



Review

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Readjustment of circadian clocks by exercise intervention is a potential therapeutic target for sleep disorders: a narrative review

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[Purpose] Circadian clocks are evolved endogenous biological systems that communicate with environmental cues to optimize physiological processes, such as the sleep-wake cycle, which is nearly related to quality of life. Sleep disorders can be treated using pharmacological strategies targeting melatonin, orexin, or core clock genes. Exercise has been widely explored as a behavioral treatment because it challenges homeostasis in the human body and affects the regulation of core clock genes. Exercise intervention at the appropriate time of the day can induce a phase shift in internal clocks. Although exercise is a strong external time cue for resetting the circadian clock, exercise therapy for sleep disorders remains poorly understood.

[Methods] This review focused on exercise as a potential treatment for sleep disorders by tuning the internal circadian clock. We used scientific paper depositories, including Google Scholar, PubMed, and the Cochrane Library, to identify previous studies that investigated the effects of exercise on circadian clocks and sleep disorders.

[Results] The exercise-induced adjustment of the circadian clock phase depended on exercise timing and individual chronotypes. Adjustment of circadian clocks through scheduled morning exercises can be appropriately prescribed for individuals with delayed sleep phase disorders. Individuals with advanced sleep-phase disorders can synchronize their internal clocks with their living environment by performing evening exercises. Exercise-induced physiological responses are affected by age, sex, and current fitness conditions.

[Conclusion] Personalized approaches are necessary when implementing exercise interventions for sleep disorders.

[Keywords] circadian clocks, sleep disorders, internal clock entrainment, external time cues, chronotypes, chrono-exercise

INTRODUCTION

Circadian clocks are endogenous biological timekeepers that control the daily cycles of various body systems ranging from molecular mechanisms to behavioral functions in living organisms. The term “circadian” is derived from the Latin words “circa” and “dies,” translating to “around the day.” Most organisms have evolved in environments characterized by a 12 h light/12 h dark cycle, and their circadian clocks represent remarkable adaptations to 24 h of repetitive light/dark conditions. Circadian clocks have three distinct criteria for classification. First, the circadian clocks must be generated internally and self-sustained under constant environmental conditions. Second, they must exhibit a period denoting the time required to complete a cycle. Finally, circadian clocks inherently adjust to environmental fluctuations to ensure stability across internal and external variations.

Although circadian clocks are endogenous biological systems, they are entrained by external time cues, primarily the solar time. Thus, circadian clocks are selectively advantageous for humans who adapt and optimize essential physiological processes for survival, such as sleep-wake body temperature, heart rate, and blood pressure in a 24-hour cycling earth environment. Endogenous circadian clocks are intertwined with nearly all aspects of human physiology, and disruption or misalignment of the internal circadian clock with the external environment is closely linked to various health conditions, including metabolic, cardiovascular, and sleep disorders¹⁻⁵. The *Clock*^{Δ19} mutant mice showed sign of hypertriglyceridemia, while the *Bmal1*^{-/-} mice showed thicker carotid artery walls that restricted blood flow^{6,7}. The most characteristic physiological period in humans that is controlled by circadian clocks is the 24-hour cycle of sleep and wakefulness. From gene regulation to behavioral functions, circadian clocks control every aspect of bodily function.

Clock gene single nucleotide polymorphisms (SNPs) have been linked to a number of sleep disorders. A more advanced sleep phase is caused by mutations in core clock genes, such as *CK1δ*, *Cry2*, and *Per2*⁸. Metabolic disorders that impair the timely transit of *Per2* are linked to

cellular overcrowding and disruption of the sleep-wake cycle. These disorders include autophagy dysregulation and excessive fat-induced cellular congestion⁹.

Currently, primary treatments for sleep disorders include a combination of pharmacological and behavioral approaches. Pharmacological interventions typically focus on neuronal stimulation pathways or core clock gene families¹⁰. Circadian behavioral therapy prioritizes aligning lifestyles with endogenous circadian clocks and incorporating timed activities such as light exposure, feeding, and exercise¹¹. Since exposure to light regulates the master clock, light therapy is a popular treatment for sleep disorders^{12,13}. The largest organ in the body, skeletal muscle has a strong circadian rhythm. Exercise affects circadian rhythms and skeletal muscle metabolism^{14,15}. Exercise can affect the expression of clock genes in the master clock, suprachiasmatic nucleus (SCN), peripheral clocks, and skeletal muscles¹⁵. Thus, exercise enhances circadian amplitude and helps adjust its phase.

This review highlights the existing literature on the potential mechanisms by which exercise can serve as an innovative and viable strategy for targeting the circadian clock associated with sleep disorders. We summarized the impact of circadian disruption on sleep disturbances and current clinical approaches. Moreover, we illustrated how the type and timing of exercise can be prescribed as a therapeutic intervention, specifically addressing individualized sleep disorders induced by circadian clock disruption.

METHODS

For this narrative review, we collected and analyzed papers via scientific paper hubs, including Google Scholar, PubMed, and the Cochrane Library. Keywords used in the searches included “Circadian clocks,” “physical activity,” “exercise,” “endurance,” “resistance,” and “strength” “chronic periods.” Studies have investigated the effects of exercise interventions on sleep disorders in both animals and humans. Most studies included in the updated bibliography were published in English only and ranged from 1989 to 2020. Articles that addressed “acute” or “cross-sectional” study designs were excluded. In addition to the computerized search, a manual search of the reference lists of the studies was performed. Furthermore, the studies that incorporated these references were disqualified due to their small sample sizes or unclear selection procedures. After removing duplicates, a thorough search yielded 17 studies that met the aforementioned criteria. Table 1 summarizes the reviewed studies. We analyzed exercise-induced circadian clock phase shifts, including sleep-wake cycle, melatonin, core clock gene regulation, and re-entrainment.

RESULTS

Mechanisms underlying the mammalian circadian clock

Mammalian circadian clocks are regulated by the tran-

scription-translational negative feedback loop (TTFL), circadian locomotor output cycle kaput (CLOCK), and brain and muscle Arnt-like protein-1 (BMAL1), which are transcription factors that regulate the expression of many circadian clock genes, including period (*Per*) and cryptochrome (*Cry*). CLOCK and BMAL1 form heterodimers via their PAS domains and transcribe period (*Per*) and cryptochrome (*Cry*)¹⁶. CRY binds to PERIOD in the cytoplasm via the CRY-binding domain at the C-terminus of PERIOD. PERIOD and CRY heterodimers, which are phosphorylated by casein kinase1 (CK1), translocate to the nucleus and inhibit *Per* and *Cry* transcription by removing BMAL1 and CLOCK¹⁷. Additionally, hyperphosphorylated PERIOD by CK1, is ubiquitinated and degraded via the ubiquitin-proteasome pathway¹⁸. The entire TTFL cycle lasted approximately 24 h. The sleep-wake cycle is one of the most prominent physiological processes regulated by the circadian clock. Early in the night, CLOCK and BMAL1 are activated, transcribe *Per*. Consequently, PERIOD synthesis began during the day and continued to increase. Over time, the PERIOD-CRY complex inhibits the CLOCK-BMAL1 complex. The following day, *Cry* and *Per* levels declined because of degradation¹⁹. Recent publications have extended our understanding of the mechanisms of the mammalian circadian clock at the genome-wide level²⁰. The circadian clock also governs daily chromatin remodeling and histone modifications²¹. The basal transcription machinery, transcription regulatory components, and RNA polymerase II exhibit daily oscillations in target genes²². Therefore, the circadian clock influences the timing of transcription factor recruitment and the transcriptional activity of target genes.

Synchronization of circadian clock by Zeitgebers

Circadian clocks are adaptive mechanisms that have evolved to help organisms optimize biological and physiological processes within a 24-hour living environment^{23,24}. Entrainment is the main part of the circadian clock that ensures that its timing remains synchronized with external cues such as stress, light, exercise, and food. This process allows organisms to adjust and align their internal rhythms with the natural environmental cycles, promoting optimal functioning and adaptation to the surrounding conditions. The most distinct environmental cue is the 24 h period of the Earth's rotation, which repeatedly results in a unique transition between light and dark environments. Consequently, circadian clocks are mainly synchronized by light-signal sensing in the SCN of the hypothalamus^{25,26}. This master clock receives light cue inputs and transmits daily signals to downstream tissues, synchronizing the peripheral clocks in the organs and tissues²⁷. Although peripheral clocks are synchronized by a master clock, each peripheral organ and tissue possesses a clock because they have distinct functions in maintaining the overall body system. In addition, the peripheral clock is synchronized with other external time signals such as stress, feeding, and physical activity including exercise^{14,15,28}.

Food intake timing is a powerful zeitgeber that regulates the circadian control of metabolic pathways. The pacemaker

Table 1. Exercise induced a circadian clock phase shift.

Exercise protocol	Subject	Main finding	Reference
Sleep–wake cycle shift			
2 h wheel running	Syrian hamsters	Free-running periods were short, and phase advances induced CT 4 and CT 11	Reebs & Mrosovsky (1989)
30 minutes of high-intensity treadmill in the morning or evening	Young adults	Morning exercise-induced phase advance shifts, but individual chronotypes also influenced the effect of timed exercise	Thomas et al. (2020)
3 h forced treadmill running or free running wheels	Mice	Maximal advances at CT 4~CT 9 and maximal delays between CT 21~CT 3	Marchant & Mistlberger (1996)
Melatonin phase shift			
3 h of moderate or 1 h of high-intensity training at night	Healthy men	Delays of melatonin onsets for both moderate and high-intensity exercise	Buxton et al. (1997)
2 h of bicycle or rowing ergometers during the waking period	Healthy adult	Plasma melatonin rhythm was phase advanced with physical exercise	Miyazaki et al. (2001)
A single episode of 3 h of nighttime pulse exercise	Young men	The nighttime exercise was associated with 1–2 h phase delays of melatonin rhythms.	Van Reeth et al. (1994)
1 hour of stair climbing (morning, afternoon, evening, or nocturnal)	Healthy men	Melatonin levels increased at the end of evening and nocturnal exercise but decreased at the end of morning exercise	Buxton et al. (2003)
Core clock gene regulation			
Wheel running at ZT 4	Syrian hamsters	Reduction of <i>mPer1</i> in the SCN at ZT 7	Maywood et al. (1999)
Free access to a running wheel	Mice	The clock gene phase was advanced, and peak levels of <i>mPer1</i> and <i>mPer2</i> expression were increased	Yasumoto et al. (2015)
One-repetition maximum isotonic knee extension	Healthy male adults	Core circadian clock genes (<i>hCry1</i> , <i>hPer2</i> , and <i>hBmal1</i>) were upregulated 6 h after exercise	Zambon et al. (2003)
Electrical pulse stimulation for 1 h	C2C12 cell <i>Bmal1</i> : luc	Stimulation at 22 h (<i>mBmal1</i> high) post synchronization (p.s) induced phase advance, and stimulation at 28 h (<i>mBmal1</i> low) p.s led to a phase delay	Kemler et al. (2020)
1 h of treadmill at ZT 5 or ZT 11	Period2: Luc mice	Timing of exercise influenced the directional response of the muscle clock phase (ZT 5 phase advance, ZT 11 phase delay)	Kemler et al. (2020)
2 h voluntary or involuntary exercise during ZT 4~ZT 6	Period2: Luc mice	PER2: LUC bioluminescence rhythm in skeletal muscle advanced 2~3 h	Wolff & Esser. (2012)
Re-entrainment			
15 min of cycle ergometer	Young adults	Exercise accelerated the re-entrainment of the body temperature rhythm to the 8 h shifted condition	Eastman et al. (1995)
2 h of bicycle in the early and middle waking period	Male adults	Exercise accelerated the re-entrainment of the sleep–wake cycle to 8 h phase-advanced new condition	Yamanaka et al. (2010)
45 min cycle ergometry at night	Young and fit males	Greater adjustment of melatonin rhythm shift to 9 h delayed new sleep–wake schedule	Barger et al. (2004)
Wheel running	Period 2: Luc mice	Exercise accelerated the re-entrainment of circadian rhythms to 8 h phase-shifted new environment	Yamanaka et al. (2008)

SCN governs the onset and offset of activities, ensuring that food intake occurs exclusively during waking hours. This arrangement synchronizes the physiological preparation of peripheral tissues for ingestion, digestion, absorption, distribution, and storage of nutrients. Melatonin originates from the pineal gland, which is downstream of the SCN, suggesting that melatonin secretion is regulated by light. Scheduled exercise is a nonphotic external time cue that effectively shifts the onset of melatonin secretion. The timing of exercise contributes to the readjustment of SCN circadian clocks with anticipated activity.

Circadian clock sleep disorders

Humans have a 24-hour sleep–wake cycle, the most representative physiological process controlled by the circadian clock. The sleep–wake cycle is mainly regulated by two mechanisms: the circadian clock and homeostasis²⁹. They are synchronized with external time cues to improve sleep quality by optimizing the sleep duration and timing. Sleep disorders are life-threatening, and more than 70 million people are diagnosed with these disorders in the U.S. Sleep deprivation interferes with physical and cognitive functions and affects personal mood³⁰. For example, circadian rhythm

sleep disorders (CRSDs) are caused by alterations in the internal circadian clock or a misalignment between external circumstances and endogenous circadian clocks⁴. Several distinctive CRSDs, such as irregular sleep-wake rhythms and advanced or delayed sleep-phase disorders have been diagnosed³¹⁻³⁴. Individuals in the delayed-sleep phase type experience a shift in sleep and wake times later than desired. In contrast, individuals with an advanced sleep phase shift sleep and wake times earlier than normal, posing difficulties in remaining awake until the desired sleep time. The irregular sleep-wake type is characterized by an unrecognizable and disorganized pattern of sleep and wake patterns. The free-running type involves a gradual delay in bedtime of a few hours each day, resulting in insomnia and difficulty waking up in the morning. Individuals with jet lag struggle to align their sleep and wake times with their desired schedules because of recent travel to new time zones. Shift workers fall asleep during the day or remain awake at night at the time required by their work schedule²⁶. Patients with CRSDs typically experience excessive daytime sleepiness, which negatively affects their quality of life by affecting work performance, personal health, and social activities. Pharmacological approaches targeting melatonin, orexin, or core clock genes are the primary treatments for patients with CRSDs. In addition, behavioral therapies, such as light adjustment, scheduled feeding, and exercise, have reported promising results.

Sleep disorder therapies

Sleep disorders are primarily treated using behavioral and pharmacological strategies. Pharmacological approaches mainly target either neural firing or core clock regulatory pathways. Melatonin initiates sleep at night, whereas orexins are neuro-activators that alert individuals during the daytime. It is predominantly synthesized and released in the pineal gland at night and its production is regulated by norepinephrine. High levels of G-protein-coupled receptors such as melatonin receptor 1 (MT1R) and melatonin receptor 2 (MT2R) are expressed in the SCN. Melatonin binds to MT1R and MT2R in the SCN and inhibits the cyclic adenosine monophosphate-protein kinase A-cAMP-responsive element-binding protein (cAMP-PKA-CREB) phosphorylation pathway, thereby inhibiting SCN neural firing^{35,36}. Melatonin administration timing is associated with a circadian clock phase shift. Melatonin administration in the late afternoon elicited a phase-advancing shift. Conversely, early morning melatonin administration delays the circadian clock. These results underscore the critical role of precisely timing melatonin intake to effectively alter circadian rhythms and sleep-wake cycles^{37,38}. Administration of tasimelteon, a melatonin receptor agonist, produced significant results, demonstrating a substantial shift in the internal circadian clock, leading to improved sleep quality³⁹. The SCN senses light through the retinohypothalamic tract, triggering orexinergic neurons in the lateral hypothalamus to secrete orexin A and orexin B. Orexin receptors 1 (OX1R) and orexin receptor 2 (OX2R) are found in neurons throughout the central nervous system^{40,41}. Orexin signaling initiates

multiple downstream cascades, including phospholipase A (PLA), phospholipase C (PLC), and phospholipase D (PLD). Consequently, the cytosolic Ca^{2+} levels increase, stimulating responses to neural firing⁴². Antagonists of orexin receptors have been found to potentially promote sleep onset by reducing cortical arousal and facilitating easier transitions between wakefulness and sleep^{43,44}. Suvorexant, an antagonist of orexin receptors, affects sleep disorders marked by difficulty in sleep onset or maintenance⁴⁵. By blocking OX1R and OX2R, it effectively suppresses orexin neuron activity, thereby promoting sleep^{24,46}.

Drugs targeting core clock components

Circadian medicine is experiencing exciting progress through direct manipulation of core oscillators. Recent studies have developed drug reagents that precisely target the fundamental components of the circadian clock. Several compounds that influence *Per* and *Cry* gene expression have the potential to modify the circadian period. The carbazole compound KL001 enhances the stability of CRY1 and CRY2 in human osteosarcoma cell lines⁴⁷. KL001 treatment extends the circadian period and reduces its amplitude. The pharmacological targeting of CK1 is promising because it is crucial for the phosphorylation of core clock components. In mice whose rhythms are disrupted by constant light exposure, the CK1 δ -specific inhibitor PF-670462 treatment can re-establish behavioral rhythms⁴⁸. Longdaysin, a ground-breaking compound, prolongs the circadian period by preventing PER1 degradation in cell cultures and zebrafish in vivo⁴⁹. REV-ERBs are nuclear receptors that play crucial roles in the circadian clock regulation. *Rev-erba* knockout (KO) mice exhibit an advanced sleep-wake pattern. Furthermore, sleep consolidation notably decreased following sleep onset, suggesting a slower build-up of homeostatic sleep requirements throughout the day⁴². Researchers identified the ideal timing for administering the *Rev-erba* agonist SR9009, demonstrating its ability to induce wakefulness during the light period⁴³.

Behavioral treatments for sleep disorder

An essential characteristic of circadian clocks is their capacity to adapt to external cues such as light, temperature, food, and exercise. Circadian clocks adjust, synchronize, and align internal biological rhythms, including their timing (phase) and duration (period), with external environmental cues like the 24-hour light-dark cycle. Therefore, circadian behavioral therapy prioritizes aligning lifestyles with endogenous circadian rhythms, focusing on timed activities, such as eating, exposure to light, and exercise, to enhance overall circadian health. Pervasive exposure to blue light at night in modern societies is a prevalent lifestyle habit that disrupts the neuroendocrine pathways of melatonin and affects the sleep-wake cycle⁵⁰. Exposure to high-intensity natural daylight is associated with sleep timing, total sleep duration, and sleep quality⁴⁴. In clinical practice, receiving several hours of bright broad-spectrum light in the morning benefits the sleep-wake cycle⁵⁰. Advancements in time-restricted feeding (TRF) have significantly impacted metabol-

ic disorders associated with disruptions in the sleep-wake cycle. TRF has emerged as a novel strategy for addressing irregularities in the sleep-wake cycle induced by diabetes. Administering TRF exclusively during the active phase effectively restored the sleep-wake cycle in diabetes mice⁴⁶. Restricting food access during the active phase has demonstrated substantial preventive and therapeutic benefits on human sleep quality and duration⁵¹.

Exercise and circadian clocks

Exercise challenges homeostasis by affecting cells, tissues, and organs. Therefore, exercise serves as a non-light external cue that can adjust the internal circadian clock and influence their timing⁵². Exercise can shift circadian clocks and is influenced by exercise type, timing, intensity, and individual chronotypes⁵³. Morning exercise advances the phase for individuals with earlier chronotypes, whereas evening exercise delays this phase. In contrast, both morning and evening exercise induced phase advances in individuals with later chronotypes⁵³. Forced treadmill exercise or a single bout of daytime wheel running induces a phase advance in the circadian clocks⁵⁴⁻⁵⁶. Patients with phase-delayed sleep problems may benefit from daytime exercise interventions as a potential treatment, which would assist in helping them revert to a more regular sleep phase. In contrast, exercising at midnight shifts circadian clocks to a delayed phase^{57,58}. Exercise influences the expression of core clock genes and changes their phases in skeletal muscle¹⁵. By utilizing exercise intervention, the SCN of the hypothalamus which regulates the master clock was shifted. Exercise interventions selectively adjusted the amplitude of *ERIOD2:LUCIFERASE* in early scheduled access to running wheel mice, but not in those with late scheduled activity or unrestricted wheel access⁵⁹. Wheel running under light exposure decreased the peak levels of clock genes *Per1* and *Per2* in the SCN⁶⁰. These findings indicate that the timing of exercise is critical for regulating molecular clocks in the SCN. Exercise acts as a powerful external factor for peripheral clocks, including the skeletal muscles. Resistance training can also influence the expression levels of core circadian clock genes in skeletal muscles. Specifically, *Cry1*, *Per2*, and *Bmal1* are upregulated in resistance exercise-trained legs compared with non-trained legs⁶¹. Male rugby players exhibited elevated average expression levels of core clock genes (*Bmal1*, *Cry1*, *Per1*, and *Per2*) in blood samples compared to sedentary males⁶². Furthermore, *Cry1* and *Cry2* genetic deletion altered the gene signature elicited by exercise and improved mice's ability to exercise⁶³.

Therapeutic potential of chrono-exercise

Light and melatonin therapies are standard treatments for CRSDs; however, exercise is beneficial for patients with CRSDs who display distinct abnormal sleep patterns. Delayed Sleep Phase Disorder (DSPD) is characterized by a significant shift in an individual's sleep and wake times, making them much later than usual. People with DSPD usually go to bed late, which leads to difficulty in waking up in the morning and feelings of excessive sleepiness during the

day. DSPD is caused by a combination of genetic, environmental, and behavioral factors. Polymorphisms in the core clock gene *hPer3* are associated with DSPD from a genetic perspective⁶⁴. Genetic mutations in the casein kinase-binding domain (CKBD) can modify the phosphorylation process of hPER3, thereby altering the circadian period length. A single nucleotide polymorphism in the 5'-untranslated region of *hPer2* and a genetic variation in CKBD of *hPer1* and are also associated with DSPD^{65,66}. Disrupted synchronization of the circadian system due to light exposure at specific times can lead to delayed sleep. DSPD is associated with increased evening and decreased morning light exposure⁶⁷. Exercise performed in the morning (ZT 4-6) shifts the PER2 phase by 2-3 hours in PER2 bioluminescence rhythms observed in skeletal muscles and lung explants¹⁵. Moreover, engaging in two hours of physical activity twice per waking period, such as cycling or rowing machines, advances the timing of melatonin secretion compared to the control group⁵⁶. Exercise induces phase advances in *Per1* and *Per2* in hamsters⁶⁰.

Advanced Sleep Phase Disorder (ASPD) is associated with significantly earlier sleep and wake times than DSPD. Individuals with ASPD typically experience fewer negative consequences, because their active phase aligns with their regular social and work hours. Genetic factors, such as mutations in CKI or PER2 phosphorylation sites, contribute to ASPD⁶⁸⁻⁷⁰. These mutations interfere with the usual phosphorylation process or accelerate phosphorylation of phosphodegron, destabilizing hPER2⁷¹. Increased sensitivity or prolonged exposure to light in the early morning contributes to the development of ASPD because light exposure plays a crucial role in regulating circadian rhythms. Subjects who engaged in three 45-minute cycling sessions at night demonstrated a substantial adjustment in melatonin oscillation, aligning with a new 9-hour delay in the sleep-wake cycle⁷². Participants were studied during nocturnal physical activity, either 3 hours of moderate-intensity exercise or 1 hour of high-intensity exercise, which led to a delay in the onset of thyrotropin and melatonin compared with the control group⁵⁷.

Irregular sleep-wake disorders are defined as the absence of a clear, consolidated sleep period, with affected individuals experiencing at least three distinct sleep episodes within a 24-hour period⁷³. Irregular sleep-wake disorders are frequently linked to the dysfunction of the central circadian pacemaker SCN or to environmental conditions that restrict exposure to strong time cues⁷⁴. Individuals with non-24 h sleep-wake disorders struggle to synchronize their sleep-wake cycles with a 24 h day. The endogenous clock is resistant to entrainment by the light-dark cycle. Most individuals with non-24 h sleep-wake disorders typically have a sleep duration slightly longer than 24 hours⁷⁵. This leads to a gradual shift in their sleep-wake patterns, making them alert at night and sleepful during the day. Exercise intervention influences this phase shift and modifies clock gene expression in both the central and peripheral clocks of the skeletal muscles. When the TTFL generates oscillations in clock genes, reduced or flattened amplitudes can lead to

an overall arrhythmicity or a singular rhythm⁷⁶⁻⁷⁸. Maximal strength training for eight days upregulates core clock genes in the skeletal muscles⁶¹. Athletes also exhibit elevated levels of core clock genes in their blood samples⁶². Acute aerobic treadmill exercise upregulated the expression of *Per1* and *Per2* in the tibialis anterior muscles of mice. Moreover, acute high-force eccentric contractions induced by electrical stimulation upregulate *Bmal1*⁷⁹.

CONCLUSIONS

Sleep disorders significantly impair sleep quality, day-time functioning, and physical and mental health. Proper management involves the diagnosis and treatment of these conditions through pharmacological interventions and lifestyle adjustments. The emerging field of chrono-exercise explores the intricate relationship between the circadian clock and exercise, offering new insights into optimizing health through timed physical activity. Exercise training has the advantages of sleep-wake phase adjustment and the up-regulation of clock gene expression. As individuals display different patterns of sleep disorders caused by a broad range of factors, from genetic mutations to irregular or shifted lifestyles, proper timing, intensity, and type of exercise (aerobic, resistant, or combined) should be considered to maximize the benefits and minimize any potential negative impacts on sleep. Thus, personalized exercise protocols for individuals with various sleep disorders should be investigated to determine the therapeutic potential of chrono-exercise. To improve overall sleep quality and wakefulness in people with shift work, social jetlag, and sleep disorders, one practical way to incorporate chrono-exercise strategies is to evaluate each person's chronotype, determine the best time to exercise based on their circadian phase, track the effects of exercise on sleep patterns, and modify the workout schedule. Thus, the advantages of exercise for circadian rhythm management and sleep health can be maximized with this personalized strategy. Additionally, physicians and exercise instructors can provide a thorough approach to managing sleep problems by incorporating the principles of chrono-exercise into their work and highlighting the important role that physical activity timing plays in circadian clocks and overall sleep quality.

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