

# Sleep Difficulties and Medications in Children With Autism Spectrum Disorders: A Registry Study

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## abstract

**OBJECTIVES:** Sleep difficulties are common in children with autism spectrum disorders, with wide-ranging effects on the child's daytime behavior. We reviewed data within our Autism Speaks Autism Treatment Network Registry to determine the prevalence of sleep difficulties and patterns of medication use.

**METHODS:** Data from 1518 children ages 4 to 10 years were analyzed to determine the number of children documented to have sleep difficulties by parent-completed questionnaires and clinician-completed forms and how these findings related to the use of sleep medications.

**RESULTS:** The Children's Sleep Habits Questionnaire total score was  $\geq 41$  (associated with clinically significant sleep problems in past research) in 71% of children. The prevalence of sleep diagnoses was less frequent (30% of children aged 4–10 years;  $P < .0001$ ). Medications for sleep were prescribed in 46% of 4- to 10-year-olds given a sleep diagnosis. The most common medication used for sleep was melatonin followed by  $\alpha$ -agonists, with a variety of other medications taken for sleep (anticonvulsants, antidepressants, atypical antipsychotics, and benzodiazepines). Children taking medications for sleep had worse daytime behavior and pediatric quality of life than children not taking sleep medications.

**CONCLUSIONS:** Parent concerns about sleep may not be reflected in the information gathered during a clinic visit, supporting the need to develop screening practice pathways for sleep in autism spectrum disorders. Furthermore, many medications taken for sleep have adverse effects, supporting the need for evidence-based interventions in this population.

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Sleep difficulties are very common in children with autism spectrum disorders (ASD), with an estimated prevalence of 50% to 80%.<sup>1-3</sup> Within the Autism Speaks Autism Treatment Network (ATN) Registry, sleep disturbance was found to be a prominent parent-reported concern from early childhood through adolescence.<sup>4</sup> Sleep has been the focus of several other ATN registry studies. In 1 investigation, poor sleep was associated with greater internalizing and externalizing behavior problems and poorer adaptive skill development.<sup>5</sup> In another analysis, children and adolescents defined as poor sleepers were also reported to have higher rates of problems with behavior than were good sleepers, including in the areas of hyperactivity, sensory issues, anxiety, and self-stimulatory behavior.<sup>6</sup> Additional studies utilizing the ATN registry documented that sleep disturbance was associated with aggression,<sup>7,8</sup> anxiety and sensory overresponsivity,<sup>9</sup> and poorer health-related quality of life.<sup>10</sup> Registry studies to date have not examined the relationship between parental concerns related to sleep assessed by using questionnaires versus those reported to clinicians. The use of medications in relation to sleep concerns has also not been examined.

Given this evidence that sleep concerns are both common and associated with daytime symptoms, it is important that primary care providers be vigilant to sleep concerns voiced by parents. However, given parents' multiple concerns regarding their children's behavior, or their belief that poor sleep is "part of autism," parents may not express concerns about sleep to their children's primary care provider.<sup>11</sup>

Even when sleep concerns are raised by parents to primary care providers, additional treatment challenges remain. Causes of sleep difficulties in

children with ASD are often complex and multifactorial.<sup>12</sup> Although some children require medications for treatment, others may require different types of interventions. For example, sleep difficulties may be related to co-occurring medical conditions (eg, epilepsy or gastroesophageal reflux)<sup>13</sup>; these can be challenging to identify in a child with ASD. Causes commonly seen in children with typical development (eg, poor sleep hygiene, behavioral insomnia of childhood) may also be present and be exacerbated by communication challenges unique to autism (eg, difficulty with transitions or with understanding parent expectations regarding sleep). Providers may not have received training, or have the time, to implement behavioral interventions for sleep in children with ASD. Facing the challenge of dealing with sleep concerns raised by a parent, providers may turn to recommending medications despite the limited evidence base for medication use in this population.<sup>11</sup>

We reviewed data from the ATN registry to compare the prevalence of parent-reported concerns about sleep captured on questionnaires with diagnoses of sleep disorders captured by clinicians. We also wished to explore medication-prescribing patterns. This understanding is critical to planning prospective studies of sleep and medication use, which will inform recommendations for evaluating and treating sleep difficulties in this population. We hypothesized that, within our sample, that (1) parent questionnaires and clinician diagnoses of sleep concerns would differ in prevalence in children with ASD, with parents more commonly reporting sleep concerns on questionnaires than to their child's clinician, and (2) the use of medications for sleep would be associated with challenging daytime behaviors and poorer quality of life.

## METHODS

This study received institutional review board approval. Review of the ATN registry documented 1518 children, aged 4 to 10 years, who were enrolled in the ATN between April 2008 and December 2013, had a Registry Diagnosis and Problems form completed by a clinician at any visit, and whose parents also completed the Children's Sleep Habits Questionnaire (CSHQ).<sup>14</sup> The ATN registry contains data from sites across North America dedicated to improving care for children with ASD. Currently there are 14 active sites. The ATN procedures include standardized collection of data such as an autism diagnosis, with all children receiving a clinical diagnosis and the Autism Diagnostic Observation Schedule (ADOS),<sup>15</sup> a diagnostic history and surveillance for co-occurring conditions associated with ASD.

On the Registry Diagnosis and Problems form, autism providers were instructed to indicate medical diagnoses or problems that were observed or, in the case of sleep, that were reported to them by a parent. On a later version of the form, instructions were clarified to the autism providers to include diagnoses and problems that were managed by an ATN clinician, even if they themselves did not manage this problem. The purpose for this change was to ensure that problems being managed by a subspecialist would be captured in the registry even if the clinicians themselves did not manage that problem. Because a preliminary analysis revealed that the prevalence of reporting sleep diagnoses was higher after the form change, we restricted our sample to cases in which the later version of the form had been completed. Thus, the current study includes 13 sites that participated in the data collection using the later version of the form. Although the Registry Diagnosis and Problems form was completed

at each clinician visit, with visits scheduled annually for 3 consecutive years, missing data did not allow us to carry out longitudinal analyses on this data set. Only 3 of the 1518 children (0.2%) in our sample had a complete set of longitudinal data (visits 1, 2, 3, and 4) from the Diagnosis and Problems form; only 41 (2.7%) had data from visits 1, 2, and 3; and only 237 (15.6%) had data from visits 1 and 2. Only 1 CSHQ and 1 Diagnosis and Problems form was included per child.

The categories of sleep disorders documented on the Registry Diagnosis and Problems form were based on the International Classification of Diseases, Ninth Revision (ICD-9), codes and included the following: behavioral insomnia of childhood, inadequate sleep hygiene, organic insomnia unspecified, sleep disturbance not otherwise specified, and other sleep disorder. The Registry Medications form documented medication use. For  $\alpha$ -agonists, melatonin, and other agents, the Registry Medications form allowed a designation that the medication was “taken for sleep.” Sleep disorders and medications were coded as present if they were documented at any visit.

The CSHQ is a validated, parent-completed questionnaire that has been used to examine sleep behavior in children with a variety of conditions.<sup>14</sup> Although initially published based on a sample of children ages 4 to 10 years, it has also been used in toddlers with ASD<sup>16</sup> and adolescents with ASD (although not formally validated in these groups).<sup>4</sup> Therefore, we restricted our sample to children ages 4 to 10 years because the CSHQ has been validated in this age group. Insomnia subscales of the CSHQ include bedtime resistance, sleep anxiety, sleep-onset delay, sleep duration, and night wakings. A CSHQ total score of  $\geq 41$  was used to define sleep disturbance on the basis of previous clinical validation studies.<sup>14</sup>

Other behavioral measures included the Aberrant Behavior Checklist (ABC), the Child Behavior Checklist (CBCL), and the Parent Proxy-Report Pediatric Quality of Life Inventory (PedsQL). The ABC is a 58-item behavioral scale that can be completed by parents.<sup>17</sup> Initially validated for ages 6 and older, it has also been validated in children as young as 14 months.<sup>18</sup> For this project, the Irritability scale was analyzed. The CBCL is a checklist parents complete to detect emotional and behavioral problems in children and adolescents. There are 2 versions, 1 for ages 1.5 to 5 years<sup>19</sup> and 1 for ages 6 to 18 years.<sup>20</sup> For this project, the Internalizing and Externalizing subscales, which are common to both versions, were analyzed. The PedsQL measures health-related quality of life in children and adolescents ranging in age from 2 to 18 years and contains 23 items encompassing physical, emotional, social, and school functioning.<sup>21</sup> The Total scale score was used for this project.

Statistical analyses were performed by using SAS software, version 9.4 of the SAS System for Windows (SAS Institute, Cary, NC). Fisher’s exact tests were performed to compare categorical variables (eg, presence of clinician-diagnosed sleep disorder versus CSHQ score of  $\geq 41$ ) at the level of individual children, and independent-samples *t* tests were performed to compare continuous variables (eg, age, sleep, and behavior scales) with medication status. In addition, *t* tests were used to compare continuous behavior scales with sleep problem status, and Fisher’s exact tests were used to compare sleep problem status by clinician diagnosis versus parent report. A  $\chi^2$  test was used to compare the percentage of sleep diagnoses and the percentage of elevated scores on the CSHQ across sites. The F test for equality of variances was used to compare the variability of the

**TABLE 1** Registry Characteristics

Variable	Values
Age, mean $\pm$ SD ( <i>n</i> ), y	6.6 $\pm$ 1.9 (1518)
Male gender	84 (1267/1515)
White race	81 (1184/1461)
Hispanic ethnicity	7 (108/1469)
IQ $\geq 70$	67 (790/1174)
ADOS Severity scale, mean $\pm$ SD ( <i>n</i> )	7.0 $\pm$ 2.0 (1324)
Sleep disorder ever captured on registry form	30 (457/1518)
CSHQ total score $\geq 41$ ever	71 (1080/1518)
CSHQ total, mean $\pm$ SD ( <i>n</i> )	46.4 $\pm$ 9.4 (1501)
Any medication ever taken for sleep	24 (371/1516)

Data are presented as percentages (*n*/*N*) unless otherwise indicated. Due to missing data, “*n*” for each variable may be less than the total sample “*N*”.

percentage of sleep diagnoses with the variability of the percentage of elevated scores on the CSHQ across sites. Significance was set at the .05 level.

## RESULTS

Table 1 presents summary characteristics of the ATN registry sample for the 2 age groups. The sample was predominantly male and white, with additional participants reported as black or African (6%), Asian (5%), and other or multiracial (9%). The sample was predominantly of non-Hispanic ethnicity (93%). The Diagnosis and Problems form captured sleep-disorder diagnoses in 30% of children. The CSHQ total score was  $\geq 41$  in 71% of children. The proportion of children with an elevated CSHQ total score was higher than the proportion of children diagnosed with a sleep disorder by an ATN clinician ( $P < .0001$ ). By using the CSHQ form as the “gold standard,” with a CSHQ score of  $\geq 41$  considered a positive finding on this form, the sensitivity and specificity of the clinician report (any problem considered positive for sleep disturbance) were 38% and 88%, respectively. The median time between completing the CSHQ and the Diagnosis and Problems form was 76 days.

Table 2 presents the percentages of sleep diagnoses in the ATN registry sample for the 2 age groups (calculations only included those who had received any sleep diagnosis). The most common diagnosis in both groups was sleep disturbance not otherwise specified.

Table 3 presents the percentages of medications indicated as “taken for sleep.” Medication use was higher in those children with sleep diagnoses captured on the Registry Diagnosis and Problems form compared with those not receiving sleep diagnoses ( $P < .001$ ). The exception was children whose sleep diagnoses were limited to either inadequate sleep hygiene or behavioral insomnia of childhood; children with 1 of these diagnoses (and no others) were not more likely to be taking medications. However, 19 of 65 children (29%) in this category were taking a sleep medication. Twenty-four percent of children were taking medications regardless of whether the Registry Diagnosis and Problems form captured a sleep diagnosis.

Apart from  $\alpha$ -agonists and melatonin, the following categories of medications were recorded on the registry form as “taken for sleep”: antidepressants, antihistamines, atypical antipsychotics, benzodiazepines,  $\beta$ -blockers, sedatives, iron supplements, and vitamins/dietary supplements (Table 3 footnote “a” lists all of the

medications reported as taken for sleep). Of those children documented to have a sleep diagnosis on the registry form, 37% of children were taking 1 medication for sleep, 7% were taking 2 medications for sleep, 2% were taking 3 medications for sleep, and <1% were taking 4 medications for sleep (total of 46% taking at least 1 medication for sleep).

Table 4 presents CSHQ and behavioral data for children taking medications for sleep compared with those who were not taking medications for sleep. All of the insomnia subscales of the CSHQ were significantly higher in those taking medications for sleep. Significantly lower (worse) scores on the PedsQL and significantly higher (worse) scores on the CBCL Internalizing and Externalizing scales and Irritability scale of the ABC were noted in those taking medications for sleep.

Table 5 presents the site-specific data. For all sites, the proportion of CSHQ scores that were  $\geq 41$  (71%) was higher than the sleep diagnoses captured on the Diagnosis and Problems form (30%). The variability of the percentage of sleep diagnoses (SD = 16.0) over the 13 sites was greater than the variability of the percentage of elevated scores on the CSHQ (SD = 6.3;  $P = .0031$ ). The rate of elevated CSHQ scores ( $P = .0018$ ) and sleep diagnoses ( $P < .0001$ ) differed by site.

## DISCUSSION

The key findings of this study support our hypotheses that sleep concerns are commonly reported by parents and clinicians, medications are commonly used for sleep difficulties, and medication use for sleep is associated with challenging daytime

**TABLE 2** Sleep Diagnoses Documented in ATN Registry

Variable	Participants, % (n) (n = 457)
Behavioral insomnia of childhood	13 (61)
Inadequate sleep hygiene	14 (65)
Organic insomnia unspecified	10 (46)
Sleep disturbance not otherwise specified	69 (315)
Other sleep disorder	13 (60)

Data are limited to the sample who received a sleep diagnosis. Because some children were given >1 sleep diagnosis, the sum of the individual categories is >100%.

**TABLE 3** Medications Recorded as “Taken for Sleep” by Participants at Any Visit by Presence of Sleep Diagnosis

Medication Class	With Documented Sleep Diagnosis, % (n) (n = 456)	Without Documented Sleep Diagnosis, % (n) (n = 1060)	P
Any medication <sup>a</sup>	46 (211)	15 (160)	<.001
$\alpha$ -Agonists	14 (63)	2 (25)	<.001
Melatonin	36 (166)	13 (136)	<.001

Data were missing for 1 child in each group; therefore, “n” = 456 rather than 457 and 1060 rather than 1061.

<sup>a</sup> Apart from  $\alpha$ -agonists and melatonin, the following medications were recorded as “taken for sleep”: amitriptyline, aripiprazole, carbamazepine, chloral hydrate, cetirizine, coenzyme Q10, diphenhydramine, fluticasone, fluvoxamine, hydroxyzine, iron supplements, lamotrigine, lorazepam, levetiracetam, mirtazapine, nortriptyline, omega-3, paroxetine, propranolol, quetiapine, thiamine, topiramate, trazadone, vitamin B-12, and zonisamide. Some children were taking >1 medication.

**TABLE 4** CSHQ and Behavioral Variables by Medication Use

Variable	Ever Taking Medications for Sleep (n = 371)	Not Taking Medications for Sleep (n = 1145)	P
CSHQ			
Total	49.7 $\pm$ 9.8	45.3 $\pm$ 9.0	<.001
Bedtime Resistance	9.4 $\pm$ 3.2	8.9 $\pm$ 3.3	.016
Sleep-Onset Delay	1.9 $\pm$ 0.8	1.6 $\pm$ 0.7	<.001
Sleep Duration	5.0 $\pm$ 1.9	4.0 $\pm$ 1.5	<.001
Sleep Anxiety	6.8 $\pm$ 2.3	6.1 $\pm$ 2.2	<.001
Night Wakings	5.0 $\pm$ 1.8	4.4 $\pm$ 1.6	<.001
Peds QL–Total	58.4 $\pm$ 14.9	64.9 $\pm$ 15.2	<.001
CBCL			
Internalizing	65.2 $\pm$ 9.4	62.8 $\pm$ 9.6	<.001
Externalizing	63.0 $\pm$ 10.8	59.7 $\pm$ 11.2	<.001
ABC-Irritability	18.0 $\pm$ 10.8	14.2 $\pm$ 9.6	<.001

Data are presented as means  $\pm$  SDs. Due to missing data, “n” for each variable may be less than the total sample “N”.

**TABLE 5** Sleep Disorders and CSHQ Results by Site

ATN Site	Total <i>N</i>	Any Sleep Diagnosis, <i>n</i> (%)	CSHQ $\geq 41$ , <i>n</i> (%)
1	137	5 (3.7)	89 (65.0)
2	223	100 (44.8)	180 (80.7)
3	140	68 (48.6)	99 (70.7)
4	72	27 (37.5)	53 (73.6)
5	91	29 (31.9)	61 (67.0)
6	109	49 (45.0)	87 (79.8)
7	137	8 (5.8)	90 (65.7)
8	198	26 (13.1)	137 (69.2)
9	109	41 (37.6)	84 (77.1)
10	114	51 (44.7)	67 (58.8)
11	70	12 (17.1)	47 (67.1)
12	49	11 (22.5)	37 (75.5)
13	69	30 (43.5)	49 (71.0)
Total	1518	457 (30)	1080 (71)

behaviors and poorer quality of life. To our knowledge, this is the largest study in children with ASD to examine sleep difficulties in relation to medication use. Additional strengths of our work are the inclusion of both younger and older children and a well-characterized sample, with careful attention to autism diagnosis.

Parent report of sleep concerns, as defined by a CSHQ score of  $\geq 41$ , was 71%, which is consistent with the prevalence reported in previously published studies of 50% to 80%.<sup>1-3</sup> The report of sleep diagnoses captured on a clinician report was much lower (30%), and when examined at a site level, was even more variable. There are several possible reasons for this discrepancy. First, because of the many needs of children with ASD, sleep concerns may be eclipsed by these other needs, especially in the limited time available at a clinician visit. Site variability may have resulted from how attuned clinicians were to asking parents about sleep, how vocal parents were about expressing sleep concerns, or other factors. Working with both primary care providers and autism medical specialists in a collaborative fashion to further develop and implement practice guidelines for sleep may be warranted. This process would include developing a standard procedure for eliciting a history

of sleep concerns from parents during a clinical visit. The ATN has developed a practice pathway for insomnia that includes attention to diagnosis as well as treatment and follow-up, although it will require comprehensive testing to determine its usefulness in clinical practice.<sup>11</sup> Second, in light of the high prevalence of reporting sleep disturbance not otherwise specified as a diagnosis, clinicians may not have been familiar with the criteria for other ICD-9 sleep diagnoses. Finally, the cutoff score of 41 used on the CSHQ may be too low for use in ASD, especially in younger children. In the initial CSHQ validation study, a total score  $>41$  differentiated children in a sleep clinic sample from children in the general population who were ages 4 to 10.<sup>15</sup> Additional work is needed to establish appropriate cutoff scores for the CSHQ in the younger and older populations.

Medications for sleep were commonly used in children, with many taking  $>1$  medication for sleep. Even those children whose Diagnosis and Problems form did not capture a sleep diagnosis had a relatively high prevalence of medication use for sleep. This finding may be due to the clinician no longer considering a sleep diagnosis active because it was adequately treated with medication. A variety of medications with the potential for side effects were taken in both

the younger and older children.

This finding supports the need for evidence-based trials of medications for sleep in this population. Medications were also prescribed in children whose forms captured a diagnosis only consistent with behavioral insomnia of childhood and inadequate sleep hygiene, although to a lesser extent than in children with other sleep diagnoses. Given that behavioral insomnia of childhood and inadequate sleep hygiene were commonly diagnosed sleep disorders, treatments that emphasize parent sleep education either alone or in combination with medications appear to be warranted.<sup>22,23</sup> These behavioral treatments, including those emphasizing a calming bedtime routine and soothing sleep environment, are also effective for other forms of insomnia, including those related to core deficits of ASD.

We found that medication use for sleep was associated with more challenging daytime behaviors and lower quality-of-life scales. It is possible that sleep disturbance itself is driving this relationship. It is also possible that a clinician would be more likely to use a medication for sleep in a child with more difficult daytime behaviors. This association of medication use for sleep with more challenging daytime behaviors and lower quality-of-life scales suggests that either (1) the sleep medications were not successfully treating sleep disturbance or (2) the sleep medications, even if successfully treating sleep disturbance, were not favorably affecting daytime behaviors and quality of life. Because of the nature of the registry, we were not able to establish causality. However, these findings underscore the need for both longitudinal and interventional studies to determine whether improvement of sleep disturbance with medications also improves daytime behaviors and quality of life.

Our finding that 46% of children aged 4 to 10 years with sleep diagnoses were taking at least 1 medication for sleep suggests that medication use for sleep is common in the ASD population. Although the literature does not provide the prevalence of sleep medication used in children without ASD, a survey of community-based pediatricians reported prescribing sleep medications more frequently for children with ASD (38% of physicians) than those with typical development (23% of physicians).<sup>24</sup> Although these survey findings likely reflect the higher prevalence of sleep problems in ASD than in the general population, our work and that of others<sup>25,26</sup> underscore the importance of regarding patients with ASD as a priority population in the treatment of pediatric sleep disturbance.

Our work has several limitations. First, the ATN registry data did not include longitudinal data needed to tease out the relationship between medication use and sleep diagnosis. As noted above, children taking

medications for sleep may not have had a sleep diagnosis captured at subsequent visits if the medication treated the sleep problem. Second, given the nature of the registry, we used broad categories to capture sleep diagnoses and medications. As mentioned earlier, clinicians may not have been familiar with the criteria for the ICD-9 codes for the different sleep diagnoses. Third, the information on which children were “prescribed” medications is not available. Thus, the data only capture children taking medication on the basis of parent report (ie, usage rates are not exactly equivalent to prescription rates). Fourth, we did not capture how many children received behavioral sleep education in conjunction with medications. Finally, the registry did not include sufficient data to assess change in sleep diagnoses or medication usage over time. The ATN recently added longitudinal data collection to better define the trajectory of sleep problems and other medical co-occurring conditions.

In summary, our findings provide support that medication use for sleep is common in children with ASD. Because many of these medications may have adverse effects, studies of interventions for sleep appear to be warranted, along with the development and implementation of guidelines for increasing clinician diagnosis of sleep disorders in children with ASD.

#### ABBREVIATIONS

ABC: Aberrant Behavior Checklist  
ADOS: Autism Diagnostic Observation Schedule  
ASD: autism spectrum disorder  
ATN: Autism Treatment Network  
CBCL: Child Behavior Checklist  
CSHQ: Children's Sleep Habits Questionnaire  
ICD-9: International Classification of Diseases, Ninth Revision  
PedsQL: Pediatric Quality of Life Inventory

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