Autism spectrum disorders and sleep disturbances in a pediatric patient

Nancy Brahm
Doug Stewart

KEYWORDS

autism, sleep disorder, pediatric

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that often presents before the child enters the educational system and is characterized by developmental deficits with impairments in three main areas [1] personal, [2] social, and [3] academic or occupational functioning.[1] The neurodevelopmental disorders represent a group of conditions with an onset early in the developmental period. Sleep disorders are commonly reported by parents of children with an ASD diagnosis with between 50% to 80% of parents reporting sleep problems with their children.[2-5] Problems can be categorized into dyssomnias (problems falling and/or remaining asleep) and parasomnias (abnormal and/or unnatural movements, behaviors, emotions, perceptions, and dreams).[4]

We report the following case of problematic sleep in a pediatric patient diagnosed with ASD, a discussion of the pharmacotherapy and nonpharmacotherapy interventions used to address this problem, and the outcomes of these interventions.

CASE PRESENTATION

A 7-year-old African-American male youth, diagnosed with ASD, was brought to clinic by his mother. The primary concern was his sleep disorder, characterized primarily by an inability to fall asleep. Specifically, his mother stated he would lie in bed for hours or wander about the house without supervision after his mother fell asleep. She feared he would overcome the door locks and elope as he had done when out in public. She reported he eloped from church a few times when supervised by others. He was estimated to have a moderate degree of intellectual disability.

His past medical history was notable for febrile seizures as a toddler and then non-febrile seizures at about three years of age. He was treated with levetiracetam for approximately 12 months, and then this medication was tapered and discontinued at about four years of age with no adverse consequences. His maternal family history is significant for type 2 diabetes mellitus (DM2) and hypertension.

Upon physical exam, a significant amount of psychomotor agitation was noted along with poor eye contact, limited expressive language, echolalia, repetitive behaviors, impulsivity, and lack of interest in interacting with others. He had no dysmorphic features and no neurocutaneous stigmata. Vital signs were within normal limits for his age and gender: heart rate 110 beats/minute, respiratory rate 22 inhalations/minute, blood pressure 108/60 mmHg and oral temperature 98.8°F. He was in the 99th percentile for height and weight (127 cm and 30.4 kg, respectively).[6] To rule out any medical concerns, comprehensive metabolic and lipid panels along with a complete blood count were done. Findings were unremarkable; all results were within normal limits.

He was the first of two children in the family. The mother was 28 years old and the sole caretaker of the children. The patient's younger sister had her first birthday about the time of the appearance of the severe sleep disorder. The sister appears to have no neurodevelopmental disorder. This patient attended a special program in the local public school for children with ASD. By the end of the various trials, he had been removed to home-schooling due to closing of the program and parental preference.

The mother reported he was relatively healthy with mildly persistent asthma well-controlled with fluticasone 110 mcg/dose used twice a day and an albuterol multidose inhaler to be used every 4 hours as needed. A previous diagnosis of atopic dermatitis was in remission. The mother did not smoke. He was toilet trained at 5 years of age, and secondary nocturnal enuresis was recently reported.

A number of medication trials were instituted to address his sleep disorder. Table 1 outlines the medication trials, the duration each agent was used, and the results of the trial. Melatonin 3 mg was initiated first by the parent without consultation with the primary care provider (PCP).

Table 1. Medication trials

Drug	Dose	Changes	Outcome
Melatonin	3 mg at bedtime	Increased dose to 5mg 3 weeks later	Discontinued after 8 week trial due to lack of effect
Clonidine Started March 2011	0.05 mg at bedtime	Titrate increasing doses in 0.05 mg increments every few weeks as needed to achieve sleep up to 0.5 mg at bedtime by week 20	Tapered dose reductions in 0.05 mg increments every five days from week 20 to week 29
Trazodone Started August 2011	50 mg at bedtime following extinction of clonidine	Increased dose to 75 mg 1 week later	Discontinued the following week later due to paroxysmal effect
Hydroxyzine Started August 2011 after trazodone discontinuation	10 mg at bedtime	Increased dose to 20 mg at bedtime 1 week later	Discontinued within 2 weeks due to lack of effect
Ramelteon Started September 2011	4 mg at bedtime	Increased dose to 8 mg at bedtime 3 weeks later	Discontinued 4 weeks later due to lack of effect
Imipramine Started October 2011	25 mg at bedtime	Increased to 37.5 mg in 1 week, 50 mg in 2 weeks, 62.5 mg in 10 weeks and 75 mg in 8 weeks	Continued good response at 75 mg at bedtime for next four months
Guanfacine HCl Started July 2012	0.5 mg at bedtime	Increased to 1 mg four weeks later	Started and continued because patient began to awaken about 3 to 4 hrs. after sleep onset

The medication trials generally resulted in improved sleep onset and variable duration of sleep for several days to weeks, and then loss of apparent effect was reported by the mother. This was true for clonidine throughout the titrations as well as the hydroxyzine trial. Trazodone produced a paradoxical effect of hyperactivity and diminished baseline sleep. Ramelteon had no effect on the patient.

Other medications considered for this patient included guanfacine, but based on the results from the clonidine titration, it was judged as not likely to be effective. However, this medication was initiated nearly one year after intervention with imipramine as an adjunctive therapy when the patient began to have middle of the night awakenings despite satisfactory sleep onset. This may be due to the blockade effects of imipramine on the re-uptake of norepinephrine and 5-hydroxy-tryptamine in addition to reduced norepinephrine plasma concentrations associated with guanfacine use.[7] In addition, guanfacine (immediate release) peaks between 1 to 4 hours but has an elimination half-life between 10 to 17 hours (adults),[8] and the elimination half-life for imipramine is approximately 19 hours.[9] The mechanisms of action and longer elimination half-lives in this combination may have and continue to help maintain sleep in this patient.

Quetiapine was also considered but rejected due to the adverse effects on weight, the potential for glucose dyscontrol, a family history of DM2, and potential movement disorders with long-term use, and the age of the patient. The PCP opted for imipramine because of concomitant nocturnal enuresis (intermittently reported) and clinician experience managing this medication.

Initial experience with imipramine produced little sustained sleep and new onset anorexia. Since the patient had a high body mass index (BMI), we persisted with a slow titration of dose, sleep improved, and anorexia resolved. His nocturnal enuresis was noted to improve before the initiation of imipramine, but we saw additional improvement-to-resolution once he had taken the medication for a few months.

Nonpharmacotherapy interventions were added. After a telephone consultation with a child psychiatrist practicing at an in-patient facility for children with ASD, the mother began using a weighted blanket obtained secondary to a consultation with the Occupational Therapist (week 24 of the medication trials). The mother was counseled on the importance of sleep hygiene recommendations and environmental conditions in his bedroom. She addressed potential contributors to sleep problems by removing distractions, such as favored toys and potential objects of obsession.

DISCUSSION

This case report highlights the challenges encountered in the intervention of sleep disorders in children with ASD. Nonresponse to treatment, paradoxical effects, other adverse drug effects, and (as in this case) only transient

improvement will be commonly seen. The mother of this patient was very diligent about compliance and reporting. She was also patient with the time course of medication adjustments, especially considering the disruption to her own sleep and potential impact on quality of life.

In a survey of community-based pediatricians (n=671), almost one-third reported alpha-agonists were the most frequently prescribed for school-aged youth with insomnia and attention-deficit/hyperactivity disorder. Children and adolescents with a diagnosis of ASD were not identified in these results, and the authors did not distinguish between agents. The need for an evidence-based approach to medication use for these agents was identified.[10]

Use of hydroxyzine was chosen based on the sedative qualities of the medication and a previous diagnosis of atopic dermatitis, also known as atopic eczema. In addition, youth with allergies have reported problematic sleep and daytime fatigue secondary to nasal obstructions. In a small sample of youth (n=14, ages 7 to 16 years) the combination of a topical steroid and antihistamine improved sleep.[11]

The efficacy of antihistamines for pediatric insomnia has not been verified by randomized controlled trials. Use in conjunction was evaluated for nocturnal cough and sleep (n=100). Using a double-blind procedure, participants were grouped by age (2–5 years, 6–11 years, 12–18 years) and randomly assigned to receive dextromethorphan, diphenhydramine, or placebo. Package dosing was followed and given 30 minutes before bedtime. Responses were recorded in a pre- and post- survey. All survey outcomes were significantly improved on the second night of the study regardless of what was used. The active arms (diphenhydramine and dextromethorphan) were not superior compared to placebo. In addition, parental sleep quality did not improve with either active arm compared to placebo.[12]

A retrospective chart review (n=40, 20 each group) comparing the effectiveness of fluoxetine and trazodone for insomnia in adolescents (aged 13–17 years) diagnosed with depression was reviewed. Researchers reported insomnia resolved more rapidly with trazodone than with fluoxetine (2.5 vs. 5.1 days).[13] Paradoxical effects were not reported.

Pediatric pharmacotherapy colleagues were consulted at intervals through these trials. The PCP had no experience prescribing ramelteon but opted to begin a trial after discussion with the clinical pharmacologists. In a review of the literature, positive results were reported in two youths, ages 7 years and 18 years old and with a diagnosis of autism.[14] In the first case report, the 7-year old male experienced delayed sleep onset (several hours) with negative results with risperidone, guanfacine, clonidine, and trazodone. Concurrent use of ramelteon (following a dosage increase to 8 mg) and olanzapine (divided doses with one at bedtime) were associated with improved sleep onset and maintenance. The second patient experienced negative sleep benefits with trials of second generation antipsychotics and diphenhydramine. Clonidine was used in divided doses. Ramelteon 4 mg was added at bedtime with improved sleep onset. No adverse effects were reported for either patient.[14]

A small randomized placebo-controlled double-blind crossover trial (n=11, 7 completing) of melatonin in children with ASD was undertaken. Seven children completed the trial. Sleep latency improved from baseline (2.6 hrs. baseline, 1.91 hrs. placebo, 1.06 hrs. with melatonin). Awakenings per night (0.35 baseline, 0.26 placebo, 0.08 with melatonin) and total sleep duration (8.05 hrs. baseline, 8.75 hrs. placebo, 9.84 hrs. with melatonin) also improved. The authors concluded that use of melatonin in children with sleep difficulties and ASD was beneficial.[15]

In a larger trial of children (n=107) ages 2 to 18 years old diagnosed with ASD, melatonin in doses ranging from 0.75 mg to 6 mg was used. Parents were counseled on sleep hygiene and reported clinical responses to melatonin in one of four categories with the results following each category: (1) sleep no longer a concern (25%), (2) improved sleep but continued parental concerns (60%), (3) sleep continues to be a major concern (13%), and (4) worsened sleep (1%). The response for one child (1%) was not determined. Mild adverse effects reported as morning sleepiness and increased enuresis affected three participants.[16]

Positive results were reported in a 12-week randomized placebo-controlled trial (n=160) involving children ages 4 to 10 years and diagnosed with ASD with the use of melatonin controlled release (CR) as monotherapy or in combination with cognitive behavioral therapy (CBT).[17] Four arms were used: (1) combination of melatonin CR and CBT, (2) monotherapy with melatonin CR; (3) CBT (4 sessions), or (4) placebo. The main outcomes were sleep latency, total sleep time, awakening after sleep onset, and number of awakenings. All active treatment groups improved in all outcome measures. Overall, melatonin treatment was most associated with decreasing insomnia symptoms and CBT with improvements in sleep latency. The combination of melatonin CR and CBT showed the

most improvement.[17] No benefits were found with melatonin use in our patient.

Nonpharmacological interventions also were implemented. Addressing tactile sensory problems included the use of a weighted blanket. The occupational therapist was integral to acquisition of the weighted blanket and instructing the parent in safe use. In children with ASD, use of sensory-based interventions has been associated with improvement in the ability to regulate behaviors, although findings are inconclusive.[18]

One of the key elements for improving insomnia is addressing sleep hygiene with a combination of behavioral, environmental, and pharmacological interventions. Behavioral changes may include the times and types of exercise, restrictions on napping and total sleep time, inclusion of a bedtime snack, and restriction of fluid intake. Environmental changes encompass room and body temperatures, noise, and the presence of light, including use of a television (and the types of programs viewed). Pharmacological interventions include limiting the use of caffeine and alcohol at bedtime. Additional interventions are limits [1] on the use of nicotine and [2] on the use of sedatives and sleeping aids used on an 'as needed' basis.[19] In school-aged children, the availability of one's own room (as opposed to sharing a room), reading as a part of the bedtime routine, avoidance of caffeine-containing beverages at bedtime, no television in the room, and a consistent bedtime routine were recommended.[20]

Addressing obstructive sleep apnea (OSA) is another nonpharmacological intervention. In addition to the challenges of disordered sleep in children with ASD, clinicians are encouraged to rule-out OSA. It has been estimated to occur in approximately three percent of the general pediatric population. The extent to which OSA occurs in the pediatric ASD population is not known.[21] The prominence of daytime drowsiness may not be readily apparent. Hyperactivity, aggression, and other behavioral problems, such as an increase in stereotypies, may be reported more frequently.[21,22] Interventions include polysomnogram diagnostic confirmation, adenotonsillectomy, if indicated, weight loss if the child is obese, and continuous positive airway pressure therapy.[21]

Additional nonpharmacological interventions include the use of light therapy if disruptions in the circadian rhythm are suspected. Problems with the sleep phase, either delayed or irregular, are characteristics of circadian rhythm-mediated insomnia.[22]

Nonpharmacologic interventions in this patient included using a weighted blanket and implementation of sleep hygiene recommendations that included addressing environmental conditions in his bedroom. In addition, a telephone consultation with the child psychiatrist helped the team reinforce the importance of exceptional sleep hygiene. Use of light therapy was not considered for this patient.

A multimodal approach is recommended to address sleep problems in children with ASD. Interventions include behavioral interventions to eliminate or modify factors that contribute to poor sleep. Examples include reducing stimulation near bedtime (i.e., limiting television and caffeine use). Introducing a bedtime routine was another recommendation, as were limiting fluid intake and controlling for noise and room temperature.[19,21] Other nonpharmacological approaches are use of light therapy and ruling-out medical problems. The use of pharmacotherapy is recognized as a treatment modality as well. As with this patient, multiple medication trials may be needed to find the most beneficial agent.

CONCLUSION

At this time, sleep remains stable in our patient with the current regimen. The plan is to reevaluate the patient as clinically indicated, based on subjective parental reports. Based on the literature reviewed and our experience, a multimodal approach with nonpharmacological and pharmacological interventions was needed. Multiple medication trials with time to evaluate the effectiveness were undertaken. With the exception of ramelteon, there have been few published reports for the use of medication for insomnia in children with ASD.

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