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## Circadian rhythms and risk for substance use disorders in adolescence

Brant P. Hasler, Adriane M. Soehner, and Duncan B. Clark

University of Pittsburgh School of Medicine, Department of Psychiatry, 3811 O'Hara Street, Pittsburgh, PA 15213

### Abstract

**Purpose of the review**—This article explores recent research in adolescent circadian rhythms, neurobiological changes influencing affective regulation and reward responding, and the emergence of substance use and related problems.

**Recent findings**—Recent findings have confirmed that adolescents with drug and alcohol problems are also beset by sleep problems, and have advanced our understanding of the relationship between sleep problems and substance involvement in this developmental period. During adolescence, a shift to later preferred sleep times interacts with early school start times to cause sleep loss and circadian misalignment. Sleep loss and circadian misalignment may disrupt reward-related brain function and impair inhibitory control. Deficits or delays in mature reward and inhibitory functions may contribute to adolescent alcohol use and other substance involvement.

**Summary**—An integration of the available research literature suggests that changes in sleep and circadian rhythms during adolescence may contribute to accelerated substance use and related problems.

### Keywords

Adolescence; sleep; circadian rhythms; reward; substance use

### Introduction

Adolescence is characterized by later preferred sleep times, parallel shifts in endogenous circadian rhythms, changes in reward responding and increased substance involvement <sup>[1]</sup>. These changes in sleep, circadian rhythms, neurobiological function and substance use are likely related. On weekdays, the inclination of adolescents toward later sleep initiation times and the early wake times imposed by school schedules results in sleep loss. Weekends are often characterized by later wake up times to make up for lost sleep. The typical repeating pattern of shifting sleep schedules from weekday to weekend induces circadian

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Author of correspondence: Brant P. Hasler, Ph.D., University of Pittsburgh School of Medicine, Department of Psychiatry, 3811 O'Hara Street, Pittsburgh, PA 15213; Phone: 412-246-5537; Fax: 412-246-5300; haslerbp@upmc.edu.

#### Conflicts of Interest:

None

misalignment, an effect referred to as “social jet lag.” During adolescence, structural and functional changes occur in the neurocircuitry involved in affective control and reward processing [2]. Sleep loss and circadian misalignment disrupts these affective and reward functions [3–7]. Among adolescents, insomnia prospectively predicts the onset of alcohol problems, and adolescents with alcohol use disorder (AUD), compared to controls, have persistent sleep difficulties, with greater variability in weekday-weekend sleep duration [8]. Recent findings suggest that the disruption of affective and reward functions due to circadian misalignment may contribute to problematic substance use [9]. Furthermore, substance use influences sleep and reward functioning. This article integrates recent findings in these areas to advance understanding of the relevance of sleep problems, circadian misalignment, affective dysregulation, and reward processing malfunction to the emergence of alcohol and drug problems during adolescence. Our review focuses primarily on findings related to alcohol, reflecting the relatively larger evidence base linking sleep, circadian rhythms, and alcohol involvement.

## Adolescent sleep and circadian rhythms

Important sleep and circadian changes occur during adolescence. Bedtimes shift later during middle school and high school, reflecting an increasing preference for later sleep times, a.k.a. eveningness [10–13]. The increase in eveningness continues until approximately age 18–20, when sleep preference undergoes a long, slow shift towards earlier sleep times, a.k.a. morningness [13,14]. These changes reflect, in part, alterations in the endogenous circadian clock, which shifts to a later (more delayed) phase during puberty [15]. Reduced sensitivity to the homeostatic sleep drive that builds during extended wakefulness may also contribute to later bedtimes in adolescents [16]. Sleep need, however, remains around 9.2 hours in adolescence [11].

Adolescents are faced with early school schedules that sharply conflict with their pre-disposed sleep timing [17]. For many, this results in difficulty falling asleep at night, curtailed sleep duration, and daytime fatigue on weekdays. Then, on the weekend, adolescents return to their preferred timing, staying up later, and sleeping in later to make up for sleep loss during the school week. Differences in weekday-weekend sleep timing, or social jet lag, are associated with mood disturbance and drug and alcohol use in both adolescents [18,19] and adults [20,21].

## Associations between sleep/circadian factors and adolescent substance involvement

Recent research has demonstrated both cross-sectional and predictive associations between sleep/circadian factors and adolescent substance involvement.

### Sleep problems/disorders

Several studies have demonstrated cross-sectional associations between self-reported sleep problems (i.e., sleep continuity disturbances, daytime sleepiness) and alcohol use/AUDs in adolescents [22,23]. More recent cross-sectional studies have linked sleep problems to consequences of alcohol use. Self-reported sleep quality over the past month was associated

with greater binge-drinking and more negative consequences of alcohol use in a sample of 261 college students [24]. In that report and a larger follow-up study, poorer sleep quality was associated with greater alcohol-related consequences in heavy drinkers [24]. The combination of poorer sleep quality and higher coping motives (e.g., to forget your worries) was associated with worse alcohol-related consequences (e.g., had a fight, argument, or bad feelings with a friend) [25].

A longitudinal study relating parent-rated childhood sleep problems predicted alcohol problems during adolescence [26,27], though another study found that self-reported insomnia complaints during adolescence did not independently predict alcohol use during young adulthood [22]. A more recent study followed 347 adolescents (age 12–19) with an AUD for five years, and observed that they reported more symptoms of insomnia and hypersomnia at follow-up relative to those reported by a reference group (n=349) [8]. At baseline, adolescents with AUDs reported greater variability in their weekday-weekend sleep duration. Among the reference adolescents without AUD, both baseline insomnia and weekday-weekend differences in sleep duration increased risk for subsequent alcohol symptoms.

### **Sleep Restriction**

Recent work suggests that the sleep restriction experienced by adolescents during school days is associated with increased use of alcohol and other drugs. Among 12,154 US high school students in the 2007 Youth Risk Behavior survey, the 68.9% teens reporting typical school night sleep durations under 8 hours were more likely to have engaged in alcohol, marijuana, and cigarette use in the past 30 days [28].

### **Eveningness and Social Jet Lag**

Eveningness, or the tendency towards a late chronotype, has been consistently linked with increased alcohol involvement in adolescents [29–34] as well as increased endorsement of various drinking motivations (e.g., drinking to conform) [35].

Social jetlag may also be associated with substance use in adolescents. Pasch and colleagues [19] studied a sample of 242 9–11<sup>th</sup> graders, reporting on cross-sectional associations between self-reported sleep, substance use, and depression. Weekday-weekend differences in bedtime and rise time were both significantly associated with higher rates of smoking, alcohol involvement and marijuana use, controlling for sleep duration. These findings partially converge with an earlier study in 388 9–12<sup>th</sup> graders [18], which reported that weekday-weekend differences in bedtime were significantly associated with the use of tobacco, alcohol, marijuana, and other drugs.

### **Circadian Data**

Adolescent studies including physiological circadian measures remain scarce. In a sample of 21 adolescents (14–19 years) with a history of substance abuse and current sleep disturbance [36], circadian alignment was quantified as the interval between dim light melatonin onset (DLMO) and wake-up time (based on wrist actigraphy). Greater

misalignment was related to greater substance use disorder (SUD) symptoms in the past month.

## Substance effects on sleep and circadian rhythms

Alcohol consumption has acute effects on sleep. Among middle aged adults, the acute effects of alcohol on sleep typically include reduced time to sleep onset (i.e., sleep latency), increased deep sleep (i.e., slow wave sleep), increased sleep consolidation, decreased rapid eye movement in the early sleep period, and sleep disruption with falling alcohol levels later in the sleep period [37]. The limited perceived benefits of alcohol initially reducing sleep latency are outweighed by sleep disruption, making alcohol a poor pharmacotherapy for sleep disturbances.

These effects of alcohol on sleep may have a somewhat different pattern in adolescents and young adults. Alcohol has biphasic stimulating and sedating properties that influence sleep effects. As blood alcohol concentration rises after consumption, a phase known as the “ascending limb,” alcohol has stimulant effects. Sedative effects occur on the “descending limb” [38]. Adolescents tend to be less sensitive to the sedating effects of alcohol [2]. Among young adults, when alcohol is consumed in the evening, compared to earlier in the day, the stimulant effect is exaggerated, increasing sleep latency [39]. Compared to placebo, young adults consuming alcohol experienced no significant change in sleep latency and they had increased wakefulness through the night [40].

Alcohol consumption acutely disrupts circadian rhythms in animal models, and is associated with altered melatonin and core body temperature rhythms in humans [41,42].

The relationship between adolescent alcohol problems and sleep difficulties often chronically persists. Hasler and colleagues [8] compared 347 adolescents with AUD and 347 reference adolescents on sleep variables at a baseline assessment and up to 5 years of follow-up visits. Adolescents with AUD had more sleep problems, including insomnia, hypersomnia and variability in weekday-weekend sleep duration, with sleep problems persisting during follow-up. Since animal studies indicate chronic effects of alcohol consumption on circadian rhythms [42], a concern is that alcohol use may further disturb circadian alignment among adolescents for whom “social jet lag” is already problematic.

## Circadian-reward mechanisms

Circadian modulation of reward function may be implicated in the development of adolescent SUDs. Paralleling the post-pubertal changes in sleep and circadian rhythms, reward-related behavior and brain function undergo dramatic alterations throughout adolescence and into young adulthood, including increased risk-taking and an apparent shift in the balance between top-down cortical regulatory capacity and bottom-up subcortical reward motivation [2,43–45]. We assert that these parallels are not entirely coincidental, particularly given burgeoning evidence of circadian regulation of the reward system. Three lines of evidence support these circadian-reward links.

### **Reward system functioning is influenced by circadian genotypes**

Circadian genes are expressed throughout the mesocortolimbic reward system, including the ventral tegmental area and ventral striatum, and disruption of these genes disrupts the reward system, including alterations in dopamine pathways (e.g., [46,47]). In animal studies, circadian gene mutants exhibit altered reward-related behavior such as increased preference for alcohol or hypersensitization to cocaine (see [48] for review). Human studies show convergent findings, including associations between a Per2 polymorphism and greater alcohol use in adult inpatients with AUDs [49]. Recent studies extend this work to adolescents, reporting that circadian gene variations are associated with increased substance use, although this may depend on environmental context. Two independent studies report that adolescents exhibit greater drinking only when they carry particular circadian genotypes (for Per1 and Per2, respectively) and experience greater life stress [50,51]. Although neither study assessed reward function as a mediator of these associations, a study by Forbes and colleagues [52] implicated Per2 in reactivity of the medial prefrontal cortex to monetary reward.

### **Diurnal rhythms are present in reward-related processes**

Daily rhythms are apparent in reward-related processes, including both behavior and the underlying physiology. Animal models demonstrate that drug and alcohol consumption, and drug-seeking behavior, exhibit daily rhythms that parallel those observed in related physiological changes in the mesolimbic dopaminergic pathway ([53–55]). In humans, alcohol consumption follows a daily pattern, peaking mid-evening for adults and somewhat later for adolescents [56,57]. This closely resembles the daily pattern of positive affect and related behaviors (e.g., socializing, laughing), which are related to activation of the reward system [58–60]. Laboratory paradigms have confirmed that the daily rhythm in positive affect reflects endogenous circadian timing, and indeed, parallels the core body temperature rhythm [61,62]. Furthermore, the latter study also reported that the heart rate response to a simple reward task showed a corresponding rhythm [62]. Emerging neuroimaging evidence supports similar daily patterns in activity of the human reward circuit [63–66].

### **Sleep and circadian disturbances are associated with reward dysregulation**

Sleep and circadian disturbances have long been noted as part of the symptomatology of AUDs and other SUDs, as well as mood disorders, all disorders characterized by altered reward function [67,68]. Sleep disturbance and sleep loss are associated with increased risk-taking and reward sensitivity [18,69], and neuroimaging studies link lower sleep quality and sleep duration to altered neural response to reward [70,71]. Furthermore, acute sleep deprivation increases the neural response to reward, with some studies also reporting an attenuated response to loss [3,6,7,72]. Similarly, “circadian” variants that are characteristic of adolescents, such as eveningness, later sleep timing, and social jet lag, are also associated with altered reward function. Eveningness is linked to altered timing and amplitude of positive affect rhythms, as well as increased risk-taking, higher novelty-seeking, and lower harm avoidance, similar to the effects of sleep loss. Neuroimaging studies in adolescents suggest that later sleep timing, greater social jet lag, and eveningness are all associated with reduced medial prefrontal cortex response to monetary reward [5,52], suggesting reduced

regulatory control. In one study, the evening-type patterns of prefrontal and striatal reactivity to reward correlated with increased alcohol use and more symptoms of alcohol dependence [5].

### Adaptive?

We speculate that both delayed circadian timing in adolescents, and circadian modulation of reward function, have adaptive roots, but may go awry in the context of circadian challenges such as early school start times. For example, others have suggested that the late sleep and circadian timing may encourage autonomy and independence by driving adolescents to be engaging the world after their parents' bedtime [73]. The circadian modulation of reward may work in concert with this, driving individuals to engage their environment and pursue rewards at times of maximal reward opportunity [74]. Circadian misalignment may distort these adaptive processes, exaggerating teens' drive to escape parental influence and their pursuit of rewards, including alcohol and other drugs.

### Implications for prevention and intervention

The high prevalence of sleep and circadian disturbances during adolescence confers an increased risk for the development of AUDs and SUDs. Preventing or treating these sleep/circadian disturbances—particularly by better matching sleep/wake schedules with internal timing—should therefore diminish risk. This can be done on an individual basis; tools are available to help teens adjust their internal timing and improve their sleep, including bright light, melatonin, and cognitive-behavioral treatments for insomnia (CBT-I). Notably, sleep hygiene recommendations, an adjunctive part of CBT-I sometimes included in current alcohol interventions, are not effective on their own [75]. CBT-I is a particularly attractive alternative to contraindicated pharmacological approaches when drug/alcohol abuse is a concern, given that it is as effective as typical sleep medications in the short-term, and perhaps more effective in the long term [76]. All of these approaches are arguably less stigmatizing than conventional drug/alcohol treatment. However, these approaches require consistent and motivated effort. Bright light treatment requires 30–60 minutes exposure after habitual rise time [77]—when adolescents are already pressed for time to get to school. Luckily, emerging technology—such as bright light goggles and visors—may allow teens to go through their normal morning routine while also getting their corrective bright light treatment.

A more efficient policy-level approach is to prevent circadian misalignment by changing school start times. Such efforts have demonstrated benefits for improving academic performance while reducing daytime sleepiness, depression, and automobile accidents [78–80].

In addition to direct sleep/circadian interventions, consideration of circadian principles during drug/alcohol treatment may be critical to consider. As noted, alcohol is relatively more stimulating when consumed in the evening [39], which may compound a tendency for adolescents to be relatively more sensitive to stimulating effects [2,40]. Prevention and intervention approaches could educate adolescents about this fact, emphasizing that self-medicating sleep problems with alcohol is likely to be particularly counterproductive for teens.

Finally, in addition to reward mechanisms, animal studies indicate that substances of abuse may entrain circadian rhythms via peripheral clocks outside of the central clock, thereby prompting substance use at particular times of day (e.g., [81]). This work has not yet been extended to humans, but one potential implication is that such rhythms may induce windows of craving that should be considered during intervention.

## Conclusion

Adolescents are prone to sleep and circadian disturbances that may partly explain their elevated risk for developing alcohol and drug problems. The mismatch between delayed internal timing and early school start times often goes unaddressed, providing a novel target for prevention and/or intervention. While effective sleep/circadian treatments already exist, these may be enhanced by a better understanding of the mechanisms underlying circadian modulation of reward processes. Future studies should include experimental studies to understand causal mechanisms, as well as prospective and longitudinal studies to tease out the bidirectional effects of sleep/circadian factors and drug/alcohol use in teens' naturalistic environments. Given the growing prevalence of smartphone use among teens, more work should be aimed at understanding the influence of smartphone use on sleep and circadian rhythms<sup>[82–84]</sup>. All these efforts are well-justified given the opportunity to correct sleep loss and circadian misalignment to shift teens' trajectory away from long-term drug and alcohol problems.

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## Abbreviations

<b>AUD</b>	Alcohol Use Disorder
<b>CBT-I</b>	Cognitive-Behavioral Treatment for Insomnia
<b>DLMO</b>	Dim Light Melatonin Onset
<b>SUD</b>	Substance Use Disorder

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**Key points**

- Developmental changes in sleep and circadian rhythms during adolescence are mismatched with school start times
- The resulting sleep and circadian disturbance is associated with increased alcohol and drug involvement
- Altered function in the reward system may partially explain the association between sleep/circadian disturbance and alcohol and drug problems
- Preventing and/or treating adolescent sleep and circadian disturbances may reduce the risk for developing alcohol and substance use disorders.