ORIGINAL RESEARCH

Effects of melatonin in children with attentiondeficit/hyperactivity disorder with sleep disorders after methylphenidate treatment

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Gabriele Masi¹ Pamela Fantozzi¹ Arianna Villafranca¹ Annalisa Tacchi¹ Federica Ricci¹ Laura Ruglioni¹ Emanuela Inguaggiato¹ Chiara Pfanner¹ Samuele Cortese²

¹IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry, Calambrone, Pisa, Italy; ²Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK

Correspondence: Gabriele Masi IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry, Viale del Tirreno 331A, 56025 Calambrone, Pisa, Italy Tel +39 05 088 6111 Fax +39 05 088 6301 Email gabriele.masi@fsm.unipi.it



Purpose: Methylphenidate (MPH), the first-line medication in children with attention-deficit/ hyperactivity disorder (ADHD), is associated with increased risk of sleep disorders. Melatonin has both hypnotic and chronobiotic properties that influence circadian rhythm sleep disorders. This study explores the effectiveness of melatonin in children with ADHD who developed sleep problems after starting MPH.

Patients and methods: This study, based on a clinical database, included 74 children (69 males, mean age 11.6 ± 2.2 years) naturalistically treated with MPH (mean dosage 33.5 ± 13.5 mg/d). The severity of sleep disorder (sleep onset delay) was recorded at baseline and after a follow-up of at least 4 weeks using a seven-point Likert scale according to the Clinical Global Impression Severity score. Effectiveness of melatonin on sleep (mean dosage 1.85 ± 0.84 mg/d) after 4 weeks was assessed using a seven-point Likert scale according to the Clinical Global Impression Improvement (CGI-I) score, and patients who scored 1 (very much improved) or 2 (much improved) were considered responders.

Results: Clinical severity of sleep disorders was 3.41 ± 0.70 at the baseline and 2.13 ± 1.05 after the follow-up (P < 0.001). According to the CGI-I score, 45 patients (60.8%) responded to the treatment with melatonin. Gender and age (children younger and older than 12 years) did not affect the response to melatonin on sleep. Patients with or without comorbidities did not differ according to sleep response. Specific comorbidities with disruptive behavior disorders (oppositional defiant disorder or conduct disorder), affective (mood and anxiety) disorders and learning disabilities did not affect the efficacy of melatonin on sleep. Treatment was well tolerated, and no side effects related to melatonin were reported.

Conclusion: In children with ADHD with sleep problems after receiving MPH treatment, melatonin may be an effective and safe treatment, irrespective of gender, age and comorbidities.

Keywords: attention-deficit/hyperactivity disorder, sleep disorders, children, melatonin, methylphenidate

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder.¹ According to the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)*,² ADHD is characterized by a persistent and impairing pattern of inattention and/or hyperactivity/impulsivity. A large body of evidence shows that ADHD is often comorbid with other psychiatric conditions, such as oppositional defiant disorder/conduct disorder, specific learning disorders, mood and anxiety disorders.³

Neuropsychiatric Disease and Treatment 2019:15 663-667

663

© 2019 Masi et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, large year agraphs 4.2 and 5 of our Terms. (http://www.dovepress.com/terms.php). Available treatments for ADHD include pharmacological and non-pharmacological strategies (including parent training programs and cognitive training). Pharmacological treatments are an important element of the multimodal therapeutic strategy for ADHD and are recommended as the first choice option in several guidelines/practice parameters, at least for severe cases,^{4–6} or as a treatment strategy for patients who have not responded to non-pharmacological interventions.^{5,6} Commonly used medications for ADHD include psychostimulants, namely methylphenidate (MPH), amphetamines and non-psychostimulant drugs (eg, atomoxetine or guanfacine).

One of the most common adverse effects during treatment with MPH is disruption of sleep patterns, including bedtime resistance, sleep-onset difficulties, night awakenings, difficulties with morning awakening, with secondary daytime sleepiness, "difficulty falling asleep" being the most frequently reported sleep disorder.⁷ Although this effect is often transitory (limited to the first weeks of treatment) in a number of children treated with MPH, in others it is persistent, which leads to stop a treatment that is otherwise effective for ADHD core symptoms.⁷

Melatonin is an endogenously produced indoleamine secreted by the pineal gland usually during darkness; its secretion is suppressed by light. Melatonin plays a key role in regulating the circadian rhythm⁸ and has many other biological functions, including chronobiotic and antioxidant properties, anti-inflammatory effects and free radical scavenging.^{9,10} Additionally, melatonin regulates the vigilance states depending on the activated melatonin receptors (MT1, MT2 or both), whereby MT2 and MT1 receptors are mainly involved in NREM and REM sleep, respectively.¹¹

Several studies have demonstrated that melatonin has both hypnotic and chronobiotic properties¹² that influence circadian rhythmicity and affect circadian rhythm sleep disorders.¹³ Because of these properties, melatonin can improve sleep-wake rhythm disturbances and decrease sleep latency in children with sleep disorders.¹⁴ Indeed, it is one of the most commonly used drugs for sleep problems in infants, children and adolescents, in particular those with neurodevelopmental disorders.¹⁵

Proof of the efficacy of melatonin in sleep latency and sleep duration in ADHD children has been supported by observational studies.¹⁶ Mohammadi et al¹⁷ explored the efficacy of melatonin in children with ADHD receiving MPH in a placebo-controlled study. This study reported a positive effect of melatonin (3–6 mg/d) on sleep latency and overall sleep disturbances, without effects on ADHD measures.

This study aimed at assessing the effectiveness of melatonin in children and adolescents with ADHD who developed a sleep problem after receiving MPH treatment (at the target clinical dose). Gender, age (pre- and post-pubertal children) and comorbidities were explored as possible elements associated with lesser effectiveness on melatonin.

Methods

Participants and procedures

This naturalistic study is based on a clinical database of 74 consecutive patients with ADHD, treated with a monotherapy of MPH (10 immediate release and 64 sustained release) (mean dosage 33.5±13.5 mg/d), who presented sleep problems (difficulty in falling asleep at bedtime, with a significant sleep onset delay), after starting stimulant treatment. Although sleep habits or difficulties were not specifically explored before starting MPH, clinically relevant sleep problems were not reported by parents in the pre-treatment clinical assessment and in the medical reports. This sample was derived from a larger cohort of about 600 consecutive youths screened and treated for ADHD in our unit for pharmacological treatments in ADHD. The diagnosis of ADHD was made at the end of the diagnostic procedure, which included a structured clinical interview according to DSM-4 criteria, the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al¹⁸) as well as the Conners' Parent (27 items rated by the parents) and Teacher Rating Scales-Revised: Short Form (28 items rated by the teachers).¹⁹ (Italian versions of the K-SADS-PL,²⁰ CPRS-R:S and CTRS-R:S²¹ are available.)

All the patients were naturalistically treated with add-on melatonin as a sleep inductor. The melatonin was used as usual in our clinical practice; information about the efficacy and tolerability of the medication was included in the medical reports; and this study is based on these reports. According to the Italian Regulatory Agency for Medications indications, the suggested dose of melatonin for sleep disorders in youth is one milligram at bedtime, and the preparations available in Italy are marketed accordingly. For this reason, starting dose was one milligram after dinner (around 8-9 pm, about 1-2 hours before bedtime), with possible increases of 0.5 mg every week, up to 5 mg/d, according to clinical needs (mean dosage 1.85±0.84 mg/d). The duration of the treatment was at least 4 weeks, with a maximum duration of 12 months, based on clinical outcomes. Twelve patients (16.2%) received a co-treatment with a behavioral psychotherapy aimed to improve cognitive, behavioral and emotional self-regulation.

The severity of the sleep disorder was recorded at baseline by a seven-point Likert scale according to the Clinical Global Impression Severity (CGI-S) score, based on parents' reports.²⁰ The patients were followed up according to a scheduled program for patients with ADHD receiving medications, with monthly visits, and the first assessment of sleep problems was 1 month after starting melatonin. Efficacy of melatonin on sleep was assessed using a sevenpoint Likert scale according to the Global Impression Improvement (CGI-I) score²² (patients with a score 1 – very much improved, or 2 – much improved, were considered responders), based on parents' reports.

All patients and their families participated voluntarily in the study after written informed consent was obtained for assessment and treatment procedures. The institutional review board of the Scientific Institute Stella Maris (Pisa) approved the study in accordance with the Declaration of Helsinki.

Statistical analyses

Subjects were compared using chi-square analysis on categorical variables and paired *t*-test on continuous variables, setting significance at 0.05 level, two tailed.

Results

Clinical severity at the baseline according to CGI-S was 3.41 ± 0.70 , after the follow-up 2.13 ± 1.05 (paired *t*-test 12.2 (74), *P*<0.001). Clinical improvement according to CGI-I was 2.35 ± 1.01 . According to a CGI-I 1 (very much improved) or 2 (much improved), 45 patients (60.8%) were considered responders.

Sixty-nine males and five females were compared according to response to melatonin, and all the five females (100%) (dose 1.8±0.8 mg/d) and 40 out of 69 males (58.0%) (dose 1.9±0.8 mg/d) were responders (χ^2 =1.9 (1), *P*=ns).

When age of the patients was considered, pre-pubertal children younger than 12 years were 42, of whom 27 (64.3%) responded to melatonin (1.6 \pm 0.7 mg/d), whereas adolescents older than 12 were 32, of whom 18 (57.2%) were responders to melatonin (2.1 \pm 1 mg/d) (χ^2 =0.2 (1), *P*=ns).

When comorbidities were considered, patients without comorbidities were 16, of whom 12 (75%) responded to melatonin (dose $1.7\pm0.8 \text{ mg/d}$), whereas patients with any comorbidity were 58, of whom 33 (56.9%) were responders (dose $1.9\pm0.9 \text{ mg/d}$) (χ^2 =1.0 (1), *P*=ns).

When specific comorbidities were considered, 34 patients presented an ODD/CD comorbidity, of whom 20 (58.8%) were responders to melatonin (1.9±0.8 mg/d), and 40 patients did not present such comorbidity, of whom 25 (62.5%) being responders to melatonin (1.8±0.9 mg/d) (χ^2 =0.007 (1), *P*=ns).

Nineteen patients presented an affective (mood and/or anxiety) comorbidity, of whom 12 (63.2%) responded to melatonin (dose 1.9 ± 1.1 mg/d), and 55 did not present

such comorbidity, of whom 33 (60%) were responders to melatonin (dose $1.8\pm0.7 \text{ mg/d}$) ($\chi^2=0.001$ (1), *P*=ns).

Finally, 19 patients presented a comorbid learning disability, of whom 9 (47.4%) were responders to melatonin (dose 1.7±0.7 mg/d), whereas 55 did not present learning disabilities, of whom 36 (65.5%) were non-responders (dose 1.9±0.9 mg/d) (χ^2 =1.3 (1), *P*=ns).

Discussion

Although MPH is the gold standard among the treatments for ADHD symptom, one of the most common AEs during treatment with MPH is disruption of sleep patterns, sometimes persistent and impairing. Melatonin can improve sleep—wake rhythm disturbances and decrease sleep latency in children with sleep disorders.

In this study, we aimed to explore the efficacy of melatonin in ADHD patients treated with MPH who developed sleep problems after starting MPH treatment to control ADHD symptoms. According to our findings, melatonin was effective in improving sleep problems in 60.8% of the patients. The efficacy was similar in males and females and in children when compared to adolescents. Furthermore, the comorbidities, frequently occurring in youth with ADHD, did not affect the efficacy of melatonin. Finally, melatonin was well tolerated, and no side effects were reported during the follow-up.

This naturalistic study has several important limitations. The most important is that we used CGI-I as an outcome measure, not a specific measure of sleep disorder severity and improvement. The lack of other methods, such as previously validated questionnaires, sleep diary and actigraphy, limits the reliability of the results. However, the methodology of reassessment of the patients, using clinical global impression in the scheduled visits (usually every month), is consistent with the naturalistic design of the study and with the routinary clinical care in the real life. Another limitation is the lack of specific information about the sleep habits before starting MPH. However, clinically significant sleep problems were not reported by parents in the first clinical reports, but only after starting stimulant treatment.

However, CGI-I is the criterion according to which usually clinicians decide treatment strategies, ie, to continue or change a pharmacotherapy. Another limitation is that, based on Italian Regulatory Agency for Medications indications, the suggested dose of melatonin for sleep disorders in youth is one milligram at bedtime, and the preparations available in Italy are marketed accordingly. The use of relatively low doses of medications in our patients may have reduced the efficacy of the treatment. However, an observational, naturalistic study suggested that in children with different neurodevelopmental disorders about two-third of the patients responded to relatively medium doses (2.5-6 mg/d), whereas doses above 6 mg added further benefit only in a small percentage of children.²³

A strength of this study is that it is based on a consecutive, unselected sample of children naturalistically treated, with few exclusion criteria (except for intellectual disability, autism spectrum disorders and schizophrenia). Most comorbid conditions, which are the rule in clinical settings but are often excluded in controlled trials, were included in the study, increasing the applicability of the study to clinical practice.

Although sleep disturbances associated with ADHD have been neglected in the past, there is now an increasing interest on this topic,²⁴ since: 1) sleep disturbances may be a source of distress for the child and the family; 2) sleep problems may worsen ADHD symptoms as well as associated emotional disorders; 3) quantitative or qualitative alterations of sleep may cause problems with mood, attention and behavior, and 4) sleep disturbances may mimic ADHD symptoms in children misdiagnosed with ADHD. For these reasons, sleep disorders may represent a target of intervention in all the children with ADHD, both receiving or not receiving stimulant treatments.

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Disclosure

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