International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.2, pp 765-777, April-June 2012

# Chronotherapeutical approach: Circadian rhythm in human and its role in occurrence and severity of diseases

**Satwara Rohan S.[1]*, Patel Parul K.[1], Shaikh Farhatjahan[1]**

**[1]Babaria Institute Of Pharmacy ,Vadodara-Mumbai NH#8 ,Varnama ,Vadodara 390240 ,Gujarat ,India. Phone: 0265 - 6599991-2-3 Fax: (O) 0265 – 2356350.**

***Corres. author: rohansatwara@yahoo.com***
***Mobile No. : 9824779744***

**Abstract:** Mammalians circadian pacemaker resides in the paired suprachiasmatic nuclei (SCN) and influences a multitude of biological processes, including the sleep–wake rhythm. Clock genes are the genes that control the circadian rhythms in physiology and behaviour. Due to that that pathophysiology several diseases like allergic rhinitis, arthritis, asthma, myocardial infarction; congestive heart failure, stroke, and peptic ulcer disease etc. give rise to day-night patterns in onset and symptoms exacerbation. The scientific study of biological rhythms and their underlying mechanisms is known as chronobiology and treatment using this concept is known as chronotherapy. The effectiveness and toxicity of many drugs vary depending on dosing time. Such chronophamacological phenomena are influenced by not only the pharmacodynamics but also pharmacokinetics of medication. Chronopharmacokinetics deals with the study of the temporal changes in absorption, distribution, metabolism and elimination of several drugs and thus takes into account the influence of time of administration on these. The role of circadian rhythms in the mechanisms of disease and the pharmacokinetics and pharmacodynamics of medications constitute a challenge to drug-discovery and drug-delivery scientists. This review represents the basic concept of circadian rhythm, mechanism and its synchronization with severity and occurrence of various diseases from viewpoint of chronopharmacology and chronotherapy.
**Keywords:** Circadian rhythm, biological clock, chronotherapy, chronopharmacokinetics.

## Introduction

A circadian clock is a highly conserved feature of life on earth, imparting an approximately 24 hr period to many biological behaviours at the cellular, tissular, and organismal levels. They serve to impose internal alignments between different biochemical and physiological oscillations. Biological functions are organized in time as rhythms with cycle durations as short as 1 second or less, as illustrated by oscillations in the electrocardiogram, and as long as 24 hours, week, month, and year. Their ability to anticipate environmental changes enables organisms to organize their physiology and behaviour such that they occur at biologically advantageous times during the day just as visual and mental acuity fluctuate, affecting complex behaviours.

The scientific study of biological rhythms and their underlying mechanisms is known as Chronobiology. The majority of health care providers are unfamiliar with this field because the teaching of biology in schools of medicine, nursing, and pharmacy is based solely on the theory of homeostasis. We are taught that our biology is maintained in a relatively constant state by inherited mechanisms that are activated when internal conditions deviate from specific set points. Chronobiology, on the other hand, teaches human biological functions and processes exhibit predictable-

in-time cyclic variability. Emerging findings from chronobiological investigations are of such importance that re-examination of several fundamental assumptions and a practice of clinical medicine is now warranted.

Chronopharmacology is the investigative science that elucidates the biological rhythm dependencies of medications. The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 h rhythms of biochemical, physiological and behavioural processes under the control of circadian clock. Such chronophamacological phenomena are influenced by not only the pharmacodynamics but also pharmacokinetics of medications. The knowledge of 24 h rhythm in the risk of disease plus evidence of 24 h rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for pharmacotherapy (chronotherapy).

The aim of review is to provide an overview of circadian rhythm, circadian pattern of various diseases, chronopharmacokinetics of several drugs and their dosing time-dependent alterations in therapeutic outcomes in treatment. The underlying mechanisms and usefulness are introduced from viewpoint of chronopharmacology and chronotherapy. [1, 2, 3]

- **Circadian rhythm of Human body**

  Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours also termed as sleep-wake cycle. This master clock network orchestrates the period and phase of the large number of acquiescent peripheral circadian clocks located in cells, tissues, and organs. The end-effect is a wonderful chronological organization of biological processes and functions.

  A biological rhythm is broadly defined by the characteristics of period, level, amplitude, and phase.

- **Period -** Period is the duration of time required to complete a single cycle. Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days. Included in this category are the ultradian (< 20 h), circadian (-24 h), and infradian (>28 h) rhythms as described below. Finally, long-period rhythms show oscillations of roughly a week, month, and year.

  **(a) Ultradian rhythms**: - Oscillations that are completed in a shorter duration of less than 24 hours are termed as ultradian rhythms (more than one cycle per day).

  **(b) Circadian rhythms**:-The term "circadian" was obtained from Latin words "circa" meaning "about" and "dies" meaning "day". Oscillations in our body that are completed within 24 hours are termed as circadian rhythms.

  **(c) Infradian rhythms**: - Oscillations that are completed in more than 24 hours are termed as infradian rhythms(less than one cycle per day). [4]

- **Phase -** Phase refers to the clocking of specific features, such as the peak and trough values, of a rhythm relative to the corresponding time scale.
- **Amplitude-** It is a measure of the magnitude of the predictable time variability due specifically to a biological rhythm or the difference between the peak (or trough) and the mean value of a circadian wave. The amplitude of rhythms may change with aging. For example, in diurnally active young adults the circadian rhythm in antidiuretic hormone (ADH), which regulates urine formation and volume, is of very high amplitude. Peak ADH concentration occurs during the night time to ensure reduced urine formation and volume during sleep; thus, in young adults urine formation and volume are much greater during diurnal activity than nocturnal sleep. However, with aging the amplitude of the ADH rhythm decreases; as a consequence, the peak of the circadian rhythm in urine formation and volume shifts to the middle of the night, resulting in frequent disturbances of sleep because of the need to urinate [5].
- **Level -** Level is the baseline around which rhythmic variation occurs. The level of circadian rhythms oscillates in a predictable-in-time manner during the month in young women and over the year in men and women, giving rise, to menstrual and annual biological rhythms.
- **Historical aspects of chronobiology and chronotherapy:**

Daily rhythms in plants and animals have been observed since early times. As early as the fourth century BC, Alexander the Great's scribe Androsthenes noted that the leaves of certain trees opened during the day and closed at night showing a clear rhythmicity. In 1729, the French astronomer Jean Jacques d'Ortous deMairan conducted the first known experiment on biological rhythms [6]. Since then, it has been proven that insects use photoperiodic information to bring their growth and dormant periods into harmony with seasons [7]. Circadian rhythms of behaviour in mammals are known to be robust and precise [8, 9].

The first supra mutation was carried out by using different mutagens onto the Drosophila melanogaster (fruit fly) and master 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 in1980s [10]. 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.

- **Mechanism and molecular basis of Biological clock**

The circadian timing system is a hierarchical network that temporally coordinates biological and physiological processes along the 24-h day. Endogenous, self-sustained, 24-h rhythmic oscillations within the hypothalamic pacemaker, the paired suprachiasmatic nuclei, are entrained to the 24-h changes in external environment through input signals from sensory organs and from other brain areas. In turn, the hypothalamic pacemaker generates behavioural rhythms and synchronizes ubiquitous clocks in peripheral organs through neuronal, physiological and endocrine output signals, resulting in measurable and therapeutically exploitable circadian variations. Thus, rhythms in hormonal secretions including cortisol, catecholamines and melatonin, autonomic nervous system activity, core-body temperature, physical and cognitive performance form a dynamic physiological network which resets and coordinates the peripheral molecular clocks. [11]

Each mammalian cell is equipped with a self-sustained molecular clock, resulting from interconnected and auto-regulatory transcriptional, post-transcriptional and post-translational loops involving a genetic network of at least 15 gene products. Alongside these identified core clock genes, at least 10 other proteins, including several kinases and the proteasomal machinery, are implicated in the control of clock protein stability and degradation, thus regulating the abundance, activity and subcellular localization of the core clock proteins. This molecular clock generates self-sustained 24-hr cyclic oscillations in individual cells, which can be entrained by internal cues, such as endocrine and temperature rhythms. One of the main outputs of the ticking molecular clock within each cell is the coordinated transcription of 10% of the genome with a circadian rhythmic pattern. The circadian transcriptome is tissue-specific, and constitutes the molecular basis of circadian rhythms in the whole organism.

The monitoring of rhythm, overcome of rhythm disruption and manipulation of rhythm from viewpoints of molecular clock are essential to improved progress and diffusion of Chronopharmacotherapy. Such approach should be achieved by the new challenges in drug delivery system that match the circadian rhythm (Chronotherapeutic-DDS). [12, 13]

Chronopharmaceutics includes pharmaceutical application of “Chronobiology” in drug delivery. Chronobiology is the study of biological rhythms and their responses to other metabolic functions of body.

- **Terminologies related to Chronotherapeutics:**

Chronotherapeutics includes the fundamentals and research into various aspects of chrono-physiology, chronopathology, chronopharmacology, chrono pharmacokinetics, chronopharmacodynamics, chronoesthesy and chronotoxicology. Broadly, chronopharmaceutics bring together Chronobiology and pharmaceutics. [14]

**1. Chronopathology (disease pathophysiology):** It is the study of biological rhythms in disease processes and morbid and mortal events.

**2**. **Chronopharmacology:** It is the study of the manner and extent to which the kinetics and dynamics of medications are directly affected by endogenous biological rhythms, and also how the dosing time affect biological punctuality and the features (period, level, amplitude, and phase) of biological rhythms. Thus it involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics.

**3**. **Chronopharmacokinetics** - This term includes both rhythmic changes in the drug bioavailability, pharmacokinetic and its excretion.

**4. Chronopharmacodynamics-** Chronodynamics refers to dosing time, i.e., rhythm-dependent, differences in the effects of medications. Such administration- time differences are due to rhythms in the free-to-bound drug fraction, number and conformation of drug-specific receptors, ion channel dynamics, and rate limiting step(s) in metabolic pathways. Both the desired/ beneficial and undesired/adverse effects of medications can vary significantly according to their administration time.

**5**. **Chronoesthesy-** Chronopharmacology studies sometimes reveal great differences in their effects with different biological times of application, even through the pharmacokinetics and concentration are the same. This phenomenon is termed chronoesthesy, which is the circadian change in the susceptibility of any biosystem to a drug (including organ systems, tumors) parasites, etc.

- **Human endocrine and exocrine secretions based on circadian rhythm:**

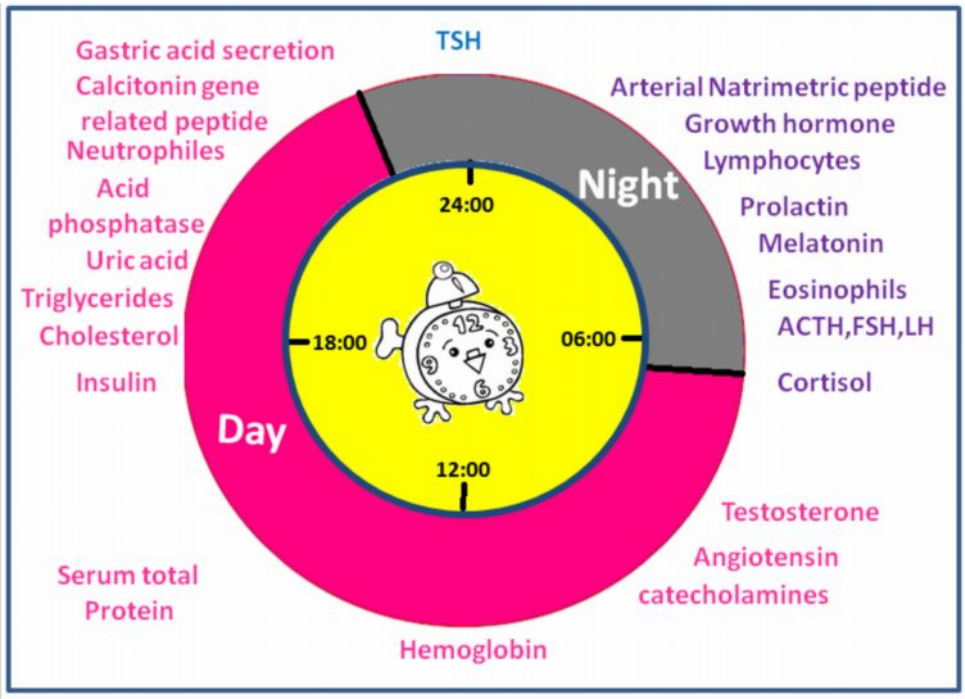


**Figure 1 Pulsatile exocrine and endocrine secretions dependent on human circadian rhythm [modified 15, 16]**

**6. Chronotoxicology** - Chronotoxicology is an aspect of Chronodynamics; it refers specifically to dosing-time, i.e., rhythm-dependent, differences in the manifestation and severity of adverse effects and thus intolerance of patients to medications. Certain classes of drugs that have high risk of adverse effects and relatively narrow therapeutic range are likely to show significant dosing-time differences in safety (i.e., Chronotoxicology).

Many hormones in the human body are secreted in a cyclical or pulsatile manner, rather than continuously as shown in above figure 1. Secretions of the anterior and posterior pituitary hormones, adrenal glucocorticoids, mineralocorticoids and catecholamines, gonadal sex steroids, parathormone, Insulin and glucagon are pulsatile in manner [17, 18]. During hormone secretion, a baseline release is combined with the pulsed release. Insulin is one good example of a pulsatile hormone release. A basal release of Insulin stimulates the synthesis of proteins and glycogen in muscle and adipose tissue. In addition, pulsatile Insulin release is observed during and following the intake of foods to regulate the body's blood glucose levels. Pulsatile release of gastrointestinal hormones, stimulated by presence of food in the gastrointestinal tract, generally causes the release of digestive enzymes from the pancreas and stomach. Many hormones including follicle stimulating hormone (FSH), leutinizing hormone (LH), leutinizing hormone releasing hormone (LHRH), oestrogen, and progesterone are also regulated in the body in pulsatile manner. Numerous biological functions in the body are thus regulated by the temporal and pulsatile release of hormones [19]. If the hormones were continuously secreted, a hormonal imbalance may arise, which would not only induce down regulation of hormone receptors on the target cellular membranes, but might also produce undesired side-effects [20].

- **Circadian rhythms in occurrence and severity of diseases:**

The diseases recently targeted for pulsatile drug delivery are those which have enough scientific background to justify chronopharmaceutical drug delivery system compared to conventional drug administration. These include asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases, diabetes, hypercholesterolemia, and neurological disorders etc. which have good circadian rhythm as shown in figure 2.

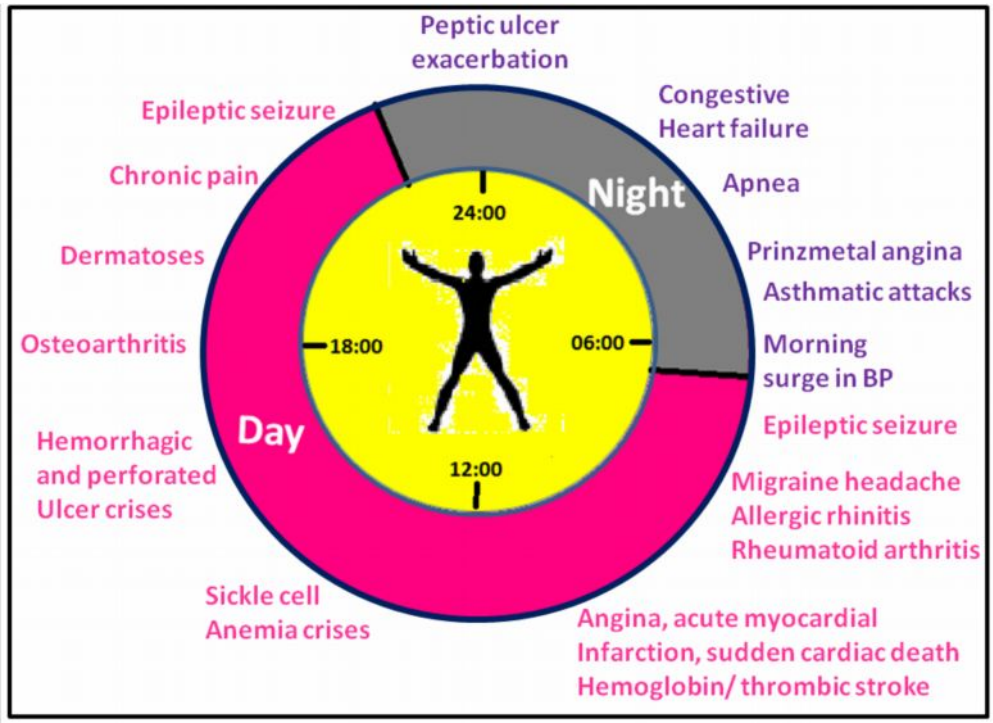


**Figure 2 The circadian pattern of various diseases [modified from 15, 16]**

**1. Bronchial asthma**

It is generally identified by airway inflammation resulting in hyper responsiveness of lower respiratory tract to various environmental stimuli [21].Airway resistance increases progressively at night in asthmatic patient. This asthma known as nocturnal asthma is an exacerbation of asthma with increase in symptoms, airway responsiveness and/or lung function [22]. In daytime antigen provokes the release of pro-inflammatory mediators from mast and eosinophil cells over the span of long hours resulting in exacerbation of inflammation, smooth muscle bronchospasm and contraction, over-stimulation of mucus glands with mucus hypersecretion of the small airways of the lung. It is a good target for chronotherapy because bronchoconstriction and exacerbation of symptoms vary on circadian fashion.

**2. Allergic rhinitis:**

Common symptoms of allergic rhinitis are sneezing, nasal rhinorrhea, red itchy eyes, nasal pruritus and nasal congestion [21].Each of the symptoms is found to occur most frequently before breakfast and in the morning and least frequently in the middle of the day. There are two phases of occurrence of allergic rhinitis i.e. early phase (developing within minutes) and late phase (manifesting after 12–16 h). The early phase happens due to release of Histamine, Prostaglandins, cytokines, TNF-α, chemotactic factors etc resulting in sneezing, nasal itch, rhinorrhea. On the other hand late phase is shown due to elaboration, adhesion and infiltration of circulating leukocytes, T cells and eosinophils evoking nasal congestion, obstruction due to the exacerbation of inflammation of the nasal, sinus and other tissue of the upper airway.

**3. Pain**

Pain control is one of the most important therapeutic priorities. Although numerous clinical practice guidelines for pain management have been published, inadequate pain relief remains a significant health care issue. It was reported that the highest threshold occurred at the end of the resting period, while the least threshold was seen at the end of the activity period. In arthritis there is circadian rhythm in the plasma concentration of C-reactive protein and Interleukin-6 of patient with rheumatoid arthritis [24]. Besides, different opioid peptides like 5-hydroxytryptamine, Bradykinin, Glutamate, NO, substance P, Cytokines and Prostanoids are involved in the activation of nociceptors [23]. Brain concentration of substance P in rat model is highest in night with compared to daytime. It was reported that levels of endogenous Opioid peptides are higher at the starting point of the day and lower in the evening both in neonate and adult human volunteers. Patients with osteoarthritis tend to have less pain in the morning and more at night. While patients with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout day. The symptoms are swelling

of finger and pain at joint. Patients with gastro-oesophageal reflux disease feel night time pain. But renal colic shows morning peak independent of gender and presence or absence of visible kidney stones.
The choice of analgesics and the route of their administration depend on the nature and duration of the pain. Aspirin, Paracetamol, NSAIDs and Morphinomimetics are indicated against nociceptive pain, while anticonvulsants, tricyclic antidepressants and local anaesthetics are used against neurogenic pain.

**4. Duodenal ulcer**
Generally gastric acid secretion is highest in the evening in duodenal ulcer patients and decreases in the early morning [24, 25]. One group of authors studied incidence of ulcer perforation for daily (circadian), weekly (circaseptan) and yearly (circannual) time effects [26]. A circadian rhythm has been found overall that was reproducible and fairly stable across seasons, decades, and days of the week. Duodenal perforations showed highest incidence in the afternoon, while gastric perforations showed a major peak around noon and a secondary peak near midnight. For duodenal ulcer perforation, the circannual pattern was characterized by a 6-month rhythm, with significantly higher incidence in May–June–July and in November– December in most subgroups. A circaseptan rhythm was not found, but there was a significantly higher incidence on Thursday–Friday as compared to Sunday–Monday.

**5. Cancer**
There are many clock genes involved in transcriptional and posttranscriptional activation and inhibition of regulatory loops that produce circadian oscillation in mammalian cells [27]. Particularly CLOCK: BMAL1 or NPAS2:BMAL1 protein dimmers are responsible for activation of the transcription of the clock genes Per and Cry. However, the clock genes Per1, Per2, Bmal1 and Rev-erbα have been found to be expressed in a few mouse models. The clock genes related rhythm alterations at the tissue level may be seen due to the desynchronization of the individual cancer cells that form into a solid tumour. The difference of minutes or hours of internal rhythm in each cell from that of its neighbours leads to such condition. A change in the molecular clock of human tumors is further supported by decreased expressions of the Per1, Per2 or Per3 genes at a single time point in comparison with reference tissues. In addition, the blood flow to affected area is higher in cancer patients than the other parts of the body. Animal studies also reveal that survival rate varies according to the circadian dosing time of different anticancer drugs [27]. Percentage of survival rate suffering acute lymphoblastic leukaemia dosed with combination of 6-mercaptopurine and methotrexate was just double in the evening dosing with compared to morning dosing [28]. Another group of authors has compared the effect of continuous infusion of 5- fluorouracil (5-FU) with circadian patterns of 5-FU administration which shows peak value at 4 a.m., 10 a.m., 4 p.m. or 10 p.m.[45,44] The study indicates that the cytotoxic effect of 5-FU is minimum for the circadian delivery. Circadian fluctuation in blood flow at the subcutaneous tumour site of rat was also investigated [29]. The result indicated that tumour blood flow in the night time was considerably higher than that of daytime. Although there were no marked differences in the mean arterial blood pressure, tumour size and body weight of rats between groups of daytime and night time. Blood flows of normal tissues like subcutis, liver, kidney, cortex, bone marrow and tumour tissues (SLC) were calculated in daytime and night time [30]. Rats were used as animal model. There were no significant differences between average blood flows in two different time zones in all normal tissues. On the other hand blood flow in tumour tissue was increased appreciably in night time in comparison with daytime. These results suggest that there is a circadian pattern in blood flow at the cancer site.

**6. Cardiovascular diseases**
In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day. Platelet agreeability is increased and Fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Because of this reason the frequencies of myocardial infarction and of sudden cardiac death are more prone during from morning to noon [31]. Ambulatory blood pressure measurements show a significant circadian variation to characterize blood pressure. This Variation is affected by a variety of external factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, hematologic and renal variables. Increased heart rate, blood pressure, imbalanced autonomic tone, and circulating level of catecholamines controlling the cardiac arrhythmias show important circadian variation and trigger the genesis of the circadian pattern of cardiac arrhythmias [32]. Atrial arrhythmias appear to exhibit circadian pattern usually with a higher frequency in the daytime and lower frequency in the night time with the abnormal foci under the same long-term autonomic regulation as normal pacemaker tissue. According to study ventricular tachyarrhythmias show late morning peak in the patients with myocardial infarction sometime in the distant past morning peak

and afternoon peak in patients with recent myocardial infarction. Myocardial ischemia, angina pectoris, acute myocardial infarction, and sudden cardiac death are also unevenly distributed during the 24 h with greater than expected events during the initial hours of the daily activity span, in the late afternoon or early evening [33]. Both pharmacokinetics and pharmacodynamics of some oral nitrates, calcium channel blocker and β-adrenoceptor antagonist medications have been shown to be influenced by the circadian time of their administration.

**7. Diabetes**

In case of type I diabetes circadian rhythms of necessity of Insulin and its action are frequently asked question from point of physiological interest and clinical importance [34]. Generally insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show cyclic rhythmicity of 8–30 min which can conclude optimal action. The basal mode of Insulin release acts on B cell in both stimulatory and inhibitory fashions. Target cell sensitivity to insulin action and hyperglycaemia may be impaired by stress hormones, cortisol, epinephrine and growth hormone. Partly intrinsic rhythmicity, dehydration and prolonged insulin withdrawal may induce a secondary feed-back signal on Insulin release which can help to raise blood glucose levels. The modulators of Insulin release and action are secreted in a circadian fashion and secondarily impress the mode of Insulin release. So, any difference between a daily maximum and minimum in plasma Insulin concentration besides its short-term rhythmicity has to be considered as a complex secondary circadian rhythm. It is in particular due to variable secondary early-morning and late-afternoon Insulin resistance.

**8. Hypercholesterolemia**

A circadian rhythm takes place during cholesterol synthesis. Cholesterol synthesis is generally higher during night time than day light. Sometimes it varies according to individuals. The maximal production occurs early in the morning, i.e., 12 h after last meal. Studies with 3-hydroxy-3-methylglutaryl-CoenzymeA (HMG-CoA) reductase inhibitors have suggested that evening dosing was more effective than morning dosing. The activity of rate limiting enzyme HMG-CoA is higher in the night time [35]. But the diurnal variations occur due to periodicity or degradation of this regulatory enzyme.

**9. Sleep disorder**

Many biological signalling e.g. sleep disorder occurring in the central and autonomous nervous systems show complex time structure with rhythm and pulsatile variations in multiple frequencies. The time of sleep required by each person is usually constant, although there is a wide variation among individuals [36]. Sleep consists of a rhythmic (circadian) combination of the changes in physiological, biochemical and psychological processes. When the circadian rhythm is disturbed, or when the individual processes are abnormal during sleep, it may result in a variety of disorders. One such example is delayed sleep-phase syndrome which is characterized by severe sleep-onset insomnia. Normally, sleep is impossible until 3 a.m. or later until there is great difficulty in awakening in the mornings at the normal time. The ability to cope up with circadian rhythm disturbances also differs from person to person. Identification of the individual variation would be of importance in dealing with certain sleep disorders.

**10. Epilepsy**

The circadian rhythm may also take a significant role in seizures of some types of epilepsy [37]. The influence of the biological clock on seizure of some partial seizures has been found in some experimental animal models. The methodology for measurement of the circadian rhythm in humans is also investigated. Behavioural Chronobiology provides the detection of probable new regulation processes concerning the central mechanisms of epilepsy [38]. Because of this fact, the circadian psychophysiological patterns of epilepsy show dynamic biological systems which recommend some intermodulating endogenous processes between observation and seizure susceptibility. Furthermore, such chronobiological studies applied to epileptic behaviour suggest the development of new heuristic aspects in the field of comparative psychophysiology.

**11. Alzheimer's disease**

Change of circadian rhythm is also seen in patients with Alzheimer's disease [39]. Individuals with Alzheimer's show less diurnal motor activity, a higher percentage of nocturnal activity, lower inter daily stability of motor activity, and a later activity acrophase (time of peak) than normal healthy individuals. Alzheimer's disease leads to pathological changes in the suprachiasmatic nucleus and thus it disrupts circadian rhythms of the brain's function. The core body temperature is also higher in patients with this disease. The circadian abnormalities are seen together with cognitive and functional deterioration in this disease. No other change has been evaluated.

**12. Parkinson's disease**

Autonomic dysfunction seen in Parkinson's disease discloses many alterations in circadian rhythm of blood pressure, amplified diurnal blood pressure

variability and postprandial hypotension [40]. But existence of circadian rhythm in this disease has not been evaluated. Clinical data shows daily fluctuations of motor activity pattern but the effect of the phase of the disease and the subsequent roles of drugs are difficult to estimate.

**13. Coagulation disorder and thrombosis**

The fluidity and retention of the blood within the circulatory system are essential for life [41]. These dual roles are obtained through the actions and interactions of multiple variables 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. Alterations in the time structure of circadian rhythms may lead to hypercoagulability and thrombosis or hypocoagulabity and haemorrhage. Haemostasis is affected by various factors such as peripheral resistance, blood flow, blood viscosity, blood pressure and heart rate. Peripheral vascular resistance decreases during afternoon resulting in rise of blood flow at that time in diurnally active personnel. The vasomotor tone of the coronary and peripheral arteries and the vasoconstrictor response to adrenaline are greater in the morning than in the afternoon. β-Thromboglobulin also shows peak concentration around 6 a.m. and low values between noon and midnight. Factor VII demonstrates prominent circadian variation with does not. The peak time of Factor IX is also reported to be around 9 a.m. The peak concentration of natural coagulation inhibitors like protein C, protein S and antithrombin occurs at 6 a.m. and lowest values occur between noon and midnight. Although rhythmic variations are seen in the Fibrinolytic systems but these may be different al local tissue level.

**14. Infectious diseases**

Periodic time-dependent changes in the incidence of infectious diseases are well known [42]. The elevation of body temperature, fever due to bacterial infections is higher in the evening while that due to viral infections is more likely in the morning. Influenza is epidemic in the winter season. It was reported that the morbidity and the mortality were greatest during the winter and least during the summer both in the Northern and Southern Hemispheres. The weight of the nasal secretions is highest in the morning in patients with cold and decreased over the day and increased again somewhat in late evening. Recently the Centers of Disease Control of the US publishes prominent patterns in meningococcal meningitis (January Peak), mumps (April Peak), pertusis (August Peak), varicella (April Peak), and typhoid (August Peak). Though the reason of the seasonal patterns of individual infectious disease is complex and multiple factors are involved, seasonal cycles in infectious diseases are generally attributed to seasonal differences in weather/atmospheric conditions, virulence or prevalence of casual pathogens, and/or variations in the behaviour of the host.

- **Circadian dependence of drug pharmacokinetics:**

The time of administration of a drug or toxic agent may influence the response of the organism. Chronopharmacology examines the influence of the moment of drug administration (hour, month, and year) on the drug and body response according to the temporal structure of the organism receiving it. Thus, the quantitative response (duration or intensity of the action) of an organism, as well as the qualitative response (i.e. inhibition or induction, increase or decrease of its effect), varies with time of administration. Moreover, the different steps in pharmacokinetics, e.g. absorption, distribution, metabolism and elimination, are influenced by different physiological functions that may vary with the time of day. Thus, pharmacokinetic parameters [including the peak drug plasma concentration [ $C_{max}$ time to reach $C_{max}$ ($t_{max}$), the area under the concentration-time curve (AUC), volume of distribution ($V_d$), protein binding, elimination half-life ($t_{1/2}$) and clearance (Cl)] which are conventionally considered to be constant in time are circadian time-dependent[46]. More recently, Shiga et al [47] documented differences in chronopharmacokinetic profiles between Propranolol, a lipophilic β-blocker, and Atenolol, a hydrophilic b-blocker, in patients with hypertension. Their results showed that Propranolol, but not Atenolol, is absorbed more rapidly after morning administration compared with evening administration. This confirms that the absorption rate of a lipophilic, but not a hydrophilic, drug is faster after the morning dosage in humans. Time-dependent changes in kinetics may result from circadian variations at each step, e.g. absorption, distribution, metabolism and elimination. At each of these steps, biological rhythms may influence the kinetics of a drug, as indicated in Table 1.

**Table 1 possible physiological factors influencing circadian dependent pharmacokinetics of the drugs**

| **Absorption** |
|---|
| Oral: Gastric pH, gastric motility, gastric emptying time, gastrointestinal blood flow, transporter. Parenteral: Transdermal permeability, ocular permeability, pulmonary permeability. |
| **Distribution** |
| Blood flow, albumin, α1-acid glycoprotein, red blood cells, and transporter. |
| **Metabolism** |
| Liver enzyme activity, hepatic blood flow, gastrointestinal enzyme. |
| **Elimination** |
| Renal, biliary, intestinal, Glomerular filtration, renal blood flow, urinary pH, electrolytes, tubular resorption, Transporter. |

**Table 2 Circadian variation in the pharmacokinetics of antibiotics in human being [56]**

| **Results** | **Antibiotics** |
|---|---|
| Higher serum levels at 9 am | Amikacin |
| Higher mean serum at 5 am ,higher trough serum levels at 9 am | Netilmicin |
| Lower urine excretion at 10 pm | Ciprofloxacin |
| Longer serum half life at midnight | Sulphamethoxazole |
| Lower renal clearance at 8 p.m higher renal cortex accumulation at 1:30 a.m. lower renal clearance at 1:30 a.m. | Amikacin |
| Higher AUC (serum) at midnight | Cefodizine |

- **Chronopharmacokinetics of drugs [56]**
- **Antiasthmatic Drugs**

Antiasthmatic drugs such as Theophylline and beta sympathomimetics should be dosed higher in the evening than during daytime when asthma is predominantly nocturnal. The Theophylline concentration peak height (Cmax) is greater and time to peak ($T_{max}$) shorter with dosing at 08:00 than at 20:00[48]. Both the first and second-generation H1-receptor antagonists of Cyproheptadine, Terfenadine, Clemastine, and Mequitazine exerted a statistically significantly longer duration of action when they were ingested in the morning (7 a.m.) than evening (7 p.m.).

- **Antibiotics**

Administration-time-dependent differences in the pharmacokinetics and toxicity of antimicrobial agents have been documented in table 2.

This is particularly true for the aminoglycosides, as their nephrotoxicity is greatest when administered during the resting period. Food intake and low urinary pH has been found to be protective of the toxicity of aminoglycosides at this time of the day[49].Knowledge of the administration-time-dependence of aminoglycosides and the underlying mechanisms can be used to develop once-a-day formulations that are significantly less toxic, in particular to the kidney, in patients who require around-the-clock antimicrobial therapy.

- **Anticancer Drugs**

In human bone marrow, skin, and oral and rectal mucosae, DNA synthesis, a stage of the cell-division cycle associated with increased susceptibility to S phase specific agents, decreases by 50% or more between 00:00 and 04:00 compared with daytime. The activity of dehydropyrimidine dehydrogenase in human mononuclear cells increases by 40% around midnight. This enzyme brings about the intracellular catabolism of 5-FU and contributes to improved tolerability of this drug between 00:00 and 04:00. In contrast, cisplatin are better tolerated between 16:00 and 20:00 than 12 h apart. The chronopharmacokinetic finding of Cisplastin seems to contribute to the decreased renal toxicity during evening administration. These findings show that the circadian stage at which anticancer drugs are given to patients should be carefully considered. One approach to increasing the efficiency of pharmacotherapy is administering drugs at times during which they are best tolerated given in table 3.

**Table 3 Tolerance to circadian based cancer chemotherapy in humans [56]**

| Drug | Cancer type | Time of optimal host Tolerance |
|---|---|---|
| Doxorubicin | Ovarian cancer | 06.00 hr (>18.00 hr)<br>06.00 hr (>18.00 hr) |
| Cisplastin | Ovarian bladder cancer | 16.00 hr-20.00 hr (>4.00-08.00 hr)<br>18.00 hr (>6.00 hr) |
| Etoposide | Solid tumor | 07.00 hr (>19.00 hr) |
| 5 fluorouracil | Solid tumor | 02.00- 10.00 hr |
| Methotrexate | Solid tumor | 08.00 hr |

- **Antiulcer Drugs**

$H_2$-blockers (Ranitidine, Cimetidine, Famotidine, Roxatidine, and Nizatidine) should be taken once a day in the late afternoon or early night when acid secretion is increasing, independently of whether the compounds have a short or a long half-life. In contrast to $H_2$-blockers proton pump inhibitors (PPI) should be dosed in the morning [50] since the increase by lansoprazole and Omeprazole in intragastric pH is more pronounced after morning than evening administration.

- **Antihypertensive drugs**

Cardiovascular drugs such as Nifedipine, oral nitrates and Propranolol, plasma peak concentration is twice as high and time to reach peak concentration is shorter after morning dosing compared with evening dosing [51]. Such a variation was not detected when sustained release dosage forms of Nifedipine and isosorbide mononitrate were used. The underlying mechanisms of their chronopharmacokinetic pattern involve a faster gastric emptying time and a greater gastrointestinal perfusion in the morning. Shiga et al documented that Atenolol, in contrast to Propranolol, is not absorbed more rapidly after morning administration compared with post-evening administration. [52] This confirms that the absorption rate of lipophilic, but not hydrophilic drugs is faster after morning dosing.

- **Anti-inflammatory drugs**

Studies on NSAIDs, e.g., Indomethacin and Ketoprofen, have also shown that these drugs have a greater rate and/or extent of bioavailability when they are given in the morning than when they are given in the evening due to better morning absorption. Earlier and higher peak concentrations were obtained when Ketoprofen and Indomethacin was given at 07:00 and 07:00 or 11:00 respectively than at other times of the day or night [53]. Greater blood flow of the gastrointestinal tract in the morning than in the evening may explain this phenomenon. Circadian changes in renal function, plasma protein binding or hepatic blood flow could also explain temporal variation in drug plasma levels. Many variables are known to influence pharmacokinetics.

- **Opioid analgesics**

Stronger analgesic effects were observed when Tramadol and Dihydrocodeine were applied in the evening to relieve painful stimuli. Peak morphine use occurred at 9 a.m. and least use at 3 a.m. in postoperative patients undergoing elective Cholecystectomies. The need for Fentanyl was lower when the surgery was done between 8 and 10 a.m. than between 11 a.m. and 3 p.m. [54]. Finally, a recent study of Meperidine reveals a circadian variation of Meperidine-induced analgesia in sickle cell anaemia patients, with maximal analgesic effect occurring with the morning dose. A prospective study reported the existence of circadian variation in the distribution of lethal Opiate overdoses in drug abusers, with a high death risk in the evening hours (03:00–09:00 h).

- **Local anaesthetics**

The duration of local anaesthesia was longest when amide-type local anaesthetic agents (Lidocaine, Ropivacaine, Mepivacaine and Betoxycaine) were applied around 3 p.m.[55] Area under the Lidocaine plasma concentration curves (AUC) was largest in the afternoon. A 60%change was found in the 24-hour plasma clearance of Bupivacaine, the clearance being greatest at 6 a.m. An administration-time-dependent variation in the transcutaneous passage of a medication was also studied. The plasma levels of Lidocaine were significantly higher in the evening than at any other time of day.

- **General anaesthetics**
  - Barbiturates

    Higher brain pentobarbital or Hexobarbital concentrations occurred when injected during the dark phase. Postsynaptic Type-A GABAergic activity is increased during nocturnal hours, corresponding to the duration of the maximal efficacy of barbiturates.

- Benzodiazepines

  The elimination half-life of Midazolam was found to be at its shortest at 14:00 h and at its longest at 02:00.

- Ketamine, Etomidate, Propofol, and Halogenated Agents:

  Action was found longer during the night than during the day. This circadian rhythm also followed a seasonal pattern between 115% in January to 54% in May– June.

- Halothane

Greatest efficacy of Halothane occurred between 24:00 and 06:00 h.

- **Anti-Migraine drugs**

Sumatriptan is a drug of choice in migraine treatment. The mean peak serum concentration following the 07:00 h administration was significantly higher than after the 19:00 h administration. AUC and AUMC were significantly higher following the 07:00 and 01:00 h administrations than after the 1900 h administration. Following administration at 07:00 h, the mean oral clearance and the apparent volume of distribution were significantly lower than after the 19:00 h administration.

- **Immunosuppressants**

A slightly increased AUC and AUMC resulting from decreased apparent clearance during the resting (PM) versus activity (AM) period were observed for Cyclosporine. A significant delay in mean residence time was observed after the PM dose, and the PM area under the moment curve was larger than the AM value. These trends and differences suggest that more sophisticated time-dependent cyclosporine dosing methods are needed to balance AM and PM drug exposure and thereby improve immunosuppressant activity.

## Conclusion:

The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 h rhythms of biochemical, physiological and behavioural processes under the control of circadian clock. The knowledge of 24 hr rhythm in the risk of disease plus evidence of 24 hr rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for drug therapy. We must strive to develop intelligent drug-delivery systems that can affect a target cell or organ system at that circadian time when it is possible to optimize desired therapeutic outcomes and minimize or avert adverse effects. There is a critical and urgent need at least in cases such as asthma, cancer and heart diseases for novel chronopharmaceutical drug products either for therapy or prevention. Such novel drug dosage forms should be effective, safe, robust (predictable drug release rate in biological systems) and clinically justified, with spatial and temporal control ability after administration by different routes. One approach to increasing the efficiency of chronotherapy is administering drugs at times during which they are best tolerated. Chrono-DDS may benefit the development of new therapeutic strategies for several diseases as well as provide insights into chronotherapy as a way to optimize current therapies. Theoretically, such ideal drug delivery system (preferably a non-invasive system with affordable cost) would potentially improve the safety, efficacy and patient compliance of old and new drugs.

The application of biological rhythm to therapy may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity. The monitoring of rhythm, overcome of rhythm disruption and manipulation of rhythm are essential to improved progress and diffusion of Chronopharmacotherapy.

## References:

1. Reinberg A, Smolensky MH. Biological rhythms and medicine. New York: Springer-Verlag; 1983. p 305.
2. Touitou Y, Haus E, editors. Biological rhythms in clinical and laboratory medicine. Heidelberg: Springer-Verlag; 1992.
3. Halberg F. Chronobiology. Annu. Rev. Physiol. 1969; 31:675-725
4. M.H. Smolensky, G.E. D'Alonzo, Biologic rhythms and medicine, Am. J. Med. 1988; 85 :34–46
5. Kallas HE, Chintanadilok J, Maruenda J, Donahue JL, Lowenthal DT. A clinical investigation of nocturnal polyuria in patients with nocturia: a diurnal variation in arginine vasopressin secretion and its relevance to mean blood pressure. Drugs Aging. 15, 1999, 429-437.
6. C.S. Pittendrigh, Temporal organization: reflections of a Darwinian clock-. Rev. Physiol. 55 (1993) 16– 54.

7. P.L. Adkisson, Internal clocks and insect diapause, Science (1966) 234– 241.
8. A. Kramer, F.C. Yang, P. Snodgrass, X. Li, T.E. Scammell, F.C. Davis, C.J. Weitz, Regulation of daily locomotor activity and sleep by hypothalamic EGF receptor signaling, Science 294 (2001) 2511 – 2515.
9. M. Menaker, Circadian rhythms. Circadian photoreception, Science 299 (2003) 213– 214.
10. Wager-smith, K. and S.A. Kay, 2000. Circadian rhythm genetics: From flies to mice to humans. Nature Genetics, 26(1): 23-27.
11. Pasquale F. Innominato , Francis A. Lévi, Georg A. Bjarnason, Chronotherapy and the molecular clock: Clinical implications in oncology, Advanced Drug Delivery Reviews 62 (2010) 979–1001
12. King, D.P. and J.S. Takahashi, 2000. Molecular genetics of circadian rhythms in mammals. Annual Review of Neuroscience, 23: 713-742.
13. Shigehiro Ohdo , Satoru Koyanagi, Naoya Matsunaga, Chronopharmacological strategies: Intra- and inter-individual variability of molecular clock, Advanced Drug Delivery Reviews 62 (2010) 885–897
14. R.V. Trivedi*, K.J. Wadher , J.B. Taksande , J.G. Mahore, M.J. Umekar chronotherapy: a concept, pauperism and approaches, International Journal Of pharmaceutical Development & Technology ,Vol. 1, Issue 1, Jan – Jun 2011 ,1-10
15. S. Ohdo, Chronopharmaceutics: pharmaceutics focused on biological rhythm, 1237 Biol. Pharm. Bull. 33 (2010) 159–167.
16. S. Ohdo, Chronotherapeutic strategy: rhythm monitoring, manipulation and disruption, Adv. Drug Deliv. Rev. 62 (2010) 859–875.
17. S.-Y. Lin, Y. Kawashima Review Current status and approaches to developing press-coated chronodelivery drug systems, Journal of Controlled Release, 2011
18. J.D. Veldhuis, Pulsatile hormone secretion: mechanisms, significance and evaluation, in: D. Lloyd, E. Rossi (Eds.), Ultradian Rhythms from Molecules to Mind: A New Vision of Life, Springer, New York, 2008, pp. 229–248.
19. G. Barbarant, K. Prank, Pulsatile patterns in hormone secretion, Trends Endocrinol. Metab. 3 (1992) 183–190.
20. S.E. Sauder, M. Frager, G.D. Case, R.P. Kelch, J.C. Marshall, Abnormal patterns of pulsatile luteinizing hormone secretion in women with hyperprolactinemia and amenorrhea: responses to bromocriptine, J. Clin. Endocrinol. Metab. 59 (1984) 941–948.
21. M.H. Smolensky, B. Lemmer, A.E. Reinberg, Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma, Adv. Drug Deliv. Rev. 59 (2007) 852–882.
22. R.J. Martin, S. Banks-Schlegel, Chronobiology of asthma, Am. J. Respir. Crit. Care Med. 158 (1998) 1002–1007.
23. B. Bruguerolle, G. Labrecque, Rhythmic pattern in pain and their chronotherapy Adv. Drug Deliv. Rev. 59 (2007) 883–895.
24. T. Saitohl, Y. Watanabe, Y. Kubo, M. Shinagawa, K. Otsuka, S.A. Ohkawa, T. Watanabe, Intragastric acidity and circadian rhythm, Biomed. Pharmacother. 55(2000) 138–141.
25. J.G. Moore, F. Halberg, Circadian rhythm of gastric acid secretion in men with active duodenal ulcer, Dig. Dis. Sci. 31 (1986) 1185–1191.
26. C. Svanes, R.B. Sothern, H. Sorbye, Rhythmic patterns in incidence of peptic ulcer perforation over 5.5 decades in Norway, Chronobiol. Int. 15 (1998) 241–264.
27. F. Levi, C. Focan, A. Karaboue, V. de la Valette, D. Focan-Henrard, B. Baron, F. Kreutz, S. Giacchetti, Implications of circadian clocks for the rhythmic delivery of cancer therapeutics, Adv. Drug Deliv. Rev. 59 (2007) 1015–1035.
28. A. Altinok, F. Levi, A. Goldbeter, A cell cycle automation model for probing circadian patterns of anticancer drug delivery, Adv. Drug Deliv. Rev. 59 (2007) 1036–1053.
29. K. Hori, M. Suzuki, S. Tanda, S. Saito, M. Shinozaki, Q.H. Zhang, Circadian variation of tumor blood flow in rat subcutaneous tumors and its alteration by angiotensin II-induced hypertension, Cancer Res. 52 (1992) 912–916.
30. K. Hori, Q.H. Zhang, H.C. Li, S. Saito, Y. Sato, Timing of cancer chemotherapy based on circadian variations in tumor tissue blood flow, Int. J. Cancer 65 (1996) 360–364.
31. G.H. Tofler, D. Brezinski, A.I. Schafer, C.A. Czeisler, J.D. Rutherford, S.N. Willich, R.E. Gleason, G.H. Williams, J.E. Muller, Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death, N Engl J. Med. 316 (1987) 1514–1518.
32. F. Portaluppi, R.C. Hermida, Circadian rhythms in cardiac arrhythmias and opportunities for their chronotherapy, Adv. Drug Deliv. Rev. 59 (2007) 940–951.
33. F. Portaluppi, B. Lemmer, Chronobiology and chronotherapy of ischemic heart disease, Adv. Drug Deliv. Rev. 59 (2007) 952–965.
34. W. Waldhausl, Circadian rhythms of insulin needs and actions, Diab. Res. Clin.Pract. 6 (1989) S17–S24.

35. P.J.H. Jones, D.A. Schoeller, Evidence for diurnal periodicity in human cholesterol synthesis, J. Lipid Res. 31 (1990) 667–673.
36. V.M. Kumar, Sleep and sleep disorders, Indian J. Chest Dis. Allied Sci. 50 (2008) 129–136.
37. W.A. Hofstra, A.W. de Weerd, How to assess circadian rhythm in humans: a review of literature, Epilepsy Behav. 13 (2008) 438–444.
38. C. Poirel, M. Ennaji, Circadian aspects of epileptic behavior in comparative psychophysiology, Psychol. Rep. 68 (1991) 783–801.
39. L. Volicer, D.G. Harper, B.C. Manning, R. Goldstein, A. Satlin, Sundowning and circadian rhythms in Alzheimer's disease, Am. J. Psychiatry 158 (2001) 704–711.
40. B. Bruguerolle, N. Simon, Biologic rhythms and Parkinson's disease: chronopharmacologic approach to considering fluctuations in function, Clin. Neuropharmacol. 25 (2002) 194–201.
41. E. Haus, Chronobiology of hemostasis and inferences for the chronotherapy of coagulation disorders and thrombosis prevention, Adv. Drug Deliv. Rev. 59 (2007) 966–984.
42. D. Beauchamp, G. Labrecque, Chronobiology and chronotoxicology of antibiotics and aminoglycosides, Adv. Drug Deliv. Rev. 59 (2007) 896–903.
43. E. Haus, Chronobiology in the endocrine system, Adv. Drug Deliv. Rev. 59 (2007) 985–1014.
44. B.C. Youan, Chronopharmaceutical drug delivery systems: Hurdles, hype or hope?, Adv. Drug Deliv. Rev. 62 (2010) 898–903
45. Z. Khan, V. Pillay, Y.E. Choonara, L.C. du Toit, Drug delivery technologies for chronotherapeutic applications, Pharm. Dev. Technol. 14 (2009) 602–612
46. Simvastatin: a one-a-day treatment for hypercholesterolemia, Pebble Beach, California, Am. J. Med, 87, 1989, 1– 59.
47. Shiga, Fujimura A, Tateishi T, Ohashi K, Ebihara A, Differences of chronopharmacokinetic profiles between propranolol and atenolol in hypertensive patients, J Clin Pharmacol, 33, 1993, 756-761.
48. Reinberg A, Pauchet F, Ruff F, Gervais A, Smolensky MH, Levi F, Gervais P, Comparison of once-daily evening versus morning sustained-release Theophylline dosing for nocturnal asthma, Chronobiol. Int, 4, 1987, 409–419.
49. Lemmer B, Circadian rhythms and drug delivery, J. Control Release. Controlled Release, 16, 1991, 63-74
50. Shiga, Fujimura A, Tateishi T, Ohashi K, Ebihara A, Differences of chronopharmacokinetic profiles between Propranolol and Atenolol in hypertensive patients, J. Clin. Pharmacol., 33, 1993, 756-761
51. Bernard Bruguerolle, Gaston Labrecque, Rhythmic pattern in pain and their chronotherapy, Adv. Drug Del Rev, 59, 2007, 883–895
52. Santini ST, Cima MJ, Langer R, A controlled-release microchip, Nature, 397, 1999, 335–338.
53. Youan BC, Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery, J. Control. Rel, 98, 2004, 337–353.
54. FDA, Electronic Orange Book, Administration, Washington, DC, 2003 , 20.
55. Leslie S, Euroceltique, SA, United States, 1982, 20.
56. Prasanthi N. I., G. Swathi, Manikirin S.S., Chronotherapeutic: a new vista in novel drug delivery systems, , international journal of pharmaceutical sciences review and research, volume 6, issue 2, January – February 2011; article-014.

*****