



## CHRONOTHERAPEUTICS DRUG DELIVERY SYSTEMS CHALLENGES TO PHARMACEUTICAL FIELD

### ABSTRACT

Chronotherapy refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease, in order to optimize therapeutic outcomes and minimize side effects. The specific time that patients take their medication is very important as it has significant impact on treatment success. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary over time. Drug pharmacokinetics can also be time-dependent; therefore, variations both in a disease state and in drug plasma concentration need to be taken into consideration in developing drug delivery systems intended for the treatment of disease with adequate dose at appropriate time but also pharmacokinetics of medication. The effectiveness and toxicity of many drugs vary depending on the dosing time. Such chronopharmacological phenomena are influenced by not only the pharmacodynamics. 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. Theoretically, such ideal drug delivery system would potentially improve the safety, efficacy and patient compliance of old and new drugs. This review points to dosing time dependent alteration in therapeutic outcomes and safety of drug.

**Keywords:** RP-HPLC, Amlodipine, Losartan, Gradient.

### INTRODUCTION

Chronotherapy considers a person's biological rhythms in determining the timing and amount of medication to optimize a drug's desired effects and minimize the undesired ones. Study of influence of biological rhythm on the effects of medication is known as chronopharmacology while the science of study of biological rhythms is known as chronobiology.

With the understanding of biological time keeping the idea came that these rhythms must affect how the body responds to drugs administered over the course of the day<sup>1</sup>. In order to increase the effectiveness of drug there are many approaches have been applied, here one of the technique is described which chronotherapeutic drug delivery system is. Many functions of the human body vary considerably in a day.

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These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep/activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period) chronopharmaceutical drug delivery systems (ChrDDS) should embody time-controlled and site-specific drug delivery systems<sup>2</sup>

The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to development of drug delivery system<sup>3</sup>.

## Biological rhythms

A biological rhythm is a self-sustaining oscillation of endogenous origin. The spectrum of biological rhythms is broad as displayed in Table 1. Short-period rhythms of a second or so are quite common; the high frequency oscillations in the electrical impulses of the central and autonomic nervous systems and the high frequency pulsatile secretions of the neuro endocrine system are but a few examples. Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days. Included in this category are the ultradian ( $\tau < 20$  h), light intensities are thought to be the majorenvironmental cue involved in circadian entrainment. Light- signals are perceived by photoreceptor cells in the retina and transmitted to neurons of the SCN via the retinohypothalamic tract. A great deal of research shows that the inherited period of the human pacemaker clock is not precisely 24 h. In fact, inmost people, it is somewhat longer, closer to 25 h. Environmental times, termed synchronizers or zeitgebers, the strongest one being the daily light-dark cycle occurring in conjunction with the wake-sleep routine, set the inherited pacemaker circadian timekeeping systems to 24h each day.<sup>4</sup>

The human circadian time structure was depicted in

**Table 1:** (Spectrum of biological rhythms)

Period ( $\tau$ )	Major rhythmic components
<b>Short</b> [ $\tau < 0.5$ h]	Pulsates ( $0.1s < \tau < 1s$ )
<b>Intermediate</b> [ $0.5 h < \tau < 6$ days]	Circadian ( $20 h < \tau < 28 h$ ) Ultradian ( $0.5 h < \tau < 20 h$ ) Infradian ( $28 h < \tau < 6$ days)
<b>Long Period</b> [ $\tau > 6$ days]	Circamensual ( $\tau \sim 30$ days) Circaseptan ( $\tau \sim 7$ days) Circannual ( $\tau \sim 1$ year)

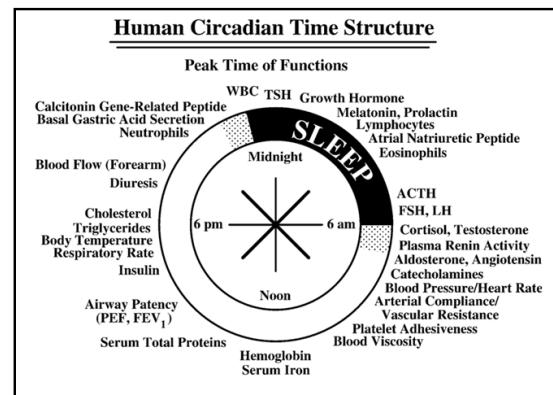
## Circadian time structure

The results of numerous biological rhythm studies help define the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock-like diagram like that shown in Fig. 1. This figure shows the peak time of a select number of human circadian rhythms in relation to the typical synchronizer routine of most

human beings-sleep in darkness from 10.30 P.M to 6.30 A.M and activity during the light of the day between 6.30 A.M and 10.30 P.M.

The peak gastric acid secretion, white blood cell count (WBC), calcitonin gene-related protein, and atrial 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 do the adrenocorticotrophic (ACTH), follicle stimulating (FSH), and luteinizing (LH) hormones. Plasma cortisol, renin activity, angiotensin, and aldosterone peak in the morning as do arterial compliance, vascular resistance, platelet aggregation, and blood viscosity. Hemoglobin and insulin concentrations peak at noon and in the afternoon, as do the spirometric measures of airways caliber FEV<sub>1</sub> (forced expiratory volume in 1 s) and PEF (peak expiratory flow rate).

The circadian rhythms of serum cholesterol and triglycerides and urinary diuresis crest early in the evening. The information conveyed in this figure clearly illustrates that the biochemistry and physiology of human beings are not constant; rather, they are variable in a predictable and coordinated manner during the 24 h.<sup>5</sup>



**Figure 1:** Human circadian time structure. Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (~6–7 a.m. to ~10–11 p.m.) alternating with nighttime sleep.

## Chronotherapy

Coordinating biological rhythms with medical treatment is known as chronotherapy, which allows for appropriate dosing of actives at the most suitable times of the day, thus improving efficacy and reducing undesirable side effects.<sup>6</sup>

### Advantages of Chronotherapy

- Chronotherapy is drug-free
- Chronotherapy is more effective when a person sleeps for several hours.
- While Chronotherapy patients often fall asleep this improves their condition and confidence as well.
- Chronotherapy is different from other treatments because it got the beginning, middle, and an end. So one can predict easily the point at which it will work.
- It gives you a new schedule like getting up and sleeping early which will be quite unusual for some days but it will give you a period to adjust psychologically
- Improved stability
- No risk of dose dumping<sup>7</sup>

### Disadvantages of Chronotherapy

- It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps or over 24 hours during the treatment.
- Person become less productive during chronotherapy and staying awake till the other schedule will be bit uncomfortable.
- Medical supervision is mandatory for this therapy.
- Large number of process variables.
- Trained /skilled person is needed for manufacturing.<sup>8</sup>

## CIRCADIAN RHYTHMS IN OCCURRENCE AND SEVERITY OF DISEASE

### 1) Bronchial Asthma

Airway resistance, bron constriction and exacerbation of symptoms increase progressively at night in asthmatic patients.

Risk of asthma attack is 100-fold greater during night time sleep than during daytime activity. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during early morning hours.<sup>9</sup>

Daily or alternate day, morning dose of glucocorticoid medications such as methyl prednisolone (Medrol) significantly moderates side effects and enhance therapeutic benefits. Oral prednisolone administered at 3 pm rather than at 8 am has been shown to be highly effective in the treatment of nocturnal asthma. Evening once daily dosing of controlled release theophylline tablets (Uniphyll 400 mg tablets) showed chronotherapeutic potential in the treatment of nocturnal and early-morning asthma. Many circadian dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms.

For example, cortisol (an anti-inflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am.

It is a good target for chronotherapy because broncho constriction and exacerbation of symptoms vary on circadian fashion. The enhanced understanding of the chronobiological impact upon the pathology of asthma, and the pharmacology and pharmacokinetics of the drugs used in its management, have led to new approaches to disease management and enhanced patient care.<sup>10</sup>

### 2) Pain

Pain threshold does not follow the same pattern in all tissues. The sensitivity threshold of the gingival to a cold stimulus was maximal at 18:00 h and reached a peak at 03:00 h (35% difference). Tooth sensitivity was lowest between 15:00 and 18:00 h, with a peak in pain intensity at 08:00 h (160% increase). Circadian rhythms in acute pain have been also recorded, such as in dental surgery, with a morning peak during the first postoperative day. The peak of morphine use occurred at 09:00 h and was the least at 15:00 h in patients undergoing elective surgery.

The peak demand for morphine or hydromorphone occurred in the early morning and was lowest during the night in postoperative gynecologic patients.<sup>11</sup>

### 3) Arthritis

Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAID's such as ibuprofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain. For osteoarthritis sufferers, the optimal time for a nonsteroidal anti-inflammatory drug such as Ibuprofen would be around noon or mid-afternoon.

The same drug would be more effective for people with rheumatoid arthritis when taken after the evening meal. There is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 of patients with rheumatoid arthritis. Symptoms of rheumatoid arthritis are most intense when awaking from night time sleep, while those of osteoarthritis are worse in the evening or at night. Chronopharmacological studies of once daily sustained release indomethacin preparation for the treatment of osteoarthritis have indicated that time of dosing influences tolerances and effectiveness<sup>12</sup>

### 4) Cardiovascular diseases

Several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. Cardiac events also occur with a circadian pattern. Numerous studies have shown an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia. BP is at its

lowest during the sleep cycle and rises steeply during the early morning awakening period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile. They have quite a marked rise in blood pressure upon awakening - called 'the morning surge' - that increase can be 3 mm Hg/hour (systolic) and 2mm Hg/hour (diastolic) for the first four to six hours after waking up. This is due to high catecholamine concentration in the early morning.<sup>13</sup>

### 5) Hypercholesterolemia

A circadian rhythm occurs during hepatic cholesterol synthesis. However, this rhythm varies according to individuals. Indeed, there is a large variation in plasma mevalonate concentrations between individuals. Therefore cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis. Many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. It seems therefore that cholesterol is synthesized during the night as well as during daylight; however the maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing. that cholesterol synthesis increases during the night. Free cholesterol levels are reported to be lowest at 2 pm to 6 pm and peak at 6 am. Chronotherapy can be achieved by timing the medication in accordance with circadian rhythm for hypercholesterolemia. Morning versus evening administration of HMG-CoA-reductase antagonists.<sup>14</sup>

### 6) Diabetes

The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been previously discussed. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion.

Providing basal insulin exogenously to patients with diabetes inhibits hepatic glucose production. Exogenous administration of mealtime doses promotes peripheral glucose uptake (i.e. it prevents postprandial increases in blood glucose concentration) as well as reducing hepatic glucose release.<sup>15</sup>

## 7) Epileptic seizure

Chronophysiology investigations considered at a rhythmometric level of resolution suggested several heuristic perspectives regarding (1) the central pathophysiology of epilepsy and (2) the behavioural classification of convulsive events. Such circulation studies also show that chronobiology rises some working hypotheses in psychophysiology and permits the development of new theoretical concepts in the field of neurological sciences. It is also well known that the brain area with the highest concentration in noradrenergic nerve terminals and nonadrenergic nerve terminals and noradrenaline (NA) have a circadian rhythm in their content of NA.<sup>16</sup>

## 8) Cerebrovascular accidents

The cerebrovascular accidents have been shown to occur on the first hours of morning between 10 am and 12 noons, and the incidence declines steadily during the evening and the midnight. A major objective of chronotherapy for cardiovascular disease is to deliver the drug in higher concentration during time of greatest need and in lesser concentrations when the need is less. ACE inhibitors are more effective when administered during night. Atenolol, Nifedipine and Amiodipine are more effective when administered at night.

The first chronotherapeutic therapy for hypertension and angina pectoris has recently been developed which matches drug delivery to the circadian pattern of blood pressure and rhythm of myocardial ischemia. Verapamil has been employed in this system where release is observed after 4-5 hours and continues for 18 hours.

Taken at bedtime, this provides optimal blood concentration between 4 a.m. And 12 noons. Data from recent studies demonstrate that antihypertensive and antianginal therapy can be designed to mimic the circadian rhythms.<sup>17</sup>

## 9) Myocardial Infarction

Onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between 6 am and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone.<sup>18</sup>

## 10) Peptic Ulcer Disease

A histamine antagonist when given at night shows the better result unlike when given at regular intervals around the clock. This is because the more acid secretion, more pain and perforation of gastric and duodenal ulcers are more subjective at night rather than in day time. It is well established that patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed, as the rate of stomach acid secretion is highest at night. The timing of administration of ulcer medications has a significant impact on their therapeutic effect.

It is well established that the patients with better the peptic ulcer disease are often experiences the greatest degree of pain in the near time that the patient go to bed. The timing of administration of ulcer medications has a significant result on their therapeutic effect shows the best chronotherapeutics drug delivery in the drug administration in the treatment of ulcer treatment which shows the right treatment a significant impact upon treatment and this will lead the according to the rhythms and biological time structure<sup>19</sup>

## 11) 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. 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.<sup>20</sup>

## 12) Allergic rhinitis

Common symptoms of allergic rhinitis are sneezing, nasal rhinorrhea, red itchy eyes, nasal pruritus and nasal congestion. Each of the symptoms was 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).

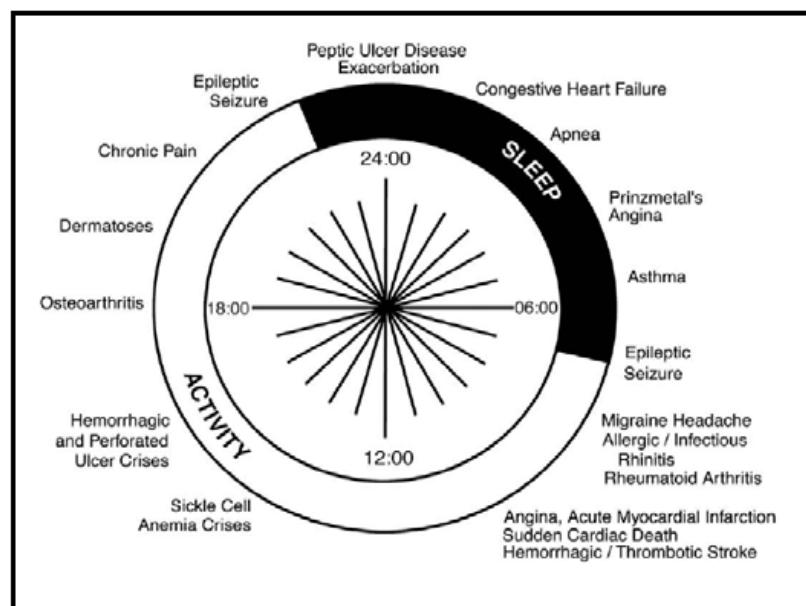
The early phase happens due to release of histamine, prostaglandins, cytokines, TNF- $\alpha$ , chemotactic factors etc resulting in sneezing, nasal itch, rhinorrhea. On the other hand late phase is shown due to elaboration, adhesion and infiltration of circulating leukocytes, T cells and eosinophils evoking nasal congestion, obstruction due to the exacerbation of inflammation of the nasal, sinus and other tissue of the upper airway.<sup>21</sup>

## 22) Sleep disorder

Many biological signalings 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. 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<sup>22</sup>



**Figure 1:** Display in the form of a 24 h clock diagram of the approximate time, in human following the diurnal activity/nocturnal sleep routine, when symptoms or events of diseases are worst or most frequently.

## Chronopharmacokinetics

Chronokinetics refers to dosing-time, i.e., rhythm-dependent, differences in the absorption, distribution, metabolism, and elimination of medication. Circadian rhythms in gastrointestinal pH can affect drug dissolution, and circadian rhythms in gastric emptying, motility, and blood flow can affect the rate, and in certain cases the amount, of drug absorption. Moreover, circadian rhythms in hepatic blood flow and enzyme activity can significantly affect drug biotransformation and metabolism, and rhythms in hepatic bile function and flow as well as renal blood flow, glomerular filtration, and tubular function can affect drug elimination. The pharmacokinetics, for example, the parameters of the time to peak concentration, peak height, elimination rate, volume of distribution and area under the time-concentration curve, of a number of medications have been found to be influenced by circadian rhythms.<sup>23</sup>

## Drug Absorption

In humans, for orally administered drugs, absorption was shown to be affected by circadian rhythm as gastric acid secretion and gastric pH, gastric motility, gastric emptying time, and gastrointestinal blood flow vary according to the time of day. These changes may have an impact on the time-dependent difference of drug absorption. For instance, circadian changes in pH may affect drug ionization according to its physicochemical properties. On the other hand, gastric emptying time is another important factor in the absorption of drugs. Gastric emptying rates were compared between morning (8 am) and evening (8 pm) in male subjects and it was found that gastric emptying  $t_{1/2}$  for the evening meal was significantly longer for solids but not for liquids compared with those of the morning meal. The increase in evening meal gastric emptying time may also cause a delay in reaching peak plasma concentrations for several drugs. Such variations may be related to the physicochemical properties of a drug, since most lipophilic drugs seem to be absorbed faster in the morning as compared to evening. The mechanisms underlying the chronokinetics of lipophilic drugs involve a faster gastric emptying time

and a higher gastrointestinal perfusion in the morning. However, such changes have not been shown for hydrophilic drugs. Feeding conditions also contributes to dosing time-dependent difference in drug absorption. Drug absorption by other than oral route of administration is also influenced by biological rhythms

**For example,** Skin permeability shows circadian time-dependent difference. For instance, in children, the skin penetration of an eutectic mixture of lidocaine (lignocaine) and prilocaine was reported to depend on the time of administration, with a higher rate of penetration occurring in the evening. Ocular absorption of topically applied beta-blockers is also demonstrated to be circadian time-dependent difference.<sup>24</sup>

## Drug distribution

Circadian changes in biological fluids and tissues related to drug distribution are documented to vary according to time of day. Blood flow depends on several regulatory factors including sympathetic and parasympathetic systems which activities are known to be circadian time dependent with a predominant diurnal effect of the sympathetic system. Thus, diurnal increase and nocturnal decrease of blood flow may explain a possible difference in drug distribution depending on dosing time. Plasma proteins such as albumin or alpha 1 glycoprotein acid have been documented to be circadian time-dependent.

The plasma concentrations of albumin and alpha 1 glycoprotein acid show peak around noon. As a result, daily variations have been reported for drug protein binding. Temporal variations in plasma drug binding may have clinical implications only for drugs that are characterized by a high protein binding (>80%) and a small apparent  $V_d$ .<sup>25</sup>

## Drug Metabolism

Hepatic drug metabolism is generally assumed to depend on liver enzyme activity and/or hepatic blood flow: both have been shown to be circadian time-dependent. Enzyme activities show circadian time-dependent difference in many tissues such as brain, kidney,

and liver. Conjugation, hydrolysis and oxidation were shown to be circadian time dependent. For drugs with a high extraction ratio, hepatic metabolism depends on hepatic blood flow. Circadian variations in hepatic blood flow induce changes in liver perfusion and, thus, temporal variations in the clearance of such drugs. Clearance in healthy volunteers shows the highest values in the early morning.<sup>26</sup>

### Drug excretion

Renal physiological functions such as glomerular filtration, renal blood flow, urinary pH and tubular resorption show circadian time-dependent difference with higher values during daytime. These rhythmic variations in renal functions may contribute to circadian dependent change in drug urinary excretion. The rhythmicity in urinary pH modifies drug ionization and may explain that acidic drugs are excreted faster after an

evening administration as demonstrated for sodium salicylate and sulfasalazine. Such variations are obviously more pronounced for hydrophilic drugs. The circadian timing system plays a key role in the changes of toxicity of drugs by influencing their metabolisms in the liver and intestine in addition to their excretion via bile flow and urine. Rats with chronic biliary drainage under a rigid lighting schedule (light on at 6 am and off at 6 pm) exhibited a remarkable circadian rhythm of bile flow, biliary concentrations and excretory rates of bile salts, cholesterol and phospholipids. On the other hand, the excretion rates of these polyamines were found to highest in the morning in healthy volunteer subjects.<sup>27</sup>

Possible physiological factors influencing circadian stage-dependent pharmacokinetics of drug

<b>Absorption</b>
<b>Oral:</b> Gastric pH, Gastric motility, Gastric emptying time, Gastrointestinal blood flow, transporter.
<b>Parenertal:</b> Transdermal permeability, Ocular permeability, Pulmonary permeability
<b>Distribution</b>
Blood flow, albumin, $\alpha$ 1-acid glycoprotein, red blood cells, transporter.
<b>Metabolism</b>
Liver enzyme activity, hepatic blood flow, gastrointestinal enzyme.
<b>Elimination</b>
Renal, Biliary, Intestinal, Glomerular filtration, Renal blood flow, Urinary pH, Electrolytes, Tubular resorption,

### Chronodynamics

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, second messenger and ion channel dynamics, and rate-limiting step(s) in metabolic pathways. Both the desired/

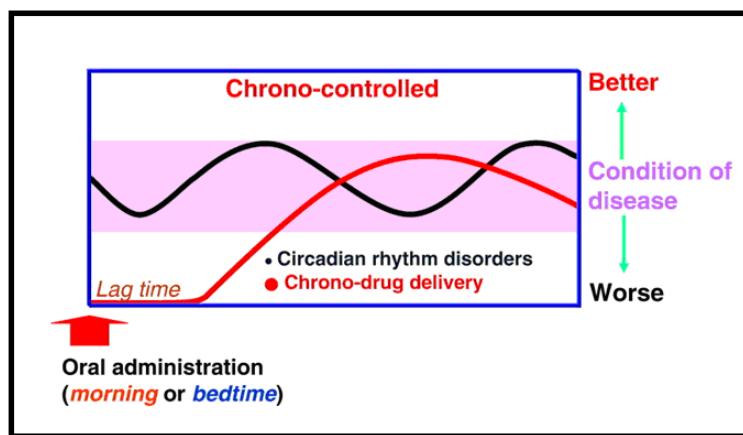
beneficial and undesired/adverse effects of medications can vary significantly according to their administration time.<sup>28</sup> Non-steroid class of anti-inflammatory drugs (NSAIDs), are prescribed to manage the pain, stiffness, and inflammation of rheumatoid and osteoarthritis. A number of clinical trials with NSAIDs have shown that they exert better therapeutic effect on the aggravating morning symptoms of rheumatoid

arthritis, and are better tolerated, when ingested around or at bedtime than in the morning upon arising. On the hand, NSAIDs are more effective in reducing the afternoon and evening peak intensity of osteoarthritis symptoms when ingested in the morning or around lunch time, although the likelihood of gastric intolerance and other adverse effects is greater when they are routinely ingested in the morning as opposed to evening.<sup>29</sup>

### 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. Classes of medications that have high risk of adverse effects and relatively narrow therapeutic range, in particular, are likely to show significant dosing-time differences in safety.

These medications are best tolerated — cause least adrenocortical suppression when ingested as a single daily dose in the morning at the commencement of the daily activity span, when a part or all of a moderate daily dose of the glucocorticoid is ingested, injected, infused, or inhaled late in the day, especially in the evening between dinner and bedtime, the risk of adrenocortical suppression is heightened, even after only a few days of treatment. These chronotoxicological findings have significantly impacted the manner in which synthetic corticosteroids are used in clinical practice. These and other findings from both human and laboratory animal studies imply that drug-delivery systems must be designed to minimize the potential risk of adverse effects of pharmacotherapies by taking into consideration their specific circadian chronotoxicologies<sup>30</sup>



### Circadian rhythm of clinical diseases

Predictable circadian variation can be useful in diagnosis of.

Sl. No	Diseases / Syndrome	Circadian rhythmcity
1	Allergic rhinitis	Symptoms worse in early morning
2	Bronchial asthma	Exacerbations more common during the sleep period
3	Arthritis rheumatoid	Symptoms are most intense rheumatoid upon awakening
4	Osteoarthritis	Symptoms worse in the middle/latter portion of the day
5	Anti cancer agents	Doxorubicin, Cisplatin, methotrexate
6	NSAIDs	Ibuprofen, Indomethacin, Tenoxicam, Acetylsalicylic acid
7	Angina pectoris	Chest pain and ECG changes more common during the early morning
8	Myocardial infarction	Incidence greatest in the infarction early morning
9	Peptic ulcers	Symptoms worse after gastric emptying and in the early morning (sleep period)
10	Stroke	Incidence greatest in early morning
11	Epilepsy	Incidence greatest in early morning

## CONCLUSION

The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 hours rhythms of biochemical, physiological and behavioral processes under the control of circadian clock. The knowledge of 24 h rhythm in the risk of disease plus evidence of 24 hours

Rhythm dependencies of drug pharmacokinetics, effects and safety constitute the rationale for pharmacotherapy. The pharmacokinetic and pharmacodynamics of medication very depending on biological rhythms. The goal of pharmacotherapy is hormonal substitution to mimic the rhythmic variation of hormone levels in healthy individuals. One approach to increasing the efficiency of pharmacotherapy is administering drugs at times during which they are best tolerated. The application of biological rhythm to pharmacotherapy 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 chrono pharmacotherapy. 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.

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