EDITORIAL

Are We Ready to Assess Circadian Phase at Home?

Commentary on Burgess et al. Home circadian phase assessments with measures of compliance yield accurate dim light melatonin onsets. SLEEP 2015;38:889–897.

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The circadian pacemaker controls the timing of many aspects of our biology. Misalignment of the circadian system as may occur in shift-workers, blind individuals, and individuals exposed to repeated cycles of jet-lag, is associated with various health disorders.[1–6] Moreover, therapeutic efficacy may depend on the timing of treatment administration relative to circadian phase, and circadian-informed treatment has been reported to be beneficial for antihypertensive medication and cancer chemotherapy.[7–10] One of the major barriers of adopting "circadian medicine" in routine clinical practice, however, has been the difficulty in assessing circadian phase at home or in an outpatient setting.

The gold standard inpatient method to estimate circadian phase is the plasma melatonin rhythm measured under constant routine (CR) conditions,[11] typically using the dim light melatonin secretion onset time (DLMO) as the phase marker.[12] The CR procedure, however, is expensive, intensive, and time-consuming, and therefore impractical for high-volume clinical use. Melatonin can be reliably assayed from saliva[13] as a proxy for plasma melatonin without the same degree of invasiveness, and salivary DLMO has been used to assess circadian phase in field-based and clinical settings.[14,15]

In this issue of *SLEEP*, Burgess and colleagues[16] report on a small but rigorous study that favorably compares the accuracy of at-home DLMO assessments with laboratory-based ones. Thirty-five healthy adults (21–62 years) were studied for 10 days, and they completed consecutive at-home and laboratory-based phase assessments twice, with the order randomized and counterbalanced and separated by 5 days. Saliva samples were collected half-hourly starting 6 h before and ending 2 h after each participant's average bedtime. Compliance to prescribed light exposure restrictions and sampling schedule was measured objectively both at home and in the laboratory.

The procedure compliance rate was high, and most participants collected every saliva sample within 5 minutes of the scheduled time. Ninety-two percent of home DLMOs were stated to be unaffected by the ambient light or by sampling errors based on objective measures of ambient light under ambulatory conditions and objectively recorded sample collection times. There was no significant difference between the home and laboratory DLMOs on average, and they were highly correlated ($r = 0.91$).

In contrast, a previous study by Pullman et al.,[17] which assessed salivary DLMO from hourly samples collected both at home and under laboratory conditions, showed that the phase assessments differed by up to 90 minutes, despite imposing dim light, posture, and activity restrictions. Unlike the study by Burgess, Pullman did not measure compliance to the restricted conditions, which may have contributed to the at-home DLMOs appearing to occur later, likely due to direct suppression by light.[18] Therefore, the study by Burgess underscores the importance of proactively and overtly monitoring compliance, especially of environmental conditions, to the success of this approach; when left to their own devices, patient compliance is much worse.[19] This degree of monitoring may put off physicians. Similarly, the extent of the restrictions necessary to obtain the high compliance rates may be considered unacceptable by many patients and limit their willingness to participate or comply with collection procedures.

In addition to potential confounds of light exposure and sample collection compliance, salivary melatonin may not be able to detect DLMO in patients with low melatonin production.[20] The relatively young age of the patients may have contributed to the remarkably low failure rate of the current study (n = 1; 3% of the population)[16] compared to the much higher failure rates found by Pullman (~35%)[17] and the ~24% failure rate reported in a larger study of ~2,000 patients in the same sleep clinic in the Netherlands.[15] Furthermore, most of the participants in the study by Burgess were moderate morning types" or "neither morning nor evening types," and would therefore be likely to have a DLMO occurring during the sampling window. A sampling interval of 6–8 h at this time may not be adequate to measure DLMO in individuals with a less typical circadian phase, as might be expected in Advanced- or Delayed Sleep Phase Disorder patients,[20,21] and even less so when trying to assess individuals with less predictable circadian phases such as shift-workers, those with jet-lag, or in blind individuals with non-24 h circadian rhythms, who would need up to 24 h of monitoring to capture the phase. In these cases, measurement of urinary 6-sulphatoxymelatonin (aMT6s), the major metabolite of melatonin, in sequential voids over 24–48 h may be preferable and has been used successfully in multiple field studies including in shift-workers (e.g., nurses,[1] oil-rig workers[22]), in unusual environments (e.g., spaceflight,[23] mission control,[2] Antarctica[24]) and in many clinical populations (e.g., blind persons,[25] breast cancer patients,[26] schizophrenic patients,[27] and children with developmental disorders[28]) as well as inpatient experimental protocols.[29]

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DLMO is a clinically relevant tool that can be used to diagnose Circadian Rhythm Sleep Disorders.[21] Therapeutic efficacy may be improved by circadian-informed treatment protocols, which requires both accurate and clinically feasible methods of assessing circadian phase. A practical and cost-effective procedure for assessing circadian phase may utilize a hybrid approach. For example, outpatient 24–48 h urine samples could be collected initially to assess circadian rhythm abnormality broadly, which can then identify the patients who need more controlled assessments at home or in the laboratory, while also determining the optimal timing for saliva sample collection. Although results from the current study are encouraging,[16] additional work on larger and more diverse clinical and subclinical populations, which are likely to exhibit a greater failure rate are necessary to design an optimal tool. The ability to assess circadian phase clinically would, however, revolutionize diagnostics and therapeutics and open a new chapter in personalized circadian medicine, and deserves a dedicated focus by our field.

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