Impact of Circadian Rhythm on Attention-Deficit Hyperactivity Disorder

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Abstract

The purpose of this research and systematic literature review is to determine if altering the circadian rhythm in people with Attention-Deficit Hyperactivity Disorder (ADHD) improves their symptoms. Up to 75% of people with childhood-onset ADHD exhibit a delayed circadian rhythm phase. This can cause difficulty in initiating and maintaining sleep, which in turn can cause excessive daytime sleepiness and further exacerbate ADHD symptoms, especially hyperactivity. Journal articles were searched in the databases of PubMed that concerned treatment aspects that would affect circadian rhythm and ADHD. Topics were further divided into themes that included melatonin, light therapy (LT), sleep hygiene intervention, and stimulant therapy effects. The search yielded 126 articles. Exclusionary criteria were articles dated prior to 2000, those not concerning all aspects used in search criteria, additional comorbidities, or those that compared participants with ADHD and those without ADHD. A total of ten articles were reviewed. The current literature revealed that advancing the circadian rhythm had improvements to both sleep and ADHD symptoms (subjectively) even when the duration of sleep time was not increased. However, most patients that were poor sleepers prior to treatment continued to be poor sleepers with treatment. Establishing good sleep hygiene showed benefits to most patients and should be addressed prior to the diagnosis of ADHD or starting therapy. Studies revealed that it can take more than eight weeks on ADHD medication to see benefits to sleep, as medication would commonly have a negative impact to sleep initially. More research needs to be conducted in this area, as most studies had more males versus females, and several were short in duration.

Keywords: circadian rhythm, ADHD, melatonin, light therapy, sleep hygiene intervention, stimulant therapy effects.

Introduction

ADHD is one of the most common mental disorders for children and adolescents, and prevalence is around five percent (Drechsler et al., 2020). Males are typically affected more than females at a ratio of three to one (Sharma and Couture, 2014). The exact etiology is unknown but deficits to the prefrontal cortex (PFC), caudate, and cerebellum have been shown. These areas regulate attention, thoughts, emotions, behavior, and actions. Imbalances of neurotransmitters (NT), specifically dopamine (DA) and norepinephrine (NE), are the main cause for ADHD symptoms to occur. People with ADHD may also have a decrease in their DA receptors, an increase of DA efflux, or a decrease in uptake of DA (Drechsler et al., 2020). Assessing and managing ADHD can prove exceedingly difficult, as presenting symptoms can vary wildly. Comorbidities, such as other mental disorders, can overlap and can further complicate the diagnosis and treatment. Oppositional defiant disorder (ODD), major depressive disorder (MDD), and anxiety disorders are some of the more common comorbidities (Drechsler et al., 2020). Children with ADHD experience problems with initiating and maintaining sleep up to 70% of the time (Sciberras et al., 2020).

ADHD Diagnosis

There is no diagnostic marker for ADHD, so there are no objective criteria for the diagnosis. The United States uses the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). The DSM-5 goes by behavioral symptoms divided into 11 symptoms for inattentiveness and nine symptoms for hyperactivity/impulsivity. Symptoms need to be present in two or more settings before age 12 for at least six months, and these symptoms must also impair their social, academic, or occupational functioning. For those under 17 years of age, they need to have at least six or more symptoms in a subtype. For 17 years of age and older, they require at least five or more symptoms. If they meet both subtypes, they fulfill the criteria to

have the combined type (Drechsler et al., 2020). Reduced school performance, antisocial problems, and substance use are common problems associated with ADHD (Corkum et al. 2020). It is estimated that four percent of children in the United States are on stimulant medications, and 60% affected will have ADHD lifelong (Peppers et al. 2016). Males are more common to have the hyperactive or combined type, with added aggression. Conversely, females tend to have the inattentive type with cognitive impairment and eating disorders (Sharma and Couture, 2014). Several rating scales are used and filled out by the patient, parent, teacher, and/or caregiver/provider. These can be great adjunct tools in assisting with the diagnosis of ADHD.

ADHD Treatment

First-line treatment for ADHD is stimulants and these facilitate the release of DA and NE and block the reuptake of both. Stimulants act on the PFC and striatum, and this creates more control over attentional resources, thus improving ADHD symptoms (Corkum et al. 2020). There are immediate release (IR) and extended release (ER) forms. However, Sharma and Couture stated that stimulants like amphetamines and methylphenidate (MPH) are 6th and 12th, respectively, of substances known to cause harm. They are also 8th and 13th, respectively, to cause dependence (Sharma and Couture, 2014). Treatment is advised for all children diagnosed because they tend to have a better prognosis if treated early and lowers potential for substance abuse later in life. Most common adverse drug reactions (ADR) include sleep issues, decreased appetite, and cardiac problems. Close monitoring of the patients' sleep, height, weight, and vital signs are important to evaluate. Drug holidays are advisable if growth deficiencies are noted. Psychosocial interventions/therapy are extremely important as adjunct treatment in people with ADHD, not only to monitor symptoms, but to also see if ADHD or the medication is causing any

issues at home or school. Sleep disorders are very prevalent (70-90%) in those with mental health issues compared to healthy children (25-40%) (Peppers et al. 2016).

Research Question

Does altering the circadian rhythm have an impact on symptoms and medication management in children and adults with attention-deficit hyperactivity disorder (ADHD)?

Research Methods

A literature review was performed using journal articles found in the databases of PubMed. Search topics consisted of literature concerning treatment aspects that would affect circadian rhythm and ADHD. Topics were further divided by themes in the literature that concerned melatonin, bright light therapy (BLT), sleep hygiene intervention, and the effects of MPH on sleep and ADHD. ADHD symptoms were added to the search for sleep hygiene intervention, and children were added for one search concerning MPH use. Each theme was searched individually to further delineate the articles, and a total of three were picked from similar articles in PubMed. Most articles were written within the past 10 years, but three dated back to the early 2000s. There was a total of 43 studies for melatonin treatment, 11 studies for BLT, 27 for sleep hygiene intervention, and 45 studies for stimulant therapy effects. Exclusionary criteria consisted of articles not concerning all aspects that were used in the search criteria, as several articles fit into this category. Studies were also excluded that concerned additional comorbidities, or those that compared participants with ADHD and those without ADHD. Studies not in English were excluded. Three studies met the criteria for melatonin, two studies for BLT, two studies for sleep hygiene intervention, and three studies for stimulant effects.

Literature Review

Melatonin's Effects on Circadian Rhythm in Patients With ADHD

Masi et al. (2019) performed a study to determine melatonin's effectiveness in children and adolescents experiencing sleep problems after starting stimulant therapy. There were 74 participants, 69 males and five females with mean ages of 11.6±2.2 years. Diagnosis of ADHD was made by clinical visits using the DSM-4 criteria, and excluded subjects with intellectual disabilities, autism spectrum disorders, and schizophrenia. All participants were on MPH, with 64 on sustained release and 10 on immediate release with mean dosages of 33.5 mg. Sleep problems were classified as sleep onset delay and poor sleep efficiency. All participants were treated with a starting dose of one mg of melatonin after supper, which was around 20:00-21:00, one to two hours before bedtime. Doses could be increased by 0.5 mg weekly, up to a maximum of 5 mg. The mean dose at 1.85 mg. Treatment lasted one month, and subjects were assessed at that time. Twelve participants also received psychotherapy to improve cognitive, behavioral, and emotional stressors.

The Clinical Global Impression Severity (CGI-S) scores assessed the severity of their sleep disorders (Masi et al. 2019). Measurements were taken at baseline and again at one month; low scores corresponded to less severity of sleep disorders. The Clinical Global Impression Improvement (CGI-I) scores assessed the efficacy of melatonin on their sleep and were measured at one month. Low scores indicated more improvements with melatonin, and scores of either one or two were considered responders to melatonin.

Baseline CGI-S scores were 3.41 and decreased to 2.13 at one month ($p<0.001$). CGI-I scores revealed that 45 participants (60.8%) were responders to melatonin. These were further broken down by sex, age, and comorbidities. All five females and 40 (58%) males were

responders. Ages less than 12 years old (n=42) revealed that 27 (64.3%) were responders. Thirty-two subjects older than 12 years old revealed that 18 (57.2%) were responders. Participants with any comorbidities (n=58) showed that 33 (56.9%) were responders. Twelve of the 16 subjects (75%) with no comorbidities were responders. This did not show any significance when sex, age, and comorbidities were considered. Melatonin showed no side effects at follow-up and was well tolerated by participants (Masi et al. 2019).

The study showed that melatonin can improve sleep problems in subjects taking MPH for their ADHD. Due to the unequal sample size of sex of the participants, it was difficult to determine if melatonin was more effective in females versus males. Melatonin seemed to be slightly more effective in children versus adolescents, but again numbers were not equal. Unequal sample size was again noted in the comorbidity section, but non comorbidity subjects seemed to respond better to melatonin. This was also a strength of this study to allow participants with other comorbidities. Additional limitations are that sleep hygiene or problems were not examined prior to starting MPH, and no objective measurements were used to assess sleep severity or improvement (actigraphy, sleep studies, etc.). No placebo was used for comparison.

Van der Heijden et al. (2007) investigated melatonin's effect on sleep, behavior, cognitive performance, and quality of life in medication-free children, ages six to 12 years old, diagnosed with ADHD and chronic sleep-onset insomnia (CSOI). One hundred and five participants were enrolled and assessed by a psychologist to determine a diagnosis of ADHD. CSOI is classified as sleep-onset issues viewed by parent or child, with symptoms at least four days per week for more than one year, and an average sleep latency of more than 30 minutes. Patients were excused from study if they had developmental disorders, chronic pain, hepatic or

renal dysfunctions, epilepsy, earlier use of melatonin, or an IQ less than 80. Subjects were not allowed use of other medications within four weeks prior to the study.

The study started with a one-week baseline period, followed by a four-week randomized, double-blind, placebo-controlled trial. Participants were randomly given fast-release melatonin (three mg if under 40kg or six mg if over 40kg body weight) or placebo (Van der Heijden et al. 2007). Medication was given at 19:00 and the child was allowed to go to bed whenever tired. Forty-four were given 3 mg, nine given six mg, and the rest given placebo; demographics and clinical characteristics were evenly distributed amongst participants. Adherence was documented after three weeks of treatment by medication counts. Measurements consisted of sleep actigraphy, sleep logs, dim light melatonin onset (DLMO), problem behavior, cognitive performance, and quality of life. These were taken during the baseline week and the fourth week of treatment. Actigraphy assessed sleep onset (minutes), total sleep time (minutes), sleep latency (minutes), and sleep efficiency (% of time spent asleep in bed). Sleep logs measured difficulty in falling asleep, with lower points indicating less difficulty. DLMO is a good marker of circadian rhythm and is when endogenous melatonin levels reach four pg/mL in the evening. These samples are taken from saliva and dim lit rooms were required upon collection. Problem behaviors were assessed by the Child Behavior Checklist (CBCL) and Teacher's Report Form (TRF), with higher scores indicating more issues. The Eriksen Task and Sustained Attention Dots Task measured cognitive performance. These assessed the patient's ability to resist distracting stimuli through reaction time (RT) and error incidence (EI), as well as sustained attention respectively. The TNO-AZL Questionnaire for Children's Health-Related Quality of Life, Parent Form (TACQOL-P) measured quality of life, with higher scores indicating a higher quality of life.

Melatonin advanced sleep onset by 26.9 minutes compared to a delay of 10.5 minutes in the group not taking melatonin ($p<0.0001$). Nearly half (48.8%) of patients taking melatonin had an advancement in sleep onset of more than 30 minutes, while only 12.8% of the placebo group had the same effect ($p=0.001$). Mean total sleep time (TST) increased to 19.8 minutes in melatonin group, while a decrease was noted of 13.6 minutes in placebo group ($p=0.01$). Sleep latency decreased by 21.3 minutes with melatonin, while an increase of 3.0 minutes occurred in placebo group ($p=0.001$). Sleep efficiency increased by 2.6% with melatonin and decreased by 2.1% in placebo group ($p=0.011$). Difficulty in falling asleep declined by 1.2 points with melatonin, while the placebo group also declined only by 0.1 points ($p<0.0001$). DLMO advanced by 44.4 minutes with melatonin, while DLMO was delayed by 12.8 in placebo ($p<0.0001$). A stronger advancement of sleep onset was seen in those with a significant delay in their baseline DLMO after melatonin treatment, and this did not occur in the placebo group ($p=0.008$, $p=0.645$ respectively) (Van der Heijden et al. 2007).

CBCL decreased to 8.0 with melatonin and decreased by 16.2 in placebo group ($p=0.083$). TRF showed equal decreases to 4.0 in both groups ($p=0.29$). The Eriksen Task/Interference Control showed reduction in RT to 17.0 milliseconds in the melatonin group, while placebo had a 9.5 reduction in RT ($p=0.37$). The EI % increased by 0.4 for the melatonin group and decreased by 0.6 in placebo ($p=0.28$). Sustained Attention testing mean task completion time and inaccuracy was $p=0.58$ and $p=0.52$ respectively. TACQOL-P had $p=0.82$. This indicated that there were no significant differences in scores between the groups for problem behavior, cognitive performance, and quality of life (Van der Heijden et al. 2007).

This study showed marked improvement in participants' sleep onset, TST, sleep latency, sleep efficiency, and their subjective view of falling asleep. Surprisingly, this did not have the

same effect on their behavior, cognitive performance, and quality of life as one would expect. The study was short in duration so this could explain why there was no improvement in behavior and cognition. Some limitations to the study include its sample size of only Dutch children, not differentiating the dosages of melatonin, no stimulant-treated patients, and nothing to evaluate for breathing or periodic limb movement disorders during sleep. Additionally, the study did not indicate how many males versus females were included in the trial.

Hoebert et al. (2009) performed a study that investigated the long-term use of melatonin in children that participated in a previous randomized clinical trial (RCT) that was conducted by Van der Heijden et al. (study listed above). The study wanted to determine the efficacy and safety of melatonin over the long-term. Parents were followed up after their child participated in the four-week randomized, double-blind, placebo-controlled study. Participants included 105 children, ages six to 12 years old, diagnosed with ADHD. Additional requirements were an IQ greater than 80 and the child also had to have chronic sleep onset insomnia (CSOI). Children were given three mg of melatonin if their body weight was below 40kg, and six mg if over 40kg. Participants were encouraged to go on a drug holiday for one week to determine if melatonin was still necessary.

Ninety-four of the 105 participants responded back, while others were either lost to follow up or no response was received. There were 70 males and 24 females, with a mean age at follow up of 12.39 years old. Follow up occurred roughly three to four years after the RCT study, with a mean follow up time of 3.66 years. Parents were given a questionnaire to fill out covering multiple items that will be explained in the results. DLMO was also assessed by using the last studies values to compare different groups of melatonin in the long-term trial (Hoebert et al. 2009).

Results showed that 61 children still used melatonin daily, while 11 children used it either two to three times per week to a few times a year (classified as occasional use). A total of 22 children discontinued melatonin completely. Discontinuation of melatonin was due to a resolution of CSOI (n=8), recommendation by physician (n=4), therapy had no effect (n=3), adverse effects (n=3), refusal by child (n=1), light therapy used instead (n=1), and for unknown reasons (n=2) (Hoebert et al. 2009). Duration of use ranged from one to 57 months, and the dose of melatonin ranged from 0.5 to 10 mg. Parents reported giving melatonin between 18:30 to 23:00. 82% took melatonin at a fixed time during the weekdays, while 65% took doses on the weekends. Caregiver's opinions showed that 87.8% believed the therapy was effective for treating their child's sleep onset issues, 70.8% thought melatonin improved their child's daytime behavior, and 60.9% thought it also improved their mood.

DLMO was used to assess participants at their baseline (pretreatment) during the previous RCT to compare the different groups of melatonin participants in the long-term trial. The eight children who stopped taking melatonin due to an improvement in their CSOI were compared to the remaining participants. Mean DLMO was 20:21 for the eight children, while a mean of 20:41 was shown in the remaining subjects (p=0.413). The 11 children with occasional use of melatonin were compared with the children taking melatonin daily. Mean DLMO was 20:11 for the occasional users, while a mean of 20:48 was shown in the daily users (p=0.037) (Hoebert et al. 2009). This showed a significant finding with daily users versus occasional users but was insignificant with those stopping the medication due to improvement in their CSOI.

Additionally, 67 children temporarily discontinued treatment over the long-term study, mainly over the holiday period. Twenty never discontinued treatment, while there were some participants who did not respond to this question. When melatonin was stopped, parents reported

a delay of sleep onset time (n=60, 92.3%), delay of wake-up time (n=20, 30.8%), daytime behavior change (n=29, 29.2%), and no change in sleep pattern (n=1, 1.5%) (Hoebert et al. 2009). No dependence or rebound insomnia was reported after discontinuing melatonin.

Adverse drug reactions (ADR) were noted in 19 participants that were attributed to melatonin. 63.2% had multiple ADR and 36.8% with 1 ADR. Ten subjects' ADR were self-limiting, while six persisted and this led to three of the six to discontinue treatment.

The study showed that melatonin can help children with ADHD and CSOI if it is continued but is likely not curative as effects did not persist once melatonin was discontinued. Most participants that discontinued melatonin had a delay in their sleep onset. This would suggest that long-term use of melatonin (exogenously) has little effect on the circadian rhythm when the medication is stopped. DLMO revealed that subjects with a more delayed DLMO responded better to melatonin than those with less of a delay in their DLMO. Long-term use of melatonin showed no serious ADR. Limitations of the study was lacking a control group. Additionally, ADR reporting was subjective and could have been due to a multitude of factors, such as starting stimulants or another medication. Participants did start the first RCT medication free, but this was not addressed during the follow-up interviews, as some of the participants would have likely started stimulant therapy for their ADHD.

Light Therapy Effects on Circadian Rhythm in Patients With ADHD

Rybak et al. (2006) performed a three-week open trial of light therapy (LT) during the fall or winter months. The study wanted to find out if using LT in the fall or winter months would improve ADHD symptoms. There were 29 participants (15 male and 14 female), with ages 20 to 60 years and a mean age of 40. Inclusion criteria for subjects had to have a clinical diagnosis of ADHD from childhood by the DSM-IV, an IQ in the normal range (85-115), and

able to provide informed consent. Subjects were excluded with an IQ < 85, neurological disorder, suicidal ideation, current substance dependence, previous LT exposure, eye conditions that would affect LT, and inability to provide consent. Several participants had psychiatric comorbidities that included major depressive disorder (MDD), seasonal affective disorder (SAD), chronic depression, and history of substance abuse. Seven subjects were on stimulants only, four were on antidepressants only, and four were taking both medications. However, these comorbidities and medications were not delineated.

Participants filled out several forms at baseline and again after the three-week trial. The Brown Adult ADD Scale and the Conners' Adult ADHD Rating Scale (CAARS) to assess ADHD, with higher scores indicating more severe symptoms. The Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version (SIGH-SAD) was used to determine current mood symptoms, with high scores indicating worse seasonality/depression. The Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ) assessed circadian rhythm, and higher scores would indicate a phase advancement to the morning hours. Sleep diaries were going to be filled out, but subjects had trouble completing the logs. Instead, the study had verbal reports with compliance of LT on day 10 and 21 of therapy. The Conners' Continuous Performance Test-II (CPT-II), Hopkins Verbal Learning Test (HVLT), Benton Judgement of Line Orientation (JLO), and the Wisconsin Card Sorting Test (WCST) were all used to assess neuropsychological measures. These included attention, processing speed, executive functioning, memory, and visual perception all with several subtypes (Rybak et al. 2006).

Results were close in the ADHD scores. The Brown Adult ADD Scale had a mean ± standard deviation (SD) of 84.7±20.4 before LT, while after LT this decreased to 71.4±24.4

(p=0.001). The CAARS had a mean ± SD of 577.9±62.5 before LT, while after LT this decreased to 535.4±95.2 (p=0.001). The MEQ increased from 46.2±10.3 to 51.2±10.2 after LT (p=0.016). SIGH-SAD showed a significant decrease from 14.5±11.3 to 7.5±7.0 (p=0.001) (Rybak et al. 2006). Neuropsychological values demonstrated an improvement in attention, processing speed, and visual perception, while verbal memory and executive functioning showed no significant improvement.

The study further correlated the changed scores in the Brown Adult ADD Scale, CAARS, MEQ, and the SIGH-SAD. Their calculations showed a significant increase in MEQ scores when the Brown Adult ADD Scale and CAARS scores decreased (55% and 52% respectively). This would indicate that ADHD symptoms decreased with the phase advancement to morning following LT. The SIGH-SAD scores showed a moderate correlation between the Brown Adult ADD Scale and CAARS scores (40% and 33% respectively), implying that phase advancement via LT improved ADHD symptoms more than their depressive symptoms (Rybak et al. 2006).

This study showed that LT may be used as an adjunct therapy in patients with ADHD and is not exclusively for patients with SAD. Advancing morningness revealed a significant improvement in ADHD symptoms and would likely benefit those patients having trouble with stimulant therapy. Limitations include having no placebo group and a small sample size. The study also did not indicate what medications subjects were taking, and no differentiation was given between medication versus no medication. Additionally, no objective measurements were used to assess sleep and it would be beneficial to see what would happen in the spring and summer months.

Rachel et al. (2017) performed an open-label trial with a small sample size of 16 participants, aged 19-64 years old, diagnosed with ADHD by the DSM-IV-TR criteria. There

were seven men and nine women. The goal was to determine if correcting delayed circadian rhythm with light therapy (LT) improves ADHD symptoms. The first week assessed subjects at their baseline, followed by two weeks of 30-minute morning LT. Dim-light melatonin onset (DLMO) was evaluated via saliva samples at baseline and after the two-week treatment of LT. Participants decreased overhead light and used glasses to block blue-wavelength light after 16:00 so melatonin onset would not be affected. Actigraphy, sleep-wake diaries, and the Pittsburgh Sleep Quality Index (PSQI) were used to quantitatively and qualitatively assess the subjects' sleep respectively. Mid-sleep time is the point between bedtime and wake time, and this was an important tool used to measure the effects of LT on the circadian rhythm. The ADHD-Rating Scale (ADHD-RS) was used to rate ADHD symptoms.

LT advanced DLMO by 31 minutes, standard error of mean (SEM) 20:36 advanced to 20:05. Mid-sleep time advanced by 57 minutes, SEM 04:37 advanced to 03:40 ($p=0.002$ and 0.004, respectively). Phase advances in DLMO and mid-sleep time demonstrated a reduction in ADHD-RS scores ($r=-0.55$ and $r=-0.53$, $p=0.027$ and $p=0.044$ respectively). Actigraphy in participants with significant DLMO phase advance ($n=8$) showed no changes in total sleep time, sleep efficiency, or wake after sleep onset. Subjects tended to have earlier sleep start times, wake-up times, and increased sleep fragmentation. The sleep-wake diaries revealed a reduction in subjective sleepiness (mean 2.97 to 2.63; $p=0.033$). The PSQI showed an improvement in sleep quality (mean 10.1 to 6.1; $p<0.001$); a reduction of the PSQI score equates to an improvement in sleep quality (Rachel et al. 2017).

This study effectively showed that LT can alter the circadian rhythm through advancing DLMO and mid-sleep times, and this in-turn demonstrated a reduction in ADHD symptoms. Altering the circadian rhythm showed no changes in total sleep time, sleep efficiency, or wake

after sleep onset. However, sleep fragmentation did increase. Subjectively, participants felt an improvement in sleep quality and a decrease in their sleepiness. The study did not differentiate those on stimulant versus no stimulant medication, and no placebo group was used. Four were on no medications, one was on the antidepressant bupropion extended release, five on short-acting mixed-amphetamine salt, four on long-acting mixed amphetamine salt, and two on Lisdexamfetamine.

Promoting Good Sleep Hygiene And Its Effects on Circadian Rhythm in Patients With ADHD

Peppers et al. (2016) performed a six-week pilot project on children with ADHD. Ages five to 11 with diagnosed ADHD meeting the Diagnostics and Statistics of Manual of Mental Health Disorders, 5th edition criteria were studied. Participants also needed a score of 42 or more on the Child Sleep Habits Questionnaire (CSHQ), as this assesses sleep and a score of 42 or more indicates a pediatric sleep disorder. Patients with obstructive sleep apnea, sleep aid medication use, or changes in their ADHD medications over the six-week period were excluded. The Vanderbilt Assessment Scale (VAS) was used to assess symptoms and behaviors of their ADHD, with higher scores indicating more severe symptoms. The CSHQ and VAS were completed at baseline and after the six-week sleep hygiene intervention.

Providers in the study reviewed the patient charts and interviewed the caregivers and child to determine eligibility. Only 23 met the criteria above, consisting of 13 males and 10 females. Twenty were on stimulant medication, six had comorbidities (anxiety, oppositional defiant disorder, learning disability, and mood disorder), and almost half had multiple home settings for sleep. The providers used the “Clinical Practice Guideline on Sleep Disorders in Childhood and Adolescent Primary Care” to establish good sleep hygiene for the patients and caregivers (Peppers et al. 2016). This included a six-minute video on sleep hygiene, and the

providers established an individualized plan for each participant. A six-week follow-up visit was scheduled to evaluate sleep and ADHD symptoms via the CHSQ and VAS scores.

The results after the six-week intervention showed both decreases in the CSHQ and VAS scores. CSHQ scores decreased mean standard deviation from 50.13 ± 7.16 to 43.74 ± 6.49 ($p<0.001$). VAS scores on questions one to nine decreased mean standard deviation from 11.39 ± 7.75 to 7.52 ± 8.41 ($p<0.001$). VAS scores on questions 10-18 decreased mean standard deviation from 9.30 ± 9.08 to 6.39 ± 8.51 ($p<0.004$) (Peppers et al. 2016).

This study showed decreases in ADHD symptoms and an increase in sleep quality and was very practical in the clinic setting. Limitations were small sample size, no placebo group, and no objective measurements of the subject's sleep, such as a sleep study or actigraphy. There was also no assessment of the parents' educational level or socioeconomic status that may certainly affect results. Follow-up visits during the first few weeks could have also benefited caregivers and patients to assess their progress.

Sciberras et al. (2020) performed a randomized controlled trial (RCT) of 244 children with ADHD with moderate to severe sleep problems; majority of participants were male (85%). The study was used to investigate if behavioral sleep intervention is effective in improving the child and caregiver's well-being long-term. Participants were aged five to 12 years old with diagnosed ADHD from the Diagnostic and Statistical Manual for Mental Disorders (DSM) IV, via the ADHD Rating Scale (ADHD-RS). They also needed to meet the American Academy of Sleep Medicine criteria of having a behavioral sleep disorder, and the parent needed to rate their child's sleep problem as moderate to severe via the Children's Sleep Habits Questionnaire (CSHQ). Children were excluded if they had a serious medical condition, developmental disabilities, suspected obstructive sleep apnea, or have been seen already by a psychologist or

sleep clinic for sleep assistance. Baseline surveys of the CSHQ were filled out by parents, with higher scores indicating more sleep problems. The Anxiety Disorders Interview Schedule for Children IV (ADISC-IV) was also filled out to assess for any comorbid conditions (autism, conduct disorders, etc.). Eighty-eight percent were taking ADHD medication and comorbidities were common.

A computer randomized patients and divided them into behavioral intervention or usual clinical care groups. The usual clinical care groups were the child's primary pediatrician. Teachers and pediatricians were not informed of the child's status in the study. Behavioral intervention consisted of two face-to-face sleep consultations held two weeks apart, with psychologists assessing the children (Sciberras et al. 2020). The first visit assessed sleep problems, discussed treatment goals, educated about sleep (sleep cycles, hygiene, etc.), and established an individualized sleep plan for the patient. Sleep diaries were filled out between each visit and were reviewed during the second visit and a follow-up phone call.

The CSHQ and ADHD-RS were taken at baseline and again one year later. The Pediatric Quality of Life Inventory (PedsQL), Strengths and Difficulties Questionnaire (SDQ), Daily Parent Rating of Evening and Morning Behavior (DPREMB), and Depression, Anxiety, and Stress Scales (DASS) were all filled out by the parents one year later. The ADHD-RS and SDQ were also filled out by the child's teachers. Seventy-five percent of participants and 81 percent of teachers responded at the 12-month follow-up. The behavioral intervention group results revealed children were less likely to have moderate to severe sleep problems compared to usual care children (28.4% versus 46.5% respectively; $p=0.03$). CSHQ had lower total scores in the intervention group compared to usual care group ($p=0.02$). Sleep onset delay and night awakenings were the most notable differences. PedsQL showed higher scores in the intervention

group ($p<0.001$), and higher scores correspond to a better quality of life. SDQ consisted of emotional and conduct problems, with lower scores indicating a decrease in behavior issues. The parent report showed lower scores in intervention group ($p=0.005$), while the teacher report showed no significant difference between the groups ($p=0.46$). DPREMB assessed daily functioning, with higher scores meaning poorer functioning. The intervention group had lower scores compared to the usual care group ($p<0.001$). DASS assessed parent's mental health, and this revealed minimal differences in scores between the groups ($p=0.55$). The parent report of the ADHD-RS showed fewer ADHD symptoms in the intervention group ($p<0.001$), while the teacher report revealed no differences between the groups ($p=0.91$) (Sciberras et al. 2020).

This study revealed that a small behavioral intervention improved the severity of participants' sleep problems, especially in sleep onset delay and nighttime awakenings. Quality of life, daily functioning, behavioral problems, and ADHD symptoms improved as well versus the control group. Limitations of the study include no objective measurements to assess the child's sleep (actigraphy, sleep study, etc.). Some patients were lost to follow-up and teachers could have changed during the 12 months, so this could have affected the minimal differences in reports on the SDQ and ADHD-RS values.

Stimulant Therapy Effects on Circadian Rhythm in Patients With ADHD

Corkum et al. (2020) conducted a trial to determine how sleep is affected by extended-release methylphenidate (ER MPH, Biphentin). Participants included children diagnosed with ADHD using the DSM-IV by psychologists and pediatricians that specialized in that field of study. Exclusionary criteria consisted of an IQ below more than one standard deviation (SD) of the mean according to the Wechsler Intelligence Scale for Children-4th edition (WISC-IV), children with neurological, genetic, metabolic, or seizure disorders, diagnosis of a sleep or

mental health disorder (except for learning disabilities), current treatment for sleep problems, or a Tanner stage of 3 or more.

Measures used for this study consisted of a demographic questionnaire that was completed by the parents. This included information on the child, parent, family variables, child's age and sex, and family socioeconomic status (SES). The Boyd-NP scale further assessed their SES, with higher scores indicating higher SES (0-100). The Conners Parent Teacher Rating Scale-Revised (Long Form) (CP/TRS-R:L) was used to assess the children's severity of their ADHD, with higher scores indicating an increase in severity. Parents completed the CPRS-R:L form, and teachers filled out the CTRS-R:L form. Actigraphy was used to measure the child's sleep/wake cycles indirectly via motor activity through a wristwatch the child wore only at night. Parents also filled out sleep logs so data could be compared with the actigraphy collection. Actigraphy measured total sleep time (TST), sleep onset latency (SOL), and sleep efficiency (SE). TST is when sleep onset starts to the end time of their sleep. SOL starts when the first 20-minute block of sleep is achieved. SE is the TST ratio to the time spent in bed, so from lights off to lights on in percentage form (Corkum et al. 2020). Polysomnography (PSG) was performed, and this monitored participants sleep via brain waves and looked for any sleep disordered breathing. PSG was performed at baseline to screen for sleep disorders and to reduce the "first night effects" when participants had to come back for their second PSG. Participants needed to have an apnea-hypopnea index (AHI) score of less than or equal to one to qualify for the study. AHI indicates how many times a person has pauses or shallow breathing per hour.

Following information collected at participants baseline, the study began with a four-week, randomized, cross-over trial where each child took two weeks of ER MPH treatment and two weeks of placebo treatment. Data was not collected at baseline, as this was used solely as a

screening tool. Information was collected about sleep and behavior during the first and third weeks of the trial. Actigraphy data was collected for six nights (weekdays only), and the second PSG occurred at the end of the first week with the child taking ER MPH or placebo (Corkum et al. 2020). PSG data was matched with the child's actigraphy and sleep logs. ER MPH and placebo were both contained in identical capsules, so identification was not possible. Participants that were less than 20 kg received a 20 mg daily dose, those that were in the 20-30 kg range were given 30mg, and over 30 kg received 40 mg. Distribution of medication began and ended on a weekend, and subjects took the medication within the first hour of waking. Only the pharmacists were aware of what type of medication was given to participants.

Twenty-three males and three females completed the trail, with a mean age of eight years old, ranging from six to 12 years of age. The impact of ER MPH on ADHD symptoms showed significant reduction in the CPRS-R:L and CTRS-R:L ADHD Index scores; $p=0.009$ and $p=0.026$ respectively. Values at baseline were 72.4 (CPRS-R:L) and 68.9 (CTRS-R:L), and these decreased to 62.9 and 58.4 in the ER MPH group. The placebo group had smaller reductions to 68.2 and 64.0 respectively. The impact of ER MPH on sleep showed significant changes in TST and SOL (both with $p=0.001$), but no significant changes to SE ($p=0.12$) in the actigraphy data. Children slept on average 30 minutes less during the ER MPH compared to placebo group, and this difference was due to the increase of 30 minutes in SOL in the ER MPH group. Conversely, the PSG data showed no significant changes in TST, SOL, or SE ($p=0.08$, $p=0.28$, $p=0.32$ respectively). Participants still had shorter TST and longer SOL in the ER MPH group (Corkum et al. 2020).

The study revealed that the TST and SOL were negatively impacted in the ER MPH group in the actigraphy data. PSG showed similar, albeit smaller, findings but were not

statistically significant. ER MPH was effective in improving ADHD symptoms based on CP/TRS-R:L data, and the dose seemed appropriate due to no adverse effects noted. Discrepancies in the actigraphy and PSG data could be due to environmental factors, and that actigraphy was taken over several days versus just one night for the PSG. This study underlined the importance of addressing any sleep problems prior to starting medication, and to monitor short and long-term effects of ER MPH on sleep. Limitations of the study include small sample size, unequal sex distribution, and limited ethnic variation. Actigraphy was not worn during the day or weekends, so this could have missed naps or changes to sleep patterns over the weekends. The study was also short term. Patients may have acclimated to the ER MPH overtime, and the TST and SOL may improve later. Missed doses could have occurred, as parents self-reported medication adherence.

Solleveld et al. (2020) conducted a 16-week double-blind, randomized controlled trial (RCT) with immediate-release methylphenidate (IR MPH). Participants included medication-naïve children diagnosed with ADHD according to the DSM-IV by a psychiatrist. The study consisted of only boys (n=48) from the Netherlands, with ages ranging from 10-12 years of age. Exclusionary criteria were comorbid psychiatric disorders requiring medication, such as stimulants, neuroleptics, antipsychotics, or dopamine receptor agonists. Neurological or medical illnesses were also excluded in the study. Participants were randomly assigned to either IR MPH or placebo for 16 weeks. Distribution was concealed to participants, providers, and researchers, which was achieved by making both medications identical in appearance. IR MPH dosages started at 0.3 mg/kg/day and increased weekly with 5-10 mg/day to a maximum of 40 mg daily, or until target clinical dose was achieved. Adherence to treatment was monitored at the 1st, 2nd,

3rd, 8th, and 12th week. If side effects occurred with dose adjustments, the psychiatrist returned the participant to the previous dose.

Actigraphy was used to assess participants at their baseline (BL), during treatment (DT), and one week after treatment was discontinued or post treatment (PT). Actigraphy measured muscle activity on the wrist to determine sleep versus awake, and this was a watch that was worn 24 hours a day for five consecutive days. BL was one week prior to trial, DT occurred at the eighth week of treatment, and PT was at week 17. Participants also filled out sleep-diaries during each actigraphy period, and this would assess subjective sleep parameters to coincide with their actigraphy. Several measurements were taken with actigraphy, but the main component of the study focused on sleep efficiency (SE). SE is defined as the ratio of total sleep time (TST) to time in bed (TIB) (Solleveld et al. 2020). Screening for sleep disorders at the participants baseline was conducted with the Holland Sleep Disorder Questionnaire (HSDQ). The Epworth Sleepiness Scale (ESS) and the Evaluation List Insomnia Therapy (ELIT) were assessed during the actigraphy recordings to subjectively determine participants sleep. Restless leg syndrome (RLS) is a common problem in patients with ADHD, and the Johns Hopkins RLS (JHRLSS) was used to assess the severity of RLS. The severity of ADHD symptoms was assessed by the Disruptive Behavior Disorder Rating Scale (DBD-RS).

All participants showed no severe sleep problems via the HSDQ at their baseline. Adherence to the trial medication did not differ between the MPH (84.89%) and the placebo (79.68%) groups ($p=0.31$). Mean MPH dose was 29.13 mg (0.86 mg/kg), while the mean placebo dose was 34.40 (0.88 mg/kg) ($p=0.07$). The titrated placebo doses were higher but were not statistically significant. MPH group had an increase in their SE at PT compared to their BL ($p=0.005$, 95% CI). Additionally, SE values were much higher in the MPH group when

compared to the placebo group at PT ($p<0.01$, 95% CI). The study also looked at BL versus the eighth week of treatment in both groups, and this showed minimal differences in SE (BL $p=0.962$ and DT $p=0.94$). Significant findings were also found concerning sleep onset latency, total sleep time, sleep start time, and final wake-up time. The MPH group had positive effects in these values versus placebo, and were more noted in PT versus DT. The ELIT sleep scores revealed a decrease in sleep complaints in both MPH and placebo groups during the trial. Excessive daytime sleepiness (EDS) decreased in the MPH group versus the placebo group in the ESS scores. However, scores in ELIT and ESS were not significant (Solleveld et al. 2020).

The DBD-RS revealed lower ADHD symptoms in the MPH group compared to placebo group both DT and PT. Mean difference of DT 4.64 ($p<0.01$, 95% CI) and mean difference of PT 4.61 ($p<0.01$, 95% CI). The DBD-RS also looked at symptoms in attention and hyperactivity, and they revealed similar findings. Concerning attention, DT versus BL showed a mean difference of 8.62 ($p<0.01$, 95% CI) in the MPH group and a mean difference of 5.29 ($p<0.01$, 95% CI) in the placebo group. PT versus BL in the MPH group revealed a mean difference of 8.5 ($p<0.01$, 95% CI) and the placebo group had a mean difference of 5.14 ($p<0.01$, 95% CI). Hyperactivity scores in both groups comparing DT versus BL revealed a mean difference of 4.7 ($p<0.01$, 95% CI). PT versus BL showed a mean difference of 4.62 ($p<0.01$, 95% CI) (Solleveld et al. 2020).

This trial suggests that MPH may not affect sleep quality in the short-term, but over the long-term can improve SE, SOL, and sleep duration in someone with ADHD. Interestingly, ADHD symptoms improved in both groups but MPH improved attention scores much more when compared to the placebo group. Participants in both groups also had less sleep problems at the end of the study. The improvement of ADHD symptoms and sleep problems may be caused

by the participants being more aware of their sleep schedules and adjusting accordingly. In any case, this shows clinical relevance about how long to try MPH prior to discontinuing use due to side effects or sleep issues. Limitations of this study is its small sample size of only medication naïve boys from the Netherlands. The study also did indicate that some participants (n=9) used melatonin but did not differentiate these participants from the others. The severity of sleep problems was subjective, as this was only screened with a questionnaire and no objective findings (like a PSG) were used. Only low to moderate doses of IR MPH were used in the study, and it would have been beneficial to observe what high doses or ER MPH would do to the results.

Weiss et al. (2021) performed a one-month double-blind trial, followed by an optional open-label six-month trial. The study used Adhansia XR (PRC-063), a long-acting methylphenidate used for ADHD management, and participants took medication once daily in the morning. Adhansia XR has peak concentrations at one and a half hours and a second peak at 12 hours and takes approximately three days to reach a steady concentration state. Participants included 177 males and 198 females that were 18 years of age (average age of 35) or older with diagnosed ADHD by the DSM. Some participants did not complete the trial, so the total number did decrease. Groups were evenly balanced by age, sex, race, BMI, and severity of ADHD symptoms. The ADHD-rating scale (ADHD-RS) and the Pittsburgh Sleep Quality Index (PSQI) were used to subjectively assess ADHD symptoms and sleep quality respectively. Higher scores in the ADHD-RS test showed more severity in ADHD symptoms. PSQI scores below five considered patients as good sleepers, and scores above five were rated as poor sleepers. No objective measurements were taken. The study excluded people with adverse reactions or those unresponsive to methylphenidate or amphetamines. Those on psychotropic or sleep medications

due to a psychiatric disorder were also excluded. Melatonin was allowed if that patient was taking the medication for at least one month prior.

The one-month double-blind trial used randomized dosages at 0 (placebo), 25, 45, 70, or 100 mg per day. During the study, participants were given a placebo or one of the four dosages of Adhansia XR. There were 333 subjects studied, with 264 being on a medicated dose of Adhansia XR and 69 taking the placebo. The groups that were medicated and on placebo were balanced based upon their severity of ADHD symptoms. The percentage of good sleepers (PSQI<5) at baseline, was 20.9% in those taking Adhansia XR (all doses) and 23.1% in those on placebo. At the end of the trial there was a small increase in good sleepers to 23.6% in those on Adhansia XR, and a much more significant increase in those taking the placebo at 35.9%. For patients taking Adhansia XR, 14% went from poor to good sleepers, 9.4% went from being good to poor sleepers, and the rest of the patients had no change. For the placebo group, 19.4% went from poor to good sleepers and 2.8% went from good to poor sleepers. Poor sleepers (PSQI>5) were noted in 65.5% on Adhansia XR and 58.3% taking the placebo at baseline and at the end of the trial. The study showed minimal improvement in both groups and no statistical differences between them ($p=0.0972$) (Weiss et al. 2021).

The optional six month open-label trial optimized Adhansia XR treatment individually ($n=184$) with dosages ranging from 25 to 100 mg per day. If the participant did not tolerate the lowest dose they were excluded from the trial. For the 184 participants, baseline PSQI scores further decreased at the end of the double-blind trial ($p<0.0001$). 57.3% were good sleepers by the end of the six months, 34.1% went from poor to good sleepers, and 5.7% went from good to poor sleepers (Weiss et al. 2021).

This study suggests that sleep should be assessed prior to medication therapy for ADHD. If a subject has poor sleep at baseline, they will likely continue to have poor sleep with therapy. However, the study also showed that the adverse effects of Adhansia XR were short-lived, and most participants' sleep improved over time. Resolution of insomnia in the Adhansia XR group was comparable to the placebo group, with resolution after 12 and 10 days respectively. The double-blind trial had participants on random dosages, so they could be under or over medicated. Dosages were optimized in the open-label trial, and this led to significant improvements to symptoms.

Discussion

The correlation of ADHD and its effects on sleep are well known, but studies examining the treatment of sleep issues caused by ADHD and/or stimulant medication are limited. Patients with ADHD are twice as likely to develop sleep complaints than those without ADHD (Weiss et al. 2021). Analyzing the studies in the literature review did show similarities and trends to sleep and ADHD, but the data was limited at times and findings showed multifactorial etiologies.

Melatonin administration is a natural way to address sleep problems. Patients with ADHD usually have a delay in sleep onset that is likely due to melatonin release that occurs later in the evening for these patients. For patients already on stimulant medication, Masi et al. (2019) showed that melatonin helped decrease sleep issues significantly. Van der Heijden et al. (2007) assessed medication naïve participants, and melatonin provided similar results. The Van der Heijden study provided much more objective measurements along with a placebo group, while the Masi trial only consisted of subjective criteria with no placebo. Both trials were over one month in duration, large sample sizes, and consisted of only children with the majority being males. The Van der Heijden (2007) study suggests that melatonin can improve sleep, however

the improvement in sleep did not help with cognitive and behavioral performance. Long term use of melatonin showed no adverse effects, and that continued use can be beneficial, but has little effect on the circadian rhythm (Hoebert et al. 2009). Parents subjectively reported that melatonin improved sleep onset, behavior, and mood. However, discontinuing melatonin almost always resulted in a rebound in delayed sleep onset. Evidence for dosing melatonin is insufficient, but a good general rule to follow would be one to five mg for children and one to ten mg for adults (Amy Meidinger, personal communication, October 31, 2022). Most experts agree that doses above 20-30 mg are no more effective than lower doses.

Light therapy (LT) is commonly used in patients with seasonal affective disorder (SAD) to treat depression. When using LT in the morning, one can advance the circadian rhythm to a more appropriate time, especially in patients with delayed sleep onset. Rybak 2006 and Rachel 2017 et al. showed similar findings with reduction in ADHD symptoms when the circadian rhythm was advanced. Participants also felt like their mood, attention, processing speed, visual perception, and sleep were improved. Interestingly, objective measurements were conflicting. Sleep actigraphy showed no changes to TST, SE, WASO, while sleep fragmentation increased (Rachel et al. 2017). DLMO did advance which would make sense with the advancement in the circadian rhythm. Studies only included adults and were equal in sexes but did not provide details about medications the participants were taking, and no placebo group was utilized. Data was extremely limited regarding LT and appears to be utilized infrequently in this population of patients. Its use may be beneficial in populations or regions where natural light is limited.

Establishing good sleep hygiene practices is the cheapest and most practical intervention in treating sleep disorders, especially in the younger population. Individualizing a plan for good sleep hygiene can be remarkably effective, as there are several factors involved with sleep

hygiene (multiple homes, differing bedtimes, parenting techniques, etc.). Peppers 2016 and Sciberras 2020 et al. had similar findings with reduction in sleep problems and ADHD symptoms. Sciberras et al. (2020) was superior in that it assessed participants over a years' time and had much more data to review and assess. Additionally, Sciberras et al. (2020) did have teachers assess the participants ADHD symptoms via questionnaires, and these did not show significant findings. These findings underscore how subjective questionnaires can be; objective data would be useful in this area. Most experts agree that addressing sleep hygiene prior to establishing diagnoses is crucial in teasing out the root cause to a patient's symptoms (Amy Meidinger, personal communication, October 31, 2022).

ADHD medication negatively affects the circadian rhythm with its DA and NE stimulation, and caution is warranted regarding taking these medications where sleep is concerned. Stimulants act on the prefrontal cortex and striatum, and this creates more control over attentional resources, thus improving ADHD symptoms (Corkum et al. 2020). Scheduling the dose can become difficult when a patient is taking extended-release methylphenidate (ER MPH) and is still having trouble concentrating later in the afternoon. Adding an immediate-release MPH (IR MPH) in the afternoon can help but may have deleterious effects to their sleep. Corkum et al. (2020) used ER MPH, and this was the only trial to conduct polysomnography (PSG) on their participants. ER MPH reduced ADHD symptoms according to both parents and teachers, while negatively affecting TST and sleep onset latency (SOL). SE was not significantly impacted. PSG showed a similar trend but not as significant compared to the actigraphy. Weiss et al. (2021) also used ER MPH over an extended period and revealed that adverse effects to participants sleep were short-lived and their sleep improved over time. However, the study suggests that those with poor sleep at baseline would continue to have poor sleep with treatment.

Solleveld et al. (2020) used IR MPH and revealed similar findings over long-term use. By the 16th week of treatment, participants had an improvement in SE, SOL, and sleep duration. These trials revealed the difficulty in determining when to increase the dose of ADHD medication, and it seems like a balancing act of addressing ADHD symptoms while trying not to significantly affect sleep. Most experts agree that increasing ADHD medication should be done in two to three weeks, rather than titrating up in just a week's time (Amy Meidinger, personal communication, October 31, 2022).

Several studies had a common trend in their findings, in that correcting delayed sleep onset revealed improvements in ADHD symptoms and sleep quality. The more holistic approaches, such as LT and good sleep hygiene practices, showed benefits to both ADHD and sleep. Sciberras et al. (2020) showed that adopting good sleep hygiene practices can have lasting effects to both ADHD and sleep. Unfortunately, there was no LT study similar in length to the sleep hygiene studies, as the LT trials were very limited and in short duration. This may have been the reason for the conflicting results of the participants' outcomes. The subjective sleep diaries showed improvement with LT, while the actigraphy showed no significant changes with more sleep fragmentation (Rachel et al. 2017). The actigraphy findings may have improved if the study was over a longer period of time. A trial of LT followed by cessation of LT would be useful to compare with the melatonin studies. LT may have similar findings to melatonin when assessing delayed sleep onset. Discontinuing melatonin showed a rebound of delayed sleep onset in 92.3% of its participants (Hoebert et al. 2009). Additionally, only children participated in the melatonin trails, while the LT studies were exclusive to adults. LT is safe for children, but no studies were found that measured this in children with ADHD. As stated above, no adverse effects were noted with long-term melatonin use (Hoebert et al. 2009). However, it would be

useful to know if chronic exogenous use of melatonin has any lasting effects to endogenous melatonin and other hormonally driven factors in the body.

Participants taking ADHD medication consistently showed negative effects to their sleep early in treatment, and only improved slightly by the second month of treatment (Solleveld et al. 2020). Solleveld et al. (2020) showed it can take up to sixteen weeks of treatment for significant findings, and one could see this being a difficult task when treating a patient, especially a child, with ADHD. Additionally, the study was not clear how long it took for titrating the target dose. Clinically, this can be very difficult when trying to titrate a patient's ADHD medication. Guidelines advise to increase dose every seven days to reach a target dose, but reaching a steady state seems to differ individually. The studies involving children that were analyzed used either fixed doses based on weight or titrated doses until a target dose was achieved. The lone adult study administered set doses as well and showed improvements in ADHD and sleep symptoms once the dose was titrated and therapy was over a month's duration. Additional data from the titrated dose trial would be beneficial if they were to include the participants' response rate to change in dose. This would help in obtaining an average in the response to therapy, and clinically help educate patients and caregivers about what to expect. Staying on a dose longer than a month may be needed to start feeling the maximum effect from the medication. Objective findings concerning sleep were only performed in studies involving children. The four-week trial found a negative impact on sleep (Corkum et al. 2020), while the 16-week trial revealed significantly more improvements to sleep (Solleveld et al. 2020). However, Solleveld et al. (2020) showed that even at the 8th week of treatment, participants did not show significant changes in their sleep efficiency. The adult trial had similar results and only improvement of sleep was noted well after the first month of treatment (Weiss et al. 2021). The studies overall tended to show that

patients should have a reduction in their ADHD symptoms relatively quickly, but their sleep can be negatively affected for up to one to four months.

Overall, the research showed the importance of addressing sleep prior to starting ADHD medication. Questionnaires were a very effective tool in assessing sleep and ADHD symptoms and are cost effective. Objective measurements, such as sleep actigraphy and PSG, only showed significant findings when measurements were taken over an extended period. Performing these studies would not be beneficial in most cases because of the cost and the length of time needed to assess sleep. The objective measurements do help rule out any sleep disturbances, so using a questionnaire that first focused on sleep would help determine if they would be indicated. Research was lacking to demonstrate differences between sexes, as most studies consisted of males. Future studies with a more balanced population of patients would be beneficial. Additionally, more research is needed in assessing sleep prior to starting treatment for ADHD and determining how many patients eventually require treatment. Developing an individualized treatment plan for patients seems to be the best method to help improve sleep issues and ADHD. Educating patients on good sleep hygiene and what to expect with ADHD medication use is crucial, as timing of symptoms and sleep improvements differed greatly. The patient and caregiver both should know that ADHD symptoms should improve relatively quickly but sleep improvements may not be fully realized in a few months.

Conclusion

Assessing sleep in ADHD patients can be extremely difficult, especially in cases where the patient has difficulty initiating sleep prior to the diagnosis. Factoring in multiple home/sleep settings complicates things even further. Several studies indicated that those patients would continue to have problems with their sleep. Adjusting to ADHD medication can take a few

months, and it may take even longer for their sleep to finally improve according to the data. This could cause poor adherence to the medication. Establishing good sleep hygiene is critical in helping these patients sleep and must be addressed prior to the diagnosis of ADHD or starting hypnotic therapy. Questionnaires are very cost-effective and easy to perform in the clinic setting. Objective measurements, such as actigraphy and PSGs, are costly and used to rule out sleep disorders. Prescription hypnotics were not examined, but the use of melatonin did show benefit in most patients. However, the data did not show this to be effective in altering the circadian rhythm, as stopping led to a rebound in delayed sleep onset. LT had similar results to melatonin use, but more research is needed in this area as this data was exclusive to adults and short in nature. Notably, advancing circadian rhythm demonstrated improvements to both sleep and ADHD symptoms even when the duration of sleep time was not increased.

Application to Clinical Practice

As clinicians, it is important to make patients with ADHD aware of the difficulty in treating their sleep issues and setting clear expectations. Conducting a thorough history and physical examination is critical in discerning issues that could be worsening their ADHD symptoms or sleep. Advancing circadian rhythm showed benefits to both ADHD symptoms and sleep, and is an appropriate treatment goal to discuss with patients and/or caregivers. Consulting with an expert in ADHD management, such as a psychologist, is a good first step in diagnosing ADHD in a patient. Once the patient is formally diagnosed, the primary care provider can take over management, but can still consult with the psychologist if the patient becomes refractory to therapy. Initiating stimulants should be at a low dose, with titrating taking place about once per week. The goal is to maximize the medications effects but also avoid side effects, such as decreased appetite and insomnia. Weekly updates from the patient and/or caregiver can be done

via phone or messaging system. Optimal therapy may take a few months, so it is vital to explain to the patient and/or caregivers to provide realistic expectations. Monthly face-to-face visits should be scheduled to review the response to treatment and note any side effects or changes to vital signs. Once the patient has reached their desired dose with therapy, a mutual decision can be made between the provider and patient/family as to routine follow-up. At minimum, the patient should be seen annually. A drug holiday may be considered if symptoms have improved or have remained unchanged for a few years.

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