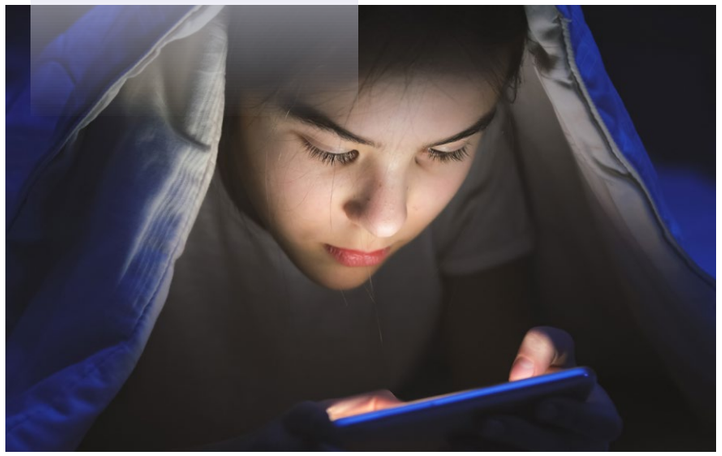
Delayed sleep-wake phase disorder

Dr Gregory Carter from the University of Texas Southwestern Medical Center at Dallas has studied delayed sleep-wake phase disorder (DSWPD) for decades. DSWPD is a circadian rhythm disorder, characterised by a late onset of sleep and wakefulness compared to conventional times or a "night owl" preference. The exact cause is unknown but a combination of genetic and environmental factors (lifestyle, such as shift work) has been suggested. Possible treatment options include melatonin and a combination of bright light therapy and cognitive behaviour therapy. Successful treatment requires personal motivation and discipline to adhere to strict schedules.

Delayed sleep-wake phase disorder (DSWPD) is characterised by an inability to fall asleep at a socially acceptable time ("night owl" preference), usually for more than two hours, and an inability to wake up at conventional early times for traditional social, school or employment schedules. This results in chronic sleep deprivation and inertia (an inability to fully wake up and stay alert in the morning), which further impairs daytime activity. DSWPD is often differentiated from chronic insomnia, as patients with DSWPD have improved subjective sleep quality and duration when they are allowed to sleep at their desired times when they do not have to wake up at conventional times. It is the most commonly diagnosed circadian rhythm sleep disorder, estimated to affect 0.2–10% of the general population.

The feeling of tiredness throughout the day can cause distress for patients and further affect those around them, as they may be tardy or miss school and work days. It is not surprising that anxiety, depression, and personality vulnerabilities are frequently found to be associated with DSWPD. For example, failure to maintain a required schedule increases the risk of interpersonal conflicts, which lower self-esteem and feelings of competence. This further reduces the capacity to enforce self-discipline to strive for achievements.



DSWPD is most commonly observed in adolescents, increases in frequency during an individual's early 20s, and decreases amongst older populations. However, DSWPD can persist in older individuals who have usually developed adaptations resulting in less distress.

THE CIRCADIAN CYCLE

The circadian clock is a 24-hour cycle that is part of the body's internal mechanism, which generates a 24-hour rhythm in gene expression (the process whereby the DNA instructions are converted into a functional product). This circadian clock regulates rhythms of metabolism, sleep, body temperature, blood pressure, and immune function, to name a few. Different systems of the body follow the circadian clock and these systems are synchronised with a master clock in the brain. The master clock is directly influenced by environmental cues, especially light. Hence, the circadian clock is inherently tied to the cycle of day and night.

The sleep-wake cycle is driven by determinants of the internal circadian rhythm. In the morning, light exposure causes the internal clock to synchronize with the day, generating alertness. This is called 'process C' or the circadian drive, which increases over the course of the day or wakefulness to counter 'process S' or the drive to sleep. 'Process S' becomes stronger the longer an individual is awake, probably due to decreased brain energy reserves from wakefulness. At the onset of sleep, 'process C' drops dramatically to allow the onset of sleep. In DSWPD, 'process C' is misaligned with the desired sleep/wake cycle and continues to strongly oppose sleep onset at the desired time even in the presence of accumulated sleep deprivation.

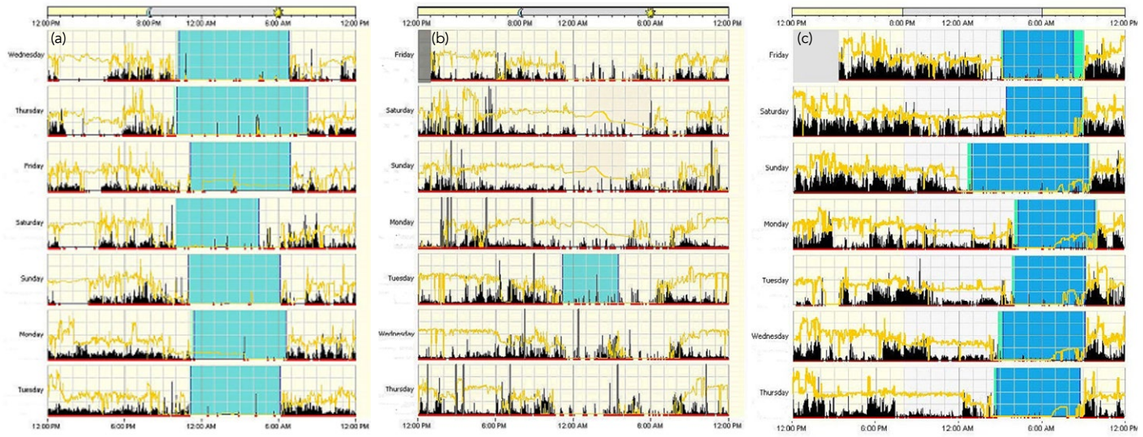


Figure 1. Contrasting images from three patients. The sleep periods are shaded in blue. The figure (a) is a patient with normal sleep. Figure (b) is a patient with severe insomnia, with sleep so disrupted that blue shading of the sleep period was not possible. Figure (c) is a patient with delayed sleep wake phase disorder whose sleep periods shaded in blue begin in the morning hours.

Delayed sleep-wake phase disorder is the most commonly diagnosed circadian rhythm sleep disorder, affecting 0.2–10% of the general population.

CAUSES OF DSWPD

The exact cause of DSWPD has remained elusive. Researchers have hypothesised that both genetic and environmental factors play a role in initiating and exacerbating this condition. A family history with the same condition has been found in approximately 40% of individuals. Polymorphism in the circadian clock gene *hPer3*, human leukocyte antigen, and *Clock* are found to be associated with DSWPD onset and progression. A 2017 study published in *Cell* identified a gene involved in the circadian clock, *CRY1*, to play a role in DSWPD. A gain-of-function mutation leads to increased CRY1 protein expression and inhibition of target genes: *Clock* and *BMAL1*. Altogether, it is associated with increased period of molecular circadian rhythms in cells and delayed sleep onset.

Decreased exposure to bright light in the morning and increased exposure to light late in the evening can exacerbate the delayed circadian phase, which causes individuals to have the desire to fall asleep and arise later than usual times. Furthermore, certain changes in lifestyle can initiate the onset of DSWPD, such as maladjustment to changes in work and social schedules, different time zones, shift work, and activities that continue into late evening.

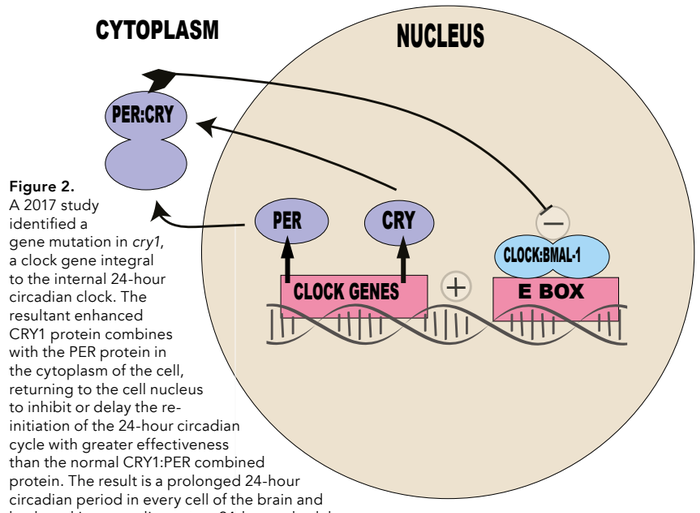


Figure 2. A 2017 study identified a gene mutation in *cry1*, a clock gene integral to the internal 24-hour circadian clock. The resultant enhanced CRY1 protein combines with the PER protein in the cytoplasm of the cell, returning to the cell nucleus to inhibit or delay the re-initiation of the 24-hour circadian cycle with greater effectiveness than the normal CRY1:PER combined protein. The result is a prolonged 24-hour circadian period in every cell of the brain and body making compliance to a 24-hour schedule more difficult.

TREATMENT OPTIONS

A 2015 paper published in the *Journal of Clinical Sleep Medicine* outlines the treatment recommendations from the American Academy of Sleep Medicine (AASM) for DSWPD according to an extensive systematic literature review and meta-analyses. This is summarised and expanded in a chapter of a 2020 book titled, 'Circadian Rhythm Sleep-Wake Disorders', authored by Dr Gregory

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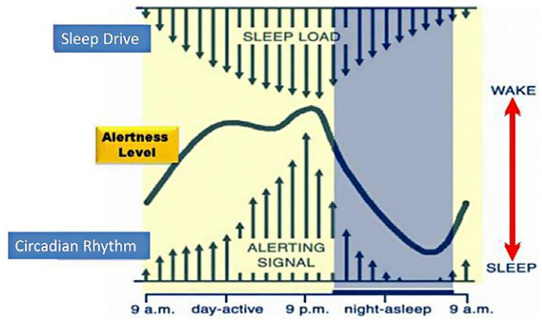
Two Process Model of Sleep Regulation



Borbély (1982)

As wakefulness persists through the day, the sleep drive gradually increases. The internal clock's circadian rhythm opposes this sleep drive with increasing force until that force drops precipitously allowing the onset of sleep. If, however, an individual wants to go to sleep while the circadian rhythm is at maximal force due to a misalignment of the circadian rhythm with the desired schedule, sleep onset is impossible.

Carter from the University of Texas Southwestern Medical Centre at Dallas.

Firstly, melatonin represents a potential therapy avenue, as it is a hormone associated with the internal circadian clock. Three reviewed investigations have contradictory information regarding the effects of melatonin and sleep improvement/circadian rhythm in adult patients. The most definitive results showed a decrease in sleep latency (the amount of time it takes to transition from full wakefulness to onset of sleep) by 43.52mins in comorbid depressed patients and 37.70mins in non-depressed DSWPD patients when 5mg of melatonin was administered.

Studies in children aged 6-12 years old when given a low dose of melatonin, ranging from 0.05mg/kg to 0.15mg/kg showed an improvement in sleep latency in comparison to the placebo group. Two randomised, placebo-controlled studies on children and adolescents with various psychiatric comorbidities showed an advancement in sleep onset time when melatonin was administered.

There is a lack of reported serious adverse effects with the use of ≤10mg/daily melatonin in healthy adults. However, adverse effects have been observed in higher doses of melatonin and in individuals with pre-existing conditions, such as headaches, somnolence, hypotension, hypertension, gastrointestinal upset, and exacerbation of hair loss. Despite low support from studies for the use of melatonin supplements, clinical experience nevertheless supports its use due to inconclusive adverse effects compared to no treatment. It has been suggested that a single dose of melatonin of 0.3mg to 3mg should be taken four hours prior to the desired bedtime.

Successful treatment depends on personal motivation to endure sleep deprivation initially and maintain a rigid schedule continuously.

A combination light therapy has also been suggested as a potential treatment option for DSWPD patients. Upon waking up, participants in a 2011 study were exposed to natural sunlight or a 1,000lux broad-spectrum lamp for 30-120mins. In counter-clockwise increments of 30mins per day, participants advanced to a target time of 0600hrs. When this time was achieved, light therapy was discontinued and participants were encouraged to maintain the same early rise time. Therefore, the success of therapy requires personal motivation to maintain a rigid schedule. Along with this, sessions of cognitive behaviour therapy were performed. Results showed that total sleep time and initial sleep latency were improved compared to patients who were on the wait list to partake in the investigation. No serious adverse effects have been reported with the use of light therapy.

Due to positive results from limited studies, it has been suggested for patients to undergo bright light therapy at 10,000lux 30mins to 4hrs after waking up and no later than 8hrs before the desired sleep onset. The light should be placed to the side of the face at a distance of about 24inches. Alternatively, sunlight exposure in the early mornings or midday for 30mins to 4hrs can also be helpful, provided appropriate UV light safeguards are used (but not including darkened glasses).

Both therapies require patients to fix their daily schedule, which would cause initial anxiety. Thus, successful treatment depends on personal motivation to endure sleep deprivation initially and maintain a rigid schedule continuously. Anti-anxiety medication can reduce motivation or complicate successful therapy. Further and continued maladaptive sleep behaviours, such as adolescent after-school jobs, blue light screen exposures from computers, television, and cell phones, stimulating substances consumed within 6hrs of desired sleep onset time, and exciting activities before bedtime, such as family discussions and phone usage, can interfere with successful treatment. Therefore, discipline from both patients and support systems are needed to ensure DSWPD is tackled.

Behind the Research

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Research Objectives

Dr Gregory Carter is involved in applied research on the use of ambulatory cardiorespiratory sleep studies.

Detail

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Personal Response

Why is there a lack of data for DSWPD treatment options, for example the lack of large-scale randomised controlled trials, and what can be done to improve this?

Large scale (100-500 subjects) randomised controlled trials of treatment options in DSWPD have been difficult to perform. The primary difficulty is the differential diagnosis of DSWPD or a delay in the circadian rhythm versus insomnia or a delay in bedtime due to another etiology such as restless legs or behavioural actions, such as the use of blue screens at bedtime, that are easily remedied by medications or changes in behaviour. Thus, screening of subjects requires an interview with a sleep medicine clinician and testing such as dim light melatonin onset to determine which volunteers are trial candidates. Drop-outs of trial subjects and subject compliance are lesser but significant difficulties. These difficulties mandate a multi-centre trial to generate the number of volunteers required with duplication of resources and expenses at each centre. The length of follow-up of each subject to evaluate maintenance of the therapeutic response would need to be at least 6 months, meaning that the trial would need to fund the resources and expenses for a minimum of two years. The bottom line then becomes funding running into several million US dollars. This cost can only be reduced by widespread presence of sleep medicine clinicians and circadian rhythm testing resources, reducing the cost of putting those resources in-place for the purpose of constructing a trial.