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CHRONOTHERAPY REVIEW: RELATION BETWEEN BODY CLOCK AND DRUG EFFECTS

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Abstract: Approximately every 24 hours, naturally occurring and autonomous biological clocks referred to as circadian rhythms arise, influencing a broad spectrum of physiological, biochemical, and behavioral processes in life forms [1, 2]. A hierarchical framework of central and peripheral clocks regulates these rhythms, with the primary pacemaker situated in the hypothalamic suprachiasmatic nucleus (SCN) [3]. Tissues including the liver, kidney, and intestines have peripheral clocks that are synchronized by neuroendocrine behaviors, food cycles, and external stimuli from the outside world [4]. Maintaining systemic homeostasis requires circadian regulation, which also helps organisms anticipate and react to daily environmental changes like light-dark cycles [5].

Disruption of circadian rhythms caused by factors like overtime, travelling continuously, or erratic lifestyles can negatively affect health and increase the risk of disorders such as cancer, cardiovascular disease, and metabolic syndrome [6]. Crucially, the pharmacokinetic (absorption, distribution, metabolism, and excretion) and pharmacodynamic (drug-receptor contact) processes are both greatly impacted by circadian oscillations, which in turn affects the toxicity and efficacy of drugs across the 24-hour cycle [7, 8]. The temporal variation in drug targets, metabolic enzyme expression, and physiological parameters underscores the necessity of aligning drug administration with the body's internal clock—a concept known as chronotherapy [9].

Recent modeling methods, like chronopharmacometrics and systems biology, have been key in understanding how different biological systems interact over time and in improving drug dosing schedules. New findings also show that drugs aimed at key parts of the body's internal clock could help treat problems related to our biological rhythms. Improved knowledge of the circadian system and its pharmaceutical impacts may lead to more specialized and successful therapies. By coordinating medication administration with the patient's biological cycles, these approaches not only aim to increase treatment effectiveness but also reduce adverse effects. The application of chronotherapy in clinical practice has the potential to drastically alter the medical environment as long as research in this area continues to advance.

INTRODUCTION:

Biological systems across virtually all organisms have evolved to adapt to the Earth's 24-hour light–dark cycle through intrinsic circadian clocks—self-sustained, entrainable oscillators that regulate physiological processes on a near-24-hour cycle. These circadian rhythms coordinate a multitude of biological functions including sleep–wake cycles, body temperature, hormonal secretions, metabolism, and immune responses, aligning internal functions with the external environment to maintain homeostasis [12,13]. The mammalian circadian system is organized hierarchically, with a central pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus synchronizing peripheral clocks located in nearly all cells and tissues [14]. These rhythms persist even in constant conditions and are modulated by zeitgebers such as light, feeding patterns, and temperature, allowing organisms to anticipate environmental changes [15].

Importantly, circadian rhythms exert profound influences on pharmacokinetics (PK) and pharmacodynamics (PD), affecting drug absorption, distribution, metabolism, and elimination. Nearly 50% of the mammalian

protein-coding genome exhibits circadian expression, leading to time-of-day-dependent fluctuations in drug targets, enzymes, and transporters involved in xenobiotic metabolism [16,17]. Consequently, the efficacy and toxicity of numerous therapeutic agents—including those used for managing cardiovascular, oncological, and metabolic disorders—vary based on the timing of drug administration [18]. This time-of-day variability forms the basis of chronopharmacology, a field that aims to improve drug effectiveness and safety by synchronizing treatment regimens with the body's internal clock [19]. For instance, antihypertensive drugs like nifedipine exhibit enhanced efficacy when taken at night due to nocturnal blood pressure surges. Similarly, corticosteroids such as prednisone are more effective when administered in the morning, aligning with endogenous cortisol peaks. Statins are typically prescribed for nighttime use, matching the body's natural cholesterol synthesis peak.

Table 1: Examples of Circadian-Dependent Drug Administration

Drug/Class	Optimal Time	Therapeutic Benefit	Reference
Nifedipine (BP med)	Night	Reduces nocturnal BP surge	[19]
Prednisone (Steroid)	Morning	Aligns with cortisol peak, minimizes side effects	[25]
Statins	Evening	Matches peak cholesterol synthesis	[25, 26]

The relevance of circadian biology in clinical pharmacology is especially notable in the context of chronic diseases. For instance, cardiovascular disorders, which remain the leading cause of global mortality, display strong circadian variation in symptoms and events such as myocardial infarction and stroke, which tend to occur more frequently during specific times of the day [20,21]. Drug efficacy and adverse event profiles for commonly prescribed cardiovascular agents like statins, beta-blockers, and antihypertensives have been shown to be significantly influenced by administration time due to circadian variations in hepatic metabolism and vascular tone [22,23].

Despite these insights, the integration of circadian principles into clinical practice remains limited. A lack of awareness among healthcare providers, alongside insufficient chronobiological consideration in drug development, hampers the implementation of personalized, time-based treatment strategies. As chronopharmacometrics—the integration of chronobiology with pharmacometric modeling—continues to advance, it holds the promise of transforming drug therapy by optimizing dosing schedules and reducing adverse effects based on individual circadian profiles [24].

This review explores the complex interplay between the circadian system and drug efficacy, summarizing current knowledge on molecular clock mechanisms, circadian influences on drug action, and emerging applications of chronotherapy to enhance treatment outcomes.

1. Historical Evolution of Chronopharmacology:

The development of chronopharmacology has emerged from centuries of observations on biological timekeeping. This timeline highlights foundational discoveries that led to our current understanding of circadian regulation and its application in pharmacology.

Table 2: Historical Timeline

Year	Milestone	Details & Contributions	Reference
1729	First Evidence of Biological Clocks	When plant of mimosa was kept in complete darkness, Jean-Jacques d'Ortous de Mairan saw regular leaf movements, which may indicate the evidence of an internal bio clock.	[27]

1751	Linnaeus' Floral Clock	Carl Linnaeus further illustrated the recurring cycles in nature by using flower opening times to build a "Horologium Florae."	[28]
1920s	Early Human Rhythm Studies	Endogenous cycles in humans were shown by the fluctuation of physiological markers such as temperature and pulse in daily rhythms.	[29]
1950s	Birth of Chronobiology	The term "circadian" was first used by Franz Halberg, who also founded the methodical study of biological rhythms in both health and illness.	[30]
1970s–80s	Pharmacological Studies in Rodents	Studies on humans and animals showed that the effects and metabolism of drugs (such as theophylline and acetaminophen) varied with the time of day.	[31]
1984–1990	SCN as the Master Clock	The suprachiasmatic nucleus (SCN) was found to be the primary pacemaker in animals through transplantation studies.	[32]
1997	Discovery of CLOCK Gene	The discovery of the clock gene in mice represented a significant advancement in our knowledge of the molecular underpinnings of circadian rhythms.	[33]
2000s	Emergence of Chronotherapy	Drug administration based on time of day gained popularity in the treatment of hypertension, asthma, and cancer.	[34]
D2017	Nobel Prize for Circadian Rhythm Research	Hall, Rosbash, and Young discovered the molecular mechanisms underlying the circadian rhythms.	[35]

2. Circadian Control of Pharmacokinetics and Pharmacodynamics:

Circadian rhythms profoundly influence the pharmacokinetics (PK) and pharmacodynamics (PD) of many drugs through their regulatory effects on physiological processes governing drug absorption, distribution, metabolism, and excretion.

1. Absorption
Circadian rhythms affect a number of physiological processes, including the absorption of medications from the gastrointestinal tract. Throughout the day, a number of variables change, including splanchnic blood flow, intestinal motility, gastric pH, and enzyme activity. For instance, the solubility and dissolution of several oral medications may be impacted by the greater stomach acidity that occurs at night. Similarly, decreased intestinal motility while you sleep can cause drugs to take longer to absorb (36,37). Because of these variances, a medicine may act very differently depending on when it is administered.

2.Distribution
Additionally, the distribution of medications throughout the body is regulated by circadian rhythms. Many medications attach to plasma proteins for transportation, and their amounts fluctuate throughout a 24-hour period. A drug's free (active) concentration in the blood may be impacted by this. Additionally, the way drugs are delivered to target areas might be changed by circadian variations in blood flow to tissues and organs. A drug's ability to reach the liver or kidneys for metabolism or clearance, for example, may be limited by decreased hepatic or renal blood flow during specific times of the day (38).

3. Metabolism:
Our primary organ for digesting drugs, the liver, is not always in the same state of operation. Its enzyme levels fluctuate in time with our circadian cycles, particularly those of cytochrome P450s. This implies that a medication taken in the morning may or may not degrade as quickly as a medication taken at night. These variations can have an impact on a drug's effectiveness and likelihood of side effects, especially for medications that need exact dosage [36,39,40].

4. Excretion
Our kidneys—the body's filtration system—don't flush out drugs at a steady pace all day. Things like glomerular filtration rate, urine flow, and active transport shift depending on the time, thanks to our circadian rhythm. These changes mean that the same drug dose might leave the body faster in the afternoon than at night, which can impact how long the drug stays active and how effective it is [36,37,40].

3. Clock Genes and Their Role in Drug Metabolism:

The ability of our body to digest drugs is not solely controlled by the organs involved; it is also intimately related to our internal biological clocks. These clocks are managed by specific genes known as clock genes, which also regulate the daily cycles of numerous physiological processes, such as drug metabolism.

CLOCK and BMAL1: The Core Timekeepers
The circadian rhythm is driven by a core transcriptional pair consisting of the proteins BMAL1 and CLOCK. The expression of several genes, including those encoding cytochrome P450 enzymes—important participants in drug metabolism, particularly in the liver—is triggered when these two proteins interact. Because of the circadian pattern of this activation, the effectiveness of medication metabolism can change with the time of day (41,42).

PER Genes: The Brakes in the Cycle
The PER1, PER2, and PER3 genes act as part of a feedback loop that keeps the CLOCK:BMAL1 activity in check. These proteins accumulate over time and then suppress the activity of CLOCK and BMAL1 to help maintain a roughly 24-hour rhythm. Studies on mice lacking PER genes have shown abnormal expression of liver enzymes, leading to significant changes in how drugs are broken down and how long they stay active in the system (43).

CRY Genes: The Rhythm Stabilizers
The CRY1 and CRY2 genes work alongside the PER proteins to fine-tune the internal clock. They play a critical role in regulating the strength and stability of circadian rhythms. Knockout models have revealed that when CRY genes are disrupted, the body loses its ability to maintain regular expression of drug-metabolizing enzymes, which affects drug absorption and clearance (44).

4. Experimental Approaches in Chronopharmacology:

1. Time-of-Day Dosing Models: Drugs are administered at different times of the day to assess how their effects changes with time.
   Applications: It helps to identify optimal dosing windows to improve therapeutic outcomes and minimize side effects. (45,46)
2. Circadian-Altered Animal Models: Use of genetically modified animals (e.g., CLOCK, BMAL1 knockout mice) or animals exposed to altered light/dark cycles.
   Applications: Investigates the role of circadian genes in drug metabolism and physiological rhythms. (47,48)
3. Telemetry and Physiological Monitoring: Continuous monitoring of body temperature, heart rate, and activity using implanted sensors in animals.
   Applications: Tracks real-time circadian physiology and responses to pharmacologic interventions. (49)
4. Transcriptomics (Gene Expression Studies): Collecting tissue samples at various times to analyze mRNA expression patterns.
   Applications: Determines how circadian rhythms influence gene networks related to ADME (absorption, distribution, metabolism, excretion). (50)
5. Proteomics (Protein Profiling): Assessing time-dependent changes in the expression and modification of proteins involved in drug processing.
   Applications: Reveals circadian regulation of key drug transporters and metabolic enzymes. (51)
6. Metabolomics (Metabolite Analysis): Measuring small molecules in blood or tissues over 24 hours to track changes in drug breakdown products.
   Applications: Identifies circadian fluctuations in endogenous metabolites and drug response profiles. (52)

5. Chronotherapeutic in Practice:

1. High Blood Pressure (Hypertension)
Imagine being able to lower your risk of heart attack just by changing *when* you take your medicine. That's exactly what a large study found when patients with high blood pressure started taking their medication at bedtime instead of in the morning. Not only did their blood pressure improve overnight, but their overall risk of heart problems dropped significantly too (53).

2. Asthma
People with asthma often notice that their symptoms get worse at night. Researchers tested whether changing the time of inhaled steroid use could help—and it did. Taking the drug in the late afternoon enhanced breathing during sleep hours and helped better manage symptoms at night (54)

3. Cancer of the colon
In a colorectal cancer clinical trial, physicians experimented with administering chemotherapy at times that corresponded with patients' biological clocks. What was the outcome? Patients on the customized timetable responded better to treatment and experienced fewer side effects than those on a regular schedule (55). It makes a compelling case for why "when" matters in cancer treatment.

4. Epilepsy
For children who were having more seizures at night, adjusting the timing of their anti-seizure medication made a big difference. By syncing the medication with the hours seizures were most likely, doctors managed to cut down the number of episodes and even reduce daytime drowsiness (56).

5. Type 2 Diabetes
In another study, patients were asked to take their metformin either in the morning or at night. Those who took it in the evening had better overnight blood sugar control and woke up with lower fasting glucose levels—just by switching the pill to bedtime (57).

6. Impact of Chronotype and Genetic Variability:

Not every person's body functions according to the same internal clock. "Morning types" are those who naturally rise early and are at their most alert in the morning, while "evening types" are those who are at their most alert in the evening. Not only are these circadian preference differences, or chronotypes, behavioral, but they also have biological roots that can influence how we react to drugs.
According to research, a person's chronotype can affect anything from side effect risk to drug metabolism. nighttime types may benefit from nighttime dosing schedules, whereas morning types may metabolize some medications more effectively in the early hours of the day (58). Therefore, knowing a patient's chronotype can be quite important when it comes to adjusting the scheduling of medications to maximize effectiveness and reduce side effects.
Genetic variation in clock genes, such as PER, CRY, CLOCK, and BMAL1, which control circadian rhythms at the molecular level, adds still another level of complexity. Variations in these genes have been linked to changes in medication response, susceptibility to disease, and even variations in the activity of enzymes involved in drug metabolism depending on the time of day (59,60). Variants in PER3, for example, have been linked to a changed susceptibility to drugs that impact the nervous system's functioning (61).
When combined, chronotype and clock gene polymorphisms show how pharmacotherapy needs to be more individualized, taking into account the patient's internal biology as well as the appropriate medicine and dosage.

7. Role of the Microbiome and Environmental Cues:

Circadian rhythms are not solely governed by our internal biological clocks—they're also significantly shaped by external cues and the gut microbiome. Studies have shown that microbial populations in the gut fluctuate throughout the day, influencing drug metabolism and immune responses (62). Environmental signals such as light, feeding patterns, and sleep-wake cycles act as *zeitgebers*, synchronizing internal rhythms with the external environment (63,64). Disruptions in these patterns—common in shift work, jet lag, or irregular eating—can desynchronize circadian rhythms, potentially reducing drug efficacy or increasing toxicity (65).

8. Advances in Chronopharmaceuticals and Drug Delivery Systems:

Modern pharmaceutical science is increasingly embracing time-based drug delivery. Technologies like pulsatile-release tablets and programmable infusion pumps are designed to align drug release with the body's biological rhythms (66). Smart drug delivery systems, including wearable biosensors and ingestible microdevices, are being developed to sense physiological changes and adjust drug release in real time (67,68). These approaches aim to improve outcomes in diseases like cancer, hypertension, and arthritis, where symptoms and drug targets fluctuate by time of day (69).

9. Chronopharmacology and Aging:

Aging brings about notable changes in circadian organization, including weakened rhythms and altered sleep-wake cycles. These changes can affect drug absorption, metabolism, and excretion, leading to variability in drug responses among elderly patients (70). Liver enzymes responsible for metabolizing many drugs may exhibit reduced circadian expression with age, and renal function—crucial for drug clearance—also declines (71). As a result, older adults are more vulnerable to adverse drug reactions if medication timing is not optimized according to their altered circadian profiles (72).

10. Regulatory Considerations and Guidelines:

Despite growing evidence supporting the role of circadian rhythms in drug response, formal regulatory frameworks around chronotherapy are still evolving. Agencies like the FDA and EMA acknowledge circadian biology's impact but lack detailed guidance on incorporating time-of-day effects into clinical trial design or drug labeling. The lack of extensive clinical data and individual circadian biology heterogeneity make it difficult to develop standard regimens for chronopharmacology. Nonetheless, interest is growing, particularly for medications like chemotherapeutics and antihypertensives that have high time-of-day dependence or limited therapeutic windows [73,74].

11. Ethical and Logistical Challenges in Chronomedicine:

Implementing time-based therapeutics introduces several ethical and practical concerns. Patients may face difficulties adhering to complex timing regimens, especially when they conflict with sleep, work, or caregiving responsibilities. There are also ethical concerns around equitable access to personalized chronotherapy, particularly in under-resourced settings. Logistically, healthcare systems may struggle to adapt workflows, especially in hospitals or nursing homes where standardized dosing schedules dominate [75,76]. Moreover, ethical considerations arise when tailoring treatment based on chronotype or genetic predisposition, especially if such information is not uniformly available or well-understood.

12. Integration with Artificial Intelligence and Big Data:

The fields of big data analytics and artificial intelligence (AI) provide exciting prospects for transforming chronomedicine. Artificial intelligence (AI) systems can model and forecast the best time to take medications for each patient by combining data from wearable biosensors, electronic health records, and individual chronotypes. Drug delivery systems that are responsive and dynamic can be made possible by the use of mobile health (mHealth) technologies to track biological rhythms in real time. Especially in the management of chronic diseases, this data-driven strategy can decrease side effects and enhance treatment outcomes [77,78]. The requirement for uniform data collection and interpretation, together with privacy issues, continue to be major implementation obstacles.

CONCLUSION:

Chronopharmacology highlights the critical role of biological timing in determining drug efficacy and safety. As our understanding of circadian biology expands, it is increasingly clear that optimal therapeutic outcomes may depend not only on the right drug and dose but also on the right time of administration. Clinical studies across diverse conditions such as hypertension, asthma, and cancer support the idea that synchronizing drug delivery with circadian rhythms can enhance efficacy while minimizing adverse effects [79,80,81].

Despite the promise, integrating time-based treatment into routine care faces regulatory, ethical, and logistical hurdles. Variability in individual chronotypes, genetic polymorphisms in clock genes, and environmental influences complicate universal dosing strategies [82,83]. However, with the rise of wearable technology, AI, and big data analytics, we are now better equipped to develop personalized chronotherapeutic models that adapt to real-time biological signals [84].

Looking ahead, a multidisciplinary approach—combining molecular biology, pharmacology, bioinformatics, and clinical sciences—will be essential to establish evidence-based guidelines and bring chronotherapy into

mainstream medical practice. With thoughtful application, chronopharmacology has the potential to become a cornerstone of precision medicine.

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