COMMENTARY

Shedding Light on the Effectiveness of Melatonin for Circadian Rhythm Sleep Disorders

Commentary on van Geijlswijk et al. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. SLEEP 2010;33:1605-1614.

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DELAYED SLEEP PHASE DISORDER (DSPD) OFTEN PRESENTS AS SLEEP-ONSET INSOMNIA AND/OR EXCESSIVE MORNING SLEEPINESS ASSOCIATED WITH the chronic inability to fall asleep typically until between 2 am to 4 am, and extreme difficulty waking up in time to meet social, school or professional obligations.[1,2] DSPD is one of the most common of the circadian rhythm sleep disorders (CRSD), affecting an estimated 1.7% of the general population,[3] 6% to 16% of adolescents and young adults, and nearly 10% of those with chronic insomnia.[4,5] Treatment of DSPD typically involves a multimodal approach using both behavioral and pharmacological treatments. Of the pharmacologic approaches, the most commonly used and recommended as a "guideline" by the American Academy of Sleep Medicine Clinical Parameters is appropriately timed melatonin administration.[2,6] However, to date there are no large multicenter randomized controlled trials of melatonin for the treatment of DSPD and controversy exists on the effectiveness of melatonin for the treatment of secondary sleep disorders, including DSPD. For example, a widely cited meta-analysis published in the British Medical Journal, concluded that there was no evidence that melatonin was effective.[7] So, why are there such discrepancies? The lack of efficacy could be due to multiple factors, including the lack of regulation of the various melatonin preparations, dose, timing of administration, and perhaps more even than expected, the wrong indication.

This issue of *SLEEP* contains the results of a small, but rigorous meta-analysis that supports the effectiveness of exogenous melatonin in advancing the rhythm of melatonin and sleep onset time, and improving sleep latency in children and adults.[8] Importantly this study sheds light on the apparently contradictory signals regarding the efficacy of melatonin in the treatment of CRSDs. There are several features of this study that are particularly noteworthy, not the least of which is that it's the first meta-analysis of the effectiveness of exogenous melatonin for the treatment of DSPD in which circadian timing was assessed prior to treatment. The randomized placebo controlled trials (RCT) included in this meta-analysis had measures of the timing of sleep and wake parameters or endogenous melatonin. Furthermore, dim light melatonin (DLMO) onset from plasma or saliva was available in the majority of the studies (6 out of 9) included in the meta-analysis. Such markers of circadian timing can be quite valuable for differentiating patients with circadian delay and misalignment from those without. One of the major challenges in clinical practice is that patients without a delay in the phase of circadian rhythms can present with symptoms of DSPD, such as sleep onset insomnia and daytime sleepiness. Indeed, alterations in homeostatic regulation or behavioral factors can manifest with symptoms similar to those of seen in DSPD.[9,10] Therefore, circadian based treatments, such as melatonin would not be expected to be effective in those without circadian rhythm disturbances. The increasing availability of objective measures of the sleep wake rhythm (actigraphy) and circadian timing (DLMO) can help meet this challenge. Indeed, DLMO testing has been shown to be a relatively simple and reliable tool for circadian phase typing in patients with DSPD.[11]

Another important feature of the van Geijlswijk et al. study is that the timing of exogenous melatonin administration was included in the assessment of effectiveness. This could explain the difference between the positive results of this meta-analysis and the negative results reported by Buscemi et al., in which circadian timing measures or the time of melatonin administration was not taken into account.[7] As predicted by the phase response curve for melatonin,[12] and confirmed in a clinical population with DSPD, the most effective time of administration is 5-6 hours prior to DLMO.[13] The results from the van Geijlswijk et al. meta-analysis confirm that administration of melatonin prior to the DLMO (1.5 to 6.5 hours) was more effective in advancing circadian timing. It surely follows that because a primary role of endogenous melatonin in humans is to inform the brain and other tissues about time of day, its effectiveness in the treatment of CRSDs will largely depend on the appropriate timing of exposure. In addition to its phase re-setting properties, the generally modest hypnotic effect of exogenous melatonin is also dependent on circadian timing.[14]

Some of the most consistent data on the effectiveness of melatonin for the treatment of DSPD arise from pediatric studies, including children with ADHD.[15] In the meta-analysis by van Geijlswijk et al., four of the nine studies were in children.[8] Despite melatonin's potential effectiveness, its use in children raises concern regarding the safety of long term treatment. Although melatonin at the low dose (1-5 mg) typically used in clinical practice appears to be generally safe, little is known about the long term effects of chronic use on health in children or adults.

The study by van Geijlswijk et al. underscores the importance of assessing circadian timing prior to treatment to estab-

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lish the diagnosis, and most importantly to specify the timing of treatment. Current diagnostic criteria for DSPD rely largely on the patient's self-reported sleep/wake time and symptoms of insomnia and excessive sleepiness. Tools such as actigraphy and salivary DLMO are becoming more readily available in the clinic and recent data support the clinical efficacy of DLMO testing in diagnosing DSPD.[11] Utilization of more precise and direct measures of circadian timing is a necessary first step towards effective treatment.

The widespread use of melatonin in clinical settings is in contrast to the surprisingly small number of studies (only 9) that met the inclusion criteria set forth in the van Geijlswijk et al. meta-analysis.[8] Although there is consistent evidence from small clinical studies that when appropriately timed, melatonin is an effective treatment for DSPD[13,16] determining the optimal schedule and dose will require further study. Large multicenter RCTs are warranted to establish the dose (very low vs. low), the timing of administration and long term safety in children and adults. With the exciting advances in the field of circadian biology and the recognition of the importance of circadian timing for health and disease, this is the perfect time to move circadian based treatments from the research bench to the bedside.

DISCLOSURE STATEMENT

Dr. Zee has indicated no financial conflicts of interest.

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