Circadian imbalance

Clinical implications and integrative treatment

Fullscript

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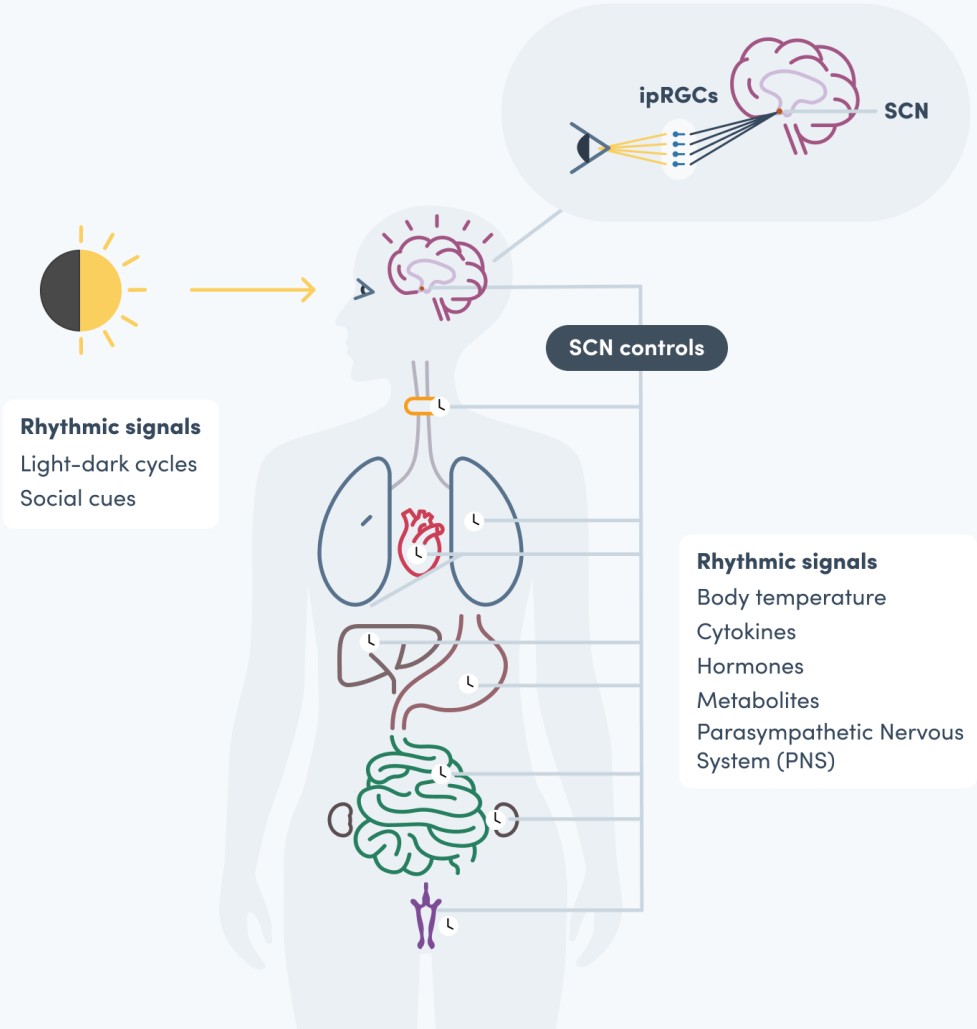
The critical nature of circadian rhythm

Understanding the impact that the circadian rhythm has on health begins with an appreciation of the suprachiasmatic nucleus (SCN). Located in the hypothalamus, the SCN acts as a circadian "pacemaker" that regulates most timing systems and rhythms in the human body, including blood pressure, body temperature, cytokine secretion, energy homeostasis, heart rate, hormone status, renal activity, and the sleep-wake cycle. [9]

Just like a quiet oscillating fan on a hot day, in the background of our lives, the SCN carries out its rhythmic tasks as the central clock that is synchronized with all of the other automated clocks of the body. But what happens when this oscillating central clock is disrupted? As the SCN-regulated circadian clock influences nearly all physiological activities, disruption can have widespread and severe consequences on human health, such as cancer, cognitive impairment, dysplasia, metabolic syndrome, and psychiatric illness. [44]

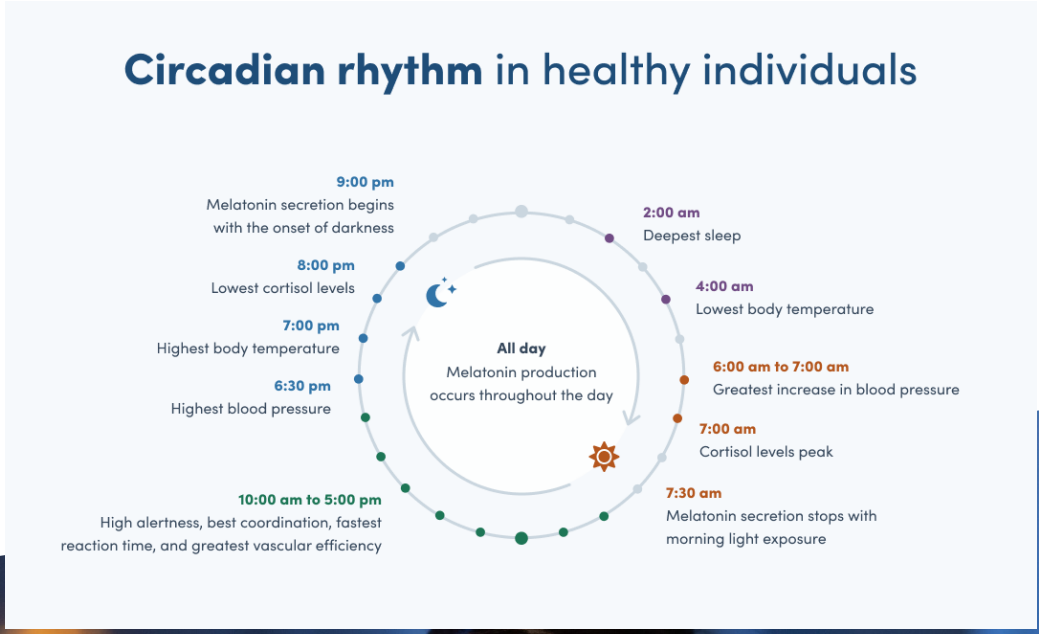
The circadian clock and human physiology



Legend

Suprachiasmatic nucleus (SCN): a region of the brain that controls circadian rhythms
Intrinsically photosensitive retinal ganglion cells (ipRGCs): receptors in the retina that respond to light

The complex transcriptional and translational circadian feedback loop takes 24 hours to complete and is synchronized with the natural day-night patterns humans have been exposed to for billions of years. [10] From a physiological perspective, the typical 24-hour cycle is depicted in the figure below.



The circadian system regulates far more than just the sleep-wake cycle; however, when this system is disrupted, the most noticeable effects are on sleep and the stress response. This is significant because both chronic stress and lack of sleep have been associated with several serious illnesses including the leading causes of disease-related mortality—cancer, diabetes, heart disease, and stroke. [32]

Many mechanisms connect circadian imbalance to poor health and disease. Each pathway of the circadian system is critical on its own, but when combined, they clearly illustrate the importance of addressing circadian imbalance in clinical practice.

"Circadian health is integral to whole-person healthcare," says naturopathic oncologist and integrative medical expert Lise Alschuler, ND, FABNO. "An integrative medicine approach can help patients who are struggling with circadian imbalance, and integrative practitioners are well-positioned to help improve circadian-based wellness in clinical practice."

A great place to start with an integrative approach is by understanding the mechanisms involved, including the genes, hormones, and proteins that play a role in circadian balance.

Underlying mechanisms

The most significant external stimulus that influences the circadian system is daylight. Daylight stimulates receptors in the retina that trigger a cascading effect of neurotransmission and protein activation in the SCN, and subsequently to all peripheral organs. [10] All cells in the human body, and approximately 10% of the genes expressed in cells and tissues, are rhythmically synchronized with the SCN. [44] The circadian system is characterized by complex feedback loops that activate genes, hormones, and proteins, which confer significant influence on health and disease.

Clock genes and proteins

Clock genes are aptly named because they help the body manage time on a molecular level. Through a self-perpetuating 24-hour cycle, the rhythmic expression of clock genes are important regulators of health as they methodically evoke responses that impact behavior, metabolism, and physiology. [4] This is the essence of circadian rhythm.

"Many of the clock genes are involved in 'housekeeping' functions of the cells and are essential to key processes such as restoring redox potential, autophagy, and cell repair," explains Dr. Alschuler, who is a professor and associate director of the Fellowship in Integrative Medicine at the University of Arizona.

Clock genes encode proteins that are a significant part of the feedback loop as they drive the oscillation of the entire circadian timing system. [20] While this system is innate, the clock is also synchronized to a person's 24-hour environment, with food and light being two key synchronizers that help regulate the protein-coding genetic activity. [4]

Neuronal firing within the SCN stimulates circadian rhythm related to genes and proteins, but it also influences hormonal activity, as noted in the following section.

Hormones

Levels of many hormones, including growth hormones, ghrelin, leptin, insulin, cortisol, and melatonin, fluctuate based on circadian rhythm. Circadian disruption, and the subsequent illnesses caused by that imbalance, occurs when there is impaired hormonal homeostasis and reversed cortisol and melatonin rhythms. [24] When the circadian system is in balance, cortisol levels peak in the morning while melatonin levels decline, and cortisol levels decline in the evening when melatonin levels peak.

"Circadian function is anchored to the daily wave secretion pattern of melatonin and cortisol," says Dr. Alschuler. "When balancing circadian rhythm in clinical practice, identifying issues with these two hormones is key."

Cortisol

Fluctuating cortisol levels throughout the day can provide an indication of circadian clock function. When the circadian clock is balanced and healthy, cortisol levels are high in the morning, decline throughout the day, are low in the evening, and increase overnight. This 24-hour cycle is modulated by the SCN via the hypothalamic-pituitary-adrenal (HPA) axis. Any disruption to that cortisol rhythm increases pro- and anti-inflammatory proteins, which can also increase the risk of a variety of disease processes. [43]

Melatonin

The hormone melatonin also influences the sleep-wake cycle. However, in contrast to cortisol, rising melatonin levels act to promote sleep at night.

The release of melatonin is regulated by light exposure. As the sun sets and exposure to sunlight declines, the SCN sends a signal to the pineal gland to produce more melatonin. When the sun rises and sunlight increases, the SCN inhibits melatonin synthesis. This flow of melatonin is a sure sign that the circadian system is operating efficiently. Evening artificial light can have the same effect as sunlight, which explains how it can disrupt the rhythmic release of melatonin. [46]

The role of melatonin extends beyond regulating the sleep-wake cycle. Melatonin, a potent antioxidant with immune-enhancing effects, also plays a role in blood pressure and cardiovascular regulation, as well as detoxification. [42] Melatonin is also neuroprotective and has anti-apoptotic and anti-inflammatory effects. [40] Given these important mechanisms, therapeutically, melatonin may also provide protection against a number of illnesses including cancer and neurodegenerative conditions. [26]

Glucose-stimulated insulin secretion

Another mechanism by which the circadian system influences health is via glucose metabolism. As the circadian system also helps control glucose metabolism, when there is a disruption in circadian rhythm, there may be a corresponding disturbance in glucose homeostasis and an adverse effect on glucose metabolism. [22] In addition, both sleep loss and elevated cortisol, key signs of circadian imbalance, have been shown to promote insulin resistance and disrupt optimal glucose metabolism, which can lead to an increased risk of obesity and type 2 diabetes. [36]

Circadian disruptors

There are many factors that can contribute to circadian imbalance, including blue light exposure in the evening, poor diet, increased stress, and impaired sleep.

The significance of sleep

"In my practice, poor sleep hygiene or a lack of understanding of the purpose of sleep seems to be the greatest disruptor of the circadian system," explains integrative mental health expert and naturopathic clinician Peter Bongiorno, ND, LAc. "Most of my patients are busy and try to extend their day into the night as much as possible, which can lead to circadian disruption."

Dr. Bongiorno feels that communicating the value of sleep to patients should be a priority in clinical practice because sleep plays a critical role in neurological function and influences systemic physiology across many other body systems. Whether there is a deficit in sleep quantity, quality, or both, sleep disruption can lead to numerous negative health effects including:

- Decreased cognitive function
- Emotional distress
- Increased HPA activity
- Increased inflammation
- Metabolic changes
- Mood disorders
- Performance deficits
- Reduced quality of life
- Somatic pain [31]

Many factors can contribute to sleep impairment, including:

- Alcohol intake
- Anxiety, worry, and rumination
- Caregiving (both the physical and emotional demands)
- Chronic pain
- Drug abuse
- Excess nighttime caffeine intake
- Excess nighttime light and/or noise exposure
- Health conditions such as obstructive sleep apnea or restless leg syndrome
- Parenting young children
- Shift work
- Some medications such as anticonvulsants, dopamine agonists, and psychostimulants
- Travel/jet lag [31]

Lack of sleep and stress often go hand-in-hand so addressing both in clinical practice is important.

The impact of stress

"The biggest circadian disruptor I have found is high and chronic stress in the absence of regular stress management," says Dr. Alschuler. "While it is not always possible to control the amount of stress in our lives, those who have an established routine of mindfulness practice—meditation, breathing exercises, movement, time in nature, etc.—can generally withstand stress to a greater extent and sustain a healthy circadian rhythm."

Circadian disruption can impact a person's ability to cope with stress, and conversely, a person's inability to cope with stress can disrupt circadian balance. [25] A rhythmic release of cortisol via the HPA axis will help dictate how well a person can manage stress.

Dietary disruptors

Research shows that dietary patterns, including what and when you eat, can impact circadian balance. For example, according to a 2020 review, eating patterns in shift workers contributed to circadian disruption. Rather than eating three scheduled meals per day within the typical 24-hour cycle, shift workers ate across 24 hours with food consumed during the nighttime hours as well. The review also stated that the food choices of shift workers include "fast" food and unhealthy snacks, which may also disrupt circadian rhythm. [7]

Since the circadian clock helps control glucose metabolism, energy levels, and other feeding factors, it makes sense that there would be a connection between diet and circadian imbalance for many patients, not just shift workers. When it comes to diet and circadian balance, it is important to consider consistency, nutrient composition, and timing. As mentioned previously, alcohol and caffeine can be circadian disrupting culprits, but a diet consisting of unhealthy fats that lacks health-promoting polyphenols can also be problematic to the circadian rhythm. [35]

Dietary circadian disruptors to reduce or avoid include:

- Alcohol
- Caffeinated foods and beverages
- Highly processed foods
- Simple sugars
- Unhealthy fats such as trans or saturated fats [35]

Consequences of disruption

As previously mentioned, the consequences of circadian disruption are significant. These consequences can include an increased risk of many illnesses including cancer, cardiovascular issues, diabetes, immunodeficiency, mental health disorders, metabolic syndrome, and neurodegenerative diseases. [44] That's why an accurate diagnosis of circadian imbalance is so critical.

Accurate diagnosis

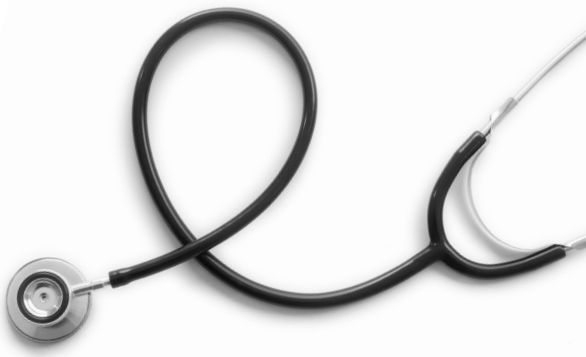
"There is no perfect way to test circadian rhythm, so establishing a diagnosis can be challenging," says Dr. Bongiorno, who has a thriving clinical practice with two locations in New York and is the author of many books on the integrative treatment of mental health disorders. "Diagnosing circadian imbalance is ultimately determined based on clinical presentation and ruling out other contributors such as anxiety, food sensitivities, and other dietary issues."

Dr. Bongiorno explains that using an integrative approach is like being on a fact-finding mission to pinpoint the root cause. "A thorough health history intake is key," he says. Dr. Bongiorno uses blood, urine, and saliva testing to identify deficiencies and cortisol function throughout the day. "I also check thyroid function and genetic SNPs such as COMT for imbalances that may play a role in circadian disruption."

In addition to blood and saliva hormone tests, the National Institutes of Health recommends a thorough evaluation of sleep habits and encourages patients to keep a sleep diary that describes the quality and quantity of nightly sleep. [33]

Just like Dr. Bongiorno, Dr. Alschuler uses an empirical diagnostic approach that evaluates presenting signs and symptoms. "I often order a four-point salivary cortisol test which provides a compelling graphic that I can share with patients to help motivate them to adopt recommended lifestyle changes," says Dr. Alschuler. "I will also typically evaluate early morning cortisol levels as increases or decreases have a fairly good predictive value of circadian dysfunction."

Diagnostic evaluations and tests will also yield information that can be used to create the patient's individualized protocol.



Integrative treatment

With a clear understanding of the bidirectional interaction that circadian rhythm has on almost all metabolic processes in the human body, an individualized integrative treatment protocol can be created by focusing on lifestyle advice, dietary supplements, and dietary recommendations. In the scientific literature, a diet that considers the circadian system is referred to as *chrononutrition*. [34]

The important role of chrononutrition

Nutrients obtained from the diet can influence the circadian clock by either encouraging and restoring synchronicity or contributing to its imbalance. One key way to influence which route will be taken is with the feeding-fasting cycle. [37] Studies now show that proper feeding of the clock requires a certain amount of fasting for it to function properly.

The now popularized concept of time-restricted feeding actually has its roots in circadian rhythm; humans historically ate within a 12-hour window during daylight hours and fasted overnight so that the body could perform metabolic tasks without the added burden of managing digestion and glucose metabolism. [29] Several studies have demonstrated that time-restricted feeding can contribute to healthy aging and weight loss, and the authors of a 2017 review concluded that it can also contribute to circadian balance. Circadian rhythms naturally become disrupted with age, so that's one way in which time-restricted feeding can rebalance the circadian system. The authors of the review also report that because a time-restricted eating pattern includes fasting, it can help promote balance. [30]

In addition to time-restricted feeding, practitioners may also want to recommend the Mediterranean eating pattern. A 2010 clinical trial confirmed that polymorphisms in specific clock genes can increase susceptibility to weight gain. The study also found that participants, who did not have the genetic variation that causes obesity, experienced weight loss as a result of following a Mediterranean diet. [18] The authors of a 2019 clinical trial involving adolescents concluded that the Mediterranean diet improved sleep quality and attributed these effects, in part, to the diet's influence on circadian rhythm. [3] The Mediterranean diet, a diet sometimes recommended for diabetes management, also helps control blood glucose levels, a significant factor involved in circadian rhythm. [8]

Finally, preliminary research infers that eating seasonal fruits and vegetables may help support circadian function. A 2019 review points to in vivo research demonstrating that the phenolic compounds found in seasonal fruits and vegetables can positively influence biological circadian rhythms. [6]

Of course, a key strategy in creating circadian balance involves addressing sleep. In addition to the diet strategies mentioned, there are lifestyle factors and dietary supplements that can help.

Enhancing sleep quantity and quality

Sleep hygiene is something that Dr. Bongiorno focuses on in his clinical practice. "With some patients, nighttime is finally when their day is quiet and calm, and they want to have that time for themselves rather than going to bed," he says. "I have to take into consideration their need for that downtime, but I also want to give them solid sleep hygiene strategies."

Dr. Bongiorno believes that blue light emitted from computers, tablets, and cell phones is the biggest culprit that induces an excitatory state at night when the body is trying to unwind. "Curbing blue light in the evening can be very helpful," he says, and he recommends avoiding blue light exposure for at least two hours before bed. "If they must use a device at night, I recommend sipping some lavender tea and reading a device with an amber hue. If ambient light is still required, using an orange bulb can also help lessen the negative impact on melatonin."

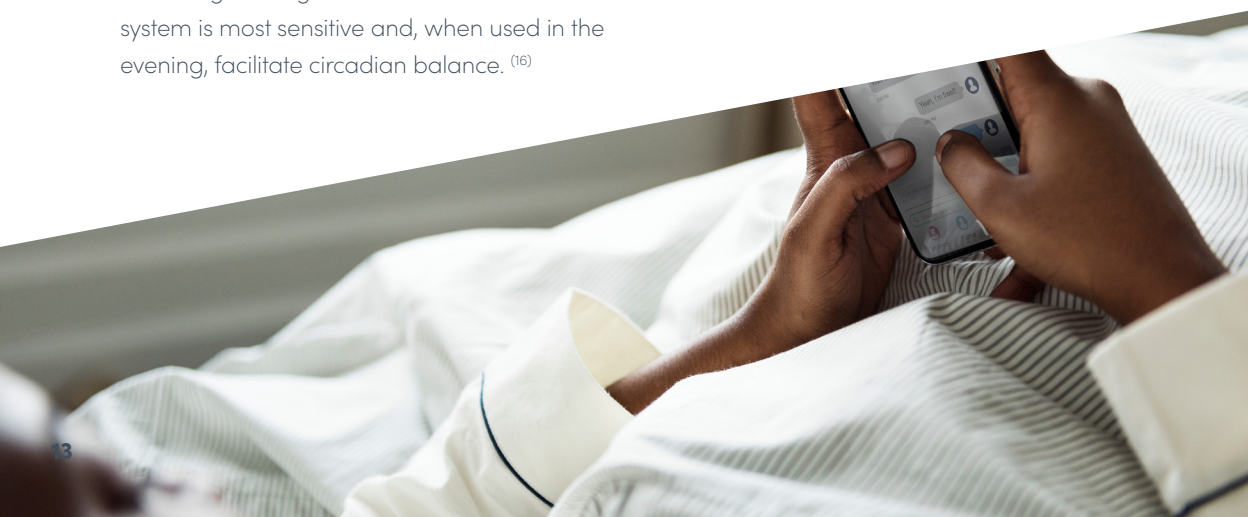
Research shows that orange light and blue light blocking glasses can help block wavelengths of light to which the circadian system is most sensitive and, when used in the evening, facilitate circadian balance. [16]

Other optimal sleep hygiene recommendations include:

- Avoiding activities that demand high levels of concentration as well as emotionally disturbing or excitatory activities before bed
- Ensuring that the bed is comfortable and the bedroom is dark, quiet, and at a pleasant temperature
- Maintaining a regular sleep-wake schedule and avoiding variations of more than two hours on the weekends
- Avoiding intake of alcohol, caffeine, tobacco, or any other excitatory substance prior to bedtime [14]

In addition to proper sleep hygiene, broad-spectrum light therapy in the morning can help enhance evening sleep, especially in individuals who have delayed sleep phase disorder, a condition characterized by an inability to fall asleep and morning sleepiness. [15]

In addition to morning light therapy for sound nighttime sleep, Dr. Bongiorno also recommends a morning exercise routine. Exercise timing is important as research indicates that for some individuals evening exercise can be disruptive to the circadian system. [40]



Dietary supplements for sleep

When it comes to dietary supplements for sleep, practitioners have several options. However, many practitioners start with prescribing melatonin, which has been shown in many clinical trials to improve sleep onset, as well as sleep quantity and quality. [15]

"There is no question that melatonin can help safely re-adjust poor circadian function," says Dr. Bongiorno. "In cases of delayed sleep phase syndrome, I will often dose melatonin at low levels in both the mid-evening and before bed to help reset circadian rhythm."

In addition to melatonin, certain medicinal herbs may be effective. According to a 2020 review of randomized, double-blind, placebo-controlled trials, herbs that can help with sleep include chamomile, hops, lavender, rosemary, and valerian. [19]

A unique oral form of lavender known as Silexan has been shown to enhance sleep. According to a 2019 clinical trial, the secondary sleep effects of lavender were due to its anxiolytic activity versus sedation. [38]

Other nutrients that may be used to encourage sound sleep include GABA, L-theanine, and 5-HTP. A 2019 clinical trial showed that the combination of GABA and L-theanine helped participants fall asleep faster and also improved non-REM sleep. [23] In vivo research demonstrated that the combination of GABA and 5-HTP helped improve sleep quantity and quality. [21]

Magnesium is also important for sleep as it is involved in more than 300 important enzyme systems including systems associated with circadian rhythm. [11] A 2012 double-blind, clinical trial demonstrated that 500 mg of magnesium daily for eight weeks improved sleep quality and quantity, as well as subjective symptoms of insomnia compared to placebo. [2]

Successful stress management strategies

Getting a good night's sleep will also help with stress, a leading circadian disruptor, but there are also many other effective stress management techniques that practitioners can share with their patients. In the scientific literature, mindfulness-based stress reduction, which is rooted in the concept of moment-to-moment, non-judgmental awareness, has received a great deal of attention thanks to the work of Jon Kabat-Zinn, PhD and other pioneers of this school of thought. Mindfulness-based stress reduction techniques, including body scanning, meditation, and various forms of yoga, have been shown to help people manage stress as well as improve outcomes associated with a variety of illnesses, including anxiety, cancer, chronic pain, depression, heart disease, insomnia, and more. [39]

Many integrative health experts believe that the answer to stress management lies with the breath. In fact, a 2018 systematic literature review found that slow deep breathing not only helps reduce stress because it impacts parasympathetic and central nervous system activities, it can also improve both physical and mental wellness on many levels. [45]

Acupuncture may also be worth considering. According to the researchers of a 2017 randomized placebo-controlled trial involving peri-menopausal patients with sleep issues, acupuncture helped improve sleep by impacting circadian balance and HPA axis hormonal changes including the release of cortisol. [17]

Dietary supplements for stress

Successful stress management and circadian rhythm function will benefit when HPA axis function is addressed. Dr. Alschuler utilizes a four-pronged approach to using dietary supplements for stress, which includes adaptogens, amino acids, minerals, and nervine herbs.

"Without a doubt, my go-to dietary supplements for stress include adaptogens, and I also typically recommend nervine herbs in tandem," says Dr. Alschuler. "Repleting minerals and amino acids also benefit circadian function because amino acids are precursors to neurotransmitters and minerals are cofactors involved in neurotransmitter synthesis. This is important because neurotransmitters, particularly serotonin, influence hypothalamic and pituitary initiation of the stress response."

By definition, adaptogens can help the human body "adapt" and resist biological, chemical, and physical stress by creating homeostasis and supporting optimal circadian balance. [28]

Withania somnifera (ashwagandha) is an adaptogen that has been featured prominently in scientific literature as it can help patients cope with stress and improve overall quality of life. [12]

Ginseng (Asian and American) is another adaptogen that has been shown to effectively regulate HPA axis hormonal changes due to stress and can also help reduce the risk of stress-associated psychological illnesses. [27]

The authors of a 2018 review concluded that *Rhodiola rosea*, another potent adaptogen, is an effective treatment for stress symptoms and can help prevent corresponding stress-related complications. [13]

Nervine herbs such as chamomile, hawthorn, lavender, lemon balm, oat seed, poppy, passionflower, skullcap, and verbena have been widely used to treat mild-to-moderate anxiety and can be effective stress management tools for some patients. [1]

Amino acids, such as L-ornithine, L-tryptophan, and L-tyrosine, are also critical when it comes to stress management as they positively influence the stress-induced imbalance between excitatory and inhibitory neurotransmitters and help regulate the stress response. [5]

Dietary supplements for circadian imbalance

The table below provides examples of nutrients and medicinal herbs that may help address circadian imbalance via improved sleep or stress.

Nutrient/medical herb	Effects
Amino acids (e.g., L-ornithine, L-tryptophan, L-tyrosine)	Positively influence stress-induced imbalance between excitatory and inhibitory neurotransmitters Help regulate the stress response [5]
GABA with 5-HTP	Improves sleep quantity and quality [21]
GABA with L-theanine	Improves sleep onset and non-REM sleep [23]
Ginseng (Asian and American)	Regulates HPA axis hormonal changes resulting from stress Reduces the risk of stress-associated psychological illnesses [27]
Lavender	Enhances sleep due to anxiolytic activity [38]
Magnesium	Improves sleep quality, sleep quantity, and symptoms of insomnia [2]
Melatonin	Improves sleep onset, quantity, and quality [15]
Nervine herbs (e.g., chamomile, hawthorn, lavender, lemon balm, oat seed, poppy, passionflower, skullcap, verbena)	Used to treat mild-to-moderate anxiety [1]
Rhodiola rosea	Reduces stress symptoms May help prevent stress-related complications [13]
Withania somnifera	Improves stress adaptation and resistance Improves overall quality of life [12, 28]

Circadian rhythm in clinical practice

Circadian balance is critical to disease prevention and optimal health. Both Drs. Alschuler and Bongiorno agree with many other integrative medical experts who feel that circadian imbalance should be prioritized by all clinicians to help prevent and reverse misalignment in this significant health system. Effective screening and diagnosis are followed by a comprehensive treatment protocol that can include recommendations for diet, lifestyle, and dietary supplements that are tailored to the individual needs of each patient.

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