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CHRONOPHARMACOLOGY: NEW INSIGHTS AND THERAPEUTIC SIGNIFICANCE

Dr. Pragati Khare[1*], Dr. Satyendra Singh[1], Dr. Sandeep Kumar Yadav[2] and Noopur Khare[3]

[1] BPS Educational Institution of Pharmacy, Etah, U.P., India.

[2]SGT College of Pharmacy, SGT University, Gurugram, Haryana, India.

[3]Bhai Gurdas Institute of Engineering and Technology, Sangrur, Punjab, India.

Abstract

The study of how biological rhythms, especially circadian cycles, affect the pharmacokinetics and pharmacodynamics of drugs is known as chronopharmacology. This field acknowledges that endogenous biological clocks cause regular variations in the body's physiological functions, such as drug absorption, metabolism, distribution, and disposal, over the 24-hour day. Consequently, the timing of administration has a substantial impact on the toxicity and effectiveness of many medications. Using a technique called chronotherapy, chronopharmacology seeks to maximise therapeutic results by coordinating drug delivery with the body's circadian rhythms. There are distinct circadian patterns in the pathophysiology and symptom severity of conditions like cancer, rheumatoid arthritis, asthma, hypertension, and sleep disturbances. Chronotherapy can improve patient adherence, reduce side effects, and increase treatment effectiveness by adjusting prescription schedules to these rhythms. The fundamental mechanics of circadian clocks have been clarified by developments in molecular biology, which have shown that many pharmacological targets and metabolising enzymes are regulated by the clock. By enabling real-time monitoring of individual biological rhythms, technological advancements such as wearable technology and biomarker assays have further made personalised chronotherapy possible. Furthermore, the creation of programmable delivery systems and controlled-release drug formulations has made it easier to administer medications at precisely the right times. Despite its potential, issues including inadequate clinical trial data and inter-individual heterogeneity in circadian cycles still exist. However, chronopharmacology is a revolutionary method that incorporates the temporal component into pharmacotherapy, providing safer and more efficient treatment plans. Chronopharmacology has the potential to be a crucial part of personalised medicine as research advances, leading to better health outcomes for a wide range of illnesses.

Keywords: Chronopharmacology, Chronotherapy, chronokinetics, infradian and chronodynamics.

Introduction

A subfield of pharmacology known as chronopharmacology examines how a drug's effects change with biological time, especially in connection to the body's circadian cycles. Endogenous, approximately 24-hour cycles in physiological and behavioural processes, including as hormone production, body temperature, metabolism, and sleep-wake patterns, are known as circadian rhythms. These rhythms are impacted by outside stimuli like light and dark and are controlled by an internal biological clock found in the hypothalamic suprachiasmatic nucleus (SCN) (Dobrek, 2021).

The basic tenet of chronopharmacology is that the time of day at which drugs are taken can have a substantial impact on how the body reacts to them. Drug-receptor interactions (pharmacodynamics) and variations in drug absorption, distribution, metabolism, and excretion (together referred to as pharmacokinetics) are examples of this. For instance, the time of day can affect how a drug is metabolised and how effective it is because of changes in the activity of liver enzymes that are involved in drug metabolism, gastrointestinal motility, renal function, and even blood flow to organs. The two primary components of chronopharmacology are chronokinetics and chronodynamics. The term "chronokinetics" describes time-dependent changes in pharmacokinetic processes, which means that a drug's identical dosage may result in varying plasma concentrations throughout the day. Contrarily, chronodynamics describes how the body's sensitivity or responsiveness to medications varies over time as a result of modifications in physiological condition, enzyme activity, or receptor density (Robles et al., 2024).

There are significant therapeutic ramifications to this time-dependent heterogeneity in medication effect. Numerous physiological functions and illnesses have a circadian rhythm. The symptoms or severity of conditions like hypertension, asthma, peptic ulcers, arthritis, and even some forms of cancer vary with time. For example, heart attacks are more common in the early morning hours, and asthma symptoms frequently get worse at night. The notion of chronotherapy allows clinicians to minimise adverse effects, improve treatment efficacy, and optimise therapeutic results by coordinating drug administration with these biological rhythms.

Antihypertensive medication use is one well-known example. Naturally, blood pressure rises in the morning and falls at night according to a circadian pattern. It has been demonstrated that taking some antihypertensive drugs in the evening as opposed to the morning improves blood pressure control throughout the day and lowers the risk of cardiovascular events. In a similar vein, chemotherapy medications can be more efficient against tumour cells and less harmful to healthy organs when given at particular times of the day (Ohdo et al., 2019). Chronopharmacology is becoming more and more significant as interest in personalised treatment increases. Drug regimens can be customised for optimal effect by taking into account a person's circadian biology. In order to improve drug timing techniques, this discipline is now investigating genetic determinants, sleep-wake cycles, and molecular clock processes.

To sum up, chronopharmacology is a significant development in both clinical practice and pharmacological science. It makes pharmacological therapy more accurate, efficient, and individualised by accounting for the body's natural biological rhythms. In the future of medicine, chronopharmacology is expected to be crucial as our knowledge of circadian biology develops (Kaşkal et al., 2025).

Chronophysiology

The field of physiology known as chronophysiology studies how time affects biological processes in living things, especially cyclic patterns that take place over a range of temporal scales, including infradian (longer than a day), ultradian (shorter than a day), and circadian (daily) rhythms. The field is based on the knowledge that nearly every physiological activity, including digestion, immunological reactions, hormone secretion, and sleep-wake cycles, exhibits time organisation. These biological rhythms are not arbitrary; rather, they are controlled by internal biological clocks, the most notable of which is the circadian clock found in mammals' hypothalamic suprachiasmatic nucleus (SCN). Nearly every cell and organ in the body has a peripheral clock that is in sync with this master clock (Coskun et al., 2023).

Therefore, chronophysiology investigates how these timing systems are created, preserved, and synchronised with the outside world, mostly by use of environmental cues called zeitgebers, such temperature and light. The light-dark cycle, which helps synchronise internal physiology with the Earth's day-night rotation, is the most potent zeitgeber for circadian rhythms. Chronodisruption is a misalignment that can occur when these cycles are disturbed, whether as a result of shift work, jet lag, abnormal sleep patterns, or prolonged exposure to artificial light. Numerous health problems, such as metabolic disorders (like obesity and diabetes), cardiovascular illnesses, mental disorders (like depression and bipolar disorder), compromised immunological function, and even cancer, are becoming more and more associated with this misalignment (Bechtel et al., 2024).

Chronopharmacology, a branch of pharmacy where the timing of drug administration is synchronised with the body's biological rhythms to optimise effectiveness and reduce adverse effects, also heavily relies on chronophysiology. For example, some blood pressure drugs work better when taken at night, which is when the body naturally regulates blood pressure. Additionally, the field informs chronotherapy, which optimises therapeutic effects by scheduling medical treatments to align with a patient's biological cycles. The expanding knowledge of chronophysiology is also influencing personalised medicine strategies, in which treatment plans are customised based on a patient's chronotype—their innate propensity for morning or evening behavior—as well as genetic and environmental variables.

Because it draws from disciplines including molecular biology, neuroscience, endocrinology, behavioural science, and chronobiology, chronophysiology is by its very nature interdisciplinary. It focusses on clock genes and their protein products at the molecular level. These genes create transcriptional-translational feedback loops that produce rhythmic gene expression across a 24-hour period. Disorders like delayed sleep phase disorder and familial advanced sleep phase syndrome might result from disruptions in these genes. Crucially, chronophysiology research is not limited to humans but rather encompasses the animal kingdom, providing valuable insights into ecological interactions and evolutionary adaptations. Timing mechanisms also affect development, reproduction, and metabolic processes in microbes and plants, demonstrating the universality of temporal regulation in life (Bangar et al., 2023).

The accuracy and use of chronophysiological research are being further enhanced by technological advancements like wearable biometric sensors, high-throughput genomics, and machine learning algorithms, which make it possible to track and analyse physiological rhythms in real time. The discoveries from chronophysiology are more pertinent than ever as the world becomes more and more round-the-clock due to

artificial illumination, digital screens, and demands from work and social interactions. They provide answers for maximising lifestyle, productivity, and well-being in balance with our internal clocks, in addition to helping to explain why specific behaviours and environmental exposures have an impact on health (Del-Valle et al., 2024).

Chronopharmacology

Chronopharmacokinetics

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Chronopharmacodynamics

A subfield of chronopharmacology called chronopharmacodynamics studies how the body's biological rhythms affect the pharmacodynamic interactions between medications and their targets, such as receptors, enzymes, or ion channels. It focusses on the time-dependent changes in the effects and effectiveness of medications. Chronopharmacodynamics examines how a drug's same concentration can have different effects based on the biological time at which it is administered, in contrast to chronopharmacokinetics, which deals with time-related changes in drug concentration within the body. Circadian rhythms—roughly 24-hour biological cycles regulated by internal clocks, most notably the central circadian pacemaker found in the hypothalamic suprachiasmatic nucleus (SCN)—are the main forces behind these oscillations.

Numerous physiological processes, such as hormone secretion, cell cycle progression, pain sensitivity, immune function, and cardiovascular dynamics, are influenced by this central clock, which synchronises peripheral clocks in different organs. These processes all contribute to the determination of a drug's efficacy or toxicity at any given time of day. The importance of coordinating pharmacological interventions with the body's endogenous rhythms to maximise results is highlighted by the relevance of chronopharmacodynamics, which is especially evident in conditions like cancer, depression, arthritis, hypertension, and asthma where symptoms clearly vary with the clock (Erkekoglu et al., 2012).

The rhythmic manifestation of pharmacological targets themselves is a crucial component of chronopharmacodynamics. A medicine operating on a specific target may have a stronger or lesser impact depending on the time of day it is provided since receptors, transporters, and enzymes involved in signal transduction pathways might display circadian rhythms in their expression, density, or sensitivity. For instance, beta-blockers used to treat heart disease and hypertension target beta-adrenergic receptors in the cardiovascular system, which exhibit time-dependent changes in responsiveness. When beta-blockers are administered at night, when sympathetic activity is lower, the therapeutic impact may be less pronounced than when they are administered in the morning, when these receptors are more receptive and active. Time-dependent changes in pain perception and alleviation can also result from circadian fluctuations in nociceptive thresholds and opioid receptor sensitivity, which can affect how effective analgesics are throughout the day. Tumour cell sensitivity to chemotherapeutic drugs can be influenced by the time-of-day dependent expression of enzymes involved in DNA replication and repair, such as topoisomerase or thymidylate synthase, in cancer therapy. Clinical studies of chronotherapy in colorectal cancer and other cancers have confirmed that

chemotherapy can be considerably more effective and less harmful when it is administered when cancer cells are at their most vulnerable and healthy cells are comparatively resistant (Ohdo et al., 2003).

Chronopharmacodynamics also heavily relies on hormonal control. Significant diurnal changes are seen in hormones like cortisol, melatonin, insulin, and catecholamines, which also affect a variety of downstream pathways that modify the effects of drugs. For example, the time of corticosteroid therapy is crucial in autoimmune disorders like rheumatoid arthritis because glucocorticoids, which have a circadian secretion pattern that peaks in the early morning, control inflammation and immunological responses. Dosing in the morning can lessen suppression of the hypothalamic-pituitary-adrenal (HPA) axis and coincides with the body's natural cortisol peak. Similar to this, the circadian rhythms of insulin sensitivity and glucose tolerance, which typically peak during the day and decrease at night, influence the chronopharmacodynamic profiles of antidiabetic medications like insulin or sulfonylureas. Because coordinating insulin supply with circadian glucose metabolism enhances glycaemic control and lowers the risk of hypoglycemia, this time-dependent variation in medication efficacy has significant implications for the design of dosage regimens in diabetes care.

The molecular circadian machinery, which includes "clock genes" like CLOCK, BMAL1, PER1-3, and CRY1-2, which control the rhythmic expression of thousands of genes involved in signalling, metabolism, and cellular function, also has an impact on chronopharmacodynamics. By altering the production of proteins that act as drug targets or have an impact on intracellular signalling cascades, these clock-controlled genes can modify the pharmacodynamic response. Changes in lifestyle, shift work, jet lag, or illness can all disrupt clock gene expression, which might change drug responsiveness and increase treatment resistance or side effects. For example, altered expression of PER2 has been associated with increased sensitivity to chemotherapeutic agents, while disruption in BMAL1 can impair glucose homeostasis and affect antidiabetic drug response. Such insights underscore the need for incorporating chronobiological markers into pharmacodynamic assessments and patient care, moving towards a more individualized and time-informed approach to therapy (Zhou et al., 2021).

Biological Rhythms

Basic temporal patterns in physiological, behavioural, and metabolic processes that take place in living things are known as biological rhythms. These cycles are essential for preserving homeostasis and guaranteeing peak performance in reaction to changes in the surroundings. Biological rhythms, which are present in all living things, including bacteria, plants, animals, and people, allow organisms to anticipate and adjust to regular changes in their surroundings, such as the daily cycle of light and dark, seasonal fluctuations, or tidal patterns. Internal biological clocks control these rhythms, which can be "entrained" or synchronised by zeitgebers—external stimuli—of which light is the most common. In disciplines including medicine, psychology, chronobiology, agriculture, and even space research, an understanding of biological cycles is crucial (Morin et al., 2025).

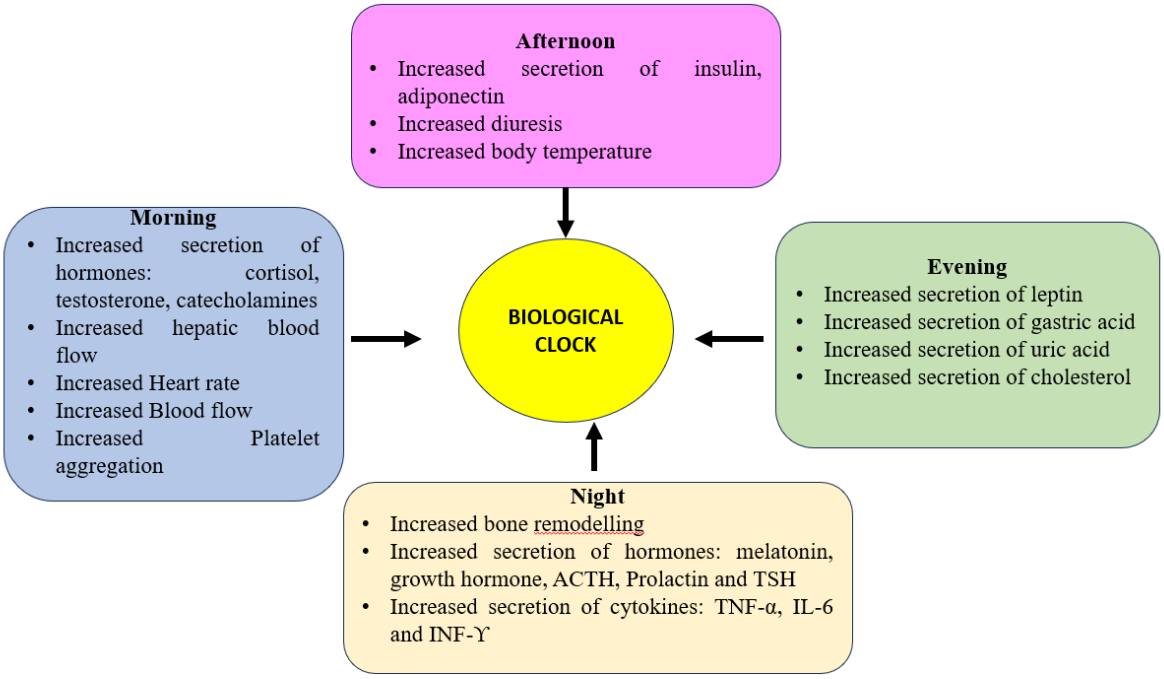

Fig. 1: Biological clock and its associated body responses

Types of Biological Rhythms

Biological rhythms are typically classified based on their frequency or duration:

1. **Circadian Rhythms**: These biological rhythms, which have a roughly 24-hour period, are the most researched. "Circadian" is derived from the Latin words diem (day) and circa (around), which means "about a day." Numerous physiological functions, including the sleep-wake cycle, body temperature, hormone secretion, metabolism, and immunological responses, are influenced by circadian rhythms. The suprachiasmatic nucleus (SCN) of the hypothalamus houses the human central circadian clock. It gets direct input from the retina to synchronise internal time with the external light-dark cycle.
2. **Ultradian Rhythms**: These rhythms happen several times a day and have a cycle of less than twenty-four hours. The heartbeat, the REM and non-REM phases of sleep, and the release of certain hormones like growth hormone and insulin are a few examples. Ultradian rhythms are crucial for maintaining regular relaxation and recuperation as well as for regulating physiological reactions (Vitaterna et al., 2001).
3. **Infradian Rhythms:** These cycles can continue for days, weeks, or months and are longer than twenty-four hours. This group includes the human menstrual cycle, seasonal affective disorder, and some animal reproductive and migratory behaviours. Infradian rhythms are frequently triggered by seasonal or lunar cues and internal hormone changes (Markam et al., 2025).
4. **Circannual Rhythms**: The yearly cycles of the Earth's orbit around the Sun correspond with these biological rhythms. Animal moulting, mating seasons, and hibernation are a few examples. In humans, mood swings, immunological responses, and metabolic activities all exhibit minor circannual patterns (Helm et al., 2013).
5. **Tidal and Lunar Rhythms**: These rhythms line up with lunar cycles (approximately 29.5 days) and tidal patterns (about 12.4 hours). They are particularly noticeable in marine life that depends on the tides for reproduction and food. For example, in order to maximise reproductive success, some fish and invertebrates time their spawning to coincide with the lunar cycle (De la Iglesia et al., 2013).

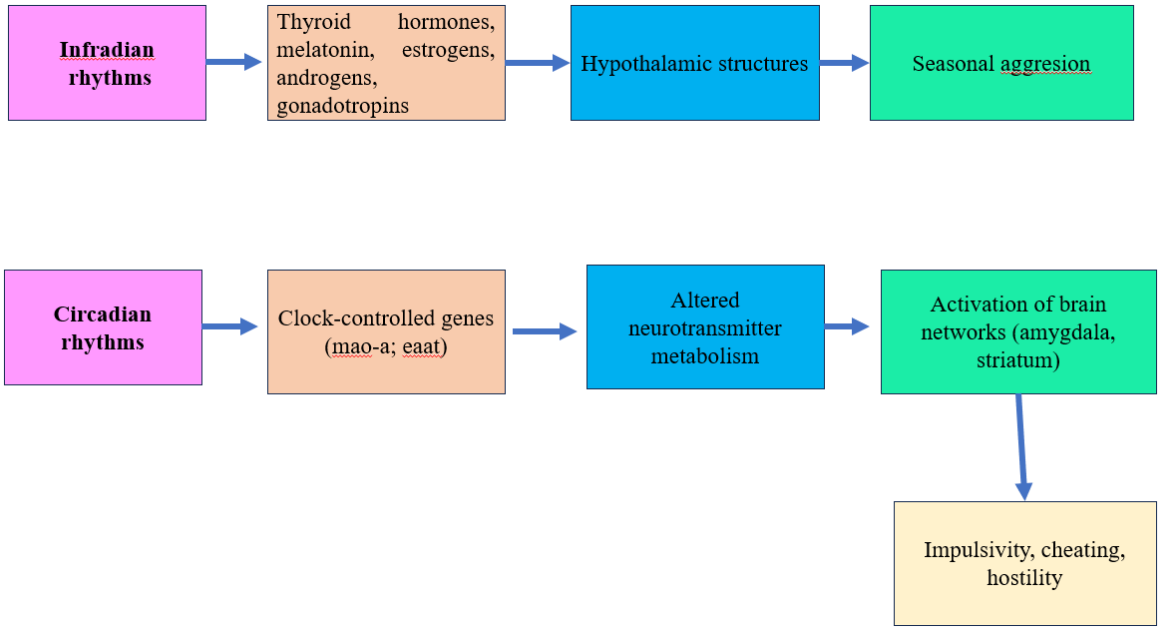

Fig. 2: Types of Circadian rhythms

Mechanisms Behind Biological Rhythms

Endogenous time systems called biological clocks regulate biological rhythms. The SCN, the primary pacemaker in mammals, is made up of roughly 20,000 neurones that use molecular feedback loops to produce rhythmic signals. Clock genes like CLOCK, BMAL1, PER (Period), and CRY (Cryptochrome) control biological rhythms at the molecular level by producing proteins that control their own transcription in roughly 24-hour cycles.

Gene expression is both activated and repressed in these feedback loops. For instance, the transcription of the PER and CRY genes is activated by a complex formed by the proteins CLOCK and BMAL1. In a self-regulating loop, PER and CRY proteins reduce their own synthesis as they build up in the cytoplasm and ultimately block the CLOCK-BMAL1 complex's activity. This inhibition is lifted when the PER and CRY proteins degrade, enabling the cycle to resume. Almost every cell in the body uses this molecular clock to create peripheral clocks that the SCN synchronises (Sanchez et al., 2022).

Zeitgebers and Entrainment

Biological clocks need to be regularly adjusted to stay in sync with their surroundings, even though they are capable of maintaining rhythms on their own. Zeitgebers (German for "time-givers") are environmental cues that control a process known as entrainment. Light is the most potent zeitgeber, resetting the SCN daily to correspond with the 24-hour solar day.

Other zeitgebers include:

• Temperature: For certain animals, daily temperature variations can aid in synchronising biological clocks.

• Food availability: Without involving the SCN, feeding regimens can synchronise peripheral clocks in organs such as the pancreas and liver

• Social cues: Human and animal biological cycles can be influenced by interactions with other creatures or social contexts.

• Physical activity: Exercise can improve synchronisation and change circadian rhythms, particularly in people who work shifts or are jet lagged (Holley et al., 1981).

Functions and Importance of Biological Rhythms

Biological rhythms are crucial for aligning internal physiology with external demands. They regulate:

• Sleep-wake cycles: Maintaining appropriate sleep and mental function.

• Hormone release: including growth hormone, insulin (glucose management), cortisol (stress), and melatonin (sleep).

• Digestion and metabolism: When to eat and when to release digestive enzymes.

• Immune function: The efficacy and inflammation of the immune system vary during the day.

• Mood and cognitive function: Throughout the day, there are variations in emotional stability, memory, and alertness.

• Reproduction: Ovulation timing, sexual behaviour, and fertility are all influenced by rhythm.

Disruption of these rhythms—known as **chronodisruption**—can lead to various health issues including insomnia, obesity, depression, cardiovascular disease, diabetes, and certain cancers (Reddy et al., 2018).

Biological Rhythms and Health

The importance of biological rhythms in preserving both physical and mental well-being is becoming more and more clear. Circadian rhythm disruption, whether from shift work, jet lag, sleep disorders, or excessive exposure to artificial light, has been associated with a higher risk of:

• Mood disorders: Disrupted circadian regulation is linked to seasonal affective disorder, bipolar disorder, and depression.

• Metabolic diseases: Circadian misalignment raises the risk of diabetes and obesity by affecting glucose metabolism.

• Cardiovascular disease: Disturbances in the circadian rhythms that regulate heart rate and blood pressure can lead to hypertension and heart attacks.

• Cancer: circadian rhythms regulate DNA repair, cell division, and apoptosis. Upsetting these cycles could encourage the growth of tumours.

Applications of Biological Rhythm Research

Biological rhythm research has produced useful applications in the fields of medicine, education, and the workplace:

1. Chronotherapy: To optimise efficacy and minimise adverse effects, drugs are administered at predetermined intervals. Antihypertensives, for example, might work better at night, and chemotherapy might be easier to handle if it is timed to the patient's circadian rhythm.

2. Shift work management: By designing better lighting and shift patterns, an understanding of biological rhythms can reduce circadian disturbance and enhance worker productivity and health.

3. Treatment for jet lag: Travellers can more easily acclimatise to different time zones by using melatonin, appropriate light exposure, and sleep scheduling based on circadian biology.

4. School start times: Teenagers' circadian rhythms are inherently delayed. It has been demonstrated that delaying the start of classes improves mental wellness, academic achievement, and sleep length.

5. Space travel: In space, astronauts encounter different cycles of light and dark. Biological rhythms must be synchronised in microgravity to sustain performance and health over extended missions (Foster et al., 2020).

Circadian Rhythm

Natural biological mechanisms called circadian rhythms repeat approximately once every 24 hours and control the sleep-wake cycle. "Circadian" is derived from the Latin words diem (day) and circa (around), which means "about a day." Nearly every living thing, including people, animals, plants, and even some microorganisms, has these rhythms, which are controlled by a biological clock. Because they affect a number of physiological functions, including hormone production, body temperature, metabolism, immunological response, and behaviour, circadian rhythms are essential for preserving the body's internal equilibrium.

The suprachiasmatic nucleus (SCN), a small area in the brain's hypothalamus, is crucial to the human circadian clock. Coordinating the timing of peripheral clocks in nearly every organ and tissue, the SCN serves as the body's master clock. It is able to synchronise internal rhythms with the external environment, particularly the light-dark cycle, because it receives direct input from the eyes through the optic nerve. The strongest environmental cue (zeitgeber) that can reset the SCN is light. The SCN is signalled by light entering the eyes in the morning to block the generation of melatonin, a hormone that encourages sleep, thereby encouraging awake. On the other hand, in the evening, darkness promotes the release of melatonin, which primes the body for sleep.

Sleep-wake cycles are controlled by circadian rhythms, which also affect mood, attentiveness, and cognitive function. Circadian cycles also govern other biological processes. For example, the hormone cortisol, which is linked to metabolism and stress, increases in the early morning to aid in the body's awakening and progressively falls throughout the day. Additionally, body temperature varies during the day, peaking in the late afternoon or early evening and falling to its lowest point in the morning (Lee et al., 2021).

Chronopharmacology and endocrinology

The study of how pharmacological effects change in accordance with the biological timing system—specifically, the circadian rhythms that regulate physiological processes—is known as chronopharmacology. Since hormone secretion follows regular daily, monthly, or seasonal patterns, endocrinology—the study of hormones and the endocrine system—is greatly impacted by these same biological rhythms. By coordinating treatment with the normal variations in hormone synthesis, receptor sensitivity, and metabolic activity, the field of chronopharmacology and endocrinology provides vital insights for improving drug therapy. This time-based strategy can promote hormonal balance, lessen side effects, and increase medication efficacy.

The body's major circadian clock, which is housed in the hypothalamic suprachiasmatic nucleus (SCN), frequently regulates the rhythmic secretion of hormones like cortisol, melatonin, insulin, thyroid hormones, growth hormone, and sex steroids. These cycles control metabolism, stress reactions, sleep-wake cycles, and reproductive processes. Pharmacological drugs that target the endocrine system must take timing into account because endocrine functions are naturally rhythmic. This is done to prevent any disruptions to these sensitive processes or to capitalise on times when hormones or receptors are most active (Mercadante et al., 2024).

The cortisol cycle is among the best-known instances of circadian effect in endocrinology. The adrenal glands secrete the glucocorticoid hormone cortisol, which has a diurnal pattern, peaking between 6 and 8 AM and

then decreasing throughout the day. Upon waking, this rhythm promotes metabolism, stress response, and alertness. In order to minimise suppression of the hypothalamic-pituitary-adrenal (HPA) axis and replicate the body's natural secretion, glucocorticoid drugs (such hydrocortisone or prednisone) are frequently given in the morning. Because corticosteroids don't correspond with the body's natural rhythm, they can cause immunosuppression, adrenal suppression, and sleeplessness when taken at night.

The treatment of diabetes mellitus is another crucial area where chronopharmacology and endocrinology meet. Throughout the day, insulin sensitivity and glucose tolerance fluctuate; they usually peak in the morning and fall at night. This means that depending on when they are administered, insulin and oral antidiabetic medications like metformin or sulfonylureas may have different effects. According to chronopharmacological principles, glycaemic control can be improved and the risk of hypoglycemia can be decreased by scheduling medicine to take place at times when insulin sensitivity is higher. Additionally, thyroid hormones exhibit diurnal oscillation; thyrotropin (TSH) in particular surges at night and troughs out at day. Determining the best time to administer levothyroxine—which is usually advised in the early morning on an empty stomach to promote uniform absorption and minimal interference—and interpreting thyroid function tests require an understanding of these changes (Chung et al., 2011).

A well-known example of a chronobiotic agent is the hormone melatonin, which controls the sleep-wake cycle and both reflects and affects circadian time. Melatonin, which is released by the pineal gland in reaction to darkness, is used medicinally to treat insomnia, jet lag, and problems of the circadian rhythm. Melatonin's effectiveness is very time-dependent; if it is given at the wrong time of day, it may cause the circadian rhythm to shift in the wrong direction or not work at all. Additionally, chronopharmacology is becoming more and more important in hormone-sensitive diseases, such prostate and breast cancer, where the timing of hormone therapy or chemotherapy can have a big impact on treatment results. For instance, circadian variations in oestrogen receptor expression may affect the effectiveness of tamoxifen, an oestrogen receptor modulator used to treat breast cancer (Arendt et al., 2019).

Chronopharmacology and cardiovascular medicine

The study of how the pharmacokinetics and effects of drugs change with the time of day they are taken is known as chronopharmacology. It is based on the knowledge that the human body functions according to internal biological clocks called circadian rhythms, which affect physiological functions like metabolism, hormone production, blood pressure control, and heart function. The use of chronopharmacology in cardiovascular medicine has important therapeutic ramifications since the timing of medication administration can impact the safety and effectiveness of therapy for disorders like thrombosis, angina, heart failure, hypertension, and myocardial infarction.

Circadian variation is strong in cardiovascular physiology. An example of this would be blood pressure, which usually rises in the morning, peaks during the day, and falls at night. The diurnal change in blood pressure is the term used to describe this phenomena. The majority of people have a normal "dip" in blood pressure when they sleep, but some patients—particularly those with diabetes or hypertension—do not experience this dipping at all. Known as "non-dippers," these people are more likely to experience cardiovascular problems.

Additionally, there are cyclic patterns in heart rate, vascular tone, and sympathetic nervous system activity. A morning surge is associated with an increased risk of unfavourable cardiovascular events, including

myocardial infarctions (heart attacks), strokes, and sudden cardiac death. Early in the morning, from 6:00 a.m. to noon, these occurrences are most common (Waris et al., 2024).

The time of cardiovascular medication delivery can be adjusted to offset peak risk periods and enhance therapeutic results in light of these predictable temporal patterns. For instance, hypertension drugs including beta-blockers, ACE inhibitors, ARBs, and calcium channel blockers, especially in non-dippers, are frequently more effective when taken in the evening or right before bed. Dosing at bedtime can improve blood pressure regulation throughout the day and lessen the morning spike, which is a crucial period for cardiovascular risk. Antihypertensive medication administered at night considerably lowers the risk of cardiovascular morbidity and death when compared to morning dosing, according to studies like the MAPEC and Hygia trials.

A common antiplatelet medication, aspirin also exhibits chronopharmacological significance. There is a higher chance of thrombotic events in the morning due to an increase in platelet activity. According to research, low-dose aspirin taken in the evening may provide better inhibition of platelet aggregation during the high-risk morning hours than dosed in the morning.

The timing of statin therapy in cholesterol management is affected by the circadian cycle of cholesterol production, which peaks at night. For optimal effectiveness, short-acting statins, such as simvastatin, should be taken in the evening. In some people, evening dosing may still be more in line with hepatic cholesterol production, even though long-acting statins like atorvastatin and rosuvastatin are less time-dependent.

Drugs like aldosterone antagonists and diuretics are frequently scheduled to optimise effectiveness and minimise negative effects when treating heart failure. For example, diuretics are typically used in the morning to prevent nocturia and sleep disturbance, and other drugs for heart failure may be tailored to the circadian patterns of neurohormonal activity and renal function.

The use of chronopharmacological concepts to cardiovascular medicine provides a potent method for treatment optimisation. Clinicians can improve treatment efficacy, minimise side effects, and possibly lower the occurrence of major cardiovascular events by coordinating drug delivery with the body's circadian rhythms. Time-based, individualised treatment could emerge as the future standard of care for cardiovascular health as chronobiology and chronotherapy research progresses (Strauss et al., 2023).

Chronopharmacology and neurology

The study of how biological timing influences a drug's activities, efficacy, and adverse effects is known as chronopharmacology. Its foundation is the knowledge that the human body uses internal timekeeping systems, namely circadian rhythms, to rhythmically control physiological functions. These changes throughout time have important clinical implications in neurology, the study and treatment of nervous system problems. Biological cycles influence several neurological processes, including sleep, mood, cognition, pain perception, neurotransmitter release, and seizure susceptibility. The efficacy of neurological treatments can therefore be significantly impacted by the time of pharmaceutical interventions, which is why chronopharmacology is an essential factor in the management of neurological disorders (Tamilanban et al., 2020).

Circadian Rhythms and the Nervous System

Circadian rhythms are both regulated and targeted by the central nervous system (CNS). The primary circadian pacemaker that synchronises peripheral clocks throughout the body is the hypothalamic suprachiasmatic nucleus (SCN). Daily variations in hormone levels, neuronal activity, attentiveness, and core body temperature are all synchronised by this master clock. Serotonin, dopamine, norepinephrine, and GABA are among the many neurotransmitters whose production, release, and receptor sensitivity vary during the day. These variations affect mood, sleep-wake cycles, neurological illness susceptibility, and cognitive function.

Circadian rhythm disruption, such as that experienced by shift workers, jet lag, sleep problems, or neurodegenerative diseases, can have a major impact on brain function and exacerbate symptoms of ailments such as multiple sclerosis, epilepsy, Parkinson's disease, Alzheimer's disease, and depression. In these situations, chronopharmacology offers resources for improving treatment plans by coordinating drug delivery with natural biological cycles to maximise effectiveness and reduce toxicity (Ma et al., 2019).

Chronopharmacology in Sleep Disorders

Circadian dysregulation is closely linked to sleep disorders, especially narcolepsy, insomnia, and delayed sleep phase syndrome (DSPS). The hormone that marks the start of sleep, melatonin, is naturally released at night and inhibited by light. When given in accordance with a person's circadian phase, therapeutic melatonin and melatonin receptor agonists (like ramelteon) work best. Melatonin can be ineffective or cause the biological clock to move in the wrong direction if it is administered too early or late. Chronotherapeutic scheduling is therefore crucial to attaining the intended sleep results. Similarly, when administered at a time that promotes the patient's natural circadian desire for alertness, modafinil, a wake-promoting drug used to treat narcolepsy and shift work sleep disorder, is more effective and more tolerated. Understanding chronopharmacology also helps with the timing of hypnotics, which, if not taken in accordance with circadian sleep-wake patterns, may result in residual sedation or cognitive impairment (Barion et al., 2007).

Chronopharmacology and Epilepsy

Another neurological disorder that is strongly impacted by circadian rhythms is epilepsy. With certain forms of epilepsy exhibiting a propensity for seizures during sleep and others during awake, seizure occurrence frequently exhibits time-of-day patterns. Changes in cortical excitability, hormone levels (such as melatonin and cortisol), and sleep architecture are all associated with these rhythms. Depending on when they are taken, antiepileptic medications (AEDs) such levetiracetam, carbamazepine, valproate, and lamotrigine might have varying therapeutic efficacy and adverse effect profiles. For instance, divided doses can be used to target seizure-prone times, while overnight dosing may lessen daytime drowsiness. According to certain research, adjusting the timing of AED treatment in paediatric patients may lessen seizure frequency and enhance behavioural results. Even though it isn't yet commonly utilised, chronotherapy shows promise for individualised treatment and reducing side effects in epilepsy (Kreitlow et al., 2022).

Chronopharmacology in Neurodegenerative Disorders

Both motor and non-motor symptoms of Parkinson's disease (PD), including tremor, stiffness, irregular sleep patterns, and mood swings, exhibit diurnal fluctuation. Levodopa, the mainstay of PD treatment, has pharmacokinetics and pharmacodynamics that are influenced by intestinal absorption, gastric emptying, and dopamine receptor sensitivity, all of which can change during the day. When the effectiveness of a medicine

decreases before the next dose is due, some individuals suffer wearing-off events. These variations can be lessened and quality of life enhanced by modifying the dopaminergic therapy's schedule, frequency, and formulation (controlled-release vs. immediate-release, for example) in accordance with circadian considerations.

Similar to this, sundowning—a condition in which agitation, confusion, and anxiety develop in the late afternoon or evening—occurs often in people with Alzheimer's disease (AD). Given this behavioural circadian disruption, strategically timing the administration of drugs like acetylcholinesterase inhibitors or antipsychotics may help reduce symptoms. Additionally, AD patients can benefit from improved sleep and cognitive stability by maintaining stable circadian rhythms through light therapy, regimented routines, and timely drug administration (Chaudhuri et al., 2013).

Chronopharmacology and Mood Disorders

Disturbances in circadian biology are intimately associated with mood disorders, especially major depressive disorder (MDD) and bipolar disorder. Depressive symptoms frequently exhibit diurnal variation or get worse in the morning. Depending on their pharmacology, antidepressants—particularly SSRIs, SNRIs, and tricyclics—can have sedative or activating effects, and the timing of their use affects both their effectiveness and tolerance.

For instance, mirtazapine, which has sedative qualities, is frequently prescribed at night, whereas fluoxetine, which can be stimulating, is typically best taken in the morning. Lithium and other mood stabilisers have been demonstrated to affect circadian gene expression in bipolar illness. By controlling clock genes like PER2, lithium is known to extend the circadian period and stabilise mood. Therefore, it's critical to maintain regular lithium dosage schedules for both mood stability and circadian alignment (Geoffroy et al., 2025).

Chronopharmacology and pain management

The study of how biological rhythms impact the actions and efficacy of drugs, known as chronopharmacology, is becoming more and more important in the treatment of pain. Circadian rhythms—natural 24-hour cycles that control physiological processes like hormone secretion, inflammation, and nerve sensitivity—have an impact on how pain is perceived and how analgesic treatment is received. Both the degree of pain and how the body reacts to painkillers are impacted by these daily variations. Enhancing patient outcomes, decreasing adverse effects, and increasing efficacy are all possible when chronopharmacological principles are incorporated into pain management.

Circadian Rhythms and Pain Perception

Pain is a dynamic experience that changes with time. Studies have demonstrated that pain sensitivity and nociceptive thresholds—the point at which a stimulus becomes painful—change with the time of day. Although this pattern may vary depending on the type and source of the pain, pain sensitivity is generally lower in the morning and higher in the evening.

The following circadian-controlled systems play a major role in regulating these fluctuations:

• Proinflammatory cytokines like IL-6 and TNF-alpha, which tend to rise during the night and early morning hours, contributing to increased pain during these times;

• Melatonin, which has analgesic and antioxidant properties and peaks at night;

• Hormones like cortisol, which has anti-inflammatory effects and peaks in the early morning.

This explains why fibromyalgia and migraine headaches may get worse at night, while rheumatoid arthritis and other illnesses tend to have more severe symptoms in the morning. These trends lend credence to the idea that the timing of analgesic treatment is important, both to align the drug's impact with times of greatest pain and to take advantage of the body's innate rhythms to augment or supplement pharmacologic effects (Sharma et al., 2023).

Chronopharmacology of Analgesic Medications

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Many people use NSAIDs to treat inflammatory pain. Circadian changes in inflammation and stomach mucosal protection affect how effective they are. In illnesses like arthritis, where pain and stiffness intensify over night and in the morning, studies indicate that giving NSAIDs in the late afternoon or evening may improve symptom control.

However, dose time also affects the gastrointestinal side effects caused by NSAIDs. Due to the highest gastric mucosal protection during the day, morning dosage may lessen gastrointestinal effects. Therefore, depending on the demands of each patient, the timing of NSAID administration must balance safety and efficacy (Ghlichloo et al., 2019).

Opioids

For moderate to severe pain, opioid analgesics like oxycodone, codeine, and morphine work on the central nervous system. They exhibit diurnal fluctuation in their pharmacokinetics (absorption, metabolism, and excretion) and pharmacodynamics (interaction with receptors). Opioid receptor sensitivity and pain thresholds have been shown to fluctuate throughout the day, impacting analgesic efficacy as well as adverse effects such as respiratory depression and drowsiness.

For example, research shows that opioids are more effective in the evening, which is also when pain sensitivity is higher. But this also increases the risk of respiratory depression at night, particularly in patients who are not familiar with opioids. Therefore, while using long-acting opioids at night, cautious dosage and supervision are crucial.

Adjuvant Analgesics

Time-dependent changes are also seen in medications that are frequently used to treat neuropathic pain, such as antidepressants (like amitriptyline) and anticonvulsants (like gabapentin or pregabalin). When taken in the evening or right before bed, these drugs might work better because they coincide with the beginning of pain at night and reduce sedation throughout the day. Evening dosing also increases adherence and improves sleep, which is frequently disrupted in individuals with chronic pain (Cohen et al., 2017).

Chronic Pain and Circadian Disruption

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- **Timed light exposure** to regulate melatonin and improve sleep;
- **Structured sleep-wake schedules**;
- **Adjusting medication timing** to match symptom peaks and natural rhythms (Bernatoniene et al., 2023).

Toward Personalized Pain Management

Individualised pain management is made possible by the integration of chronopharmacology into clinical practice. Healthcare professionals can schedule medication to match with times of greatest demand and physiological receptivity by evaluating a patient's pain pattern, chronotype (morning or evening preference), and lifestyle.

Real-time monitoring of circadian patterns and symptom changes is now possible thanks to technological advancements like wearable sensors, smartphone apps, and digital pain diaries, which provide tools for more precisely customising treatment.

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Chronopharmacology and oncology

In order to maximise effectiveness and minimise toxicity by coordinating therapy with the body's natural cycles, chronopharmacology examines how the timing of drug delivery impacts the pharmacokinetics and pharmacodynamics of pharmaceuticals. Because of the circadian fluctuation in tumour biology, medication metabolism, DNA repair processes, and the patient's own physiology, chronopharmacology has attracted a lot of attention in oncology, the field that deals with cancer treatment. By comprehending and taking advantage of these time-dependent fluctuations, patients' quality of life can be improved, side effects can be decreased, and therapeutic outcomes can be improved.

Circadian Rhythms in Cancer Biology

Numerous cellular functions that are important to the development of cancer are regulated by circadian rhythms, including as metabolism, apoptosis, DNA damage repair, and cell cycle progression. Important genes in these pathways, including PER, CLOCK, BMAL1, and CRY, are part of the molecular clockwork that controls the expression of genes in a rhythmic manner.

The natural circadian clocks of tumour cells are frequently disrupted, which can result in unchecked proliferation and treatment resistance. The host's regular circadian rhythms, particularly in the liver and gastrointestinal tract—two important organs involved in drug metabolism and clearance—remain unaltered, nevertheless, and have an impact on the processing of anticancer medications. This disparity offers a therapeutic window during which the timing of medication administration can be changed to optimise the destruction of cancer cells while preserving healthy tissue (Rajan et al., 2024).

Chronopharmacokinetics and Chronopharmacodynamics in Cancer Therapy

There is diurnal variation in the pharmacokinetics of chemotherapeutic medicines, or how the body absorbs, distributes, metabolises, and excretes medications. Throughout the day, there are variations in gastrointestinal absorption, liver enzyme activity, kidney function, and plasma protein levels. For instance, the concentration of active medications and metabolites is affected by the activity fluctuations of enzymes involved in drug metabolism, such as cytochrome P450s. Circadian rhythms also affect chronopharmacodynamics, or how medications interact with their targets. Day-to-day variations in DNA synthesis rate, repair mechanisms, and tumour cell sensitivity to chemotherapy impact the cytotoxicity and adverse effect profiles of the medicines.

Clinical Evidence for Chronotherapy in Oncology

Numerous clinical trials have assessed chronotherapy, or time-adjusted chemotherapy treatment, with promising outcomes.

1. **Colorectal Cancer:** Treatment of colon cancer with oxaliplatin, 5-fluorouracil (5-FU), and leucovorin is one of the most well-researched cases. It has been demonstrated that chronomodulated delivery, which involves giving these medications at particular times of the day, improves therapeutic efficacy while lowering toxicities such peripheral neuropathy, neutropenia, and mucositis. According to studies, adverse effects can be minimised without sacrificing tumour control by giving oxaliplatin in the afternoon or evening, when normal cells are less sensitive.

   2. Breast Cancer: Agents such as doxorubicin and cyclophosphamide have been investigated in chronotherapy techniques. It may be possible to reduce cardiotoxicity and improve tumour response by timing these medications to coincide with circadian changes in cardiac vulnerability and DNA repair.

2. **Leukemia and Lymphoma:** The circadian timing of medications such as methotrexate and cytarabine can affect bone marrow toxicity and treatment outcomes in haematological malignancies (Ozturk et al., 2017).

Benefits of Chronotherapy in Oncology

The enhanced therapeutic index, which maximises tumour death while minimising side effects, is chronotherapy's main benefit. Chronotherapy minimises dose-limiting toxicities that often complicate cancer treatment by delivering chemotherapy when cancer cells are more susceptible and normal tissues are more resistant. This could lead to better results by enabling either more aggressive schedules or higher cumulative doses.

By reducing adverse symptoms including nausea, exhaustion, and immunosuppression, chronotherapy can also improve patient quality of life by promoting better treatment adherence and fewer disruptions.

Challenges and Considerations

Although chronotherapy has potential, a number of obstacles prevent its widespread use:

• Interpatient variability: Depending on a person's age, lifestyle, genetics, and illness status, their circadian rhythms vary. It is currently not common practice to precisely analyse each patient's biological clock in order to tailor chronotherapy.

• Real-world problems: Chronomodulated medication delivery frequently necessitates specialised clinical setups and programmable infusion pumps, both of which can be resource-intensive.

• Tumour heterogeneity: Cancer cells may become resistant to the impacts of time of day or lose their ability to regulate their circadian rhythm.

• Drug half-life: Unless formulations are made especially for chronotherapy, long half-lives of medications may mask timing effects (El-Tanani et al., 2024).

Chronopharmacology and immunology

Chronopharmacology is the study of how drug administration timing affects pharmacological effects by synchronising with biological cycles in the body. Because circadian rhythms have a considerable impact on immune function, this technique is especially important in the field of immunology. Throughout the 24-hour day-night cycle, the immune system's activity fluctuates, impacting the body's reaction to infections, inflammation, and immunomodulatory treatments. By comprehending these rhythms, medication scheduling can be optimised to boost the immune system or lessen excessive inflammation, increasing therapeutic effectiveness and lowering unwanted effects.

Circadian Regulation of the Immune System

The hypothalamus's core biological clock and the immune cells' peripheral clocks work together to tightly regulate the immune system's circadian rhythm. Circadian genes, including PER, CRY, BMAL1, and CLOCK, control the immune-related genes' rhythmic expression. Important facets of immune function are influenced by this rhythmicity, such as:

• Leukocyte trafficking: Throughout the day, the quantity of immune cells in circulation, including neutrophils, monocytes, and lymphocytes, varies, usually reaching its maximum during the resting phase.

• Production of cytokines: Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 exhibit diurnal fluctuation, frequently rising in the early morning or at night.

• Antigen presentation and adaptive immunity: The immune system's reaction to infection or immunisation is influenced by the efficacy of antigen-presenting cells and T cell activation, which also fluctuates during the day.

This inherent rhythmicity affects vulnerability to infection and the progression of immunological-mediated illnesses by causing immune responses and inflammation to be greater or weaker depending on the time of day (Ayyar et al., 2021).

Chronopharmacology in Immune Modulation

The timing of immunomodulatory medications can affect their efficacy and adverse effect profiles due to the circadian variations in immunological activity.

Vaccination

Research has indicated that the timing of vaccinations has an impact on the immunological response. For instance, compared to afternoon immunisation, morning vaccination may elicit a greater antibody response. Higher antigen-presenting cell activity and improved adaptive immune activation in the morning are assumed to be the causes of this. Therefore, scheduling vaccinations optimally may increase their effectiveness, which is crucial for susceptible groups like the elderly.

Corticosteroids

A common immunosuppressant for autoimmune and inflammatory disorders is corticosteroids. A clear circadian rhythm is followed by their natural equivalent, cortisol, which peaks in the early morning and decreases throughout the day. Corticosteroids can lessen hypothalamic-pituitary-adrenal (HPA) axis suppression and minimise adverse effects such adrenal insufficiency when administered in accordance with this natural rhythm, usually in the morning. In conditions like rheumatoid arthritis, when morning stiffness and inflammation peak early in the day, chronotherapy of steroids helps reduce symptoms (Walton et al., 2021).

Biologic Agents and Immunotherapy

Chronopharmacological optimisation may also be advantageous for biologic treatments, such as monoclonal antibodies and cytokine inhibitors used in autoimmune illnesses (e.g., anti-TNF medicines, IL-6 inhibitors). Although clinical research in this field is still in its infancy, timing dosing to correspond with peak cytokine levels or immune cell activity may increase efficacy and decrease side effects (Raychaudhuri et al., 2009).

Chronopharmacology in Infectious Diseases

Host-pathogen interactions are also impacted by circadian rhythm. The time of day might affect an individual's susceptibility to infections and reaction to antimicrobial treatments. For instance, host circadian rhythms affect how some bacteria and viruses replicate.

Antimicrobial drugs may be most effective when given when host immune responses are at their peak or when pathogen multiplication is at its highest. Moreover, infection control may be enhanced by using chronotherapy to optimise immunomodulatory adjunct medicines like interferons or vaccinations (Rijo-Ferreira et al., 2022).

Molecular Fundamentals of Circadian Clocks

The Earth's rotation causes regular daily changes in the environment, which organisms can predict and adjust to thanks to the circadian clock, an inherent timekeeping system. Usually lasting around 24 hours, this biological clock coordinates rhythms in metabolism, behaviour, and physiology. Circadian clocks are produced and sustained at the molecular level by a network of interrelated transcriptional-translational feedback loops (TTFLs) made up of core clock genes and proteins. Although the precise components differ, these molecular clocks are impressively conserved throughout species, from humans to cyanobacteria (Pilorz et al., 2018).

Core Molecular Components of Circadian Clocks

- A transcriptional-translational feedback loop involving multiple core clock genes and their protein products is at the centre of the circadian clockwork in animals. CLOCK, BMAL1, PER (Period), and CRY (Cryptochrome) proteins are the main constituents.

  • Two transcription factors that form a heterodimer in the nucleus are BMAL1 (Brain and Muscle ARNT-Like 1) and CLOCK (Circadian Locomotor Output Cycles Kaput). This complex starts the transcription of target genes by binding to E-box sites in their promoters.

• The Period (Per1, Per2, Per3) and Cryptochrome (Cry1, Cry2) genes are two examples of these target genes. The cytoplasm is where the Per and Cry mRNAs are translated into proteins.

- • Following a lag, the proteins PER and CRY group together to form complexes that return to the nucleus and stop the CLOCK:BMAL1 complex from working. The feedback loop is closed by this repression, which lowers the transcription of Per and Cry.

  • A new cycle starts as the PER and CRY proteins break down over time, releasing CLOCK:BMAL1 from inhibition. This negative feedback loop, which produces the molecular oscillation that underlies circadian rhythms, takes about twenty-four hours to finish (Takahashi et al., 2017).

Additional Feedback Loops

Auxiliary loops supplement the main negative feedback loop, giving the clock more resilience and fine-tuning.

• A secondary feedback loop that controls Bmal1 expression is formed by the proteins REV-ERB (α and β) and ROR (Retinoic acid receptor-related Orphan Receptors α, β, and γ). Rev-Erbα and Ror gene transcription is activated by CLOCK:BMAL1. RORs increase Bmal1 transcription, while REV-ERB proteins suppress it. The clock's stability and accuracy are enhanced by this antagonistic control, which also fine-tunes the oscillation of BMAL1 protein levels.

• Additional clock-controlled genes (CCGs) that CLOCK regulates: BMAL1 connects the circadian clock to many physiological activities, including hormone synthesis, DNA repair, metabolic processes, and cell cycle.

Post-translational Modifications

Post-translational modifications (PTMs) are essential for establishing the stability, localisation, and activity of clock proteins; the molecular clock is not only controlled at the transcriptional and translational levels. One important alteration is phosphorylation. PER proteins are phosphorylated by kinases like casein kinase 1δ/ε (CK1δ/ε), designating them for ubiquitin-proteasome system destruction. The time of nuclear entrance and PER protein accumulation is regulated by this mechanism.

• Disorders like familial advanced sleep phase syndrome (FASPS) can be caused by changes in the circadian period caused by mutations in CK1δ/ε or PER phosphorylation sites.

• Additional PTMs that support clock protein turnover and function include acetylation, ubiquitination, sumoylation, and poly(ADP-ribosyl)ation (Relógio et al., 2011).

Input and Output Pathways

Light is the most significant of the external cues, or zeitgebers, that synchronise circadian clocks. In animals, the retinohypothalamic tract carries light information to the hypothalamic suprachiasmatic nucleus (SCN), the master circadian pacemaker, via specialised retinal ganglion cells that express the photopigment melanopsin.

• The SCN synchronises systemic physiology through neurological and hormonal signals by coordinating peripheral clocks found in almost all tissues; exposure to light causes the SCN to induce the production of the Per1 and Per2 genes, which resets the clock phase.

Peripheral clocks modulate metabolism, detoxification, and cardiovascular rhythms by controlling local tissue activities in organs like the liver, heart, and lungs (Helfrich-Förster et al., 2020).

Molecular Clock in Peripheral Tissues

Nearly every cell has a molecular clock that is controlled by comparable feedback loops, even if the SCN serves as the master clock.

The same core components (CLOCK, BMAL1, PER, and CRY) underpin peripheral clocks, which are sensitive to systemic cues like hormones, body temperature, and feeding schedules. This multi-oscillator system enables precise control of local physiology, guaranteeing tissue-specific circadian rhythms that complement the organism's overall temporal program.

Circadian Clock and Health

Significant physiological repercussions may result from interference with the molecular clock's components: • Sleep problems, metabolic syndrome, cardiovascular diseases, cancer, and mental disorders have all been connected to genetic mutations or changes in clock gene expression.

Understanding the molecular basis of circadian clocks has opened avenues for chronotherapy, where drug administration is timed to maximise efficacy and minimise side effects. • Circadian misalignment, as observed in shift work, jet lag, or irregular sleep patterns, impairs molecular clock function and increases the risk of chronic diseases (Fagiani et al., 2022).

Chronopharmacology of Arthritis

Chronic joint inflammation, pain, stiffness, and functional impairment are hallmarks of arthritis, especially rheumatoid arthritis (RA) and osteoarthritis (OA). Patients frequently report greater pain and stiffness in the early morning hours, and these symptoms show clear circadian patterns. Optimising therapeutic efficacy and reducing side effects need an understanding of the chronopharmacology of arthritis, or how the timing of drug delivery affects treatment outcomes.

Circadian Rhythms in Arthritis Symptoms

The severity of arthritis symptoms fluctuates throughout the day, largely influenced by the body's internal biological clock. In RA, pro-inflammatory cytokines such as **interleukin-6 (IL-6)** and **tumor necrosis factor-alpha (TNF-α)** peak during the night and early morning, contributing to the classic morning stiffness and heightened pain sensitivity. This nocturnal rise in inflammation correlates with circadian variation in immune system activity and hormone levels, including the early morning nadir of anti-inflammatory hormones like **cortisol**.

Osteoarthritis symptoms also show daily variation, with pain intensity frequently increasing after periods of rest, such as in the morning, due to joint stiffness and mechanical factors (Cutolo et al., 2016).

Principles of Chronopharmacology in Arthritis Treatment

In order to increase effectiveness and decrease toxicity, chronopharmacology seeks to align medicine delivery with the body's circadian rhythms and symptom patterns. This entails scheduling arthritis medications to combat the highest levels of pain and inflammation, which are frequently experienced at night or in the early morning.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The first-line treatment for arthritic pain and inflammation is NSAIDs. Chronotherapy studies have demonstrated that by addressing the nocturnal spike of inflammatory cytokines, NSAID dosages taken in the evening or before bed can dramatically reduce morning stiffness and pain. For instance, meloxicam or

indomethacin sustained-release formulations taken at night offer superior symptom control in the early hours of the morning compared to morning dosage.

By limiting medication exposure during times of elevated stomach vulnerability, this approach not only increases patient comfort but may also lessen gastrointestinal adverse effects (Shah et al., 2024).

Glucocorticoids

Strong anti-inflammatory medications called glucocorticoids, such as prednisone, are frequently prescribed for RA. Taking glucocorticoids late at night or in the early morning hours optimise their anti-inflammatory impact during the cytokine surge, lowering morning stiffness and pain because endogenous cortisol levels normally peak in the early morning.

In order to match corticosteroid action with peak inflammation, modified-release prednisone formulations that release the medication 3–4 hours after consumption (usually given at nighttime) have been created. This improves symptom alleviation while limiting overall steroid exposure and side effects.

Disease-Modifying Antirheumatic Drugs (DMARDs) and Biologics

The underlying immunological processes of arthritis are the focus of DMARDs and biologic medicines (such as methotrexate and TNF inhibitors). There is little information on their chronopharmacology, however there is evidence that administering them at a time that corresponds with circadian immunological activity may increase effectiveness and decrease side effects.

For instance, taking methotrexate in the evening may increase its effectiveness and tolerability. Similarly, circadian patterns of cytokine production and immune cell function may help optimise the timing of biologic therapy, but further study is required (Paolino et al., 2017).

Chronopharmacology of Sleep Disorder

Sleep disorders are a broad category of illnesses that interfere with regular sleep cycles, such as narcolepsy, insomnia, restless legs syndrome, and circadian rhythm sleep-wake disorders (CRSWDs). These conditions can have a significant impact on general health, cognitive function, and quality of life. Pharmacotherapy is frequently used to treat sleep problems, and knowing chronopharmacology—the timing-dependent effects of medications—is essential to maximising therapeutic benefits and reducing side effects. This paper investigates how the treatment of sleep disorders is influenced by chronopharmacological concepts.

Circadian Rhythms and Sleep Regulation

The circadian rhythm and the homeostatic sleep drive are the two main mechanisms that control sleep-wake cycles. The hypothalamic suprachiasmatic nucleus (SCN) controls the circadian system, which plans the time of sleep and awake over a 24-hour period. Physiological processes are synchronised with environmental cues like temperature and light by this endogenous clock.

Sleep disorders can arise from a mismatch between the internal clock and the external environment caused by disruptions in circadian rhythms, which can be brought on by shift work, jet lag, or inherent circadian disorders. Pharmacological therapies can enhance the quality of sleep and daytime functioning by taking into account the timing of drug delivery in relation to circadian phases (Karna et al., 2020).

Chronopharmacology of Common Sleep Medications

Hypnotics and Sedatives

Medications such as benzodiazepines, non-benzodiazepine receptor agonists (e.g., zolpidem), and melatonin receptor agonists are commonly prescribed for insomnia. The main way that chronopharmacology directs their usage is by coordinating the start and duration of the medicine with the patient's circadian phase and sleep cycle.

• Z-Drugs and benzodiazepines: By strengthening GABAergic inhibition, these medications aid in the beginning and maintenance of sleep. By giving these medications just before bed, their maximum sedative effects coincide with the ideal sleep duration, minimising awakenings during the night. Inappropriate scheduling, however, may result in tolerance or lingering sedation during the day.

• Agonists for Melatonin and Melatonin: The pineal gland secretes the hormone melatonin, which tells the brain that night has arrived. It is used to treat sleep-wake disorders related to the circadian clock, including jet lag and delayed sleep phase syndrome (DSPS). Melatonin can increase sleep initiation and advance the circadian phase when administered 1-2 hours before to the planned bedtime. Because administration during the day may result in undesirable phase shifts, timing is crucial (Golombek et al., 2015).

Wake-Promoting Agents

Wake-promoting medications like modafinil and armodafinil are used to treat conditions including narcolepsy and shift work disorder that are characterised by excessive daytime sleepiness. The timing of its delivery is designed to optimise awareness throughout the patient's waking hours and prevent disruptions to their subsequent sleep.

Chronotherapy in Circadian Rhythm Sleep-Wake Disorders

The objective of circadian rhythm sleep-wake disorders, such as advanced or delayed sleep phase syndromes, is to re-align the internal clock with environmental and social needs. When it comes to timing the administration of medications and light therapy to restore circadian rhythms, chronopharmacology is essential. Patients with delayed sleep phase syndrome (DSPS) have trouble sleeping until late at night and waking up in the morning. An earlier sleep onset can be promoted by advancing the circadian clock with timed melatonin treatment in the early evening.

Patients with Advanced Sleep Phase Syndrome (ASPS) go to sleep and wake up sooner than they would like to. The circadian clock is delayed by evening bright light exposure, timed melatonin antagonists, or deliberate avoidance of morning light (Schwartz et al., 2009).

Significance of Chronopharmacology

In order to maximise therapeutic results, chronopharmacology—the study of how pharmacological effects change based on biological timing and circadian rhythms—has become an essential field. The understanding that the human body functions on intricate, inherent, time-dependent cycles—mostly circadian rhythms—that affect drug absorption, metabolism, efficacy, and toxicity is what makes it significant. Almost every physiological process, including hormone production, enzyme activity, immunological reactions, and cell regeneration, is impacted by this temporal fluctuation. Clinicians and researchers can optimise medicine administration to particular times of day by understanding these biological rhythms, which minimises side effects and maximises efficacy.

Many diseases, for instance, show circadian patterns in their pathophysiology and symptom intensity; for instance, cancer cell division occurs according to daily cycles, hypertension frequently peaks in the early morning, and asthma symptoms typically increase at night. By coordinating the timing of medications with the body's natural rhythms, a technique known as chronotherapy, chronopharmacology takes use of these patterns. This strategy can significantly enhance medication performance. For example, antihypertensive medications administered at night are more successful at reducing cardiovascular events and controlling morning blood pressure spikes than those administered in the morning. Similar to this, chemotherapy can increase tumour kill rates while preserving healthy cells and reducing side effects by scheduling it to target cancer cells during their most vulnerable stages (Colita et al., 2024).

Recent Advances in Chronopharmacology

Significant progress has been made recently in the field of chronopharmacology, which examines how the effects and metabolism of medications change in response to biological timing and circadian rhythms. These advancements in drug formulation, clinical treatments, molecular biology, and personalised medicine are revolutionising the prescription and delivery of pharmaceuticals. Safer and more effective treatments have been made possible by an understanding of and ability to use the temporal patterns of physiology and disease. A thorough analysis of some of the most noteworthy recent developments in this developing topic may be found below.

Molecular Insights and Circadian Biology

The growing comprehension of the molecular mechanics behind circadian clocks has been one of the key factors propelling advancements in chronopharmacology. Numerous clock-controlled genes involved in drug metabolism, immunological response, and cell cycle regulation have been discovered, along with core clock genes like CLOCK, BMAL1, PER, and CRY, thanks to developments in genetics and molecular biology. The scientific basis for chronotherapy has been established by the discovery that many pharmacological targets and metabolising enzymes are regulated in a circadian fashion.

Recent studies have shed light on how clock protein post-translational changes (such as phosphorylation and acetylation) control the accuracy and stability of circadian rhythms, which in turn affects how drugs work. Furthermore, research on the peripheral clocks of organs like the liver, kidney, and heart has shown toxicity and drug metabolism rhythms that are particular to each tissue. This information lends credence to the notion that treatment outcomes can be enhanced by coordinating drug delivery with both local organ clocks and the brain's master clock (Yu et al., 2022).

Technological Innovations: Wearables and Biomarkers

Chronopharmacology has been transformed by the combination of wearable technologies and digital health tools, which allow for the continuous monitoring of circadian biomarkers including body temperature, heart rate variability, and activity-rest cycles. By offering customised circadian profiles, these gadgets assist medical professionals in figuring out when to provide medications based on each patient's unique rhythm. Personalised chronotherapy is being advanced by the discovery of biomarkers, such as clock gene expression patterns in peripheral blood, particularly in complicated disorders like autoimmune diseases and cancer. Large datasets are analysed by machine learning algorithms to forecast each patient's drug response time, which helps to improve treatment plans (Gubin et al., 2025).

Novel Drug Formulations and Delivery Systems

The development of chronotherapeutic drug delivery systems, which release pharmaceuticals in accordance with circadian cycles, has been the focus of pharmaceutical innovation. These consist of: • Controlled-release pills and tablets intended to postpone or maintain the release of a medication.

• Programmable infusion pumps that deliver medications intravenously at predetermined intervals.

• Delivery using nanoparticles that delivers medications to particular tissues in a time-dependent fashion. These kinds of devices are especially useful for medications that have limited therapeutic windows or that have serious adverse effects (Butler et al., 2024).

Conclusion

Our knowledge of how drugs function in the dynamic milieu of the human body has been completely transformed by chronopharmacology, the study of the relationship between biological time and pharmacological action. Recognising that circadian cycles control physiological processes, such as medication absorption, metabolism, distribution, and elimination, chronopharmacology highlights that "when" a drug is delivered can be just as important as "what" drug is given and in "what" quantity. This temporal dimension brings about a paradigm shift away from conventional pharmacotherapy and towards chronotherapy, a more advanced, time-aware method. Enhancing medication efficacy is important, but so are reducing side effects, increasing patient compliance, and eventually raising the standard of care overall (Robles-Piedras et al., 2024). Asthma symptoms increase at night, cardiovascular events peak in the early morning, and many malignancies have regular cell cycle progression—diseases with distinct circadian patterns are becoming more widely acknowledged. In a variety of illnesses, such as hypertension, cancer, rheumatoid arthritis, metabolic disorders, and sleep problems, therapeutic outcomes have significantly improved when drug delivery is tailored to these biological rhythms. The mechanistic underpinnings of chronopharmacology have been greatly illuminated by the developments in molecular chronobiology, especially the identification of core clock genes and associated regulatory networks. The discovery of circadian variations in drug targets and metabolic enzymes—two important factors influencing therapeutic action and toxicity—has been made possible by this molecular insight. Furthermore, the understanding that local drug metabolism is influenced by peripheral clocks in different tissues highlights the intricacy and the need to take organ-specific timing into account when designing a treatment plan. Advances in technology have helped chronopharmacology become more widely used in therapeutic settings. Individual circadian markers may now be continuously monitored thanks to wearable technology and digital health platforms, allowing for customised chronotherapy that takes into account each patient's own biological rhythms rather than depending only on averages from the community (Lee et al., 2021).

In addition, the creation of programmable and controlled-release drug delivery systems enables accurate temporal targeting of pharmaceuticals, maximising therapeutic windows and minimising adverse effects. Even with these encouraging developments, there are still obstacles in the way of completely incorporating chronopharmacology into standard medical treatment.

These include the practical challenges of arranging medication delivery in accordance with biological clocks, the lack of awareness among clinicians, and the heterogeneity in individual circadian rhythms caused by hereditary and environmental variables. Furthermore, in order to create evidence-based guidelines, extensive clinical trials that validate chronotherapy procedures across a range of populations and conditions are still required. However, chronopharmacology has a promising future and could transform personalised treatment. Even more accuracy in medication therapy is possible when chronopharmacological concepts are combined with pharmacogenomics and biomarker-driven methodologies (Adepu et al., 2021).

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