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# Editorial: Circadian rhythm sleep-wake disorders: Pathophysiology, comorbidity, and management

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circadian rhythm sleep-wake disorders, circadian disruption, delayed sleep-wake phase disorder, comorbidity, depression, melatonin, melatonin receptor agonist

## Editorial on the Research Topic

[Circadian rhythm sleep-wake disorders: Pathophysiology, comorbidity, and management](#)

Circadian rhythm sleep-wake disorders (CRSWDs) are not stand-alone entities—they are often accompanied by various neuropsychiatric phenomena, ranging from minor symptoms to major psychiatric or neurological disorders. More often, circadian disruptions can be hidden players in various disorders, including psychiatric and physical ones. Recent studies have revealed that circadian disruptions/disorders and other disorders have a bidirectional relationship, suggesting some shared pathophysiology.

In this context, the focus of this Research Topic has been on CRSWDs and other conditions related to the circadian system. [Otsuki et al.](#) conducted a retrospective study to examine the relationship between delayed sleep-wake phase disorder (DSWPD) and decreased social zeitgebers during the pandemic in Japan. They found that symptoms of DSWPD, as assessed by the clinical global impressions—severity of illness, were worse after the pandemic began, suggesting that not only biological clock regulation in the narrow sense but also environmental factors have substantial contribution in this condition. [Tomishima et al.](#) conducted a web survey regarding the epidemiology of the risk of DSWPD. Their results showed that it has a similar prevalence as previous studies in Western countries. Interestingly, this was determined using the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), originally developed to assess circadian-related symptoms in bipolar disorder (1). The same authors have previously validated BRIAN for the screening of DSWPD in their study (2), and their studies suggest that the phenotype of DSWPD is characterized by neuropsychiatric symptoms besides the deviation of the sleep-wake phase itself. [Takaesu et al.](#) studied major depressive disorder (MDD) in terms of the delayed sleep-wake phase and found that it was associated with functional impairments and a deterioration in the quality of life. Their results might lead to important considerations regarding the source of circadian disturbance in MDD. Circadian misalignment may be at the upstream in etiology and bring cognitive and social dysfunction, or it may be the result of weak social zeitgeber (as [Otsuki et al.](#) reported), or a third hypothesis would be that the alteration of homeostatic building up in MDD (3) might be the root of both of them. [Hirose et al.](#) reported a study of locomotor activities of DSWPD and found that it was altered at the ultradian level compared to healthy people. This is similar to MDD, as shown in the previous study (4), and suggests that DSWPD is not a simple circadian phase disorder. This might also bring some suggestion as to the recent findings that a substantial portion of patients with DSWPD do not have delayed melatonin rhythm, and thus, behavioral components should be weighed in this condition (5).

Besides CRSWDs, Li et al. studied the relationship between neuropsychiatric symptoms and sleep quality in people with cerebral small vessel disease (CSVD). They found a significant association between these factors, which suggests that brain-organic changes may be at the root of both and that there may be shared alteration in neuropsychiatric homeostatic processes. Interestingly, CSVD has also been reported to have relevance to the circadian rhythms of rest-activity (6, 7) or blood pressure (8). This might have another way of association with the alteration of neuropsychiatric homeostasis. This area of research may be worthy of further study in the future. Ichba et al. studied the effect of periocular skin warming on the sleep of patients with insomnia disorder. They reported that the intervention could shorten the sleep onset latency and promote heat dissipation on distal limbs. It is well-known that thermoregulation is under circadian control, and a previous study reported that experimental circadian interventions shortened sleep onset latency in healthy subjects *via* warming distal limbs (9). The present study suggested that this process could be manipulated afferently (i.e., from the peripheral side) in a sophisticated manner, which is interesting for both clinical and etiological considerations.

The melatoninergic function plays an essential role in the central circadian regulatory mechanism, and exogenous melatonin has been used to treat CRSWDs. Palagini et al. reviewed the previous studies on melatonin usage for a broad range of psychiatric conditions and made expert consensus recommendations. Although the evidence so far is still insufficient to cover these conditions fully, it is encouraging that exogenous melatonin seems a promising intervention for their comorbid sleep disorders. The effects of melatonin or ramelteon, a selective MT1 and MT2 receptor agonist, on the symptoms of various psychiatric conditions, have been studied (10), and a recent meta-analysis showed that ramelteon has a preventative effect for relapse of depression in bipolar disorder (11). Melatonin has chronobiotic and soporific properties (10), and whether melatonin receptor agonists work for these conditions *via* direct circadian manipulation (i.e., phase shifting or stabilizing) or not should be investigated further. Polymeropoulos et al. reported that tasimelteon, another selective MT1 and MT2 receptor agonist, could alleviate jet lag disorder in real-life transmeridian travel. Tasimelteon has been reported as a potent compound in circadian modification and approved for treating non-24-h sleep-wake rhythm disorder in the US and Europe (12). The result of the present study is also encouraging because this latest melatonin receptor agonist might potentially expand its usage. There have also been several studies regarding the therapeutic

effects of tasimelteon on other conditions, including depression (13). Further studies might also be warranted on its efficacy on CRSWDs' comorbidities.

The articles on this Research Topic have added interesting knowledge to sleep and psychiatric disorders in the context of circadian mechanisms. These should provide further insight into this, a little, complicated theme and inspire researchers to continue exploring it.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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## Conflict of interest

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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