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Review Article

Chronopharmacology: A new way to treat disease

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ABSTRACT: Chronopharmacology aims at the use of biological rhythms in the clinical treatment to enhance both effectiveness and tolerance and minimizes the side effects of a drug by determining the best biological time for its administration. It involves bot h the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. Rhythmicity has been detected in several physiological variables such as pulse, temperature, blood pressure and hormonal secretions like diurnal variation insulin effects on blood glucose. The goal of chronopharmacology is to optimize the therapeutic effect and control or reduce the adverse effects without altering the functioning of the drug in the body. Auto-induction, auto- inhibition and food effects are considered to be the reasons of chronopharmacology. The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 hrs rhythm of biological, physiological and behavioral processes under the control of the circadian clock. Now a day, the chronopharmacological principle is used in the therapy of various diseases such as angina, hypertension, asthma, peptic ulcer, diabetes, migraine, etc. This article aims to introduce chronopharmacology, their terminologies, causes and need of it, biological clock and biological rhythms in various biological systems and the dependence of diseases on biological rhythms.

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INTRODUCTION

Functions of the human body vary day to day and adverse effects of dosing timing of medications about these variations can lead to changes in both the disease biological rhythm [1]. Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities. The goal of chronopharmacology is to improve our understanding of periodic and thus predictable (e.g. circadian) changes in both desired effects (Chronoeffectiveness) and tolerance (Chronotolerance) of medications. The science dealing with the phenomenon of biological rhythmicity in the living organism is called chronobiology. The branch dealing with the pharmacological aspects of chronobiology is termed as Chronopharmacology which may be subdivided into chronotherapy, chronopharmacokinetics and Chronotoxicity [2].

Important Terminology [3]

Chronopharmacology 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 of medications affect biological timekeeping and the features (period, level, amplitude, and phase) of biological rhythms.

Chronokinetics refers to dosing-time, i.e. rhythm-dependent, differences in the absorption, distribution, metabolism, and elimination of medications.

Chronodynamics refers to dosing-time, i.e., rhythm-dependent, differences in the effects of medications.

Chronesthesy refers to medications and other chemical substances typically exhibit dose and/or concentration-response relationships. Chronesthesies are demonstrable by the direct application of medications to their sites of action and by differences in the blood/tissue concentration–biological response to medications when administered at different times during the 24 h.

Chronotherapeutics refers to the application of chronobiological principles in the treatment of diseases. Chronotherapeutics takes into account biological rhythm determinants in (i) disease pathophysiology (chronopathology), (ii) chronopharmacology (chronokinetics, chronodynamics, chronesthesy, and chronotoxicology) of medications, and (iii) attributes (period, phase, amplitude, and level) of the human biorhythmic time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects. The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness.

Advantages of Chronotherapy [4]

- Chronotherapy is drug-free
- It is more effective when a person sleeps for several hours.
- While Chronotherapy patients often fall asleep this improves their condition and confidence as well.
- •It is different from other treatments because it got the beginning, middle, and end. So, one can predict easily the point at which it will work.
- It gives a new schedule like getting up and sleeping early which will be quite unusual for some days but it will give a period to adjust psychologically.

Disadvantages of Chronotherapy [4]

- It develops a non 24 hours of the sleep-wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment. It's not quite common but the degree of risk is not known.
- A Person may also be deprived of sleep sometimes.
- The Person becomes less productive during chronotherapy and staying awake till the other schedule might be a bit uncomfortable.
- Person will have to take some time off from your busy normal schedule as its time taking therapy.
- Medical supervision is mandatory for this therapy and regular consulting of sleep specialists is recommended.
- Person has to keep himself awake till the next sleep schedule so he has to get himself busy so that he stays awake till the other schedule.
- A Person undergoing therapy may feel unusually hot or cold sometimes.
- The Patient needs to consult the doctor regularly to avoid side effects.

Ideal characteristics of Chronotherapy [4]

- Non-toxic within approved limits of use
- Should have a real-time and specific triggering biomarker for a given disease state
- Should have a feedback control system (e.g. self-regulated an adaptative capability to circadian rhythm and the individual patient to differentiate between awake – sleep status)
- Biocompatible and biodegradable, especially for parenteral administration
- Easy to manufacture at an economic cost.
- Easy to administer into patients to enhance compliance with the dosage regimen.

Causes for Chronopharmacology

There are different reasons for this which may be summarized as:

Autoinduction – A repetitive dose of a drug induces or increases enzymes responsible for its elimination, thereby increasing its clearance. This is called as autoinduction. It is dependent on the dose and concentration of the drug. It has several therapeutic consequences. It affects the time to achieve steady-state and limits one's ability to use information from a single dose to predict kinetics after a repeated dose or continuous administration. Carbamazepine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration that either oral bioavailability decreases or clearance increase with time [5].

Autoinhibition – It may occur during the course of the metabolism of certain drugs. In this case, the metabolites formed an increase in concentration and further inhibit the metabolism of the parent drug. In biochemistry, this phenomenon is called as product inhibition or allosteric inhibition or feedback inhibition [5].

Food Effects – Gastric emptying is slowed or delayed by food, often resulting in a decrease in the peak concentration and an increase in the time of its occurrence following a single dose of the drug. It is a major cause of circadian variations in th e case of patients who tends to eat more in the evening than at breakfast. Usually, when absorption is slowed by food, the rate of input into the liver and concentration of drugs entering the liver are lowered and prolonged and this metabolism is lower [1].

Need for Chronopharmacotherapy

It is required to monitor therapy to limit the duration of therapy especially in cases where patients are already having compromised renal, cardiac, and hepatic or any other function of the body. Any type of accumulation of drugs in these organs causes greater toxicity which may lead to diminished function of the organ. Thus, the chronopharmacotherapy becomes a very important part of the treatment of several diseases particularly those effecting targeted body parts [5].

Steps involved in the evaluation of Chronopharmacology [1]

- Identification of its occurrence: its cause should be identified to know which type of variation is seen. This

step also clarifies the point that whether the effect is due to a biological clock or not.

- Determination of the parameter affected: the pharmacokinetic parameters which are affected need to be known. However, more than one parameter may be affected but a need arises to study for all the possible parameters.
- Mechanism of non-linearity: there are different types of variations because of which non-linearity in the pharmacokinetic profile is seen. To implement chronopharmacotherapy it is necessary to first identify the mechanism and then take measures to solve it.

HUMAN CIRCADIAN RHYTHM

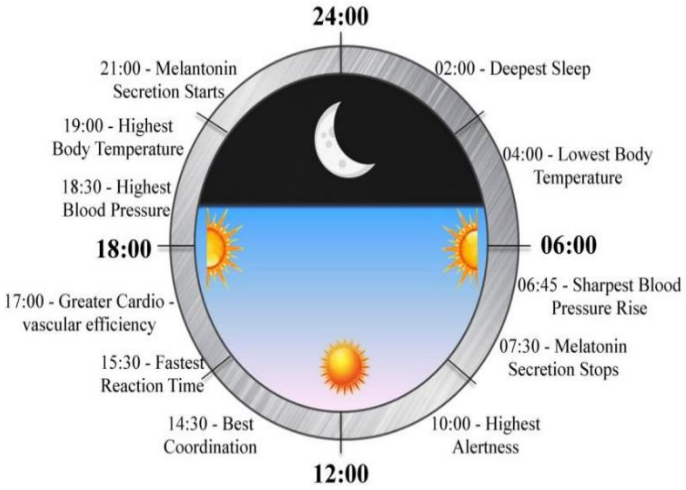

Fig. 1: Human circadian cycle

According to the human daily working cycle that rhythm is based on sleep-activity cycle or solar/lunar corresponds to a person's daily, monthly, seasonal or adaptations which is influenced by our genetic makeup yearly biological clock or to maximize the health and affects the body's functions day and night (24-hour benefits and minimize the adverse effects). Circadian rhythms occur in certain diseases given when the right amount of drug is delivered to conditions like depression, rheumatoid arthritis, and the correct target organ at the most appropriate time [6]. Hippocrates already noticed in 400 B.C. that daytime sleepiness is indicative of disease, and night time sleeplessness can indicate pain and suffering [7].

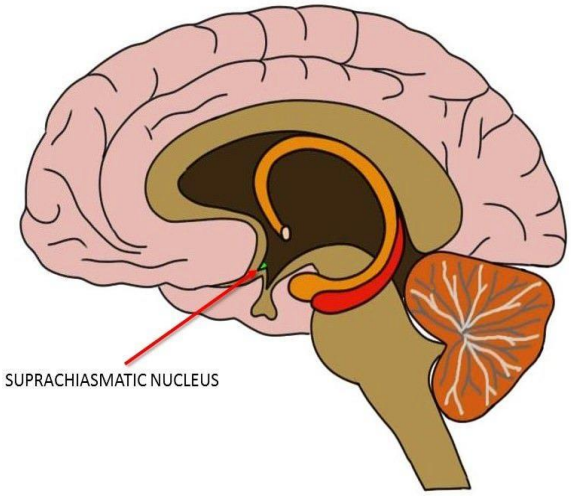

Fig. 2: Location of SCN

The Supra Chiasmatic Nucleus (SCN) of the anterior hypothalamus is the site of the identified as a center that generates circadian activities. Like any timing system, the circadian clock is made up of three components –an input pathway adjusting the time, a central oscillator generating the circadian signal, and an output pathway manifesting itself in circadian physiology and behavior. Clock genes are the genes that control the circadian rhythms in physiology and behavior. Three mammalian clock genes (Per1, Per2, and Per3) are rhythmically expressed in the SCN. Per1 and Per2 are induced in response to light [8].

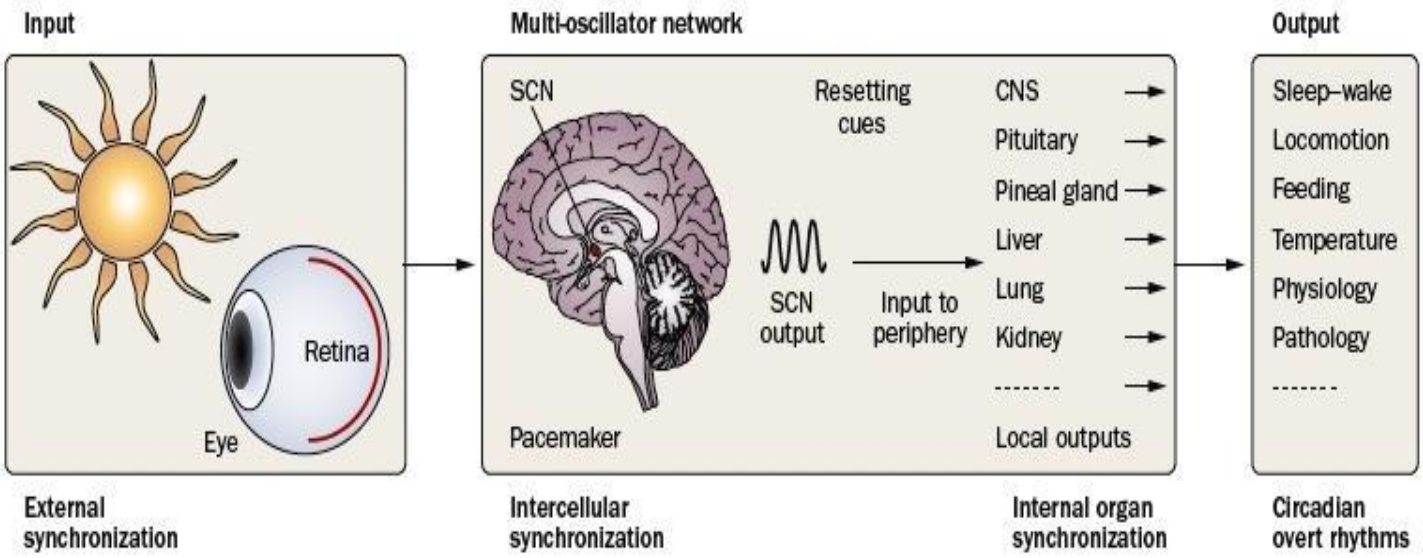

Fig. 3: Response diagram [9]

There are a variety of methods to ascertain the timing of biological clocks –

- Melatonin provides the most reliable and consistent measure of the circadian pattern and can be measured in the plasma, saliva, or urine.
- Because secretion of the hormone is acutely suppressed by light exposure, the measurement of the time of onset of the daily melatonin rise during low-light exposure is a more reliable measure of the circadian phase.
- The dim-light melatonin onset (DLMO) has been used to assess alterations of the circadian phase in a variety of diseases.
- Other markers, such as core body temperature, and cortisol may also serve as biomarkers for circadian rhythms.

BORHYTHM

A biorhythm is a hypothetical cycle in physiological, emotional, or intellectual well-being or prowess. "Bio" pertains to life and "rhythm" pertains to the flow with regular movement. It is defined by the characteristics of the period, level, amplitude, and phase [3].

Table 1: Types of Biological Rhythms

Period (τ)	Major Rhythmic Components
Short (τ < 0.5 hr)	0.1 sec < τ < 1 sec τ ≈ min Pulsatiles (1 min < τ < 0.5 hr)
Intermediate (0.5 hr < τ < 6 days)	Ultradian (0.5 hr < τ < 20 hrs) Circadian (20 hrs < τ < 28 hrs) Infradian (28 hrs < τ < 6 days)
Long (τ > 6 days)	Circasepatan (τ ≈ 7 days) Circamensual (τ ≈ 30 days) Circannual (τ ≈ 1 year)

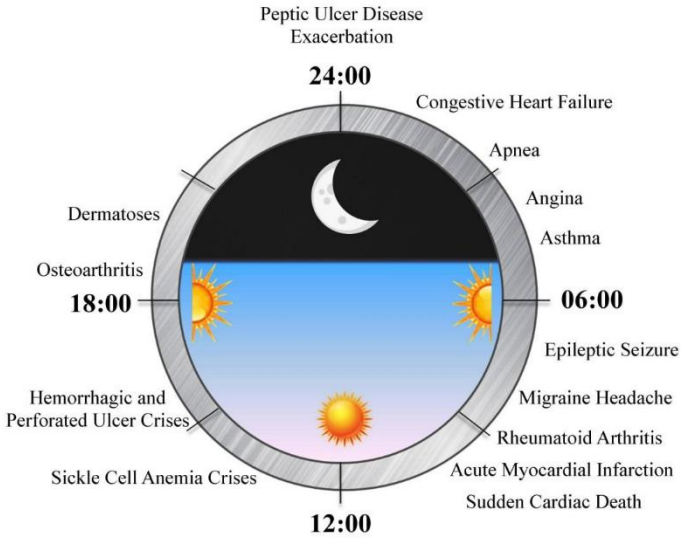

Fig. 4: Peak time of Chronic Medical Conditions

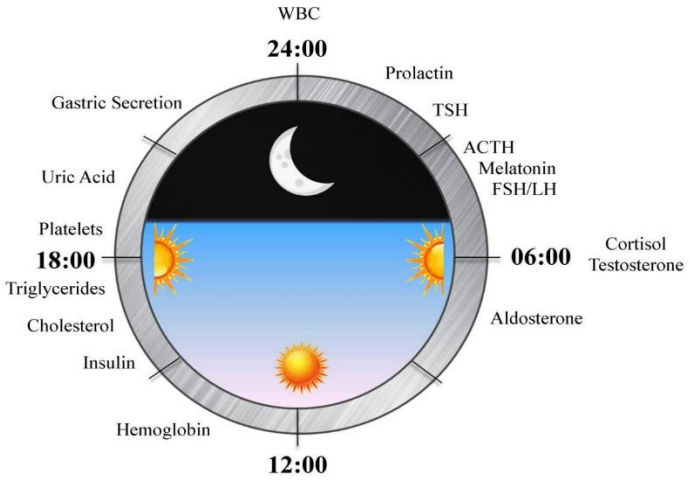

Fig. 5: Peak time of various hormone secretion

BIOLOGICAL RHYTHMS OBSERVED IN VARIOUS BIOLOGICAL SYSTEMS

The basic physiological process governing the drug action the absorption of the distribution the metabolism and the excretion are controlled by the following systems of the body. Hence it is important to know the circadian rhythms in these systems and their effect on drug action [2].

Cardiovascular system

Like several electrophysiological phenomena, cardiovascular activities show a circadian rhythm. Based on the influence of external stimuli and endogenous homeostatic mechanisms, the cardiac electrophysiological properties change diurnally and enable the cardiovascular system to adapt accordingly with the rest –exercise cycles. Cardiovascular functions such as heart rate and blood pressure show 24 hrs variation e.g. in case of blood pressure are highest in the late afternoon and gradually decrease in the evenings to attain the lowest values at night, which can be qualified to the circadian rhythms in the nervous and endocrine system [2]. Myocardial infarction (MI) occurs more frequently in the morning as a result of the concomitant unfavorable timing of several physiological parameters and/or biochemical conditions. Most of the cardiac ischemic conditions and acute myocardial infarctions occur usually between the morning and the noon. The time of day of onset of platelet agreeability, nonfatal myocardial infarction, and sudden cardiac death had prominent circadian rhythms with a primary peak in the morning and a secondary peak in the evening [10].

Urinary system

The urinary system which plays a pivotal role in the elimination of a drug has many instances of circadian rhythms altering e ither the clearance or the urinary flow causing nephrotoxicity. Aminoglycosides can produce renal toxicity with chronic administration. Because these antibiotics are primarily eliminated by renal excretion, diminishing renal function with time may cause greater drug accumulation and more toxicity. There is a need to monitor therapy to limit the duration of therapy, especially in patients who already have compromised renal function.

Theophylline causes an increase in the renal flow by increasing the clearance levels and thereby increases in the urine flow and renal excretion. Carbamazepine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration indicates that either oral bioavailability decreases or clearance increase with time [3].

Gastrointestinal system

The gastrointestinal motility, the intraluminal pH, blood flow to the stomach and enzymatic action are not the only factors that influence the gastrointestinal absorption of the drug. It even depends on the circadian rhythms and all the above-mentioned factors are also influenced by the time of the day. Most of the drugs we generally take are lipophilic and they are found to have more rate of absorption in early mornings rather than any hour of the day [3].

Hepatic system

The anti-depressant nartryptalline which is injected into significant presystemic hepatic metabolism accumulates in a highly predictable manner on multiple oral dosing. The clearance levels of acetaminophen are decreased due to the effect of circadian rhythms and thus resulting in the hepatotoxicity [3].

Respiratory system

Chronopharmacological studies statistically show that the development of asthma symptoms and many types of bronchospastic attacks is more common from midnight to early morning i.e. 2 AM to 6 AM every day. Chronophamacotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours. E.g. Theophylline is taken once a day in the evening causes theophylline blood levels to reach their peak and improve lung function during the difficulty early morning hours. Studies have also proved that a single dose administered in those early hours is equally effective as four doses in a day [3].

DISEASES SHOWING DEPENDENCE ON BIOLOGICAL RHYTHM

Asthma – Bronchial asthma is a chronic airway inflammation characterized by paroxysms of coughin g, wheezing, and dyspnoea. Chronopharmacological studies statistically show that the development of asthma symptoms and many types of bronchospastic attacks is more common from midnight to early morning from 2AM and 6AM every day. Chronopharmacotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours. Several drugs for asthma have been developed based on chronopharmacology. One example is the bronchodilator uniphyl, long-acting theophylline taken once a day in the evening causes theophylline blood levels to reach their peak and improve lung function during the difficult early morning hours. Numerous investigations have demonstrated the usefulness of chronotherapy for asthma, especially for patients with nocturnal asthma [3]. Long term oral administration of corticosteroids at 8AM and 3PM is more effective in controlling nocturnal asthma. Inhaled corticosteroids of single daily dose at 5:30 PM were nearly as effective as four doses a day. Oral corticosteroids should be administered around 3 PM to achieve peak pulmonary anti-inflammatory efficacy between 3 AM and 6 AM [7].

Diabetes – Biologists have found that a key protein that regulates the biological clocks of mammals also regulates glucose production in the liver and altering the levels of this protein can improve the health of diabetic mice. The additional function of the cytochrome is the regulation of gluconeogenesis according to the diurnal activity and feeding levels. So modulating cytochrome levels can also help decrease the diabetic effect on the patients [3].

Arthritis – Rheumatoid arthritis can be distinguished from osteoarthritis by the time of day when the patient's joints are most painful. Rheumatoid arthritis – Morning stiffness between 8 AM to 11 AM is a characteristic feature of rheumatoid arthritis. Taking long-acting NSAIDs like flubiprofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and minimizes or averts their side effects. Osteoarthritis – People with osteoarthritis, the most common form of the disease, tend to have less pain in the morning and more intense in between 2 PM to 8 PM. For osteoarthritis sufferers, the optimal time for a non-steroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon [4].

Cancer – The tumor cells and the normal cells differ in their chronobiological cycles. This fact is the basis for the chronopharmacotherapy of cancer. Based on a study which suggested that the DNA synthesis in the normal human bone marrow cells has a peak around noon while the peak of DNA synthesis in lymphoma cells is near midnight, an S-phase active cytotoxic therapy at late nights was administered and it was found that there is a decrease in the tumor cell count with a little effect on normal cells [3].

Allergy – The allergic reactions both local and systemic are mediated through interactions of immune and inflammatory responses. Such responses during the day are usually coordinated by adrenocortical function and steroid release with high amplitude daily rhythms. Scientists now believe that the symptoms of allergic rhinitis, and even the skin testing results, can vary according to the time of day [3].

Peptic ulcer – Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night. While gastric, small bowel motility and gastric emptying are all slower at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for H2 antagonists. Bedtime H2-receptor blockade using Chronotherapy overcome problems of sustained or profound decrease of 24-hr intragastric acidity including the threat of enteric infection and infestation, potential bacterial overgrowth with possible N-nitrosamine formation [4].

Mood Disorders – The deprivation of sleep in the half of the night and the timed exposure today light-intensity and artificial light still experimental therapies, may ease the depression premenstrual or during menopause and benefit both women and men with seasonal and other mood disorders.

Such a variation was not detected in the mood disorders when sustained release dosage forms of nifedipine and isosorbide mononitrate were used [4].

Sleep Disorders – Many biological signals like sleep disorders occurring in the central and autonomous nervous systems show the complex time structure with rhythmic and pulsatile variations in multiple frequencies. Sleep mainly consists of a rhythmic combination or circadian changes in physiological, biochemical and psychological processes.

When the circadian rhythm is disturbed or when the individual physiological or psychological processes are abnormal during sleep it may result in a variet y of disorders. The circadian rhythm disturbances also differ from person to person and identification of the individual variation would be important in dealing with certain sleep disorders [4].

Alzheimer's Disease – The change of circadian rhythm is also seen in patients with Alzheimer's disease. Individuals with Alzheimer's symptoms show less diurnal motor activity and a higher percentage of nocturnal activity which shows the lower inter daily stability of motor activity and activity of macrophages peak time than normal health y individuals. The core body temperature is also higher in patients and the circadian abnormalities are seen together with cognitive and functional deterioration in this disease [4].

Parkinson's Disease – Parkinson's disease discloses many alterations in the circadian rhythm of blood pressure; amplified diurnal blood pressure variability and postprandial hypotension are due to autonomic dysfunction. But the existence of circadian rhyt hm in this disease has not been evaluated in clinical data because the daily fluctuations of the motor activity pattern of the phase of the disease and the subsequent role of drugs are difficult to estimate [4].

Table 2: Biological Rhythm and the manifestations of clinical diseases [7]

Biological System	Disease/Syndrome	Biological Rhythmicity	Treatment
Respiratory	Asthma	Exacerbation more common during sleep period between 4 AM and 6 AM.	Albuterol or Tulobuterol in early morning
	Hypertension	Incidence greatest in the early morning between 4-6 AM.	Captopril, Clonidine or other medication in morning
Cardiovascular	Myocardial Infarction	Incidence greatest in the early morning	Cardiovascular active drugs before waking
	Strokes	Incidence higher in the morning	Cardiovascular active drugs before waking
	Sudden Cardiac Death	Incidence higher in the morning after awakening	Cardiovascular active drugs before waking
	Angina Pectoris	Angina attacks occur 30 times more often between 2 AM and 4AM.	Larger doses of Nitroglycerin early in the morning
	Peptic Ulcer	Worse in late evening and early morning hours	H_2 blockers during the night

CONCLUSION

The major objective of this article is to inform biologists, clinicians, pharmaceutical scientists and other professionals about the importance of biological clocks and chronopharmacology to human health and disease. Chronopharmacology is a developing science that gives much hope for better the effectiveness of drug therapy and reducing the incidence of toxic drug reaction. It also motivates the investigator to develop new tools for the treatment of cardiovascular diseases, respiratory disorders, hormonal disorders, etc. There is growing evidence that circadian rhythmicity influences disease symptoms, diagnostic test results and even the body response to drug therapy.

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