However, the importance of certain lifestyle variables in the prevention and treatment of mental illness is increasingly being addressed in a variety of professional guidelines and national health policy texts. For example, to lower the risk of depression (including postnatal depression), the UK Chief Medical Officers' Physical Exercise Guidelines and the US Physical Activity Guidelines for Americans both suggest doing at least 150 minutes of moderate-to-vigorous physical exercise each week. (Vancampfort et al., 2019).



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Therapeutic Implications and Future Directions

The physiology of sleep is altered by autonomic deficits, and sleep disorders can impact autonomic processes. The diagnosis and prognosis of sleep disorders, as well as sleep disorder therapies, have not, however, been thoroughly examined with an emphasis on this reciprocal relationship. Medicinal treatments are commonly used to treat sleep problems, to help patients fall asleep by boosting their GABA levels. Nevertheless, these drugs unnaturally alter autonomic tone, and prolonged usage exacerbates the drop in systolic blood pressure and raises heart rate (Nardone et al., 2020). Current neuromodulation techniques work well to restore regular sleep patterns without running the danger of addiction. While LF (25 Hz) deep-brain stimulation of the PPT lengthens the duration of REM sleep, repetitive transcranial magnetic stimulation decreases cortical hyperexcitability and rebalances neurotransmitter release by engaging the local neural network with alternating currents. These neuromodulation techniques, however, are unable to counteract erratic autonomic changes linked to compromised sleep physiology (Du et al., 2019; Sharma et al., 2018). With an emphasis on maximising the most suitable neural target, stimulation regimens, and candidate symptoms to treat, more noninvasive therapeutic techniques of brain stimulation for sleep disorders are now being developed (Fisicaro et al., 2020). This section examines the neurostimulation research in the domains of sleep medicine and autonomic regulation, but the currently available methods only provide limited cross-therapeutic benefits.

CPAP as a therapeutic approach

For individuals with moderate-to-severe OSA, nasal continuous positive airway pressure (CPAP) is the gold standard of care. By functioning as a pneumatic splint that maintains the upper airway open while you sleep, CPAP can stop OSA

episodes (Bragazzi et al., 2019). CPAP enhances attentiveness, sophisticated cognitive performance, and several mood subscales when compared to a placebo (Barnes et al., 2004). However, overall compliance is frequently low, and CPAP adherence may be subpar. Actually, 25–50% of patients with OSA do not sustain optimal adherence to CPAP, and 15–30% do not accept CPAP treatment right from the start (Collard et al., 1997). The use of CPAP is not entirely tolerable, even with the latest machines and interface (mask) devices (Gulati et al., 2017).
Social and personality characteristics have been examined in a prospective observational study to see if they are related to CPAP compliance (Mahoney et al., 2022). Socioeconomic status, personality, or education did not significantly correlate with CPAP compliance in this research (Panel: et al., 2015). Patients with depression, on the other hand, need more intense care and are less likely to comply optimally with CPAP therapy.

Genetic and biomarker-based personalized treatments

Biomarkers that mimic the functioning of the central nervous system at the level of neuronal activity are necessary for personalised treatment in psychiatry. In addition to being used to separate patients from healthy individuals, electroencephalography (EEG) during sleep or resting-state conditions and event-related potentials (ERPs) have also been used to predict treatment outcomes in a variety of psychiatric disorders, providing insights into individualised therapy approaches. The baseline EEG indicators for major depressive disorder and attention-deficit hyperactivity disorder are the main focus of this review. It discusses paroxysmal EEG patterns and epileptiform discharges, quantitative EEG characteristics within the main frequency bands, connection indicators, ERP components, and possible biomarkers from EEG sleep research and vigilance management that may aid in identifying positive treatment outcomes.
Additionally, the different markers are examined in light of their possible (Olbrich et al., 2016).
The innovative and profoundly revolutionary discipline of "personalised sleep medicine" addresses each person's unique sleep-related medical requirements. In order to maximise sleep quantity and quality and successfully treat sleep disorders, this innovative framework transcends conventional one-size-fits-all methods and acknowledges the unique physiological and psychological traits of every individual. Recognising and addressing the various elements that affect sleep, including genetic predispositions, behaviour and lifestyle choices (diet, exercise, and drug and stimulant use), environmental factors, and underlying medical disorders, forms the basis of this strategy (Genderson et al., 2013; Sejbuk et al., 2022). Personalised sleep medicine can provide more precise diagnoses, focused therapies, and proactive management techniques that better suit the requirements of each patient by taking these factors into account. It is remarkable how quickly new technologies are being developed and incorporated into this industry. A better knowledge of sleep patterns and the introduction of new tools, particularly digital ones, are driving personalised sleep medicine forward and providing creative solutions for problems connected to sleep (Cheung et al., 2023). To collect comprehensive information on sleep patterns, amount, quality, and disruptions, wearable technology, smartphone health apps, and sophisticated diagnostic tools are being used more and more. Continuous monitoring and analysis are made possible by these technologies, which yield a multitude of data that may be efficiently utilised to customise interventions and therapies (Vijayan et al., 2021). Furthermore, the possibilities of personalised sleep medicine have been significantly improved and expanded with the introduction of advanced data analysis tools, including machine learning and artificial intelligence (AI) (Bragazzi et al., 2019). Large datasets may be more easily interpreted thanks to these technologies, which provide subtle insights into sleep patterns and possible diseases. They enable medical professionals to create highly individualised treatment programs that precisely match each patient's unique sleep profile. Furthermore, this subject greatly benefits from a greater comprehension of sleep science, which includes the study of circadian rhythms and sleep

physiology (Foster, 2020). These fields of study are revealing new facets of the intricate relationship between sleep and general health and wellbeing, offering important insights that can guide individualised treatment plans. To put it simply, personalised sleep medicine is at the forefront of a revolution in healthcare that prioritises individualised treatment and uses science and technology to enhance sleep quality (Ryba-White et al., 2021). Given that adequate sleep is essential for overall health and well-being, this strategy not only more successfully treats sleep problems but also improves people's quality of life in general (Ramar et al., 2021).

Role of chronotherapy and lifestyle interventions

The deliberate administration of drugs in uneven doses across time, such as throughout the day, is known as chronotherapeutics. 76 To determine the drug-delivery pattern, dose, and administration time to maximise desired and/or minimise adverse effects, chronotherapeutics considers (a) rhythmic changes in disease pathophysiology, (b) the chronopharmacology (chronokinetics, chronodynamics, chronesthesy, and chronotoxicology) of medications, and (c) endogenous determinants of the individual's circadian time structure (Baglioni et al., 2020). Chronotherapeutics is based on the idea that the body's daily rhythms affect how well treatments work. It looks at four main areas: first, the body's internal clock and how it controls daily cycles; second, how diseases and symptoms change throughout the day; third, how medicines work at different times of day, including how they are released and how they affect the body; and fourth, new ways to deliver medicine that can be timed properly. At first, people tried simple methods like giving medicine at different times of the day using traditional pills that released medicine slowly over 12 hours or once a day in the morning or evening. But as more research was done, it became clear that better systems are needed. These systems should be easy to use, respond to signs in the body that show when medicine is needed, and be affordable for both patients and healthcare organizations. In the future, these systems will need to deliver multiple medicines, each responding to different body signals, so they can work well with the body's natural rhythms to treat diseases more effectively (Smolensky et al., 2011). Chronobiotics: A chronobiotic is a chemical compound that may either avoid the disruption of circadian rhythms following environmental changes or retrain short-term dissociated or long-term desynchronised rhythms. More precise definitions have recently been put forth: "a substance that adjusts the timing of internal biological rhythms" or, more precisely, "a substance that adjusts the timing of the central biological clock" are the terms used to describe a chronobiotic. It must be distinguished from a hypnotic, which is a medication that promotes and sustains sleep (Moser et al., 2006). The body's endogenous rhythms may be phase delayed by up to an hour daily in the absence of continuous circadian pacemaker control, which can have a major effect on general health. Sleeping and waking patterns, as well as other circadian rhythms, can be seriously disrupted by abnormal phase positions, which are a hallmark of diseases of the circadian rhythm (Driscoll et al., 2007; Lack & Wright, 2007). The International Classification of Sleep Disorders has categorised certain sleep disorders as circadian rhythm sleep disorders (CRSDs) (Driver & Hawari, 2018). Time zone change syndrome (often known as "jet lag"), advanced sleep phase syndrome, non-24-hour sleep/wake rhythm disorder, delayed sleep phase syndrome, and shift work sleep disorder are all examples of circadian rhythm sleep disorders. All of these illnesses have been linked to disturbances in the circadian phase position of plasma melatonin levels. According to Warman and Arendt, chronotherapy can be used to treat advanced sleep phase disorder, delayed sleep phase syndrome, other CRSDs, seasonal affective disorder, circadian desynchronisation brought on by Arctic winter darkness, and resetting the rest/activity rhythms of blind individuals for whom light does not act as a zeitgeber (Warman & Arendt, 2017). In the field of chronotherapy, mathematical modeling has shown promise in optimizing the timing of chemotherapy treatments based on the circadian rhythms of patients to improve efficacy and minimize toxicity. These

models streamline the interpretation of complex drug interactions and timings, making it far more feasible to align treatments with circadian cycles for improved survival outcomes

Enhancing Diagnosis and Personalized Treatment

Beyond autoscoring, AI has the potential to transform sleep medicine by facilitating better management of sleep disorders, early identification, and individualised therapy. Beyond the apnea-hypopnea index alone, artificial intelligence (AI) is being used to enhance the diagnosis of sleep disorders such as obstructive sleep apnoea (OSA) (Serrano Alarcon et al., 2021). Polysomnography, which necessitates an overnight stay in a sleep lab or at-home sleep apnoea testing, is the traditional method of diagnosing OSA. These days, scientists are creating AI models that can identify OSA with easier-to-use and less expensive techniques. For instance, blood oxygen levels (SpO2) may now be accurately monitored by smartwatches, providing a possible tool for early OSA identification (Almarshad et al., 2023; Zhao et al., 2022).

Furthermore, utilising basic indicators like age, sex, and body mass index, AI-based prediction models have demonstrated a respectable level of performance in identifying those who are at risk of getting OSA (Yang et al., 2024). Furthermore, by evaluating clinical and polysomnographic data, AI has shown potential in supporting narcolepsy diagnosis and subtyping (Kuan et al., 2022). A potential strategy for improving patient adherence and results is the use of AI and ML to customise therapy for sleep disorders (Shen et al., 2022). Large datasets may be analysed by AI algorithms to find patterns and connections between patient characteristics, sleep physiology, and treatment outcomes. With the use of this thorough study, OSA may be precisely phenotyped and endotyped, opening the door to the development of specialised treatment plans that highlight the disorder's distinctive features.

Essential features associated with OSA, including as upper airway collapsibility, decreased muscle reactivity, a low arousal threshold, and poor ventilatory control, may be predicted by machine learning models (BaHammam, 2024). In order to investigate the relationship between four major OSA endotypes and the severity of OSA as determined by polysomnography, a recent study presented a novel data-driven methodology that uses supervised machine learning and unsupervised multivariate principal component analysis (Nemati et al., 2014). Understanding how common polysomnographic and clinical factors could predict these endotypes was another goal of the investigation. Treatment approaches can be directly customised by knowing a patient's unique endotype.

In order to match patients with the therapy that would most likely work best for them, a machine learning model was used, for example, to predict the outcomes of various treatment approaches, such as dental appliances. ML algorithms have proven to be highly accurate in forecasting OSA patients' adherence to CPAP therapy (Brennan & Kirby, 2023). Clinicians can customise treatments to meet the needs of each patient by using AI to find connections between therapy responses and patient features through the analysis of huge datasets. This individualised approach to sleep treatment has the potential to transform patient care by enhancing quality of life and results.

Conclusion

Sleep is controlled by a complex system that works together using chemicals in the brain, hormones, your body's natural day-night cycle, and changes in gene activity. When this system doesn't work properly, it can lead to poor sleep and various sleep problems. These issues can affect your brain, body, and heart in serious ways. New research in genetics and how systems work has helped scientists understand how things like brain chemicals, genes that control your body clock, and the immune system play a role in conditions like insomnia, narcolepsy, sleep apnea, and restless legs. This knowledge is changing how we treat sleep disorders, moving away from just treating symptoms to using more targeted and personalized approaches, including looking at specific molecules, testing for markers, and using time-based treatments. Moving forward, the focus should be on turning these findings into effective

and individualized treatments to help reduce the impact of sleep disorders worldwide. A variety of sleep disorders are caused by disturbances in the intricate molecular, genetic, and environmental processes that regulate sleep. Even if the present treatment only partially relieves the problem, personalised sleep medication may be possible by combining molecular insights with cutting-edge technology like wearable monitoring, artificial intelligence, and targeted medicines. Additionally, research might concentrate on creating precision methods, novel therapies, and biomarkers to shift the focus of sleep health from symptomatic treatment to predictive and preventative measures.

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