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TIME-OPTIMIZED DRUG DELIVERY: THE ROLE OF CHRONOTHERAPY IN MODERN THERAPEUTICS

Sadhana M. Deokar *, Gitanjali D. Batwal, Priyanka P. Chopde and Priya V. Nagare

Rajmata Jijau Shikshan Prasarak Mandal College of Pharmacy, Dudulgaon, Pune - 412105, Maharashtra, India.

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Correspondence to Author:
Ms. Sadhana M. Deokar

Assistant Professor,
Rajmata Jijau Shikshan Prasarak Mandal College of Pharmacy,
Dudulgaon, Pune - 412105,
Maharashtra, India.

E-mail: snpawar75@gmail.com

ABSTRACT: Circadian clock is an impressive timing system responsible for the control of several metabolic, physiological and behavioral processes. Chronotherapeutic is an approach that aligns the timing of drug delivery with the rhythms of diseases or disorders to optimize therapeutic responses and minimize side effects. This method ensures the purposeful and controlled release of medications in varying amounts over a 24-hour period. Chronotherapeutic drug delivery systems are becoming increasingly important in pharmaceutical technology, as they reduce dosing frequency and toxicity while delivering drugs in sync with the circadian rhythm (CR) of specific diseases, ensuring optimal treatment when symptoms are at their peak. Eventually, the benefit goes to the patient due the compliance and convenience of the dosage form. Chronotherapy is the conveying drugs in the body at the target site by maintaining perfect synchronicity with circadian rhythms. Chronotherapy refers to the use of circadian, ultradian, in radian& seasonal or other rhythmic cycles in the application of therapy. Some of the conditions, which may be significantly benefited, are hypertension, myocardial infarction, bronchial asthma, peptic ulcer, arthritis, duodenal ulcer, diabetes, neurological disorder, cancer and hypercholesterolemia. Chronobiology is the branch of science that studies periodic phenomena in living organisms and their adaptation to biological rhythms. These rhythms can occur annually, monthly, daily, or at even shorter intervals. Daily rhythms lasting 24 hours are known as circadian rhythms. This review highlights chronobiology, chrono pharmacology, and the chrono kinetics of various drugs, as well as their applications in the treatment of different diseases, known as chronotherapeutic.

INTRODUCTION: The term "chrono" mainly refers to the research that every metabolic occurrence experience rhythmic variation in time [6]. Chronotherapeutics is a therapy that involves timing the *in-vivo* availability of a drug to coincide with the rhythms of a disease or disorder in order to maximize therapeutic responses and minimize side effects.

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This approach aims to deliver medications in different amounts over a 24-hour period in a profound and intentional manner [7]. In order to maximize desired effects and reduce unfavorable ones, pharmacotherapeutics considers the rhythm determinants of the human circadian time structure when determining the drug-delivery pattern, dosage, and administration time [8, 9].

Circadian rhythms are naturally occurring, self-sustaining oscillations that have a 24 hour periodicity. They control a variety of bodily processes, including hormone synthesis, metabolism, and sleep patterns. Human physiological functions change rhythmically, following the body's inherent biological clock.

Biological Clock: A biological rhythm is a self-sustaining oscillation of endogenous origin [10]. The term circadian comes from Latin word Circa means 'about' and Dian means 'day'.Circadian rhythms are the most vital type of biological rhythms and hold significant importance for both humans and animals. They play a crucial role in regulating body temperature, heart rate, blood pressure, organ blood flow, pulmonary and kidney functions, as well as the levels of neurotransmitters, hormones, enzymes, electrolytes, and glucose [5]. The study of biological rhythms and their underlying mechanisms is known as chronobiology [11]. The best known and most studied biological rhythm patterns in humans are the circadian rhythms with a frequency of about 24 h [12]. Chronobiology refers to the study of the biological rhythms and mechanisms in living systems. This science considers that the bioprocesses and functions of all living organisms exhibit predictable variability over time. Biological rhythms enable adaptation to environmental conditions and are driven by empirical, physiological, and molecular biological mechanisms [13]. There are mainly three different types of biological rhythms which are observed in humans such as:

Ultradian: These are the cycles shorter than a day. e.g. 90 minutes sleep cycle

Circadian: This lasts for over 24 hours. e.g. sleeping and waking patterns.

In Radian: cycles longer than 24 hours. e.g. monthly menstruation Seasonal: such as seasonal affective disorder (SAD), this causes depression during the short days of winter in susceptible people [14].

Circadian Time Structure: The temporal organization of humans is defined in part by the findings of a multitude of biological rhythm studies. One way to visualize the human circadian time structure is to plot the peak time of 24 hour rhythms on a clock-like diagram such as the one presented in **Fig. 1.** This figure plots the peak time of a particular set of human circadian rhythms relative to the average synchronizer routine of most humans, which consists of sleeping in the dark from 10.30 P.M. to 6.30 A.M. and being active during 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 natriureticpeptide occurs late at night or early in sleep. During sleep, levels of growth hormone, thyroid-stimulating hormone (TSH), blood lymphocytes, eosinophils, and plasma melatonin and prolactin peak, along with hormones like adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Plasma cortisol, renin activity, angiotensin, and aldosterone levels peak in the morning, along with arterial compliance, vascular resistance, platelet aggregation, and blood viscosity. Hemoglobin and insulin concentrations reach their peak around noon and in the afternoon, as do spirometry measures of airway caliber, such as FEV1 (forced expiratory volume in 1 second) and PEF (peak expiratory flow rate).

Serum cholesterol, triglycerides, and urinary diuresis reach their peak levels 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 [15].

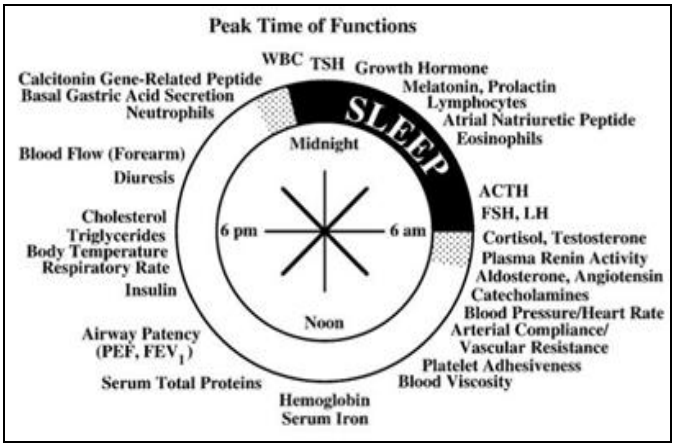

FIG. 1: HUMAN CIRCADIAN TIME STRUCTURE

Implication of Circadian Rhythm in Diseases: The concept of homeostasis has its roots in the early history of medical study, before techniques, technologies, and diagnostic instruments were developed enough to emphasize the significance of inter- and intra-individual variability. Different organ systems have different circadian rhythms, which are not homeostatic in nature. Consequently, day-night cycles impact the prevalence and intensity of numerous chronic illnesses [16].

Potentially affecting the approach taken to treat them. Numerous illnesses exhibit the intensity of their symptoms around the clock and are influenced by the biological rhythm [17]. Nighttime is the peak time for peptic ulcer and gout episodes. Conditions include asthma, congestive heart failure, and acute pulmonary edema deteriorate at night [18, 19]. When you wake up in the morning or during the night, you may notice more symptoms of rheumatoid arthritis and allergic rhinitis [20, 21, 22]. Morning time is a prevalent time for fatal pulmonary embolisms, strokes, and hypertensive crises [23, 24]. In the morning, depression is also more prevalent [25]. The severity of osteoarthritis symptoms increases with daily activities, peaking in the late afternoon and evening [26]. In the afternoon as opposed to the morning, bleeding ulcers are more common [27].

Chronobiology: Scientific constraints known as "chronobiology" are used to study and quantify the biological clock's processes, which include significant cyclical indicators of life in unicellular and multicellular organisms [28].

Chronopharmacology: The timing of chronotherapeutic medications to complement illness cycles and minimize adverse effects is closely linked to *in-vivo* drug accessibility. It focuses on the discovery that pharmaceutical pharmacokinetics and pharmacodynamics, as well as peak-to-trough rhythmic behavior in illness symptoms and risk factors, is symbiotic [28]. Patients with rheumatoid arthritis and related crippling joint disorders may have better pain relief from non-steroidal anti-inflammatory drugs (NSAIDs) if they take their prescription prior to, during, or within five to seven hours of the onset of pain. Patients with arthritis may get relief from morning discomfort by taking NSAIDs prior to bed. In a similar vein, asthma medicine appears to be taken at night rather than during the day. Numerous factors that depend on the circadian rhythm appear to be involved in the worsening of nocturnal asthmatic symptoms. Studies show that the body absorbs theophylline more slowly at night. An increased understanding of the chronobiological influence on asthma pathology has also enhanced modern disease control techniques. Both healthy and sick tissues are cytotoxic to anticancer medicines [29]. Traditionally, cancer treatments entail administering medications in accordance with hospital schedules and staff work hours (Levi *et al.* 2010). Contrarily, chronotherapy involves administering each medication in accordance with a delivery pattern that adheres to exact circadian periods in order to maximize both efficaciousness and tolerability (Levi and Okar 2011). Chrono modulated delivery schedules have been a major part of this [30].

Chronotherapy: Chronotherapy is the practice of aligning medical treatment with the body's natural rhythms. It helps ensure medications are given at the best times of the day, improving their effectiveness and reducing side effects [31]. The basis for pharmacotherapy, or chronotherapy, is the understanding of the role that the 24 hour rhythm plays in disease risk and the data indicating the dependence of medication pharmacokinetics, effects, and safety on the 24 hour rhythm. Taking medications at the periods when they work best and/or are most well-tolerated is one way to improve the effectiveness of pharmaceutical treatment. When using a specially designed drug delivery method to synchronize drug concentrations to rhythms in disease activity, together with the proper timing of traditionally prepared tablets and capsules, a medicine can be used in chronotherapy. Drugs have different pharmacokinetic and pharmacodynamic properties based on biological rhythms [4].

Ideal Characteristics of Chronotherapy:

- Should possess an identifiable and timely triggering biomarker for a particular illness state.
- Non-toxic within authorized usage limits.
- Feature a feed-back control mechanism (e.g., self-regulated and adaptive capacityto).
- Biodegradable and biocompatible, particularly when used parenterally.
- Simple and affordable to produce.
- Easy to follow, helping patients stick to their dosing schedule [32].

Advantages:

1. Drugs are not used in chronotherapy.

2. When a patient sleeps for several hours, chronotherapy works better.

3. Despite the fact that sufferers with chromophyll frequently fall asleep, this helps them feel better and more confident.

4. Chronotherapy has a beginning, middle, and end, which sets it apart from other forms of therapy. Thus, it is easy to forecast when it will start to function [3].

5. It provides you a new routine, such as rising and sleeping earlier, which for a few days will be rather uncommon but will allow you time to acclimate mentally.

Disadvantages:

The patient sleeps for more than 24 hours throughout the therapy, which causes a non-24-hour sleep waking syndrome to emerge afterwards. Although the level of danger is unknown, it's not very prevalent.

1. A person may occasionally lack sleep.

2. A person's productivity decreases throughout chronotherapy, and staying up late till the alternate schedule is a little unpleasant.

3. Because treatment requires time, you will need to take a break from your hectic routine.

4. This treatment requires medical monitoring. Additionally, routine consultation with sleep specialists is advised.

5. A person must stay awake till the following sleep schedule. He must thus occupy himself in order to stay awake till the other timetable.

6. The therapist may occasionally cause the patient to feel abnormally hot or chilly.

7. Need to see a doctor frequently to prevent negative consequences [33].

Chronotherapy of Diseases:

Asthma: This condition is marked by inflammation of the airways, which makes the lower respiratory tract hyperresponsive to different environmental stimuli. In the patient, airway resistance gradually gets worse at night. The most prevalent illness when there is a significant time-varying circadian variation is asthma. The prevalence of asthma symptoms is higher during the early morning hours. Asthma symptoms are 50–100 times more prevalent at night. Asthma flare-ups throughout the night are indicative of altered biological functioning because of bronchial patency circadian cycles, hyperreactivity of the airways to acetylcholine, histamine, and house dust, and plasma levels of cortisol, adrenaline, histamine, and cyclic AMP. The sustained release theophylline, transdermal tulobuterol patch, and once-daily inhalation of the glucose corticosteroid caledonite have all been demonstrated to be beneficial in [34].

Cardiovascular Disease: When a person has cardiovascular disease, their morning capillary resistance and vascular reactivity are higher and subsequently decrease. Relative hypercoagulability of the blood is caused by increased platelet aggregation and decreased fibrinolytic activity in the morning. Additionally, blood pressure peaks in the early morning hours of the day and falls during the sleep cycle. According to these observations, the 24 hour period is also unevenly distributed in terms of myocardial ischemia, angina pectoris, acute myocardial infarction, congestive cardiac failure, and sudden cardiac death. The early afternoon and early evening are the times of day when the greatest expected events occur. Early in the morning is when sympathetic activity and the Renin-Angiotensin-Aldosterone Axis peak. Physical and other external factors that affect the ANS Differences are also influenced by l activity, emotional state, meal, and sleep/wake schedule. Now a days, novel drug delivery systems are available for chronotherapeutic antihypertensive products such as calcium channel blockers, β-adrenoceptor antagonists, and oral nitrates, whose pharmacokinetics and pharmacodynamics are influenced by circadian rhythm. These products release the drug during the vulnerable period between 6 am and noon after medication administration at 10 pm [35, 36, 37].

Myocardial Infarction: Research has indicated that the onset of myocardial infarction is more common in the morning, with 34% of cases happening between 6 A.M. and noon. Mornings are more common for acute cardiac arrest and transitory myocardial ischemia.

It has been proposed that the rise in platelet aggregation, cortisol, catecholamine release, and vascular tone are the reasons of these observations [38, 39].

Cancer: Research on both humans and animals indicates that chemotherapy may be less harmful and more successful if cancer medications are given precisely at certain times that maximize tumor cell cycles while being less harmful to healthy tissue. When tumors are tiny and developing at their fastest rate, as well as when they are larger and expanding more slowly, the regular circadian shifts in tumor blood flow and cancer growth are important. The time of chemotherapy administered on a circadian rhythm has a significant impact on drug toxicity patterns and severity, maximum tolerated dosage, average dose intensity, tumor response quality and frequency, and cancer patient survival. Cancer chrono genetic therapy has been found effective in suppressing tumors *in-vivo*. For example, it has been shown that CLOCK genes dictate sensitivity to the anticancer drug cyclophosphamide [40, 41].

Peptic Ulcer: The gastrointestinal tract's many processes follow circadian cycles, with the production of stomach acid peaking at night. Small Owel movement, stomach emptying, and gastric acid production all slow down during night. A key element in the healing of duodenal ulcers is the suppression of nocturnal acid production. Therefore, the suggested dosage for H2 antagonists for an active duodenal ulcer is once daily at bedtime. Chronotherapy, which blocks H2 receptors at night, can solve issues with a prolonged or significant drop in intragastric acidity for 24 hours, therefore reducing the risk of infection and infestation of the intestines, bacterial overgrowth, and the potential creation of N-nitrosamine [42].

Arthritis: Rheumatoid arthritis and osteoarthritis can be differentiated by the time of day when a patient experiences the most pain in their joints. Rheumatoid arthritis is characterized by morning stiffness, but osteoarthritis symptoms are often greater in the afternoon and evening. Non-steroidal anti-inflammatory medications (NSAIDs) are given late at night, which is better for the therapy, in order to relieve the stiffness and morning discomfort associated with rheumatoid arthritis. When taken in the morning, the novel cyclooxygenase-2 inhibitors successfully ease the symptoms of osteoarthritis, and when a small portion of the dose is given in the evening, improved outcomes are observed in cases of rheumatoid arthritis. Chronotherapy for all types of arthritis uses standard treatment, which includes corticosteroids and non-steroidal anti-inflammatory drugs. However, the timing of the drug's dosages is matched to the disease's rhythms, ensuring that the drug's peak blood levels coincide with the peak of pain [43, 44].

Hypercholesterolemia: Even when fasting, the nighttime hours are when greater rates of cholesterol ingestion associated with hypercholesterolemia and hepatic cholesterol genesis occur. It has been observed that the free cholesterol levels are lowest between 2 and 6 p.m. and greatest in the morning and early afternoon when HMG-CoA reductase antagonists are administered [45].

Allergic Rhinitis: In the early morning, symptoms such as sneezing, runny nose, and nasal congestion are usually more severe. Maximum relief may be given at the moment when the patient most needs it if the drug's administration can be coordinated with the biological time structure that has the peak pharmacologic activity and coincides with the period of greatest discomfort [46].

Mood Disorders: Both men and women with seasonal and other mood disorders may benefit from the partial nighttime sleep deprivation and the scheduled exposure to artificial light and daytime light intensity. These treatments may also lessen depression that occurs before or after menopause. When isosorbide mononitrate and nifedipine were administered in sustained release dose forms, no such difference was seen in the mood disorders [47].

Diabetes: The circadian rhythms of insulin and its activity are clinically and physiologically significant in type I diabetes. Thus, insulin is released in a pulsatile manner, however it can occasionally be erratic. Insulin can exhibit its ideal activity within a cyclic rhythmicity of 8-30 minutes. The insulin release mode is influenced by the circadian rhythm of secretion of the insulin

release and action modulators. Thus, there is a short-term rhythmicity difference between the maximum and lowest plasma insulin concentration, and a complicated secondary circadian rhythm that varies between early morning and late afternoon insulin resistance [48].

Sleep Disorders: The central and autonomous neurological systems produce a variety of biological signals, including sleep disorders, which exhibit a complicated temporal structure with pulsating and rhythmic fluctuations in several frequencies. The primary components of sleep are circadian, rhythmic alterations in physiological, biochemical, and psychological processes. Numerous illnesses may arise from disruptions to the circadian cycle or aberrant physiological or psychological processes that occur during sleep. Additionally, circadian rhythm disruptions vary from person to person, and treating specific sleep problems would require identifying each individual variance [49].

Epileptic: The circadian rhythm is also a major factor in epileptic episodes. Humans and animals have both been shown to be affected by the biological clock while experiencing certain partial seizures. Because the circadian psycho-physiological patterns of epilepsy show dynamic biological systems that show some intermodulation endogenous processes between observation and seizure susceptibility, behavioral chronobiology allows the detection of new regulation processes that concern central mechanisms of epilepsy. When chronobiologic investigations are applied to epileptic behavior, new heuristic features in the field of comparative psychophysiology may be developed [50].

Alzheimer's disease: Individuals suffering from Alzheimer's disease also exhibit a shift in their circadian rhythm. Compared to normal healthy persons, those with Alzheimer's symptoms have reduced inter-day consistency in motor activity and a larger percentage of nighttime activity, as well as decreased peak time activity of macrophages. The core body temperature is also greater in patients and the circadian anomalies are noticed associated with cognitive and functional decline in this disease [51].

Parkinson's disease: Autonomic dysfunction is responsible for postprandial hypotension and increased diurnal blood pressure fluctuation. Parkinson's disease is characterized by several changes in the circadian rhythm of blood pressure. However, the existence of a circadian rhythm in this condition has not been assessed in clinical data due to the difficulty in estimating the daily changes of the disease's phase-specific motor activity pattern and the consequent involvement of medications [52].

TABLE 1: DISEASES REQUIRING CHRONOTHERAPEUTIC DRUG DELIVERY

Disease	Chronological Behaviour	Drug Used
Cardiovascular disease	Blood pressure reaches its lowest levels during the night or early morning upon waking	Nitroglycerin, Calcium blocker, ACE Inhibitors
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonyl urea, Insulin, Biguanide
Asthma	Attacks are more likely to occur during the night or in the early morning hours	Antihistaminic
Arthritis	Pain in the morning and more pain at night	NSAIDS, Glucocorticoids
Peptic ulcer	Pain at night, when stomach is empty, or after eating	H2 blockers, Proton pump inhibitors
Hypercholesterolemia	Cholesterol synthesis is typically higher at night than during the daytime	HMG CoA reductase inhibitors

CONCLUSION: Diseases having a chronological pathophysiology are not well treated by conventional dosage formulations. Conversely, the circadian rhythm of a number of disorders can be easily mimicked by CDDS. Several methods, including time-controlled release systems, stimuli-induced systems, and external stimuli-dependent systems, are used to create efficient CDDS. Numerous pharmaceutical companies are developing chronotherapeutic delivery systems, and several chronotherapeutic drugs are already on the market, suggesting that chronotherapeutic delivery systems have a bright future [53]. Chrono pharmaceutics promises better patient outcomes and improved disease management in the future. The major drawback of these systems is their reliance on human action to trigger drug release. Therefore, an ideal chronotropic system should be

self-regulating, capable of being taken at any time, and able to account for environmental factors such as sleep wake cycles, light dark phases, and activity rest status [54]. Circadian disorders typically necessitate chrono pharmacotherapy, which is simply and extremely efficiently achieved with a pulsatile drug delivery system. With the development of pulsatile drug delivery, the achievement of safe and efficient therapy can be guaranteed [2]. Drug exposure, side effects, and efficacy have all been shown to be influenced by dosing timing. Numerous disease processes also exhibit rhythmic alterations across 24 hour or other durations. Over the last two decades, a great deal of information has been discovered on how circadian rhythms are created inside individual cells and how they affect drug metabolism, detoxification, and effectiveness [55].

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