Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Effects of melatonin in children with attention-deficit/hyperactivity disorder with sleep disorders after methylphenidate treatment

This article was published in the following Dove Medical Press journal:
Neuropsychiatric Disease and Treatment

Gabriele Masi[1]
Pamela Fantozzi[1]
Arianna Villafranca[1]
Annalisa Tacchi[1]
Federica Ricci[1]
Laura Ruglioni[1]
Emanuela Inguaggiato[1]
Chiara Pfanner[1]
Samuele Cortese[2]

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

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]

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

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/NDT.S193891

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 rhythm[8] 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 properties[12] 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 al[17] 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 al[18]) 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:S[21] 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 seven-point Likert scale according to the Global Impression Improvement (CGI-I) score[22] (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±0.7 mg/d), whereas adolescents older than 12 were 32, of whom 18 (57.2%) were responders to melatonin (2.1±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±0.8 mg/d), whereas patients with any comorbidity were 58, of whom 33 (56.9%) were responders (dose 1.9±0.9 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±0.7 mg/d) (χ^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.

Acknowledgment

This research was supported by a donation from Humana Italia SpA to the IRCCS Stella Maris.

Disclosure

GM was in an advisory board for Angelini, has received research grants from Lundbeck, FB Health, and Humana Italia, and has been a speaker for FB Health and Otsuka. SC declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH), a non-profit organization, in relation to lectures delivered for ACAMH, and from the Healthcare Convention for Educational Activity on ADHD. The authors report no other conflicts of interest in this work.

References

1. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol*. 2014;43(2):434–442.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
3. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet*. 2005;366(9481):237–248.
4. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921.
5. National Institute for Health and Care Excellence [webpage on the Internet]. Attention deficit hyperactivity disorder CG72; 2008. Available from: http://www.nice.org.uk/CG72. Accessed March 1, 2018.
6. Taylor E, Dopfner M, Sergeant J, et al. European clinical guidelines for hyperkinetic disorder ? first upgrade. *Eur Child Adolesc Psychiatry*. 2004;13(S1):17–30.
7. Cortese S, Holtmann M, Banaschewski T, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry*. 2013;54(3):227–246.
8. Gordon N. The therapeutics of melatonin: a paediatric perspective. *Brain Dev*. 2000;22(4):213–217.
9. Mauriz JL, Collado PS, Veneroso C, Reiter RJ, González-Gallego J. A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives. *J Pineal Res*. 2013;54(1):1–14.
10. Porfirio MC, Gomes de Almeida JP, Stornelli M, Giovinazzo S, Purper-Ouakil D, Masi G. Can melatonin prevent or improve metabolic side effects during antipsychotic treatments? *Neuropsychiatr Dis Treat*. 2017;13:2167–2174.
11. Comai S, Ochoa-Sanchez R, Gobbi G. Sleep-wake characterization of double MT_1/MT_2 receptor knockout mice and comparison with MT_1 and MT_2 receptor knockout mice. *Behav Brain Res*. 2013;243:231–238.
12. Wirz-Justice A, Armstrong SM. Melatonin: nature's soporific? *J Sleep Res*. 1996;5(2):137–141.
13. van Geijlswijk IM, Korzilius HP, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. *Sleep*. 2010;33(12):1605–1614.
14. Appleton RE, Gringras P. Melatonin: helping to mend impaired sleep. *Arch Dis Child*. 2013;98(3):216–217.
15. Hartz I, Furu K, Bratlid T, Handal M, Skurtveit S. Hypnotic drug use among 0–17 year olds during 2004–2011: a nationwide prescription database study. *Scand J Public Health*. 2012;40(8):704–711.
16. Anand S, Tong H, Besag FMC, Chan EW, Cortese S, Wong ICK. Safety, tolerability and efficacy of drugs for treating behavioural insomnia in children with attention-deficit/hyperactivity disorder: a systematic review with methodological quality assessment. *Pediatr Drugs*. 2017;19(3):235–250.
17. 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(2):87–92.
18. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age Children-Present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–988.
19. Conners CK. *Conners' Rating Scales: Revised Technical Manual*. Multi-Health Systems Inc ed. NY: North Tonawanda; 1997.
20. Kaufman J, Birmaher B, Rao U, Ryan N. *Test K-SADS-PL – Intervista diagnostica per la valutazione dei disturbi psicopatologici in bambini e adolescenti*. Trento: Erikson; 2004.
21. Nobile M, Alberti B, Zuddas A. *Conners' Rating Scales-Revised-Italian Version*. Giunti OS. ed; 2007.
22. Guy W. *ECDEU Assessment Manual for Psychopharmacology, revised*. Rockville, MD: US Department of Health, Education and Welfare; 1976.
23. Ayyash HF, Preece P, Morton R, Cortese S. Melatonin for sleep disturbance in children with neurodevelopmental disorders: prospective observational naturalistic study. *Exp Rev Neurother*. 2015;15(6):711–717.
24. Kirov R, Brand S. Sleep problems and their effect in ADHD. *Expert Rev Neurother*. 2014;14(3):287–299.