

Circadian disruption and human health

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Circadian disruption is pervasive and can occur at multiple organizational levels, contributing to poor health outcomes at individual and population levels. Evidence points to a bidirectional relationship, in that circadian disruption increases disease severity and many diseases can disrupt circadian rhythms. Importantly, circadian disruption can increase the risk for the expression and development of neurologic, psychiatric, cardiometabolic, and immune disorders. Thus, harnessing the rich findings from preclinical and translational research in circadian biology to enhance health via circadian-based approaches represents a unique opportunity for personalized/precision medicine and overall societal well-being. In this Review, we discuss the implications of circadian disruption for human health using a bench-to-bedside approach. Evidence from preclinical and translational science is applied to a clinical and population-based approach. Given the broad implications of circadian regulation for human health, this Review focuses its discussion on selected examples in neurologic, psychiatric, metabolic, cardiovascular, allergic, and immunologic disorders that highlight the interrelatedness between circadian disruption and human disease and the potential of circadian-based interventions, such as bright light therapy and exogenous melatonin, as well as chronotherapy to improve and/or modify disease outcomes.

Circadian (*circa*, “about,” and *diem*, “day”) rhythms are endogenous oscillations with an approximately 24-hour cycle. Circadian rhythms in physiology and behavior are organized by a central “master” clock, the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus, that coordinates alignment between external synchronizing agents with circadian clocks in other brain regions, as well as in peripheral tissues. Circadian rhythms are modulated by endogenous (genetic, physiological) as well as environmental (light) and behavioral (activity, feeding) factors. In this Review, we use “circadian disruption” as a nonspecific umbrella term to describe a disturbance, dysregulation, or problem that negatively affects circadian function, but as Vetter has pointed out, there is a need for clearer terminology and quantification of circadian disruption (1). It is becoming increasingly clear that circadian disruption in humans can result in broad and significant consequences for mental and physical health (2, 3). Furthermore, changes in circadian function are often accompanied by sleep-wake disturbances, which also contribute to poor health outcomes. The interrelationship between circadian rhythms and human disease can create a vicious cycle between disease expression and circadian disruption, as exemplified in immunologic (4, 5), cardiometabolic (6), neurodegenerative, and psychiatric disorders (7).

General mechanisms of circadian disruption

In humans, measures of circadian disruption include the phase (timing), relationship between internal-internal or internal-external rhythms (alignment), the period and amplitude of circadian rhythms. Disturbance of circadian phase alignment and amplitude are the most common measures that have been associated with adverse health consequences. As outlined in Figure 1, circadian disruption can occur at multiple levels, from intrinsic changes at the molecular, cellular, tissue, or system level to misalignment among different organizational levels and/or with behavioral and environmental cycles. The “molecular circadian clock” refers to genes that maintain autoregulatory feedback loops in which oscillating outputs regulate their own expression (circadian locomotor output cycles kaput [*CLOCK*], brain and muscle ARNT-like [*BMAL*], period [*PER*], rev-erb/nuclear receptor subfamily 1, group D [*NR1D*], and cryptochrome [*CRY*]; ref. 4).

Biomarkers of circadian rhythm and circadian disruption

Although the SCN rhythm cannot be directly measured in humans, the timing of melatonin onset and amplitude measured in plasma or saliva, or the melatonin metabolite 6-sulfatoxymelatonin in urine, are gold standard biomarkers of circadian rhythms. The collection of 24-hour urine samples is particularly useful to assess circadian amplitude of melatonin in special populations, such as pediatric patients in whom blood or salivary samples might be difficult to obtain (8), and has been shown to be a useful treatment-responsive biomarker of circadian disruption in neurologic diseases, such as Alzheimer's disease (AD) (9) and pediatric epilepsy (10). Although less direct, other commonly used measures include rest/activity cycles derived from actigraphy, and other hormonal, metabolic, and cardiovascular rhythms (7).

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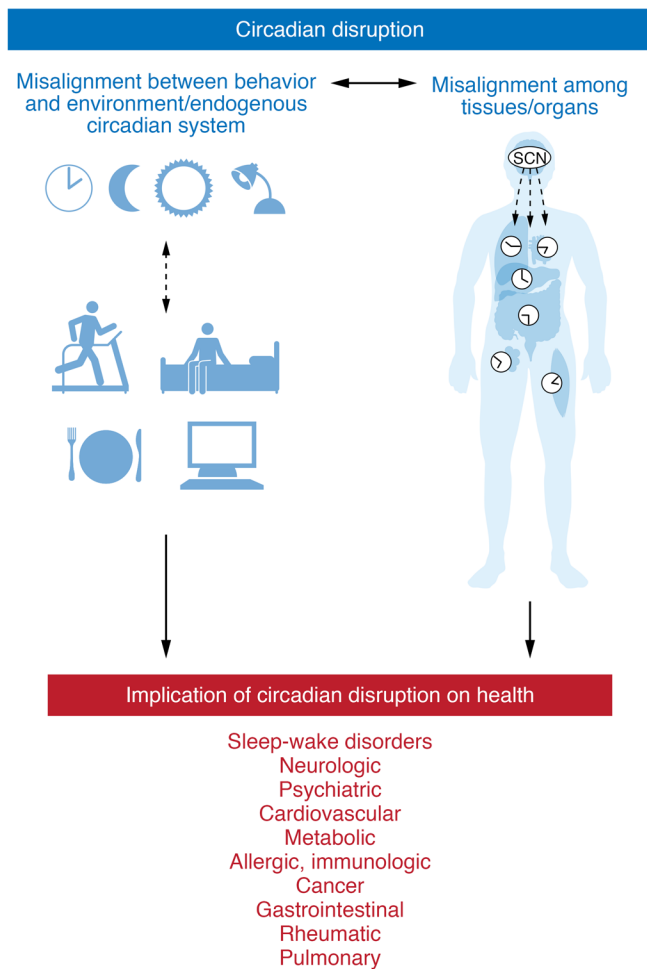


Figure 1. Schematic of the interrelationships between circadian disruption and human disease. As depicted on the top left, circadian disruption can result from misalignment of external factors (such as the natural light/dark cycle, social and work requirements, and behaviors such as sleep and meal timing) with the master circadian clock located in the suprachiasmatic nucleus (SCN), as well as with endogenous circadian clocks in other tissues. Common examples of chronic external-internal misalignment include social jet lag, shift work, and misalignment due to inappropriately timed light exposure (evening or night). The top right image depicts the SCN and the peripheral clocks throughout the body. The SCN integrates light and nonphotic stimuli to synchronize the timing of other brain and body clocks with the environment and behaviors. Disturbances at these various organizational levels result in circadian disruption. Disturbance in the phase and amplitude of circadian rhythms can occur at the molecular, cellular, and organismal levels. On the bottom are examples of the impact of circadian disruption and the bidirectionality between circadian disruption and the classical circadian sleep-wake disorders and other chronic medical disorders.

Part of this gap stems from the lack of multicenter randomized clinical trials and longitudinal population studies that directly focus on circadian disorders, as well as the limited number of well-established patient-reported outcomes and scalable human biomarkers of circadian disruption. Additionally, research targeting clinical circadian rhythm requires an age-based approach, as there are prominent differences in circadian phase and amplitude, as well as stability of rhythms across the lifespan.

In this Review, we use an evidence-based “bench-to-bedside” approach, applying research in circadian disruption to the risk for, and therapeutics for, some of the most prevalent and pressing human diseases. We apply this model to highlight selected examples of research findings from preclinical and clinical work that are ripe for translation and implementation in the clinic, and development of guidelines for public health. Lastly, we discuss strategies for integrating biological timing in medicine to optimize and personalize the care of individuals with circadian rhythm sleep-wake disorders, as well as disruption of the circadian system within the context of chronic disease.

The following discussion is organized by key disease areas of circadian disruption in human health: neurologic, psychiatric, metabolic, cardiovascular, and allergic/immunologic. We highlight the epidemiologic and background evidence supporting the connection between circadian disruption and human health and then apply the bench-to-bedside model to discuss examples of targetable mechanisms to enhance circadian health in these disorders.

Neurologic disorders

Circadian disruption is common in neurologic disorders, affecting the development, expression, and severity of disease. There is mounting evidence linking circadian disruption with cerebrovascular disease, epilepsy, migraine, multiple sclerosis, neurodegenerative disorders, and neurodevelopmental disorders (7). Beyond its association with disease severity, circadian disruption increases the risk for neurologic disorders across the lifespan (18).

Neurodevelopmental disorders

Circadian disruption and poor sleep quality are common in neurodevelopmental disorders, including autism spectrum disorders (ASDs) and rare genetic neurodevelopmental disorders such as

Public health implications of circadian disruption

The public health implications of circadian disruption are enormous owing to the number of people affected and the mounting evidence of circadian disruption’s association with serious adverse health outcomes. Populations in the US at risk for circadian disruption include the approximately 16% of adults who usually work a nondaytime schedule (11), the approximately 70% who work indoors (12), the estimated 99% affected by light pollution (13), and the growing sector of adults aged 65 and older (14). This topic is also important for policy decisions that affect the general population, such as the public and scientific debate regarding daylight saving time and its potential health and safety risks (15). “Chronotype” refers to one’s preferred timing of sleep and activity, and evening chronotypes (“night owls”) are more likely to experience circadian disruption because of a mismatch between their internal clock and their social or professional responsibilities, and have increased risk of all-cause mortality compared with morning types (16). Shift work increases risk for poor mental and physical health and is considered “probably carcinogenic” (7), and therefore has implications for both individual health and occupational health policies.

Circadian knowledge from basic science is robust, but less is available in the areas of clinical and population health (17). There remains a notable gap in translating this science to directly impact health, both for individuals and for population-based decisions.

Angelman, Williams, Prader-Willi, fragile X, and Smith-Magenis syndromes. ASDs are relatively common and have been associated with several biomarkers of circadian disruption, including misaligned cortisol rhythm and lower-amplitude melatonin rhythm (19). A leading hypothesis is that ASD induces dysfunction of melatonin synthesis (19). In fact, single-nucleotide polymorphisms (SNPs), such as in melatonin receptors *MTNR1A* and *MTNR1B*, may cause ASD (20), and other clock gene SNPs appear to modulate the association between severity of ASD and severity of the sleep disruption/circadian disruption (20). Smith-Magenis syndrome (SMS) is caused by a deletion in 17p11.2, which encompasses the gene encoding retinoic acid induced 1 (*RAI1*) (21). Mice deficient in *RAI1* have a shortened period, which appears to be due to *RAI1*'s activation of core clock gene transcription (22). In humans, *RAI1* is implicated in the regulation of melatonin secretion (21). Children with SMS exhibit an inversion of the endogenous melatonin rhythm and sleep/wake cycle (23).

One strategy to suppress the morning level of melatonin in SMS includes administration of a β_1 -adrenergic antagonist (24). Melatonin supplementation is also a core strategy to realign the circadian system and improve sleep and cognitive outcome measures (25). Melatonin supplementation for realignment (i.e., phase shifting) typically occurs at lower doses of ≤ 1 mg of immediate-release formulations given several hours before bedtime (26), whereas doses greater than 1 mg of extended-release versions just before bedtime are used for the soporific effect (27). In ASD, Malow et al. found in children with autism that treatment with melatonin significantly improved sleep quality using oral pediatric prolonged-release melatonin at starting doses of 2 mg titrated up to 5 mg after 3 weeks and up to 5–10 mg/d if needed after that (28).

Neurodegenerative disorders

Increasing evidence indicates a bidirectional relationship between circadian disruption and neurodegeneration, such as in traumatic brain injury, AD, Parkinson's disease (PD), and Huntington's disease. Circadian misalignment and decreased amplitude of several rhythms have been shown to predict the development of neurodegenerative diseases, such as AD and PD (29–31). In this section we focus on the most common age-related neurodegenerative diseases, AD and PD.

PD. In mouse models of PD, SCN neurons had decreased activity, and this may contribute to lower amplitude and/or misalignment of circadian rhythms (32). Dopamine has an important role in the regulation of centrally generated circadian rhythmicity via direct effects on retinal circadian rhythms (33), as well as via its effect on melanopsin-containing photoreceptors in the retina (34). In nonhuman primate models, depletion of dopamine disrupted rhythmicity, and this appeared to be further exacerbated by misalignment of environmental and behavioral rhythms (35). Circadian disruption in patients with PD can occur at any stage of the disease, and can include changes in the phase and amplitude of rest/activity and melatonin rhythms (36). The circadian disruption may even occur prior to the onset of clinical motor symptoms, suggesting a possible role in disease pathogenesis (37, 38).

Given circadian rhythmicity in the pharmacokinetics of levodopa (39), a dopamine precursor indicated for the management of PD symptoms, timing of dosing could potentially help

optimize effectiveness and decrease side effects. Mathematical models are being developed to integrate biomarkers of circadian disruption, such as clock gene expression and timing of light exposure, to predict the impact on neurotransmitters, such as dopamine, and help in timing treatment and choosing drug targets (40). Tested circadian-based therapeutics include bright light therapy, which improves mood (41), sleep quality, and daytime alertness (42). Interestingly, bright light therapy twice daily for 14 days also increased objective levels of physical activity (42) as well as enhanced sleep and improved disease control (43). In PD, melatonin has been primarily used for its soporific effects (44).

Dementia and AD. AD is associated with circadian disruption at multiple organizational levels, including loss of SCN neurons (31) and impaired function of light input pathways (degeneration of the intrinsically photosensitive retinal ganglion cells; ref. 45). Environmentally there is decreased exposure to light and structured activity. These and other factors can contribute to the low amplitude and misalignment of circadian rhythms at multiple levels of organization (7, 31, 46–53), which in turn have been shown to correlate with the degree of neurologic impairment (54, 55). In mice, misalignment between feeding rhythms and the SCN results in memory impairment (56), which improves with timed feeding schedules (57). Furthermore, there is evidence for misalignment of neuronal activity in different brain regions, such as between the SCN and hippocampus (58, 59). The evidence that circadian disruption increases the risk for cognitive decline and AD (30) raises the possibility that improving circadian function may decelerate age-related cognitive impairment.

Light therapy, specifically morning blue-enriched light, might be effective for improving sleep quality and cognitive function (60), and evidence indicates that light therapy reduces neuroinflammation and oxidative stress to improve sleep and cognition (61). Indeed, these circadian-based therapies, including sleep behavior modifications (62), are increasingly becoming part of standard of care for AD, and might combat cognitive decline (30). Increasing daytime light exposure might improve rhythmicity and help consolidate sleep (63). In a systemic review and meta-analysis, melatonin supplementation appeared to significantly improve scores on the Mini-Mental State Examination in nine studies of mild AD (64). However, the evidence is weak, and a recent Cochrane review found that melatonin, even at higher doses, did not improve sleep measures compared with placebo (65).

Psychiatric disorders

Circadian disruption is common in psychiatric disease, including schizophrenia and mood disorders, such as depression, bipolar disorder, and seasonal affective disorder (21, 66, 67). In this section, we focus on mood disorders as common examples of the role of circadian disruption in the development of psychiatric disorders and the potential of circadian-based psychiatric therapeutics. Other published reviews in this area (21, 66, 67) delve deeper into psychiatric disorders that are outside the scope of this Review, including substance use disorders (21).

Mood disorders

The link between circadian disruption and mood disorders is well established (68–70). Seasonal affective disorder is characterized

by the onset or worsening of depression during the fall and winter months, when the daily duration of daylight decreases (66), and patients are symptomatic as a result of seasonally induced circadian misalignment. Accurate assessment of circadian phase and therapy to shift phase might improve depressive symptoms (68). Another example is delayed sleep-wake phase disorder (DSWPD), in which misalignment between the onset of melatonin and bedtime resulted in increased odds of depressive symptoms (OR = 4.31, 95% CI = 1.75–10.64) and DSWPD exacerbation (71). “Circadian depression” is a recently coined term used to describe this potential clinical phenotype that requires circadian-targeted treatment for specific mood disorders, as evidenced by specific rhythmicity/seasonality to symptoms, clinical course, objective circadian parameters, and treatment responses (72).

Preclinical evidence further demonstrates the bidirectional relationship between mood disorders and the circadian system in mice, in which manipulation of serotonin receptors themselves induced circadian disruption (73). External circadian factors, such as light at the wrong time in a mouse model, also induce signs of depression (74), mediated by intrinsically photosensitive retinal ganglion cells and their projections to hypothalamic, preoptic, and limbic regions, such as the amygdala (75). In humans, functional MRI studies found that light suppresses amygdala activity, but improves connectivity within the prefrontal cortex (76), which suggests a potential mechanistic explanation of the effect of light on mood. Other circadian mechanistic contributors to mood disorders in humans include altered clock gene expression (77) and genetic polymorphisms in clock genes (78) (e.g., *PER3* rs57875989 is associated with anxiety; ref. 79). As a separate point, synchronizing timing of the brain clock with the external environment can decrease depression (80). A recent study of thousands of patients in several large cohorts identified that earlier sleep midpoint was associated with a 23% lower risk of depression (80).

Circadian-based approach to psychiatric therapy

The findings described above support the potential of circadian-based treatment approaches for psychiatric disease. In fact, psychiatric drugs, such as selective serotonin reuptake inhibitors, have differential effects in various light conditions in humans (81). Chronotype also influences therapeutic efficacy. For example, patients with bipolar disease who respond to lithium tend to be “morning larks” (82), and lithium might strengthen circadian amplitude in those that are responders (83, 84). Interestingly, lithium-induced circadian disruption in some nonresponders might be overcome by circadian entrainment with synchronizing agents or zeitgebers (83). The use of bright light therapy is relevant across many mood disorders, such as major depression (85), bipolar disorder (86–88), and seasonal affective disorder (89, 90). It is important to note that the efficacy of bright light therapy in clinical trials for mood disorders is variable, and is dependent on the type of light used, the timing of usage, and patient adherence (91). It is worth a brief mention of burgeoning literature on attention deficit hyperactivity disorder (ADHD) that suggests that phase advancing via bright light can correct circadian disruption without inducing changes in sleep and improves symptoms of ADHD (92), which might also be accomplished by phase advancing with melatonin (93).

Metabolic disorders

The intimate relationship between the circadian system and metabolism is crucial for optimizing energy extraction and utilization from food during the active period and processing stored energy during the rest phase to maintain stable glucose levels during the overnight fast. The impact of circadian disruption on metabolic disorders has been an area of intense research. Several high-impact reviews (94–97) summarize the close coupling of circadian regulation and metabolism. In this Review, we focus on the negative-feedback loop between circadian disruption, diabetes, and obesity.

Metabolism and diabetes

It is well established that circadian dysregulation affects metabolism at the genetic, cellular, and system levels, resulting in impaired glucose tolerance and insulin resistance and increased risk of metabolic syndrome and diabetes (98). Core clock gene disruption, such as in *Clock*^{Δ19} mutant mice, demonstrates the profound impact of the *Clock* gene mutation on metabolism, with the development of obesity and metabolic syndrome (99). Loss of *Bmal1* increases insulin sensitivity (95), as well as tissue-specific mechanisms of misalignment (100). In fact, social jet lag (the shifting of bedtimes between work and free days) has also been associated with the metabolic syndrome and with increased glycosylated hemoglobin (101). Misalignment in those with later chronotype might explain why they are more likely to be overweight and have type 2 diabetes (102, 103). Even among patients with type 2 diabetes, those who are evening types have poorer glycemic control (104–106). These studies suggest that discrepancies between internal timing and social timing can lead to metabolic impairment.

The timing of food consumption also directly impacts blood glucose levels. For example, eating the same meal at breakfast, lunch, or dinner will result in the lowest glucose spike at breakfast, doubled at dinner (94). In fact, a continuous glucose infusion demonstrated that blood glucose levels are highest overnight when the body is not expecting to receive glucose. Experimental human studies that induced circadian disruption recapitulated the increased glucose levels, despite controlled food intake and increased insulin levels (6, 107). Circadian misalignment also reduces glucose tolerance and impairs insulin sensitivity (108–110), providing a potential mechanism to explain the increased risk of diabetes in shift workers (107). Another population at risk for circadian misalignment is pregnant women, and a higher risk of gestational diabetes was observed in those with a later sleep midpoint (111).

The timing, intensity, and wavelength of light exposure can also modulate metabolic function, with evening blue-enriched light having the strongest negative impact by increasing blood glucose levels (112). Indeed, several studies have demonstrated that dim light conditions during the daytime and/or excessive evening light disrupts metabolic clocks, such as in patients with diabetes in whom blood sugar levels are more difficult to control (113, 114). Enhanced daytime light exposure and promotion of dim light in the evening to improve circadian alignment is one strategy that might improve metabolism and cardiometabolic disease control (114). In addition, recent evidence from preclinical and clinical studies indicates that time-restricted feeding and timed exposure to light may be important strategies to align the timing

of energy intake with clock-regulated metabolic rhythms. Such circadian-based approaches have the potential to improve metabolic health and maybe even weight regulation (115–117).

Obesity

Considering the strong association of obesity with *Clock*^{fl/fl} mutation in mice, it is not surprising that *CLOCK* gene variants, such as rs6820823, rs3792603, rs11726609 (118), and rs1801260 (119), are associated with elevated BMI in humans. Polymorphisms of *CLOCK*, such as rs3749474, might be identified to more effectively personalize weight loss treatment, such as with restriction of dietary fat intake (120). Polymorphisms in genes encoding melatonin receptors are also associated with metabolic dysfunction and obesity (121–125), and the relationship between nighttime food consumption and obesity might be partly mediated by these melatonin receptor polymorphisms (126). Potential mechanisms linking circadian disruption to weight gain and obesity in night shift workers include a decrease in daytime energy expenditure after night shifts (127), compounded by dysregulation of hormonal (leptin/ghrelin) signaling to eat (128).

Shift workers are an at-risk population for metabolic disorders, type 2 diabetes, and obesity (129–131). In a systematic review of shift work and metabolic syndrome, there was an association between metabolic syndrome and shift work (OR = 1.29, 95% CI = 1.06–1.52) (132). Social jet lag is associated with overweight, and the greater the discrepancy in bedtimes, the greater the prevalence (101, 133).

As a method to improve circadian alignment, particularly between central and peripheral metabolic tissues, time-restricted feeding of animals, even animals on a high-fat diet, improved circadian function (134). Time-restricted feeding is also a proposed strategy to prevent metabolic diseases (135, 136). A recent study suggests a correlation between insulin sensitivity and the proportion of calories consumed in the morning (137), which should be considered in relation to melatonin rhythms (138). Taking a step further, a systematic review of time-restricted feeding in humans in seven studies found that it resulted in a mean weight loss of 2.88 kg (95% CI = –3.96 to –1.80) (139), although the effects on weight loss are highly dependent on the specific intervention protocol (135).

Cardiovascular disorders

A landmark 1985 *New England Journal of Medicine* paper described the timing of myocardial infarctions (MIs; commonly known as heart attacks), with a higher likelihood of events occurring between 6 am and noon (140). Further research identified similar timing of this risk in stroke (141) and ventricular arrhythmias (142). This vulnerable morning time is not explained by behavioral triggers alone, i.e., feeding, sleep, etc. (143–145). Rather, it appears to be due in part to circadian regulation of prothrombotic factors, such as platelets and prothrombotic plasminogen activator inhibitor-1 (PAI-1) (146, 147). Because the circadian system regulates the timing of cardiovascular (CV) function, when circadian disruption is present there is a profound impact on CV health.

Acute CV events and CV risk

Circadian misalignment between environmental or behavioral rhythms and central or peripheral clocks has been shown to

increase the risk for cardiovascular disease (CVD). Animal models demonstrate that arrhythmias and CV events manifest in conditions of circadian misalignment (6).

Myocardial infarction and stroke. In humans, circadian misalignment might induce hypertension and inflammation (as exemplified with biomarkers such as C-reactive protein) (148), which in part may explain the epidemiology data linking shift work with MI and stroke (149). In mouse models of stroke, one functional consequence of longer duration of “shift work” is upregulated inflammatory mediators and ultimately worse stroke severity (150). The modulation and interaction between CVD and circadian disruption is exemplified by the finding that in patients with type 2 diabetes, the *CLOCK* rs4580704 SNP is associated with increased lifetime risk of stroke (151). Evidence indicates that CV damage and risk for CV events in night shift workers is due to a putative circadian disruption-induced IL-6-mediated inflammatory mechanism (152), as evidenced by increased carotid intimal-medial thickness (153). Other types of circadian disruption, including social jet lag or late chronotype, increase risk factors for CVD, such as increased resting heart rate and hypertension (103, 154, 155), and are associated with an increased prevalence of CV diseases (16).

Hypertension. Circadian regulation of blood pressure occurs in the nondisrupted state by increased nocturnal parasympathetic (156) tone that provides cardioprotective nocturnal blood pressure dipping (157–159). Misalignment, such as in one small study of social jet lag, can alter parasympathetic tone during sleep (160). A review of studies in shift workers affirms that this circadian disruption induces increases in sympathetic tone and downregulation of cardioprotective parasympathetic tone (161). Indeed, experimental induction of circadian misalignment in humans increases blood pressure (6, 108, 149).

Arrhythmias. With regard to arrhythmia, 44% of the sinus node transcriptome has diurnal variation (162). In one mouse study, unnaturally restricting feeding to the rest period unmasked long QT syndrome (163). Additionally, housing mice in non-24-hour-light/dark cycles, even under stable entrainment (similar to shift work conditions) induced phase misalignment between the environment and internal circadian timing, and this phase misalignment was the driver of the cardiac abnormalities, including prolonged QT interval (164).

Circadian-based therapeutic strategies for CVD. Strategies to boost circadian amplitude and stable alignment are potentially beneficial. Considering the vulnerable time window of CV events and a hypothesized circadian link, murine studies identified that expression of the core clock gene *Per2* appears to be protective against myocardial ischemic and reperfusion injury (165–167). Central and peripheral PER2 expression can be induced by light activation of melanopsin receptors in retinal ganglion cells (165, 168, 169), and bright light therapy to increase PER2 amplitude might protect against ischemic injury (167, 170) and reduce platelet aggregation (171).

In humans, bright light therapy in the morning can indeed induce PER2 expression in buccal or plasma samples (170). This finding as well as mechanistic animal studies led to a proof-of-concept study in humans using bright light therapy (10,000 lux from 8:30 to 9:00 am every morning for 5 days) to evaluate CV risk pathways. The researchers found they could target the vulnerable morning time window for CV events by decreasing clot-

ting time and downregulating several procoagulant pathways as measured on proteomics of blood samples, including tissue inhibitor of metalloproteinase (TIMP-1), PDGFA/B, and platelet factor 4 (PF4) (171).

Furthermore, manipulation of the timing of therapies, or chronotherapy, for CVD has been gaining attention. Therapeutic attempts to combat hypertension via time-based treatment have received considerable attention; even nighttime exercise has been tested as a possible strategy (172). A recently published study with a large sample of hypertensive patients followed for about 6 years identified that bedtime treatment decreased risk of all measured CV events (stroke, MI, heart failure) (173). Although there has been some controversy over the study design (174), a systematic review of ten published trials also supported evening dosing of blood pressure therapy (175). It should be considered, however, that pharmacokinetics differs between anti-hypertensives, and translating these findings to clinical practice should consider the half-life and time to peak action. Further prospective studies that evaluate the benefits of evening dosing for specific populations are needed (176). In comorbid conditions such as obstructive sleep apnea, morning dosing might still be preferable (177).

CV risk in children

Although pediatric populations are not well studied, this group offers a unique opportunity for intervention to avoid accumulation of CV damage and to decrease long-term CV risk. With regard to CV circadian rhythms, children are unique in that rhythms vary widely by age (178), and the timing of CV events, such as arrhythmias, in children might be different from that in adults (179). Specific pediatric diseases such as type 1 diabetes and prematurity can further induce internal misalignment and CV risk, creating a feedback loop between disease expression and circadian disruption (180, 181). Obese children have lower-amplitude circadian rhythms, and even when BMI is controlled for, inflammation inversely correlates with the strength of the rhythm (182). Cardioprotective physiology, such as nocturnal blood pressure dipping, is also important in children yet appears to be disrupted by several pediatric disease states (183–185). Because adolescents are susceptible to phase delays (8, 186, 187), circadian misalignment is commonly associated with greater metabolic effects in this population (188, 189) and potentially effects on the CV system (190).

Modifiable behavioral factors such as screen time at night, alcohol use, and consistently early school start times (191) might be targeted to modulate this CV risk. Race/ethnicity might also modulate the relationship between circadian misalignment and metabolic effects in adolescents (192), and is an important factor to consider in the study of circadian disruption.

Immunologic disorders

Circadian control of the immune system is an area of important investigation that shows the intimate relationship between the circadian system, the immune system, and sleep (193–202). It follows that circadian disruption has been associated with immune disorders (203). In this Review, we highlight the relationship between circadian disruption, asthma (204), and other allergic diseases (205).

COVID-19

The COVID-19 pandemic offers an example of the interrelationship between human health and circadian disruption in immunology. Specifically, circadian misalignment, such as shift work, might increase the risk of being infected with SARS-CoV-2 (206–208). Although there are no data specific to COVID-19, time of day of infection with pathogens appears to alter susceptibility (209, 210). Upon infection with SARS-CoV-2, severe disease (like other severe illnesses) appears to induce circadian disruption by obliterating normal rest/activity rhythms (211). It is speculated that active SARS-CoV-2 infection might also dampen melatonin rhythm and alter timing of clock gene expression, resulting in misalignment and upregulation of the damaging inflammatory cytokine expression (212). In terms of therapy, the circadian system might have the potential to improve COVID-19 disease outcomes (212–214). For example, morning administration of antiviral therapy (darunavir/ritonavir) might be more effective in reducing inflammation, as measured by biomarker C-reactive protein (215).

Asthma

In *Clock*- or *Bmal1*-mutated mice, misalignment between clock genes and organs results in defects of the epithelial barrier of the skin (216), intestine (217), and airways (218). Furthermore, deletion of a downstream target of *Bmal1*, *Rev-Erba*, results in clock gene and cellular misalignment, leading to diminished antiviral responses and increased allergen responsiveness, translating to an asthma-like phenotype (219, 220). Misalignment between environmental rhythms and the SCN also appears to increase asthma risk in shift workers (OR = 1.23, 95% CI = 1.03–1.46) (221). The mechanism behind the increased risk for asthma in shift workers might also be one of genetic susceptibility to circadian disruption. For example, there is an association of clock gene variants, such as *TIMELESS*, with asthma in children (222), and higher odds of asthma are noted in morning-chronotype shift workers who had to work nights (221). This argues for the consideration of circadian chronotype in the design of personalized shift work schedules to improve health. Importantly, hypoxia in asthma or in other conditions is one disease-induced factor that appears to further promote circadian misalignment owing to tissue-specific, time-dependent transcriptional changes (223).

Although there are limited data, time can be harnessed to personalize therapy for asthma, via chronotherapy (Figure 2). For example, the package insert for montelukast, a leukotriene receptor antagonist therapy, suggests that evening administration might improve efficacy (224). Paying attention to time can even adjust the risk of side effects from therapies. Bavishi et al. described an increased rate of cutaneous reaction to allergy shots (subcutaneous allergen immunotherapy) in the afternoon compared with morning (225).

Other allergic diseases

Here we describe other common allergic diseases, such as anaphylaxis (226), atopic dermatitis (4), and allergic rhinitis (227). In a mouse model of passive cutaneous anaphylaxis (226), multiple mechanisms of circadian disruption lowered the threshold for allergic reaction and altered the rhythmic pattern of reactions; these included mutations of *Per2*, mast cell-specific *Clock* mutation, and time-restricted feeding (during the rest interval)

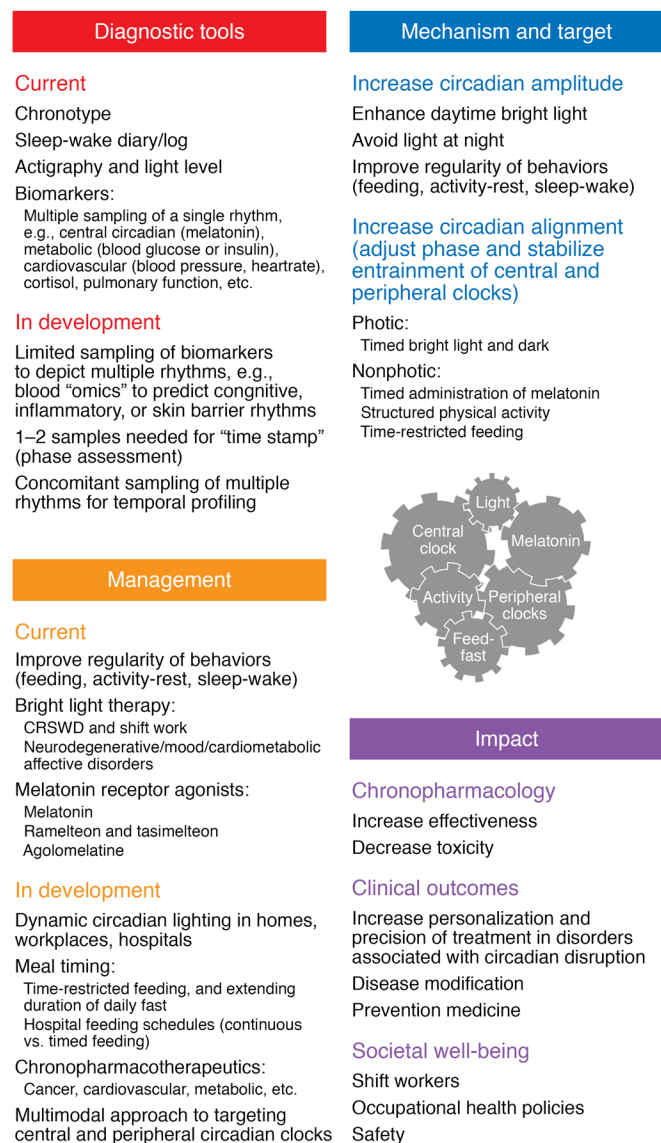


Figure 2. A multimodal approach to address circadian disruption and its effect on health. Diagnostic approaches, including current tools, rely primarily on self-reported and behavioral measures and require time-intensive multiple sampling of biomarkers to obtain a 24-hour profile. However, tools in development seek to assess circadian phase using a single time sample of multiple rhythms. Circadian-based therapies, such as timed bright light exposure and exogenous melatonin, are commonly used to align the phase of external/behavioral rhythms with endogenous central and peripheral clocks. In addition, time-restricted feeding can enhance alignment among peripheral clocks and improve metabolic health. In development are multimodal approaches to target central and peripheral clocks with dynamic circadian lighting, time-restricted feeding and drugs to align and stabilize circadian entrainment, and chronopharmacotherapy to optimize efficacy and tolerability of medications. CRSWD, circadian rhythm sleep wake disorder.

has similar effects to corticosteroid, i.e., there is suppression of IgE-mediated allergic reactions in mouse mast cells and decreased basophil reactivity in human basophils of allergic rhinitis patients (237). This suggests an exciting role for circadian therapeutics in targeting allergic and immunologic disease. In a mouse model of pulmonary fibrosis, drugging the clock gene by inhibition of *Rev-Erba* might inhibit myofibroblast activation and potentially prevent fibrosis (238).

Conclusion

The accumulating bench-to-bedside-to-population research highlights the magnitude and interrelatedness of circadian disruption in human disease, and the opportunity for circadian-based approaches to prevent and optimize individual and societal health. In addition to disease-specific effects of circadian disruption, transdiagnostic effects are noted as a result of particular sleep/circadian constructs (e.g., late/evening chronotype, social jet lag). Given this, adverse health outcomes are unlikely to occur in isolation, and therapeutic strategies such as melatonin supplementation or bright light therapy might be used concordantly to treat multiple conditions. However, few clinical trials have been conducted with only weak treatment recommendations for circadian disorders.

The discovery of the genetic underpinnings of circadian rhythms, together with the findings that this clock genetic machinery exists in virtually all cells and tissues and regulates metabolic, immune, and neural processes and pathways, has fundamentally changed our view of the importance of circadian health in medicine. Circadian medicine is a relatively new concept, but is rapidly gaining momentum throughout the world. In parallel with translational research, there is a clear need to identify biomarkers that are clinically relevant, but also scalable at the population level. Rapid development of technology for wearables and environmental sensors, coupled with artificial intelligence, will allow us to assess circadian timing of multiple rhythms at different organizational levels in real time to gain insight into the interaction between environment, behavior, and central and peripheral clocks in health and disease. Finally, clinical trials and a narrowing of the bench-to-bedside gap are needed. For example, although about 1000 genes are involved as drug targets or in drug metabolism/transport (239), only a few of the most commonly prescribed treatments in medicine have time-of-day indications for dosing (240). This is not

in mice (228–230). This supports the hypothesis that circadian disruption due to multiple mechanisms might increase the risk of severe allergic reaction.

Because of the nighttime predominance of allergic disease (4), the degree of nocturnal disruption defines disease severity level for asthma and allergic rhinitis and directly impacts treatment decisions by physicians (231–233). Targeting of allergic disease should include assessment of timing of symptoms, such as asthma flare, classically around 4 am (the timing of lung function nadir and increased lymphocyte counts in the lung) (234, 235). Allergic rhinitis symptoms peak between 4 and 6 am, a time when pollen counts are high; patient is recumbent (sleeping); and when inflammatory rhythms are upregulated — all of which can increase edema of the upper airway (227). Atopic dermatitis (eczema) symptoms also appear to peak in the evening, with overnight scratching peaking approximately 3 hours after bedtime (236).

Preclinical human testing has also garnered evidence supporting the therapeutic strategy of “drugging the clock,” such as via a selective casein kinase inhibitor. In mast cells, this

because the therapies do not work better with timed administration, but rather because clinical trials are lacking to determine optimal timing. We have a good blueprint for how to integrate circadian timing in medicine, and now is the time to move disease-specific research forward.

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