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REVIEW ARTICLE

Circadian aspects in the aetiology and pathophysiology of insomnia

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Summary

Because the endogenous circadian pacemaker is a very strong determinant of alertness/sleep propensity across the 24 h period, its mistiming may contribute to symptoms of insomnia (e.g., difficulties initiating sleep and maintaining sleep) and to the development of insomnia disorder. Despite the separation of insomnia and circadian rhythm disorders in diagnostic nosology implying independent pathophysiology, there is considerable evidence of co-morbidity and interaction between them. Sleep onset insomnia is associated with later timed circadian rhythms and can be treated with morning bright light to shift rhythms to an earlier timing. It is also possible that the causal link may go in both directions and that having a delayed circadian rhythm can result in enough experiences of delayed sleep onset to lead to some conditioned insomnia or insomnia disorder further exacerbating a delayed circadian rhythm. Early morning awakening insomnia is associated with an advanced circadian phase (early timing) and can be treated with evening bright light resulting in a delay of rhythms and an improved ability to sleep later in the morning and to obtain more sleep. There is some evidence suggesting that sleep maintenance insomnia is associated with a blunted amplitude of circadian rhythm that may be treated with increased regularity of sleep and light exposure timing. However, this is an insomnia phenotype that requires considerably more circadian research as well as further insomnia clinical research with the other insomnia phenotypes incorporating circadian timing measures and treatments.

KEYWORDS
circadian rhythms, delayed sleep–wake phase disorder, early morning awakening insomnia, evening types, insomnia, sleep onset insomnia

WHAT IS CIRCADIAN?

Stemming from the Latin origin, "circa" in English translates to "about", and "dien" means "a day". Thus, circadian rhythms are near-24 h daily oscillations in virtually all living processes. Endogenous circadian rhythms (body clocks) have been investigated in humans for over half a century (Aschoff, 1965). More than 40 years ago the strength of the circadian clock on alertness/sleepiness was dramatically demonstrated. Experiments in a time-free controlled laboratory environment when participants were allowed to self-select bedtimes in a "free-running" condition showed that when sleep was initiated at different circadian phases the length of sleep obtained could more than double (Czeisler et al., 1980). When sleep opportunities were carefully controlled to occur at all circadian phases in the "forced-desynchrony" studies, it

was shown that after equal amounts of prior wake time, sleep latency was more than four-times longer when sleep onset occurred close to the core-body temperature maximum phase in the evening "wake-maintenance" circadian zone than when sleep was allowed at the temperature minimum circadian phase (Dijk & Czeisler, 1994; Lack & Lushington, 1996; Lavie, 2001). The impact of the circadian rhythm timing on sleep propensity led to the early suggestion that a desynchrony between the timing of the circadian system and choice of bedtimes could lead to insomnia (Strogatz et al., 1987).

THE "TWO PROCESS" MODEL

The two major biological determinants of sleep propensity (the two-process model) consist of accumulated time awake or time asleep (sleep homeostasis or Process S) and circadian rhythm phase (Process C). A summary and four decades of historical perspective on its development has been published recently by one of its founders (Borbely, 2022).

In the two-process model, the circadian influence is probably stronger than the homeostatic sleep drive, at least over 36 h of total sleep deprivation (Dawson & Reid, 1997; Strogatz et al., 1986). The strong influence of the circadian rhythm factor is not well understood by the public or by health practitioners and leads to one of the barriers in implementing treatments when circadian rhythms factors are likely to play a role in insomnia disorder. For example, an early illustration of the strength of the circadian factor was interpreted by the authors, not as the effect of the circadian rhythm factor (Process C), but as the hours awake (Process S). Forty young healthy participants were subjected to 28 h of total sleep deprivation during which they performed a cognitive psychomotor tracking task every half-hour throughout the 28 h (Dawson & Reid, 1997). The authors focussed on the period from 13 to 23 h of wakefulness and showed a steady decline in performance to levels comparable to an elevated blood alcohol concentration (>0.08%) that would be considered illegal for driving a vehicle. The thrust of the message was that loss of sleep should be considered as a serious contributor to impaired performance, as much as our society considers drink driving. It is one of the most cited articles in the sleep area (>800 citations to date) and in the media. However, it is also important for the public, and public safety and welfare authorities, to understand that the main source of impairment was not the hours awake, but the circadian rhythm effect as is evident in Figure 1.

The focus on the period at 13 to 23 h of wakefulness shows a dramatic decline in performance that is equivalent to increasing blood alcohol concentrations. Yet a broader perspective of all the data shows increasing performance from 1 to 12 h of wakefulness and another more rapid increase from 25 to 29 h of wakefulness. An unconfounded assessment of the effect of the hours awake would control for circadian timing by comparing a greater time awake but at the same circadian timing. The performance at 29 h of wakefulness should be compared with 5 h of wakefulness exactly 24 h previously (same circadian phase) but after an additional 24 h of wakefulness to test the effects of time awake. This comparison shows very little decline of performance even with the additional 24 h of wakefulness. Additionally, the performance at 29 h is markedly better than at 25 h of wakefulness, despite being awake for an additional 4 h. This variation of performance across 29 h of wakefulness demonstrates the strength of the circadian rhythm effects on performance, probably more than the time awake. Therefore, the involvement of this strong circadian process (C) should be considered in the aetiology of insomnia.

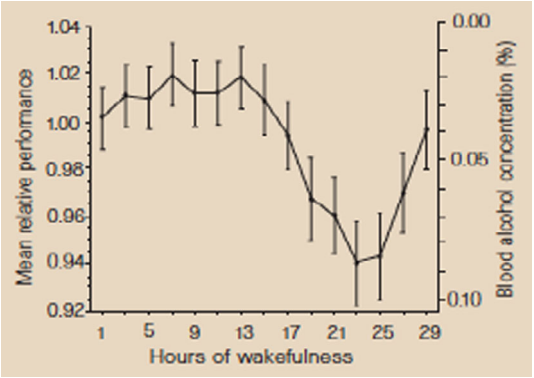

FIGURE 1 Psychomotor tracking task during 29 h of sustained wakefulness expressed as mean relative performance and the percentage blood alcohol concentration equivalent. Error bars ± SEM (taken from Dawson & Reid, 1997)

ARE CIRCADIAN RHYTHM DISORDERS REALLY SEPARATE FROM INSOMNIA DISORDERS? FROM THE PERSPECTIVE OF CIRCADIAN RHYTHM DISORDERS

In the nosology of sleep disorders (Diagnostic and Statistical Manual of Mental Disorders-5 [DSM5], International Classification for Sleep Disorders-3 [ICSD3]) insomnia and circadian rhythm sleep disorders are listed separately, suggesting a different pathophysiology (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2022). The most common circadian disorder, delayed sleep–wake phase disorder (DSWPD), is defined as presenting a sleep/wake pattern that is delayed from conventional sleep times (~23:00h – 07:00h) by more than 3–4 h. For example, the bed period of a patient with DSWPD may extend typically from 02:00h to 10:00h or later, thus obtaining an adequate amount of sleep, when permitted to sleep-in to those later than conventional times. However, when attempting sleep at an earlier conventional sleep time, patients with delayed sleep–wake phase disorder have difficulty initiating sleep. The conventional wisdom has suggested that the robust circadian rhythm research offers an obvious aetiology of the clinical symptoms of delayed sleep–wake phase disorder, a comparable delay of their circadian rhythms or body "clock". It is said that when sleeping at their optimal circadian phase (i.e., 3–4 h later), they sleep normally, (i.e., have no difficulty initiating sleep). However, someone with

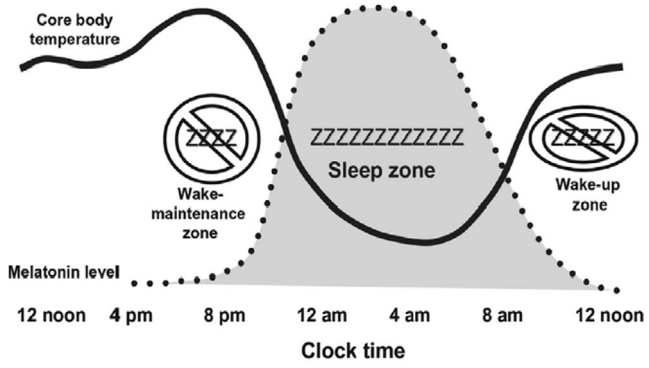

FIGURE 2 Circadian rhythm of melatonin and core body temperature of a conventionally timed sleeper (i.e., ~23:00h to 07:00h). Core temperature is strongly and positively associated with the circadian rhythm of alertness. Thus, the nadir of core temperature is the optimal sleep time and the two core temperature peaks (i.e., maximum daily alertness) before and after the sleep zone are associated with sleep inhibition, that is, wake maintenance and wake-up zones, respectively

DSWPD can present with sleep onset insomnia symptoms when attempting to fall asleep at an earlier, conventional, sleep time that coincides with their circadian delayed evening wake maintenance zone (Figure 2). In this case delayed sleep–wake phase disorder may present with sleep onset insomnia only if meeting socially appropriate sleep times that are inappropriate for their circadian timing. Hence it is assumed that the sleep onset difficulty is only a function of a delayed circadian rhythm and not caused by insomnia symptoms that should be evident, regardless of circadian phase of attempted sleep. So why should we consider circadian rhythm aspects in the discussion of the pathophysiology of insomnia?

Evidence suggests that even when initiating sleep at their appropriate circadian phase, patients with delayed sleep–wake phase disorder still exhibit abnormally long sleep onset latencies (e.g., >30 min Lovato et al., 2016; Saxvig et al., 2013; and >20 min Murray et al., 2019), significantly longer than good sleepers at their typical sleep time (Rahman et al., 2009). Therefore, patients diagnosed with delayed sleep–wake phase disorder still show clinical symptoms of sleep onset insomnia even when sleeping at their ideal circadian late times.

DSWPD AND SLEEP ONSET INSOMNIA (SOI) OVERLAP

To understand the development of sleep onset insomnia, it would be helpful to describe the typical clinical history of those with delayed sleep–wake phase disorder. Most would have a history of forced awakenings to make social (e.g., family, work, etc.) obligations or to attend school at a time earlier than they would prefer, given their delayed circadian rhythm. On nights preceding these early forced awakenings, they may strategically aim for an earlier sleep onset time to obtain an adequate amount of sleep before the necessary earlier awakening time. However, they typically have trouble falling asleep at this earlier bedtime because it falls into the evening "wake maintenance zone" close to the maximum core-body temperature phase of their circadian rhythm. The wake maintenance zone is associated with an increased core body temperature and increased alertness, the net effect of which inhibits sleep onset (Dijk & Czeisler, 1994; Lack & Lushington, 1996; Lavie, 2001). This frequent difficulty in initiating sleep with earlier bedtimes is not a pleasant experience. It is associated with frustration at the failure to fall asleep and worry that their window of sleep opportunity (given the fixed forced awakening time the next morning) is shrinking the longer it takes to fall asleep. On these nights, the bedroom environment and the conscious desire to fall asleep is associated with frustration and worry leading to the "fight-or-flight" response from activation of the sympathetic division of the autonomic nervous system and hypothalamic/pituitary/adrenal (HPA) axis. Thus, with repeated nightly associations the "fight-or-flight" response becomes classically conditioned to be elicited automatically with the presentation of the antecedent conditions (e.g., bedroom, time of night, desire to fall asleep, etc.) developing a more enduring insomnia disorder that will operate independently of the circadian rhythm phase. Therefore, at least some patients with delayed sleep–wake phase disorder are likely to have developed some chronic sleep onset insomnia arising from the many occasions they have attempted to sleep during their circadian wake-maintenance zone. There is clear evidence that those presenting with sleep onset insomnia show a delayed circadian rhythm as measured by their core body temperature (Morris et al., 1990).

However, it is important to consider that the relationship between delayed sleep–wake phase disorder and sleep onset insomnia is bi-directional. We have illustrated how patients with delayed sleep–wake phase disorder may, over time, develop insomnia symptoms as a result of conditioned responses. On the other hand, those with sleep onset insomnia and no indication of circadian misalignment can, over time, disrupt their circadian rhythm timing. For example, patients with sleep onset insomnia may engage in additional late-night activities (e.g., work, gaming, interacting with others, reading in bed with a bright bedside light, watching TV on a big screen, etc.). Often, these behaviours are associated with time-cues (e.g., light from device or overhead lights) that in turn delays the timing of the circadian rhythms and perpetuates the inability to fall asleep. The mechanisms by which this link between insomnia and disruption of circadian rhythms occurs have had little research focus to date and warrant further empirical investigation.

THE PUZZLING "NON-CIRCADIAN" DSWPD

Despite the wealth of experimental circadian research providing a very plausible explanation for the delayed sleep initiation in delayed sleep–wake phase disorder when attempting sleep at an inappropriately early circadian phase, a large percentage of clinically diagnosed DSWPD patients do not, in fact, have abnormally delayed circadian rhythms. In a large clinical trial that had recruited 186 with delayed

sleep–wake phase disorder, Sletten et al. (2018) found that 62 (33%) did not have abnormally delayed melatonin circadian rhythms. Furthermore, Micic et al. (2017) found among 16 clinically diagnosed delayed sleep–wake phase disorder patients more than half (56%) had both DLMO and a core body temperature minimum timing the same as the control participants (~21:00h and 05:00h, respectively). This apparent anomaly raises doubts about the dependence of sleep initiation difficulties in DSWPD being due simply to a delay of circadian rhythms. The predicted evening "wake-maintenance zone" for these "non-delayed" DSWPD patients, based on normative data, would be the conventional 18:00h–21:00h period ending at least 2 hours before their preferred sleep onset time of 23:00h. However, when hypothetically challenged with a bedtime at this preferred early sleep onset time, the estimated sleep latency was prolonged (>1 h) for the patients with delayed sleep–wake phase disorder (Micic et al., 2016).

There seem to be two possible explanations for this substantial percentage of DSWPD patients who do not have an abnormally delayed endogenous circadian rhythm: (1) an abnormal phase angle between endogenous circadian timing and the sleep/wake cycle and (2) the presence of chronic sleep onset insomnia. While an abnormal phase angle is an interesting possibility for these "non-circadian" DSWPD patients, it would have to be confirmed by carefully controlled experimental circadian studies as well as research to identify their phase response curve to light pulses. The other plausible explanation of the delayed sleep/wake pattern of the "circadian" and "non-circadian" DSWPD is that they are manifesting a chronic sleep onset insomnia (SOI) disorder. The earlier section (SOI) depicted the scenario leading to the development of a conditioned insomnia response based on some delay of the circadian rhythm contributing to the initial sleep onset difficulties. Although in the "non-circadian" DSWPD patients circadian timing is within the normal range, it is somewhat later than normal and may be contributing to some extent to sleep onset problems. It should be recognised that a wide range of physiological and psychological variables can contribute to sleep onset difficulties on any one night and that individuals vary considerably in the source of these contributing causes of difficulties. It may be that the patients with "non-circadian" delayed sleep–wake phase disorder were more reactive to the developing difficulties initiating sleep and developed more rapidly a conditioned or habitual insomnia response. Once this difficulty is severe or frequent enough it becomes self-perpetuating. Each night of sleep onset difficulty is experienced as a threat and elicits a "fight-or-flight" reaction. It reinforces the association and strengthens the probability of occurring in the bedroom environment when attempting sleep. Therefore, the discovery of these "non-circadian" DSWPD patients suggests the presence of sleep onset insomnia in the circadian rhythm disorder of delayed sleep–wake phase disorder.

Therefore, from the perspective of those diagnosed with circadian rhythm disorders, in particular DSWPD, there is evidence suggesting a degree of sleep onset insomnia contributing to their delayed sleep/wake pattern. Even when sleeping at their ideal circadian rhythm phase at least some of them show sleep onset difficulties of extended sleep onset latencies. In summary, the experimental investigations of people with circadian rhythm disorder of delayed sleep/wake phase suggests multiple contributors to sleep onset insomnia including circadian rhythm phase delay as well as conditioned insomnia, in which the relative strengths of these contributors can vary between individuals.

FROM THE PERSPECTIVE OF THOSE DIAGNOSED WITH INSOMNIA

Insomnia disorder nosologies have traditionally recognised three main nocturnal insomnia symptoms: difficulty initiating sleep, difficulties maintaining sleep, and difficulties with awakening earlier than intended. Circadian rhythm factors have been associated with all three of these phenotypes. Sleep onset insomnia has been associated with a delay of the timing of circadian rhythms, sleep maintenance difficulties with reduced amplitude of core temperature rhythms, and early morning awakening insomnia with early timed circadian rhythms.

Sleep onset insomnia

Considerable evidence links sleep onset insomnia with a delayed circadian rhythm. This was first shown in a laboratory controlled constant routine protocol to eliminate the effects of sleep/wake and activity on the core temperature rhythm (Morris et al., 1990). They found that those diagnosed with sleep onset insomnia had an endogenous core temperature rhythm timed about 4 h later than the healthy good sleepers. The good sleepers with an objective sleep onset latency of 11 min were attempting sleep almost 2 hours after their predicted evening wake-maintenance zone, while those with insomnia (SOL = 42 min) were attempting sleep onset in the middle of their predicted wake-maintenance zone (Morris et al., 1990). They suggested this previously unrecognised circadian delay was contributing to their sleep onset insomnia, as Strogatz et al. (1987) had earlier suggested. Wright et al. (2006) found in a large study of sleep onset insomnia ($N = 84$) that the group had an average dim light melatonin onset (DLMO) time at 22:06 h which was 76 min later ($t = 6.61$, $df = 245$, $p < 0.001$) than for normal, good sleepers at 20:50 h (Burgess et al., 2008). Wright et al. (2006) subdivided their sleep onset insomnia sample into those with a normally timed dim light melatonin onset ($N = 38$, 20:51 h) and those who were more delayed ($N = 46$, 23:08 h) and found that only the delayed insomniacs showed significant correlations ($p < 0.001$) between their dim light melatonin onset times and sleep timing ($r = 0.43$–0.53). There was no correlation between the dim light melatonin onset time and sleep timing (all $p > 0.40$) in the early circadian timed sleep onset insomnia sub-group. They suggested that the sleep onset insomnia of the early, normally timed DLMO group may arise more from a conditioned insomnia that is independent of the effects of circadian timing and that in the later DLMO timed group circadian phase is contributing more to the degree of the insomnia. It is tempting to see parallels with the normally timed dim light melatonin onset group here and the "non-circadian" DSWPD group and the later timed DLMO group similar to the "circadian"

DSWPD group. However, the later DLMO group in the Wright et al. (2006) study did not have sleep patterns late enough to qualify as DSWPD. They were diagnosed as having sleep onset insomnia. The main point here is that a large percentage (55%) of this sleep onset insomnia cohort had a delayed circadian rhythm and the amount of delay of the rhythm is related to the delay of their sleep pattern and difficulty initiating sleep.

Other research has confirmed the later circadian rhythms in those with sleep onset insomnia. Van Veen et al. (2010) found those with sleep onset insomnia compared with healthy controls had a mean dim light melatonin onset time 101 min later and were attempting sleep about an hour earlier in the circadian phase. Van der Heijden et al. (2005) compared ADHD children with ($N = 66$) and without ($N = 20$) sleep onset insomnia. Those with insomnia had a dim light melatonin onset 45 min later and were attempting to sleep only 15 min after dim light melatonin onset compared with children without insomnia who were attempting sleep 35 min after dim light melatonin onset. They suggested that the children with sleep onset insomnia were attempting sleep at a relatively earlier circadian phase and their insomnia had a circadian rhythm contribution.

Early morning awakening insomnia

Those without difficulty initiating sleep but who wake before they intend to and cannot re-initiate sleep are suggested to have an advanced (early timed) endogenous circadian rhythm (Strogatz et al., 1987). Clinically this type of insomnia manifests as earlier than normal bedtimes and difficulty staying awake until that early bedtime. Patients would like to be able to stay alert until a later, more conventional, bedtime but struggle to do so often failing with an unintentional nap in front of the TV or reading in a lounge chair. When they do turn out the lights, they fall asleep quickly and sleep well for a few hours. These few hours of sleep reduce their homeostatic sleep drive but, before being able to discharge it entirely, their circadian system has entered an early timed alert zone (Dijk & Czeisler, 1994; Lack & Lushington, 1996). This early timed alert zone terminates their sleep before accumulating adequate sleep. This early morning awakening insomnia is often associated with daytime symptoms of sleepiness as well as fatigue.

The timing of the early awakening insomnia sleep pattern would be described as definite morning types (Horne & Östberg, 1977) whose preliminary physiological data suggested an advanced core temperature rhythm. Other earlier studies showed that those with early morning awakening insomnia had phase advanced circadian rhythms. Lack et al. (1996) carefully selected a group of ten middle-aged early morning awakening insomnia participants and compared them with eight age-matched good sleepers in a 26 h experimental modified constant routine. The routine allowed the unmasked assessment of the endogenous core temperature rhythm in addition to the endogenous melatonin rhythm. The modification allowed the objective sleep propensity rhythm to be measured with half-hourly 10 min sleep opportunities. Although the actigraphically measured home sleep onset times did not differ between groups, the wake-up times were 2.5 h earlier and the total sleep time 2 h less for the insomnia group. The laboratory protocol showed that the insomnia group had temperature rhythm markers about 4 h earlier. The good sleepers had a more typical temperature nadir at 04:00h while the insomnia group was at 00:20h. In addition, the melatonin rhythm markers were about 2.5 h earlier and the sleep propensity rhythm phase markers were about 2 h earlier in the insomnia group. In summary, the early timed circadian rhythms of early morning awakening insomnia would make it difficult for them to continue sleeping in the later morning and would result in a reduced total sleep time. This is strong evidence of a circadian rhythm contribution to the pathophysiology of this type of insomnia.

Other early studies were consistent with this result. Kerkhof and van Vianen (1999) in a study of 80 chronic insomnia patients measuring ambulatory oral temperature found differences in the nature of the insomnia symptoms depending on the timing of their temperature rhythms. Those whose peak temperatures were earlier (14:00h) had more awake time in the later part of the sleep period and less total sleep time. On the other hand, those with relatively late temperature maximums had mainly a problem with longer sleep onset latencies at the beginning of their sleep periods.

More recently the pathophysiological involvement of circadian rhythm mistiming has again been recognised by Flynn-Evans et al. (2017). They compared 68 primary insomnia patients with 18 age-matched good sleepers. Although the bedtimes and wake-up times of the two groups did not differ, the insomnia group had longer sleep latencies and more wake time with about 2 h less total sleep time. The insomnia group had a later DLMO and a considerable percentage of them (32%) were attempting to sleep before or within 1 hour of their dim light melatonin onset. Typically, good sleepers attempt sleep about 2 h after their DLMO and have short sleep latencies. The insomnia participants attempting sleep at an abnormally early circadian phase had exceptionally longer sleep latencies. They suggested that these insomnia participants were attempting sleep within their wake-maintenance zones. Kim et al. (2020) have also shown a relation between the timing of DLMO and sleep maintenance problems. The earlier the dim light melatonin onset, the more wake time was experienced after initial sleep onset.

Sleep maintenance insomnia

First it should be recognised that although the sleep symptoms of insomnia have traditionally been categorised as initial sleep onset, sleep maintenance, and early awakening difficulties these are somewhat arbitrary distinctions and not mutually exclusive. Patients can experience one, two, or all three symptoms all the time or different symptoms on different days or slower changes between symptoms over longer time spans. Second, the operational distinctions between these symptoms, particularly between sleep maintenance and early awakening difficulties, has not yet achieved a good consensus. For example, patients mainly with an early awakening difficulty will often

show early awakenings before their final awakening rather than necessarily a "solid" sleep up until their final awakening and thus have some sleep "maintenance" symptoms. Probably the main defining characteristic of those who can be categorised as having sleep maintenance insomnia (as opposed to early morning awakening) is the ability to reinitiate another sleep bout late in the sleep period and finally awaken at about their intended wake time.

An early attempt to measure the core body temperature rhythm in sleep maintenance insomnia (Lack et al., 1985) used a portable monitor of rectal temperature in ambulatory participants over a period of a week. The average 24 h ambulatory rhythms of rectal temperature were compared between eight "poor sleepers" of various types of sleep difficulties with age-matched good sleepers. They found no differences in the mean core body temperature across the daytime hours but significantly elevated temperatures across the early sleep period. However, this uncontrolled ambulatory monitoring study could not rule out the possibility that the periods of wakefulness in the insomnia group could have caused the overall elevated sleep period temperatures since sleep, itself, causes a decrease in core temperature and wakeful periods an increase (Barrett et al., 1993).

To control for this sleep/wake effect as well as other activity effects on ambulatory measured core temperature, Lushington et al. (2000) used a laboratory controlled constant routine protocol to assess the endogenous core temperature rhythms of sleep maintenance insomnia. Sixteen older sleep maintenance insomnia patients were compared with 16 age-matched good sleepers. The insomnia group showed similar core temperature to the good sleepers across the typical daytime but a lesser decrease of core temperature during the night time sleep period and thus a reduced amplitude of the endogenous core temperature rhythm. Since daytime administration of melatonin produces peripheral vasodilation, reduced core temperature, and increased objective sleepiness in good sleeper and insomnia groups (Gilbert et al., 1999; Lushington et al., 1997; Van Den Heuvel et al., 1998), it could be suggested that the insomnia patients have an impaired nocturnal secretion of melatonin. However, the same group (Lushington et al., 1998) found no differences in total or nocturnal melatonin production between a large group ($N = 56$) with sleep maintenance insomnia compared with an age matched group ($N = 52$) of good sleepers. Furthermore, they found no correlations between total or nocturnal melatonin outputs with any diary sleep variables. They concluded that the large differences of melatonin production between individuals are unrelated to sleep. Therefore, the possible explanation of deficient melatonin production to account for the impaired endogenous drop of nocturnal core body temp was not supported. Instead, an explanation involving an attenuation of the amplitude of core body temperature rhythm perhaps also involving nocturnal physiological or metabolic activation seems worthy of consideration. In any case, it appears that there are likely to be some circadian rhythm pathophysiology in sleep maintenance insomnia as well as in the other two insomnia types.

It has been suggested that irregularity or night-to-night variability of sleep timing leads to a reduced amplitude of circadian rhythms and, as a result, is detrimental to sleep quality and possibly a contributor to sleep maintenance insomnia. It is generally the case that good sleepers tend to have more regular sleep and wake times than poor sleepers and that effective CBTi interventions to treat insomnia include regularising bed and rise times (Bei et al., 2016). Those who have greater irregularity of sleep timing, often associated with a delayed sleep pattern, have a reduced amplitude of 24 h light exposure, greater impairments of daytime functioning (Lack, 1986; Phillips et al., 2017), impaired mental health (Bei et al., 2016; Fang et al., 2021; Murray et al., 2019; Swanson et al., 2023), and even increased physical health risks (Scott et al., 2023). However, contrary to the initial assumption of greater sleep timing variability leading to lower amplitude rhythms and reducing sleep quality, Baehr et al. (2000) showed that more evening types with typically more variable sleep timing, when kept on a fixed schedule actually had higher amplitude core body temperature rhythms. Therefore, the role of night-to-night variability of sleep timing on circadian amplitude in sleep maintenance insomnia is still largely unexplored, as is the possible role of regularising sleep timing on circadian rhythm amplitude and improvement of sleep maintenance insomnia and mental health.

INSOMNIA TREATMENT STUDIES USING CIRCADIAN INTERVENTIONS

We have suggested a possible causal involvement of circadian pathophysiology in certain types of insomnia, sleep onset insomnia from a circadian phase delay, early morning awakening insomnia from a circadian phase advance, and sleep maintenance insomnia from a blunted circadian amplitude. However strong the association, the implied causal involvement needs experimental manipulation to strengthen this circadian aetiology.

Morning bright light treatment for sleep onset insomnia

Although several studies have established that morning bright light can phase advance the circadian rhythms and sleep period of patients diagnosed with delayed sleep–wake phase disorder (Cole et al., 2002; Lack et al., 2007; Rosenthal et al., 1990; Watanabe et al., 1999), few studies have attempted morning bright light for sleep onset insomnia. Guilleminault et al. (1995) carried out a small randomised control trial of 30 insomnia patients allocated to three different arms: (1) sleep hygiene (also including some stimulus control instructions), (2) sleep hygiene and afternoon exercise, or (3) sleep hygiene and morning bright light. They were selected for the difficulty of falling asleep or awakenings in the first third of their sleep. After 4 weeks the morning light therapy group showed greater increases of total sleep and greater improvement of sleep latency than the other two groups. Although they did not measure circadian timing, they attributed the greater treatment effectiveness of the morning light group to a likely phase advance of the circadian system.

Lack et al. (2007) carried out a small (8 per group, age = 29 years) randomised control trial using either morning bright light (2500 lux) or dim (100 lux) red light on 7 consecutive mornings starting an hour before their typical weekday wake time. Compared with the dim light control group the bright light group showed significant phase advances of dim light melatonin onset and actigraphy measured sleep onset time, a significant decrease of sleep onset latency, and increase in total sleep time with no differences in wake-up times. These improvements continued to the 3 week follow-up. The bright light treatment group also showed greater decreases in daytime sleepiness and other detrimental daytime functioning measures. These participants did not meet the criteria for delayed sleep–wake phase disorder, yet did have somewhat later bedtimes (~midnight) and wake times (08:00–09:00h) than normal. They did fulfil the criteria for chronic insomnia disorder with a mean sleep latency of approximately 1 h, with about 7 h of total sleep time, that is an hour less than recommended for this young adult age group.

In a clinical environment, likely without circadian phase measures, a circadian phase delay may not have been suspected and CBTi would have been indicated for treatment. The dim light melatonin onset measured before treatment in this experimental study was about midnight that is more than 2 hours later than one would expect given their sleep period timing. If dim light melatonin onset or other circadian timing information were available clinically (Dijk & Duffy, 2020; Scott et al., 2023), then chronobiologic treatment would also be indicated and this study (Lack et al., 2007) shows it would have had a therapeutic effect on reducing clinical insomnia symptoms. In fact, both groups showed significant decreases in the Insomnia Severity Index (ISI) measures which may have arisen from the early consistent wake time used for the administration of morning light. This is one of the elements of stimulus control therapy (Bootzin, 1972) of a fixed early morning wake time and the improvement of ISI in the control group would be consistent with the possibility that some element of conditioned insomnia was also present in this patient sample. In summary, both these initial promising studies suggest that with more comprehensive information available including circadian phase measure, a more comprehensive and effective therapy, including the treatment of circadian mistiming, can be an effective adjunct to the treatment of sleep onset insomnia.

Phase advances in the circadian system can be achieved with bright light administered during typical wake-up times. There is now substantial evidence that phase advances can also be achieved with a low dose (0.3–3.0 mg) of rapidly absorbed melatonin administered in the late afternoon and early evening about 3 h before the endogenous dim light melatonin onset or, without dim light melatonin onset evidence available, about 6 h before the expected sleep onset time or 10 h before midsleep calculated from sleep diaries (Burgess, 2010; Lewy et al., 1998; Lovato et al., 2016). The use of early evening melatonin administration has been considered mainly for the treatment of delayed sleep–wake phase disorder. However, in these studies there is evidence that it is also effective for treating the sleep onset insomnia often associated with delayed sleep–wake phase disorder. Sletten et al. (2018) administered 0.5 mg quick release melatonin for the treatment of 54 DSWPD patients compared with a matched group of 50 DSWPD patients administered placebo. Administration was scheduled at an hour before their post-treatment desired bedtime of about 21:30h and 22:30h, respectively. Their pre-treatment dim light melatonin onsets and habitual bedtimes were 22:50h and 01:00h, respectively. At baseline these DSWPD patients had sleep onset insomnia even at their late habitual bedtimes, averaging sleep onset latencies of 42 min by diary measure and 21 min by actigraphy. During treatment they were instructed to go to bed at their desired earlier bedtimes resulting in increases of sleep latency at these earlier bedtimes, but the melatonin treated group showed a significantly lesser increase of sleep latency. The melatonin group also showed greater decreases of insomnia severity index and subjective daytime impairments. In sub-samples of both groups follow-up dim light melatonin onset measures showed a greater phase advance in the melatonin group than in the placebo by 30 min, however, this was not a significant group difference in these smaller sub-samples. They attributed the greater sleep improvements from melatonin treatment largely to the sleep promoting effects of melatonin when administered before the dim light melatonin onset (Gilbert et al., 1999). For our purposes the Sletten et al. (2018) study illustrated again that patients with delayed sleep–wake phase disorder sleeping at their typical delayed times still manifest sleep onset insomnia and that this insomnia could be effectively treated with circadian intervention tools of rescheduling and evening melatonin.

Evening bright light therapy for early morning awakening insomnia

The earliest circadian intervention for the treatment of insomnia appears to be by Campbell et al. (1993) with the use of 12 evenings of bright light for the treatment of chronic sleep maintenance insomnia in 16 older patients. Without changing the amount of time in bed the group showed a decrease of wake after sleep onset (~60 min), an increase in total sleep time and sleep efficiency (from 78% to 90%). Although these participants were not recruited for early morning awakening insomnia per se, the assumption of the study was that a phase delay resulting from evening light therapy would reduce the amount of wake time in the latter part of their sleep periods and that was confirmed.

This promising start to the use of circadian treatments for insomnia coincided with another pilot study using only two nights of evening bright light exposure (Lack & Wright, 1993). Nine participants with symptoms of chronic early morning awakening insomnia had their sleep measured objectively with actigraphy before and after treatment as well as endogenous core temperature rhythm and melatonin rhythms before and after treatment in a 26 h laboratory constant routine protocol. The participants were treated with two evenings of bright (2500 lux) white light from 20:00 h to 24:00 h. Following treatment both the circadian rhythms delayed by 2 h. Their sleep onset times did not change but wake-up times were delayed by 72 min and their total sleep time was increased by 73 min. A decade later the same group (Lack et al., 2005) used the same treatment and

measurement protocol but included a dim (<100 lux) red light control condition in a randomised control trial and extended the follow-up period to 4 weeks. Again, the bright white light exposed group showed delays (>2 h) of both temperature and melatonin rhythms, while the dim red light condition showed no change. The active treatment group also showed a greater decrease of wake time, delay of final wake time, and increased total sleep time measured by diary and actigraphy. Furthermore, there were improvements in daytime measures with the active treatment group showing fewer days of depression symptoms over the 4 week follow-up period.

Not all studies of this type have successfully improved the sleep in chronic insomnia. Suhner et al. (2002) recruited 15 older participants with chronic sleep maintenance insomnia and treated them with 10 nights of 2 h of evening bright light. Following this treatment, they found a 94 min delay in the temperature rhythm from 03:00 to 04:33h. This was accompanied by delays of both sleep onset and wake times but no change in the total sleep time or sleep efficiency. The lack of a significant improvement in sleep parameters in this study compared with the previous three studies does not have an obvious explanation. The timing of the light exposure was chosen specifically to be more easily administered at home for 2 h each night ending about an hour before bedtime compared with Lack and Wright (1993) and Lack et al. (2005) in which the light was administered for 4 h including an hour past the participants' typical bedtime. This more demanding but more acute (2 nights) treatment seems to have produced a greater circadian phase delay (~2 h) despite the much greater amount of actual light treatment time (20 h) in Suhner et al. (2002). Yet the earlier treatment study by the same group (Campbell et al., 1993) using the same light administration procedure was able to achieve a circadian phase delay of >2 h. A notable difference with the Suhner et al. (2002) study is that with a lesser circadian phase delay as well as some delay of the sleep period means that the treatment resulted in a smaller delay of phase angle between sleep period and the core temperature rhythm. The Suhner et al. (2002) study delayed the temperature nadir in the sleep period just over an hour (64 min), whereas the other three more effective studies delayed it in the respective sleep periods by 80 min (Lack & Wright, 1993), 130 min (Lack et al., 2005), and 158 min (Campbell et al., 1993). Therefore, the more effective treatments with evening bright light for early morning awakening or sleep maintenance insomnia appears to require a delay of the circadian nadir of core temperature rhythm into the last 2 hours of the sleep period. This would locate the maximum circadian drive for sleep (Dijk & Czeisler, 1994; Gradisar & Lack, 2004; Lack & Lushington, 1996) in the last few hours of sleep, thus counteracting the diminished homeostatic sleep drive and helping to decrease wakefulness and to extend the final wake up time.

CONCLUSIONS ABOUT CIRCADIAN RHYTHM PATHOPHYSIOLOGY OF INSOMNIA

It is important to emphasise the strength of the circadian system in determining alertness and sleep propensity across the 24 h period. If the timing is out of synchrony with the attempted sleep time it has been associated with difficulties falling asleep and sleep onset insomnia when sleep is attempted at an earlier circadian phase than normal (e.g., in the evening wake-maintenance zone). When sleep is attempted at a later circadian phase than normal, problems in maintaining sleep are found to result in more awake time particularly in the last half of the sleep period, and problems with premature early final awakenings from sleep. If the attempted sleep period seems to be appropriately timed in sync with the optimal timing of the circadian system, there is evidence that a degraded quality and continuity of sleep can be associated with a reduced amplitude of the endogenous core body temperature rhythm.

The implied causal relationship between circadian disruption and insomnia is likely to be bi-directional. Once insomnia disorder develops, largely through psychological factors, it can lead to circadian disruption. For example, a stress induced sleep onset insomnia can cause later light exposure in the evening and morning and lead to circadian phase delay which in turn perpetuates the sleep onset insomnia.

This evidence of an association between types of insomnia and circadian rhythm disruption is strengthened by the few treatment studies using bright light therapy to re-time the body clock to a time more in sync with the desired sleep period. The use of morning bright light to phase advance circadian rhythms has been successful in treating sleep onset insomnia. There are a few studies that have shown effective treatment of early morning awakening and sleep maintenance insomnia with evening bright light treatment. All these studies were effective in re-timing the body clock of these chronic insomnia cases and improving the quality and quantity of sleep and daytime functioning in most cases. Although more studies investigating the association and treatment of circadian rhythm disruption in cases of insomnia are needed and welcomed (Riemann et al., 2017), the evidence so far would suggest the utility of being alert to possible comorbid circadian pathophysiology in cases of insomnia (Espie, 2023; Van Maanen et al., 2016). This would involve the use of measures to identify circadian rhythm timing and amplitude to confirm suspected pathophysiology. Such attention would enable the appropriate chronobiologic treatments of bright light therapy and possibly low dose melatonin administration at least as an adjunct therapy to cognitive behavioural therapy (Swanson & Raglan, 2023) to improve overall treatment effectiveness for chronic insomnia.

AUTHOR CONTRIBUTIONS

Leon Lack: Conceptualization; investigation; writing – original draft; writing – review and editing; supervision; visualization. **Gorica Micic:** Conceptualization; writing – review and editing; visualization; investigation. **Nicole Lovato:** Conceptualization; investigation; writing – review and editing.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in [repository name] at [DOI], reference number [reference number].

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