

## Human Circadian Rhythms and their Health Implications

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### ABSTRACT

*Biological rhythms represent fundamental property of most living organisms ranging from several forms of bacteria and single-cell organisms to multicellular plants and animals. Our body comprises of a whole system of biological clocks that coordinate beautifully with each other and also with the central clock that remains entrained with the external environment so that we live in harmony with our environment. In this article, we present an overview of the biological rhythms seen in organisms followed by a description of the human circadian system. The importance of the circadian system in metabolism affecting our metabolic health and behaviour has also been discussed. This review also covers how disruption of these circadian rhythms could cause several diseases in our body and includes some corrective measures for their treatments.*

**Keywords: Human Circadian Rhythm, Metabolic Disorders, Jet Lag, Shift Work, Sleep Disorder**

### 1. Introduction

#### 1.1. Overview of Biological Rhythm

For millions of years, organisms live in a complex environment of many interacting components. Environmental factors continually and most often predictably change from one moment of time to the next. Rotation (24 hrs) and revolution (365.25 days) of earth around sun and that of moon around the earth regulate the periodic oscillations of geophysical events

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like day and night (solar day), lunar month, year, season and tidal flow and ebb etc. Life on earth has been subjected to strict regimen of these cyclic changes since its very origin. Through evolutionary time, these environmental cycles have left their stamp on the basic biology of the organisms. About 3 billion years ago in the course of evolution of life, the recurring solar day and geophysical pattern served as a template upon which were fashioned biological sequences of casually related events. For successful survival, organisms have evolved mechanism(s) to make use of the highly predictable environment by timing their biological functions for successful survival. Those who failed to evolve the mechanism to respond and to adapt to ever changing environment probably perished.

The revelations of temporal organisations in biomes are known as 'biological rhythms' which are ubiquitous among living organisms. The science that objectively quantifies and investigates mechanism of biological time structure, including rhythmic manifestation of life is called "Chronobiology" (Halberg *et al.*, 1972). Persons studying the patterns of rhythms that repeat themselves cyclically are called "Chronobiologists". Rhythms are present among organisms from prokaryotic to eukaryotic plants and animals and in higher vertebrates including human. They are found at all levels of biological organisation from the lowest to the highest levels which include from the cell, tissue, organ system to activities of an organism as a whole. Bioperiodicity is also evident in behaviour and in changing responsiveness of the organisms to all factors of the environment, drugs etc. (Brown, 1972). The bioperiodicity may be of varying duration ranging from a fraction of seconds to years.

The biological rhythms can be categorized into different types on the basis of duration of each cycle:

**(a) Circadian rhythm:** A rhythm of approximately a day (~24 hours) such as sleep-wake cycle.

**(b) Infradian rhythm:** A rhythm of more than the period of circadian rhythm, i.e. with a frequency less than one cycle in 28 hours, e.g. the half weekly cycle (circasemiseptan) of sudden human death, estrous cycle.

**(c) Ultradian rhythm:** A rhythm with a period of less than that of circadian rhythm (less than 20 hours) e.g. pulsatile episodic secretion of hormones.

**(d) Circaseptan rhythm:** A rhythm with a period of about a week. Some hormonal rhythms follow a roughly weekly cycle, as do patterns of kidney transplant rejection.

**(e) Circatriginton or Circamensual rhythm:** A rhythm with a period of about a month, e.g. human menstrual cycle.

**(f) Circannual rhythm:** A rhythm with a period of about a year (~365.25 days). Seasonal and reproductive rhythms in some animals follow a circannual cycle.

**(g) Diurnal rhythm:** This rhythm is an extension of circadian rhythm but the individuals must be in synchrony with the day and night cycle where they awake and function normally during daylight hours and sleep during night hours. Note that it is possible to have a circadian cycle without being diurnal but not vice versa.

Cues providing information to organisms about periodicity of environmental variables are called 'Zeitgebers' (German word 'time givers'). Zeitgebers are the entraining agents defined as those cyclic environmental cues that can entrain free running, endogenous rhythms. Depending on their habitat conditions, different organisms use different environmental cues as zeitgebers (Dixit and Singh, 2016). In most terrestrial organisms, the daily light-dark cycle is used as zeitgeber which is not surprising since daily light-dark cycle is usually the most consistent environmental cue. Others may use temperature cycle, food availability, social factors etc. as zeitgebers. Circadian rhythms persist in the organisms even in the absence of these periodic external information suggesting that they are endogenous. They are built into organisms and programmed into their genetic material being the products of genes. The biological clock is a part of our body, which generates a number of biological responses regulated by cycles. Its control centre is located in the supra chiasmatic nuclei (SCN) of the hypothalamus in the brain. In particular, it regulates body temperature and the cycle of sleeping and wakefulness with waking occurring in the morning and the need for sleep at night. Various studies indicate that SCN play a major role in generating circadian rhythms in mammals. Therefore, it is also known as the 'master clock'. SCN are small paired structures located in the anterior hypothalamus above the optic chiasma. They receive visual inputs for light-dark entrainment, mostly directly through the retinal pathway. Thus, the circadian organisation has three components- a pacemaker, an input for entrainment of the pacemaker and an output pathway for the expression of overt rhythm.

Among vertebrates, most observed form of biological rhythm is circadian rhythm. A circadian rhythm is an endogenously driven oscillating biological rhythm that resets approximately every 24 hours and can synchronize the body functions with the external temporal environment by photic (light) and non-photic (e.g. temperature, food etc.) cues (Czeisler

and Gooley, 2007; Dixit and Singh, 2014). It helps to optimize our energy use, therefore promoting survival (Foster and Wulff, 2005). It is derived from the Latin words *circa*=around, *dien*=day (Halberg, 1959). This 24-hour system exists in many forms of life on earth and is conserved throughout evolution (Loudon, 2012). The circadian cycle regulates changes in various performances, endocrine rhythms, behaviour, sleep timing etc. (Duffy *et al.*, 2001). The interesting thing about circadian rhythms is that even in the absence of external stimuli, almost 24-hour rhythms are maintained (Czeisler and Gooley, 2007).

### **1.2. Human Circadian Rhythms**

Before going further with human circadian rhythm, let's just take a short glimpse of some eminent scientists and their valuable contributions towards the development in the field of Chronobiology. A renowned Swiss botanist, Augustin Pyramus de Candolle (1778-1841) was honoured as the first person to describe a research that demonstrated the endogenous nature of circadian rhythms. Candolle studied the rhythm of the folding and opening of the leaves of sensitive plant. He observed that the rhythm persisted under continuous illumination and noticed that the period of the rhythm (i.e., duration of the cycle) was shorter than 24 hours. He demonstrated the existence of endogenous circadian clock. Also, a group of three workers, Jurgen Aschoff, Franz Halberg and Colin Pittendrigh carried out very influential research in modern circadian physiology. Aschoff's discovery and interpretation of the phenomenon of "spontaneous internal desynchronization" (Aschoff *et al.*, 1967; Aschoff and Wever, 1976) was a driving force in circadian physiology for decades. Halberg was the creator of the terms "circadian" (Halberg, 1959) and "chronobiology" (Halberg, 1969). Most of our current understanding of the operation of the circadian clock is derived from Pittendrigh's work with flies (Pittendrigh, 1954; 1966) and rodents (Pittendrigh and Daan, 1976; Daan and Pittendrigh, 1976).

Kleitman (1963) was the first to study human circadian rhythms. In 1938, he performed an experiment on two subjects deep within an underground cave, the Kentucky's Mammoth Cave considered as the longest known cave on earth. These people were shielded from periodic environmental cues and lived on non-24-hour sleep/wake, light/dark and meal schedules. They were kept out from the influence of the earth's 24-hour day. He measured the daily rhythm of their body temperature and revealed that in one of the subjects, the circadian temperature rhythm was endogenously generated, persisting for a month with a near 24-hour period despite imposition of a 28-hour rest/activity schedule. These facts strongly suggest that a physiological rhythm could oscillate even in the absence of periodic changes in the environment. This study therefore established the endogenous and physiologic nature of human

circadian rhythms for the first time.

Among various rhythms in human body, sleep/wake cycle is perhaps the most overt manifestation of circadian rhythms. Other rhythms control much of the human body's normal functions, including performance, behaviour, endocrine secretions, heartbeat, and body temperature. Considering various reports, the frequency of heart attack peaks between 6 a.m. and noon (Muller *et al.*, 1985; Rocco *et al.*, 1987) and people having asthma suffer most prevalent attack at night time (McFadden, 1988). Interestingly, most human babies are born predominantly in the early morning hours (Glattre and Bjerkedal, 1983; Kaiser and Halberg, 1962). While these patterns do not necessarily indicate that the events are driven by the circadian pacemaker, they do suggest temporal order in the functioning of the human body. This temporal organization appears to be beneficial; the human body is prepared for routine changes in state, such as awakening each morning, rather than simply reacting after shifts in demand (Moore-Ede, 1986). In addition, these regular cycles in the body present considerations for diagnosis of health problems and for the timing of medical treatment (Halberg, 1977; Minors and Waterhouse, 1987).

Apart from the above mentioned physiological functions, many other findings suggested that the secretions of several hormones also occur in a cyclic fashion (Van Cauter, 1989; Dixit and Singh, 2013). For example, the daily surges of prolactin and growth hormone appear to be triggered by sleep (Van Cauter, 1987). Sex hormones are secreted at varying levels throughout the day, the pattern of secretion reflecting the fertility, reproductive state and sexual maturity of the individual. Glucose concentration in the blood peaks late at night or early in the morning (Van Cauter, 1989) and insulin secretion peaks in the afternoon (Nejean, 1988). These physiological variables are not the only human functions that exhibit circadian rhythms. In addition, human performance, including psychological processes and mental functions, also exhibits circadian fluctuations (Colquhoun, 1981). Diverse components of human performance, including memory, reaction time, manual dexterity, and subjective feelings of alertness, have been dissected experimentally to ascertain when they peak during the course of a day and how they are affected by circadian rhythm disruption. According to Robert (1995, 2000), the human immune response also follows a circadian cycle (Fig. 1). All these functions are primarily regulated by the circadian clock, a cluster of nerves located on the hypothalamus in the brain. This circadian clock relies on environmental cues to regulate its function, primarily light cues from the day/night cycle. Abrupt shifts in routine, such as shift changes, or travel resulting in jet lag can alter the sleep wake cycle and have a detrimental effect on human health. If the alterations in biological

rhythms are strong enough they may lead to various disorders that affect human health.

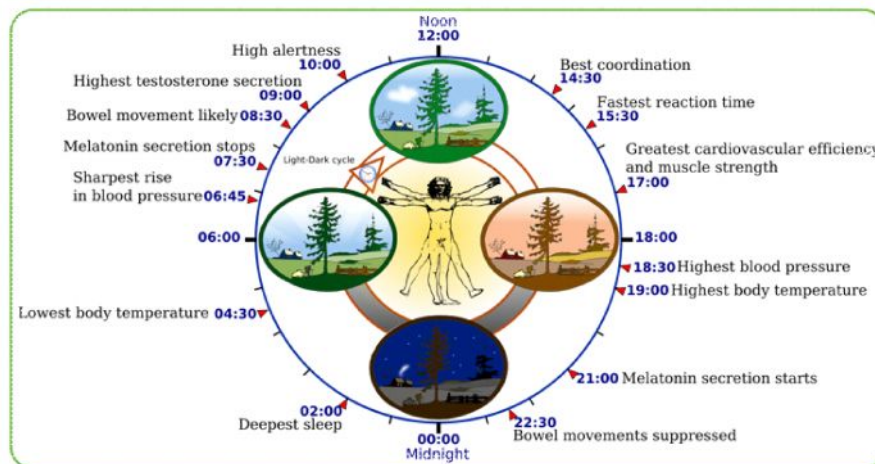


Fig. 1: Human circadian rhythms (source: [http://en.wikipedia.org/wiki/Circadian\\_rhythm](http://en.wikipedia.org/wiki/Circadian_rhythm)).

## 2. Disruption of Circadian Rhythms and Health Implications

Circadian rhythms can be maintained and free run in the absence of a source of entrainment. However, misalignment of internal oscillations with the external environment results into circadian rhythm de-synchronization. This is circadian disruption. It is caused by circadian misalignment between internal clocks and external cues or loss of circadian rhythmicity due to deregulation of clock genes (Srinivasan *et al.*, 2010). When body rhythms conflict with those in the environment, function is compromised until the rhythms are realigned. Circadian rhythms are controlled by a cyclical expression of circadian genes, and mutations in these genes result in a modification/disruption of the circadian oscillator. Thus, circadian rhythm disruption occurs by both genetic (polymorphisms in core clock genes) as well as environmental factors (such as light at night or artificial light), increasing the risk of various metabolic syndromes, health diseases and disturbance in hormone release (Fig. 2). As melatonin rhythm is entrained by light cues, light exposure at inappropriate time results in suppression of melatonin at times when it is normally released (Arendt, 2010). Further, low frequency electromagnetic (EM) waves emitted from power lines and electrical appliances have been found to disrupt our circadian rhythms, affecting melatonin rhythms by interfering with its production and secretion

(Brainard *et al.*, 1999). The invention of artificial light has revolutionized ways of living by altering behavioural and social attitudes, including sleep patterns (Vollmer *et al.*, 2012). Even though artificial light is not as efficient as natural light in circadian rhythm entrainment (Kohyama *et al.*, 2011), it can contribute to circadian disruption (Czeister and Gooley, 2007). Association between disruption of the circadian clock and risk of metabolic syndrome, obesity and Type 2 diabetes has been well established (Arble *et al.*, 2015). Also, circadian disruption in humans may increase diabetes risk via inflammatory mechanisms independent of sleep loss, leading to decreased insulin sensitivity without compensatory increase in insulin secretion (Qian and Scheer, 2016). Several environmental and genetic factors can cause disruption of the circadian rhythms. This disruption could contribute to multifactorial diseases such as cancer, cardiovascular disease and metabolic syndrome (Fig. 2).

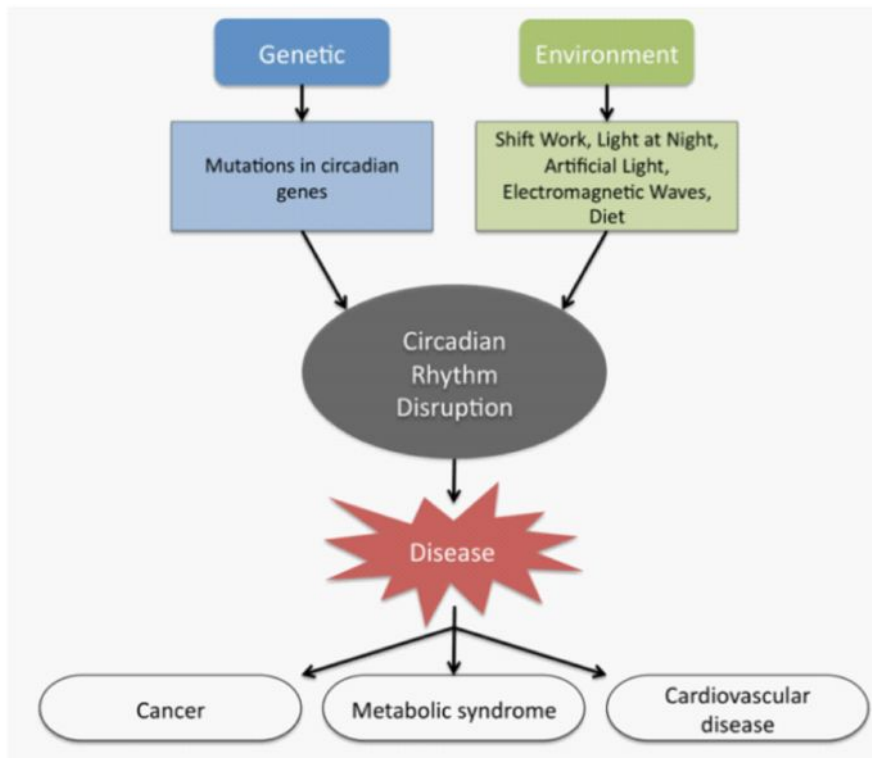


Fig. 2. Circadian rhythm disruption and its consequences adapted from Rüger and Scheer (2009).

High causes of mortality in modern societies have shifted from infectious or communicable to non-infectious or non-communicable chronic diseases like hypertension, hyperlipidemia, diabetes, cancer, coronary artery disease and diseases of chronic inflammation (Mokdad *et al.*, 2004). Non-communicable diseases (NCDs) have been found to be the leading causes of death since 2008, accounting for almost 65% of all causes of death worldwide (WHO, 2010). Cardiovascular disease (CVD) is one of the most significant causes of death in developed countries caused by circadian disruption (Prasai *et al.*, 2008; Paschos and Fitzgerald, 2010). The cardiovascular system in man exhibits daily and seasonal rhythms. Heart rate, cardiac output and blood pressure show daily rhythms (Durgan and Young, 2010). The SCN stimulates the pineal gland to produce melatonin at night. Higher chance of developing heart failure or cardiac death is found to occur in patients with lower nocturnal concentrations of melatonin (Sahna *et al.*, 2005). An interesting study by WHO (2010) has shown that urban dwellers are more prone to NCDs as compared to rural dwellers in developed and developing countries and this difference may be due to the modern changes in lifestyle. Urban dwellers are found to consume more processed and convenient foods, and have less physical activity (WHO, 2003). As a result, these people are more prone to obesity, diabetes and hypertension due to the imbalance of energy intake and expenditure (Sobngwi *et al.*, 2002). It has been observed that a deregulation of the sleep-wake cycle affects the number of circulating lymphocytes (Redwine *et al.*, 2000) and the resulting immune changes cause many adverse health effects. These inflammatory responses have been implicated as risk factors in diseases including obesity, diabetes, cancers, neurodegenerative and cardiovascular complications (Sarkisian *et al.*, 2017). Further, epidemiological observations have linked circadian rhythms with cancer risk e.g. women working with more hours per week or year at night show increased risk of breast cancer. In addition, urbanization is associated with night shift work and its link to metabolic syndrome (a multifactorial NCD) has been established (Pietrojusti *et al.*, 2010). We can see a significant change in lifestyle since the industrial revolution and as societies become more industrialized, the demand for day/night activities and services increase (Parliament Office of Science and Technology (POST), 2005). Extreme use of computers, particularly at night, is another aspect of modern life that leads to circadian disruption and should be reduced. Abnormalities in sleep/wake rhythms, appetite and social rhythms have been observed in depressive disorders, schizophrenia, bipolar disorder, anxiety disorders, seasonal affective disorder (SAD), and a variety of other

central nervous system (CNS) disorders (Lamont *et al.*, 2007; McClung, 2007).

Chronotherapeutics is the prevention and treatment of disease based on knowledge of circadian rhythms. It helps in improved diagnosis of diseases by monitoring daily oscillations in vital signs (Refinetti, 2006). Chronopharmacological treatments of hypertension, cancer and asthma exemplify the use of chronobiological information to maximize pharmacological effects and minimize side effects. Some selected circadian disorders and their treatments are listed below:

**2.1. Circadian Rhythm Sleep Disorders:** These are very common disorders caused by misalignment between the sleep period and the physical or social 24-h environmental cycle. The blind individuals and night-shift/rotating-shift workers are more prone to develop these sleep disorders. The circadian rhythm sleep disorders (CRSD) include:

- i. Delayed sleep phase (common in adolescents)
- ii. Advance sleep phase (often in the elderly)
- iii. Sleep-wake cycle irregular pattern
- iv. Non 24-h sleep-wake cycle.
- v. CRSD due to work at irregular hours

**(i) Delayed Sleep Phase Disorder (DSPD):** DSPD is characterized by a delay or late sleeping and waking, on most nights, a condition in which the endogenous circadian pacemaker is not aligned to the desired sleep-wake schedule, with sleep and wake occurring earlier or later than desired. This desynchrony is referred to as phase misalignment (Dijk and Czeisler, 1995) and is thought to arise due to a delay in the circadian pacemaker (American Academy of Sleep Medicine, 2014). DSPD causes longer than normal circadian period (e.g., 25 h) (Campbell and Murphy, 2007). Its prevalence in the general population is 7 to 16 per cent. The teenagers and individuals around 20 years of age are most commonly affected (Duffy and Czeisler, 2002; Garcia *et al.*, 2001). About 10 per cent of patients with chronic insomnia seem to have DSPD (American Academy of Sleep Medicine, 2005). It is also associated with a number of negative health consequences and significant functional impairments like job performance, financial difficulties and marital problems in adults (Alvarez *et al.*, 1992). Adolescents with DSPD show poorer school performance (Saxvig *et al.*, 2012), dysfunctional school behaviours and under achievement (Szeinberg *et al.*, 2006) and are more

likely to engage in smoking (Glozier *et al.*, 2014), excessive alcohol (Saxvig *et al.*, 2012) and caffeine use (Lovato *et al.*, 2013). A useful way of treating DSPD is to further delay sleep initiation, at a rate of two or three hours every 2 days, until the desired time of sleep period (ideally from 2330 to 0700 h) is achieved. As prolong wakefulness seems to be easier for the patients than to anticipate sleep, so this method may be an acceptable one. The patients can also be treated with phototherapy (exposure to bright light), applied during 1 or 2 h at the desired waking up time by setting a timer to turn bright lights on which can help to readjust the biological clock after a few days. Timed melatonin administration is also recommended for DSPD treatment. A dose of 0.3 to 3 mg of melatonin late in the afternoon advances the sleep phase (Sack *et al.*, 2007).

**(ii) Advanced Sleep Phase Disorder (ASPD):** ASPD is a rare disorder than DSPD and is characterized by 3- to 4-h advanced sleep onsets and wake times relative to desired normal times on most nights (Sack *et al.*, 2007; Reid *et al.*, 2001). It may be associated with a shorter-than-normal circadian period (e.g., <24 h) (Jones *et al.*, 1999). Its prevalence in general population increases with age (American Academy of Sleep Medicine, 2005) and is estimated to affect about 1 percent of middle aged adults and the elderly persons. Persons suffering from ASPD engage in the use of alcohol, sedatives, hypnotic agents or stimulants to treat insomnia and sleepiness symptoms, which can lead to abuse of these substances. The simplest measure to treat ASPD is to delay sleep time, at a rate of one to three hours every 2 days, until the desired sleep period is achieved. The elderly population can indulge themselves in physical, mental or social activities that can keep them awake until the desired sleeping time. Phototherapy, applied late in the afternoon for one or two hours, can readjust the biological clock within a few days. Exposure to artificial light in winter months may compensate the seasonal variations of light/dark cycle duration and also in locations at high latitudes (Sack *et al.*, 2007).

**(iii) Irregular Sleep-Wake Rhythm:** Persons affected by the irregular sleep-wake type of CRSD have an undefined pattern of sleep-wake rhythm. This type shows either chronic insomnia or sleepiness, depending on the particular necessity at that moment. Patient's sleep consists mostly of naps at any time of day or night instead of one consolidated sleep period. This pattern is mostly seen in association with neurological diseases, such as dementia, and in children with intellectual disabilities. It is the result of inadequate sleep hygiene and lack of exposure to synchronizing external agents, such

as sunlight, physical and social activities, particularly in the elderly (Martinez and Lenz, 2010). Strict compliance with desired time of sleep period together with filling waking hours with physical and social activities, can correct irregular sleep-wake rhythm. Intense light, applied for one or two hours at the desired waking time, can synchronize internal clocks. A dose of 3 mg of melatonin late in the afternoon can be useful to control this symptom in children with psychomotor deficit (Sack *et al.*, 2007).

**(iv) Non 24-h Sleep-Wake Syndrome:** This disorder, also known as non-entrained or free-running type CRSD is characterized by sleep symptoms that occur as a result of the longer (approximately 25 h) duration of the circadian timing mechanism cycle. Lack of light signal in individuals unable to receive the light-dark external cues for the circadian clock system is one major factor causing this syndrome in which individuals do not keep a regular 24-h sleep-wake schedule. This syndrome, occurring mostly in blind individuals and rarely in individuals with normal vision (mostly teenager males) show free running circadian rhythms (Hayakawa *et al.*, 2005). Abuse of alcohol, hypnotic, sedative, and stimulant agents exacerbate the disorder and it can become chronic if left untreated. It can also lead to depressive symptoms and mood disorders. Such syndrome is common in blind persons and individuals with irregular light-dark patterns because of night-shifts or rotating schedules. Administration of melatonin at low physiological doses (around 0.5 mg), late in the afternoon can regulate non 24-h sleep-wake syndrome (Skene and Arendt, 2007).

**(v) CRSD due to work at irregular hours**

**(a) Jet lag disorder:** Circadian rhythm disruption in travellers lead to jet lag or time zone change syndrome. It is caused by the temporary divergence between the environmentally adequate sleep-wake cycle and the endogenous cycle generated by the circadian timing mechanism, usually after a trip during which at least two time zones are crossed. Though, some people recover quickly, others take time. Our body's clock will eventually reset itself, but this often takes a few days; starting from one to two days after the arrival and resolves spontaneously within one week. The affected people complain of insomnia or sleepiness, impaired alertness, cognitive problems, malaise, fatigue, disorientation, mental dysfunction, tiredness, loss of concentration, anxiety, depression, irritability, mood disorder and gastrointestinal illness. This disorder affects all age groups, though older people can present more pronounced symptoms. The severity of jet lag

symptoms correlates with the number of time zones crossed. More the number of time zones, the more severe the symptoms. Chronic jet lag can also have serious effects on memory function, which elevate the cortisol levels and significant cognitive impairments (Cho, 2001). It has been known that jet lag cause a shift in behavioural, physiological, and hormonal rhythms in humans (Desir *et al.*, 1981) and it is of great interest to circadian researchers due to the quick misalignment and need for subsequent re-entrainment of the circadian system. People travelling to a different time zone should be re-entrained to the new LD cycle. Exposure to light or light avoidance at a particular time can help to synchronize local clock time to internal clocks. In the first days, travellers to the East should avoid light at destination in the hours corresponding from 2100 to 0300 h at their origin, i.e., at the time of melatonin peak in their internal clocks and they should receive bright light when the hour at origin is between 0500 and 1100 h. People flying to the West should avoid light from 0500 to 1100 origin time and they should be exposed to bright light between 2100 and 0300 h origin time (Chesson *et al.*, 1999). Caffeine is useful to reduce fatigue (Beaumont *et al.*, 2004). Travellers crossing more than four time zones are recommended to take melatonin (Buscemi *et al.*, 2006). Maintaining hydration, eating fruits, taking naps and avoiding ingestion of alcohol are useful suggestions (Waterhouse *et al.*, 2007). Outdoor exercises have also been reported to decrease jet lag symptoms in airline pilots (Shiota *et al.*, 1996).

**(b) Shift work disorder:** Increased work demands in this century has resulted in the formation of a work-driven on-demand “24-hour society” in which regular sleep-wake cycles are not considered a necessity. The invention of electric lights has made light omnipresent 24 hours a day and permitted round-the-clock shift work. Many people across the world are employed as shift workers (Bureau of Labor Statistics, 2005) and are forced to adopt a work-rest schedule that does not match the 24 hour solar day, resulting in “circadian misalignment”. As diurnal species, humans typically sleep at night and are awake during the day. Consequently, engaging in shift work often induces conflict between people’s internal body clocks and the actual time of day. These conflicts make shift workers work when their body is preparing for sleep, and sleep when their body is preparing for wakefulness. Working at irregular hours often causes sleep disorders characterized by complaints of insomnia, excessive sleepiness, shortened total sleep time and inadequate sleep quality. This disorder, besides impairing work performance, also increases the risk of accidents due to decreased alertness (Schwartz and

Roth, 2006) and also causes physical and mental health diseases such as hypertension (Pickering, 2006), breast cancer, uterine and cervical cancer (Haus, 2006) and cardiovascular diseases (Morikawa *et al.*, 2005; Karlsson *et al.*, 2001, 2005; Tuchsien *et al.*, 2006; Haupt *et al.*, 2008; Prasai *et al.*, 2008; McCubbin *et al.*, 2010). Shift-workers favour irregular eating times and are therefore associated with altered insulin sensitivity and higher body mass leading to increased risk for obesity and inflammation (Delezie and Challet, 2011). Therefore, night shift work is a real health hazard. The hazards of artificial light are not limited to disturbance of entrainment only but disrupted sleep-wake schedules lead to constant light exposure at night that can result in severe disruption to melatonin rhythms. Further, night shift work is clearly most important in certain occupations like healthcare and aviation industries where people are mostly awake for many hours and are often unable to maintain sleep patterns that correspond to the natural human circadian rhythm. This may develop fatigue leading to many accidents and unwanted situations. Many studies have shown that the development of metabolic syndrome (Pietrojusti *et al.*, 2009) and incidence of coronary heart disease (CAD) (Kawachi *et al.*, 1995) were strongly associated with night shift work in nurses. Furthermore, the number of people experiencing circadian disruption on a daily or weekly basis is expected to increase as the trend for a nonstop 24 hour society spreads and more and more people voluntarily shift to more nocturnal activity. Approximately, 20 per cent of the work force in industrialized countries works during variable hours and that 2 to 5 per cent of these workers suffer from some sort of sleep disorder (American Academy of Sleep Medicine, 2005). It is advised that at least 48 hours should be given between shift changes to ease the transition between shift changes and less frequent rotations should be considered. Developing a regular schedule, avoiding caffeine or physical activity before sleep, and wearing eye masks/ear plugs while sleeping ensure good sleep quality. Appropriate exposure to bright light, dim light and darkness can help in the alignment of circadian rhythm to shift work. Especially in case of night shift workers, exposure to intense light during work and avoidance of light by the use of dark glasses while leaving work can prevent melatonin secretion at night and stimulate it during the day and thus help to synchronize sleep to melatonin secretion. To fight insomnia, short-term use of a hypnotic agent or melatonin prior to sleeping can be helpful (Sack *et al.*, 2007). To avoid sleepiness, one can take nap before the shift or during the shift break or can take caffeine (Wyatt *et al.*, 2004).

It is important to mention little about what measures should be taken to avoid circadian disruption and resulting disorders and diseases, i.e., prevention. In all CRSDs, it is fundamental to enforce the adequate use of sleep hygiene measures (Table 1).

**Table 1. Sleep hygiene measures for patients with circadian rhythm sleep disorders.**

<p>Show consideration for the biological clock:</p> <ul style="list-style-type: none"> <li>Maintain regular hours for sleeping and getting up, using an alarm clock.</li> <li>Avoid variations of over 2 h in getting up time on weekends.</li> <li>Avoid staying in bed for over 7.5 h, including naps.</li> <li>Exercise at least 6 h before sleeping.</li> </ul>
<p>Relax and sleep:</p> <ul style="list-style-type: none"> <li>Avoid exciting or emotionally disturbing activities near bed time.</li> <li>Avoid activities that demand a high level of concentration immediately before going to bed.</li> <li>Avoid mental activities such as thinking, planning, or recollecting in bed.</li> </ul>
<p>Beware of drugs and disruptive environments:</p> <ul style="list-style-type: none"> <li>Prior to sleeping, avoid products that contain alcohol, tobacco, caffeine or any substance that acts on the CNS.</li> <li>Ensure that the bed is comfortable, with mattress, sheets, and covers appropriate for the temperature.</li> <li>Ensure that the bedroom is dark and quiet, with a temperature around 24°C (ranging from 17 to 27 °C)</li> </ul>

### 3. Conclusion

Clocks throughout our body control ~24 hour rhythms of behaviour (sleep/wake cycle, eating patterns, physical and social activity) and physiology (hormone release, metabolism, muscle capability, attention/alertness etc.). These are referred to as biological rhythms which are produced in almost every cell of our body and are coordinated by a specialised area of brain known as the suprachiasmatic nucleus (SCN). These internal rhythms are coordinated with environmental cues such as light exposure, food intake and activity. Maintaining robust biological rhythms is very important for our health. The importance of circadian timing has been demonstrated both

through evolutionary relevance and observed health implications of disrupted clock systems. Light affects the master clock (SCN) by resetting it in our brain. Biological rhythm disruption is caused by erratic behaviour or by conflicting timing of our internal rhythms and our environment (such as light and food). Common reasons for mismatch include jet lag, shift work, exposure to artificial light at night and erratic eating and sleeping patterns. Disrupted biological rhythms can have huge negative impacts to our health including increased risk for cardiovascular diseases, cancer, diabetes, obesity, sleep disorders, and depression etc. We can maintain a healthy clock by eating within 10-12 hours/day, getting exposure to sunlight in the mornings, trying to go to bed and wake up at the same time each day and exercising regularly but not too late.

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