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Impact of Circadian Rhythm on ADHD

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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 exacerbating 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, 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 ranges 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)
- Imbalances of neurotransmitters (NT), specifically dopamine (DA) and norepinephrine (NE), are the main cause for ADHD symptoms to occur

Statement of the Problem

- Children with ADHD experience problems with initiating and maintaining sleep up to 70% of the time (Sciberras et al., 2020)
- There is no diagnostic marker for ADHD, so there's no real objective criteria for the diagnosis. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) is used by the United States
- First-line treatment for ADHD are stimulants and these facilitate the release of DA and NE and block the reuptake of both
- Most common adverse drug reactions (ADR) include sleep issues, decreased appetite, and cardiac problems

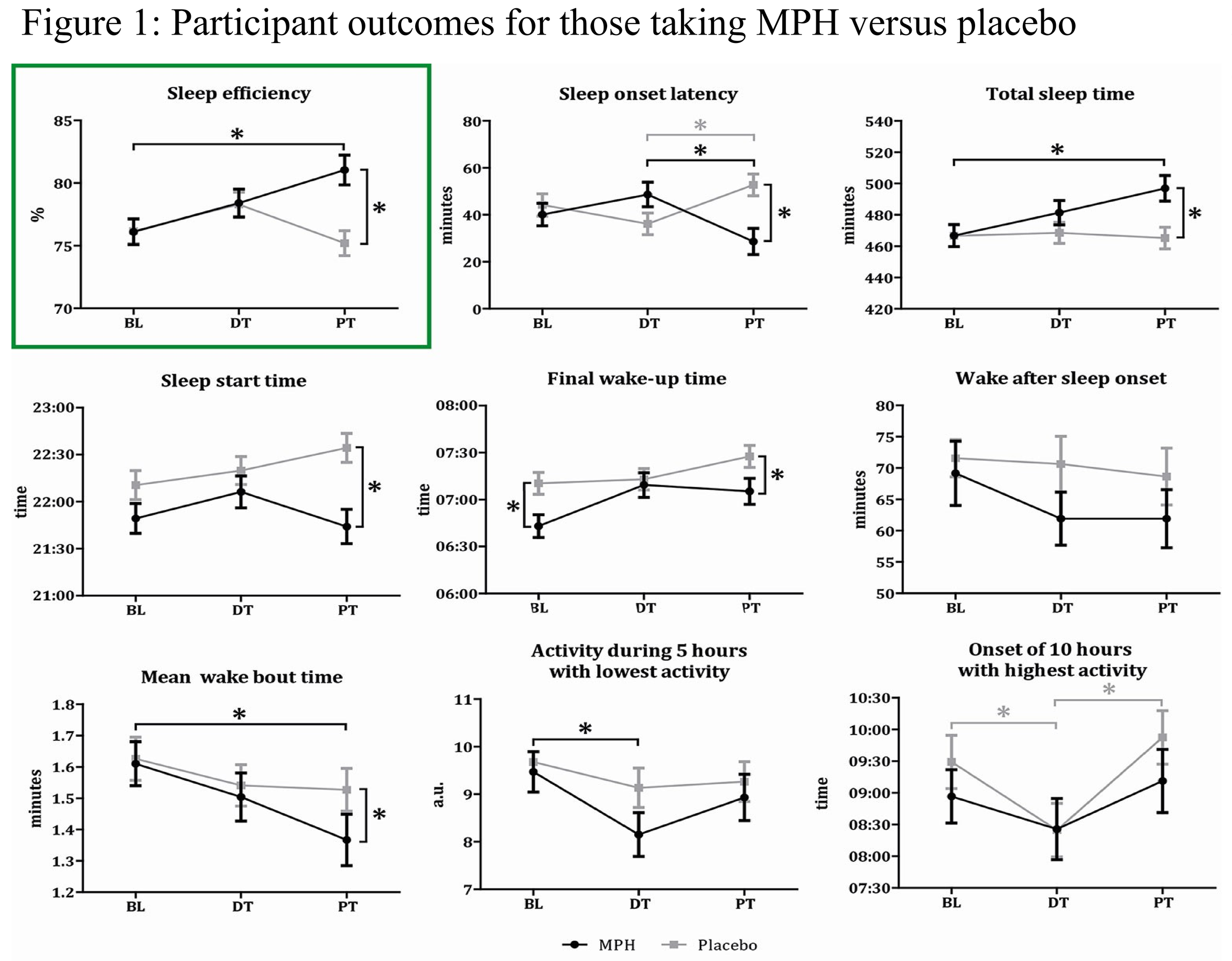
Research Question

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

Literature Review

- Masi et al. (2019) found that children and adolescents with ADHD on stimulant medication, responded well to melatonin and the response was better without additional comorbidities
- For medication naïve ADHD participants, Van der Heijden et al. (2007) found melatonin advanced sleep onset by 26.9 minutes compared to a delay of 10.5 minutes in placebo group (p<0.0001), however this did not help behavioral or cognitive function
- Hoebert et al. (2009) observed the long-term use (>3 years) of melatonin in Van der Heijden's study. This showed benefits with little side effects, and parents subjectively noting improvement in sleep, behavior, and mood
  - Discontinuing melatonin resulted in a rebound of delayed sleep onset in 92% of participants, suggesting it's ineffectiveness with circadian rhythm
  - Behavior and mood did improve with longer term use of melatonin
- LT advanced circadian rhythm to morning and ADHD participants subjectively felt like their mood, attention, processing speed, visual perception, and sleep improved (Rybak et al. 2006 and Rachel et al. 2017)
  - Surprisingly, objective sleep measurements did not show improvements to sleep and sleep fragmentation increased
- Individualizing a plan for good sleep hygiene practices showed a reduction in ADHD symptoms and sleep problems (Peppers et al. 2016)
  - Sciberras et al. (2020) further delineated this idea when comparing sleep behavioral intervention versus general clinical care
- Stimulant therapy's effects on circadian rhythm in children revealed negative effects on sleep in the first month (Corkum et al. 2020)
- However, as seen in Figure 1, Solleveld et al. (2020) showed that sleep slowly started improving beyond the 8 weeks of treatment in children
- Weiss et al. (2021) had similar findings concerning adults (Figure 2)
  - During the 1-month trial, they found minimal improvement in both the stimulant and placebo group with no statistical differences (p=0.10)
  - However, the 6-month trial showed improvements to their sleep (p<0.0001)

Figure 1: Participant outcomes for those taking MPH versus placebo



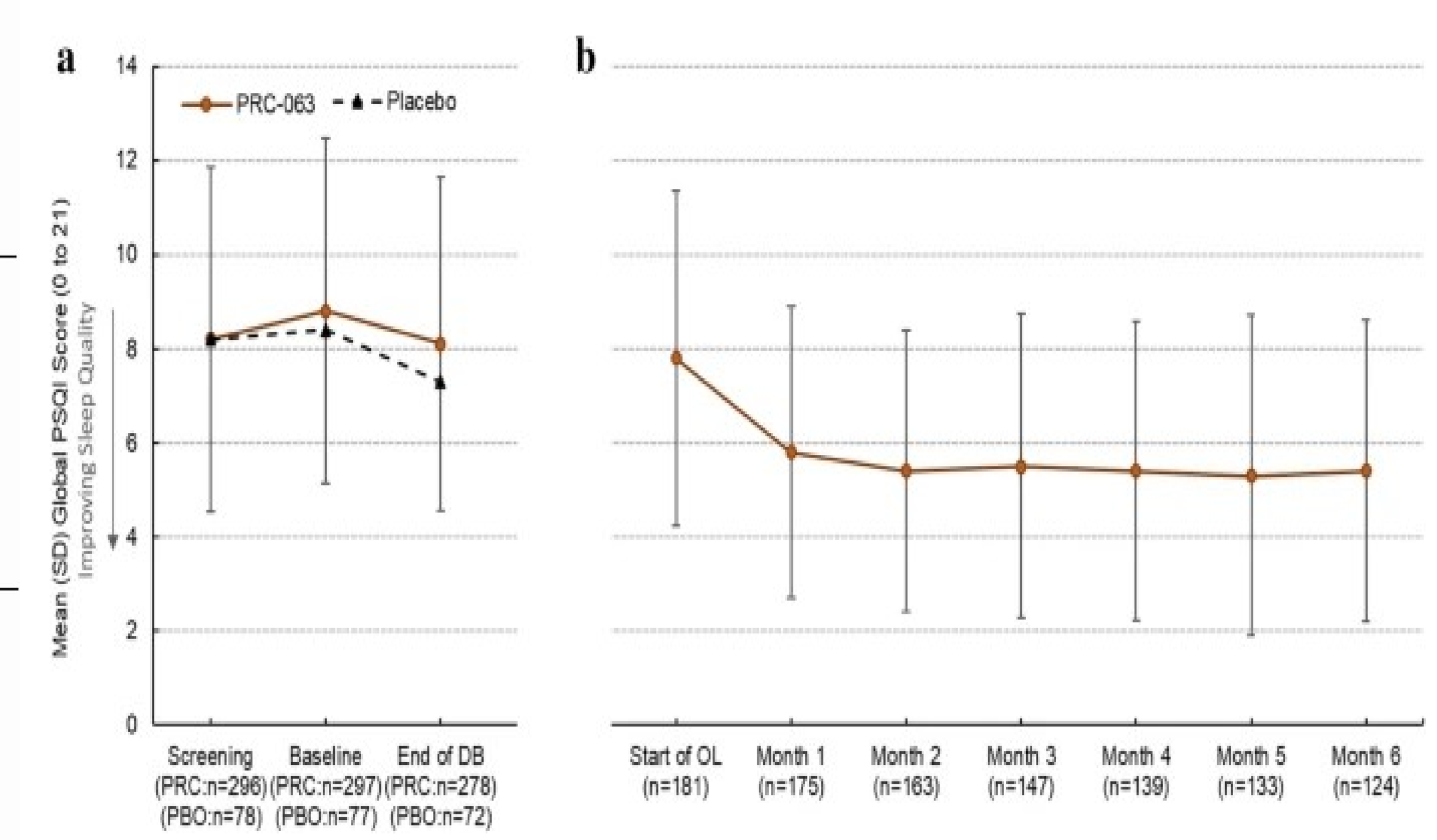
BL, baseline; DT, during treatment; PT, post-treatment. Asterisks indicate a significant difference between the two conditions ($p < 0.05$). Black lines indicate the MPH treated subjects, gray lines the placebo treated subjects.

Note: Adapted from "Effects of 16 Weeks of Methylphenidate Treatment on Actigraph-Assessed Sleep Measures in Medication-Naive Children With ADHD", by Solleveld et al. 2020. Front Psychiatry. 2020 Feb 28

Discussion

- Research showed the importance of addressing sleep in patients with ADHD. Questionnaires are a very cost-effective tool in the assessment of sleep and ADHD symptoms, while objective measurements needed to be taken over a long time period to show significant findings. Objective measurements were good at ruling out any sleep disturbances but have little utility in the long-term treatment of ADHD. Melatonin was effective in treating delayed sleep onset and caused rare side effects. However, this did not seem to change the circadian rhythm as patients still had sleep issues when discontinuing melatonin. LT studies revealed subjective improvement in patients, but objective findings revealed an increase in sleep fragmentation.
- Establishing good sleep hygiene is critical in teasing out the root cause of sleep problems, and studies showed improvements to both sleep and ADHD symptoms when this was addressed during office visits.
- ADHD medication had deleterious effects to sleep, however sleep did seem to improve past the 2-month mark in treatment.

Figure 2: Stimulant therapy versus placebo in 1-month trial and additional 6-month trial



Global Pittsburgh Sleep Quality Index (PSQI) score during **a** the double-blind (DB) study and **b** the open-label (OL) extension study. *PBO* placebo, *PRC* PRC-063, *PSQI* Pittsburgh Sleep Quality Index, *SD* standard deviation

Note: Adapted from "Effect of a Multi-Layer, Extended-Release Methylphenidate Formulation (PRC-063) on Sleep in Adults with ADHD: A Randomized, Double-Blind, Forced-Dose, Placebo-Controlled Trial Followed by a 6-month Open-Label Extension" by Weiss et al. 2021. CNS Drugs. 2021 June

Applicability to Clinical Practice

- Advancing circadian rhythm showed benefits to both ADHD symptoms and sleep, and therefore 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 at diagnosing ADHD in a patient. Once the patient is formally diagnosed, their primary care provider can take over management, but can still consult with psychology if symptoms are refractory to treatment.
- Guidelines to optimize stimulant therapy
  - Start at low dose and titrate up every 1-2 weeks
  - Maximize therapy while avoiding side effects (insomnia/appetite)
  - Weekly updates from patient/caregiver via phone/messaging system
  - Educating patient/caregiver that optimization may take a few months
  - Schedule monthly face-to-face visits to assess response
    - Look for side effects or changes to vital signs
  - If desired dose is reached, mutual decision can be made for further visits
    - At minimum, patient should be seen annually
  - Trial off medication if stable symptoms for a few years

References

- Corkum, P., Begum, E., Rusak, B., Rajda, M., Shea, S., MacPherson, M., Williams, T., Spurr, K., & Davidson, F. (2020). The effects of extended-release stimulant medication on sleep in children with ADHD. J Can Acad Child Adolesc Psychiatry. Mar;29(1):33-43. Epub 2020 Mar 1. PMID: 32194650; PMCID: PMC7065567. https://pubmed-ncbi-nlm-nih-gov.ezproxylr.med.und.edu/32194650/
- Drechsler, R., Brem, S., Brandeis, D., Grünblatt, E., Berger, G., & Walitza, S. (2020). ADHD: current concepts and treatments in children and adolescents. Neuropediatrics. Oct;51(5):315-335. doi: http://dx.doi.org/10.1055/s-0040-1701658. Epub 2020 Jun 19. PMID: 32559806; PMCID: PMC7508636
- Fargason, R., Fobian, A., Hablitz, L., Paul, J., White, B., Cropsey, K., & Gamble, K. (2017). Correcting delayed circadian phase with bright light therapy predicts improvement in ADHD symptoms: A pilot study, Journal of Psychiatric Research, Volume 91, Pages 105-110, ISSN 0022-3956, https://doi.org/10.1016/j.jpsychires.2017.03.004
- Hoebert, M., van der Heijden, K., van Geijlswijk, I., & Smits, M. (2009). Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. J Pineal Res. Aug;47(1):1-7. doi: http://dx.doi.org/10.1111/j.1600-079X.2009.00681.x. Epub 2009 May 27. PMID: 19486273
- Masi, G., Fantozzi, P., Villafranca, A., Tacchi, A., Ricci, F., Ruglioni, L., Inguaggiato, E., Pfanner, C., & Cortese, S. (2019). Effects of melatonin in children with attention-deficit/hyperactivity disorder with sleep disorders after methylphenidate treatment. Neuropsychiatr Dis Treat. 15:663-667. https://doi.org/10.2147/NDT.S193891
- Peppers, K., Eisbach, S., Atkins, S., Poole, J., & Derouin, A. (2016). An intervention to promote sleep and reduce ADHD symptoms. Journal of Pediatric Health Care, Volume 30, Issue 6, 2016, Pages e43-e48, ISSN 0891-5245, https://doi.org/10.1016/j.pedhc.2016.07.008 https://www.sciencedirect.com/science/article/pii/S0891524516301638
- Rybak, Y., McNeely, H., Mackenzie, B., Jain, U., & Levitan, R. (2006). An open trial of light therapy in adult attention-deficit/hyperactivity disorder. J Clin Psychiatry. Oct;67(10):1527-35. doi: http://dx.doi.org/10.4088/jcp.v67n1006. PMID: 17107243
- Sciberras, E., Mulraney, M., Mensah, F., Oberklaid, F., Efron, D., & Hiscock, H. (2020). Sustained impact of a sleep intervention and moderators of treatment outcome for children with ADHD: A randomised controlled trial. *Psychological Medicine, 50*(2), 210-219. doi: http://dx.doi.org/10.1017/S0033291718004063
- Sharma, A. & Couture, J. (2014). A Review of the Pathophysiology, Etiology, and Treatment of Attention-Deficit Hyperactivity Disorder (ADHD). *Annals of Pharmacotherapy*. 48(2):328-350. doi: http://dx.doi.org/10.1177/1060028013510699
- Solleveld, M., Schrantee, A., Baek, H., Bottelier, M., Tamminga, H., Bouziane, C., Stoffelsen, R., Lucassen, P., Van Someren, E., Rijsman, R., & Reneman, L. (2020). Effects of 16 weeks of methylphenidate treatment on actigraph-assessed sleep measures in medication-naive children with ADHD. Front Psychiatry. Feb 28;11:82. doi: http://dx.doi.org/10.3389/fpsyt.2020.00082. PMID: 32184743; PMCID: PMC7058799
- Van der Heijden, K., Smits, M., Van Someren, E., Ridderinkhof, K., & Gunning, W. (2007). Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry. Feb;46(2):233-41. doi: http://dx.doi.org/10.1097/01.chi.0000246055.76167.0d. PMID: 17242627
- Weiss, M., Surman, C., Khullar, A., He, E., Cataldo, M., & Donnelly, G. (2021). Effect of a multi-layer, extended-release methylphenidate formulation (PRC-063) on sleep in adults with ADHD: A randomized, double-blind, forced-dose, placebo-controlled trial followed by a 6-month open-label extension. CNS drugs. Jun;35(6):667-679. doi: http://dx.doi.org/10.1007/s40263-021-00814-z. Epub 2021 May 31. PMID: 34057707; PMCID: PMC8219576

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