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Chronopharmacology: From Circadian Biology to Optimized Drug Therapy

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Abstract. Chronopharmacology examines how biological time shapes drug disposition, target sensitivity, and therapeutic outcomes. Chronotherapeutic strategies have entered clinical practice in hypertension, rheumatoid arthritis, asthma, and cancer. Existing reviews, however, largely catalogue clinical evidence without systematically integrating how the circadian regulatory network, from core molecular oscillators to peripheral tissue outputs, affects pharmacokinetics and pharmacodynamics. This review summarizes the multi-level circadian mechanisms in mammals and uses this framework to examine the circadian basis of drug pharmacokinetics and pharmacodynamics. We systematically searched PubMed and Web of Science for chronopharmacology literature published between 1972 and 2025. The mammalian circadian system is organized around *CLOCK*/BMAL1-PER/CRY transcription-translation feedback loops, with the suprachiasmatic nucleus (SCN) integrating light and feeding signals and coordinating peripheral clocks through autonomic, endocrine, and behavioral pathways. Circadian regulation of hepatic drug metabolism, the morning peak in myocardial infarction, and clock-dependent immune responses illustrate how biological time shapes drug response. At the same time, the conflicting MAPEC/Hygia and TIME trial findings in hypertension chronotherapy indicate that universal dosing-time rules are limited. We conclude that dosing time should be evaluated as a drug- and patient-specific precision medicine variable rather than a one-size-fits-all rule.

Keywords: chronopharmacology, circadian rhythm, pharmacokinetics, drug metabolism, precision medicine

1. Introduction

Most prescribing decisions treat time of day as a logistical detail. Yet mammalian physiology is organized around approximately 24-hour rhythms that coordinate sleep, feeding, hormone secretion, cardiovascular function, immunity, metabolism, tissue repair, and cellular proliferation [1-6]. These rhythms are not cosmetic fluctuations around a stable baseline. They change the internal environment in which drugs are absorbed, transported, metabolized, eliminated, and translated into clinical effects. Chronopharmacology therefore asks a practical question: can drug therapy be improved by matching administration time to biological time?

The idea is not new. Daily variation in drug toxicity and efficacy was described before the molecular clock was understood [7, 8]. What has changed is the explanatory framework. Discovery

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of core circadian genes and transcription-translation feedback loops made it possible to connect dosing-time effects with rhythmic gene expression, nuclear receptors, metabolic enzymes, transporters, and disease processes [9-14]. Modern chronopharmacology now spans molecular biology, pharmacometrics, clinical pharmacology, behavioral medicine, wearable technology, and implementation science.

The central paradox is that circadian mechanisms are well supported in animal models and human physiology, yet clinical evidence has been inconsistent when translated into dosing rules. In hypertension, ambulatory blood pressure studies and the MAPEC and Hygia trials supported bedtime dosing, but the subsequent TIME trial found no significant cardiovascular benefit of evening administration [15-17]. In oncology, chronomodulated chemotherapy reduced toxicity and improved survival in some colorectal cancer trials [18-22]; however, tumor and host clocks can differ in phase [20], so fixed infusion times cannot be universally applied. These conflicting results share a common root: most trials scheduled treatment by clock time rather than by each patient's biological phase. This is why the present review starts from molecular mechanisms and builds a systematic account of the circadian basis of drug therapy.

We conducted a systematic search of PubMed and Web of Science using terms including circadian clock, chronopharmacology, drug metabolism, and chronotherapy, covering literature published between 1972 and 2025 and focusing on human and mammalian biology and clinical drug use; plant and veterinary chronobiology were excluded. The core argument is that dosing time should be treated as a drug- and patient-specific precision medicine variable rather than a universal rule. The review is organized by mechanistic progression. Section 2 moves from the core TTFL oscillator through SCN cellular coupling and input-output integration to peripheral clocks that regulate drug metabolism. Sections 3 and 4 use this framework to examine circadian regulation of pharmacokinetics and pharmacodynamics, using the nocturnal CYP2E1 peak relevant to acetaminophen metabolism and the nighttime peak in hepatic cholesterol synthesis relevant to statins as representative examples. Sections 5 and 6 analyze how clock disruption in disease reshapes pharmacological rhythms. Sections 7-10 discuss wearable monitoring and the translational prospects of individualized chronotherapy scheduling.

2. Circadian biology underlying drug therapy

The circadian system is hierarchically organized. The suprachiasmatic nucleus (SCN) in the anterior hypothalamus functions as the master pacemaker, receiving light information from intrinsically photosensitive retinal ganglion cells through the retinohypothalamic tract [1, 2]. The SCN synchronizes behavioral and physiological rhythms through neural, endocrine, autonomic, and behavioral outputs, in addition to temperature rhythms. Light is the dominant zeitgeber for the SCN, while feeding, activity, sleep timing, and medications can strongly influence peripheral clocks [3, 4].

At the molecular level, circadian rhythms arise from interlocking transcription-translation feedback loops (TTFLs). CLOCK and BMAL1 activate transcription of the Period (Per1-3) and Cryptochrome (Cry1-2) genes. PER and CRY proteins accumulate, translocate to the nucleus, and repress CLOCK/BMAL1 activity, creating a cycle of roughly 24 h [9-11]. Auxiliary loops involving REV-ERB and ROR regulate Bmal1 transcription and connect the clock to lipid metabolism, inflammation, mitochondrial function, and xenobiotic pathways [12-14]. Post-translational modification by casein kinase 1 and other enzymes tunes period length, amplitude, and phase.

The circadian system can be understood as three nested levels: the molecular oscillator within individual cells (the TTFL), the cellular coupling network of the SCN, and the time-signaling pathways through which the central clock broadcasts phase to peripheral tissues.

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2.1. The core molecular oscillator: transcription-translation negative feedback loops (TTFLs)

The molecular core of circadian rhythms is a transcription-translation negative feedback loop (TTFL) involving Clock, Bmal1, Period (Per1-3), and Cryptochrome (Cry1-2) genes [9-14, 23]. This loop is the fundamental engine of rhythm generation. Several interlocking loops maintain circadian balance: a positive arm in which CLOCK/BMAL1 heterodimers drive transcription through E-box elements [9, 10]; a negative arm mediated by delayed feedback from PER/CRY/CK1δ/ε repressor complexes [24, 25]; auxiliary REV-ERB/ROR and DBP/E4BP4 loops that stabilize period and couple the clock to drug-metabolizing enzyme rhythms [12, 26, 27]; and post-translational modifications that link metabolism and clock function bidirectionally [28-31].

2.1.1. Positive and negative regulatory arms: CLOCK/BMAL1 and the PER/CRY/CK1δ/ε repressor complex

The positive arm is built around the *CLOCK*/BMAL1 heterodimer. *CLOCK* and BMAL1 dimerize in the cytoplasm, translocate to the nucleus through nuclear localization signals, and bind E-box elements (5'-CACGTG-3') in the promoters of target genes. They recruit histone acetyltransferases such as p300/CBP to open chromatin and initiate transcription of roughly 5-20% of expressed genes [9-11].

After *CLOCK*/BMAL1 binds E-box elements, it recruits coactivators such as p300/CBP to remodel chromatin and drive rhythmic transcription of clock genes, including Per, Cry, *Rev-erbα*/β, *Rorα*/γ, *Dbp*, and *E4bp4* [9]. Through these coactivators, *CLOCK*/BMAL1 rhythmically controls several classes of targets: the negative regulators *Per1*/2/3 and *Cry1*/2; the auxiliary loop components *Rev-erbα*/β (Nr1d1/2) and *Rorα*/γ; the PAR bZIP transcription factors *Dbp* and *E4bp4* (Nfil3); and numerous clock-controlled genes (CCGs) that encode metabolic enzymes, transporters, nuclear receptors, ion channels, and neurotransmitter receptors. CCGs are the direct effectors through which the clock system shapes physiological output [14].

The negative arm is executed by PER/CRY/CK1δ/ε repressor complexes. Newly translated PER proteins bind CK1δ/ε and undergo multisite phosphorylation, and PER and CRY proteins assemble into repressor complexes [9, 10, 32-34]. Multistep PER phosphorylation has opposing effects: phosphorylation within the familial advanced sleep phase syndrome (FASPS) region stabilizes PER and promotes CRY assembly, whereas phosphorylation within a degradation region (degron) promotes recognition by the β-TrCP ubiquitin ligase and degradation by the 26S proteasome [9, 11, 32-34]. As PER and CRY accumulate, they form large repressor complexes with CK1δ/ε and enter the nucleus. CRY binds *CLOCK*/BMAL1 at E-box promoters and inhibits *CLOCK*/BMAL1-dependent transcription without dissociating the complex, whereas PER-containing complexes can displace *CLOCK*/BMAL1 from DNA [24, 25]. After several hours in the nucleus, the PER/CRY complex is progressively phosphorylated and degraded through ubiquitin-proteasome pathways. Once PER/CRY levels fall below the threshold required to inhibit *CLOCK*/BMAL1, transcription of E-box target genes resumes and a new round of Per/Cry transcription begins, completing a cycle of approximately 24 h.

In addition, DEC1/2 (BHLHE40/41), bHLH transcription factors activated by *CLOCK*/BMAL1, compete for E-box elements in the *Per1* promoter and provide an additional layer of negative feedback [35].

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2.1.2. Auxiliary feedback loops: REV-ERB/ROR and DBP/E4BP4

REV-ERBα/β (NR1D1/2) are nuclear receptor repressors rhythmically activated by *CLOCK*/BMAL1. REV-ERB proteins bind RORE elements in the *Bmal1* promoter and recruit NCoR/histone deacetylase corepressor complexes to suppress *Bmal1* transcription [12]. RORα/γ act as transcriptional activators that compete for the same RORE elements and promote *Bmal1* expression [13]. REV-ERB and ROR peak approximately 12 h apart and act antagonistically on the same RORE elements, with REV-ERB repressing and ROR activating *Bmal1* transcription [12, 13]. This antagonistic balance locks *Bmal1* transcription into an approximately 24-h cycle. Mice lacking both REV-ERBα and REV-ERBβ show disrupted circadian rhythms, confirming that this loop is required for rhythm stability [26].

DBP and E4BP4 (NFIL3) are rhythmically transcribed under *CLOCK*/BMAL1 control [36, 37]. DBP peaks during the subjective day, whereas E4BP4 peaks during the subjective night. The two factors compete for D-box elements (5'-TTATGTAA-3') in target promoters and thereby shape the rhythmic expression of metabolic and detoxification genes. In the liver, PAR bZIP transcription factors regulate the rhythmic expression of drug-metabolizing enzymes, including Cyp2b and Cyp3a family members [27, 38]. The DBP/E4BP4 loop is especially relevant to chronopharmacology because it is the main transcriptional conduit through which the core clock drives rhythmic drug-metabolizing enzyme expression [38].

2.1.3. Post-translational modification: the molecular interface linking metabolic state to the clock

Beyond CK1δ/ε, several metabolic sensor kinases and epigenetic modifiers tune the TTFL. AMPK, GSK3β, and the NAD+-dependent deacetylase SIRT1 regulate clock protein stability and activity, forming a bidirectional interface between metabolism, the clock, and drug metabolism [28-31].

2.2. Cellular and network mechanisms of the SCN

A TTFL within an individual nucleated cell is only the basic unit of rhythm generation. The SCN can serve as the master pacemaker in mammals because its approximately 20,000 neurons are integrated by specialized intercellular coupling into a population clock with high precision, high amplitude, and resistance to noise [39].

The SCN is a small paired nucleus in the anterior hypothalamus, located on either side of the third ventricle immediately above the optic chiasm [1]. On the basis of neuropeptide phenotype and input-output connections, it can be divided into two functional subdivisions: the core expresses vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP) and receives direct retinal input through the retinohypothalamic tract (RHT); the shell expresses arginine vasopressin (AVP), receives VIP/GRP input from the core, and projects integrated timing signals to downstream brain regions [40, 41].

SCN neurons generate spontaneous action-potential rhythms with an approximately 24-h period even without external input: firing is high during the subjective day (6-10 Hz), and SCN neurons are mostly electrically silent at night [42]. BK potassium channel expression is rhythmic in the SCN and may be regulated by *CLOCK*/BMAL1 through E-box or other regulatory elements: Kcnma1 expression peaks in the middle of the night, and BK currents contribute to the nightly hyperpolarization, whereas blocking BK conductance reduces daytime peak firing rate, creating bidirectional coupling between electrical activity and the molecular clock [42, 43].

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2.2.1. Phase synchronization between core and shell: VIP/VPAC2 neuropeptide signaling

VIP neurons in the core rhythmically express and release VIP, and VIP/VPAC2 signaling is required for SCN cellular synchrony [44, 45]. Released VIP diffuses to neighboring neurons and binds the Gs-coupled receptor VPAC2, activating adenylyl cyclase, raising cAMP, and rapidly inducing Per1 and Per2 expression [45, 46]. This cascade converges on the same downstream pathway used by light to reset the SCN through the RHT; VIP therefore acts as an endogenous zeitgeber that transfers light-induced phase information from the core to the shell. In Vipr2-knockout mice, SCN neurons retain their individual TTFL molecular rhythms but become completely desynchronized from one another, causing severe behavioral rhythm disruption [45].

2.2.2. AVP signaling as an integrative output of the shell

After receiving VIP input from the core, AVP neurons in the shell become phase-synchronized, and their own TTFL drives circadian transcription of Avp. AVP acts through two release modes. In classical axonal release, AVP neurons project densely to three downstream targets, the paraventricular nucleus (PVN), dorsomedial hypothalamic nucleus (DMH), and organum vasculosum of the lamina terminalis (OVLT), and transmit time signals through V1a receptors to regulate corticotropin-releasing hormone (CRH) release (hypothalamic-pituitary-adrenal (HPA) axis drive) and activity rhythms [47]. In dendritic release, AVP is secreted directly from shell neuron dendrites into the extracellular fluid and enters the cerebrospinal fluid and circulation [48].

2.3. Clock input pathways: molecular cascades of environmental zeitgebers

Light is the strongest zeitgeber in mammals [3, 4]. Intrinsically photosensitive retinal ganglion cells (ipRGCs) express the photopigment melanopsin (encoded by Opn4) and are most sensitive to blue light around 480 nm [49, 50]. ipRGCs do not contribute to image-forming vision; their axons form the retinohypothalamic tract (RHT), which projects directly to the SCN core. Light signals are transmitted to SCN neurons via the RHT, where synaptic transmission involves the neurotransmitters glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) [19]. Glutamate resets the SCN clock at night, with nitric oxide as a downstream mediator [51]. Glutamatergic and PACAPergic inputs converge on the transcription factor cAMP response element-binding protein (CREB); phosphorylated CREB binds cAMP response elements (CREs) in the Per1 and Per2 promoters, rapidly inducing clock gene expression [52, 53]; mPer1 transcript levels rise within minutes after a 30-min light pulse [54].

Glucocorticoids are secreted rhythmically by the adrenal cortex under SCN control [55], with a sharp rise beginning 2-3 h before awakening and peaking shortly after waking [56]. Their synchronizing effect on peripheral clocks is well established: glucocorticoids can effectively shift peripheral oscillators in cultured cells and in vivo [1, 3, 5], and clock repressors such as CRY interact with the glucocorticoid receptor (GR) to coordinate circadian transcription [5, 6]. Their effects on the SCN itself are tightly restricted: although a subset of SCN neurons express GR, expression levels are far lower than in classical target tissues such as liver and pituitary [57], and 11β-HSD1 is expressed in the human hypothalamus, including the SCN region, where it can locally modulate glucocorticoid signaling by converting cortisone to cortisol [58].

Feeding time is a strong zeitgeber for metabolic peripheral oscillators in the liver, gut, and adipose tissue. Unlike light, which primarily acts on the SCN, timed feeding can reset the liver clock independently of the SCN: when mice switch from nocturnal to daytime feeding, the Per1 and Per2

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peaks in the liver shift by approximately 12 h, whereas the SCN rhythm is largely unaffected [59-61]. The underlying mechanisms include at least two pathways. In the metabolite pathway, feeding signals entrain liver clock genes such as Per2 [62], and CLOCK transactivates the Pparα gene through E-box-rich regions [63]. In the hormonal pathway, insulin/IGF-1 drives PERIOD protein synthesis through PI3K/mTORC1 signaling [64], whereas BMAL1 translation is regulated by S6K1-mediated phosphorylation downstream of mTOR [65].

2.4. Clock output pathways

After integrating VIP/GRP-coupled input, the SCN shell broadcasts timing information through three parallel output pathways: the autonomic nervous system, endocrine hormones, and behavior, maintaining phase coherence among peripheral clocks [66, 67]. Autonomic pathway: the SCN projects multisynaptically to the PVN, which relays to spinal sympathetic and parasympathetic neurons. In the liver, for example, postganglionic fibers release norepinephrine, which acts on hepatic α1- and β-adrenergic receptors to rapidly induce Per1 expression [68]. Endocrine pathway (slow and widespread): in the pineal-melatonin pathway, darkness activates pineal β-adrenergic receptors through the SCN-spinal cord-superior cervical ganglion route, initiating transcription of arylalkylamine N-acetyltransferase (AANAT), the rate-limiting enzyme of melatonin synthesis, via cAMP/PKA/CREB [69]. Melatonin not only carries SCN output but also feeds back to the SCN: MT1 melatonin receptors (Gi/o-coupled) acutely suppress SCN firing without phase resetting, whereas MT2 melatonin receptors, also coupled to Gi/o proteins, mediate phase advances of SCN circadian rhythms through Gβγ→PLC→DAG/IP3→PKC signaling [70, 71]. Through the sleep-wake cycle, the SCN indirectly influences feeding time, which in turn is an independent zeitgeber for peripheral clocks (Section 2.3).

In the forebrain SCN and in some peripheral tissues, NPAS2 can substitute for CLOCK and heterodimerize with BMAL1. Its PAS-B domain binds heme and acts as a redox sensor, allowing the SCN to integrate metabolic state with clock signaling [72, 73].

2.5. Tissue specificity of circadian rhythms

All nucleated cells share the same core TTFL circuit (*CLOCK*/BMAL1↔PER/CRY) and are synchronized by the SCN [1, 9, 10], yet different tissues generate strikingly different rhythmic physiological outputs: the liver drives the nocturnal peak in drug metabolism, the heart drives the morning peak in cardiovascular events, and the immune system drives clock-dependent immune surveillance and tissue repair [74-78]. This tissue specificity has two molecular bases. First, because chromatin accessibility and transcription factor repertoires differ, *CLOCK*/BMAL1 binds different E-box enhancer programs in different tissues and drives tissue-specific clock-controlled gene (CCG) expression [79, 80]. Second, the auxiliary REV-ERB/ROR and DBP/E4BP4 loops differ in abundance and target gene repertoires across tissues, translating the same core timing signal into different metabolic and physiological outputs [12, 26, 27, 36]. The following sections focus on the liver and heart, which are most relevant to chronopharmacology, and briefly describe clocks in lung, kidney, and immune tissue.

The liver clock is the central regulator of drug metabolism rhythms. Approximately 43% of protein-coding genes show circadian transcription in at least one tissue, and the liver contains the greatest number of circadian genes (3,186) among the 12 organs profiled [14]. CYP3A4 and MDR1 (encoding P-glycoprotein) are direct transcriptional targets of the PAR bZIP factors DBP, thyrotroph embryonic factor (TEF), and hepatic leukemia factor (HLF), which drive their circadian expression

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with an amplitude of approximately 2.5-fold [38]. Rhythmic expression of efflux transporters such as P-glycoprotein (P-gp; ABCB1) and MRP2 (ABCC2) affects first-pass metabolism and biliary excretion in the liver and intestine [81, 82]. Multi-omics studies further show that as non-alcoholic fatty liver disease (NAFLD) progresses to cirrhosis and hepatocellular carcinoma, liver clock amplitude declines stepwise, with markedly reduced Rev-erbα and Bmal1 rhythmicity already present at the NAFLD stage [83]. REV-ERBα also regulates rhythmic transcription of cholesterol metabolism and bile acid synthesis genes in hepatocytes through RORE elements, coupling hepatic metabolic state directly to the clock [12, 26, 84].

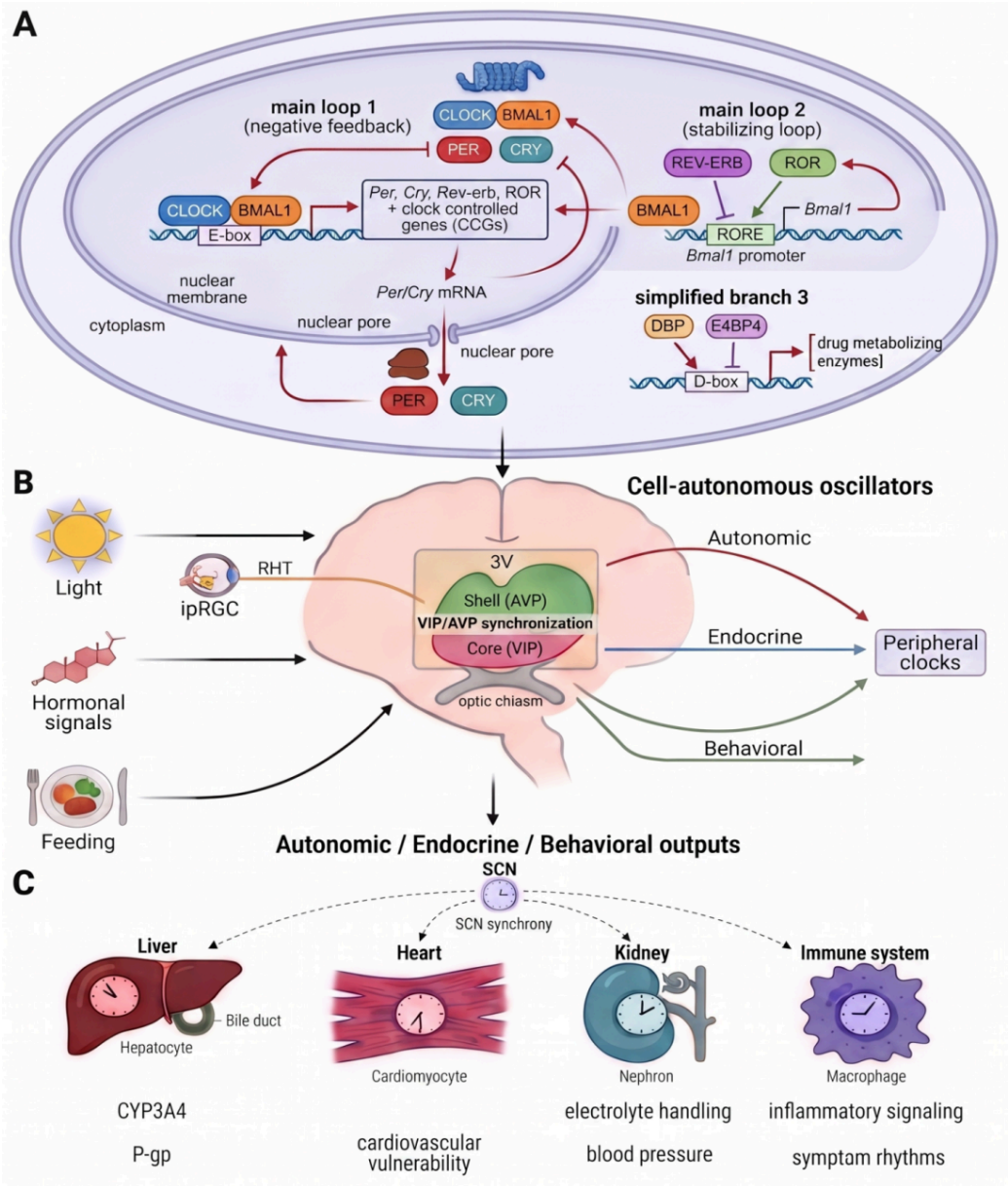


Figure 1. Multi-level circadian mechanisms underlying drug response: (A) core oscillator, (B) SCN network, (C) tissue-specific outputs

The immune clock controls circadian rhythms in cytokine production, leukocyte trafficking, and inflammatory responses [74-78]. REV-ERBα suppresses the induction of inflammatory genes such as IL-6 and CCL2 [74, 75, 77], whereas BMAL1 directly represses CCL2 expression and thereby

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limits Ly6C-high inflammatory monocyte recruitment [76, 77]; together these mechanisms help explain nocturnal worsening of asthma [85, 86] and morning stiffness in rheumatoid arthritis [78, 87, 88]. The kidney clock regulates circadian rhythms of urinary sodium and potassium excretion and thereby contributes to blood pressure rhythms [61, 89]. The cardiac clock contributes to the morning peak in myocardial infarction onset [90]. Together, these mechanisms constitute the multi-level circadian architecture that regulates drug response, as summarized in Figure 1.

3. Circadian regulation of pharmacokinetics

Chronopharmacokinetics describes dosing-time differences in drug concentration-time profiles. These differences can occur at every stage of absorption, distribution, metabolism, and excretion [91-94].

Absorption varies with gastric pH, gastric emptying, intestinal motility, bile acid secretion, mucosal blood flow, epithelial permeability, and transporter expression [91, 93]. Oral drugs with narrow absorption windows or strong transporter dependence may show time-of-day differences in exposure [95]. Food timing is particularly important because feeding is both a pharmacokinetic modifier and a peripheral clock entrainment signal [8]. Night eating, shift work, or irregular meals can desynchronize hepatic and intestinal clocks, making clock time less informative than biological time [19].

Distribution is influenced by daily rhythms in plasma proteins, tissue perfusion, membrane permeability, body temperature, and blood-brain barrier transport. These effects are usually smaller than those of metabolism or renal clearance for most drugs, but they may matter for highly protein-bound, central nervous system, or cardiovascular drugs. Circadian variation in albumin, alpha-1-acid glycoprotein, and regional blood flow can alter free drug concentration even when total concentration appears stable [91, 92].

Metabolism is the dominant chronopharmacokinetic mechanism. Hepatic clocks regulate phase I and phase II enzymes through direct clock gene control and nuclear receptors including PXR, CAR, PPARs, REV-ERB, and ROR [38, 59, 81, 84, 95-98] (Section 2.5). Hepatic CYP2E1 expression rises from the late light phase into the early dark phase [59], and dosing-time-dependent acetaminophen hepatotoxicity has been linked to this circadian regulation [59]. The active metabolite SN-38 causes less intestinal toxicity after daytime irinotecan administration because ABCC2/MRP2 efflux transporter expression in the intestinal epithelium is rhythmic and daytime efflux is more efficient [81]. Among statins, short-half-life drugs such as simvastatin and lovastatin are usually taken in the evening to match the nocturnal peak in hepatic cholesterol synthesis [99].

Excretion also varies by circadian phase. Renal blood flow, glomerular filtration, tubular secretion, urinary pH, sodium handling, and transporter expression follow daily rhythms [61, 89]. These rhythms are relevant for drugs cleared substantially by the kidney, including diuretics, lithium, and some antibiotics, and for medications where nocturnal adverse effects or sleep disruption are clinically important.

The practical implication is that clock time, dosing interval, food timing, formulation, and half-life should be considered together [92]. A short half-life drug targeting a rhythmic process may be highly timing-sensitive [19]. A long half-life drug may show less peak-trough timing dependence, but timing can still matter if adverse effects are phase-dependent or if the formulation is designed for delayed release [3, 5, 8].

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4. Circadian regulation of pharmacodynamics

Chronopharmacodynamics describes dosing-time differences in the relationship between drug concentration and effect. A drug may have identical exposure but different response if the target pathway, counter-regulatory physiology, or disease activity changes with circadian phase [93, 94].

Target abundance and sensitivity can oscillate. Adrenergic tone, renin-angiotensin-aldosterone activity, endothelial function, platelet reactivity, bronchial responsiveness, pain processing, seizure susceptibility, insulin sensitivity, and inflammatory cytokines all show daily variation [56, 85, 86, 90, 100-107]. Thus, the best time for a drug is often determined by the rhythm of the disease process rather than by drug concentration alone.

Inflammation provides a clear example. Immune cell trafficking and cytokine release are under circadian control, and symptoms of rheumatoid arthritis often peak in the early morning. Modified-release prednisone taken at bedtime can release glucocorticoids during the early morning cytokine rise, reducing morning stiffness while better matching endogenous inflammatory timing [87, 88]. In asthma, airway narrowing and inflammatory activity often worsen at night, supporting evening or bedtime timing for selected therapies in some patients [108-110].

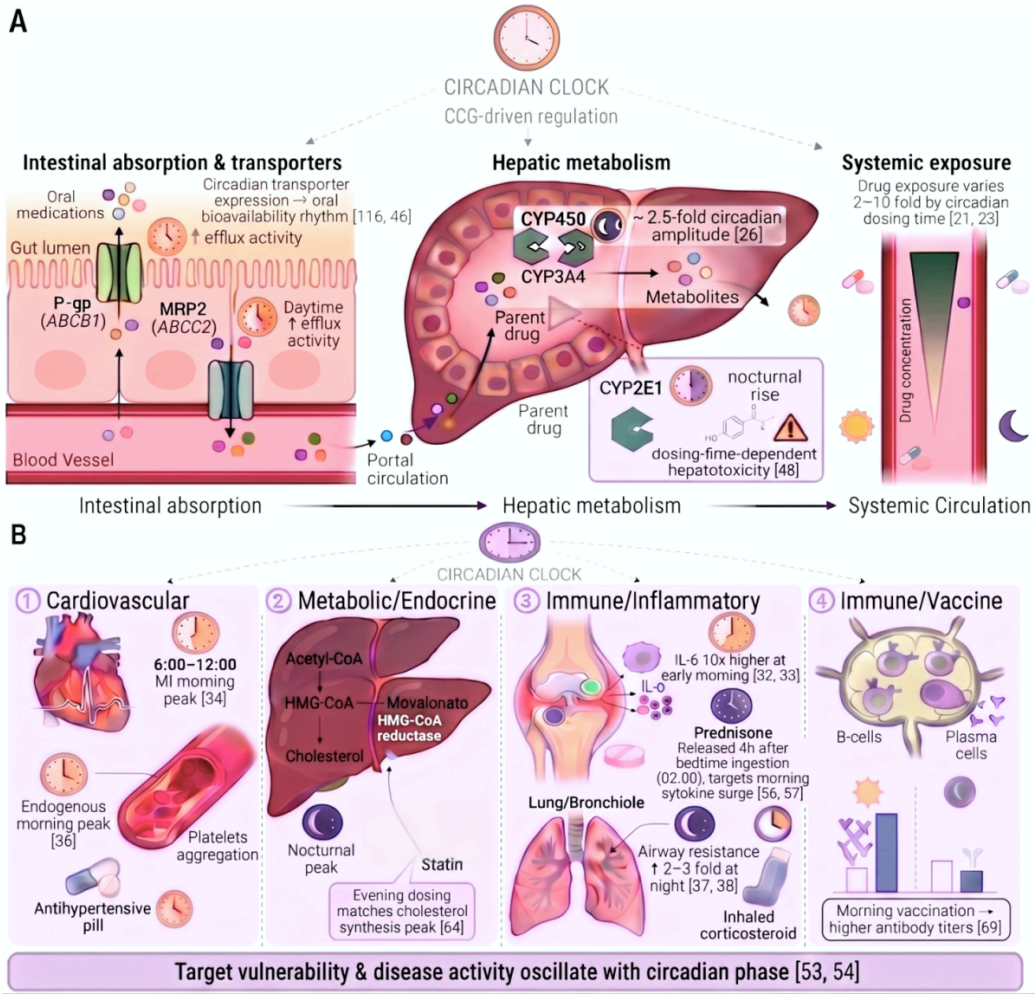


Figure 2. Circadian regulation of drug pharmacokinetics and pharmacodynamics: (A) drug disposition, (B) target vulnerability and disease activity

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Cancer illustrates both promise and complexity. Cell-cycle progression, DNA repair, apoptosis, detoxification, and bone marrow tolerance are rhythmic in normal tissues and may be altered in tumors [18-22]. Chronomodulated chemotherapy aims to deliver cytotoxic exposure when tumor vulnerability is high and normal tissue vulnerability is lower. Clinical trials in colorectal and other cancers have shown timing-dependent toxicity and sometimes efficacy, but results vary by sex, regimen, tumor biology, and implementation capacity [18-22, 111]. Figure 2 summarizes how circadian clocks regulate drug absorption, metabolism, exposure, and pharmacodynamic target vulnerability.

5. Disease states and special populations

Disease can disrupt circadian organization and thereby change drug response. Cardiometabolic disease is associated with altered sleep, feeding rhythms, autonomic tone, blood pressure dipping, insulin sensitivity, and inflammatory signaling [15, 90, 100, 105]. In type 2 diabetes, disruption of β-cell clocks impairs glucose-stimulated insulin secretion and contributes to disease risk [112]. In NAFLD, hepatic clock amplitude is attenuated, with reduced rhythmic expression of Rev-erbα and Bmal1 [83]. Chronic kidney disease is associated with circadian disruption that can alter renal function and blood pressure control [89]. In inflammatory disease, cytokines such as TNF-α can suppress clock gene expression, for example by reducing Per2 expression [75]; disrupted sleep and blood pressure rhythms accompany this process, and rhythmic fluctuations in glucocorticoid signaling feed back to clock genes, creating a bidirectional inflammation-clock vicious cycle [76-78, 87]. Clock mutant mice develop obesity and metabolic disease [3], and circadian disruption is closely linked to obesity and metabolic syndrome in experimental models [5].

Cancer may uncouple tumor rhythms from host rhythms. Tumor clocks can be damped, shifted, or genetically altered, while host tissues retain rhythmic tolerance patterns [18-22]. This creates an opportunity for chronotherapy but also explains why a fixed clock-time infusion may not fit every patient. Tumor clock phase varies widely among patients, and tumors are often poorly entrained to host circadian rhythms [20].

Special populations require caution. Older adults often have lower rhythm amplitude, earlier circadian phase, fragmented sleep, and reduced sensitivity to photic zeitgebers [113]. Shift workers may have misalignment between social time, sleep time, feeding time, and internal circadian phase [114]. Patients with insomnia, sleep apnea, jet lag, or neurodegenerative disease may deviate from standard circadian assumptions: polymorphisms in CLOCK, PER2, and PER3 are associated with insomnia susceptibility [115], and Vipr2-knockout mouse models show that defects in VIP/VPAC2 signaling can directly disrupt SCN network synchronization [45]. Children differ from adults because sleep architecture and metabolic and endocrine timing develop with age. In all these groups, dosing based only on clock time can be misleading; biological phase and daily routine often provide more reliable guidance.

6. Clinical applications across therapeutic areas

6.1. Cardiovascular drugs

Cardiovascular physiology is deeply rhythmic. Blood pressure usually falls during sleep and rises after awakening; myocardial infarction, stroke, arrhythmia, platelet activation, and vascular tone show morning patterns in many populations [90, 100, 104]. Chronotherapy has therefore been studied for antihypertensives, statins, antiplatelet drugs, diuretics, and beta-blockers.

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Hypertension evidence is mixed and clinically important. MAPEC and Hygia suggested that bedtime administration of at least one antihypertensive improved asleep blood pressure and cardiovascular outcomes [15, 16]. However, concerns were raised about design, generalizability, and implausibly large effect sizes. The TIME trial, a large pragmatic randomized trial, found no difference in major cardiovascular outcomes between evening and morning dosing of usual antihypertensive therapy [17]. Current interpretation should be cautious: bedtime dosing may be useful for selected patients with nocturnal hypertension or non-dipping patterns, ideally guided by ambulatory blood pressure monitoring [116], but routine universal bedtime dosing is not established.

Statin timing depends on half-life and cholesterol synthesis rhythm. Shorter half-life statins such as simvastatin and lovastatin are commonly taken in the evening because hepatic cholesterol synthesis is greater overnight, whereas longer half-life statins such as atorvastatin and rosuvastatin are less timing-sensitive [99]. Antiplatelet timing has been studied because platelet reactivity rises in the morning, but clinical outcome evidence is insufficient for broad timing mandates [117]. Diuretics are usually taken earlier in the day to avoid nocturia, although individualized timing may be needed for resistant hypertension or heart failure.

6.2. Endocrine and metabolic drugs

Endocrine pharmacology is naturally chronotherapeutic because hormone secretion is rhythmic. Glucocorticoids are the clearest example. Morning dosing more closely resembles endogenous cortisol and reduces adrenal suppression compared with late-day dosing, while modified-release hydrocortisone and prednisone can be used to better mimic physiological profiles in adrenal insufficiency or inflammatory disease [87, 88, 118].

Insulin sensitivity, glucose tolerance, hepatic glucose production, incretin responses, and meal timing vary across the day [105, 112]. Diabetes therapy should therefore consider meal timing, sleep timing, hypoglycemia risk, and chronotype. Evening hyperglycemia, dawn phenomenon, nocturnal hypoglycemia, and shift work may require individualized basal insulin timing or continuous glucose monitoring-informed adjustment. Thyroid hormone is commonly taken fasting in the morning, but bedtime dosing can be effective if separated from food, calcium, iron, and other interacting agents [119].

6.3. Immune, anti-inflammatory, and pain therapies

Inflammation is rhythmic, and many inflammatory symptoms peak at predictable times. Modified-release prednisone for rheumatoid arthritis targets early morning cytokine activity and has demonstrated reductions in morning stiffness [87, 88]. Nonsteroidal anti-inflammatory drug timing can be individualized to symptom peak and gastrointestinal risk, although evidence varies by drug and disease. Antihistamines are often timed according to symptom pattern and sedating properties. Biological agents have long half-lives, so clock-time administration may be less important than for short-acting drugs, but circadian immune tone may still affect vaccine responses and infusion reactions [76-78, 120].

Pain chronotherapy is promising but underused. Osteoarthritis pain, neuropathic pain, migraine, and postoperative pain can show daily variation. Timing analgesics to anticipated symptom peaks may reduce rescue dosing, but implementation requires patient-specific symptom diaries and attention to sleep disruption, renal risk, and gastrointestinal safety.

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6.4. Oncology

Chronomodulated oncology aims to exploit differences between rhythmic host tolerance and tumor vulnerability. Infusion schedules for 5-fluorouracil, oxaliplatin, irinotecan, and related regimens have been tested in colorectal cancer and other malignancies [18-22, 111]. Some studies found reduced mucosal or hematologic toxicity and sex-specific survival signals, while others failed to show consistent superiority over conventional schedules.

The field's challenge is not lack of biological rationale but lack of scalable personalization. Tumor clocks may not match host clocks, and patient circadian phase may vary because of age, cachexia, hospitalization, corticosteroids, pain, sleep disruption, and feeding schedules. Future oncology chronotherapy should combine wearable monitoring, biomarker-based phase assessment, pharmacokinetic models, and programmable infusion systems.

6.5. Central nervous system drugs

Neuropsychiatric disorders often involve circadian disruption, and many CNS drugs influence sleep, arousal, cognition, and hormonal rhythms. Hypnotics are explicitly timed to sleep onset. Antidepressant timing is usually guided by activating or sedating effects, adherence, and sleep complaints. Lithium has renal and circadian considerations; once-daily evening dosing is sometimes used to reduce renal lithium exposure, but monitoring remains essential [121]. Antiseizure therapy may be timed to seizure patterns when events cluster during sleep or awakening, although evidence depends on syndrome and drug half-life.

6.6. Respiratory and gastrointestinal drugs

Asthma symptoms often worsen at night because of circadian changes in airway caliber, inflammation, autonomic tone, and cortisol [108-110]. Evening dosing of selected bronchodilators or anti-inflammatory therapy can be useful, although modern long-acting inhalers reduce timing sensitivity. Gastroesophageal reflux and acid secretion often worsen overnight. Proton pump inhibitors are generally dosed in the morning, whereas H2-receptor antagonists may be useful in the late afternoon or at bedtime to target the circadian increase in acid secretion [91, 93, 109]. Figure 3 maps the timing schedules and evidence discussed across these therapeutic areas.

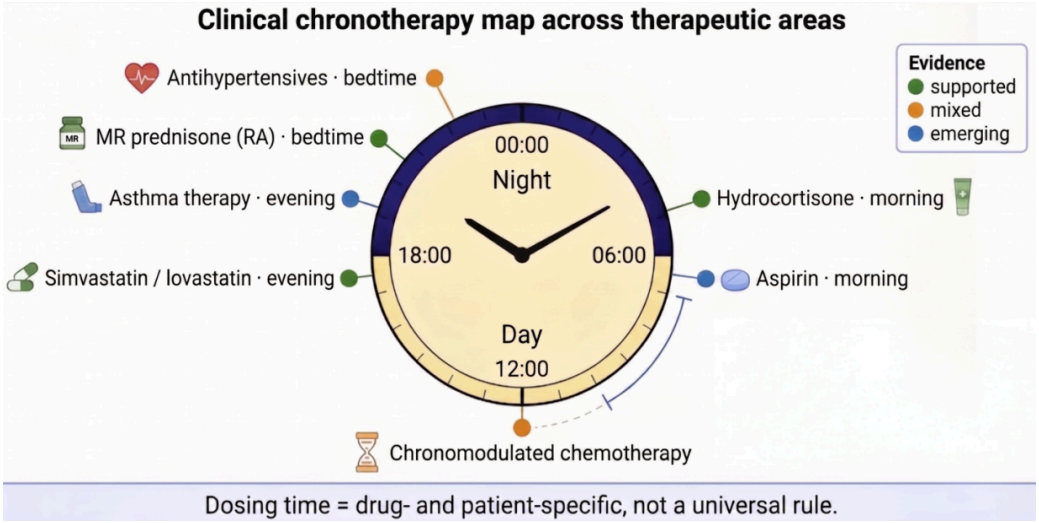


Figure 3. Clinical chronotherapy across therapeutic areas

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7. Technologies and tools for translation

Chronopharmacology requires measurement. Traditional markers include sleep diaries, actigraphy, core body temperature, dim-light melatonin onset, cortisol rhythm, ambulatory blood pressure, glucose monitoring, and timed laboratory sampling [3, 4, 103, 114]. Wearable devices now provide continuous data on activity, sleep, heart rate, skin temperature, and sometimes oxygen saturation or glucose, enabling practical rhythm phenotyping outside specialized laboratories.

Basic research tools include clock gene reporters, tissue-specific knockouts, organoids, single-cell transcriptomics, proteomics, metabolomics, and computational rhythm detection algorithms [38, 59, 81, 84, 89, 95-98]. Clinical tools include smart pill boxes, programmable infusion pumps, timed-release formulations, digital reminders, therapeutic drug monitoring with sampling-time annotation, and electronic decision support.

However, technology must not outrun evidence. A wearable-derived chronotype is not automatically a validated dosing biomarker. Clinical implementation should prioritize drugs with plausible timing sensitivity, meaningful therapeutic windows, measurable outcomes, and feasible adherence strategies.

8. Chronopharmacology, formulations, and precision medicine

Time-optimized therapy can be achieved by changing administration time, but formulations may be more reliable. Delayed-release, pulsatile-release, osmotic, multiparticulate, and programmable delivery systems can target drug release to a future biological window. This is useful when the desired exposure occurs during sleep or when inconvenient dosing times would impair adherence [8, 87, 118].

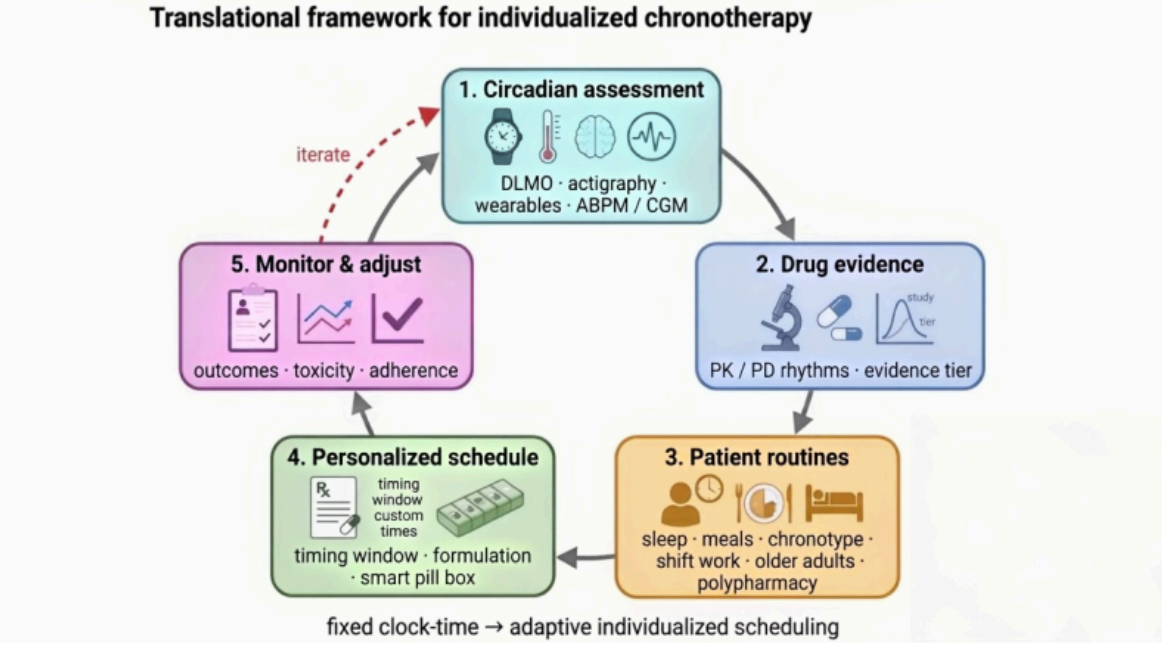


Figure 4. Translational framework for individualized chronotherapy

Chronopharmacology also intersects with pharmacogenomics. Genetic variation in CYP enzymes, transporters, receptors, and clock genes may modify both average exposure and rhythmic amplitude [91-94]. A patient may be a poor metabolizer at all times, but the clinical consequence

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may still vary by phase if the disease process or toxicity pathway is rhythmic. Integrating genotype, chronotype, organ function, disease rhythm, and formulation is a logical next step for precision dosing. Figure 4 outlines the workflow for translating circadian assessment and drug evidence into individualized dosing schedules.

9. Barriers and solutions

Several barriers limit clinical adoption. First, evidence is uneven. Many studies are small, use surrogate outcomes, or compare clock times without measuring biological phase. Second, interindividual variability is large. Morning dosing for one patient may correspond biologically to late in the circadian morning, while the same clock time in a shift worker may correspond to biological night. Third, adherence may worsen if timing instructions are complicated. Fourth, clinicians lack decision-support tools that combine drug properties, disease rhythms, and patient routines. Fifth, guidelines often avoid timing recommendations unless evidence is strong.

Solutions are feasible. Trials should measure circadian phase or at least sleep-wake timing, food timing, and chronotype. Outcomes should include efficacy, toxicity, adherence, quality of life, and implementation burden. Ambulatory monitoring should be used when the disease endpoint is rhythmic, such as blood pressure, glucose, asthma symptoms, or pain. Electronic health records can store patients' preferred sleep schedules and shift-work status. Pharmacists can help translate timing recommendations into realistic medication schedules. Formulation development should prioritize clinically meaningful timing problems rather than novelty alone.

10. Future directions

Over the next decade, chronopharmacology should move from fixed clock-time rules toward adaptive, individualized scheduling. Key priorities include large pragmatic trials for high-use drug classes, validation of wearable-derived circadian biomarkers, integration of therapeutic drug monitoring with sampling time, sex- and age-specific analyses, and better models for shift workers and patients with sleep disorders. Oncology needs trials that align chronomodulated infusion with individual host rhythms and tumor biology. Cardiovascular medicine needs evidence distinguishing nocturnal hypertension phenotypes from general hypertension populations. Endocrine and inflammatory conditions need formulations that match physiological or pathological hormone and cytokine rhythms without increasing regimen complexity.

Artificial intelligence may help identify rhythm phenotypes and predict timing response, but models must be transparent, clinically validated, and linked to actionable decisions. The goal is not to make every medication schedule more complex. It is to identify when timing meaningfully changes the benefit-risk balance and to make that timing easy for patients to follow.

11. Conclusion

Chronopharmacology adds biological time to pharmacotherapy [106]. Circadian clocks regulate pharmacokinetic processes, including absorption, distribution, metabolism, and excretion, and regulate pharmacodynamics through rhythmic target sensitivity, disease activity, and tissue tolerance [1, 8, 94]. Clinical evidence supports timing-based optimization in selected settings, but not every plausible chronotherapy improves outcomes [22]. The most defensible approach is drug-specific, patient-specific, and evidence-graded. Chronopharmacology will become clinically useful when circadian assessment, formulation science, digital monitoring, pharmacogenomics, and pragmatic

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trials converge into simple prescribing decisions. In precision medicine, the right time should stand alongside the right drug, dose, and patient.

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