

*Short communications*

## Challenges and Gaps in the Treatment of Advanced Sleep Phase Disorder: A Call for Further Research and Understanding

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### SUMMARY

People with circadian rhythm disturbances are at an elevated risk of mental disorders, and conversely, those with mental disorders are more susceptible to the circadian disruption. A steady circadian cycle of sleep and wakefulness that is phase-shifted relative to the prior local solar time may be characterized by a short endogenous circadian period. Advanced sleep-wake phase disorder (ASPD) is characterized by a substantial advancement of the sleep-wake cycle phase, followed with sleep-related symptoms. ASPD is a challenging sleep-wake disorder to manage, with current treatment options varying in efficacy and potential side effects. Further research is needed to identify effective treatment options and to elucidate the underlying mechanisms of ASPD. More research is needed to better understand the underlying mechanisms of ASPD and the molecular and metabolic changes associated with aging that may contribute to the development of the disorder.

**Keywords:** advanced sleep phase syndrome, circadian rhythm sleep disorder, sleep phase chronotherapy, melatonin, light therapy

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## FINDINGS

People with circadian rhythm disturbances are at an elevated risk of mental disorders, and conversely, those with mental disorders are more susceptible to the circadian disruption. Dysregulation of neurotransmitter systems such as serotonin, dopamine, and norepinephrine, which have been implicated in the pathophysiology of many mental disorders, have been found to be associated with circadian sleep-wake cycle disorders (1). In addition, changes in the expression of clock genes that control circadian rhythms have also been linked to the onset of psychiatric diseases. There is a complex and multifaceted relationship between circadian disruption and mental health, which requires a deeper understanding of the underlying mechanisms and the development of targeted therapeutic interventions.

A steady circadian cycle of sleep and wakefulness that is phase-shifted relative to the prior local solar time may be characterized by a short endogenous circadian period. Advanced sleep-wake phase disorder (ASPD) is characterized by a substantial advancement of the sleep-wake cycle phase, followed with sleep-related symptoms. The identification of these patients in a clinical setting is challenging, not only because of the diagnostic criteria, but also because patients may perceive an advanced sleep phase as an advantage rather than a problem when it comes to social life rhythms. This may be the reason why ASPD, until now, has been considered to be extremely rare in the general population.

We are writing to draw attention to the gaps in our knowledge of the treatment of ASPD, a circadian rhythm sleep disorder characterized by a shift of the sleep-wake cycle to an earlier time (2). Despite being a common disorder, there is a lack of research in the area of ASPD treatment. More research is needed to identify effective treatment options, as current treatment guidelines for circadian rhythm sleep-wake disorders are limited.

The lack of understanding of the underlying mechanisms is one of the major gaps in our knowledge of the treatment of ASPD. The two-process model of sleep regulation provides a framework for understanding the complex interaction of circadian and homeostatic processes in sleep regulation (3). However, the intricacies of the various factors modulating processes in people with

ASPD remain largely unexplored. Genetic, lifestyle, and environmental factors all contribute to the sleep-wake cycle. In particular, clock genes play an important role in regulating circadian rhythms. These rhythms are responsible for maintaining the sleep-wake cycle (4). In addition, environmental factors such as light exposure and social cues are known to have an impact on the regulation of circadian rhythms, which is crucial for the maintenance of mental health (5).

In 2015, the American Academy of Sleep Medicine (AASM) published a clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders, including ASPD. However, there is limited information in the guideline on the effectiveness of different treatment options and the long-term effects of these options on sleep quality and health outcomes (6). There is a need for further research to address these gaps in our understanding.

There are a few treatment options available for ASPD, including bright light therapy, melatonin, and chronotherapy. However, the evidence for their effectiveness is limited and conflicting. Bright light therapy involves exposure to bright light in the morning to advance the circadian rhythm, while melatonin is a naturally occurring hormone that can help regulate the sleep-wake cycle (7). Additionally, while light therapy has been shown to be effective in delaying the sleep-wake cycle in delayed sleep-wake phase disorder, its efficacy in ASPD is limited. Bright light exposure has been suggested as a potential treatment for ASPD, but the evidence is mixed. One study found that timed bright light exposure did not alleviate sleep maintenance insomnia in older adults (8), while another found that evening bright light delayed circadian rhythms and prolonged sleep in early morning awakening insomnias (9). Bright light therapy is a commonly used treatment for ASPD, with studies showing a significant improvements in sleep onset time and total sleep time (8). However, some patients may experience side effects such as headache, nausea, and eye strain.

Another theoretical option is melatonin, which can improve sleep quality and reduce sleep onset time. However, it can also cause side effects such as dizziness, headache, and nausea (10). Based solely on expert consensus, the 2007 AASM Practice Guidelines mention the administration of a modest dose of melatonin during early morning awakening and fi-

nal morning awakening as an option for ASPD. No new studies have been identified (6).

Chronotherapy (sleep regimen) involves the gradual shifting of bedtime and wake-up times over several days until a normal schedule is achieved. However, only one case report demonstrated this option. It can be difficult to implement because it requires a controlled environment and strict adherence to a schedule (11,12).

Aging is associated with changes in several physiological processes, including circadian rhythm regulation and metabolism, which could potentially contribute to the development of ASPD (13). Understanding the molecular and metabolic changes associated with aging and ASPD may provide insight into potential therapeutic targets for this disorder. The importance of treating ASPD in the elderly cannot be overstated. Aging is associated with changes in circadian rhythms and an increased prevalence of circadian rhythm sleep disorders,

including ASPD (14). Sleep disorders can impair the ability to perform daily activities, increase the risk of falls and accidents, and have a significant impact on the quality of life of older people (15). Effective treatment options for ASPD can significantly improve the quality of life.

In conclusion, ASPD is a challenging sleep-wake disorder to manage, with current treatment options varying in efficacy and potential side effects. Further research is needed to identify effective treatment options and to elucidate the underlying mechanisms of ASPD. More research is needed to better understand the underlying mechanisms of ASPD and the molecular and metabolic changes associated with aging that may contribute to the development of the disorder. Investigation of these changes could provide valuable insights for the development of targeted treatments and improvement in the quality of life of people with ASPD.

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## Izazovi i nedostaci u lečenju poremećaja uznapredovale faze spavanja: poziv na dalja istraživanja i razumevanje

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### SAŽETAK

Kod ljudi sa poremećajima cirkadijalnog ritma postoji povećan rizik od mentalnih poremećaja i, obrnuto, ljudi sa mentalnim poremećajima podložniji su cirkadijalnim poremećajima. Stalan cirkadijalni ciklus spavanja i buđenja koji se fazno pomera prema prethodnom lokalnom solarnom vremenu može se karakterisati kratkim endogenim cirkadijalnim periodom. Poremećaj uznapredovale faze spavanja–buđenja (engl. *advanced sleep phase disorder* – ASPD) odlikuje znatno napredovanje faze ciklusa spavanja–buđenja, praćeno simptomima vezanim za spavanje. ASPD je izazovan poremećaj spavanja–buđenja, jer ga nije lako regulisati, a trenutne opcije lečenja razlikuju se po efikasnosti i potencijalnim neželjenim efektima. Potrebna su dalja istraživanja da bi se pronašle efikasne opcije lečenja i razjasnili osnovni mehanizmi ASPD-a. Kako bi se bolje razumeli osnovni mehanizmi ASPD-a, kao i molekularne i metaboličke promene povezane sa starenjem koje mogu doprineti razvoju ovog poremećaja, neophodno je sprovesti dodatna istraživanja.

**Ključne reči:** sindrom uznapredovale faze spavanja, poremećaj cirkadijalnog ritma spavanja, hronoterapija faze spavanja, melatonin, terapija svetlošću