DLMO: Assessing Sleep and Circadian Disorders

Measuring the Circadian Clock
The most reliable measure of the timing of the central circadian clock in humans is the onset of the evening melatonin production measured in dim light, i.e., dim light melatonin onset, DLMO.

DLMO is believed to accurately represent the timing of the central circadian clock (suprachiasmatic nucleus, SCN), as the secretion of melatonin from the pineal gland is controlled by the SCN. Typically, melatonin levels begin to increase in the 2–3 h before the usual onset of nocturnal sleep, peak in the early morning hours, and decrease to daytime levels around usual waking.

The most noticeable feature of circadian rhythms is the sleep/wake cycle. But there are other circadian rhythms including swings in many hormones throughout the day, the body temperature cycle, appetite and the times of best alertness. Ideally these rhythms are in sync with each other and with the light-dark cycle in nature. Most humans are awake during daylight hours and sleep during darkness - it's the ideal scenario for overall health.

DLMO is a convenient phase marker to measure, as it can be obtained noninvasively from saliva, and can require only a relatively short window of sampling of ~6–8 hours.

For all of these reasons, the use of DLMO to assess circadian phase is proving to be a valuable tool for both researchers and clinicians alike.

Circadian Rhythm Sleep Disorders
Circadian Rhythm Sleep Disorder (CRSD) is an abnormality of the body’s internal clock, in which a person is unable to fall asleep at a normal evening bedtime, although able to sleep reasonably well at other times dictated by their internal rhythm. They cannot fall asleep when desired, so they complain of insomnia. They have trouble waking up when desired, so they complain of excessive sleepiness. It takes some insight to make the connection that the problem may be with the timing of sleep rather than the sleep itself.

One factor common to these disorders is inflexibility: even when physically tired or sleep deprived, sufferers cannot make up for lost sleep outside of their hard-wired sleep times. This factor is generally misunderstood by people who do not suffer from these disorders, leading to a conclusion that those who do are just lazy or haven’t tried hard enough to live on society’s schedule.

Some people are flexible and can adjust to sleeping on practically any schedule. Still, they may prefer to wake up early (often called “larks”) or stay up late (“night owls”). But other people cannot adjust, and forcing themselves to be awake at the wrong time for their body can make them ill. They have a Circadian Rhythm Sleep Disorder.

In addition to the sleep/wake cycle, the internal coordination of the various other rhythms may also be faulty. For example, some hormones may be on a different daily cycle than others, and this lack of coordination between systems may produce other symptoms in addition to the sleep disorder. This is believed to be the cause of the discomfort of jet lag.

CRSD Subtypes
The International Classification of Sleep Disorders Revised (ICSD-R) lists 6 subtypes of circadian rhythm sleep disorder:

- Delayed Sleep-Phase Syndrome
- Non-24-Hour Sleep-Wake Disorder
- Advanced Sleep-Phase Syndrome
- Irregular Sleep-Wake Pattern
- Shift Work Sleep Disorder
- Jet Lag Syndrome

At-Home Testing DLMO
While commonly performed by patients in sleep clinics for many years, the at-home option for patients to perform saliva collections at home is a reality now for clinicians assessing circadian rhythm disorders.

Patients are required to restrict certain foods and activities on the day of collection. The start time of the 8 hourly saliva collections starts 5 hours previous to the typical time of falling asleep. Restriction of light to > 30 lux is critical to a successful collection procedure, given that excess light will suppress melatonin. The patient stays awake for the entire collection process, freezes the samples, then ships them to the lab in a thermal container.

Device apps like multi-timers and light meters can be downloaded to ensure compliance. Detailed patient test
instructions help ensure total compliance with the technical requirements of the pre-analytic phase.

**Phase Shift Types**

The laboratory calculates the melatonin onset threshold based on the patient's own baseline measurements. The timing of the melatonin rise (if present) is then interpreted on the report. The interpretation guidelines on the report are a tool for clinicians to identify patients who may be suffering from an abnormal or shifted circadian sleep phase. If an individual's melatonin results exceed the DLMO threshold prior to 2 hours before expected sleep onset, they are identified as Advanced Sleep Phase. Delayed Sleep Phase is suggested if the DLMO threshold is crossed within 1 hour prior to, or any time after their typical sleep onset time.

Calculating DLMO has been previously performed using the fixed threshold method, which involves looking for the time at which rising melatonin levels cross a previously determined threshold, typically set at 3 or 4 pg/mL for saliva. We use the variable threshold method, aka “3k method” to calculate DLMO. This method employs establishing the mean of the first three low day-time samples, and setting the threshold as 2 Standard Deviations above this mean for each person's own measurements. This method has been shown to allow for measurements in individuals that are 'low secretors' who do not make sufficient melatonin to reach the fixed threshold values, while also allowing for DLMO estimation in individuals that have day time melatonin measurements above the fixed threshold.

**Advanced Sleep Phase**

Also known as the advanced sleep-phase type (ASPT) of circadian rhythm sleep disorder or advanced sleep phase syndrome (ASPS), this is a condition in which patients feel very sleepy and go to bed early in the evening (e.g. 6:00–8:00 p.m.) and wake up very early in the morning (e.g. around 3:00 a.m.). People with ASPD are unable to stay awake until their desired bedtime and unable to stay asleep until their desired waking time. They will complain to a sleep clinician of early morning insomnia and falling asleep early in the evening. When someone has advanced sleep phase disorder their melatonin levels and core body temperature will cycle hours earlier than an average person.

**Delayed Sleep Phase**

Delayed sleep phase disorder (DSPD), more often known as delayed sleep phase syndrome and also as delayed sleep-wake phase disorder, is a chronic dysregulation of a person's circadian rhythm (biological clock), compared to those of the general population and societal norms. The disorder affects the timing of sleep, peak period of alertness, the core body temperature rhythm, and hormonal and other daily cycles. People with DSPD generally fall asleep some hours after midnight and have difficulty waking up in the morning. People with DSPD probably have a circadian period significantly longer than 24 hours.

**Therapy for Impaired Circadian Patterns**

Possible treatments for circadian rhythm sleep disorders include:

- Behavior therapy or advice about sleep hygiene where the patient is told to avoid naps, caffeine, and other stimulants. They are also told to not be in bed for anything besides sleep and sex.
- Dark therapy, for example the use of blue-blocking goggles, is used to block blue- and blue/green wavelength light from reaching the eye during evening hours so that the production of melatonin is not decreased or eliminated.
- Melatonin or other short term sleep aids or wake-promoting agents can be beneficial; melatonin is a natural neurohormone responsible partly and in tiny amounts for the human body clock. The melatonin agonist Tasimelteon, trade name Hetlioz, has been approved in the USA solely for the treatment of non-24-hour sleep–wake disorder in totally blind people.
- Bright light therapy may progressively advance or delay sleep time. Bright light protocols supervised by a clinician help many patients restore normal patterns.