

Melatonin for Insomnia in Children With Autism Spectrum Disorders

Ivy M. Andersen, MD, JoAnna Kaczmarek, MD, Susan G. McGrew, MD,
and Beth A. Malow, MD, MS

We describe our experience in using melatonin to treat insomnia, a common sleep concern, in children with autism spectrum disorders. One hundred seven children (2–18 years of age) with a confirmed diagnosis of autism spectrum disorders who received melatonin were identified by reviewing the electronic medical records of a single pediatrician. All parents were counseled on sleep hygiene techniques. Clinical response to melatonin, based on parental report, was categorized as (1) sleep no longer a concern, (2) improved sleep but continued parental concerns, (3) sleep continues to be a major concern, and (4) worsened sleep. The melatonin dose varied from 0.75 to 6 mg. After initiation of melatonin, parents of 27 children (25%) no longer reported sleep concerns at follow-up visits. Parents of 64 children (60%) reported improved sleep, although continued to have concerns regarding sleep. Parents of 14 children (13%)

continued to report sleep problems as a major concern, with only 1 child having worse sleep after starting melatonin (1%), and 1 child having undetermined response (1%). Only 3 children had mild side-effects after starting melatonin, which included morning sleepiness and increased enuresis. There was no reported increase in seizures after starting melatonin in children with pre-existing epilepsy and no new-onset seizures. The majority of children were taking psychotropic medications. Melatonin appears to be a safe and well-tolerated treatment for insomnia in children with autism spectrum disorders. Controlled trials to determine efficacy appear warranted.

Keywords: sleep; pervasive developmental disorder—not otherwise specified; Asperger syndrome; melatonin

Sleep problems in children with autism spectrum disorders are common, with a prevalence of 44–83%,¹ and contribute to significant morbidity in children and to familial stress. The most frequent sleep problems in autism spectrum disorders, derived from parentally completed questionnaires and sleep diaries, include sleep-onset insomnia, sleep-maintenance insomnia, and irregularities of the sleep–wake cycle, including early morning awakenings.^{1,2} Melatonin, an endogenous pineal hormone, regulates human circadian rhythms by its action on the suprachiasmatic nucleus in the hypothalamus. Melatonin plays an important role in the sleep–wake cycle, and exogenous melatonin has been used successfully to promote sleep

in children with neurodevelopmental disorders, including Angelman syndrome,³ Smith–Magenis syndrome,⁴ and Rett syndrome,⁵ with minimal adverse effects. Adverse effects of melatonin including enuresis, depression, and excessive daytime somnolence have been reported, with 1 report noting increased seizures in children with profound mental retardation, epilepsy, and sleep–wake cycle disorders.⁶ The optimal effective melatonin dose in children is unclear, with some reports advocating doses of 10 mg or higher.⁷

Blood melatonin and nocturnal excretion of 6-sulphatoxymelatonin, the predominant metabolite of melatonin, are reduced in children with autism,⁸ thereby supporting a role for melatonin supplementation to promote sleep in these children. Several small studies of supplemental melatonin for promoting sleep have included children with autism spectrum disorders,⁹ and 1 prospective investigation was limited to children diagnosed with Asperger syndrome.¹⁰ One recent study showed effectiveness of combined sustained and fast release melatonin in promoting and maintaining sleep in medication-free children with autism spectrum disorders.¹¹ However, the numbers of children in all of these reports have been relatively small (1–42 children). The objective of this investigation is to describe our experience in using melatonin to treat insomnia in a

From the Sleep Disorders Division (IMA, JK, BAM), Department of Neurology and Kennedy Center, and Department of Pediatrics (SGM), Vanderbilt Children's Hospital, Vanderbilt University School of Medicine, Nashville, Tennessee.

Address correspondence to: Beth A. Malow, MD, MS, Vanderbilt University, Department of Neurology, Medical Center North, Room A-0118, 1161 21st Avenue South, Nashville, TN 37232-2551; e-mail: beth.malow@vanderbilt.edu

Andersen IM, Kaczmarek J, McGrew SG, Malow BA. Melatonin for insomnia in children with autism spectrum disorders. *J Child Neurol*. 2008;23:482-485.

large series of 107 children with autism spectrum disorders, emphasizing issues related to safety and tolerability.

Methods

Approval was obtained through the Institutional Review Board at Vanderbilt University to review the electronic medical records of a single pediatrician (S.G.M.) specializing in autism spectrum disorders in Nashville, Tennessee. One hundred eighty children (2–18 years of age) with a clinical diagnosis of autism spectrum disorders based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria¹² were identified in whom use of supplemental melatonin was suggested for treatment of reported sleep concerns. The use of supplemental melatonin was confirmed in 107 children based on the active medication record during follow-up clinical visits. Participants received a clinical diagnosis of autism spectrum disorders from psychologists or clinicians based on parent interviews, child observation, and direct testing. Because childhood bipolar disorder is an evolving diagnostic entity, we excluded these children from our cohort. The dosage and response to melatonin was determined from follow-up clinic notes documenting parental report of sleep concerns.

Melatonin was given 30 minutes to 1 hour before bedtime, and dosed according to the following protocol developed by the pediatrician specializing in autism spectrum disorders. Children less than 6 years of age were started on 0.75 to 1 mg of melatonin. The parents were instructed to increase melatonin by 1 mg every 2 weeks (up to 3 mg) if no response was noted at the lower dose. Children 6 years of age or older were started on 1.5 mg of melatonin, and parents were instructed to increase the dose to 3 mg after 2 weeks if no clinical response was seen at the lower dose. In all children, if no response was seen after 4 weeks, the parents were instructed to increase the melatonin dose to 6 mg. If parents noted daytime sleepiness in their child during melatonin treatment, they were instructed to contact the pediatrician's office so that melatonin could be lowered if necessary. In children with coexisting psychiatric disorders requiring treatment with medications, these medications were started first before melatonin treatment. Parents were instructed to begin melatonin, dosed as indicated above, if sleep problems persisted after 2 weeks in their children, despite the use of these psychotropic medications. Clinical response to melatonin was determined through chart review of clinic notes and parental sleep diaries and categorized as (1) sleep no longer a concern, (2) improved sleep but with continued parental concerns, (3) sleep continues to be a major concern, and (4) worsened sleep.

Sleep problems were categorized as sleep-onset insomnia, sleep-maintenance insomnia, or both based on parental complaints. The diagnostic subgroup of autism spectrum

disorders (autistic disorder, pervasive developmental disorder—not otherwise specified, or Asperger syndrome) along with information on the use of other psychotropic, sedative–hypnotics, and antiepileptic medications was established. Information on the use of sleep hygiene, presence or absence of epilepsy, mental retardation, and other psychiatric diagnoses was documented. Age, gender, autism spectrum disorders subgroup, the type of sleep concern, the presence of mental retardation, seizures, other psychiatric diagnoses, and the use of psychotropic medications were compared across groups using analysis of variance (for age) or χ^2 analyses (for the categorical variables).

Results

Participants

Children were predominantly male (80%) and white (60%), although there were 6% African Americans and 34% with unknown race. Autistic disorder was diagnosed in 71% of subjects, pervasive developmental disorder—not otherwise specified in 19%, and Asperger syndrome in 5%. The average age of onset of sleep disturbance was 6.7 ± 3.8 years, and the average age at start of melatonin was 8 ± 3.9 years. Follow-up visits occurred every 2–6 months, and children were followed up for an average of 1.8 ± 1.4 years after initiation of melatonin. The characteristics of children were similar in each response category to melatonin in terms of age, diagnostic subgroup of autism spectrum disorders, presence or absence of seizures, other psychiatric diagnosis, mental retardation, and sleep problems identified, and confirmed use of sleep hygiene measures. ($P > .1$).

In all children, sleep-onset insomnia alone (23%), sleep-maintenance insomnia alone (8%), both sleep-onset and sleep-maintenance insomnia (68%), or early awakenings (1%) were reported. Epileptic seizures were documented in 21 children (20%), although only 4 children were noted to have refractory epilepsy. Coexisting psychiatric diagnoses were reported in 31 (29%) children, and included attention deficit disorder with hyperactivity, obsessive–compulsive disorder, depression, oppositional defiant disorder, and anxiety disorder.

Melatonin Response and Adverse Effects

The majority of parents reported an improvement in their child's sleep with melatonin treatment. Parents of 27 children (25%) no longer reported sleep concerns at follow-up visits after initiation of melatonin. Parents of 64 children (60%) reported improved sleep; however, they continued to have concerns regarding sleep during follow-up clinic visits. The majority of parents reported an improvement in their child's sleep at the first follow-up clinic visit after initiation of melatonin. This response was

sustained during later follow-up visits in most children, although 18 children had only 1 documented follow-up visit after initiation of melatonin. In 7 children, melatonin was reported by parents to initially improve sleep, although sleep problems returned after 3–12 months, despite dose escalation. Parents of 14 children (13%) continued to report sleep problems as a major concern. One child's parent reported worse sleep after starting melatonin (1%), and 1 child had an undetermined response (1%). The single child with worse sleep had reports of increased early morning waking.

Only 3 children had adverse effects after starting melatonin, which included parental report of morning sleepiness, "fogginess," and increased enuresis. There was no reported increase in seizures after starting melatonin in children with pre-existing epilepsy and no new-onset seizures.

Coexisting Medications and Sleep Hygiene Counseling

Ninety-six (90%) children were taking psychotropic medications during melatonin treatment (Table 1). Forty-five (42%) children were medication-free before starting melatonin, and of these children, 34 were started on other psychotropic medications 2–6 months after melatonin was initiated. In 17 children (16%), psychotropic medications were begun before melatonin, for treatment of coexisting conditions. As noted in the protocol above, parents were instructed to begin melatonin if sleep problems persisted in their children despite the use of these medications. There was no statistical difference in melatonin response between the children who were medication-free when started on melatonin and those who were taking psychotropic medications when started on melatonin. Sleep hygiene techniques, including maintaining a regular bedtime and wake time, establishing a bedtime routine, and avoiding stimulating activities before bedtime, were suggested with the start of melatonin in all children. Confirmation of parental compliance with sleep hygiene recommendations was documented in 65 (58%) of children.

Melatonin Dosage

Melatonin dose ranged from 0.75 to 6 mg. Forty-seven children were started on melatonin at doses of less than 3 mg. In these children, 19 required a dose increase to 3 mg for effect on sleep. Twenty-four children were started on 3 mg, and 1 child required a dose increase to 6 mg for effect on sleep, whereas 1 child required a dose decrease to 1.5 mg secondary to reported grogginess. Seven children were started on doses above 3 mg; of these, 3 children had their doses decreased to 1.5–3 mg with continued improvement in sleep. The majority of children were started on immediate-release melatonin. Only 10 children started on an extended-release formulation; chart review indicated predominantly sleep-maintenance problems in most of these children.

Table 1. Medication Used Concurrently With Melatonin

	Number of Children ^a
Medication-free	11 (10%)
Antidepressants ^b	60 (56%)
Antipsychotics ^c	68 (64%)
Sedative-hypnotics ^d	50 (45%)
Antiepileptics ^e	36 (34%)
Stimulants ^f	46 (43%)
On 1 class	26 (24%)
On 2 classes	33 (31%)
On 3 classes	25 (23%)
On 4 classes	12 (11%)

a. Numbers do not add up to 100% as some children were on more than 1 medication.

b. Citalopram (37), paroxetine (24), fluvoxamine (17), buspirone (12), fluoxetine (8), mirtazapine (7), sertraline (4), escitalopram (2), and venlafaxine (2).

c. Risperidone (48), aripiprazole (23), olanzapine (22), quetiapine (13), ziprasidone (7), clomipramine (3), haloperidol (1), benztropine (1), and lithium (1).

d. Clonidine (39), diphenhydramine (12), clonazepam (8), zolpidem (4), zaleplon (2), alprazolam (2), esopiclone (1), lorazepam (1), and diazepam (1).

e. Oxcarbazepine (21), sodium valproate (14), carbamazepine (8), levetiracetam (7), topiramate (6), lamotrigine (4), tiagabine (2), and zonisamide (1).

f. Methylphenidate (26), dextroamphetamine (22), guanfacine (15), atomoxetine (11), dextromethorphan (3).

Discussion

Melatonin, a dietary supplement, was found to be a safe and well-tolerated treatment of both sleep-onset insomnia and sleep-maintenance insomnia in children diagnosed with autism spectrum disorders. Relatively few and minor adverse effects were reported after starting melatonin, including the absence of new-onset or worsening of previous seizures, despite the high prevalence of seizures in this population. One strength of our sample is that tolerability was documented in a large number of children across a wide age range, diagnoses (autistic disorder, pervasive developmental disorder—not otherwise specified, Asperger syndrome), and in the presence of multiple psychotropic medications.

Although the design of our study does not allow us to assess efficacy, we were impressed that almost all children treated with melatonin and sleep hygiene were reported by their parents to have a beneficial response. Furthermore, this beneficial response was noted at melatonin doses of 3 mg or less in many children. This finding is divergent from previously reported average effective controlled release and immediate release doses of 5.7 mg and 7 mg in children with sleep-wake cycle disorders.⁷

The nature of our study (retrospective and not placebo-controlled), the heterogenous sample, and the presence of confounding variables (eg, concurrent medications, variability of dose, and formulation of melatonin) does not allow us to attribute the reported improvement in sleep to the efficacy of melatonin alone. Despite these limitations, 1 of the strengths of our sample is that it is large and mirrors clinical practice as well as the clinical population treated (eg, children with coexisting psychiatric conditions who require

psychotropic medications in addition to melatonin). Regarding medication use, it should be noted that, when melatonin was added to psychotropic medications, it was because the child was continuing to experience sleep difficulties while taking these psychotropic medications. Therefore, we believe that the observation of improved sleep with administration of melatonin, even in cases where the child was taking psychotropic medications, is still meaningful. Furthermore, we did not find a significant difference in response to melatonin in children who were medication-free before treatment compared with children who were on stable dosage regimens of psychotropic medications before treatment, although we recognize that our small sample size may have limited our ability to detect a statistically significant difference in groups. Future prospective studies will need to carefully control for coexisting medications, as well as for the formulation of melatonin and the dose administered. In addition, these controlled studies will need to account for the effects of sleep hygiene counseling.

Several additional limitations of our study should be noted. First, because melatonin is classified as a dietary supplement and is not regulated by the Food and Drug Administration, formulations may have varied with respect to bioavailability within individual children. Second, we relied upon parental report of clinical response to melatonin. The use of validated measures of sleep, such as polysomnography or actigraphy, would have strengthened parental observations. However, our prior work supports the use of parental reporting of sleep concerns in children with autism spectrum disorders as a reliable indicator of sleep problems, with parental report consistent with polysomnography results.¹³

Despite these limitations, our study provides support that melatonin may be a safe and effective treatment of insomnia for children with autism spectrum disorders. Future prospective randomized blinded placebo clinical trials of melatonin in children with autism spectrum disorders appear warranted. These studies will need to carefully control for the formulation of melatonin, assess dose–response, and account for the effects of sleep hygiene counseling.

Acknowledgments

Dr Shlomo Shinnar provided helpful suggestions about the manuscript. The authors reported no conflicts of interest.

This work was presented in part at the Associated Professional Sleep Societies Annual Meeting, June 2006, Salt Lake City, Utah.

References

1. Richdale AL. Sleep problems in autism: prevalence, cause, and intervention. *Dev Med Child Neurol.* 1999;41:60-66.
2. Williams G, Sears LL, Allard AM. Sleep problems in children with autism. *J Sleep Res.* 2004;13:265-268.
3. Zhdanova, IV, Wurtman RJ, Wagstaff J. Effects of a low dose of melatonin on sleep in children with Angelman syndrome. *J Pediatr Endocrinol Metab.* 1999;12:57-67.
4. Wheeler B, Taylor B, Simonsen K, Reith D. Melatonin treatment in Smith-Magenis syndrome *Sleep.* 2005;28:1609-1610.
5. Miyamoto A, Junichi O, Takahashi S, Okuno A. Serum melatonin kinetics and long-term melatonin treatment for sleep disorders in Rett syndrome. *Brain Dev.* 1999;21:59-62.
6. Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet.* 1998;27:351:1963-1964.
7. Jan JE, Hamilton D, Seward N, et al. Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. *J Pineal Res.* 2000;29:34-39.
8. Tordjman S, Anderson GM, Pichard N, et al. Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder. *J Biol Psychiatry.* 2005;57:134-138.
9. Jan JE, Esperzedl H, Appleton RE. The treatment of sleep disorders with melatonin. *Dev Med Child Neurol.* 1994;36:97-107.
10. Paavonen EJ, Nieminen-von Wendt T, Vanhala R, et al. Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder. *J Child Adolesc Psychopharmacol.* 2003;13:83-95.
11. Giannotti F, Cortesi F, Cerquiglini A, Bernabei P. An open-label study of controlled-release melatonin in treatment of sleep disorders in children with autism. *J Autism Dev Disord.* 2006;36:741-752.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Text Revision. Washington, DC: American Psychiatric Association; 2000.
13. Malow BA, Marzec ML, McGrew SG, et al. Characterizing sleep in children with autism spectrum disorders: a multidimensional approach. *Sleep.* 2006;29:1563-1571.