HHS Public Access

Author manuscript

J Child Psychol Psychiatry. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

J Child Psychol Psychiatry. 2018 December ; 59(12): 1248–1251. doi:10.1111/jcpp.12956.

Delayed Circadian Rhythm Phase: A Cause of Late-Onset ADHD among Adolescents?

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Abstract

Late-onset attention-deficit/hyperactivity disorder (ADHD) has been a topic of significant debate within our field. One question focuses on whether there may be alternative explanations for the onset of inattentive and/or hyperactive symptoms in adolescence. Adolescence is a developmental period associated with a normative circadian rhythm phase delay, and there is significant overlap in the behavioral and cognitive manifestations and genetic underpinnings of ADHD and circadian misalignment. Delayed circadian rhythm phase is also common among individuals with traditionally-diagnosed ADHD, and exposure to bright light may be protective against ADHD, a process potentially mediated by improved circadian timing. In addition, daytime sleepiness is prevalent in late-onset ADHD. Despite these converging lines of evidence, circadian misalignment is yet to be considered in the context of late-onset ADHD – a glaring gap. It is imperative for future research in late-onset ADHD to consider a possible causal role of delayed circadian rhythm phase in adolescence. Clarification of this issue has significant implications for research, clinical care, and public health.

In the last two years, a significant debate has arisen in our field regarding the occurrence and validity of a "late-onset" Attention-Deficit/Hyperactivity Disorder (ADHD) phenotype, characterized by the emergence of ADHD symptoms during adolescence. At the heart of this controversy is the traditional conception of ADHD as a neurodevelopmental disorder with onset prior to age 12. The primary evidence for late-onset ADHD consists of four population studies that have consistently demonstrated emergence of ADHD in adolescence, leading researchers to suggest that a late onset of symptoms may represent the "rule rather than the exception" among adults with ADHD. Analysis from a multi-site treatment evaluation study (Multimodal Treatment of ADHD; MTA) also identified cases of ADHD onset in adolescence; however, symptoms were transient (i.e., emerging in adolescence and ceasing prior to adulthood) and/or better explained by substance use or other psychiatric conditions (Caye et al., 2017).

Two theoretical frameworks have been proposed to explain the emergence of ADHD in adolescence: (1) a complex phenotype, which highlights unstable interactions between neurobiological and environmental pressures over time that result in ADHD onset at

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different points over the lifespan (e.g., underlying ADHD symptoms are attenuated in childhood under certain environmental conditions, such as parental support, and manifest when supports are later removed, resulting in late-onset), and (2) a restricted phenotype, which questions whether potential underlying contributors to ADHD symptoms, such as substance use and other psychiatric disorders, should be considered as causes, or alternatively, exclusionary conditions in conceptualizations of late-onset ADHD (Caye et al., 2017). In either framework, one question remains paramount: is late-onset ADHD a "true" phenotype of ADHD or a manifestation of other physical, mental, and environmental problems that develop during adolescence?

Thus, an acknowledged threat to the late-onset ADHD phenotype concept is the presence of other medical or psychiatric conditions which may "mimic" ADHD symptoms and explain ADHD emergence later in life. For example, conditions such as depression and substance use, which are both associated with inattention, represented a primary explanation for late onset of ADHD symptoms in the MTA study, and were not consistently ruled out in population studies assessing late-onset ADHD (Caye et al., 2017). Another potential explanation for ADHD symptom onset in adolescence that has not been considered is *delayed circadian rhythm phase*. Delayed circadian rhythm phase is common in adolescence and refers to an endogenous preference for later sleeping and waking times (Roenneberg et al., 2004). Circadian phase delays – particularly more extreme delays - often result in a misalignment between an adolescent's internal circadian rhythm and social time, which interferes with social and school performance (e.g., school; Kelley et al., 2015), as well as social jetlag (i.e., variability in sleep/wake schedule across weekdays versus weekends), a phenomenon which independently interferes with daytime functioning (Coogan and McGowan, 2017).

There are several reasons to critically consider a role of circadian rhythm misalignment in late-onset ADHD. First, delayed circadian rhythm phase is prevalent and impairing among adults with traditionally-diagnosed (childhood-onset) ADHD. Up to 75% of adults with childhood-onset ADHD exhibit delayed circadian rhythm phase, including a rise in salivary dim-light melatonin onset (DLMO) and alterations in core body temperature and actigraphy-measured sleep-related movements occurring approximately 1.5 hours later in the night than healthy adults. In addition, adults with childhood-onset ADHD exhibit a delay in early morning cortisol rise (i.e., a hypothalamic–pituitary–adrenocortical (HPA) marker of circadian phase), with secretion occurring two hours later than healthy controls. Adults with childhood-onset ADHD are also frequently "night owls" who display delayed circadian preference and increased alertness in the evening (Kooij, 2017, Coogan and McGowan, 2017).

Among adults with childhood-onset ADHD, this circadian rhythm delay and greater evening alertness disrupts sleep (i.e., difficulties initiating and maintaining sleep), results in accumulating sleep debt and daytime sleepiness, and interferes with the timing of meals and activity patterns, which in turn may increase ADHD severity (Kooij, 2017), particularly hyperactivity. Indeed, links between delayed circadian phase and hyperactivity are also observed in healthy adults without ADHD, suggesting that the circadian delay-ADHD relationship may occur across a continuum of psychiatric health (Bijlenga et al., 2013).

When circadian rhythm delays are treated by bright light therapy, ADHD severity is reduced in adults with childhood-onset ADHD (Coogan and McGowan, 2017). These findings have led researchers to suggest that ADHD and sleeplessness resulting from delayed circadian phase in adulthood may represent “two sides of the same physiological and mental coin” (Kooij, 2017).

Second, the primary evidence for late-onset ADHD focuses on the emergence of ADHD symptoms during adolescence. Three of the four population-based studies concluded with the last point of data collection occurring in young adulthood (ages 17–19), suggesting the symptoms emerged between the ages of 12 (DSM cutoff for ADHD) and late adolescence. In addition, results from the MTA study suggested that for the majority of individuals displaying late-onset ADHD, symptoms were time-limited to the adolescent period and remitted prior to adulthood (Caye et al., 2017). Adolescence is also characterized by normative shifts toward delayed circadian preference in the general population, with variability in the extent of this shift across individuals, such that some individuals shift more toward eveningness than others. For most individuals, circadian preference subsequently shifts again – returning toward morningness – in early adulthood. Indeed, this occurrence is believed to represent a primary biological marker signaling the end of adolescence (Roenneberg et al., 2004). This pattern pinpoints adolescence as a developmental window wherein risk for both delayed circadian phase and emergence of late-onset ADHD symptoms may co-occur. Interestingly, an investigation with adults with childhood-onset ADHD indicated that delayed sleep phase was age-related for healthy controls (i.e., specific to adolescence) but not adults with ADHD, wherein delayed sleep phase tended to be chronic across adulthood (Bijlenga et al., 2013), suggesting the biological shift marking the end of adolescence may not have occurred for these individuals.

Third, there is remarkable overlap in the behavioral and neurocognitive deficits observed in adolescents with ADHD and those with sleep loss resulting from delayed circadian phase, suggesting a strong potential for circadian rhythm misalignment to mimic ADHD symptoms. Specifically, among adolescents, sleep loss occurring in the context of normative circadian misalignment results in increased daytime sleepiness as well as difficulties with attention, distractibility, emotional regulation, memory, and impulsivity/risk-taking (Kelley et al., 2015), symptoms that are also observed in individuals with ADHD. Indeed, adolescents with delayed sleep phase and/or eveningness chronotype preference exhibit higher rates of ADHD symptoms compared to adolescents without circadian delay. Interestingly, among adults, the relationship between eveningness chronotype and ADHD severity may be mediated by social jetlag; however, this has yet to be studied among adolescents (Coogan and McGowan, 2017). Similarly, adolescents with delayed circadian phase and/or eveningness chronotype preference also display poorer school performance, which may be due to circadian disruptions to attention and cognition. Interestingly, when the timing of cognitive testing is aligned with adolescents’ circadian preferences, their performance on executive functioning tasks, including risk-tasking, inhibitory control, and working memory, is enhanced (Kelley et al., 2015).

Fourth, research supports a common genetic basis underlying the expression of delayed circadian phase and ADHD. Specifically, polymorphisms in genes regulating the internal

circadian clock that have been related to circadian phase delay have also been associated with ADHD symptoms, particularly the T3111C single-nucleotide polymorphism (SNP) of the CLOCK gene in adults and children. There is also preliminary support for an association between a PERIOD 2 (PER2) polymorphism and ADHD symptoms in children, although the association did not reach significance at the study- or genome-wide level and warrants replication. Finally, one study examined the molecular rhythmic expression of BMAL1 and PER2 genes in adults with childhood-onset ADHD using oral mucosa sampling, and found rhythmic expression of both genes among healthy adults, but not those with ADHD (Coogan and McGowan, 2017).

Fifth, visual detection of bright light in the environment is integral to the regulation and synchronization of circadian rhythms to the solar day in humans, and adequate alignment between light exposure, the biological circadian clock, and human daytime behaviors is critical for survival, health, and adaptation to the environment. Links between light exposure and cognitive functioning, including attention and executive functioning, are also well-established. Specifically, light exposure appears to *directly* result in increased attention, alertness, and vigilance, as well as *indirectly* support the same cognitive processes through the impact of light detection on circadian rhythmicity (LeGates et al., 2014).

Regarding ADHD, there is evidence to suggest that ADHD prevalence rates are lowest in regions of the world where exposure to solar intensity is highest. Indeed, in one study, solar intensity was found to have a dose-response relationship with ADHD prevalence, explaining up to 41% of the variance in ADHD prevalence among children and up to 57% of the variance among adults, suggesting that exposure to bright light may be protective against ADHD, and this effect which may be driven by improvement in circadian regularity and timing (Arns et al., 2013). In addition, adults with childhood-onset ADHD may be hypersensitive to light, resulting in prolonged use of sunglasses throughout the year, which may also interfere with dopamine and melatonin regulation and circadian functioning (Kooij, 2017).

Sixth, a study assessing prevalence of late-onset ADHD in clinical settings found high rates of excessive daytime sleepiness among individuals with a late-onset ADHD presentation (~60%). In addition, for most of the individuals with late-onset ADHD criteria, onset of both daytime sleepiness and ADHD occurred in adulthood, suggesting that the emergence of these symptoms may coincide (Lopez et al., 2017). Daytime sleepiness frequently results from delayed circadian phase and thus, may be an indicator of circadian misalignment in late-onset ADHD.

Taken together, this evidence begs the question: Could delayed circadian phase, emerging more so for some adolescents than others, result in a late-onset ADHD presentation? There are at least two mechanisms by which circadian rhythm misalignment in adolescence might contribute to late-onset ADHD. First, delayed circadian phase may *directly* result in onset of “ADHD-like” symptoms for some adolescents; for example, those who experience greater shifts toward eveningness. For example, individuals may be predisposed to experience delayed circadian rhythm phase due to variants in clock genes. During adolescence, these genetic variants may determine the expression of delayed circadian phase, and misalignment

between intrinsic circadian rhythms and social time (e.g., school start time) may result in sleep loss, social jet lag, daytime sleepiness, and perhaps reduced light exposure, as these adolescents may sleep more during the day (e.g., weekends, after school naps). Sleep loss may then result in the appearance of symptoms that mimic ADHD, including poorer attention and greater impulsivity and distractibility. This explanation is consistent with the restricted phenotype framework, which suggests that alternative explanations (in this case, circadian rhythm misalignment) may account for the appearance of ADHD-like symptoms in adolescence (Caye et al., 2017).

Alternatively, delayed circadian phase may *indirectly* result in late-onset ADHD. For example, circadian misalignment may serve as a neurobiological stressor, not stable over time but specific to adolescence, which triggers the expression of underlying ADHD traits. Specifically, individuals may be predisposed to both delayed circadian phase and ADHD due to variants in clock genes. During adolescence, these variants determine the expression of delayed circadian phase, which then contributes to sleep loss, social jetlag, daytime sleepiness, and reduced light exposure. Sleep loss may then result in increased psychosocial stress; for example, by impairing academic, emotional, or social functioning (Kelley et al., 2015). Increased stress, in turn, may potentially result in ADHD onset by triggering expression of underlying genes, increasing the severity of subthreshold symptoms, and/or altering the trajectory of neural maturation. This hypothesis is consistent with the broad phenotype framework of late-onset ADHD (Caye et al., 2017). It should be noted that the proposed mechanisms are speculative and require empirical examination, as described below. In addition, it is important to note that relationships between delayed circadian phase and ADHD symptoms are likely to be bidirectional; for example, adolescents struggling with inattention are also more likely to stay up late to complete work, consume more caffeine, and overuse nighttime technology, which may in turn impact sleep timing (Lunsford-Avery et al., 2016).

Taken together, evidence suggests consideration of circadian rhythm misalignment is vital to informing our understanding of late-onset ADHD. From a research perspective, it is important to clarify whether circadian rhythm misalignment in adolescence represents (1) a better explanation for the occurrence of ADHD-like symptoms emerging later in development, (2) a neurobiological stressor triggering onset of a “true” ADHD phenotype, or both. Longitudinal studies evaluating ADHD symptoms though childhood, adolescence, and adulthood and including measures of circadian preference and/or objective measures of circadian timing (e.g., DLMO) may assess the extent to which circadian misalignment is present in individuals with late-onset ADHD as well as the temporal order of onset of circadian misalignment, stressors, and ADHD symptoms.

Experimental treatment outcome studies may also shed light on whether circadian misalignment directly results in ADHD-like symptoms. For example, if adolescents exhibit both late-onset ADHD and circadian misalignment, investigating the impact of circadian rhythm treatments, such as melatonin and/or bright light therapies, on ADHD severity in the absence of ADHD-specific treatments (e.g., stimulants) may elucidate whether delayed circadian phase is contributing to an ADHD-like presentation. If ADHD symptoms remit following circadian intervention, this would suggest that symptoms were due to circadian

misalignment rather that a true ADHD presentation. Additional treatment outcomes studies comparing the efficacy of circadian treatments and traditional ADHD interventions on ADHD severity would further clarify this issue.

Clinically, enhanced understanding of delayed circadian phase and its role in ADHD onset may critically impact how we assess and treat adolescents and adults presenting with a concern about ADHD. If circadian misalignment plays a causal role in the emergence of ADHD symptoms in adolescence, best-practice evaluations for ADHD may benefit from circadian rhythm assessment, which would aid differential diagnosis. Additionally, treatments targeting circadian misalignment such as light therapy and/or melatonin may be more appropriate than traditional ADHD interventions such as stimulants. Finally, from a public health standpoint, if late-onset ADHD symptoms result from circadian misalignment, accurate diagnosis may contribute to lower healthcare costs through implementation of effective treatments (reducing frequency of subsequent visits) and elimination of unnecessary ADHD-specific interventions that may not provide benefit to the patient. These are open questions for scientific inquiry; however, from the reviewed evidence, it is clearly imperative for models of late-onset ADHD to account for the potential influence of circadian rhythms on changes in behavior and attention over the lifespan.

Acknowledgements

Dr. Lunsford-Avery receives funding for studies on sleep and ADHD from the National Institute of Mental Health grant K23-MH-108704. Dr. Lunsford-Avery has received consulting fees from Behavioral Innovations Group. Dr. Kollins has received research support and/or consulting fees from the following commercial sources: Akili Interactive, Bose, Jazz, KemPharm, Medgenics, Neos, Otsuka, Rhodes, Shire, and Sunovion.

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