

## Review on Chronotherapeutics - A New Remedy in the Treatment of Various Diseases

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**Abstract:** There is an impact of circadian rhythms in the symptoms of certain diseases like asthma, arthritis, depression, ulcer, allergic rhinitis, sleep disorders etc. The human body follows the solar/ lunar adaptations known as biological clock. The biological clock follows the main rhythm known as circadian rhythm. If the circadian rhythms dysfunctions it can greatly affect the function of the brain and behavior cognition. This can be improved by the chronotherapeutics approach. The recent interest is occur in the field of chronotherapeutics is to match the circadian rhythms of the disease for the successful treatment of disease. Mostly the drugs were given in the morning because more symptoms of the diseases are occurring during the morning hours. The impact of chronotherapeutics in the optimal treatment of diseased patients is evaluated because in this method the treatment is done at right time with right medication at right targeted site and in the right concentration.

**Key words:** Chronotherapeutics • Circadian rhythms • Chronotherapeutics drug delivery • Biological clock

### INTRODUCTION

Many functions of the human body vary day by day and these types of variations cause the changes in both in disease state and in plasma drug concentrations. The pain is increases when sleep disturbances are occur due to the hormonal levels are at peak .Human circadian rhythm is based on sleep-activity cycle or solar / lunar adaptations which is influenced by our genetic makeup and affects the body's functions day and night (24-hour period) [1]. The dependence of our body functions in the certain diseased states depends on the circadian rhythm. Circadian rhythms occur in the certain diseased conditions like depression, rheumatoid arthritis, myocardial infarction, peptic ulcer etc. Chronotherapeutic drug delivery systems main goal is to meet the therapeutic needs of the treatment according to the pathological conditions. Number of hormones mainly estrogen and progesterone is released by the brain in the morning, while melatonin and cortisol are released during sleep. Blood pressure and heart rate are highest during the hours of 6.00 a.m. to 12.00 noon [2]. Many diseased symptoms occurred during the morning hours because most of the hormones and cytokines are released during this time period.

Chronotherapeutics is the discipline concerned with the delivery of drugs according to the intrinsic activities of a disease over a certain period of time because the biochemical, physiological and pathological variations over a 24h period in humans have been occurred. Chronotherapeutics deals with the medical treatment according to the human daily working cycle that corresponds to a person's daily, monthly, seasonal or yearly biological clock or in order to maximize the health benefits and minimize the adverse effects. The main goal of chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness. Optimum therapy is given when the right amount of drug is delivered to the correct target organ at the most appropriate time. If symptoms of a disease are varied the circadian rhythms also varied the drug release. In the treatment of many diseases chronotherapeutics drug delivery offers a new approach in the pharmacologic interventions design for the effective treatment in the different types of diseases. The importance of the chronobiologic factors in the normal functioning of the body increases the awareness. The chronotherapeutics approach is based on the re-synchronizing the circadian rhythms that control, synthesize and release the important catecholamine and indoleamine neurohormone. Mostly the heart attacks and

strokes occur 7am and noon. This is elevated with increases in the pulse rate, blood pressure and platelet aggregability while plasma fibrinolytic ability is low during the day.

**Chronotherapeutics:** In 1960s first chronotherapeutic formulation was introduced for the treatment of the various diseases. So, the corticosteroid was formulated as a first conventional tablet [3]. US, Asia, Europe are the countries where as the first chronotherapeutic formulation theophylline is used for the treatment of chronic obstructive pulmonary disease, conventional evening H<sub>2</sub>-receptor antagonist for the treatment of the peptic ulcer. Like theophylline the hyperlipidemia should be treated by the cholesterol formulation [4]. The “chronotherapeutics” term is mainly new in the field of drug delivery and in the treatment method. It is defined as the widespread term in which disease follow the circadian rhythm which undergoes the metabolic changes. Chronotherapeutics is defined as the method in which drug availability is matched with the rhythms of the disease according to the time structure which results in the maximum therapeutic effects and less adverse effects. It is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic activity and pharmacokinetics of many drugs [5]. Chronotherapeutics is based on the clock known as biological clock which control many vital activities of the physiological organs of the human body. The potential benefits of chronotherapeutics have been used in the management of a number of diseases particularly benefit the patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases and peptic ulcer disease [6]. Circadian rhythms are the main rhythm in the chronotherapeutics and the dysfunction of circadian rhythms can affect the brain functioning and it can be improved by the chronotherapeutics approach. There are number of conditions which show a circadian pattern and adjusting the administration of drugs according to the circadian rhythm of the disease state. Some of the conditions, which may be significantly benefited through this treatment, are given below:

- Hypertension
- Myocardial infarction
- Cerebrovascular accidents
- Bronchial asthma
- Peptic ulcer
- Arthritis

- Hypercholesterolemia
- Allergic rhinitis
- Alzheimer’s disease
- Sleep disorders
- Cardiovascular diseases
- Blood coagulation and thrombosis

For the successful treatment of various diseases depend upon the day time or month in which the medicines are taken or different type of surgery are performed. Asthma and arthritis are the diseased conditions that depend on the treatment of the biological clock or the calendar. Rhythms are mainly depending on the solar or lunar system that changes the night to day and this lead to the seasons into another. Mainly human body’s internal clock is dedicated to genetic make up. These changes affects the body’s blood pressure, blood coagulation, blood flow and other body functioning’s. Chronotherapeutics is the scientific domain that study, especially when drugs produce their best effective and least side effects. Biological rhythm markers have been identified to guide the chronotherapy of many diseases. Some medications are work better if they are administered with day and night pattern and biological clock [7].

**Human Circadian Time Structure:** The human circadian time structure is always peak for 24 hr as shown in figure. This figure also shows that the peak time of human circadian rhythm in the synchronization with the routine -sleep in darkness from 10: 30 pm to 6:30 am and activities during the light of the day between 6: 30 am and 10:30pm. These rhythms are help in defining the temporal organization of the human beings. The human circadian time structure is to depict the peak time of 24-h rhythms on a clock basal gastric acid secretion, white blood cell count (WBC), calcitonin a gene-related protein and arterial natriuretic peptide occurs late at night or early in sleep. Growth and thyroid stimulating hormone (TSH), blood lymphocyte and eosinophil number and plasma melatonin and prolactin crest during sleep as the adrenocorticotrophic (ACTH), follicle stimulating (FSH) and luteinizing (LH) hormones and plasma cortisol, renin activity, angiotensin and aldosterone are peak in the morning. The circadian rhythms of serum cholesterol and triglycerides and urinary diuresis crest early in the evening. The information given in this figure illustrates that the biochemistry and physiology of human beings are not constant; that they are variable in a predictable and coordinated manner during the 24 h. To initiate a physiological process of an organism at an appropriate

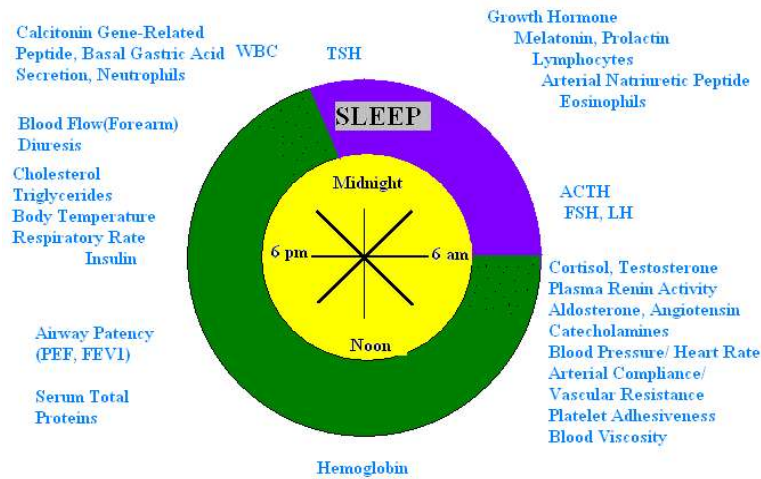


Figure of Human Circadian Time Structure

phase of the daily environmental cycle the biological timer can act as an alarm. The circadian clock can act as an instrument for the estimation of the day and night length and for seasonal phenomena it also act as clock for changing the day and night length which can be regulated appropriately [8]. All the human circadian cycle are synchronized to the rhythmic light dark cycles occur on a daily basis. In biological, physiological and biochemical processes the 24 hr cycle signals are absent externally. The tissues extract from liver, lungs are grown externally in the culture dish i.e. *in vitro* were not under the control of the SCN and circadian rhythms also could not persist [9]. The SCN can regulates the entire 24hr signals that are originate from the temporal organization of cells, tissues and whole organisms through neural or neurohormonal signals. Mostly the cells and body tissues can perform the activity on the basis of circadian rhythm. [10]. The circadian pacemaker is located in the cells of specific structures of the organisms. These structures are present in the pineal gland in the mammalian glands. In mammalian cells, the circadian clock resides in two clusters of nerve cells called the superchiasmatic nuclei which are the site of primary regulation of circadian rhythmicity in mammals. The SCN act as a master pacemaker regulating other rhythmic systems that consists of the other human activities. [11]

**Molecular Basis of Circadian Rhythms:** The first mutation was carried out by using different mutagens onto the *Drosophila melanogaster* (fruit fly) and filamentous fungus *Neurospora*. Then the resulting mutant organisms were obtained as a result of rhythm abnormalities. This mutagenesis process led to the

discovery of the first circadian clock mutants, which were called period and frequency. The genes that are used for the mutagenesis carried the mutations in the organisms which were cloned in 1980s [12]. Researchers isolated the genes in mammals i.e. mammalian homologs and in 1994 researchers began to found screening in the mouse and the first mouse circadian mutation called circadian clock [13]. In 1997 the gene affected by these mutation became the first mammalian circadian clock gene to be cloned. In the molecular biology and genetics led to the cloning of mammalian “clock” genes and the discovery of new cerebral sites that contain the circadian oscillators. Although the effects of SCN lesions on numerous rhythms have been shown their effects on sleep are less. Thus SCN lesions disturb the pattern of sleep in rats but have only minimal effects on the animals’ amount of sleep need [14]. Sleep is an independent mechanism to control the two processes:

(1) The propensity of sleep modulated by circadian clock and (2) a homeostatic control that reflects the duration of waking i.e. “sleep debt”. The sleep studies in mice carrying changes i.e. mutations in two of the genes influencing circadian cycle clock genes indicated that these mutations resulted in changes in sleep regulation [15].

**Mechanisms of Biological Time Keeping:** The pair of supra chiasmatic nuclei are situated in the hypothalamus and the pineal gland controls the circadian rhythms and master clock network. [16,17]. The rhythmic activities of specific, so-called, clock genes, like *per1*, *per2*, *per3* and their gene products are the cyclic or nocturnal secretion of melatonin from the pineal gland that comprises the

central timekeeping mechanism. This master clock network operates the period and phase of the multitude of peripheral circadian clocks located in cells, tissues and organ-systems. The temporal organization of biological processes and functions is exquisite which the end affects of the organization. Biological timekeeping is an evolutionary adaptation to an environment that is organized in time, displaying discrete and important cyclic phenomena. Thus, the temporal organization of biological processes and functions during the 24- h period ensures the peak functioning of the diurnal human species during daytime activity and repair during nocturnal cycle and the menstrual cycle, it ensures fertility and perpetration of the species; and during the year it ensures a biological adjustment to predictable-in-time changes and challenges associated with the different seasons of the year.

**Various Diseases and Chronotherapeutics:** The chronobiological studies have established the relationship between the circadian rhythm and all the human body functions. Now a days the chronotherapeutics used in the management of number diseases like asthma, cancer, cardiovascular diseases, peptic ulcer and rheumatoid arthritis. [18] The chronotherapeutics is an area in which medicines are delivering at precise intervals at the simple rate which may show the enormous benefits. Drugs that are formulated as chronotherapeutics are regulated by the Food and Drug Administration.

**Here's a Description of Some Diseases in Which Chronotherapeutics Are Used:** Asthma: Asthma is the most common disease in which the large circadian variation are occur with respect to the time. There is an increased incidence of asthma during the early-morning hours is well known to emergency, paramedics, pediatricians and parents of children with asthma. The symptoms of asthma occur 50 to 100 times more times than during the day often at night. Some studies involving that asthmatic patients self-administered the  $\beta_2$  agonist through the inhaler [19] found a 300-fold difference among the hourly frequencies of bronchodilator administration of the same drug. Many circadian dependent factors in asthma appear to contribute to the worsening of nocturnal asthmatic symptoms. In many studies [20] use of a timed-release formulation of theophylline (Theo-24) are used for achieving the therapeutic drug concentrations during the night and avoiding the toxic levels during the day when the dose was ingested or taken at 3 p.m. The other studies

[21] show that a single dose of inhaled corticosteroids are administered at 5:30 p.m. rather than 8 a.m. was nearly as effective as four times doses taken a day. In an oral prednisone formulation has been shown its effectiveness in improving the several features of nocturnal asthma when administered at 3 p.m. rather than 8 a.m. [22] Normal lung functioning undergoes a circadian changes and this reaches a low point in the early morning hours and the dip is particularly shows in people with asthma. In the asthma the main goal of chronotherapeutics is to getting the maximal effects from bronchodilator medications during the early morning hours example is the bronchodilator Uniphyll which is a long-acting theophylline preparation manufactured by Purdue Frederick Co. of Norwalk, Conn. and approved by FDA in 1989. Administration through inhaling once a day in the evening, Uniphyll is a theophylline preparation that causes the blood levels to increase and reach their peak levels and this improves the lung function during the difficult early morning hours. There are other bronchodilators that act similarly to address the early morning dip in lung function. The main key of asthma treatment is chronotherapy this treatment improves the daytime manifestations and less improvement in the night time symptoms. [23, 24]

**Arthritis:** Rheumatoid arthritis can be distinguished from osteoarthritis by the time of day when the patient's joints are most painful and morning stiffness is characteristic feature of rheumatoid arthritis whereas symptoms are often worse in the afternoon and worse in evening in osteoarthritis. [25] Non-steroidal anti-inflammatory drugs are taken for relieving the morning pain and stiffness of rheumatoid arthritis so the medicines are taken late at night and it is better for the treatment. Majority of medicines are work better for evening osteoarthritis pain if taken around noon. The new cyclooxygenase-2 inhibitors are effectively relieve the osteoarthritis symptoms when taken in the morning and better results are obtained in rheumatoid arthritis when small part of the dose is taken in the evening. [26] With the varying ingestion time resulting in the effect that is the four fold improvement in tolerance and doubling of analgesic effectiveness. Chronobiological patterns have been observed with morning stiffness and arthritic pain in patients. The people who suffer from arthritis tend to have less pain in the morning and more at night but in rheumatoid arthritis the pain mostly increases at morning and decreases as the day goes on. In recent animal studies it is showing that joint inflammation in rats fluctuates over a 24-hour period support these

observations by both patients and physicians because in chronotherapeutics the treatment is mainly based on these fluctuations then these fluctuations are matched with the rhythms of the diseases. Chronotherapy for all forms of arthritis uses standard treatment that includes the non-steroidal anti-inflammatory drugs and corticosteroids but in the treatment the dosages time are match with the rhythms of disease which are timed to ensuring that the highest blood levels of the drug coincide with peak pain. For mostly sufferers of arthritis the administration of ibuprofen non-steroidal anti-inflammatory drug and the optimal time around noon or mid-afternoon. The same drug shows the effectiveness in people with arthritis mainly rheumatoid arthritis when taken after the evening meal this shows the long term effect. The exact dose of ibuprofen would depend on the severity of the patient's pain and his or her individual physiology, diet, morphology and its surroundings. [27-29]

**Peptic Ulcer Disease:** In the past time histamine (H<sub>2</sub>) antagonists were administered at regular intervals around the clock based on the basis of pharmacokinetic properties and circadian rhythm because maximal acid secretion, peptic ulcer disease, pain and perforation of gastric and duodenal ulcers are more common at night administration of these drugs at bedtime is more effective. Nocturnal administration of the peptic ulcer medicines is not only reduces the acid secretion more effectively but also promotes the ulcer healing and reduces ulcer recurrence. [30] It is well established that the patients with the peptic ulcer disease are often experiences the greatest degree of pain in the near time that the patient go to bed as the rate of stomach acid secretion is highest at night [31]. The timing of administration of ulcer medications has a significant result on their therapeutic effect and this shows the best chronotherapeutics drug delivery in the arthritis treatment which shows the right treatment according to the rhythms and biological time structure. [32]

**Hypercholesterolemia:** The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors were firstly introduced in the morning doses for the reevaluation of the circadian rhythm of cholesterol biosynthesis. [33] The higher rates of cholesterol intake during the hypercholesterolemia and hepatic cholesterol genesis occur during the evening hours even in the fasting state also. The free cholesterol levels have been reported to be lowest at 2 p.m. to 6 p.m. and peak at 6 a.m and morning

versus evening administration of HMG-CoA reductase antagonists. [34] Some marketed preparations like Lescol, Mevacor, Prachol and Zocor showed that evening dosing frequency of these medications is more effective than morning dosing. On the basis of the studies it is recommended that five of the six currently approved HMG-CoA reductase inhibitors can be administered between the evening meal and bedtime; atorvastatin calcium or Lipitor may be an exception because of its long elimination half-life. [35]

**Cancer:** The antineoplastic drugs causes the cytotoxic effects on healthy and diseased tissues as the biological rhythms of both healthy and tumor cells influence the susceptibility of the normal and malignant cells to the cytotoxic agents. It has been shown that 'susceptibility rhythms' or the biological rhythms for drugs differ in between the healthy tissue and cancerous tissues. Acute lymphoblastic leukemia is one of the most untreated diseases which show the improved clinical results with chronotherapy. In some studies [36] it is found that the risk of relapse was 2.56 times higher in the children who are treated with the chemotherapy in the morning than in receiving the same treatment within the evening. [37] The mechanism for improving the outcomes with evening dosing is thought to be pharmacodynamic and pharmacokinetic result shown in the clinical trials. [38] Therefore the 'correct' timing of drug treatment may reduce the drug toxicity increasing the maximum drug tolerance and ultimately the chronotherapy results in better tumor management. In addition to considering the pharmacologic and pharmacokinetic properties of the drug and the clinicians may also recognize the rhythmic changes in DNA and RNA synthesis because the RNA translational activity and mitotic activity may influence the tumor cell susceptibility and it appears the timing of drug administration in the treatment of cancer which have a significant impact upon treatment and this will lead the success and this includes the patient's ultimate survival.[39,40] The optimal timing of cancer surgery, particularly for breast cancer, has come under study it is believe that in perimenopausal women, surgical cure of breast cancer is more likely if surgery is performed in the middle of a women's menstrual cycle in the week and experts believe that an improved outcome is hormone related. In the first half of the menstrual cycle, estrogen levels are high and progesterone is not produced and in the second half, progesterone rises and estrogen falls so it is believed that progesterone may inhibit the production of some enzymes that help the cancer to spread. Probably

the most impressive results of chronotherapy were obtained in a clinical trial involving patients with colorectal cancer. [41-43] An essential step toward further developments of circadian-timed therapy has been originated in the treatment of cancer and the recent advancement in the chronotherapeutics.

**Allergic Rhinitis:** Symptoms of allergic rhinitis (e.g. nasal congestion, sneezing, running nose) are typically more severe in the early-morning hours. [44, 45] showed that a morning dose of antihistamine, is more effective than placebo, but not effective as the same dose given in the evening. If the administration of the drug can be matched with the biological time structure which have the peak pharmacologic activity are matching the time of greatest discomfort, optimum relief may be provided at the time when it is needed most of the patient.

**Mood Disorders:** The deprivation of sleep in the half of the night and the timed exposure to daylight-intensity and artificial light still experimental therapies, may ease the depression pre menstrual or during menopause and benefit both women and men with seasonal and other mood disorders. Such a variation was not detected in the mood disorders when sustained release dosage forms of nifedipine and isosorbide mononitrate were used. The underlying mechanisms for the chronotherapeutic pattern involve a faster gastric emptying time and a greater gastrointestinal perfusion in the morning hours according to the biological time structure. Atenolol, in comparison to the propranolol is not absorbed more rapidly after morning administration compared with evening administration [46]. This confirms that the absorption rate of lipophilic, but not hydrophilic, drugs is faster after morning dosing [47].

**Cardiovascular Diseases:** The cardiovascular events are more commonly occur in the morning [48] and the incidence of sudden cardiac death is upto the 70% between 7 a.m. and 9 a.m. than during the rest of the day. Similarly the stroke and ventricular arrhythmias occur with greater frequency in the morning hours due to the plasma catecholamines and cortisol, as well as vascular tone and effective circulating volume, are also highest in the morning hours. In the morning hours the blood pressure increases with a higher incidence and it is mainly increased in the early morning hours. The blood pressure declines from mid afternoon and is minimum at midnight.[49,50] In most of the hypertensive patients, a marked rise in blood pressure upon awakening is occur

which is called the morning or 'a.m.' surge.[51] Systolic blood pressure rises approximately 3 mmHg/h for the first 4-6 h p while the rate of rise of diastolic blood pressure is approximately 2 mmHg/ h.[52] In few years, two large prospective studies are assessed that cardiovascular end points using nocturnal dosing of antihypertensive agents. In the studies of the heart outcomes prevention evaluation trial, [53] showed that nightly dose of ramipril (in addition to other medication), compared with a regimen not including an angiotensin-converting enzyme inhibitor, which significantly decreased all cardiovascular outcomes. [54] The first chronotherapeutic agent for hypertension and angina pectoris are controlled onset extended release verapamil (Covera-HSTM, Pharmacia, Peapack, USA), was recently developed and marketed to match the chronotherapeutic drug delivery to the circadian B.P. and myocardial ischemia rhythms. The formulation are wrapping in the entire tablet in a water-soluble delay coat that disintegrated when exposed to gastrointestinal fluids over a 6-8 h period. After administration of the medication at bedtime, very little verapamil would be absorbed during the night, but by 8-12 h the patient was likely to awaken because there would be an abundant delivery of verapamil. [55, 56] This results in several clinical trials this shown that verapamil is effective in reducing the blood pressure in population which are at high risk for hypertension and target-organ damage. The Chronotherapeutic Oral Drug Absorption System (CODAS™) formulation of verapamil was recently developed. Once-daily administration of the CODAS significantly reduced the morning BP and the formulation is also taken at bedtime and is used for a multiple-bead pharmaceutical system. Each bead is coated with a non-enteric release-controlling polymer that delays the delivery of verapamil into the gut for 4-5 h after administration and thereby provides a morning peak concentration with little adsorption during the night. [57] Onset of myocardial infarction has also increases in the morning, with 34% events occurring between 6 a.m. and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. [58]

**Diabetes:** In type I diabetes the circadian rhythms of insulin and its action are of physiological interest and clinical importance [59]. So, insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show its cyclic rhythmicity of 8-30 min which can show the optimal action. The release of insulin from basal mode acts on B cell in both stimulatory and inhibitory state and target cell sensitivity of insulin action and hyperglycemia is impaired

by stress hormones, cortisol, epinephrine and growth hormone. The intrinsic rhythmicity and dehydration have prolonged the insulin withdrawal induce a secondary feed-back on insulin release can help to raise the blood glucose levels. The modulators of insulin release and action are secreted in a circadian pattern and impress the mode of insulin release. So difference between maximum and minimum plasma insulin concentration has short-term rhythmicity and complex secondary circadian rhythm is variable early-morning and late-afternoon insulin resistance.

**Sleep Disorders:** Many biological signals like sleep disorder occurring in the central and autonomous nervous systems this shows the complex time structure with rhythmic and pulsatile variations in multiple frequencies. The time of sleep required in each person is usually constant although there is a wide variation among the humans sleep [60]. Sleep mainly consists of a rhythmic combination or circadian changes in physiological, biochemical and psychological processes. When the circadian rhythm is disturbed or when the individual physiological or psychological processes are abnormal during sleep it may result in a variety of disorders. Delayed sleep-phase syndrome which is characterized by severe sleep-onset known as insomnia [61]. Normal sleep is impossible until 3 a.m. or later there is a great difficulty in awakening during the morning hours at the normal time. The circadian rhythm disturbances also differ from person to person and identification of the individual variation would be important in dealing with certain sleep disorders.

**Epilepsy:** The circadian rhythm also plays a significant role in seizures of epilepsy [62]. The influence of the biological clock on seizure of some partial seizures has been found in animals or humans. The methodology for the measurement of the circadian rhythm in humans is also investigated. The behavioral chronobiology provides the detection of new regulation processes that concerns the central mechanisms of epilepsy [63] because the circadian psycho physiological patterns of epilepsy show dynamic biological systems which show some intermodulating endogenous processes between observation and seizure susceptibility. Such chronobiologic studies applied to epileptic behavior and this suggests the development of new heuristic aspects in the field of comparative psychophysiology.

**Alzheimer's Disease:** The change of circadian rhythm is also seen in patients with Alzheimer's disease [64].

Individuals with Alzheimer's symptoms show less diurnal motor activity and higher percentage of nocturnal activity which show the lower inter daily stability of motor activity and activity of macrophages peak time than normal healthy individuals. Alzheimer's disease leads to pathological changes in the suprachiasmatic nucleus and it disrupts the circadian rhythms of the brain's function. The core body temperature is also higher in patients and the circadian abnormalities are seen together with cognitive and functional deterioration in this disease.

**Parkinson's Disease:** Parkinson's disease discloses many alterations in circadian rhythm of blood pressure; amplified diurnal blood pressure variability and postprandial hypotension are due to autonomic dysfunction [65]. But existence of circadian rhythm in this disease has not been evaluated in clinical data because the daily fluctuations of motor activity pattern of the phase of the disease and the subsequent role of drugs are difficult to estimate.

**Coagulation Disorder and Thrombosis:** The fluidity and retention of the blood within the circulatory system are essential for life [66] and these dual roles are obtained through the actions and interactions of multiple variables in blood which together form the haemostatic system. Circadian rhythm has been found in many components of circulatory and haemostatic systems such as muscle cells, aorta, peripheral vascular muscle and endothelium and these alterations in the time structure of circadian rhythms may lead to hypercoagulability and thrombosis or hemorrhage. Homeostasis is affected by various factors such as peripheral resistance, blood flow, blood viscosity, blood pressure and heart rate. The peripheral vascular resistance decreases during afternoon hours resulting in rise of blood flow at that time is diurnally active. The vasomotor tone of the coronary and peripheral arteries of the vasoconstrictor response to adrenaline is increasing in the morning than in the afternoon. Beta-thromboglobulin also shows the peak concentration around 6 a.m. and low values between noon and midnight. Factor VII are prominent in circadian variation with highest values between 8 a.m. and noon but its antigen concentration. The peak time of Factor IX is also around 9 a.m. and the peak concentration of natural coagulation inhibitors like protein C, protein S and anti thrombin occurs at 6 a.m. and lowest values occur between noon and midnight. The rhythmic variations are seen in the fibrinolytic systems but these may be different all local tissue level.

## CONCLUSION

With an increasing awareness of the benefits of chronotherapeutics and mounting the evidence for the impact of circadian rhythms in the treatment of various diseases, there is an important medication that synchronise with the hormonal release and the night-time surge of inflammatory components. The availability of prednisone has brought hope for the treatment of various diseases. It also remains to be determined role of circadian rhythms and the use of chronotherapeutics may also play a role in determining an optimal treatment algorithm in other diseases, such as polymyalgia rheumatica, asthma, hypertension, myocardial infarction and peptic ulcer.

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