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Circadian Rhythms and Insomnia

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Abstract

Because our circadian rhythms have a strong influence on sleepiness/alertness, inappropriate timing of these rhythms with respect to the attempted sleep period can produce insomnia. Relatively delayed circadian rhythms have been associated with sleep-onset insomnia and advanced or early timed rhythms have been associated with early morning awakening insomnia. Therefore, management of these insomnias need to include treatments, such as bright light and melatonin, that will retime the circadian rhythms to be more in synchrony with the timing of sleep.

Keywords: Circadian rhythms, Delayed sleep phase, Advanced sleep phase, Insomnia, Bright-light therapy, Melatonin

Introduction

When there is a disparity between the timing of an individual's endogenous circadian rhythm and their preferred sleep–wake schedule, persistent or recurrent sleep difficulties can occur [1, 2]. This mismatch can lead to insomnia, decreased total sleep time and impaired daytime functioning. Difficulty in initiating sleep is associated with a delayed or late-timed circadian rhythm relative to the intended sleep time, while early morning awakening is associated with a relatively early timed or advanced circadian rhythm.

Normal Biological Determiners of Sleep

The two major biological determiners of sleep are sleep homeostasis and circadian rhythms [3]. Sleep homeostasis simply refers to the build-up of sleep drive or pressure during continued wakefulness much as going without food increases hunger or food-seeking drive. Similarly, the process of

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sleeping reduces sleep drive as eating reduces hunger drive. Independent of this determiner of sleep is the circadian rhythm system. Circadian rhythms (circa = about, dian = a day) refer to the 24-h oscillations in virtually every biochemical, hormonal, and physiological variable including core body temperature, cortisol, melatonin, sleep/wake cycle and sleepiness. An illustration of these rhythms is shown in Fig. 18.1, and indicates the normal relationship between the sleep period and two extensively researched circadian rhythms of core body temperature and melatonin hormone levels. All three rhythms (sleepiness, temperature, and melatonin) as well as almost every other biological and behavioral rhythm are being driven in synchrony by the central body clock, the suprachiasmatic nucleus (SCN). This is a small nucleus in the anterior hypothalamus that receives direct input from the retinas of the eyes [4]. The SCN controls the timing of the melatonin synthesis in the pineal gland [5] which then, through circulating plasma melatonin, feeds back to the SCN helping to maintain circadian rhythmicity [6].

In a controlled, constant environment the circadian rhythms oscillate unabated showing a strong endogenous origin. However, environmental stimuli and our own behavior can influence the timing of the rhythms and are called Zeitgebers or time givers.

Effects of Circadian Rhythms on Sleep

Our circadian rhythms exert a very strong effect on our subjective and objective sleepiness, that is, how sleepy we feel, how quickly we will fall asleep, and how likely we will awake. In a normally entrained person (e.g., someone with normally timed circadian rhythms) the sleep period occurs approximately between 11 P.M. and 7 A.M. Figure 18.1 indicates maximum circadian sleep propensity between 1 and 6 A.M., associated with high melatonin levels and the minimum core temperature (Tmin) [7]. Wake-up time usually occurs soon after the core body temperature begins to rise. Of particular relevance to circadian rhythm sleep disorders are two circadian periods of

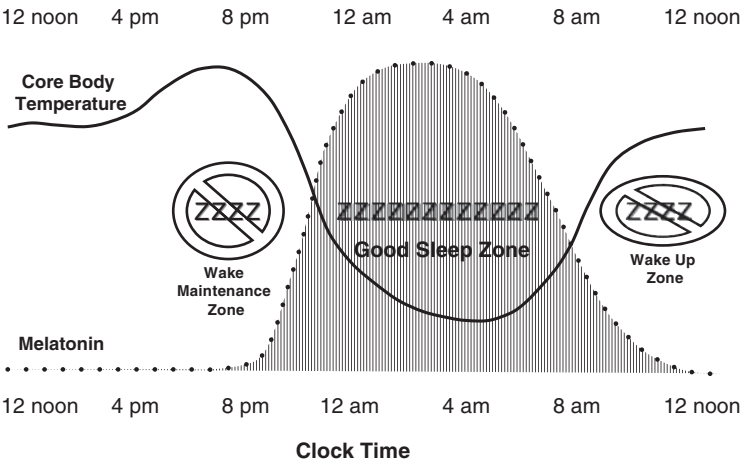

Figure 18.1 Graphical representation of the core body temperature (*solid line*) and melatonin (*dotted line*) rhythms over a 24-h period with the major sleep period indicated by the row of Zs and wake-maintenance and wake-up zones by "*not allowed*" signs over a short row of Zs

sleeping difficulty that surround the sleep-conducive period [8–11]. These are indicated in Fig. 18.1 as the wake-maintenance zone, a 3–4-h period normally between 6 and 10 P.M. when it is difficult to fall asleep and a less intense and longer wake-up zone when it is difficult to stay asleep.

Another important feature of our circadian rhythm is its period length, or time taken to complete one oscillation. Recent research has suggested that the endogenous period length of most young adults is somewhat longer than 24 h and is on an average 24.2 h [12] and considerably longer (over 25 h) for someone with a delayed sleep-phase disorder [13]. The clinical implication is that, in the absence of time cues or other entraining stimuli such as morning light, most young adults will have a tendency for their circadian rhythms to drift later, or phase delay, possibly resulting in sleep difficulty.

Insomnias Related to Circadian Rhythm Mistiming

Disturbances of the relationship between the endogenous sleep–wake rhythm and the preferred sleep–wake pattern within an individual can lead to chronic sleeping difficulties. If individuals have a delayed circadian rhythm but attempt to sleep during the earlier "normal" sleep time, they would be attempting to fall asleep during their evening wake-maintenance zone. Sleep initiation would be inhibited and, if the individual has to adhere to a normal awakening time, for example, to meet social or work obligations, total sleep time would be reduced. Several nights of reduced sleep will result in daytime impairment and distress.

Conversely, some individuals may have an early timed or phase-advanced circadian rhythm resulting in their wake-up zone occurring as early as 3 A.M. and therefore, sleep is curtailed earlier than desired. This also can lead to a reduced total sleep time, distress, and daytime impairment.

Circadian Rhythm Delay in Sleep-Onset Insomnia

The main feature of sleep-onset insomnia is difficulty of initiating sleep at the start of the sleep period. A delayed sleep phase can lead to chronic difficulties falling asleep at night as well as difficulty not being able to awake in the morning at a conventional time. If sleep onset is delayed over many nights and weeks, frustration and anxiety can develop and become associated with bedtime. This will lead to learned or psychophysiological insomnia (see Chap. 11) and contribute to the development of chronic insomnia [2].

There is increasing evidence for a circadian rhythm delay in sleep-onset insomnia. Morris and colleagues [14] found that sleep-onset insomniacs who took longer than 45 min to fall asleep also had a delay of their circadian core body temperature rhythm of approximately 2.5 h later than a control group of good sleepers. They were attempting to fall asleep within their predicted "wake-maintenance zone" in comparison to the control group who had bed times at least 2 h following this zone. More recent evidence supports this finding. In one study, 55% of individuals who experienced sleep-onset insomnia had markedly delayed (>2 h) melatonin rhythms [15]. In another study, sleep-onset insomniacs with average bedtimes at 12:25 A.M. and sleep latency of 60 min had an average melatonin onset at 12:15 A.M., over 3 h later than normal [16]. Therefore, sleep-onset insomnia appears to be associated with a

2–3 h delay of circadian rhythms as well as their associated wake-maintenance zone impairing the initiation of sleep.

Then the attempt to wake in the morning for work or domestic obligations, for example at 7 A.M., would be doubly difficult, because of insufficient sleep and trying to arise at the time of maximum circadian sleepiness, for that phase-delayed individual. In fact, when the opportunity arises, sleeping-in to a late time is made easier because the delayed circadian rhythm will have a delayed wake-up zone that, in this example, would not occur until about midday. However sleeping-in later in the mornings to catch up on lost sleep can further exacerbate the circadian phase delay because the removal of morning light while asleep releases the brakes on the tendency to phase delay [17–19].

Clinical Manifestations

Figure 18.2 shows the sleep pattern of an individual who presented to our clinic with sleep-onset insomnia. On weeknights the person was going to bed between 11:30 P.M. and midnight but taking between 60 and 90 min to fall asleep. Due to study commitments, he set the alarm for 7:30 A.M. and needed to be out of bed by 8 A.M. However, on most occasions he slept through the alarm. When he did get up earlier, he only obtained 5 h sleep. On the weekend, he stayed up on Friday and Saturday nights and slept in very late on Saturday and Sunday mornings. These sleep-ins typically result in greater difficulty falling asleep on Sunday night and difficulty in awaking Monday morning.

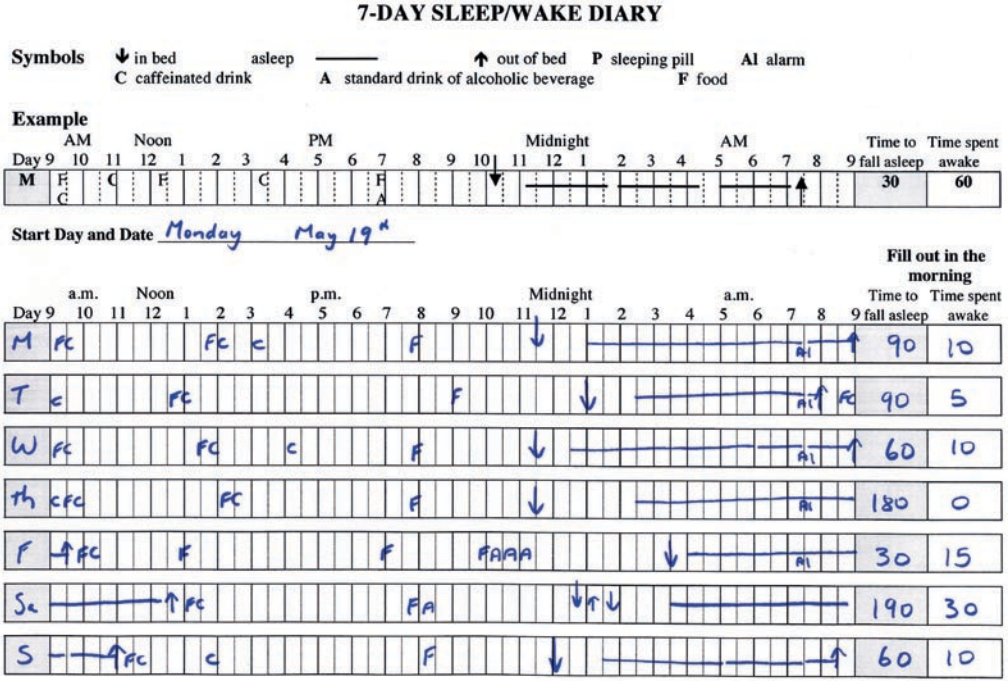

Figure 18.2 Example of a 7-day sleep/wake diary illustrating a typical client with mild-moderate circadian rhythms phase delay who experienced sleep-onset insomnia. Symbols are explained at the top of the diary

Apart from difficulty getting up in the morning, the client was beginning to feel very anxious and restless after going to bed. Individuals with sleep-onset insomnia often report being unable to "switch off" due to a racing mind. They can also feel as though they have lost control over their ability to fall asleep and feel frustrated and/or anxious. Repeatedly experiencing these feelings while attempting sleep can produce a conditioned or learned (psychophysiological) insomnia (see Chap. 11). Management of this type of insomnia will, therefore, require a multifaceted approach.

Circadian Phase Advance in Early Morning Awakening Insomnia

Chronic early morning awakening insomnia has been associated with an advanced circadian rhythm and with wake-up times ranging from 4:29 to 5:53 A.M., and total sleep times reduced to about 5 h [20–23]. Participants also experienced symptoms of daytime tiredness. Circadian rhythm timing of both temperature and melatonin rhythms was found to be advanced with temperature minima between midnight and 2:20 A.M. and urinary dim light melatonin onset (DLMO) ranging from 8:20 to 10:00 P.M. [21–23]. When compared to age-matched control groups, the insomniacs' temperature rhythms were significantly earlier by nearly 4 h and DLMO times earlier by more than 2 h.

Clinical Manifestations

People with chronic early morning awakening insomnia tend to experience overwhelming evening sleepiness and morning awakenings earlier than desired [2]. Although they could fall asleep in the early evening, they usually attempt to delay bedtime to a more socially acceptable time. Despite this, they will still awaken early and be unable to fall back to sleep. The total amount of sleep obtained can then be as little as 5–6 h leading to daytime sleepiness, fatigue, and other symptoms of sleep loss such as impaired motivation and concentration.

Figure 18.3 shows the sleep/wake pattern of a sleep clinic client who experienced early morning awakening insomnia. In the evening she experienced overwhelming sleepiness and, on four evenings, she unintentionally fell asleep briefly in front of the television. After going to bed, she experienced no difficulty falling asleep. However, after only 5– 6 h sleep, she woke and was unable to fall back to sleep. On average, she lay in bed for over an hour before getting up. Again, this can cause anxiety, frustration, and helplessness. During the day she felt fatigued, irritable, and unable to concentrate.

Management

Insomnia associated with delayed or advanced circadian rhythms needs a multifaceted approach combining behavioral, cognitive, and circadian-directed therapies. For those with sleep-onset insomnia and concomitant delayed circadian phase, appropriate treatments would include strategies to advance their circadian rhythms and sleep/wake pattern as well as psychological therapies for possible concomitant psychophysiological insomnia. Similarly, therapies to improve the sleep and daytime functioning of those with early morning awakening insomnia would include strategies to delay the circadian rhythm as well as cognitive behavior therapy.

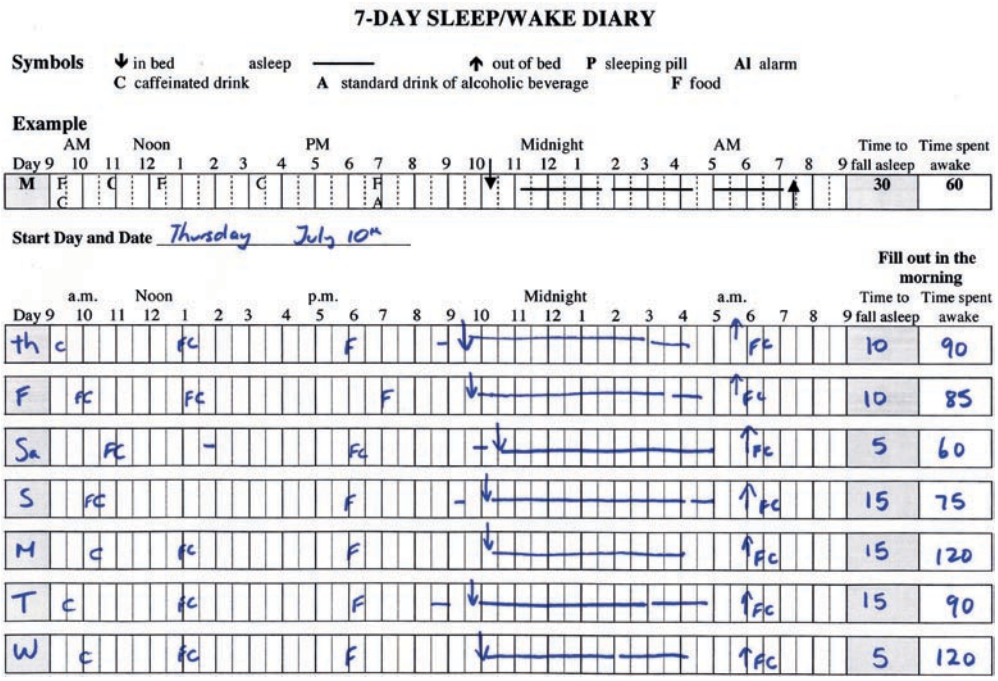

Figure 18.3 Example of a 7-day sleep/wake diary illustrating a typical client with an advanced circadian rhythm who experienced early morning awakening insomnia. Symbols are explained at the top of the diary

Retiming the Circadian Rhythm

The retiming of an individual's circadian rhythm may be achieved via zeitgebers (time givers) such as bright-light and exogenous melatonin or melatonin agonists.

Bright Light

Light entering the eye is the most powerful zeitgeber for retiming circadian rhythms. As a therapeutic tool, the light source may be sunlight or an artificial light device such as a commercially available light box. The timing of the light stimulus is crucial for effective treatment [24–27]. Studies have shown that bright light before the temperature minimum will produce a phase delay and bright light after the temperature minimum will produce a phase advance, that is, a shift to an earlier time. Therefore, bright morning light (after the Tmin) is recommended for those with an abnormally late rhythm and evening bright light (before the Tmin) for those with an early circadian rhythm and sleep pattern.

Morning outdoor light is recommended for those with sleep-onset insomnia. If an artificial light source is needed, broad spectrum white light boxes have been used to retime circadian rhythms. However, more recently it has been shown that shorter wavelength light, (blue–green light between 450 and 525 nm) is the effective part of the white light spectrum [28–30] with one study showing a phase-advancing effect in a group of mildly delayed sleepers [31]. However, clinical studies using these light wavelengths for sleep-onset insomnia have not yet been conducted.

Morning Light Therapy for Sleep-Onset Insomnia

In therapy, we suggest that the bright-light stimulus of about 1-h duration initially be administered immediately after awakening at the unconstrained ad lib wake time. The timing of awakening and the start of bright-light therapy should then be advanced earlier each morning by 15 min until the desired wake-up time has been reached. In our example (Fig. 18.2), the initial light exposure would start at 9 A.M. and then advanced by 15 min each day to the target wake-up time of 7:30 A.M. From our experience [31] we suggest continuing with 30 min of light exposure each morning with light therapy at that target wake time for at least 2 weeks. This will allow time for the apparently slower advancing sleep-onset time to "catch up" and finally result in adequate total sleep time. After therapy we suggest that clients continue to maximize light exposure in the morning, for example, by not wearing sunglasses on their way to work. We also advise dim light and quiet activities in the evening to avoid possible phase-delaying effects of evening bright light.

Evening Light Therapy for Early Morning Awakening Insomnia

Two studies have administered evening bright light to adults experiencing early morning insomnia [32, 33]. In these studies, light was administered for 4 h until midnight or 1:00 A.M. This produced delays in circadian rhythms as well as final wake-up times and increased total sleep time. As a long-lasting therapeutic intervention, we suggest that clients stay up for an hour later than their habitual bedtime with maximum ambient light. If available, an artificial light source of higher intensity would be recommended to achieve quicker results. We advise keeping active in the evening to prevent unintentional napping. We also advocate that clients, in this case, avoid bright morning light and may need to wear dark glasses or blue light blocking glasses if they wish to go outside in the first hours after awakening.

Melatonin

Other zeitgebers that have been shown to phase change circadian rhythms and sleep/wake schedules are exogenous melatonin and more recently melatonin agonists. As with light therapy the timing of melatonin ingestion is important. A recent study [34] suggested that the effects of melatonin administration and bright light are additive. However, to complement the effects of light therapy the timing of Melatonin administration must be 180 degrees or about 12 h different than that of light administration [35]. For phase advancing those with sleep-onset insomnia, melatonin ingestion should be in the evening approximately 4 h prior to the onset of endogenous melatonin or 6 h prior to habitual sleep-onset time [34–37]. For assisting phase delays in early morning awakening insomnia melatonin can be ingested at first awakening during the night [35, 38].

Although exogenous melatonin appears safe with short-term use, there is scant information about its long-term administration [39]. Some adverse side effects that have been reported following melatonin administration include headaches, dizziness, nausea, and drowsiness. [39]

More recently, Melatonin receptor agonists also have been shown to produce a phase change in healthy adults [40–42] and can also decrease sleep-onset

latency in those with insomnia [43–47]. However, their efficacy in treating insomnia associated with circadian rhythm disorders is yet to be evaluated.

Cognitive-Behavioral Therapy

In addition to morning bright-light therapy to address the circadian delay of sleep-onset insomnia it would be efficacious to use Stimulus Control Therapy instructions to address the conditioned insomnia likely to be present with this chronic insomnia [48, 49] (see Chap. 22). This will minimize the amount of time spent awake in bed trying to fall asleep and reassociate the bed with sleep rather than wakefulness and worry. As the circadian rhythm advances, the time of evening sleepiness and sleep onset will also gradually advance. Avoiding sleeping-in by keeping a consistent wake-up time is also necessary to reduce the likelihood of another phase delay.

For those experiencing early morning insomnia, in addition to evening bright-light therapy we suggest including a form of Bedtime or Sleep Restriction Therapy to minimize time in bed awake [50] (see Chap. 22). Staying up an hour later than habitual bedtime to administer evening bright light would be one part of this bed-restriction therapy. In addition, the client should get out of bed after their habitual sleep duration if they have already awoken or get out of bed at their first awakening if that has exceeded their habitual sleep duration. For example, the recommended protocol for our client in Fig. 18.3 would be evening light until 11–11:30 P.M. and "out of bed time" either on awakening if it is later than 5:30 A.M. or at 5:30 A.M. if already awake. Over the week(s), spontaneous wake-up time will get later and total sleep time will increase.

Conclusions

Circadian rhythm phase delays and phase advances are suggested as etiological factors for chronic sleep onset and early morning awakening insomnia, respectively. Circadian rhythm timing can be altered with Zeitgebers such as bright blue/green light or melatonin/melatonin agonists. Morning bright light and evening melatonin can advance or time earlier the circadian rhythms, thus serving as a treatment for the phase-delayed rhythms of sleep-onset insomnia. Evening bright light and morning melatonin administration can phase delay circadian rhythms and thus serve as treatment for early morning awakening insomnia. Because chronic insomnia from any etiological beginnings is likely to be perpetuated by learned or psychophysiological insomnia, treatment needs to be multifactorial and, in this case, include the appropriate cognitive/behavioral therapies.

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