



Melatonin effects on sleep disorders in children with attention deficit hyperactivity disorder

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ABSTRACT

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Attention deficit hyperactivity disorder is one of the most common psychiatric disorders in childhood. Around 25-50% of these children suffered from some kind of sleep disorder especially with chronic form of insomnia. The physicians usually have a plan for improving hyperactivity and attention deficit of this disease but unfortunately, they forget to manage the sleep disorders, which are a major part of patients' problems. Nowadays, we know that there is a noticeable relationship between attention deficit hyperactivity disorder and sleep disorders and by improving these children's sleep, not only the daily functions improve, but also the symptoms of attention deficit hyperactivity disorder maybe become better. Thus, it is needed to avoid the administration of psychostimulants, which have recognized side effects. Moreover, having better sleep, we will see a better relationship between children and their parents and finally a rise in the standard of life of family members, which is a very important goal in our treatment. This review article evaluates available evidence on sleep medication in children with attention deficit hyperactivity disorder to present an appropriate guidance for this high prevalence problem.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric

disorder of childhood and it can impair the quality of life of children and their

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parents (1,2). Nearly 25-50% of these children experience sleep problems and the correlation between ADHD and sleep disorders was approved (3,4). Delayed sleep onset, sleep resistance and daytime sleepiness are the major part of sleep disorders in children with ADHD (3). Although pediatric insomnia can impact educational programs, social functioning, overall health and family relationship, the doctors usually focus on improving hyperactivity, attention deficit and impulsiveness and unfortunately forget to manage their concomitant sleep disorders (4,5). In addition, not only insomnia may become aggravated by the treatment with psychostimulants medication but also sleep problems may potentially exacerbate ADHD symptoms (3,4,6).

Although the diagnosis of sleep disorders is clinical, we can use the neurophysiological evaluation, especially polysomnography, in order to confirm the symptoms (4).

We know that serotonin and melatonin, two neuroendocrine mediators, which may be culprit in ADHD developing, are both thought to regulate circadian rhythms that is very important in sleep disorders (7). Currently available research results indicate that melatonin can be effective in the treatment of insomnia (6).

This review article evaluates available evidence on sleep medication in ADHD children to present an appropriate guidance for this high prevalence problem.

Main part

It is clear that the clinicians who visit the ADHD children should have enough attention to sleep disorders of these patients as much as other problems. Weiss MD (2006) and Bendz LM and Scates AC (2010) suggested that the first-line therapy for insomnia in ADHD patients included the ruling out the differential diagnoses, optimizing ADHD stimulant

treatment, initiating good sleep hygiene and behavioral therapy (5,8). In their opinion, pharmacotherapy was a final choice in the treatment course of this disorder (8).

If we notice to the physiopathogenesis of the ADHD, we understand that this disease has a neuroendocrine base and serotonin and melatonin perform a critical role in this way. In addition, one of the most important functions of the melatonin is its antioxidant specificity (9). Because of the relationship between sleep-wake cycle and circadian rhythms, the circadian system may be disturbed in ADHD. According to some reports, their observations revealed the significant differences between the ADHD and control group in the melatonin rhythm waveform (2). In 2011, Nováková et al. used the rhythm of the pineal hormone melatonin as an acceptable marker of the system in order to assess whether the circadian system of ADHD children differed from that of controls (2). In a clinical trial research on children, Saliva got sampled every two hours up to 24 hours and the level of the melatonin was compared between ADHD and control children. According to this research, the differences between the ADHD and control group were noticeable in the melatonin rhythm waveform, but they had not seen these differences in nocturnal melatonin peaks.

Based on the importance of the melatonin role in ADHD, Chaste et al. (2011) checked all the genes of the melatonin pathway -AA-NAT, ASMT, MTNR1A, MTNR1B and GPR50 - in 321 individuals from Sweden including 101 patients with ADHD and 220 controls from the general population (9). Although they could find several gene mutations in ADHD patients, there was no prominent difference compared with the general population. Evaluating these evidences, they suggested a splice site mutation in ASMT (IVS5+2T>C) and one

stop mutation in MTNR1A (Y170X), which specifically found in ADHD.

In one study in Spain by Molina-Carballo et al. (2013), the effect of the chronic administration of prolonged release methylphenidate (PRMPH) on daily variations in blood serotonin and melatonin was evaluated. A total of 179 children (136 males, 42 females) between the ages of 5 and 14 years were enrolled in a controlled quasi-experimental open clinical study (7). Finally, they revealed that chronic treatment with prolonged release methylphenidate induced subtle changes in the daily fluctuations and concentrations of both serotonin and melatonin. This study ensured the importance of the role of melatonin in ADHD patients and the need to study about it.

In order to use medication as a help in improving the sleep disorders in ADHD children, a number of researchers used several agents. For instance, in 2013, Barrett et al. evaluated the effects of zolpidem, L-theanine and clonidine in a systematic review on five studies (10). The data showed that both of them had a poor response in reducing sleep latency and increasing total sleep time, however sleep efficiency was improved by L-theanine. They sound many side effects with zolpidem leading to the dropout of a large number of participants in all of studies. Considering the clonidine, it was noticeable that it reduced insomnia. The other drug, which was evaluated in this review, was melatonin. Studies showed that melatonin exhibited a positive response in these patients with reduction in sleep latency, higher total sleep time and higher sleep efficiency.

In 2001, Smits et al. performed a study to establish the efficacy of melatonin treatment in childhood sleep onset insomnia (11). They enrolled 40 elementary school children, 6 to 12 years of age, who suffered from chronic

sleep onset insomnia more than 1 year ago in a double-blind, placebo-controlled study. In patients who received melatonin, mean lights-off time, diary sleep onset, actigraphic sleep onset, melatonin onset and increasing total sleep time advanced 34, 63, 75, 57 and 41 minutes, respectively. There were no significant differences in the treatment groups in the change of sleep latency, wake-up time and sustained attention reaction times. The research indicated that short-term melatonin administration was relatively safe and significantly more effective than placebo in pupils with sleep disorders.

A total of 105 medication-free children, ages 6 to 12 years, with rigorously diagnosed ADHD and chronic sleep onset insomnia participated in a trial using 3 or 6 mg melatonin or placebo for 4 weeks by Van der Heijden et al. (2007) (12). They indicated that there was an advance in sleep onset, dim light melatonin onset and total time asleep. They believed that melatonin could advance circadian rhythms of sleep-wake and endogenous melatonin and enhanced total time asleep in children with ADHD and chronic sleep onset insomnia.

Mostafavi et al. (2012) studied on 50 children aged 7-12 with melatonin (3 or 6 mg based on weight) combined with ritalin (1mg/kg) and placebo combined with ritalin (1mg/kg) in a double blind randomized clinical in Iran (13). They showed significant changes in sleep latency (23.15 ± 15.25 vs. 17.96 ± 11.66 ; $P=0.047$) and total sleep disturbance score (48.84 ± 13.42 vs. 41.30 ± 9.67 ; $P=0.000$) before and after melatonin administration, respectively.

Another research in Iran by Mohammadi et al. (2012), which performed on children with age range of 7-12 years who had ADHD that were randomly introduced in the research - group 1 received melatonin and methylphenidate and the other took placebo instead of melatonin-indicated that the mean

sleep latency and total sleep disturbance scores were improved in first group (14).

Weiss et al. (2006) studied on 27 children (6-14 years of age) with ADHD who were under ritalin therapy and initial insomnia (>60 minutes) and the researchers evaluated the efficacy of the sleep hygiene in improvement of sleep disorders (8). Nonresponders to sleep hygiene educations were randomized to a 30-day double-blind, placebo-controlled, crossover trial of 5-mg melatonin. The study indicated a significant reduction of 16 minutes in initial insomnia with melatonin relative to placebo. Researchers believe that a combination of sleep hygiene and melatonin is a safe and effective treatment for initial insomnia in children with ADHD taking stimulant medication.

A systemic review by Bendz LM and Scates AC in 2010 suggested that melatonin was a well-tolerated and efficacious treatment option for pediatric patients with chronic sleep-onset insomnia (SOI) and ADHD because melatonin regulated circadian rhythm sleep disorders such as SOI in children with ADHD (5).

In several researches not only the efficacy of melatonin on sleep disorders were evaluated, but also the other potentials were studied. For instance, in 2012 Mostafavi et al. revealed that appetite was significantly correlated with sleep duration in melatonin group. In addition, mean height and weight were significantly increased in melatonin-treated children before and after the trial. These effects may be attributed to circadian cycle modification, increasing sleep duration and the consequent more growth hormone release during sleep (13).

Weiss MD and Salpekar J (2010) believed that sleep disorders can be considered as a potential factor in the exacerbation of ADHD symptoms and active usage of sleep hygiene and also using some specific pharmacological agents such as melatonin

could control some ADHD related symptoms such as irritability (3). Similarly, Betancourt-Fursow de Jiménez et al. (2006) indicated that they could expect that the symptoms of ADHD were decreased by improving the children's sleep. Therefore, it is clear that the doctors may diminish the amount or avoid the administration of psychostimulants, which have considerable side effects (4).

Szeinberg et al. (2006) evaluated the results and efficacy of long-term treatment with melatonin in adolescents (33 patients with age range of 10-18 years) with delayed sleep phase syndrome. Although they revealed its successfulness without any adverse effects in adults (15), the others believed that there were no good data concerning the safety and efficacy of long-term melatonin use in children (16).

Although there were some complications such as mild headache and generalized epilepsy, which reported by a number of studies (11), the others presented no significant adverse events by this drug (12, 16). In addition, several studies showed that enormous problem of ADHD children such as impaired attention and cognition, hyperactivity behavior, quality of life, appetite and food intake were not affected by melatonin prescription (11-14).

Conclusion

Finally, similar to some studies (6), we concluded that although the efficacy of melatonin in sleep disorders of children with ADHD was approved, there were not appropriated preparations of melatonin for children usage and we did not have evidence-based guidelines about the dosage and timing of intake in this age group. In addition, the researches, which evaluated the possible impact of melatonin intake on puberty and its effects on the endocrine system, were not considerable. Therefore,

we can conclude that using melatonin in children with ADHD and SOI should be reserved for children with persistent insomnia that their daily functions are severely impacted.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Wu EQ, Hodgkins P, Ben-Hamadi R, et al. Cost Effectiveness of Pharmacotherapies for Attention-Deficit Hyperactivity Disorder. *CNS drugs*. 2012;26:581-600.
2. Nováková M, Paclt I, Ptáček R, et al. Salivary melatonin rhythm as a marker of the circadian system in healthy children and those with attention-deficit/hyperactivity disorder. *Chronobiol Int*. 2011;28:630-637.
3. Weiss MD, Salpekar J. Sleep problems in the child with attention-deficit hyperactivity disorder: defining aetiology and appropriate treatments. *CNS Drugs*. 2010;24:811-828.
4. Betancourt-Fursow de Jiménez YM1, Jiménez-León JC, Jiménez-Betancourt CS. Attention deficit hyperactivity disorder and sleep disorders. *Rev Neurol*. 2006;42:S37-51.
5. Bendz LM, Scates AC. Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. *Ann Pharmacother*. 2010;44:185-191.
6. Holvoet E, Gabriëls L. Disturbed sleep in children with ADHD: Is there a place for melatonin as a treatment option? *Tijdschr Psychiatr*. 2012;55:349-357.
7. Molina-Carballo A, Naranjo-Gómez A, Uberos J, et al. Methylphenidate effects on blood serotonin and melatonin levels may help to synchronise biological rhythms in children with ADHD. *J Psychiatr Res*. 2013;47:377-383.
8. Weiss MD, Wasdell MB, Bomben MM, et al. Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. *J Am Acad Child Adolesc Psychiatry*. 2006;45:512-519.
9. Chaste P, Clement N, Botros HG, et al. Genetic variations of the melatonin pathway in patients with attention-deficit and hyperactivity disorders. *J Pineal Res*. 2011;51:394-399.
10. Barrett JR, Tracy DK, Giaroli G. To sleep or not to sleep: A systematic review of the literature of pharmacological treatments of insomnia in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2013;23:640-647.
11. Smits MG, Nagtegaal EE, van der Heijden J, et al. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. *J Child Neurol*. 2001;16:86-92.
12. Van der Heijden KB, Smits MG, Van Someren EJ, et al. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry*. 2007;46:233-241.
13. Mostafavi SA, Mohammadi MR, Hosseinzadeh P, et al. Dietary intake, growth and development of children with ADHD in a randomized clinical trial of Ritalin and Melatonin co-administration: Through circadian cycle modification or appetite enhancement? *Iran J Psychiatry*. 2012;7:114-119.
14. Mohammadi MR, Mostafavi SA, Keshavarz SA, et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. *Iran J Psychiatry*. 2012;7:87-92.
15. Szeinberg A, Borodkin K, Dagan Y. Melatonin treatment in adolescents with delayed sleep phase syndrome. *Clin Pediatr (Phila)*. 2006;45:809-818.
16. Cummings C; Canadian Paediatric Society, Community Paediatrics Committee. Melatonin for the management of sleep disorders in children and adolescents. *Paediatr Child Health*. 2012;17:331-336.