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Authors

Truong, Kimberly K
Lam, Michael T
Grandner, Michael A
et al.

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Timing Matters: Circadian Rhythm in Sepsis, Obstructive Lung Disease, Obstructive Sleep Apnea, and Cancer

Kimberly K. Truong[1], Michael T. Lam[2], Michael A. Grandner[3], Catherine S. Sassoon[1,4], and Atul Malhotra[5]

[1]Department of Medicine, University of California, Irvine, Orange, California; [2]Department of Medicine, University of California, San Diego, San Diego, California; [3]Department of Psychiatry, University of Arizona, Tucson, Arizona; [4]Pulmonary and Critical Care Section, Veterans Affairs Long Beach Healthcare System, Long Beach, California; and [5]Division of Pulmonary, Critical Care, and Sleep Medicine, University of California, San Diego Health Sciences, San Diego, California

Abstract

Physiological and cellular functions operate in a 24-hour cyclical pattern orchestrated by an endogenous process known as the circadian rhythm. Circadian rhythms represent intrinsic oscillations of biological functions that allow for adaptation to cyclic environmental changes. Key clock genes that affect the persistence and periodicity of circadian rhythms include *BMAL1/CLOCK*, *Period 1, Period 2*, and *Cryptochrome*. Remarkable progress has been made in our understanding of circadian rhythms and their role in common medical conditions. A critical review of the literature supports the association between circadian misalignment and adverse health consequences in sepsis, obstructive lung disease, obstructive sleep apnea, and malignancy. Circadian misalignment plays an important role in these disease processes and can affect disease severity, treatment response, and survivorship. Normal inflammatory response to acute infections, airway resistance, upper airway

collapsibility, and mitosis regulation follows a robust circadian pattern. Disruption of normal circadian rhythm at the molecular level affects severity of inflammation in sepsis, contributes to inflammatory responses in obstructive lung diseases, affects apnea length in obstructive sleep apnea, and increases risk for cancer. Chronotherapy is an underused practice of delivering therapy at optimal times to maximize efficacy and minimize toxicity. This approach has been shown to be advantageous in asthma and cancer management. In asthma, appropriate timing of medication administration improves treatment effectiveness. Properly timed chemotherapy may reduce treatment toxicities and maximize efficacy. Future research should focus on circadian rhythm disorders, role of circadian rhythm in other diseases, and modalities to restore and prevent circadian disruption.

Keywords: chronobiology disorders; sepsis; obstructive lung disease; obstructive sleep apnea; neoplasms

Endogenous rhythms that approximate 24 hours play important regulatory functions in human biology and physiology (1). Because these rhythms likely evolved as a response to the environmental changes between day and night, these rhythms have been given the name circadian (i.e., circa = around, dia = day) (2). A key oscillation of these circadian rhythms in humans is the sleep-wake cycle, which not only emerges endogenously but also provides feedback

to the circadian system (1). Central influences to this system are governed by a central pacemaker in the suprachiasmatic nuclei in the hypothalamus and subsidiary peripheral pacemakers in nearly every cell of the body (3, 4). Many circadian rhythms are autonomous and self-sustained by transcriptional–translational antiregulatory loops that generate molecular oscillations of clock genes, such as *BMAL1*, *CLOCK*, *Period 1*, *Period 2*, and *Cryptochrome* (4). It is evident that interactions among clock

components vary in a tissue-specific manner.

Environmental cues such as light, feeding-fasting cycles, and social interactions exert strong influences on both central and peripheral clocks (5, 6). The rhythmic oscillation of sleep and wakefulness, in the context of other circadian processes, represents an important physiologic phenomenon that serves to synchronize biologic functions with each other and with the external environment (Figure 1A).
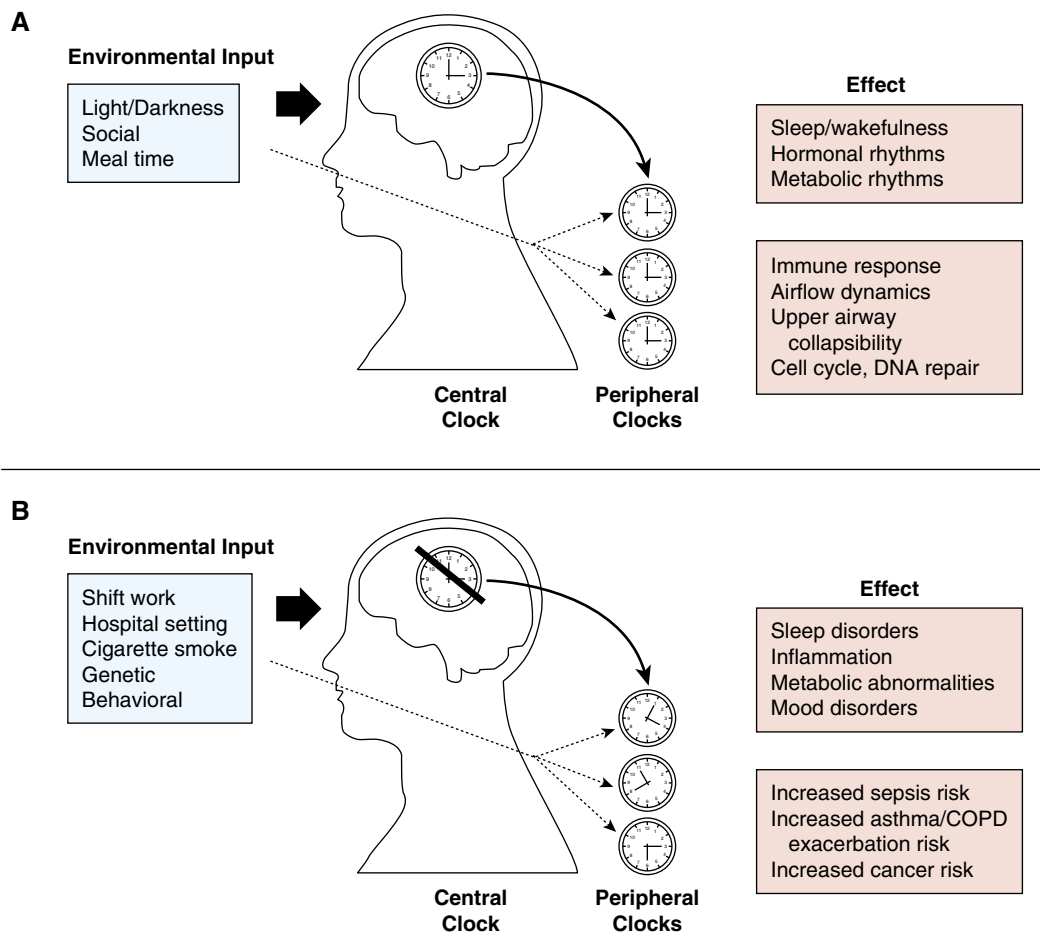
Figure 1. Simplified depiction of (*A*) normal circadian rhythm and its inputs and effects, and (*B*) disrupted circadian rhythm and its inputs and effects. Environmental inputs such as light/darkness, socialization, and meals influence central and peripheral circadian clocks. Disrupted circadian clocks may lead to various negative health outcomes. COPD = chronic obstructive pulmonary disease.

In addition to synchronizing the sleep–wake cycle, circadian rhythms play an important role in the onset and severity of diseases. Many diseases have well-documented diurnal variability. Myocardial infarction, ischemic stroke, and sudden cardiac death all peak in frequency between the hours of 8:00 A.M. and 10:00 A.M., compared with the hours between 9:00 P.M. and 11:00 P.M. (7–9). Many other diseases, including hypertension, seizures, and asthma, have been shown to exhibit a day–night variation in disease presentation as well (10).

Much of the current evidence demonstrating negative health outcomes from circadian rhythm disruption in real-world situations is from studies of shift workers (Figure 1B). By virtue of the difficulty of maintaining nonstandard schedules, shift workers are often sleep deprived in addition to being exposed to a misalignment between internal and external circadian cues. Sleep loss affects neurocognitive performance (11, 12), behavior (13), and cardiometabolic disease risk (14). Furthermore, sleep loss leads to changes in circadian rhythms in central and peripheral tissues in association with disruptions of energy metabolism (15). In short- and long-term studies of shift workers, unfavorable alterations in lipid and carbohydrate metabolism, insulin resistance, growth hormone, and corticosteroid secretion patterns (16–18) and increased risk of cancer have been reported (19–21). Similar to shift workers, patients in the intensive care unit (ICU) also experience circadian rhythm disruption due to noise, patient care interaction, mechanical ventilation, pain,

medications, artificial light, and the illness itself (22, 23).

The goal of this review is to describe the circadian rhythmic processes related to common medical conditions: sepsis, obstructive lung diseases (asthma and chronic obstructive pulmonary disease [COPD]), obstructive sleep apnea (OSA), and malignancy, with the hope of improving therapeutic efficiencies and patient care. We briefly review the normal circadian rhythm physiology related to the disease and the clinical relevance of circadian rhythm disruption during disease state. The review also highlights the therapeutic implications of the sleep–wake cycle and chronotherapy—a concept of delivering treatment on the basis of the circadian timing of the disease process to maximize therapeutic efficacy and minimize toxicity.

Sepsis

Normal Circadian Rhythm of Immune Cells

Like other cell types in the body, immune cells have an endogenous circadian clock. Light and dark cycles influence the immune functions of natural killer cell activity, lymphocyte proliferation, and monocyte proliferation (24, 25). Levels of inflammatory mediators such as IL-6, tumor necrosis factor, and IFN-γ have a diurnal variation (26). Eight percent of all mRNA transcripts in macrophages have a 24-hour period oscillating expression. This translates to a concept called "circadian gating." The capacity of a cellular function, such as the magnitude of immune response to pathogen, becomes time-dependent throughout the day (27, 28). Toll-like receptor 9, a recognition receptor for DNA of bacterial and viral pathogens, has been observed to peak during activity phases of mammals and reach a nadir during sleep. When sepsis was induced in mice by colon puncture, more severe forms of sepsis, increased number of bacterial burden, and earlier mortality were observed when toll-like receptor 9 expression was highest (29).

Figure 2. Circadian effect on mortalities from animal model of septic shock. Mortality rate from septic shock exhibited a strong diurnal pattern dependent on the timing of the septic challenge (*black line*) (31). The diurnal variation diminished when subjects were housed in conditions with constant lighting (*red dashed line*) (39). Knockout of *Period 2* also abolished the diurnal variation even when the subjects were housed in normal 12-hour light/12-hour dark conditions (26).

Circadian Rhythm and Sepsis

Sepsis is a complex syndrome of systemic inflammatory response when the host immune system recognizes pathogen-specific molecules. This process leads to rapid activation of proinflammatory cascades in promoting pathogen clearance through complement pathways, mobilization of leukocytes, phagocytosis, and release of reactive oxygen species and antimicrobial peptides. Activation of antiinflammatory processes is equally important, as unchecked inflammation leads to hypotension, multiorgan failure, and death (30).

The circadian effect on sepsis is well documented in controlled animal experiments. Halberg and colleagues (31) tested the circadian effect of sepsis by inoculating equivalent doses of endotoxin in mice at different times of the day. When endotoxin was injected at 4:00 P.M., the survival from septic shock was less than 20%. When the same dose of endotoxin was given at 12:00 A.M., the survival was greater than 90% (31) (Figure 2). This finding
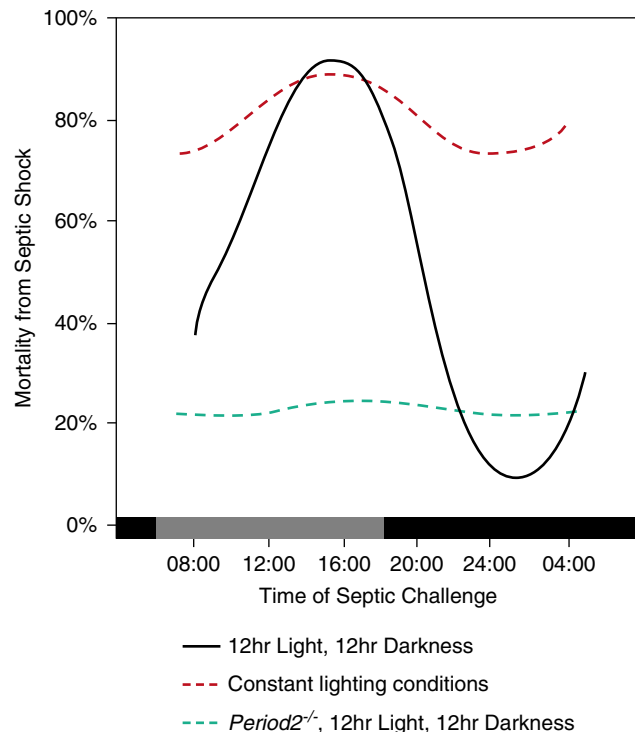
seems to be dependent on the circadian physiology, because genetic disruption of *Period 2*, a key circadian clock gene, abolishes the diurnal effect of endotoxin on survival (26). Melatonin, a major hormone of circadian rhythm, is also an important mediator of the inflammatory response seen in sepsis. Deletion of melatonin receptors in experimental sepsis generated a greater inflammatory response in mice (32). Exogenous melatonin increased survival of sepsis in a melatonin receptor–dependent fashion (33).

How sepsis affects the circadian clock is still under investigation. Circadian rhythm may be suppressed during acute inflammatory illness, as evidenced by suppression of circadian clock genes in peripheral leukocytes for at least 17 hours after inoculation of endotoxin in mice (34). This finding may explain why diurnal variation of melatonin was blunted in ICU patients with sepsis compared with ICU patients without sepsis (35). Furthermore, injection of endotoxin disrupted sleep by decreasing non-REM sleep and doubling

the amount of wakefulness during the night (36).

Genome-wide transcriptional profiling of lung tissues showed cytokine production and leukocyte trafficking exhibited a circadian rhythm (37). Genetic knockouts of *BMAL1*, a prototypical circadian clock gene, altered the rhythmic expression of IFN-γ and myeloperoxidase in granulocytes. *BMAL1* is also important for the circadian pattern of granulocyte infiltration into the endotoxemic lungs (26, 37).

Sleep deprivation may also impact risk and severity of sepsis (Figure 1B). Animals undergoing septic challenge are less likely to recover when their 12/12 hour light/dark cycle is replaced by constant light or constant darkness (38, 39). In humans, systemic C-reactive protein, IL-1, and IL-6 were increased in sleep-deprived individuals (40–42). Individuals deprived of 24 to 88 hours of sleep had impaired immediate antibody response to hepatitis and influenza vaccines, suggesting an attenuated

antigen-specific immune defense with sleep disruption (43, 44). Collectively, these studies highlight circadian clock realignment and sleep quality improvement as a crucial role in therapy in sepsis.

Implications on Treatment of Sepsis

Restoring the circadian rhythm in patients is an underused aspect in sepsis treatment. Melatonin is one of the main endogenous mediators of the circadian rhythm, with beneficial antioxidative and antiinflammatory effects. A randomized controlled trial among 24 ICU patients with respiratory failure showed oral melatonin to increase sleep time and quality (45).

Melatonin also has effective antioxidative and antiinflammatory effects. In a small randomized controlled trial of 20 infants with sepsis, Gitto and colleagues (46) assessed the antiinflammatory effect of melatonin. Blood leukocyte count and absolute neutrophil count were significantly decreased in infants with sepsis receiving 20 mg melatonin (47). Infants with sepsis treated with melatonin had an 80% decrease in C-reactive protein compared with control infants. A higher proportion of melatonin-treated infants had full recovery from sepsis within 48 hours. In a second study, IL-6, IL-8, and tumor necrosis factor-α levels were significantly lower in melatonin-treated newborns with respiratory distress syndrome, further supporting the antiinflammatory effects of melatonin (48). Melatonin has no major toxicity and is rapidly cleared at high doses after oral administration (46–49). Melatonin may be a highly promising tool in the ICU to promote healthy circadian rhythm, improve immunity, and improve sepsis outcomes.

Regarding light therapy in the ICU, various studies have failed to show objective benefit. Wunsch and colleagues (50) showed that the presence of a window in an ICU did not improve functional status, length of stay, or mortality in 789 critically ill patients with subarachnoid hemorrhage. However, the authors mentioned limitations of their study included not taking into account sedation, delirium, limited light exposure after transferring out of the ICU, and a study cohort with acute brain injury, which may make external stimuli less important. Another study reported that in patients with severe sepsis,

outdoor light did not entrain melatonin secretion pattern (51). The authors noted that the environmental light levels were low (maximum of 200 lux). The white light intensity most reliably shown to entrain the circadian rhythm is 10,000 lux for at least 30 minutes or 2,500 lux for at least 1 hour (52–54).

Obstructive Lung Disease

Circadian Rhythm in Asthma

Nighttime worsening of asthma has been historically recognized. A Roman physician in the fifth century, Caelius Aurelianus, noted: "On the heavy breathing and wheezing which is called Asthma by the Greeks, this disease is a burden…during the winter and at night more than during the day or the spring" (55). Clinically, asthma exacerbations frequently occur in the early hours of the morning, around 4:00 A.M. Dyspnea-induced nighttime awakening occurs in more than 75% of respondents in a large survey of individuals with asthma (56). In a 1-year review and a 2.5-year review of deaths due to asthma in adults, approximately 70% of asthma-related deaths occurred between 12:00 A.M. and 6:00 A.M. (57, 58).

Physiologically, airway caliber and inflammation also follow circadian patterns. Peak expiratory flow (PEF) as a measure of airway obstruction has been shown to fluctuate over a 24-hour period in both healthy patients and patients with asthma. Airway obstruction worsens during the night, with patients with asthma having a 51% larger change in PEF during nighttime than control patients (59). In addition, Bonnet and colleagues (60) revealed the circadian variation of airway responsiveness, with maximum bronchial responsiveness to methacholine and histamine bronchial challenge at 3:00 A.M. and 4:00 A.M. When transbronchial biopsies were performed in patients with and without asthma at 4:00 P.M. (when lung function is optimal) and 4:00 A.M. (when airflow limitation is highest), the tissue biopsies of nocturnal patients with asthma had a pronounced circadian variation in alveolar eosinophil number per unit volume, with a significantly higher eosinophil number at 4:00 A.M. than 4:00 P.M. (61). Bronchoalveolar lavage (BAL) studies show higher numbers of macrophages, neutrophils, lymphocytes,

and CD4$^+$ T cells have also been reported in alveolar tissue at 4:00 A.M. than at 4:00 P.M. (62, 63). The increase in inflammatory cells correlates with the overnight increase in airflow obstruction.

Sleep deprivation alone does not have an effect on circadian variation of lung function, suggesting that an endogenous circadian pacemaker is responsible for the diurnal variations (64). Many other factors are associated with the nocturnal exacerbation of asthma (Figure 3). The robust circadian rhythms of cortisol dip during the night and the vagal tone increase during sleep are believed to contribute significantly to the diurnal variation in airway inflammation and reactivity (65, 66). Cortisol binding and steroid responsiveness appear impaired in nocturnal asthma, resulting in impaired endogenous antiinflammatory processes (67). Other factors, such as late phase response to allergen exposure, nighttime predominance of gastroesophageal reflux, sleep apnea, and lung volume changes during sleep, may also play a role in nocturnal asthma symptoms (68–70).

Chronotherapy for Asthma

Chronotherapy provides a reasonable approach to treatment of asthma by taking into account the diurnal nature of the disease (Table 1). Systemic corticosteroid therapy has been found to be most efficacious for nocturnal asthma when administered at 3:00 P.M. In a study by Beam and colleagues (71), prednisone at 50 mg was administered to patients with asthma at 8:00 A.M., 3:00 P.M., or 8:00 P.M., and FEV$_1$ and BAL fluid were studied. The 3:00 P.M. administration of prednisone was associated with significantly increased nocturnal FEV$_1$ and decreased neutrophils, eosinophils, lymphocytes, and macrophages in the BAL fluid. The 8:00 A.M. and 8:00 P.M. prednisone administration were ineffective in improving FEV$_1$. Another study administered methylprednisolone at a dose of 40 mg to patients with asthma at 3:00 A.M., 7:00 A.M., 3:00 P.M., or 7:00 P.M. and found that administration at 3:00 P.M. led to greatest increase in PEF (72).

Several studies have looked at chronotherapy of inhaled corticosteroids. Triamcinolone of 800 μg administered at 3:00 P.M. to 5:30 P.M. was found to be equivalent to conventional 200 μg four times per day (73, 74). Furthermore, triamcinolone of 800 μg at 8:00 A.M. did not
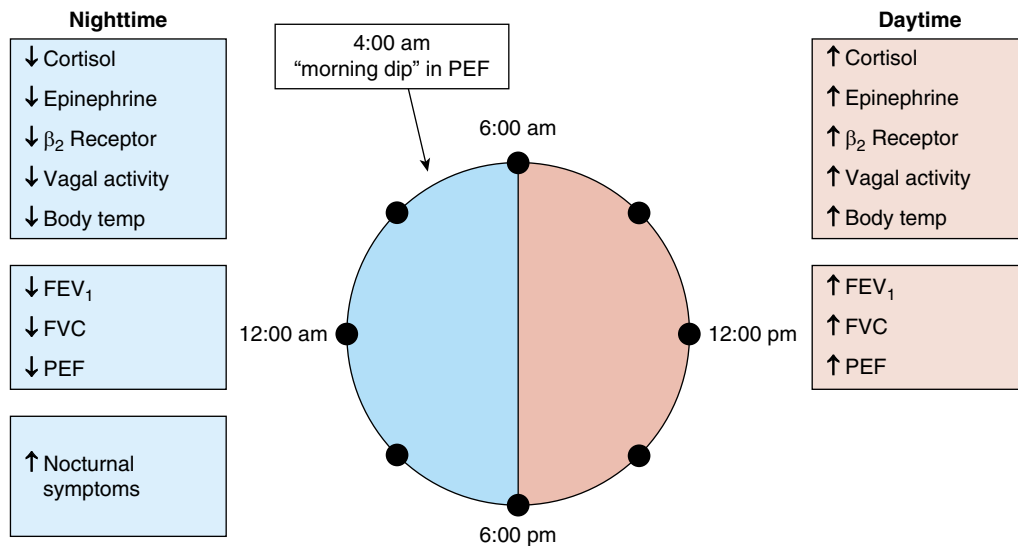
Figure 3. Diurnal depiction of neuroendocrine factors and airway dynamics associated with nocturnal asthma exacerbations. PEF = peak expiratory flow; Temp = temperature.

improve morning or evening peak expiratory flow rate (74). Despite giving a higher dose at one time, there were no differences in adrenocortical suppression or systemic side effects between the groups. Similarly, the efficacy and safety profile of inhaled beclomethasone dipropionate for patients with moderate asthma is the same when administered twice per day (conventional) or as a single dose in the afternoon or at bedtime (75). For mometasone furoate, the effect of evening regimen at 200 μg on FEV$_1$, morning PEF, FVC, and forced expiratory flow between 25% and 75% of vital capacity (FEF$_{25-75\%}$) was equivalent to 200 μg twice daily. Of note, when mometasone furoate was given in the morning at 200 μg, it demonstrated no differences compared with placebo (76, 77).

The concept of chronotherapy has also been shown in other treatment agents for asthma. For long-acting β$_2$-agonist salmeterol, 100 μg given at night is as effective as 50 μg twice a day in averting nighttime bronchial asthma attacks in otherwise difficult-to-control patients (78). The leukotriene receptor antagonist montelukast improves FEV$_1$ when dosed in the evening compared with the morning (79). Once-daily dosing in the evening of theophylline, compared with twice-daily and round-the-clock dosing, improves both asthma symptoms and PEF (80). Inhaled tiotropium showed no significant differences in effect on airway caliber when administered once daily in the morning versus the evening (81). However, the long half-life of tiotropium may mask its circadian-dependent effects.

Understanding the diurnal nature of the pathophysiology and the diurnal effect

Table 1. Evidence for chronotherapy in asthma by medication class

Class	Medication	Suggested Time	Effect	Reference
Systemic steroids	Oral prednisone	3:00 P.M.	Significantly increased nocturnal FEV$_1$ when compared with 8:00 A.M. and 8:00 P.M. administration	71
		3:00 P.M.	Decreased inflammatory cells in BAL fluid	71
	Intravenous methylprednisolone	3:00 P.M.	Greatest increase in PEF when compared with 3:00 A.M., 7:00 A.M., and 7:00 P.M. administration	72
Inhaled steroids	Triamcinolone	3:00 P.M.	Once per day at 3:00 P.M. equivalent to four times daily	73, 74
	Beclomethasone	Afternoon	Single dose in afternoon same efficacy as twice daily	75
	Mometasone	Evening	Significantly increased FEV$_1$, morning PEF, FVC, FEF$_{25-75\%}$; morning dose and placebo showed no difference	76, 77
Long-acting β$_2$-agonist	Salmeterol	Evening	One dose at night is equivalent to twice-daily dosing	78
Leukotriene receptor antagonist	Montelukast	Evening	Improved FEV$_1$ when compared with morning administration	79
Inhaled antimuscarinic	Tiotropium	N/A	No difference between morning and evening administration	81

Definition of abbreviations: BAL = bronchoalveolar lavage; FEF$_{25-75\%}$ = forced expiratory flow between 25% and 75% of vital capacity; N/A = not applicable; PEF = peak expiratory flow.

of treatment is important in management of asthma. When assessing response to therapy, knowing the timing of when patients take their medications is crucial, as treatment at certain times of the day may not be effective (74, 76). Furthermore, having to take only one dose per day significantly simplifies treatment regimen. This approach helps patients with adherence.

Circadian Rhythm in COPD

The link between circadian rhythm and chronotherapy in COPD is less established, especially given the heterogeneous nature of the disease. Similar to asthma, the diurnal variation in symptom severity has been observed during COPD exacerbations, with elevated risk for intubation during early morning hours in the emergency department (82). Exciting research is emerging showing environmental risks of COPD, such as tobacco smoking, can affect components of the circadian clock (83), which may lead to chronic inflammatory responses (84). As future studies elucidate the interrelationship between circadian rhythm and COPD, new therapeutic targets and approaches may emerge in COPD treatment.

OSA

OSA affects conservatively 10% of the U.S. population and is defined by obstruction of the upper airway during sleep, leading to chronic intermittent hypoxemia and sleep fragmentation. OSA has also been linked to metabolic syndrome, hypertension, stroke, and cancer. Animal models that mimic conditions of OSA show altered metabolic, inflammatory, and autonomic changes with associated autonomic risk (85). The impact of the circadian system on OSA is unclear, but it may influence apnea occurrence and duration in the early morning compared with late afternoon. In two separate studies, higher upper airway critical closing pressure (86) and prolonged apnea events (87) were consistently found to be greater in the morning than in the evening or afternoon. The mechanism is still unclear, but this knowledge provides a possible novel therapeutic modality for sleep apnea. Future studies to examine circadian rhythms in patients with OSA and timing of cardiometabolic risk incidence in OSA are needed (88).

Cancer

Circadian Rhythm Disruption and Tumorigenesis

Cell cycle regulation, apoptosis, and DNA repair, among other important processes for tumorigenesis, follow circadian rhythms. This notion has been shown in rapidly dividing cells of skin, gut, pancreas, reproductive organs, and bone marrow in humans and animals (89–94). Disruption of the circadian rhythm is linked with deregulated cell proliferation and the progression of cancer (95, 96). A large number of animal studies have shown cancer development in animal models of circadian disruption (94, 97–100). It was reported that both pancreatic carcinoma and osteosarcoma xenografts grew at a faster rate in animals with suprachiasmatic nuclei lesions (101). In humans, *BMAL1/CLOCK*, *Period 1*, and *Period 2* are human circadian clock genes found to maintain a rhythmic pattern of cell proliferation and repair of DNA damage (94, 100–102).

A recent case-cohort study looking at lung cancer did not reveal increased risk among rotating night shift workers (103); however, multiple international prospective cohort studies have shown an increased risk in breast cancer and prostate cancer in night shift workers (104–107). The World Health Organization's International Agency for Research on Cancer concludes, "shiftwork that involves circadian disruption is probably carcinogenic to humans" (Group 2A classification) (108). In 2009, night shift workers with breast cancer were awarded compensation in Denmark (107). More recently, an American Medical Association policy statement recognized circadian disruption due to occupational light as a cancer risk and has encouraged lighting technologies at home and at work to minimize circadian disruption (109).

Future prospective investigations are important to solidify current knowledge and shed light on pathophysiology of circadian disruption on cancer risk in humans.

Chronotherapy for Cancer

Because most chemotherapy agents target a certain stage in the cell cycle, properly timed chemotherapy delivery may reduce treatment toxicities and maximize efficacy (Figure 4). Several clinical trials looking at various chemotherapy agents showed promising results in reducing toxicity and improving treatment efficacy (Table 2). Two phase III trials showed chronomodulated chemotherapy reduced the incidence of severe mucositis by 80% and halved the incidence of peripheral neuropathy (110, 111). In breast cancer,
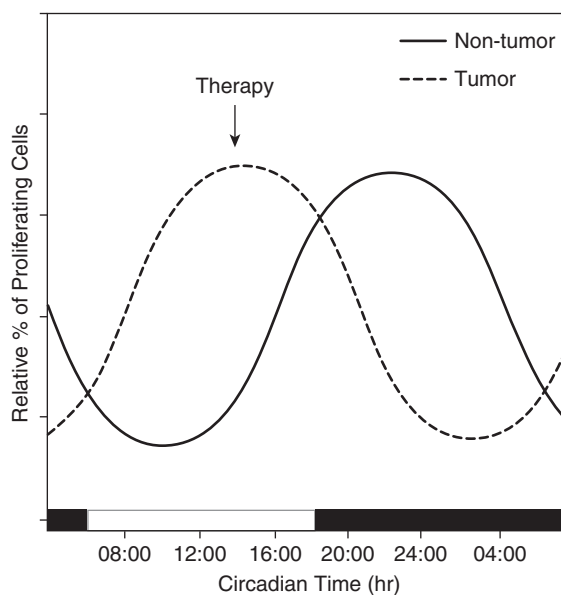
Figure 4. Concept of chronotherapy in cancer therapy. The timing of proliferation is different between tumor and nontumor cells (95). Chemotherapy with time-specific delivery (*arrow*) maximizes therapeutic potential while minimizing effect on normal cells.

Table 2. Evidence for chronomodulated chemotherapy by cancer type

Cancer Type	Trial Design (No. of Patients)	Intervention	Endpoint	Results	References
Breast	Randomized, multicenter (90)	Time of delivery of vinorelbine	Toxicity	Leukopenia significantly less if maximum delivery at 5:00 P.M.	112
Colorectal	Randomized, multicenter (92)	5-FU + LV 4:00 A.M., oxaliplatin 4:00 P.M. vs. continuous infusion	Toxicity	Severe stomatitis decreased by fivefold with chronotherapy schedule (18 vs. 89%, $P < 0.001$)	110
	Randomized, multicenter (186)			Severe stomatitis decreased by fivefold with chronotherapy schedule (14% vs 76%, $P < 0.0001$)	111
	Randomized, multicenter (92)		Tumor response rate	Response rate significantly higher in chronotherapy schedule (53 vs. 32%, $P < 0.05$)	110
	Randomized, multicenter (186)			Response rate higher in chronotherapy schedule (51 vs. 29%, $P = 0.003$)	111
	Phase III (564)		Survival	Risk of death in men decreased by 25% with chronotherapy (18 vs. 21 mo, $P = 0.02$) Risk of death in women increased by 38% with chronotherapy (19 vs. 16 mo, $P = 0.03$)	118
Endometrial	Phase II (33)	Doxorubicin 6:00 A.M., cisplatin 6:00 P.M.	Toxicity	Well tolerated with 60% response rate	117
	Phase III (342)		Efficacy	No difference in response rate (46% in standard group vs. 49% in chronotherapy group, $P = 0.26$) Decreased leukopenia (75% in standard group, 64% in chronotherapy group; $P < 0.05$), and granulocytopenia (81% in standard group, 74% in chronotherapy group; $P < 0.05$)	113
Lymphoblastic leukemia	Retrospective cohort (118)	6-MP and MTX before 10:00 A.M. vs. after 5:00 P.M.	Disease-free survival	Increased long-term survival for evening group; risk of relapse 2.6 times greater for morning group	114
Pancreas	Phase I (16)	5-FU 4:00 A.M. vs. continuous infusion	Toxicity	Acceptable toxicity at 4:00 A.M.	115
Rectal	Single center, nonrandomized (28)	5-FU administered at 9:00 P.M. × 5 d, with radiation, followed by surgery	Toxicity, efficacy	High response rate with minimal toxicity; 7% with grade III toxicities, 52.6% with significant downstaging	116

Definition of abbreviations: 5-FU = fluorouracil; 6-MP = 6-mercaptopurine; LV = leucovorin; MTX = methotrexate.

leukopenia was significantly less common if chemotherapy was delivered at 5:00 P.M. compared with other times of day (112). Studies of patients with rectal cancer, pancreatic cancer, endometrial cancer, and lymphoblastic leukemia also demonstrate the safety of chronomodulated chemotherapy and support the benefits of minimized toxicity and positive response rate (113–117). One phase III study found that chronomodulated chemotherapy for patients with metastatic colon cancer had a stark sex difference: risk of death increased by 38% in women and decreased by 25% in men (118). Rigorous studies of chronomodulated therapy will help identify patients who could receive maximal benefit from therapy.

As more is learned about chronotherapy for oncologic patients, personalized chronotherapy may become a central goal in the field of oncology. After decades of chronotherapy research, technologic advances now allow chronomodulated drug delivery through programmable pumps and oral multiunit preparations (119, 120).

Table 3. Summary

Many physiology and pathophysiology of disease processes exhibit circadian patterns, involving behavioral or functional variations that cycle every 24 h.
Immune responses due to sepsis vary at different times of the day. Circadian disruption, demonstrated by genetics models and sleep deprivation in humans, affects the severity of immune response.
Airflow obstruction tends to worsen in the early morning, corresponding to circadian changes of pulmonary function and abundance of immune cells in the airway.
Upper airway collapsibility and apnea length follow an endogenous circadian pattern in obstructive sleep apnea and are worse in early morning.
Many properties of tumorigenesis, such as cell proliferation and DNA repair, are regulated in a circadian fashion. Chronic circadian disruption in shift workers increases cancer risk.
Chronotherapy, the practice of giving treatment at specific times, has been shown to be beneficial, with reduced toxicity in treatment of asthma and chemotherapy for various malignancies.

Conclusions

Remarkable progress has been made in the understanding of circadian rhythms in common but debilitating medical conditions, including sepsis, obstructive lung disease, cancer, and OSA (Table 3). Circadian rhythms affect these conditions, misalignment of circadian rhythms results in adverse consequences, and direction of therapy toward entrainment of healthy circadian rhythms results in increased positive outcomes. Specifically, chronotherapy is a promising approach.

Future Research

Circadian rhythm disruption is common, and the health consequences due to circadian disruption cannot be ignored. The mechanisms of circadian disruption leading to health consequences in humans are not fully understood, and there is a paucity of therapeutic options for correcting misalignment or deentrainment of patients' circadian rhythms. Future translational and clinical research in circadian rhythm disorders on modalities to restore or prevent circadian disruption is indispensable to optimizing and personalizing medical treatments. ■

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