

# Review: Identification and Management of Circadian Rhythm Sleep Disorders as a Transdiagnostic Feature in Child and Adolescent Psychiatry

Martijn Arns, PhD , J.J. Sandra Kooij, MD, PhD , Andrew N. Coogan, PhD 

**Objective:** Sleep disturbances are highly frequent features in a range of child and adolescent psychiatric conditions. However, it is commonly not clear if such sleep problems represent symptomatic features of, comorbidities of, or risk factors for these conditions. It is believed that underlying dysfunction in the daily biological (circadian) clock may play important roles in the etiology of many sleep disorders, and circadian rhythm changes are reported in a number of neuropsychiatric conditions. The aim of this review was to explore the key identifying features of circadian rhythm disorders (CRDs) in child and adolescent psychiatry and address how such disorders may be managed in the clinic.

**Method:** A narrative review was conducted of the extant literature of CRDs in children and adolescents with psychiatric conditions.

**Results:** Key biological and social factors that contribute to CRDs in children and adolescents, and the cognitive and neurobehavioral consequences resulting from insufficient sleep were outlined. The roles of melatonin and other chronotherapeutic and behavioral interventions for the management of CRDs were also outlined. Further, the importance of careful investigation of circadian rhythm abnormalities in shaping the most effective treatment plan according to chronobiological principles was highlighted.

**Conclusion:** CRDs are common in children and adolescents with psychiatric conditions and arise out of complex interactions between biological and social factors. Careful clinical attention to and management of CRDs in child and adolescent psychiatry have the potential for significant benefit not only in the domain of sleep but also in a range of cognitive, affective, and behavioral outcomes.

**Key words:** ADHD, circadian, light, melatonin, sleep

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**S**leep and circadian rhythm problems, including difficulty falling or staying asleep, excessive daytime sleepiness, and excessively short or long sleep, are widely reported across diagnostic categories of *DSM-IV* and *DSM-5*. As such, sleep disturbances may constitute one of the most frequent symptoms in child and adolescent psychiatry as well as adult psychiatry.<sup>1</sup> Sleep disturbances form part of the diagnostic criteria of depressive and bipolar disorders in *DSM-5* and are common in anxiety and psychotic disorders, addiction, and post-traumatic stress disorder. Historically, sleep disturbances have been regarded as consequences of primary psychiatric disorders and have received insufficient attention from both researchers and clinicians relative to their prevalence and impact: What if sleep disturbance is a precipitating factor in the expression of the vulnerability for psychiatric disorders in a person and is much more important than previously thought?<sup>2</sup> This would open up new venues for better treatment of psychiatric conditions and for prevention of

their first manifestation. Given the developmental time course of the most prevalent psychiatric disorders, the contribution of sleep disturbances during childhood and adolescence may be particularly important as a point for intervention. Further, successful management of sleep disorders and disturbances in young people may improve psychological and physical daytime functions and ultimately improve clinical and psychosocial outcomes.<sup>2–4</sup>

Sleep-wake behavior arises from an interplay between endogenous circadian processes and sleep homeostatic factors, in concert with social and environmental influences.<sup>5</sup> The circadian system is an intrinsic biological timekeeper that imposes a 24-hour temporal architecture on behavior and physiology. An important function of the circadian clock is to promote wakefulness during the day and consolidation of sleep during nighttime hours, resulting in an average of 7–8 hours of sleep and 16–17 hours of wakefulness for adults.<sup>5,6</sup> This interplay, illustrated in Figure 1, is also referred to as the 2-process model.<sup>7</sup> Sleep pressure builds up during the day

(depicted as process S), and the circadian wakefulness drive cycle is a near 24-hour rhythm (depicted as process C). These 2 processes, especially their interaction, play a crucial role in sleep-wake regulation where the likelihood of falling asleep is highest when the distance between both processes is maximum, ie, when sleep pressure is high and circadian rhythm-determined wakefulness is low. Misalignment of either process will thus have ramifications for sleep-wake regulation, eg, when process C is shifted to later times, a person will be capable of falling asleep only at a later time, despite being very tired (as indicated by the accumulation of sleep pressure, or process S). In addition to the interaction between circadian and homeostatic factors in regulating the sleep-wake cycle, environmental and social factors play key roles, with social schedules and imperatives and modern technology, such as the use of light-emitting devices at night, increasingly emerging as areas of interest in sleep medicine.<sup>8</sup>

## METHOD

A narrative review was conducted of the extant literature of circadian rhythm disorders (CRDs) in children and adolescents with psychiatric conditions.

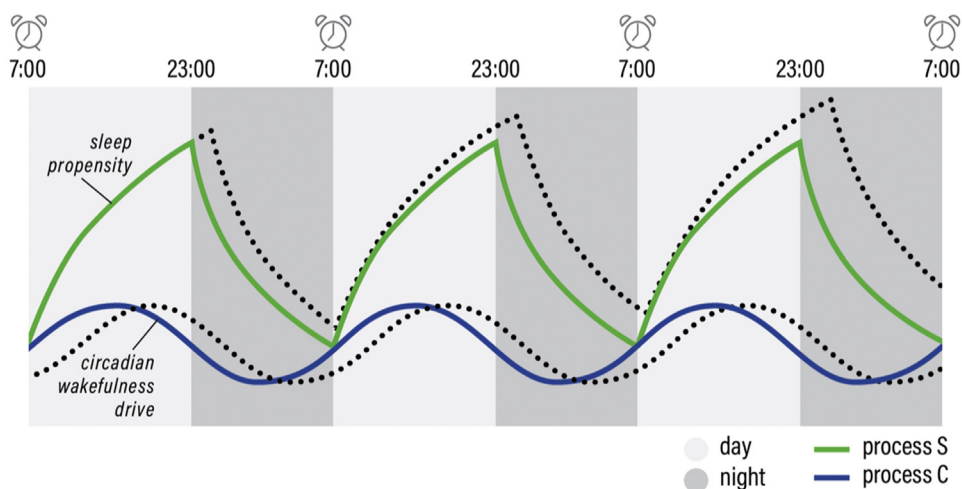
## RESULTS

### Circadian Rhythm Disorders

The circadian clock is normally synchronized (entrained) to recurring time cues in the environment (zeitgebers), with the most important one being the light-dark cycle.

Breakdown of optimal synchronization between internal circadian rhythms and external cycles can result in circadian misalignment, in which the timing of the external light-dark cycle no longer aligns with the phase of the endogenous circadian clock; the most obvious example of this is jet lag following rapid transit across a number of time zones. Such misalignments may be transient and resolve once internal clocks are allowed to resynchronize to external cycles. Another mechanism by which circadian misalignment may arise is via reduced responsivity and entrainment of the circadian system to zeitgebers, with the most striking being situations in which the circadian clock free runs according to its endogenous period, which may be approximately, but not exactly, 24 hours.<sup>9</sup> The phase of entrainment of the circadian clock with reference to the environmental light-dark cycle is manifested as a person's chronotype, describing the preferred timing of sleep-wake behavior across the 24-hour cycle. People with later (evening) chronotypes exhibit preference for later wake times and later sleep onset times, while people with early (morning) chronotypes prefer earlier wake and sleep onset times. A chronotype exists as a normally distributed spectrum in the general population<sup>9</sup> and is partly genetically determined (heritability estimates are approximately 10%–50%<sup>10</sup>). A chronotype is also strongly influenced by ontogeny and sex, with the greatest sex difference during adolescence/early adulthood<sup>11</sup> (a higher percentage of adolescents are classified as having an evening chronotype relative to adults, and

**FIGURE 1** Two-Process Model of Sleep



**Note:** Two-process model of sleep, indicating a normal (green and blue) and a delayed (dotted lines) circadian rhythm (adult sleep wake times taken as a reference). Process S indicates sleep pressure; process C indicates the circadian wakefulness drive. The larger the distance between process S and process C, the more likely the moment of sleep initiation or falling asleep. With a delayed circadian rhythm, sleep initiation is delayed, and given wake times are unchanged, there is a progressive increase and accumulation of sleep pressure across days (also termed accumulation of sleep debt). Times in figure are based on the 24-hour clock. (Modified from Bijlenga *et al.*<sup>2</sup>) Please note color figures are available online.

this effect is more pronounced in boys than girls<sup>12</sup>). If the circadian clock does not appropriately entrain to the daily light-dark cycle, CRDs characterized by inappropriate or suboptimal timing of behavior, sleep, and physiology may arise with implications for physical and psychological health. In the following subsections, we review the etiology, manifestation, and management of CRDs in children and adolescents occurring as primary conditions or as comorbidities with common psychiatric disorders.

### Circadian Clock and CRDs

The master circadian oscillator is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus,<sup>13</sup> and the SCN clock entrains to the light-dark cycle via photic information transferred to the SCN by the retinohypothalamic tract, a monosynaptic input to the SCN from a subset of retinal ganglion cells.<sup>13</sup> Besides rod and cone photoreceptor cells in the retina, there are more recently discovered retinal photoreceptor cells that are responsible for the non-image forming perception of light intensity.<sup>14</sup> These are the M1 type, intrinsically photosensitive retinal ganglion cells (ipRGCs), which modulate, among others, the pupillary reflex and the release of melatonin and project to the SCN.<sup>15</sup> The photopigment melanopsin in these ipRGCs is most sensitive to visible light of shorter wavelengths (400–500 nm, the blue light range of the spectrum).<sup>16</sup> In addition to projection to the SCN, the ipRGCs also project to sleep-promoting neurons in the ventrolateral preoptic nucleus and superior colliculus.<sup>17</sup> As the SCN entrains to the appropriate environmental zeitgebers, it then synchronizes multiple brain and peripheral clocks that together give rise to whole-organism circadian rhythms in behavior and physiology.<sup>18</sup>

While light is the dominant zeitgeber for the circadian system, humans also entrain to nonphotic zeitgebers, such as mealtimes, social cues,<sup>19,20</sup> and exercise.<sup>19</sup> The effects of photic and nonphotic zeitgebers on circadian phase are determined by the circadian phase during which these cues are presented; for example, the impact of evening light differs from the impact of early morning light, which differs from the effect of light during the afternoon; morning bright light advances the phase (phase advances) of the circadian clock, and evening bright light exposure delays the phase of the circadian clock leading to later sleep onset time (Figure 1).<sup>15</sup> Man-made electric lighting that preferentially triggers the ipRGCs (ie, 400- to 500-nm blue light, mostly light-emitting diodes, LEDs) in the evening, is associated with circadian phase delays, and thus in the assessment of delayed sleep phase in young people, careful consideration should be given to the use light-emitting devices in the evening as a potential source of such delays.

### Genetic and Molecular Basis of Circadian Rhythmicity

The genetic and molecular basis of circadian rhythmicity has been remarkably elucidated over the past 2 decades, and the core molecular circadian clockworks consist of a series of interlocking feedback and feedback transcriptional loops involving a panel of clock genes that code transcription factors (eg, *CLOCK*, *BMAL1*, *PER1/2/3*, *CRY1/2*). The temporal dynamics of these loops result in molecular cycles with periods close to 24 hours, which in turn imposes rhythmicity on a large proportion of the transcriptome in a tissue-dependent manner. Of interest for CRDs are a number of studies that link rare, but highly penetrant polymorphisms in circadian or circadian-related genes and signaling pathways: familial advanced sleep phase syndrome, an inherited condition characterized by a 4-hour phase advance of the sleep-wake cycle, is associated with polymorphisms that alter the stability of the *PER2* gene.<sup>21,22</sup> In familial delayed sleep phase disorder (DSPD), a dominant coding polymorphism in the *CRY1* gene with an allele frequency of 0.6% in the general population is associated with delayed and/or fragmented sleep-wake rhythms through a gain-of-function molecular phenotype that results in lengthening of the circadian period.<sup>23</sup> These studies illustrate that single polymorphisms can result in heritable extreme phase advances or delays of the sleep/wake cycle. However, the majority of CRDs are neither as extreme nor familial in nature. If such CRDs are considered as the tails of the normal distribution of a chronotype, understanding the determinants of the chronotype should be instructive in the etiology of CRDs. Genome-wide association studies have implicated up to 351 loci in chronotypes, although in common with many other genome-wide association study findings on behavioral traits, the total variance in chronotypes associated with these polymorphisms is low.<sup>24</sup>

### CRDs and Short Duration Sleep

CRDs such as DSPD and advanced sleep phase disorder are suspected when sleep onset and offset times are shifted by 3–6 hours relative to conventional sleep-wake timing within the particular social context; for example, this may translate to sleep onset times between 2 AM and 6 AM in adults with DSPD according to International Classification of Sleep Disorders guidelines.<sup>5</sup> DSPD and advanced sleep phase disorder may not impact sleep duration in contexts where people are allowed sufficient compensatory accommodations in morning routines (such as work or school start times) to preserve sufficient sleep duration and to counteract the later sleep onset times and longer sleep latencies.<sup>5</sup> However, in children and adolescents, smaller phase delays and advances (2–3 hours) are considered consistent with the presence of a CRD, especially when total sleep duration is reduced considerably (eg, owing to real-world

inflexibility in school start times). As such, some of the adverse daytime consequences of CRDs may be mediated through chronic short sleep duration (the accumulation of sleep debt across days [Figure 1]).

Occasional sleep deprivation (eg, not sleeping for 1 or 2 nights) exerts detrimental effects on cognitive functioning, and comparable effects are found after sustained sleep restriction (eg, persistent reduced sleep duration), which probably better mirrors real-world circumstances.<sup>25</sup> Sleep-restriction studies demonstrate substantial impairment of sustained attention and working memory<sup>26,27</sup>; 2 weeks of restricting sleep to 6 hours per night leads to cognitive impairments that were equal to 2 nights of full sleep deprivation.<sup>25</sup> In contrast to participants who were sleep deprived, sleep-restricted participants were unaware of their cognitive deficits.<sup>25</sup> Resultant cognitive deficits, most specifically inattention, needed a longer duration of normal sleep to fully recover than the duration of the initial sleep restriction.<sup>26,27</sup> Sleep restriction studies have also been conducted in children, albeit not as extensively as in adults, and in general these studies demonstrate impairments of attention<sup>28–31</sup> and behavioral dysregulation after 1 week of sleep restriction.<sup>27</sup> Contrasting a sleep-restriction and sleep-extension regimen in a group of adolescents with attention-deficit/hyperactivity disorder (ADHD) resulted in large effects on inattentiveness, oppositional symptoms, and sluggish cognitive tempo, demonstrating a potential causal link between sleep duration and symptoms often seen as characteristic in ADHD.<sup>32</sup> With respect to the amount of sleep children currently achieve, a systematic review with data from 690,747 children from 20 countries demonstrated that children today sleep 1 hour 15 minutes less than a century ago.<sup>33</sup> Therefore, a greater proportion of children than ever may have chronic sleep restriction, a conjecture that is further evidenced by a trend over the last 10–15 years of increased signs of drowsiness in the daytime in healthy children as quantified objectively with EEG.<sup>34</sup> Cross-sectional studies in children have clearly demonstrated associations between longer sleep duration and better executive function and school performance; conversely, shorter sleep is associated with more internalizing and externalizing behavior problems (summarized in a meta-analysis of 35,936 children<sup>35</sup>). Adolescents who go to bed later display poorer academic performance,<sup>36</sup> and several studies have demonstrated that by delaying high school start time by 30–90 minutes, sleep duration increased by 29–45 minutes, with subsequent reductions in daytime sleepiness, depressed mood, and caffeine use<sup>37,38</sup> and a reduction of 70% in the number of car crashes among teen drivers.<sup>25</sup> These effects appear to be mediated through later wake times but not later sleep onset times, indicating that delaying school start time

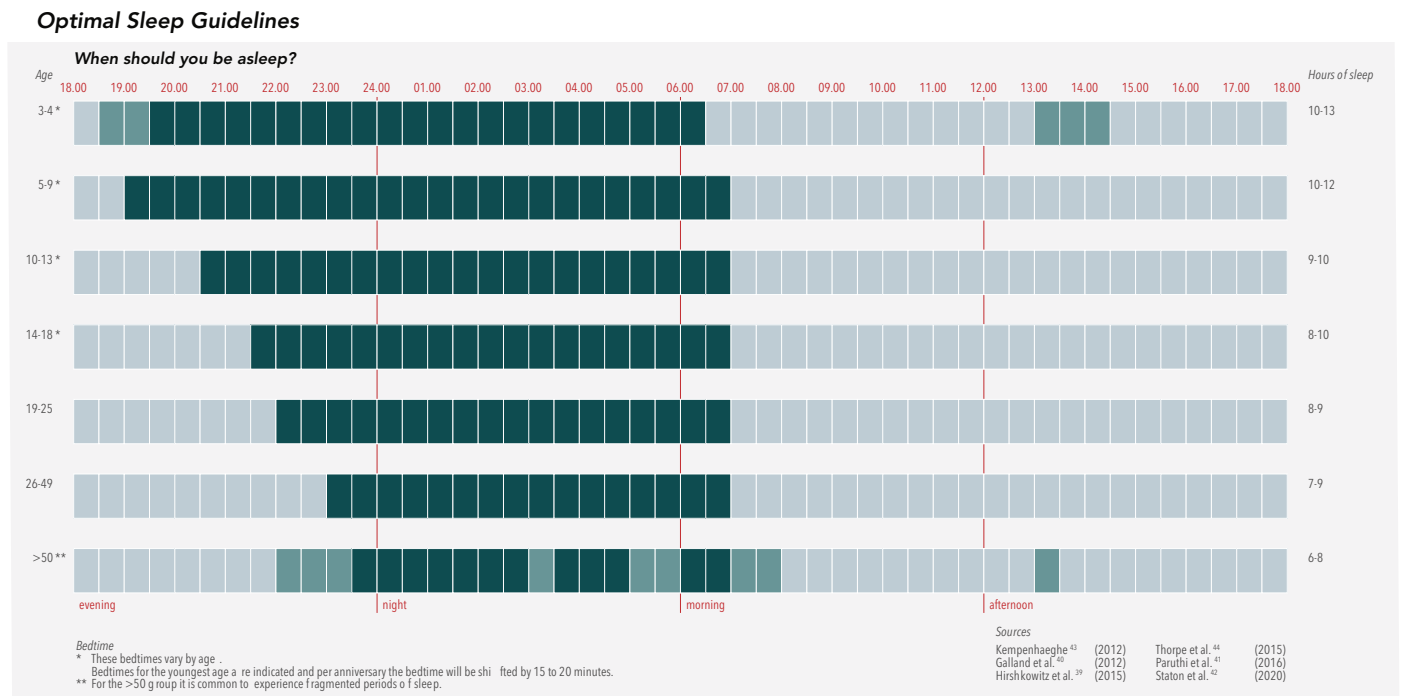
does not lead to later sleep schedules.<sup>37,38</sup> As such, in the assessment of CRDs in young people, careful attention should be paid to aspects of their school and social schedules, especially aspects that may be tractable, such as bedtimes and timing of sleep on school-free days.

In child and adolescent psychiatry, it can often be hard to gauge what age-appropriate bedtimes and what an age-appropriate number of hours of sleep per night are. Figure 2 shows recommended bedtimes during the working week and sleep duration for different age groups. These estimates were derived from several sources and guidelines,<sup>39–44</sup> and a graphic version that is regularly updated can also be downloaded from the Brainclinics Foundation (<https://brainclinics.com/sleep-materials/>) for further reference.

### Social Factors and CRD Symptoms

Both advanced and delayed sleep phases highlight an important issue for CRDs: alterations in circadian phase per se may not be detrimental, but they may be detrimental in the context of competing and conflicting environmental and social cycles that generate conflict between the internal circadian phase and the socially determined exposure to photic and nonphotic zeitgebers. There is evidence that people with DSPD are more likely to have circadian desynchrony than people with advanced phase sleep disorder, given the morning bias in schedules in many societies.

Clearly the more extreme the underpinning phase delay or advance, the greater the potential mismatch and the greater the resultant symptoms of daytime sleepiness, fatigue, and impaired affect and cognition may be. Such a concern is not only pertinent to people with more extreme phases of circadian entrainment, but also is pertinent to people with a typical phase of circadian entrainment but who experience a conflict between this biological time and social imperatives in a phenomenon that has been termed social jet lag (formally defined as the difference in time of midsleep on work and free days).<sup>45</sup> Owing to puberty-associated changes in chronotype, adolescents and young adults have the greatest social jet lag as they tend to have more delayed circadian rhythms.<sup>46</sup> For adolescents, social jet lag typically arises owing to a conflict between biologically driven late phase of circadian entrainment (manifesting as a preference for later bedtimes) and forced early waking because of school or college start times during the school week. On days without such enforced waking (eg, the weekend), the timing of sleep for adolescents is a function of their later circadian phase combined with catch-up longer sleep durations to address accumulated sleep debt during the school week. In such a scenario, earlier school start times will result in greater social jet lag, as will the need for longer commutes that would predispose to earlier forced waking times. It is important to

**FIGURE 2** Recommended Age-Appropriate Bedtimes and Wake-up Times

**Note:** Recommended age-appropriate bedtimes and wake-up times as well as number of hours of sleep per night (on the right). Dark shading indicates sleep times, and lighter colors in the youngest (3–4 years) and oldest (>50 years) age groups indicate exchangeable times, ie, when someone naps during the day, sleep pressure in the early evening is probably lower. For the >50 years age group, lighter colors further indicate higher occurrences of fragmented sleep that are common at older ages. Also, if sleep offset times are different, eg, 8 AM instead of 7 AM, other times shift along as well. These recommendations have been derived from recommendations and guidelines from the American Academy of Sleep Medicine (AASM),<sup>41</sup> the Center for Sleep Medicine in Kempnaeghe, and the latest systematic reviews and meta-analyses on sleep duration and napping.<sup>39–42,100,101</sup> Times in figure are based on the 24-hour clock, graphic and future updates can be downloaded from the Brainclincs Foundation website: <https://brainclincs.com/sleep-materials/>. Please note color figures are available online.

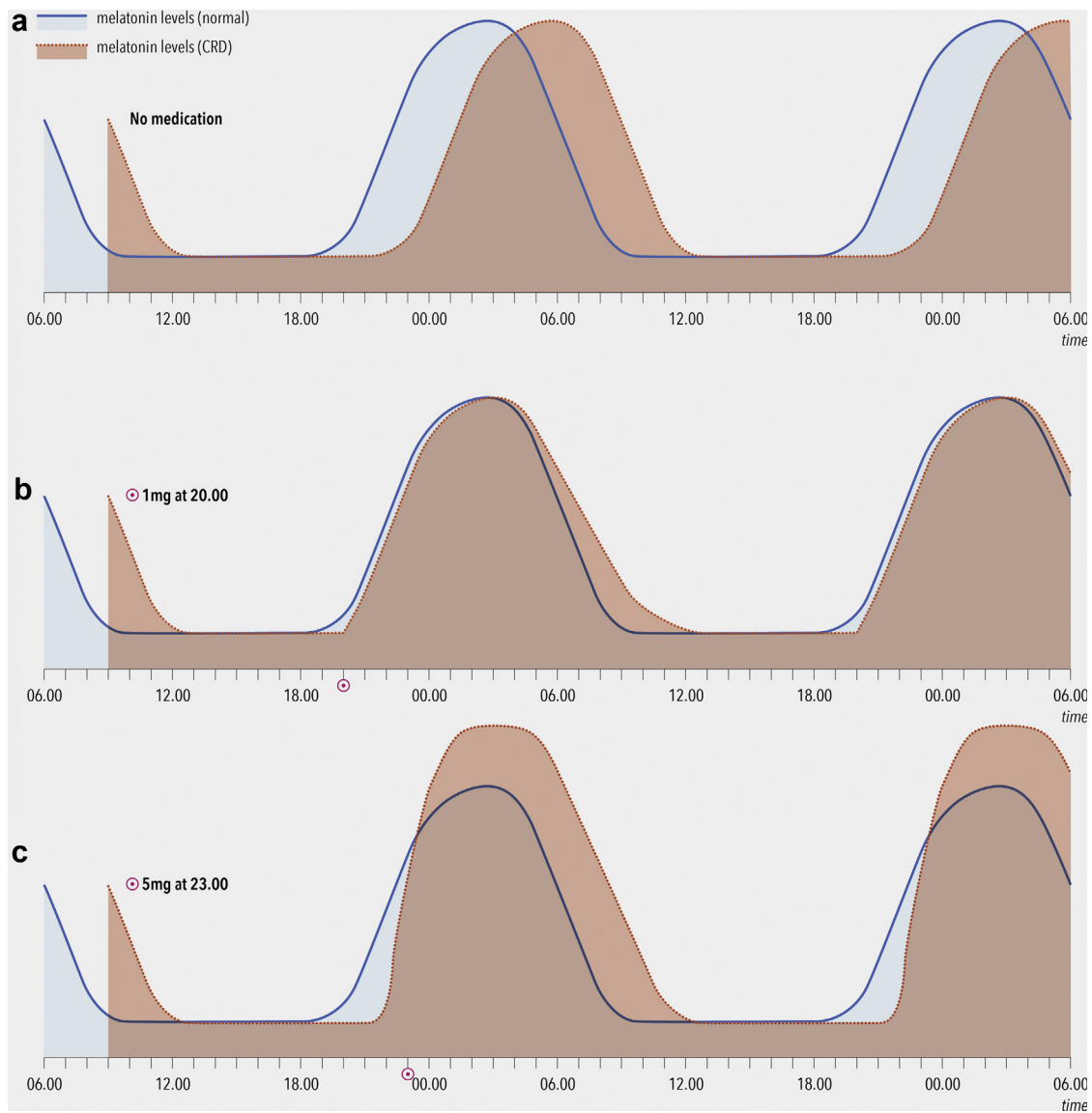
recognize that adolescents' later wake times during the weekend is strongly shaped by their intrinsic circadian phase<sup>11</sup>; that is to say it is a more naturalistic sleep schedule relative to their intrinsic circadian rhythms than that enforced on them during the school week. Social jet lag is associated with shorter sleep, poorer sleep quality,<sup>47</sup> and adverse psychosocial physical health outcomes for young people (eg, seasonal and nonseasonal depression<sup>48</sup> and cardiometabolic risk<sup>49</sup>). There are promising indications that interventions that alter the social schedule to better fit the circadian rhythm can result in reduced social jet lag, longer sleep, and improved psychosocial outcomes; for example, delaying the start of the high school day may result in longer sleep and better educational performance.<sup>50</sup> As such, in assessing CRDs in young people, attention should be focused on social circumstances as much as biological factors.

### Circadian Rhythm Changes Across Common Psychiatric Diagnoses in Young People

As noted above, sleep disturbances are very common in young people with diagnoses of neurodevelopmental or affective disorders. Circadian rhythm changes may underpin

some of these sleep disturbances and may be of importance themselves as various aspects of affect and cognition operate under significant circadian control.<sup>51,52</sup> Further, later chronotype is associated with traits and behaviors that may be of importance for psychopathology, including greater emotional lability,<sup>53</sup> aggression and antisocial behavior,<sup>54</sup> and risky behaviors and addiction.<sup>55,56</sup>

Young people with depression are reported to be twice as likely to have delayed sleep onset (defined as between 2 AM and 6 AM<sup>57</sup>). Delayed sleep phase is reported to be present in 62% of young people with bipolar disorder and 30% of young people with unipolar disorder (compared with 10% in the control population<sup>58</sup>). Blunting of the locomotor circadian rhythm may be a state marker for the development of episodes of unipolar or bipolar depression.<sup>57</sup> In a normative population of preadolescent children, evening chronotype was associated with more sleep problems, greater daytime sleepiness, and greater depressive symptoms<sup>59</sup>; similar findings are reported for adolescents, with the influence of depression on chronotype being greatest after puberty and later chronotype predicting subsequent depressive episodes.<sup>60</sup> Later chronotype in

**FIGURE 3** Different Dosing and Timing Regimens for Melatonin Prescription

**Note:** Effects of various dosing and timing regimens of exogenous melatonin application in people with circadian rhythm disorder (CRD) (adults in this example; same principle applies to youth). (a) Endogenous melatonin cycles over 2 days for people with normal circadian rhythms (blue) and people with delayed circadian rhythms (orange). (b) When exogenous melatonin is considered in patients as a treatment to normalize circadian timing, a low dose (1 mg) early in the evening several hours before dim light melatonin onset (8 PM) normalizes the melatonin transcription by providing a small boost early in the evening, whereby endogenous production takes over and achieves physiologically relevant melatonin transcription. (c) When a high dose (5 mg) is provided 1 hour before bedtime (as is often done in practice), an overdrive of melatonin is seen, which might result in short-term relief due to the hypnotic effects as well as hangover/sleepiness in the morning, albeit this will not result in longer-term chronobiotic effects.<sup>95</sup> Times in figure are based on the 24-hour clock. Please note color figures are available online.

adolescents may be differentially associated with depression compared with anxiety, and observations of associations between anxiety symptoms and later chronotype may be driven by comorbid depressive symptoms.<sup>60</sup>

In children with ADHD, although chronotype differences have not been reported compared with controls, later chronotype in children with ADHD was more associated with sleep problems,<sup>61</sup> and the normalization of delayed sleep onset resulted in normalized inattention.<sup>62,63</sup> Later

chronotype in adolescents with ADHD has also been reported to be associated with more sleep problems and daytime sleepiness.<sup>64</sup> As such, assessment of chronotype in the clinic may be useful in managing sleep problems in young people with ADHD. A recent systematic review reported that later chronotype/delayed sleep phase and irregular sleep-wake rhythms are associated with autism spectrum disorder, although there is a relative paucity of studies in this area to date.<sup>65</sup>

While this has by no means been an exhaustive review of this important topic, we highlight that circadian rhythm changes may be a transdiagnostic feature for many common conditions in child and adolescent psychiatry and may warrant systematic evaluation in routine clinical practice.

#### Application Example: CRDs, Sunlight, and ADHD

Intense natural light in the morning acts as a zeitgeber that phase advances the circadian clock and as such can counter phase delays.<sup>66</sup> People who are typically exposed to more outdoor (natural) light go to sleep earlier and sleep more than people typically exposed to indoor (nonnatural) light.<sup>67</sup> However, it has been described that 73%–78% of patients with ADHD present with difficulty falling asleep or late sleep onset,<sup>61,62,68,69</sup> adding evidence to the hypothesis that ADHD is associated with a delayed circadian phase, as demonstrated by a delayed onset of the sleep hormone melatonin in the evening in both children and adults. Also, synchronization to daylight is compromised during the daytime by photophobia leading to the wearing of sunglasses in adults with ADHD.<sup>70</sup> Congruent with this concept, 2 pilot studies in which morning bright light therapy was applied in adults with ADHD demonstrated an advanced circadian phase and subsequent improvements in ADHD symptoms.<sup>63,71</sup> Consistent with this, Arns *et al.*<sup>72–74</sup> observed a strong geographical correlation between higher sunlight intensity and a lower prevalence of ADHD across the United States and in other countries. This relationship is explained by the fact that sunlight intensity serves as an important cue for the brain's circadian rhythm regulation, where high daylight intensity is a stronger cue than low daylight intensity to synchronize the circadian rhythm. People with a genetic disposition to a lengthening of the sleep cycle may therefore profit from stronger synchronization cues, such as a large contrast in light between day and night: high sunlight intensity and dark evenings and nights, leading to a better synchronized circadian rhythm, better sleep, and thus less severe ADHD symptoms.

## DISCUSSION

### Assessment and Treatment of CRDs in Young People in the Clinic

Screening, diagnostic assessment, and treatment of sleep disturbances in child and adolescent psychiatry are important. Sleep diaries can be used to record important factors, such as day-to-day variability in sleep timing and duration. Various screening questionnaires are available, such as the Children's Sleep Habits Questionnaire (CSHQ)<sup>75</sup> and the Holland Sleep Disorders Questionnaire (HSDQ), which is normed and validated against polysomnography<sup>76</sup> and is also available in multiple languages including English.<sup>76</sup> These questionnaires screen for sleep onset delay and

circadian rhythm sleep disorders as important indicators for CRD. The presence of other sleep problems identified by these questionnaires (eg, insomnia, sleep duration, parasomnia) should prompt attention to the possible presence of CRDs and appropriate follow-up. Questions on sleep timing (bedtime, sleep onset time, variable or fixed bedtime, sleep onset latency, weekend catch-up sleep, napping during daytime, sleeping through, wake-up time, sleep duration, sleep quality, sleepiness during daytime) should complement questions on sleep environments, household composition, and individual and household sleep habits and evening activities). If on initial investigation it appears that social and behavioral factors and poor sleep hygiene are not the primary drivers of abnormal sleep phase, objective measures of sleep-wake behavior, such as wrist actigraphy and/or the determination of the dim-light melatonin onset (DLMO) in saliva for confirmation of a delayed circadian rhythm/sleep phase, may be indicated. DLMO quantifies melatonin concentrations from saliva and can objectively determine the time when melatonin production is initiated and hence is a reliable measure of circadian phase.<sup>77</sup> Wrist actigraphy is especially useful to objectively assess sleep-wake behavior and timing over weekdays and weekend days and can help detect sleep maintenance problems of which children and parents are often unaware.

With regard to treatment approaches for CRDs, sleep hygiene should be part of psychoeducation for all patients presenting with CRDs and their caregivers. Sleep hygiene consists of measures that promote better sleep duration and quality through sleep-friendly environments and behaviors and involves directions for the timing and amount of caffeine and use of other substances; maintenance of consistent sleep schedules; and keeping bedrooms dark, quiet, and well ventilated. Sleep hygiene may also promote circadian entrainment via increased exposure to natural bright light in the morning and during the day and minimizing late evening light exposure through the use of blackout blinds and preventing unnecessary exposure to man-made blue light sources in the evening. Software tools such as Night Shift (Apple Inc., Cupertino, California) and f.lux (<https://justgetflux.com/>) that reduce the short wavelength visible light component of light-emitting diodes may be useful in reducing the phase-delaying potential of light-emitting device use in the evening. The wearing of orange-tinted glasses from 7 PM also restricts blue wavelength light incident on the retina and counters evening light-induced phase delays.<sup>78</sup> However, while sleep hygiene is widely recognized as an important behavioral approach for better sleep, poor sleep hygiene is often not believed to be the primary cause, nor sleep hygiene the only treatment, of CRD.<sup>79</sup>

Chronotherapy (interventional approaches primarily targeting the circadian clock) for delayed sleep phase involves phase resetting of the internal clock by the use of early morning bright light exposure and/or exogenous evening melatonin or may involve tailoring the time of dosing of certain therapeutics to enhance their efficacy and/or decrease their side effects. According to circadian theory, an underlying phase delay may be countered with early morning bright light exposure and midevening melatonin treatment, and phase advances can be countered with early morning melatonin and evening light exposure. This was elegantly demonstrated in a study by Lewy *et al.*<sup>80</sup> on seasonal affective disorder in which approximately two thirds of patients had an underpinning phase delay, while one third had a phase advance; tailoring of the light therapy/melatonin to the underlying phase resulted in correction of the phase and decrease in depressive symptoms. In children and adolescents, there are indications that chronotherapy may be useful in the treatment of CRDs either as stand-alone or adjunct approaches. Richardson *et al.*<sup>81</sup> reported a randomized controlled trial for green or red light therapy delivered through specialized glasses to adolescents and young adults with delayed sleep phase disorder, which resulted in earlier times of sleep onset, shorter sleep latency, and improved daytime functioning. Further, light therapy in DSPD also reduced cognitive insomnia symptoms and psychological distress.<sup>81</sup> Another randomized controlled trial of morning bright light therapy paired with cognitive behavioral therapy in children and adolescents with DSPD found moderate-to-large improvements in sleep timing, duration, latency and sleepiness and fatigue compared to wait-list controls; these effects persisted for 6 months. Light therapy aimed at resetting the circadian rhythm usually consists of bright white or blue light boxes with an intensity of 10,000 lux, at a distance of 20–40 cm from the eyes. Light therapy aimed at phase-advancing the circadian rhythm should comprise 2–3 weeks of light exposure for 30 minutes every morning at the same time, preferably between 7 and 8 AM. The number of days of light therapy may be an important factor shaping the efficacy of light therapy in DSPD.<sup>82</sup> Weekend sleep schedules and light exposure, late bed times and evening light exposure may also be important factors in determining the efficacy of chronotherapy in adolescents.<sup>83,84</sup> As light-emitting device use is now highly prevalent among adolescents, due consideration should be given to the use of such devices in the late evening as a potential source of phase-delaying photic stimulus to the circadian clock that may confound the successful application of morning light therapy.<sup>85</sup> Recently discovered higher-than-expected levels of inter-individual variability in circadian responsiveness to evening light<sup>86</sup> indicates that

careful circadian phenotyping in DSPD may increase the efficacy of chronotherapeutic approaches.

Another important chronotherapeutic approach is the timed use of melatonin or melatonin agonists. Endogenous melatonin is usually secreted during the dark period and is suppressed by nocturnal light. Melatonin has chronotherapeutic, antioxidant, anti-inflammatory, and free radical scavenging properties.<sup>87</sup> Plasma melatonin is hardly detectable in the first months after birth, with a clear day-night difference emerging after 3 months,<sup>88</sup> followed by increasing nocturnal levels of melatonin peaking at 1–3 years of age, after which melatonin levels progressively decrease until adulthood with further moderate declines into old age.<sup>88,89</sup> The decreasing plasma levels from childhood into adolescence are mainly explained by increased body size.<sup>89,90</sup> Exogenous melatonin has several properties: it can act as a chronobiotic (a substance that is capable of entraining circadian rhythms); however, the exact dosing time is crucial for such uses.<sup>91–93</sup> Burgess *et al.*<sup>93</sup> demonstrated that low-dose (0.5 mg) melatonin taken 2–4 hours before DLMO, or 9–11 hours before sleep midpoint, resulted in maximum phase advances, relative to a higher dose (3 mg). A similar lack of dose effect (0.05–0.15 mg/kg) on phase-advancing effect (compared with placebo) was demonstrated by van Geijlswijk *et al.*,<sup>94</sup> highlighting that timing is more important than dosage. Administration of 5 mg of melatonin to children between 6 and 7 PM<sup>69</sup> and 5 mg to adults between 3 and 10 PM has been found to be effective in reducing sleep onset latency.<sup>92</sup> However, using DLMO, the window for optimal administration of melatonin to achieve phase advances is 3–5 hours before DLMO,<sup>87</sup> and the earlier it is prescribed within that window the larger the phase advance.<sup>69</sup> Given that time from DLMO to sleep initiation is 1.0–2.7 hours,<sup>69,93</sup> this translates to a time approximately 4–6 hours before the desired or age-appropriate bedtime (Figure 2) to make optimal usage of the phase-advancing effects of melatonin. Exogenous melatonin taken several hours before bedtime can thus phase advance the circadian clock; however, when taken 6–15 hours after DLMO, thus in the morning, melatonin will phase delay the circadian clocks.<sup>92</sup>

In higher doses (>5 mg), melatonin also exerts putative hypnotic (soporific) properties, reported as early as in 1996.<sup>91</sup> Furthermore, at higher doses, the chronobiotic effect of melatonin might be lost,<sup>95</sup> or when a high dose is given too late, with melatonin levels persisting through the morning, it might actually result in phase delay (Figure 3).<sup>92</sup> Therefore, in patients with CRDs, low-dose melatonin (0.5–1.0 mg), appropriately timed 4–6 hours before the desired bedtime, is preferred to prevent the more hypnotic effects and focus on the chronobiotic effect.



These recommendations contrast with advice from the European Food and Safety Authority in 2010 and 2011<sup>87</sup> that has contributed to the controversy of the “high-dose 1 hour before,” versus “low-dose longer before bedtime” doctrine. Finally, many of the melatonin preparations are extended-release formulations; however, the added value of such formulation has also been doubted, as it is not clear whether these result in chronobiotic or somnolent benefits over immediate-release formulations.<sup>87</sup>

Overall, the evidence base for the efficacy of chronotherapy in CRDs in children and adolescents remains underdeveloped, although the prevalence of DSPD in youth in general is reported to be as high as 16%.<sup>96</sup> As such, there is a need to strengthen the evidence base to afford frontline clinicians guidelines for the targeted use of chronotherapy in the management of CRDs in young people. Melatonin use for chronotherapy appears to be safe and effective,<sup>87,97,98</sup> although there is a need for high-quality randomized controlled trials to strengthen the evidence base for its clinical use for primary and comorbid CRDs in young people.<sup>99</sup>

## Summary

CRDs are prevalent in child and adolescent populations, including in children with neurodevelopmental disorders such as ADHD, mood disorders, and autism spectrum disorder, and impact daily functioning, including attention, working memory, mood, and externalizing behaviors. For the diagnosis, assessment, and prevention of CRDs, questionnaires and subjective instruments are important but may be augmented by objective measures via actigraphy devices or biological measures, such as DLMO. The impact of social and school schedules, modern media, and lighting sources combined with a trend for children to spend less time outside (reduced sunlight exposure) may contribute to CRDs and should be carefully assessed in young people presenting with potential CRDs. Simple management measures that target

such factors include sleep hygiene and psychoeducation for patients and their caregivers, increasing exposure to morning light by simple means such as change of transport to school to walking or cycling, and reducing exposure to blue light in the evening with blue light-blocking features in devices or with blue light-blocking glasses. If such preventive measures do not help sufficiently, chronotherapeutic approaches should be tried, such as timed bright light therapy in the morning (30 minutes of 10,000 lux at a distance of 20–40 cm to the eyes or light glasses<sup>100</sup>), behavioral interventions such as a structured sleep-wake schedule,<sup>101</sup> or melatonin. It is important that melatonin dosing and timing be implemented appropriately, with preferably a low, nonsedating dose of melatonin 4–6 hours before the desired sleep time.

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Dr. Arns is with Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience, Research Institute Brainclinics, Brainclinics Foundation, Nijmegen, and Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, the Netherlands. Dr. Kooij is with Amsterdam University Medical Center, Amsterdam, and PsyQ, Expertise Center Adult ADHD, the Hague, the Netherlands. Dr. Coogan is with Maynooth University, Ireland.

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### Author Contributions

*Conceptualization:* Arns, Coogan

*Writing – original draft:* Arns, Kooij, Coogan

*Writing – review and editing:* Arns, Kooij, Coogan

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Correspondence to Martijn Arns, PhD, Brainclinics Foundation, Bijleveldsingel 32 6524 AD, Nijmegen, The Netherlands; e-mail: martijn@brainclinics.com

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