Sleep and Sleep Disorders 3

Circadian rhythms and disorders of the timing of sleep

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The daily alternation between sleep and wakefulness is one of the most dominant features of our lives and is a manifestation of the intrinsic 24 h rhythmicity underlying almost every aspect of our physiology. Circadian rhythms are generated by networks of molecular oscillators in the brain and peripheral tissues that interact with environmental and behavioural cycles to promote the occurrence of sleep during the environmental night. This alignment is often disturbed, however, by contemporary changes to our living environments, work or social schedules, patterns of light exposure, and biological factors, with consequences not only for sleep timing but also for our physical and mental health. Characterised by undesirable or irregular timing of sleep and wakefulness, in this Series paper we critically examine the existing categories of circadian rhythm sleep–wake disorders and the role of the circadian system in their development. We emphasise how not all disruption to daily rhythms is driven solely by an underlying circadian disturbance, and take a broader, dimensional approach to explore how circadian rhythms and sleep homoeostasis interact with behavioural and environmental factors. Very few high-quality epidemiological and intervention studies exist, and wider recognition and treatment of sleep timing disorders are currently hindered by a scarcity of accessible and objective tools for quantifying sleep and circadian physiology and environmental variables. We therefore assess emerging wearable technology, transcriptomics, and mathematical modelling approaches that promise to accelerate the integration of our knowledge in sleep and circadian science into improved human health.

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Introduction

Circadian rhythm sleep–wake disorders are characterised by sleep that occurs too early (advanced sleep–wake phase disorder), too late (delayed sleep–wake phase disorder), progressively shifts from day to day (non-24 h sleep–wake rhythm disorder), or follows no consistent pattern (irregular sleep–wake rhythm disorder) with respect to an individual's desired sleep timing, or that required by social and occupational demands (panel 1).[1,2] Jet lag and shift work disorder are other categories of circadian rhythm sleep–wake disorders that are primarily motivated by social and behavioural factors. Patients with this group of disorders often seek help due to difficulties initiating or maintaining sleep or difficulties waking up at appropriate times. Circadian rhythm sleep–wake disorders are important differential diagnoses in individuals presenting with insomnia symptoms.

Dysfunction of the endogenous circadian timekeeping system (panel 2) is commonly believed to influence misalignment of sleep with light–dark cycles and social schedules. In this Series paper, we discuss emerging clinical and scientific understanding to focus on a more nuanced perspective in which the circadian system is reciprocally influenced, and often over-ridden by, behavioural and environmental factors. We also highlight insights into the causal role played by circadian dysfunction in the development and maintenance of disease beyond the classic sleep–wake disorders to include neuropsychiatric and metabolic disorders.[33,34]

Despite substantial progress in our understanding of circadian biology over the past 50 years, the integration of these advances into improved understanding, recognition, and treatment of sleep-timing disorders remains slow.[35] Innovations that identify and target the mechanisms underlying abberant sleep-circadian timing are necessary and provide a considerable unexplored opportunity for improving every domain of human health, including cognition, mood, metabolism, and immunity.

The first and second papers in this Series are published in *The Lancet* and discuss excessive daytime sleepiness[36] and insomnia,[37] and the fourth paper is published in *The Lancet Neurology* and discusses an evolutionary perspective of sleep function.[38]

Regulation of sleep and wakefulness

Determinants of sleep timing

The timing of sleep in the real world reflects the interaction of the circadian system with social schedules,

Search strategy and selection criteria

We searched PubMed for the exploded MeSH headings "circadian rhythm" and "sleep disorder, circadian rhythm" and combined them with the terms "prevalence", "pathophysiology", "assessment", "treatment", "management", "light therapy", "chronotherapy", "melatonin", "orexin", "shift-work", "dementia", "Parkinson's disease", "depression", and "bipolar disorder", without language restrictions. We also searched Google Scholar and the Cochrane Library using the term "circadian rhythm sleep wake disorder" for further studies, using the same date restrictions. We focused on clinical human studies published between Jan 1, 2015, and Feb 15, 2021, and, when possible, cited meta-analyses and systematic reviews published since 2015. We have also referenced important studies published before Jan 1, 2015.

Panel 1: *International Classification of Sleep Disorders* (3rd edition) diagnostic criteria for circadian rhythm sleep–wake disorders

1 A chronic or recurrent pattern of sleep–wake rhythm disruption primarily caused by an alteration of the circadian system or a misalignment between the endogenous rhythm and the desired or required sleep–wake schedule
2 A sleep–wake disturbance (eg, insomnia, excessive daytime sleepiness, or both)
3 Association with substantial impairment or distress in at least one domain of functioning (eg, social or occupational)

Except for jetlag disorder, symptoms need to be present for at least 3 months. The sleep disturbance should also not be better explained by other sleep disorders, medical disorders, or psychiatric disorders.

light–dark exposure, genetic factors, sex, developmental age, and the homoeostatic pressure for sleep. In clinical practice, identifying which combination of these variables are perturbed remains a challenge.

Most commonly assessed using self-report measures (panel 3), sleep timing and duration are normally distributed among the population. In general, sleep timing is later and sleep duration is longer on non-work days, compared with days when an individual has work or school commitments. Variability between individuals can be considerable, particularly in the absence of social constraints, with sleep onset in extreme-early and extreme-late sleepers being different by as much as 10 h. Twin and family studies suggest that up to 50% of variability in preferred sleep time is heritable.[47] With the exception of rare mutations with large effects in families with extreme early or late sleep preference, however, current evidence suggests that sleep timing in the wider population is affected by multiple pleiotropic genes, each with a modest effect size.[48]

In neonates, sleep–wake patterns follow an ultradian rhythm, with circadian sleep–wake and melatonin rhythms emerging from around age 3 months.[49] Sleep timing delays in adolescence,[50] with women reaching their latest sleep timing approximately 1·5 years earlier than men (at around age 20 years), and subsequently becomes progressively earlier during adulthood.[51,52] Although earlier bed and rise times and decrements in sleep quality and duration accompany healthy ageing,[53] current evidence suggests that changes in sleep homoeostasis, rather than circadian period, underlie these changes.[54]

In societies living without electric light, wake time is aligned with sunrise.[55] In societies with widespread access to electric light, however, sleep timing is primarily aligned with clock time, is associated with work or social schedules, and has little seasonal variation. There is continued debate as to whether sleep followed a biphasic pattern with a prolonged nocturnal awakening in premodern societies before the invention of high-intensity manufactured light.[56,57]

Contribution of the circadian system to sleep timing

Although affected to some extent by voluntary control, the timing, duration, and structure of sleep, and the ease with which we fall asleep, are all modulated by the circadian phase of the central pacemaker, located in the suprachiasmatic nucleus (panel 2).

Laboratory studies show that the circadian system provides an escalating wake-promoting signal throughout the biological day, during which time concentrations of cortisol decrease, core body temperature increases, and concentrations of melatonin remain low or undetectable.[58,59] Therefore, in healthy individuals the peak circadian wake-promoting signal, also called the wake maintenance zone, occurs in the evening between approximately 1900 h and 2200 h (figure 1). Soon after this peak, the circadian wake-promoting signal rapidly dissipates (accompanied by melatonin release and decreasing body temperature).[58,59,64] For an individual sleeping between 2300 h and 0600 h, the circadian sleep-promoting signal is strongest at approximately 0400 h to 0600 h, coinciding with the core body temperature nadir, and approximately 2 h before habitual wake time and cortisol peak.

The circadian system also influences sleep structure so that the propensity for rapid eye movement sleep is highest shortly after the lowest core body temperature, just before the cortisol peak. Circadian control of sleep extends to specific sleep oscillations, including sleep spindles[59] and slow waves,[65] and has been implicated in memory consolidation and metabolite clearance from the brain.[66] Circadian rhythmicity also modulates vigilance, cognition, and brain activity during wakefulness.[67,68]

The circadian system interacts with another process, sleep homoeostasis, which tracks the increase and decrease of sleep debt during wakefulness and sleep. Our ability to initiate and maintain sleep and wakefulness is affected by the combined effects of circadian phase and homoeostatic sleep pressure.[59] For example, we can stay awake for 16 h during the circadian day, when accumulating sleep debt is counterbalanced by the escalating circadian wake-promoting signal. Conversely, we struggle to stay awake for a similar duration in the circadian night, when high homoeostatic sleep pressure coincides with a low circadian drive for wakefulness. The interaction between circadian rhythmicity and sleep homoeostasis, as formalised in the two-process model of sleep regulation,[69,70] is crucial to understanding disorders of sleep timing and daytime vigilance. Neural systems responsible for sleep–wake switching[61,71] have recently been incorporated into mathematical models that quantitatively predict the effects of light on sleep timing[72,73] and are promising tools for understanding disorders of sleep–wake regulation.

Panel 2: Principles of circadian regulation

Periodicity: circadian rhythms are self-sustained oscillations of biological systems that persist in the absence of external 24 h cues and complete a full cycle approximately once a day. They allow the organism to anticipate periodic changes in the environment and optimally align behaviour, such as feeding, fasting, sleep, and wakefulness, and the physiological and biochemical processes that support them within the 24 h day. In humans, circadian rhythms in physiology and behaviour have evolved to support a diurnal temporal niche and promote the occurrence of sleep in the night and wakefulness in the day. Sleep is just one process that is affected by circadian control. Body temperature; vascular tone; renal excretion; metabolism; glucose, lipid, and endocrine regulation; immune responses; alertness; mood; cognition; brain oscillations; and functional MRI-assessed brain activation in response to tasks all display circadian modulation. These rhythms maintain homoeostasis of physiology throughout the 24 h day and maintain optimal waking function during the daytime. For example, despite substantial diurnal variations in food and fluid intake, circadian regulation of gluconeogenesis and renal function supports the maintenance of plasma glucose and osmolality within a narrow range.

Circadian timing is a fundamental property of cellular function. 43–82% of all protein-coding genes show rhythmic expression, with substantial organ-specific variation in the expression of transcripts.[3,4] Expression of genes associated with the stress response, endocrine activity, and immune activity peak during the biological day, whereas genes linked to methylation, chromatin remodelling, and RNA processing are expressed during the biological night.[4-6] These rhythms are generated at a cellular level by a set of genes, known as clock genes, which code for proteins that inhibit their own transcription in a negative feedback loop.[7] Precise and robust oscillations are an emergent property of the central pacemaker, a cluster of neurons located in the suprachiasmatic nucleus of the hypothalamus[8,9] that orchestrates the timing of oscillators in peripheral tissues through behavioural, neuroendocrine, and autonomic outputs.[10] Nonetheless, other brain regions, peripheral tissues, and organs also exhibit their own specific rhythmic organisation affected by local oscillators, but also by behavioural cycles and their associated systemic factors.[11]

Entrainment: in carefully controlled studies of sighted individuals, the average intrinsic period of the human circadian pacemaker is 24·15 h (SD 0·2 h) and is comparable across different age groups.[12,13] The intrinsic period is shorter in women than in men by around 6 min.[14] A canonical property of circadian systems is their use of environmental cues, known as zeitgebers, to adjust for deviations in period and control of phase of the internal rhythm with respect to the external world, thereby preventing them from drifting out of alignment. In normal conditions, this adjustment results in synchronisation of endogenous circadian rhythms with the environment cycle, also known as entrainment. In humans, the light–dark cycle is the primary force by which internal and external rhythms maintain a constant temporal relationship, also known as a phase of entrainment.[15] Light information is detected primarily by a specific population of non-image forming, melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) that project directly to the suprachiasmatic nucleus via the retinohypotholamic tract. ipRGCs are most sensitive to short wavelength light (approximately 480 nm) but also receive inputs from rods and cones.[16] Light alters the firing rate of neurons in the suprachiasmatic nucleus and activates molecular signalling pathways that alter the transcription of clock genes that establish the phase of the circadian cycle.[8] The phase response curve describes the differential direction and magnitude of phase shifts as a function of the timing of light exposure: light in the evening delays (slows down) the circadian clock and the associated sleep-propensity rhythm, whereas light in the morning advances (speeds up) the circadian clock.[17–19] The human circadian system is sensitive to even dim evening light: a single 6·5 h pulse of an intensity similar to domestic indoor lighting (approximately 100 lux) induced 50% of the maximal delay in melatonin phase achieved by 10 000 lux light.[20] In controlled laboratory conditions, electronic light-emitting devices can delay the circadian phase by up to 1·5 h.[21] In addition to these phase-shifting effects, light also directly increases arousal, reduces sleep propensity, and modulates mood and cognition.[22] These effects are mediated by projections from ipRGCs to the suprachiasmatic nucleus or projections to other hypothalamic nuclei involved in sleep-circadian regulation, including the ventrolateral preoptic nucleus and subparaventricular zone, alongside other areas involved in mood regulation, including the medial amygdala.[23] Through their action on melatonin receptors in the suprachiasmatic nucleus, exogenous melatonin and its analogues increase sleep propensity[24] and can phase shift[25] and entrain[26,27] the circadian clock. As illustrated in some totally blind individuals, other non-photic signals, including exercise, mealtimes, and social activity,[28] also contribute to circadian entrainment, albeit more weakly than light.

Defining circadian disruption: although there is no formally accepted definition, in this Series paper we use the term circadian disruption to describe atypical timing of the central pacemaker relative to external time due to phase advance or delay, or an inability of the circadian system to entrain to environmental cues, which results in misalignment of the sleep–wake cycle relative to desired or required schedules (or, if conventional sleep timing is enforced, misalignment between the internal circadian rhythm and sleep episodes). We also use the term circadian disruption to describe desynchrony between the timing of the central pacemaker in the suprachiasmatic nucleus with peripheral oscillators elsewhere in the body, and to describe a reduction in amplitude of internal physiological rhythms.

(Continues on next page)

(Panel 2 continued from previous page)

Physiological and environmental determinants of individual differences in circadian timing: the timing of a circadian rhythm relative to a zeitgeber (eg, the light–dark cycle) depends on the strength of the zeitgeber, how sensitive the organism is to that zeitgeber, and the amount of change required to entrain the internal circadian period with the zeitgeber period. An individual with a circadian period that is much longer than the 24 h light–dark cycle will therefore be entrained at a later phase, or be more delayed, than someone with a period of around 24 h,[29,30] and more so when the light–dark cycle has a low amplitude or the individual is relatively insensitive to light. A 50-fold difference in sensitivity to light on a logarithmic scale has been reported at the individual level;[31] therefore, the same timing and intensity of light exposure could have different interindividual effects on the phase of entrainment.[32]

A spectrum of sleep and circadian rhythm dysfunction

Whether disorders of sleep timing come from factors that are external or internal to an organism, or from the interaction between them, provides a useful framework for understanding these disorders and their underlying mechanisms.

At one end of the spectrum are prevalent extrinsic social and environmental influences on sleep-circadian misalignment, particularly shift work (which 10–30% of adults in high-income societies do).[74] Working at night necessitates the displacement of wakefulness, light exposure, and food intake to night-time and the displacement of sleep, dark exposure, and fasting to daytime. The circadian system and associated physiological rhythms do not readily adapt to these displacements.[75] Another ubiquitous extrinsic cause of circadian misalignment is self-selected exposure to evening light and reduced exposure to daylight. Manufactured light has allowed the extension of the photoperiod into the evening and night, liberating humans from the natural light–dark cycle and affecting our circadian system. Due to the sensitivity of the circadian system to evening light, most people living with electrical light will have at least some degree of phase delay, with those with a long circadian period experiencing the largest degree.[73] Through a combination of both the phase delaying and direct alerting effects of evening light, sleep is delayed, while wake time is unable to move in parallel due to work or school commitments. This results in systematically shortened sleep that occurs at an earlier circadian phase. Despite being known as social jet lag,[76] the root cause of this process is exposure to evening light. Similarly, slow accumulation of homoeostatic sleep pressure during adolescence results in late sleep timing and late circadian phase[50] in teenagers but they are still required to wake at an early circadian phase for school, which has negative consequences on academic performance and health.[77]

At the other end of the spectrum are intrinsic mechanisms that can affect all levels of the circadian hierarchy.[78] The considerable range of interindividual sensitivity to light (panel 2) suggests that some individuals are more susceptible to the effects of light on the circadian system, with age, sex, chronotype, genetic polymorphisms, and ocular factors underlying these differences.[79] The circadian system can fail to synchronise to the 24 h day if its input pathways are disrupted, resulting in the circadian system expressing its intrinsic period—as observed in non-24 h sleep–wake rhythm disorder in totally blind people.[80] In the suprachiasmatic nucleus, polymorphisms and mutations in clock genes (figure 1) can generate short or long intrinsic periods,[81,82] resulting in an atypical phase relationship (phase angle) between circadian rhythmicity and sleep timing. Processes that damage the suprachiasmatic nucleus and its networks, including neurodegeneration,[83] can lead to reduced amplitude of oscillations in the suprachiasmatic nucleus and peripheral clocks, and corresponding sleep–wake propensity and physiological rhythms. Internal desynchrony between central and peripheral oscillators can arise from aberrant timing of sleep–wake with feeding and fasting cycles relative to internal physiological and endocrinological rhythms.

In the real world, circadian disruption arises from a complex blend of extrinsic and intrinsic factors (figure 2). Variables that predispose an individual to later bed and wake times also lead to self-selected increased exposure to evening light and decreased exposure to morning light, delaying the circadian clock even further. Similarly, an individual with a preference for particularly early or late sleep times might choose a night-shift pattern of work, further accentuating circadian misalignment and desynchrony. Underlying biological differences are therefore amplified by interactions with the environment, leading to circadian disruption of large magnitudes, considerable interindividual variations in sleep phenotype, and a diagnosis of circadian rhythm sleep–wake disorders.

Circadian rhythm sleep–wake disorders

Using current criteria, diagnosis and treatment of circadian rhythm sleep–wake disorders can be made solely by assessment of sleep phenotype through clinical interview, sleep diaries, and actigraphy (panel 4) but does not mandate biomarkers of endogenous circadian physiology or assessment of sleep with polysomnography. Although most experts in the field would assert that circadian rhythm sleep–wake disorders in their classic

Panel 3: **Measuring behavioural and biological rhythms**

Measures of sleep timing and behavioural rhythms

- Sleep diaries[39,40] document subjective sleep onset and offset; number and duration of night awakenings; and subjective sleep quality, latency, and number and duration of naps from which the timing and regularity of sleep can be measured; sleep diaries are non-invasive, low-burden, and relatively inexpensive; at least 1 week of recording (ideally longer) is required
- The self-report Horne-Östberg Morning-Eveningness Questionnaire[41] assesses diurnal preference or chronotype; it is a measure of preferred or actual timing of activities and sleep, which is normally distributed and correlated with circadian period and phase, and is also influenced by other factors (such as homoeostatic sleep drive)
- Actigraphy uses a wrist-worn accelerometer to capture rest–activity rhythms, from which the timing and regularity of sleep can be estimated;[42] actigraphy is non-invasive, low-burden, and relatively inexpensive and some devices sample amounts of light; at least 1 week of recording (ideally longer) is required
- Consumer-grade wearable and mobile technologies are becoming ubiquitous and are attracting increasing interest as population-level biomarkers of sleep;[43,44] further validation studies are required before these devices can be used in clinical settings[45]
- None of these measures directly assess robust markers of the circadian clock and all are strongly influenced by social schedules; in most clinical situations, neither the timing of sleep nor chronotype necessarily reflect the phase of entrainment of the circadian pacemaker, and are not sufficient to establish a circadian disturbance, but could provide a useful starting point before more detailed examination

Biomarkers of suprachiasmatic nucleus phase and the endogenous circadian rhythm of sleep propensity

- Melatonin secretion is a robust marker of circadian phase[46] and can be sampled through serial salivary assays, serum assays, or 24 h collection of urinary 6-sulphatoxymelatonin; dim-light melatonin onset, measured in light less than 10 lux (ideally less than 5 lux), allows the circadian phase to be estimated from a section of the melatonin cycle, most suitably in entrained individuals when expected phase is probably close to normal; this method does not work in individuals with shift work, jetlag, or non-24 h sleep–wake rhythm disorder in which phase could occur anywhere across the circadian cycle; for these individuals, urinary collection during a period of 24 h or more is most appropriate
- Melatonin, cortisol, and core body temperature rhythm are driven by the suprachiasmatic nucleus, which also generates the circadian sleep propensity rhythm; environmental and behavioural rhythms, however, can obscure the underlying endogenous rhythm in a process known as masking (eg, light suppresses melatonin secretion and activity and sleep substantially modify the core body temperature rhythm); for the biomarker to accurately reflect the true endogenous circadian rhythm, masking effects should be minimal (eg, by reducing light exposure or lying down and prohibiting sleep)
- Core body temperature, but not skin temperature, is a robust marker of circadian phase and associated circadian rhythm of sleep propensity in highly controlled laboratory conditions, but is not appropriate in an outpatient setting due to masking effects
- Although not yet available, reliable markers of peripheral clocks will also be required before peripheral clock misalignment can be differentiated from masking effects of misaligned behaviour on peripheral rhythms

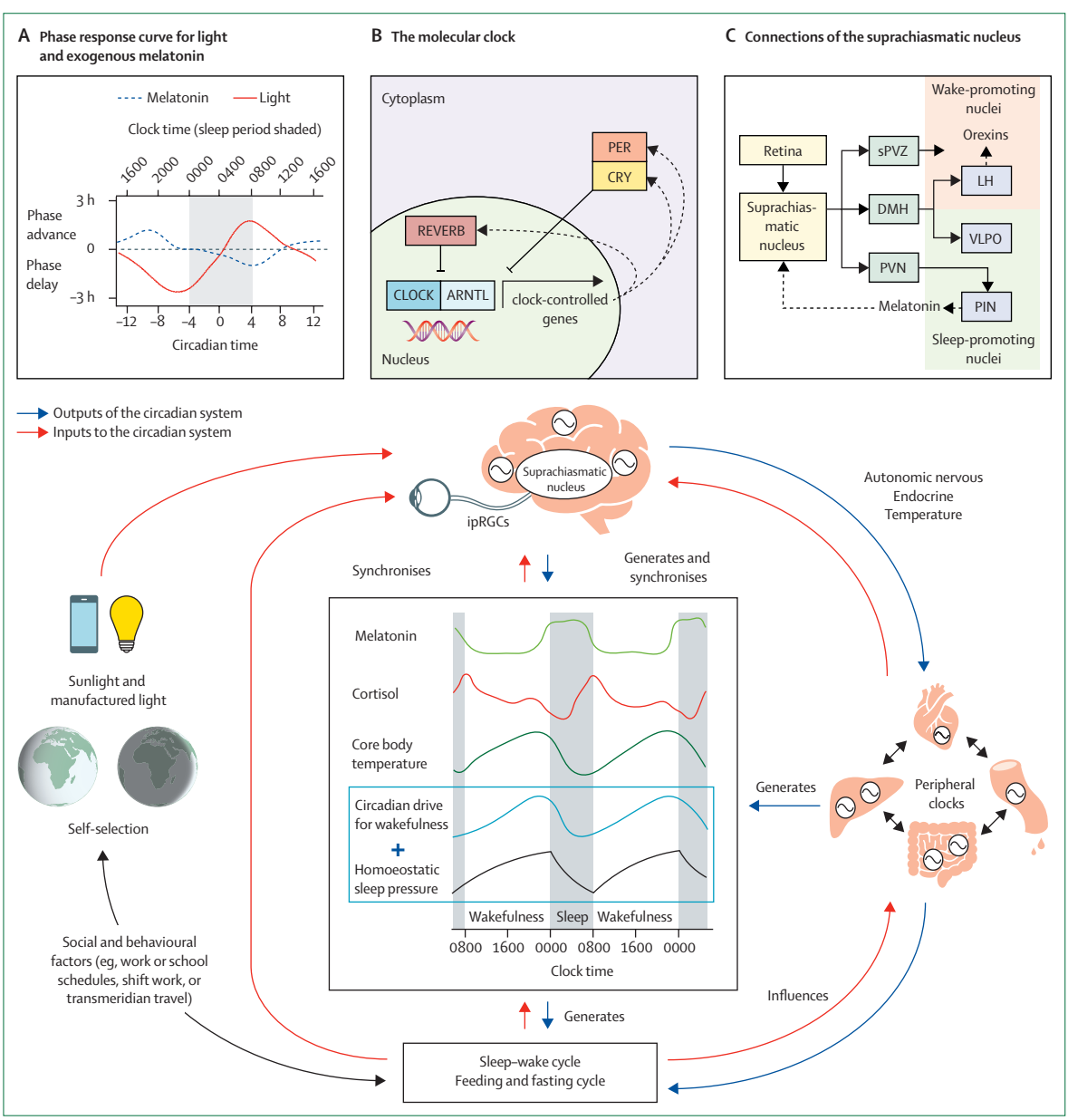
form are underpinned by a disturbance in the circadian system, its phase of entrainment, or its alignment with the environment (figure 3), in clinical practice this basis usually remains unknown and does not differentiate between intrinsic and extrinsic causes. Therefore, development and implementation of appropriately timed interventions are hindered. Consequently, a substantial lack of clarity exists in our understanding of the pathophysiology, classification, diagnosis, and treatment of circadian rhythm sleep–wake disorders.[35] These disorders probably represent a subset of a broader spectrum of disturbances in the circadian timing system. Few studies have examined the prevalence, causes, and consequences of circadian rhythm sleep–wake disorders, restricting our understanding of its effect at a population level. In part, the paucity of epidemiological data arises from ambiguity over definitions and cutoffs for desired and socially acceptable sleep times, which have been inconsistently operationalised across diagnostic systems.[35]

Delayed sleep–wake phase disorder

First described as a variant of insomnia,[92] individuals with delayed sleep–wake phase disorder have persistent difficulty with falling asleep at socially appropriate times and struggle to wake when required on work or school days (table). Prevalence estimates vary depending on sample and diagnostic criteria, ranging between 0·17 and 1·53% in the general population, between 3·3 and 7·3% in adolescents, and decreasing to 0·7% between ages 40 years and 64 years.[99] These data reflect the physiological trajectory of phase delay observed in adolescence, and the subsequent progressive phase-advance observed in adulthood. The underlying causes of delayed sleep–wake phase disorder remain uncertain. Several studies have reported a later dim-light melatonin onset in those with delayed sleep–wake phase disorder than in controls.[114,115] This finding is consistent with a delayed opening of the so-called sleep gate, when circadian propensity for wakefulness declines, and explains the difficulty in

initiating sleep at a socially appropriate time (when circadian wake propensity still remains high). Approximately half of a sample of patients with delayed sleep–wake phase disorder and non-24 h sleep–wake rhythm disorder had significantly longer periods of melatonin and temperature rhythms,[30] suggesting that circadian period is a causal factor in some, but not all, patients. A 2017 study described a subgroup of 43% of individuals with delayed sleep–wake phase disorder without significant delay in dim-light melatonin onset, which occurred at an appropriate clock time, similar to controls (figure 3).[88] This subgroup with non-circadian delayed sleep–wake phase disorder might have an intrinsically later phase of the sleep propensity rhythm relative to the phase of entrainment of the suprachiasmatic nucleus, or different mechanisms affecting delayed sleep phase, including psychophysiological hyperarousal observed in insomnia and differences in sleep homoeostasis.

Measurement of circadian phase could also identify patients who have been misdiagnosed with insomnia who could be more accurately diagnosed as having delayed sleep–wake phase disorder.[89,115] Nevertheless, circadian phase is itself reciprocally influenced by the timing of sleep–wake behaviour and light exposure; delayed circadian phase could therefore also occur as a consequence of behavioural factors (eg, sleep onset insomnia) affecting delayed sleep.[116]



Advanced sleep–wake phase disorder

In contrast to delayed sleep–wake phase disorder, individuals with advanced sleep–wake phase disorder complain of difficulty staying awake in the evening and awakening too early in the morning.[117] Although previously considered to be exceedingly rare,[118] more recent conservative prevalence estimates range between 0·04%[84] and 0·25%[119] and are likely to be highest in older people and those with dementia. Some individuals might find advanced sleep times to be more compatible with social and occupational schedules and would therefore be less likely to seek treatment than individuals with delayed sleep. Furthermore, although an extreme early sleep phase has been reported in 0·33% of patients presenting to a sleep clinic,[84] not all patients consider this early sleep phase an impairment and so do not meet diagnostic criteria for advanced sleep–wake phase disorder.

Non-24 h sleep–wake rhythm disorder

Non-24 h sleep–wake rhythm disorder occurs in both blind and sighted individuals, but is a fundamentally different disorder in the two groups.

As light is the primary environmental cue in humans, it is unsurprising that more than half of totally blind people have non-entrained melatonin, cortisol, or temperature rhythms.[120,121] Light is unable to reach and entrain the suprachiasmatic nucleus, which results in the circadian pacemaker reverting to its endogenous period. However, the majority of blind people maintain a stable 24 h sleep–wake schedule aligned with social convention, and have cyclic insomnia and daytime sleepiness as their circadian sleep–wake propensity rhythm passes in and out of alignment with their enforced sleep cycle.[122] The remaining group (approximately 40%) of blind people with apparently entrained sleep–wake rhythms are hypothesised to have either circadian periods that are very close to 24 h (and therefore appear entrained) or are synchronised by non-photic cues, such as exercise and social activity[123] (panel 2). A subset (approximately 5%) of people with no light perception are entrained by light via residual non-visual photoreception in intrinsically photosensitive retinal ganglion cells.[124,125] Non-24 h sleep–wake rhythm disorder is rare in blind people with some light perception and in those with pathology that does not affect or impair the retinal ganglion cell layer.[121]

Non-24 h sleep–wake rhythm disorder can also occur in sighted individuals, where it is caused by an atypical exposure to light–dark cycles that lengthen the circadian day, rather than no light exposure. The disorder is therefore caused and expressed in fundamentally different ways in people with and without light perception. Prevalence of non-24 h sleep–wake rhythm disorder in sighted people is unknown but can be challenging to diagnose and is likely to be under-recognised,[126] particularly in populations with psychiatric disorders. Sleep onset generally occurs progressively later, reflecting the period of the unentrained pacemaker that in most individuals is longer than 24 h,[14] alongside superimposed behavioural factors.[108]

Irregular sleep–wake rhythm disorder

Irregular sleep–wake rhythm disorder is characterised by a fragmented and unpredictable rest–activity profile, with no single consolidated sleep episode within the 24 h day (table 1). The disorder almost always occurs in the context of neuropsychiatric disorders, including schizophrenia,[127] autism spectrum disorder,[128] and Alzheimer's disease.[129] Rest–activity fragmentation correlates with clinical severity of dementia,[130] although

Figure 1: **The human circadian timekeeping system**

Comprising a hierarchy of cell-autonomous oscillators, the circadian system influences the timing of almost every aspect of physiology and behaviour, including daily rhythms in melatonin, cortisol, temperature, and the circadian drive for wakefulness. The circadian wake-promoting signal interacts with the homoeostatic sleep process to generate the sleep–wake cycle.

The suprachiasmatic nucleus is synchronised with environmental cycles primarily by light input via intrinsically photosensitive retinal ganglion cells. Crucially, social and behavioural factors, including sleep–wake, feeding, and light exposure cycles, also feed back to the circadian clock to modify circadian phase. Peripheral oscillators maintain coherence through autonomic nervous system, endocrine, and temperature signals emanating from the suprachiasmatic nucleus, but can also be directly entrained by behaviours such as feeding, thereby separating them from the central pacemaker. (A) The suprachiasmatic nucleus is differentially sensitive to the phase-shifting effects of light, depending on the circadian phase at which exposure occurs.[18] Light exposure before the crucial phase at the core body temperature minimum results in phase delay, whereas light exposure after this crucial point results in phase advance. The phase response curve for orally administered melatonin is nearly opposite to the phase response curve for light: in an entrained individual living under typical conditions, melatonin administered in the afternoon or early evening advances circadian phase, whereas melatonin administered in the morning leads to a phase delay.[60]

(B) The molecular clock is regulated by a transcriptional-translational feedback loop that completes one cycle approximately every 24 h, consisting of a positive loop, in which the transcription factor *BMAL1* heterodimerises with *CLOCK* (or *NPAS2* in the brain) and binds to E-box promoter elements in clock-controlled genes. These genes include the core clock genes period (*PER1*, *PER2*, and *PER3*) and cryptochrome (*CRY1* and *CRY2*), whose proteins dimerise and repress their own transcription, forming the negative loop. *CLOCK* and *BMAL1* affect additional loops, including feedback via the Rev-Erbα nuclear receptors (which repress *BMAL1* transcription) and *ROR* nuclear receptors (which enhance *BMAL1* transcription), and are responsive to hormones and metabolites.

(C) The suprachiasmatic nucleus generates the 24 h sleep–wake propensity rhythm through indirect projections to sleep-promoting and wake-promoting nuclei. Wake-promoting regions in the brainstem and hypothalamus receive excitatory inputs via relays in the ventral sPVZ and DMH. The suprachiasmatic nucleus also affects rhythmicity in the orexins—neuropeptides that are released from the LH and strongly excite wake-promoting pathways, such as the histaminergic system.[61] The sleep-promoting VLPO, located in the anterior hypothalamus and active during rapid eye movement and non-rapid eye movement sleep,[62] receives inhibitory input from the suprachiasmatic nucleus. Control of other canonical circadian outputs, including the autonomic nervous system, cortisol, and melatonin, is exerted via projections from the suprachiasmatic nucleus to the PVN. The rhythms of cortisol and melatonin affect rhythmicity in gene transcription and physiology in the periphery and melatonin, released by the PIN, feeds back to the suprachiasmatic nucleus. The suprachiasmatic nucleus innervates a wide range of other brain regions, including those involved in emotion, motivation, and reward.[63] Many of these regions also contain local circadian oscillators,[8] further extending the mechanisms of circadian control on sleep and arousal. DMH=dorsomedial nucleus of the hypothalamus. ipRGCs=intrinsically photosensitive retinal ganglion cells. LH=lateral hypothalamus. PIN=pineal gland. PVN=paraventricular nucleus. sPVZ=subparaventricular zone. VLPO=ventrolateral preoptic nuclei.

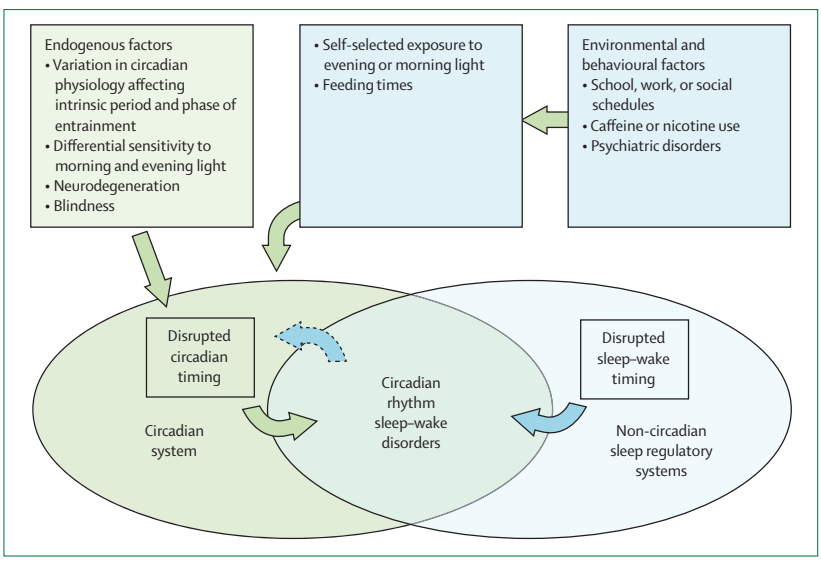


Figure 2: **Pathways to the development of circadian rhythm sleep–wake disorders**
Circadian rhythm sleep–wake disorders were thought to develop primarily as a result of disruption to the circadian system. However, they are now also understood to develop from environmental and behavioural variables that dysregulate non-circadian sleep regulatory systems, including the homoeostatic sleep process, which affect a secondary shift in circadian timing. Circadian rhythm sleep–wake disorders therefore develop as a result of the combined effect of dysfunction in both circadian and non-circadian sleep regulation. In particular individuals, sleep timing that is chronically misaligned or non-entrained with light–dark cycles has been described, even although circadian timing remains appropriately phased, showing how the underlying circadian rhythm can be overridden by behavioural factors and dissociated from sleep timing.

not all studies have shown attenuation of amplitude of the rest–activity and melatonin rhythms. The number of neurons in the core region of the suprachiasmatic nucleus in patients with Alzheimer's disease correlates with amplitude of the rest–activity rhythm.[112]

Irregular sleep–wake rhythm disorder is frequently cited as a cause for an individual being placed in an institutional setting. Although its true prevalence is unknown, irregular sleep–wake rhythm disorder is probably substantially under-recognised in nursing home populations.[35] Given the high personal, caregiver, and economic burdens of irregular sleep–wake rhythm disorder and its relationship with psychopathology and poor functional outcomes, further research into the causes, identification, consequences, and treatment of the disorder is urgently needed.

Consequences of sleep-circadian disruption on health

Circadian disruption has been implicated in the development of cancer, metabolic diseases, inflammatory diseases, cardiovascular diseases, sleep disorders, and neuropsychiatric disorders.

Insights from shift work

Few shift workers, unless working in atypical environments (such as oil rigs),[131] fully adapt their internal clock to their work schedules.[75,90,132] Sleep, feeding, and light exposure thus occur at the non-optimal circadian phase, and long-term night shift workers have curtailed sleep, impaired waking performance, and mood and gastrointestinal disturbance akin to jet lag. Approximately 27% of shift workers meet formal criteria for shift work sleep disorder,[133] although in practice, almost all shift workers will experience the negative effects of sleeping, waking, and eating at an inappropriate circadian phase. Furthermore, this classification does not capture the many other health sequelae arising from shift work.

Working during the biological night, alongside the additional acute and chronic sleep loss, increases the risk of workplace accidents by 40–100%.[134,135] Shift workers are at approximately 20–35% increased risk of breast, prostate, and colorectal cancers,[136,137] type II diabetes,[138] coronary heart disease,[139] and depression.[140,141] The magnitude of these effects vary by shift pattern and

Panel 4: **Clinical assessment of circadian rhythm sleep–wake disorders**

Clinical interview

- Useful screening questions: on a long weekend or holiday, with few responsibilities or obligations, when would you go to bed and when is your final awakening?[84] At what time of day do you feel most alert and energetic?
- Explore the degree of impairment in social and occupational function
- Be aware of possible diagnoses of circadian rhythm sleep–wake disorders in individuals with neuropsychiatric disorders, including brain injury, bipolar disorder, schizophrenia, Parkinson's disease, and dementia, in whom the diagnosis of circadian rhythm sleep–wake disorders could be overlooked
- Consider differential and comorbid diagnoses, particularly insomnia, depression, anxiety disorders, post-traumatic stress disorder, and obsessive compulsive disorder
- The Horne-Östberg Morning-Eveningness Questionnaire,[41] which assesses diurnal preference, and other validated questionnaires screening for shift work disorder[85] and non-24 h sleep–wake rhythm disorder in blind individuals,[86] could be supportive

Investigations

- Obtain prospective daily sleep diaries or wrist actigraphy for at least 7 days (preferably longer) across both school or work nights and free nights; if non-24 h sleep–wake rhythm disorder is suspected, at least 2 weeks of sleep diary or actigraphy is required (preferably longer);[1,2] if the patient is unable to complete their own sleep diaries, caregiver documentation is necessary
- Measurement of circadian biomarkers using serial salivary dim-light melatonin onset is important in distinguishing between phase-advanced and phase-delayed rhythms; urinary 6-sulphatoxymelatonin profiles have been shown to be valuable in shift work, jetlag, and non-24 h sleep–wake rhythm disorder; a low-amplitude melatonin rhythm might be seen in irregular sleep–wake rhythm disorder

number of years worked in shift work. Even modest misalignment between sleep–wake timing and clock time is associated with obesity[142] and cardiometabolic derangement,[143,144] suggesting that shift work has a substantial effect at the population level.

Laboratory studies have elucidated some of the putative mechanisms underlying the negative health consequences of shift work. Desynchrony of sleep–wake and endogenous circadian rhythmicity leads to raised blood pressure,[145] reduced insulin sensitivity and release[146] (in some studies to the prediabetic range),[145,147] and elevated postprandial lipid and glucose concentrations.[148] One mechanism associating shift work with an elevated risk of breast cancer is the so-called light-at-night hypothesis, which posits that exposure to light at night leads to melatonin suppression that could affect oncogenesis,[148] although short sleep and molecular clock disruption are also implicated. When sleep is experimentally displaced from melatonin rhythms by 12 h, more than 97% of normally rhythmic blood transcripts became arrhythmic—most of which were those associated with regulation of transcription and translation,[6,149] although the melatonin rhythm was not affected. Simulating another consequence of shift work, 1 week of reduced sleep duration resulted in reduced rhythmicity and amplitude of expression in similar sets of genes.[5] These findings were observed in constant routine conditions, implying that sleep restriction affects the endogenous circadian component of rhythmicity. Mistimed and shortened sleep, and associated changes in light exposure and feeding, could therefore allow disease by diminishing coherence between oscillations that are normally in alignment and dampening the amplitude of molecular rhythms and their associated physiological processes.

Circadian rhythm sleep–wake disorders and neuropsychiatric disorders

Disturbances in the timing, duration, and quality of sleep and in the amounts of energy, activity, and appetite during the day are prominent symptoms that are present in a range of neuropsychiatric disorders.[33,130] Anatomical and neurotransmitter systems implicated in mental disorders overlap with systems underlying circadian regulation, and psychiatric symptoms and disturbances in sleep and its timing precipitate and maintain one another.[150] In particular, longitudinal markers of diurnal and circadian rhythm predict fluctuations in clinical status in mood disorders[151,152] and are modifiable factors. Measurement of endogenous circadian phase in addition to longitudinal sleep monitoring has rarely been performed in existing studies, restricting insight into underlying mechanisms of disease.

Strong associations between delayed sleep–wake phase disorder and depression,[88,153] bipolar disorder,[154] obsessive compulsive disorder,[155] and attention-deficit hyperactivity disorder[156] have been reported. Individuals with delayed sleep–wake phase disorder with delayed circadian phase show higher neuroticism scores[157] and greater depressive symptoms[88,153] than do individuals with delayed sleep–wake phase disorder without delayed endogenous markers, implicating misalignment between the circadian rhythm, light–dark, and social cycles with personality traits and mood. In our experience, social anxiety and social phobia are over-represented in patients with delayed sleep–wake phase disorder and non-24 h sleep–wake rhythm disorder. Withdrawal behaviours and a preference for being awake during the night with concomitant self-selection for evening light exposure might be causal factors.[80] Conversely, 34% of sighted individuals with non-24 h sleep–wake rhythm disorder subsequently developed depression, pointing to a reciprocal relationship between circadian desynchrony and mood.[102] Comorbidities associated with advanced sleep–wake phase disorder are fewer than in delayed sleep–wake phase disorder, although both migraine and depression have been reported in familial subtypes of advanced sleep phase.[81,158]

In 91 105 participants from the UK Biobank cohort,[159] flattened amplitude of rest–activity rhythms was associated with an increased risk of lifetime depressive disorder and bipolar disorder. Future longitudinal studies testing causal associations with other actigraphic parameters, including phase and variability of the

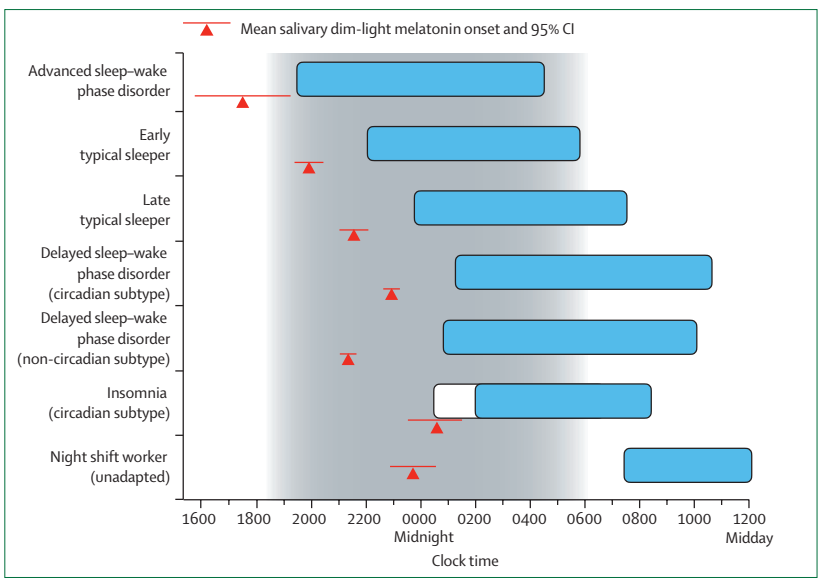


Figure 3: **Phase relationships between dim-light melatonin onset and main sleep episode in relation to timing of sunset and sunrise in local time at the spring equinox**

In the first four groups, sleep onset occurs approximately 2 h after dim-light melatonin onset and is therefore appropriately aligned with the circadian sleep–wake propensity rhythm. However, the circadian phase itself can be atypically advanced (as in advanced sleep–wake phase disorder)[87] or delayed (as in the circadian subtype of delayed sleep–wake phase disorder),[88] resulting in sleep timing that is substantially earlier or later than desired.

In non-circadian delayed sleep–wake phase disorder, dim-light melatonin onset occurs at a conventional time, although sleep onset is atypically delayed with regard to the sleep–wake propensity rhythm. This pattern has been reported in approximately 40% of patients with delayed sleep–wake phase disorder.[88] Similarly, a subgroup of up to 20% of patients with insomnia try to initiate sleep at too early a circadian phase (when the promotion of wakefulness is still high), leading to long sleep latencies, indicated by the white box.[89] Circadian phase does not adapt to environmental cycles in the majority of permanent night shift workers,[90] with the main sleep episode occurring up to 12 h out of phase with melatonin release.

	Key clinical features	Associated clinical features	Comorbid diagnoses	Hypothesised pathophysiology and known pathophysiology
Delayed sleep–wake phase disorder	Persistent difficulty falling asleep and waking up at socially appropriate or desired times; sleep inertia (impaired alertness) when waking up in time for school or work; when able to follow preferred schedules, sleep times are delayed (eg, from 0400 h to 1200 h) with normal sleep quality and duration and little daytime impairment	Poor academic performance; depression; absenteeism from school; increased use of alcohol, tobacco, caffeine, and hypnotic medications[93,94]	Sleep onset insomnia, mood disorders, anxiety disorders, psychosis spectrum disorders, phobias, obsessive compulsive disorder, attention-deficit hyperactivity disorder, autism spectrum disorder, post-traumatic stress disorder	A gain of function mutation in *CRY1* (leading to a longer circadian period in a cell system)[95] and the shorter allele in *PER3*[96,97] have been associated with evening chronotype and delayed sleep–wake phase disorder; a subgroup of patients with delayed sleep–wake phase disorder with delayed sleep phase but normal circadian timing has been described;[88,98] withdrawal behaviours; preference for being awake at night; increased caffeine and nicotine use; increased exposure and sensitivity to light at night; reduced sensitivity to light in the morning; longer circadian period; aberrant phase of entrainment between circadian and sleep–wake phases; atypical accumulation and dissipation of homoeostatic sleep drive[98,99]
Advanced sleep–wake phase disorder	Difficulty staying awake in the evening and awakening too early in the morning, with sleep times typically more than 2 h earlier than desired; when allowed to occur at preferred times, sleep quality and duration are normal	Family history and increasing age	Dementia, migraine	Heightened sensitivity to the phase-advancing effects of morning light and reduced sensitivity to evening light are possible mechanisms, although convincing evidence for these putative causes is currently scarce; the discovery of families with extreme advanced sleep phase that followed a Mendelian pattern of inheritance led to the identification of mutations in circadian genes including the *CK1δ/ε* binding region of *PER2*[100] and *CK1* itself;[101] mutations in *PER3*, *CRY2*, and *TIMELESS* have been identified,[81] indicating a genetic basis for advanced sleep–wake phase disorder in at least a subset of individuals
Non-24 h sleep–wake rhythm disorder in blind individuals	Most blind patients with non-24 h sleep–wake rhythm disorder maintain 24 h sleep–wake schedules but have cyclical episodes of insomnia, good sleep, and excessive daytime sleepiness	Total blindness (no intact visual photoreception and no intact non-visual photoreception)	Not available	Inability of the circadian system to entrain to environmental cycles due to an absence of input from the main zeitgeber, light; the circadian system expresses its intrinsic period (which in most cases is more than 24 h), and sleep disturbance occurs as the circadian rhythm passes in and out of alignment with the enforced sleep cycle
Non-24 h sleep–wake rhythm disorder in sighted individuals	Most commonly, progressive 1–2 h delays in sleep onset and wake times each day are observed	Poor academic performance; depression; absenteeism from school; increased use of alcohol, tobacco, caffeine, and hypnotic medications;[93,94] 72–85% of cases are men, with onset most commonly occurring during adolescence[80]	Mood disorders, personality disorders, and psychotic disorders have been reported to precede non-24 h sleep–wake rhythm disorder onset[102]	Delayed sleep phase is a risk factor that precedes development in 13–26% of people with non-24 h sleep–wake rhythm disorder;[80,102] non-24 h rhythms have been reported to develop in patients receiving phase-delay chronotherapy for delayed sleep–wake phase disorder;[103] *PER3* polymorphisms have been associated with non-24 h sleep–wake rhythm disorder;[104] non-24 h sleep–wake rhythm disorder and delayed sleep–wake phase disorder in sighted individuals could share a common cause, including inappropriate timing of light exposure, a long circadian period, and a delay in sleep relative to circadian phase,[105] allowing the phase-delay portion of the circadian cycle to be more strongly illuminated, lengthening the circadian period; in case reports, traumatic brain injury[106] and chemotherapy[107] have been suggested to cause non-24 h sleep–wake rhythm disorder; sighted individuals with non-24 h sleep–wake rhythm disorder but entrained endogenous circadian phase have been described,[108] in whom sleep delay is proposed to develop because of environmental and behavioural factors, such as a preference for minimising social interaction by being awake during the night and asleep during the day
Irregular sleep–wake rhythm disorder	Sleepiness with frequent daytime naps but difficulty sustaining consolidated sleep at night; total sleep time per 24 h period is essentially normal for age[109]	The effect of irregular sleep–wake rhythm disorder on quality of life, general health, and economic costs have not been adequately studied, but are suggested to be substantial;[110] fragmented and irregular sleep could be an early biomarker of and risk factor for developing dementia[111]	Neurodegenerative disorders (including Alzheimer's disease); neurodevelopmental disorders; psychosis spectrum disorders	Hypothesised to develop because of an attenuated circadian amplitude or reduced circadian input to sleep-regulatory centres; the homoeostatic sleep process is then relatively unopposed, leading to multiple short sleep fragments; blunted amplitude (reduced robustness of the circadian signal) can happen due to dysfunction of the inputs to the suprachiasmatic nucleus (eg, low light intensity during the day that can occur in institutional settings or through retinal or optic nerve pathology), dysfunction of the suprachiasmatic nucleus itself (eg, degeneration or loss of coherence between neurons),[112] or dysfunction of outputs of the suprachiasmatic nucleus (eg, pathology affecting melatonin secretion in the pineal gland)[113]

Table: **Circadian rhythm sleep–wake disorders: features, associations, and mechanisms**

rest–activity cycle and the extent to which changes in behavioural rhythms are caused by an underlying circadian disturbance, are warranted. Depression is also sensitive to seasonal changes, with approximately 8% of patients having depressive episodes in autumn or winter months,[160] correlating with shortening of the photoperiod. Polymorphisms in circadian genes in bipolar disorder including *CLOCK*, *TIMELESS*, and *RORA*, have been reported.[161] An approximately 7 h phase advance in cortisol rhythm and *PER1* and *BMAL1* expression in mania and a 4–5 h phase delay in bipolar depression have been shown, which normalised upon subsequent treatment of mood.[162] Current evidence therefore suggests delayed circadian phase to be associated with

depression and advanced circadian phase to be associated with mania.[163] Although pharmacological and non-pharmacological treatments often normalise these discrepancies,[163–165] whether atypical phase relationships between sleep and circadian rhythm in mood disorders are primary or arise secondary to behavioural factors remains unclear. This knowledge gap shows the need to integrate longitudinal endogenous circadian biomarkers into the diagnosis and treatment of both circadian rhythm sleep–wake disorders and psychiatric disorders.

Rest–activity fragmentation was found in the early preclinical phase of Alzheimer's disease,[129] and longitudinal studies suggest that greater disruption in behavioural rhythms is a risk factor for developing dementia or Parkinson's disease.[130,166] Circadian disruption could therefore be a common pathway to neurodegeneration and cognitive decline, exerting effects through a range of mechanisms (including amyloid β dynamics, inflammation, glymphatic clearance, and oxidative stress) in a deleterious cycle.[167]

Treating circadian rhythm sleep–wake disorders through the application of circadian principles

The 2015 guidelines from the American Academy of Sleep Medicine[2] are based primarily on findings from small trials and case series, alongside empirical approaches extrapolated from our understanding of circadian physiology. The report from a 2021 expert workshop notes that the evidence base guiding treatment of circadian rhythm sleep–wake disorders remains inadequate.[35]

Chronotherapy was developed as a strategy for improving sleep timing in delayed sleep–wake phase disorder by delaying the sleep opportunity by 3 h every day until the desired bedtime is reached.[168] Successful treatment of advanced sleep–wake phase disorder by gradual phase advance has also been reported,[169] but systematic clinical trials have not been performed. Treatment can be challenging, however, with substantial motivation required to maintain adherence with desired sleep schedules and difficulty in controlling the confounding effects of light. The American Academy of Sleep Medicine guidelines did not recommend this intervention due to an insufficient amount of evidence.[2]

In accordance with predictions from the phase response curve to light in humans, 2 h of 2500 lux light in the mornings and light-blocking glasses in the evening in delayed sleep–wake phase disorder advanced circadian phase by 1 h 25 min, compared with a 10 min advance in control individuals.[170] The magnitude of effect is not always sufficient to move sleep to preferred times, and more studies are needed before light therapy or light avoidance can be recommended as a sole intervention in delayed sleep–wake phase disorder.[2] Similarly, although the current understanding of the human circadian system implies that avoidance of manufactured light in the evening (including light from screens) could stop progressive phase delay in delayed sleep–wake phase disorder and non-24 h sleep–wake rhythm disorder, there is not yet any clarification as to what avoidance means—although a 2022 expert review suggested it meant less than 10 melanopic lux at the eye.[171] There is also high variability in the effectiveness of different light-avoiding products, such as changing screen output or wearing blue-light blocking glasses. Until better evidence is available, however, advising patients to minimise exposure to light, particularly blue-enriched light from electronic devices, for 2–3 h before bedtime is a sensible approach.

Some evidence exists for evening light therapy in advanced sleep–wake phase disorder.[117,172] Systematic reviews and meta-analyses of light therapy in dementia[173] and psychiatric disorders[174] have generally found positive effects of evening bright light therapy on sleep, circadian rhythm, and psychological and behavioural outcomes, although there is substantial inconsistency because of heterogeneous studies of short duration and small sample size.

Exogenous melatonin has sleep-facilitating effects that are more pronounced when administered during the day and in early evening, when endogenous production is absent or very low.[175,176] Melatonin also acts as a chronobiotic, however, with an opposite effect on circadian phase to that of light. Administration of low-dose, rapid-release melatonin in the late afternoon or early evening induces maximal phase advance of the sleep–wake propensity rhythm; administration on waking leads to maximal, albeit small, phase delays.[60] Evidence is sufficient to weakly recommend evening melatonin at doses ranging from 0·5 mg to 5 mg in delayed sleep–wake phase disorder in children and adults,[2] but not morning melatonin in advanced sleep–wake phase disorder. There are no clear recommendations on timing of administration of melatonin. As a general rule, in the absence of circadian markers patients with delayed sleep–wake phase disorder are typically advised to take immediate-release melatonin approximately 5–6 h before the current sleep onset time to induce maximal phase advances. As sleep timing advances, however, the time of melatonin administration might also advance into the late afternoon or early evening, at which point risk of sleepiness becomes a concern. To minimise this risk, we suggest melatonin is taken 1–3 h before sleep onset time, and patients should be advised not to take melatonin when alertness is required—eg, within 8 h of driving. Melatonin is widely available in the USA as a supplement, but is only available as a prescribed, slow-release formulation in most other countries. Despite widespread use, safety information is lacking, particularly for children, adolescents, and people who are pregnant.[177] We therefore recommend that melatonin is administered with clinical supervision, especially in these groups.

The melatonin agonists ramelteon, agomelatine, and tasimelteon have also been developed. For blind individuals with non-24 h sleep–wake rhythm disorder, melatonin[26,178] (0·5–10 mg, fast-release preparation) and tasimelteon[27] (20 mg, no specifications for preparation) administered at a fixed clock time 1 h before target bedtime induced entrainment. In sighted individuals with non-24 h sleep–wake rhythm disorder, stabilisation of sleep–wake rhythms with melatonin (0·5–1 mg) administered 2 h before target bedtime and bright light therapy for 1 h after predicted wake time has been suggested on the basis of evidence from a case series.[126] For individuals with irregular sleep–wake rhythm disorder, available evidence suggests that melatonin has a benefit in children with neurodevelopmental disorders but no efficacy in dementia,[179] for which the risks of depression and sedation outweigh the benefits.[2]

There is little evidence to support the use of hypnotic medications in circadian rhythm sleep–wake disorders, and an evidence base for the effects of orexin antagonists on circadian outcomes has yet to be established.

For all interventions, timing is key. In the absence of circadian biomarkers, however, judging the optimal timing for inducing maximal phase shifts is challenging and is estimated from sleep timing, with a risk of mistiming treatment.[91] Multicomponent interventions—eg, combined evening melatonin and morning light therapy in delayed sleep–wake phase disorder—appear to be more effective than single-component approaches. However, an improved understanding of the mechanisms underlying each constituent treatment remains necessary. Rapid relapse invariably follows treatment discontinuation, so approaches to augmenting and maintaining adherence with treatment, including psychological therapies,[180] will be valuable.

Future directions

Despite compelling evidence for the role of circadian disturbance across a range of disorders, clinical implementation of circadian science remains slow. One barrier is education and training; sleep-circadian medicine currently forms a very small part of the medical[181] and clinical psychology[182] curricula. Another barrier is measurement; accurate longitudinal objective assessment of endogenous circadian rhythms is rarely done and assessment of sleep timing and light exposure are not routinely implemented. Circadian rhythm sleep–wake disorders, especially those with a recurring but long rest–activity period, such as non-24 h sleep–wake rhythm disorder, could be underdiagnosed.

Validated markers of endogenous circadian phase, including salivary, blood, or urinary melatonin or cortisol assays, are available. They are, however, considered complex and expensive, and are not routinely implemented. Serial sampling during approximately 6–24 h is necessary and, for plasma and salivary melatonin, should be obtained in dim light to avoid masking effects. Urinary measures during 24 h can provide more flexibility in field-based assessments. These methods are arguably no more costly or onerous than other, more commonly used investigations in sleep medicine, such as polysomnography, and therefore the primary barrier to their implementation might be how they are perceived. Nonetheless, novel approaches that assess endogenous circadian phase at scale using less invasive, point-of-care tests are necessary.[183]

Rest–activity timing should be used with caution when assessing circadian rhythm sleep–wake disorders, and further insights into the mechanisms underyling these disorders at the individual and population levels could be gained by harnessing multivariate, longitudinal data streams from increasingly ubiquitous mobile and wearable devices.[43,45] Continuous sensor data from consumer technologies, including movement, heart rate, light, and geolocation, can enrich understanding of how sleep-circadian regulation interacts with real world environmental and behavioural variables, such as light exposure and exercise.[184,185] Another promising approach uses mathematical models to integrate passively gathered light information and rest–activity data to identify causal factors underlying sleep timing phenotypes.[185–188] Evaluation of these novel methods against gold standard markers of circadian phase will be essential before they can be implemented in clinical practice. These real world data can be combined with measures of the sensitivity to light (assessed, for example, by melatonin suppression and pupillometry in controlled conditions)[79] and genetic variants, such as *PER3* genotype, (shown to modulate response to melatonin in delayed sleep–wake phase disorder)[189] of an individual to design personalised therapeutic interventions.

One emerging method for assessing circadian rhythmicity uses multivariate, transcriptomic biomarkers to estimate circadian phase using transcripts from whole blood[190,191] or monocytes[192] that predict melatonin phase within approximately 1–2 h. Accuracy is enhanced by collecting two samples approximately 12 h apart. Evaluation of these methods in conditions in which sleep and light are displaced, such as shift work, is required. Two other essential circadian parameters, intrinsic circadian period and amplitude, are poorly characterised by current methods, and novel approaches for assessing these parameters are also needed.[183] Finally, technology for the assessment of sleep physiology at scale in patient populations is in development and could overcome the paucity in information on sleep structure in circadian rhythm sleep–wake disorders.

Widespread measurement of valid and robust markers of endogenous circadian rhythmicity and sleep physiology will allow the role and diagnostic boundaries of circadian dysfunction to be defined more clearly and improve the search for effective treatments. Field

studies have shown that the phase of entrainment has a considerably wider range than is commonly known. For example, despite living in the same time zone and being considered entrained to the 24 h day, phase angles of entrainment, as assessed by dim-light melatonin onset, spanning 7 h in insomnia patients[89] and 9 h in undergraduate students[193] have been found. Even in highly controlled laboratory conditions, this range is approximately 5 h.[30,32,194] Such variability has clear and systematic influences on sleep latency, timing, and duration and time course of daytime alertness,[195,196] with several clinical implications.

First, many individuals could be living with unrecognised sleep-circadian misalignment and the circadian system might contribute more extensively to the development of other disorders, such as psychiatric disorders, metabolic disorders, or cardiovascular disease, than we are currently aware. For example, up to 20% of individuals with a diagnosis of insomnia initiate sleep at too early a circadian phase and are likely to meet delayed sleep–wake phase disorder criteria,[89] as are a subgroup of individuals with depression. Second, only those with extreme sleep-circadian phenotypes meet current diagnostic criteria for circadian rhythm sleep–wake disorders, thereby excluding many individuals living with circadian misalignment, substantial disturbances in sleep timing, and other circadian-mediated sequelae. For example, during the COVID-19 pandemic, people with an evening chronotype were more susceptible to developing mental health disorders and sleep disturbance than earlier chronotypes.[197] Adopting a dimensional (rather than categorical) approach to assessing the contribution of circadian disruption across a range of disorders, alongside a greater awareness of circadian disruption as a treatable but often hidden comorbidity to other disorders, will begin to address the inconsistencies in this field.

Conclusions

The relevance of circadian biology to sleep–wake timing and wider health is increasingly apparent. Challenges to the circadian system include insufficient light exposure during the day, too much light at night, and long-term shift work, leading to mistimed sleep, diminished circadian amplitude, and weaker coherence within oscillator networks. Circadian disturbance contributes not only to the development of circadian rhythm sleep–wake disorders, but also to the development of a broad range of disorders, including cardiometabolic and inflammatory disease, cancer, mood dysfunction, and cognitive dysfunction, through mechanisms that are not yet fully elucidated. The finding that outcomes from surgery, side-effects from chemotherapy, or vaccine efficacy vary according to the time of day at which they are administered[198,199] highlights the need for medicine to pay closer attention to the temporal dimension.

The scope for developing novel interventions is broad. Circadian rhythmicity has a biological basis but is responsive to modifications to behavioural and environmental factors.[116] At the policy level, the effects of daylight savings time, work schedules, and delayed school start times on sleep-circadian health remain active areas of debate. Optimising the timing, intensity, quality, and composition of light from a circadian, and not just visual, perspective will require collaboration between architects and the lighting industry.[171]

Rigorous approaches to developing cognitive-behavioural therapies for circadian rhythm sleep–wake disorders include mini-treatment experiments, in which effective strategies that reverse disorder-maintaining factors are identified and subsequently incorporated into multicomponent interventions.[200] Further research into how shortened and fragmented sleep mediates the relationship between circadian dysfunction and disease, together with treatments that target both sleep and circadian dimensions, are necessary. Novel agents that target the melatonin, orexin, and serotonergic systems show promise with regard to treatment. Increasingly, we live with the demands of a 24 h society. In this context, we must increase the attention given to our most fundamental of attributes, the evolution of our physiology around the 24 h day, to improve the understanding, recognition, and treatment of human disease.

Contributors

All authors developed the outline for this Series paper and contributed to the writing and editing of this paper. NM prepared the final version of this paper, which all authors approved.

Declaration of interests

SWL has received consulting fees from EyeJust, Rec Room, Six Senses, and Stantec; has current consulting contracts with Akili Interactive, Apex 2100, Consumer Sleep Solutions, Hintsa Performance, KBR Wyle Services, Light Cognitive, Lighting Science Group Corporation/HealthE, Look Optic, Mental Workout/Timeshifter, and View; has received honoraria and travel or accommodation expenses from MIT, Roxbury Latin School, and University of Toronto; and travel or accommodation expenses (no honoraria) from Wiley; has received royalties from Oxford University Press; holds equity in iSleep; has received an unrestricted equipment gift from f.lux Software; holds an investigator-initiated grant from f.lux Software; has a Clinical Research Support Agreement and a Clinical Trials Agreement with Vanda Pharmaceuticals; is an unpaid Board Member of the Midwest Lighting Institute (non-profit); is co-investigator on National Institutes of Health grants (R01HL159207, R03AG071922, R21NR018974); was a Programme Leader for the Cooperative Research Centre for Alertness, Safety, and Productivity, Australia, through an adjunct professor position at Monash University (2015–19); has served as a paid expert in legal proceedings related to light, sleep, and health; and has several patents related to circadian applications. D-JD has consulted for and received research support from pharmaceutical and non-pharmaceutical companies with an interest in developing treatments for sleep and circadian rhythm disorders; was a paid consultant to or received research support from F Hoffmann-La Roche, Pfizer, Eli Lilly, Novo Nordisk, Ono Pharma UK, Janssen Research and Development, GW Pharma, Phillips Lighting, H Lundbeck, Merck, Vanda Pharmaceuticals, Cephalon, Servier, UCB, Procter & Gamble, and Ferring Pharmaceuticals; and is supported by the UK Dementia Research Institute which is funded by the UK Medical Research

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