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Role of Chronotherapy in Disease Control and Prevention

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Abstract: Circadian (24 h) and other period rhythms possess a key role in biological activities and processes. Evolving ideas from the scientific field of chronobiology, the study of biological rhythms, which has been dominating medical teaching, research, and practise for a significant portion of the 20th century, they are now challenging the concept of homeostasis, or consistency of the internal milieu. Rhythms of the circadian cycle in the physiology of the gastrointestinal system, critical organs, and body tissues may result in changes in the pharmacokinetics and effects of treatments depending on the time they are administered. As a result, the pharmacokinetics and dynamics of the same medication taken in the same dose and under the same circumstances in the morning and evening may differ. Chronotherapy, or enhancing the effectiveness and safety of pharmaceuticals by distributing their concentrations over the course of a day in synchrony with the biological rhythms that determine disease, is now possible due to new advances in technology. Chronotherapy aids in the control and prevention of disease.

Keywords: Chronotherapy, Diseases in CNS, CVS, Respiratory, UTI systems, Chronobiology

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Introduction

A biological rhythm is any occurrence that occurs repeatedly in a biological system at roughly regular periods. The idea is sufficiently not defined to be helpful in enumerating a broad range of occurrences that may represent quite distinct underlying systems. Restrictive descriptions that are based on the chosen criteria are needed in order to categorise rhythms. Rhythms can be differentiated based on: (a) A characteristic like frequency; (b) The ecological system (like a population) in which the rhythm is seen; (c) The timing of the rhythm; (d) The nature of the rhythm-generating process; and (e) the purpose that the rhythm serves. Biological rhythms range in frequency ranging over numerous logarithmic units from a single cycle per millisecond to one

cycle every several years. Biological rhythms can be seen in cells, tissues and organs. Exogenous rhythms are comparable to forced oscillations of passive systems, i.e., systems that can only oscillate when external periodic disturbances or signals (driving force) are present, and whose oscillations cease once the input becomes steady. On the other hand, endogenous rhythms are frequently compared to active systems that have oscillations that persist unabated when the energy source is maintained (Aschoff *et al.,* 1980).

There are four rhythms: (a) Diurnal rhythms are the synchronisation of the circadian rhythm with day and night. Circadian rhythms are the cycle of physiological and behavioural rhythms, such as sleep; (b) Biological rhythms known as ultradian rhythms occur more frequently and last for a shorter period of time than circadian rhythms; (c) Physiologic rhythms that persist longer than 24 h, such as the menstrual cycle, are known as infradian rhythms; and (d) Circadian: One year's worth of rhythms. It is also known as "seasonal rhythm" (Aschoff *et al.,* 1980).

What is Circadian Rhythm?

When there are no 24 h signals from the environment, free running circadian rhythms appear. This shows that the beat is not synchronised by a cyclical change in the physical environment. In order to distinguish diurnal rhythms that are merely a reaction to 24 h environmental changes from those that remain under constant environmental conditions, a diurnal rhythm should not be considered to be circadian. Yet, since nearly all diurnal rhythms are discovered to be circadian, there is little practical reason to discriminate between diurnal and circadian rhythms. Furthermore, there is no language that categorises circadian rhythms according to the nature of the external stimulation that synchronises the cycle.

The ability of rhythms to persist in the absence of a Zeitgeber or other external time signal. strongly suggests the existence of a biological clock or other internal mechanism for keeping time (Aschoff *et al.,* 1960).

A groundbreaking illustration of the SCN's function came from the discovery made in the early 1970s that disrupting and abolishing endocrine and behavioural circadian rhythms in rats could be accomplished by damaging (i.e., lesioning) the SCN (Klein *et al.,* 1991). Furthermore, by transplanting SCN from other animals into the mice with the lesioned SCN, researchers were able to partially restore the circadian rhythms. Similar investigations in hamsters demonstrated that the restored rhythms expressed clock characteristics (such as the duration or amplitude of the rhythm) of the donor rather than of the host, proving the SCN's role as a master pacemaker controlling other rhythmic systems (Ralph *et al.,* 1990). In order to comprehend 24 h timekeeping, researchers had to focus on the clock in the SCN, which they did after learning that it is the site of fundamental regulation of circadian rhythmicity in mammals.

But more recently, scientists have been astounded to discover that circadian rhythms can persist in isolated livers, lungs, and other organs cultivated in a culture dish (i.e., *in vitro*), which are not controlled by the SCN (Yamazaki *et al.,* 2000). These results imply that the majority of biological cells and tissues may be capable of circadian activity regulation. The SCN is the primary circadian pacemaker that controls how cells, organs, and the entire organism are organised into a 24 h time frame. However, these results do not reduce the importance of this position. The SCN emits signals that operate on other nerve cells (i.e., neural signals) or that are also carried to other organs via the blood (i.e., neurohormonal signals), which are the physiological mechanisms underlying this coordination. As of this writing, it is still unknown exactly how the SCN "talks" to the rest of the body or what the characteristics of the circadian signal are (Stokkan *et al.,* 2000).

Human physiological and behavioural processes are almost entirely rhythmic, which results in striking diurnal cycles in human performance levels. Whether brought on by

voluntary circumstances (like shift work or quick time zone changes) or involuntary circumstances (like illness or advanced age), a disturbed circadian rhythmicity in humans has been linked to a variety of mental and physical disorders and may have a detrimental effect on safety, performance, and productivity. In fact, sleep-wake cycle abnormalities may be connected to many negative impacts of altered circadian rhythmicity. The circadian clock affects some rhythmic processes more than the sleep-wake state does, whereas other rhythms are more reliant on the sleep-wake state.

The timing of sleep and wakefulness for the majority of animals is synchronised with all other circadian-controlled rhythms, including the timing of the sleep cycle. But, because of a special cognitive aptitude, humans may ignore their intrinsic biological clock and its rhythmic outputs. Negative consequences may result when the circadian rhythms that regulate the sleep-wake cycle are out of sync (such as during shift work or quick time zone changes).Sleep problems can happen for a variety of known and unknown reasons, in combination to the sleep disturbances brought on by jet lag or shift work. It is also frequently unclear if sleep disruptions are a cause of or a symptom of the illness, despite the fact that disrupted sleep is a defining feature of many human mental and physiological disorders, particularly affective disorders. Although the significance of these rhythm abnormalities in the development (i.e., causation) of the disease is uncertain, other circadian rhythm abnormalities are frequently linked to numerous disease states (Roenneberg *et al.,* 2003).

Chronobiology is a branch of biology that studies when biological events, particularly recurring or cyclical ones, occur in specific organisms. Suprachiasmatic nucleus or nuclei (SCN) is a collection of nerve cells in the hypothalamus of the brain that produces and regulates circadian rhythmicity in mammals (Bunney *et al.,* 2013). Daily rhythms in plants and animals have been noticed since ancient times, according to chronopharmaceutics. Androsthenes, a scribe to Alexander the Great, observed that certain trees' leaves opened during the day and closed at night, demonstrating a clear rhythmicity, as early as the fourth century BC (Luca *et al.,* 2013). Chronopharmacokinetics examines the temporal changes in pharmacokinetic parameters and, as a result, considers how the timing of administration affects these various processes. Many studies have been done on chronokinetics in the last ten years (Wirz-Justice *et al.,* 1999). Chronopharmacodynamics – it has long been understood that pharmacokinetics dosage time dependence (or chronopharmacokinetics) exists. Recent research has shown that the daily rhythmicity of drug-metabolizing enzymes and transporters (DMETs) expression is a crucial determinant of chronopharmacokinetics (Bunney *et al.,* 2012).

Role of Chronotherapy in Diseases:

Central Nervous System:

The suprachiasmatic nucleus (SCN), a core clock in mammals with a circadian timing system, gets information about light through a particular channel as well as data about other pertinent environmental signals, such as the timing of food. Through a number of routes, including arousal centres, the SCN communicates with the rest of the brain. The central clock can control rhythms throughout the body due to its effective combination of output channels, and most tissues have cell-autonomous molecular clocks. As a result, all biological systems are impacted by a broad temporal framework. The idea that this temporal structure is crucial for human health is one of the foundational ideas of the circadian science (Bendeti *et al.,* 2007).

It has been found that people with severe mood disorders have irregular circadian rhythms, which are controlled by the clock gene machinery (Bunny *et al.,* 2013). The symptoms of the severe mood illness can be quickly alleviated by chronotherapeutic therapies that change clock gene mechanisms. About 60% of patients with

affective disorders experience a quick improvement in their gloomy mood after manipulating their sleep-wake cycle (Luca *et al.,* 2013). The duration of sleep is changed by a complete or sleeping too less, and the timing of sleep is altered by partial sleep deprivation or phase advance (Wirz-Justice *et al.,* 1999). Sleep deprivation therapy's (SDT) cause quick yet brief effects (Bendetti *et al.,* 2007). However, a recovery night should activate the aberrant clock gene machinery again since SDT possibly resets it (Janugade *et al.,* 2009). For instance, treating bipolar depression with a combination of lithium, light therapy, and sleep deprivation (Bendetti *et al.,* 2007). Sleep deprivation during the first half of the night and timed daytime exposure to artificial light and light intensity are both relatively new phenomena.Treatments may lessen premenstrual sadness or menopause, which will assist both women and men who suffer from seasonal and other mood problems. The mood disorders were not reduced when isosorbide mononitrate and nifedipine were taken in sustained release dose formulations (Janugade *et al.,* 2009). numerous bodily signals, such as sleep disorder in the autonomous and central neurological systems, demonstrating how intricate time is framework with pulsating and cyclic changes in various frequencies, the disruption of the circadian cycle when a person's physiological condition changes During sleep, psychological processes are aberrant. It could lead to a number of disorders. Additionally, circadian rhythm problems vary from person to person and the person's identification variation would be crucial in addressing specific sleeping issues (Singh *et al.,* 2010). Parkinson's disease reveals many changes to the blood's circadian rhythm increased diurnal blood pressure; hypertension variability and post-meal low blood pressure caused by autonomic dysfunction. But the presence of the disease's circadian cycle has not been studied with clinical data due the daily variations in the phase's motor activity pattern of the illness and the ensuing function of medications are challenging to estimate (Mandal *et al.,* 2010).

Cardiovascular system:

Different 24 h cycles of activity are observed in heart rate, blood pressure, circulating catecholamines, blood coagulation markers, vascular endothelial function, and the autonomic nervous system (Cooke-Ariel *et al.,* 1998; Thosar *et al.,* 2018). There is a change in several cardiovascular functions in the morning . It is significant that these mornings rhythm changes line up with the development of CVD. Morning (6 a.m.–12 noon) appear to see a rise in unfavourable cardiovascular events, such as abrupt cardiac arrest, ventricular arrhythmias, stroke, and myocardial infarction (Thosar *et al.,* 2005; Hemida *et al.,* 2007; Thosar *et al.,* 2018). People who have a heart attack in the morning often have a larger infarct size and a worse prognosis compared to people who have a myocardial infarction later in the day (Tofler *et al.,* 1987). Hypertension is one of the cardio vascular disease. In the population, 35% of adult and 90% of elderly people have this disorder. It has been proven that Stroke and coronary heart disease risk are both increased by high blood pressure and may even contribute to kidney failure, and that treating high blood pressure lowers both morbidity and mortality (Chobian *et al.,* 2003). The management of hypertension may be improved by taking into account diurnal blood pressure variation, using novel antihypertensives, and treating the condition when it is still in its early stage.

The only method that allows for blood pressure regulation over a 24 h period is ambulatory blood pressure monitoring (ABPM) (Thosar *et al.,* 2018), and identifies physiologic and pathologic fluctuations in blood pressure that occur during the day and night (Hemida *et al.,* 2007). Compared to the ABPM, the office blood pressure reading is a worse indicator of target organ damage (Thosar *et al.,* 2018). The likelihood of arterial stiffness (Li *et al.,* 2008), left ventricular hypertrophy (LVH), heart failure, myocardial infarction, microalbuminuria, and vascular dementia (Hemida *et al.,* 2007) is higher in subjects with reduced blood pressure decline,

nondippers (10% decline of the daily value), or those with nocturnal hypertension (Li *et al*., 2007). Additionally, the sudden increase in blood pressure could overburden the vascular system, increasing the chance of an atherosclerotic plaque rupture. Actually, dangerous events like a stroke, myocardial infarction, or sudden cardiac death tend to occur in the morning (Patel *et al.,* 2008).

Night time hypertension may be caused by a variety of causes, including an excessive salt consumption, obesity, renal dysfunction, sleep apnea, or disturbances of the autonomic nervous system (Suarez-Barrientos *et al.,* 2011). The release of melatonin, whose endogenous levels should be at their peak, is believed to be reduced when the overnight blood pressure falls insufficiently. Human circadian melatonin synthesis is impaired and relative melatonin deficiency is brought on by night time light exposure (Butt *et al.,* 2009), which confuses the biological clock and causes chronodisruption (Reiter *et al*., 2006; Reiter *et al.,* 2007), biological circadian rhythms and temporal organisation. One of its effects could be a nondipping BP pattern. Due to circadian changes and evening blood pressure disturbances, the majority of people should not take all of their antihypertensive taking all morning meds (Erren *et al.,* 2009), morning blood pressure management (Thosar *et al.,* 2018). Several antihypertensive medications fail morning blood pressure management (Thosar *et al.,* 2018).

Chronotherapy's potential role in lowering cardiovascular events is still unknown. The Ambulatory Blood Pressure Monitoring and Cardiovascular Events (MAPEC) project, which includes 3000 adult hypertensives, investigates whether chronotherapy will have any additional effects on cardiovascular prognosis beyond lowering clinic-determined daytime or ABPM-determined 24 h mean blood pressure levels (Suarez-Barrientos *et al.,* 2011). It is an exciting and potentially ground-breaking trial. The perhaps favourable findings of this study might change how hypertension is treated in light of the innate variances in blood pressure-regulating mechanisms.

In cardiovascular disease, capillary resistance and vascular reactivity are also higher in the morning and decline later in the day. In the morning, there is a relative increase in blood coagulability due to increased platelet aggregation and decreased fibrinolytic activity. Additionally, blood pressure rises sharply during the early morning wakeup time and is lowest throughout the sleep cycle. According to these results, myocardial ischemia, angina pectoris, acute myocardial infarction, congestive cardiac failure, and sudden cardiac death are also unevenly distributed over the course of a 24-hour period, with more events likely to happen in the early morning or late afternoon.

Vascular responsiveness and capillary resistance are both increased in cardiovascular disease. greater in the morning and decreases throughout the day. Morning fibrinolytic activity declines and platelet aggregation is stronger, increasing blood's ability to clot. Additionally, blood pressure rises sharply during the early morning wakeup time and is lowest throughout the sleep cycle. These findings show that myocardial ischemia, angina pectoris, acute myocardial infarction, congestive cardiac failure, and sudden cardiac death are also unevenly distributed over a 24-hour period, with more expected events anticipated to occur in the early morning or late afternoon. The peak of sympathetic activity and the Renin-Angiotensin-Aldosterone axis occur in the early morning. Variations in ANS are also influenced by other factors such as diet, physical activity, emotional state, and sleep/wake schedule. There are currently chronotherapeutic oral nitrates, for example, antihypertensive medications. Adrenoceptor and calcium channel blocker opposing force whose pharmacokinetics and the circadian cycle has an impact on pharmacodynamics. New drug delivery devices are available, releasing medication during susceptible times from 6 am until noon following the administration of around 10 pm, take

medication (Lemmer *et al.,* 1992; Muller *et al.,* 1998; Hermida *et al.,* 2008).

Respiratory system:

There is controversy around the relative contributions of the circadian and sleep systems to asthma (Tofler *et al.,* 1987), and this problem has not yet been resolved. Initially, it was suspected that sleep systems played the major role. In a study of shift workers, there appeared to be an immediate phase change in the circadian rhythm of peak expiratory flow (PEF), causing the reduction in airway function to remain related to the sleep period (Tofler *et al.,* 1987). However, studies involving nocturnal sleep deprivation have shown a variety of results and conclusions (Clark *et al.,* 1977, Ballard *et al.,* 1989). The most thorough research on this topic has been on changes in lower-airway resistance throughout the night (Clark *et al.,* 1977). Even while the growth is more pronounced during sleep, asthmatics' resistance will consistently increase throughout the night, whether they sleep or not. These results are corroborated by the observation that asthma attacks start substantially less frequently in the first half of the night (Catterall *et al.,* 1986). These records enable us to draw beneficial inferences. First, it seems possible that both circadian and sleep factors contribute to asthma. Additionally, a neural regulatory system linked to sleep undergoes normal alteration as a result of the novel drop in airway function throughout the night. Notably, airway function peaks during periods of increased sleepiness in the afternoon (Montplaisir *et al.,* 1982), and diminishes when sleep pressure subsides during sleep. Sleep appears to be important in the aetiology of asthma, and asthma patients can experience difficulties falling asleep. According to reports, patients with lung diseases or asthma frequently complain about having trouble staying asleep, having poor sleep quality, and being overly sleepy during the day (Hetzel *et al.,* 1980, van Keimpema *et al.,* 1995). Recent, significant research indicates that, even when controls are made for the aforementioned confounders within the analysis, people with asthma are more likely to complain of difficulty falling asleep, early morning awakenings, daytime sleepiness, and daytime fatigue. Studies also reveal that although there is a considerable decrease in patient sleep efficiency compared to a healthy individual in the general population, asthma has no significant effects on the distribution of sleep stages or on sleep delays (Catterall *et al.,* 1986), by this we can say that asthmatic individual suffer from reduced sleep efficient drugs that are used for the asthma β2-Agonists, Theophylline, and Anticholinergic Therapy.

When an airway is blocked or becomes more blocked, theophylline is taken to lessen any negative side effects. It is also given once in the evening to manage nocturnal asthma and comes in the form of SR formulation (Fitzpatrick *et al.,* 1991). Another aspect of theophylline therapy is its capacity to work in conjunction with inhaled corticosteroids as a part of a chronotherapeutic regimen. This interaction is crucial as these inhaled corticosteroids are used by people with severe asthma who were unable to control their nocturnal asthmatic symptoms. For the treatment of asthma, a variety of tablet formulations for the prolonged release of agonists were used (D'Alonzo *et al.,* 1990). Similar to theophylline, little to no information is available on how to evaluate or include a long-acting 2-agonist oral instruction to an inhaled corticosteroid using chronotherapeutic approaches. Salmeterol and formoterol, two long-acting 2-agonists for the treatment of these medications have less side effects than long-acting oral medications (Muir *et al.,* 1992; Rabe *et al.,* 1993), for nocturnal asthma (D'Alonzo *et al.,* 1990, Fitzpatrick *et al.,* 1990). In patients with persistent asthma, salmeterol improves daytime cognitive function and sleep quality (Fitzpatrick *et al.,* 1990, Muir *et al.,* 1992). Glycine 16 polymorphism (Szefler *et al.,* 1991), which is connected to the downregulation of 2 receptors that takes place throughout the night in nocturnal asthma (Selby *et al.,* 1997), must be taken into consideration in any

advancements in 2-agonist therapy. Due to their ability to lower the disease's elevated nightly parasympathetic tone, medications that inhibit the vagal nerve system may be beneficial in the treatment of nocturnal asthma (Turki *et al.,* 1995). Two inhaled cholinergic antagonists, oxitroprium and ipratropium bromide, have been shown in numerous investigations to lessen the morning decline in airflow in asthmatics (Morrison *et al.,* 1988, Coe *et al.,* 1996). Upon learning about them, corticosteroids have been utilised in a chronotherapeutic manner, as their long-acting or long-term oral administration at 8:00am and 3:00pm are more effective than the same doses administered at 3:00pm and 8:00pm in treating nocturnal asthma (Wolstenholme *et al.,* 1989).

According to other research, taking a single dosage of prednisone at 3:00 pm enhances lung function and reduces airway inflammation more efficiently than taking the same amount at 8:00 am and 8:00 pm (Reinberg *et al.,* 1983). Corticosteroids can be effective both when taken orally and when breathed (Beam *et al.,* 1992).

Asthma:

Inflammation of the airways is one of its characteristic of lower body parts which become hyperresponsive as a result of exposure of the respiratory system to numerous environmental stressors. At nights, airway resistance gradually increases in the patient. Most people have asthma. Condition where there is significant circadian fluctuation happens in relation to time. There is rise in asthma prevalence in the early morning hours. The shifting condition of things at night is circadian rhythms which are responsible for biological activity in bronchial patency; hyper-reactivity of the airways to dust in the home, histamine, and acetylcholine; and histamine, epinephrine, cortisol, and cyclic AMP (Pincus *et al.,* 1995).

Gastrointestinal Tract:

List of diseases:

GI Diseases and GI carcinogenesis are circadian based therapeutic interventions which includes pharmacotherapy, chronotherapy. Melatonin in GI diseases (Muir *et al.,* 1992). There is a link between shift work, which is practised by an estimated 16% of the population, and a number of illnesses, including those that influence metabolic functioning. Working shifts was associated with an increased risk of being overweight, obese, and developing type 2 diabetes (T2D), in a meta-analysis covering more than 300000 population (Smolensky *et al.,* 1999, Lui *et al.,* 2018). It was interestingly found that several metabolic organs, including the pancreatic islets, liver, adipose tissue, skeletal muscle, and the gastrointestinal (GI) tract, express cell-autonomous clocks that collaborate with one another to regulate diurnal metabolic homeostasis (Zyonic *et al.,* 2006; Hoogerwerf *et al.,* 2007; McCarthy *et al.,* 2007; Marcheva *et al.,* 2010; Rey *et al.,* 2011; Petrenko *et al.,* 2017; Vetter *et al.,* 2018). The GI tract plays a distinctive role in the "metabolic clock" since it is positioned to be the first point of nutrient contact after meal ingestion. Although digestion and food absorption are effective- to be the key tasks of the gut, this integrated system of different tissues also plays a crucial role in preventing metabolic inflammation by maintaining barrier integrity and by having a functioning immune system.

We concentrate on addressing how the GI tract regulates circadian biology. All of the body's nucleated cells have been shown to express clock genes on their own (Rakshith *et al.,* 2016).

Peptic ulcer:

Peptic ulcer production is characterised by desynchronosis, which is a disruption of the gastrointestinal tract's regular rhythmic activities. By applying this theory, anti-ulcer therapy's efficiency is increased by 10–15%, greatly lengthening the duration of clinical remission. The results of the earlier pH monitoring should be taken into consideration while differentiating the antisecretory treatment chronoregime. Patients are advised with excessive stomach acidity to take antisecretory medications (proton pump inhibitors, M-anticholinergics, and H2-receptor blockers). The majority of their stomach acid is

secreted once a day in the late afternoon or early evening. Astringents, coatings, and reparants should be applied later in the day, ideally in two steps.

Both at night and during the day, antacids are beneficial. Antisecretory medications should be administered twice daily to patients with high levels of gastric secretion, and their administration in the evening should be preceded by the peak hour of stomach acidity (7–8 pm). Famotidine, ranitidine, and other H2-receptor blockers can be given once at night (7–8 pm) in the spring and summer to prevent ulcer exacerbations, whereas gastrotsepin and other M-cholinoblockers can be introduced once at night (7–8 pm) in the fall (Marthenoc *et al.,* 2020).

Circadian rhythms affect a number of gastrointestinal tract activities, with gastric acid production rising during night. While less bowel motility, stomach emptying is slower at night. The treatment of duodenal ulcers depends in large part on the suppression of nocturnal acid. For active duodenal ulcers, a once-daily dose at bedtime is advised when using H2 antagonists. The risk of intestinal infection and infestation, potential bacterial overgrowth, and probable N-nitrosamine formation are all problems that can be resolved by chronotherapy, which is administered at night to inhibit H2 receptors (Timoffev *et al.,* 2012).

Urinogenital Tract:

Under the control of an organism's sleep/wake cycle, the pineal gland secretes N-acetyl-5-methoxytryptamine (melatonin) (Timoffev *et al.,* 2012). The suprachiasmatic nucleus (SCN) in the hypothalamus receives the light stimulation, which is subsequently sent on to the pineal gland by the retina's ocular cells. Melatonin is primarily secreted at night and is inhibited by light. It interacts with the SCN's master clock and peripheral clocks in many organs, including the kidneys, having an impact on circadian rhythmicity and controlling a variety of biological processes (Humphries *et al.,* 1991).

In addition, biochemical processes that are either receptor-mediated or receptor-independent safeguards the kidneys. It controls mitochondrial metabolism, encourages the production of ATP, and guards against nitrative damage to the mitochondria. Melatonin plays a significant function in chronic injury by inhibiting pro-inflammatory mediators and starting an anti-inflammatory protective action (Rahman *et al.,* 2018). Furthermore, melatonin maintains the bioavailability of nitric oxide (believed to decline in hypertension) through acting on the melatonin receptor MT2 to enhance endothelium-dependent vasorelaxation in the mesenteric arteries (MAs) of spontaneously hypertensive rats (SHRs) (Hrenak *et al.,* 2015). In mice, long-term melatonin treatment increased the expression of vasoprotection-related markers and reduced inflammation and oxidative stress (Qui *et al.,* 2018). Melatonin is an essential regulator of the circadian sleep-wake cycle due to its pleotropic effects in addition to levels that peak at night and progressively fall during the day in healthy individuals. In contrast, older individuals have lower levels of circulating melatonin. Moreover, melatonin's acrophase is impacted by a number of clinical conditions, such as the CKD-related non-dipper type of hypertension (Agabiti-Rosei *et al.,* 2017).

Chronotherapy in a Rare Disease Such as Smith-Magenis Syndrome:

A complex neurodevelopmental condition called Smith-Magenis syndrome which comprises intellectual disability. The RAI1 gene is located on chromosome 17p11.2, which is the source of 90% of the cases; other cases are attributable to mutations in the same gene.

It is interesting to note that behavioural problems tend to be more severe - the speech delay and sleep disturbances. Sleep disorders link overnight agitation to excessive daytime sleepiness. They are supported by a cycle of melatonin secretion that is reversed. However, combining the morning intake of beta-blockers with the night time consumption of melatonin may

significantly improve the circadian rhythm issues (Patil *et al.,* 1984; Smith *et al.,* 1986; Russcher *et al.,* 2017).

According to one of the earliest research on sleep disturbances, 62% of SMS users experienced sleep difficulties, including trouble going asleep, difficulty remaining asleep, and numerous nighttime awakenings (Stratton *et al.,* 1986). Sometimes, paradoxical sleep—or REM sleep—was completely absent (Greenberg *et al.,* 1991). Since then, numerous research have investigated SMS users' sleep cycle and supported earlier findings. They also presented the idea of an abnormal chronology of the light-dark cycle, which involves the necessity for many daytime naps in addition to early bedtimes and early wakeups ((Greenberg *et al.,* 1991; Greenberg *et al.,* 1996; Smith *et al.,* 1998; De Leersnyder *et al.,* 2001).

Neuro-developmental problems of sleep are typically multifactorial and poorly understood. There is an intriguing general disruption of the sleep-wake pattern in SMS, along with melatonin secretion that was inverted. The pineal gland primarily produces melatonin from 5-hydroxytryptamine (5-HT). The pineal gland often secretes at its highest levels in the middle of the night. Dosing plasma melatonin and urinary metabolites revealed that nearly all SMS patients experienced a phase change in their melatonin circadian rhythm (Smith *et al.,* 1998, De Leersnyder *et al.,* 2001). Melatonin secretion started at roughly 6 AM and peaked at around 12 PM, with an offset at around 8 PM (Smith *et al.,* 1998).

The description of a successful therapy for SMS disruptive sleep disorder is that the Light inhibits the generation of melatonin because it is stimulated by changes in luminosity. This light-driven process passes through the retinohypothalamic tract from the retina to the suprachiasmatic nuclei of the hypothalamus. The primary biological clock of mammals resides in these nuclei, which also produce the circadian rhythms of the body. There have been several clock genes identified. They are in charge of all environmental-driven circadian rhythms. These genes' expression oscillates roughly every 24 hours in accordance with the circadian rhythm (Potocki *et al.,* 2000). Only a little amount of melatonin is secreted during the night in SMS, with an aberrant peak in secretion occurring about noon (Potocki *et al.,* 2000; De Leersnyder *et al.,* 2001; Piggins *et al.,* 2005). So, finally to an assumption that the sleep-wake circadian rhythm problems in SMS patients are caused by a malfunctioning clock gene.

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