# Effect of Light and Melatonin and Other Melatonin Receptor Agonists on Human Circadian Physiology

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**KEYWORDS**

• Advance • Agonist • Circadian • Delay • Light • Melatonin

**KEY POINTS**

- Circadian timing has a profound influence on mental health, physical health, and health behaviors.
- Individual patients suspected of misaligned circadian rhythms can vary in their suitability for light, melatonin, and other melatonin receptor agonist treatment.
- Prescribing a relatively consistent light/dark cycle is often the first step in treatment.
- Key features of light treatment to consider include timing, intensity, duration, color, light avoidance, and choosing a light device to best accommodate patient motivation for treatment.
- Key features of exogenous melatonin and other melatonin receptor agonist treatments to consider include timing, dose, fast or slow release formulations, and purity.

## INTRODUCTION

Multiple varieties of light devices and multiple formulations of exogenous melatonin are commercially available without prescription in the United States. Light devices are most commonly used by patients with seasonal affective disorder, who represent approximately 1% to 2% of the North American general population.[1] Similarly, approximately 2% of US adults use exogenous melatonin, most typically as a sleep aid.[2,3] There are also several melatonin receptor agonist formulations available via prescription in various countries around the world.

Light, melatonin, and other melatonin receptor agonists can significantly impact circadian ("body clock") physiology, particularly the *timing* of circadian rhythms. Circadian timing in turn has a widespread and profound influence on mental and physical health (eg, Refs.[4–6]). For example, there are projections from the central circadian clock to peripheral tissues,[7,8] and the circadian clock has a direct influence on sleep[9] and inflammatory processes.[10] The central circadian clock also influences circadian clocks in peripheral systems.[11] The focus of this review was on the use of light, melatonin, and other melatonin receptor agonists to shift central circadian timing in patients in whom misaligned biological rhythms are thought to play a role, and the practical issues surrounding their use. Light can also suppress melatonin[12] and increase alertness,[13]

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and exogenous melatonin can increase circulating levels of melatonin,[14] but here we restrict our focus to circadian phase shifting, as this is most often the aim of light and melatonin treatment. We intend for this review to complement rather than replace clinical recommendations on the use of light, melatonin, and other melatonin receptor agonists to treat circadian rhythm sleep disorders (Ref.[15]), depression (eg, Refs.[16,17]), and/or insomnia (eg, Ref.[18]). We provide a brief review of the human circadian system, followed by a summary of the patient characteristics and safety issues to consider before recommending light treatment, melatonin, or other melatonin receptor agonists to patients. We then review the characteristics of light that are relevant to circadian physiology, and practical aspects of light treatment and conversely, light avoidance. The important features of exogenous melatonin and other melatonin receptor agonists are then described, followed by practical aspects of melatonin treatment and, briefly, how melatonin can be combined with light treatment to increase shifts in circadian timing. We end with a consideration of how to evaluate patient outcomes after treatment.

## THE CENTRAL CIRCADIAN SYSTEM

The central circadian system can be conceptualized as having 3 components: (1) input pathways that provide signals to synchronize the endogenous central clock to the external environment, (2) the central clock, which generates the rhythms, and (3) output pathways or rhythms that convey the central clock signal to other regulatory systems in the brain and body (**Fig. 1**). In terms of input pathways, the strongest resetting agent is light. Light is captured by the 5 retinal photoreceptors (rods, blue cones, green cones, red cones, and the intrinsically photosensitive retinal ganglion cells [ipRGCs]) and the signal is transmitted to the central circadian clock.[19] Other "nonphotic" stimuli, such as exogenous melatonin, can also be used to shift circadian timing. Here we refer to *exogenous melatonin* as melatonin that people typically ingest, after which it enters the circulation and is believed to shift circadian timing by binding to melatonin receptors on the central clock.[20]

The central circadian clock is located in the suprachiasmatic nuclei (SCN) in the hypothalamus.[21] More than 70% of humans have an endogenous period greater than 24 hours (on average ~24.2 hours).[22,23] Thus, for most humans, their internal body clock takes more than 24 hours to complete 1 cycle, meaning that they have an endogenous tendency to drift later ("phase delay") each day. This is perhaps most commonly seen in the later sleep times that often occur on the weekend or work-free days.[24] A gradual later drift in circadian timing is also seen in totally blind individuals, as light does not reach their internal circadian clock.[25] Thus, daily input signals are required to shift the clock earlier ("phase advance") to synchronize the clock's timing to the external 24-hour day.

The output circadian rhythm often measured to infer the timing of the central circadian clock in humans is the endogenous melatonin rhythm. We use the term *endogenous melatonin* to refer to internally produced melatonin. The endogenous melatonin rhythm is believed to accurately represent the timing of the central circadian clock, as the secretion of melatonin from the pineal gland

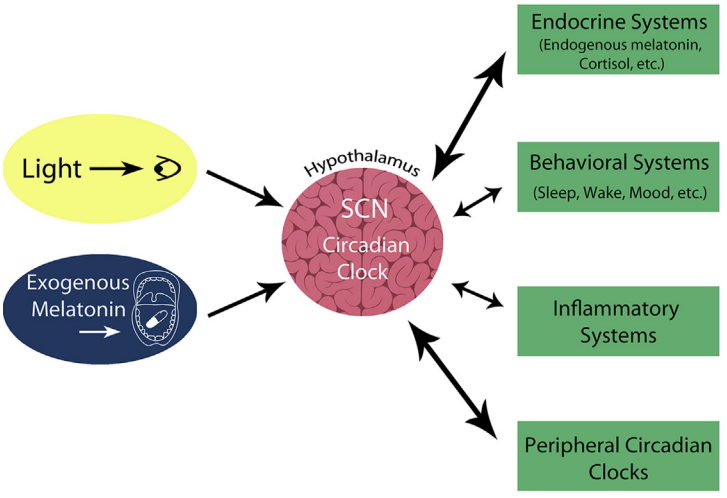


**Fig. 1.** The 3 components of the circadian system: (1) input pathways such as light and exogenous melatonin, which provide timing signals to the central circadian clock; (2) the central clock, SCN in the hypothalamus, which generates the rhythms; and (3) the output rhythms, which include endogenous melatonin and molecular peripheral circadian clocks contained in most tissues. Many of these output rhythms can feedback to the central circadian clock.