Characterization of Sleep Habits and Medication Outcomes for Sleep Disturbance in Children and Adults With Angelman Syndrome

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Accessibility
Characterization of sleep habits and medication outcomes for sleep disturbance in children and adults with Angelman syndrome

Running Title: Sleep Disorder and Treatment in Angelman Syndrome

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Abstract

The objectives of this study were to characterize the sleep habits of 50 clinically referred individuals with Angelman syndrome (AS) and to retrospectively compare the effectiveness/tolerability of the three most commonly prescribed sleep medications in the sample.

An experienced physician assigned a Clinical Global Impressions-Severity scale (CGI-S) score for each subject’s AS-specific symptoms. Caregivers completed the Child Sleep Habits Questionnaire (screen for sleep problems in school-aged (4-10 years) children), a screening assessment for sleep problems. Caregivers provided information about medication trials targeting disturbed sleep, with the physician assigning a CGI-Improvement scale (CGI-I) score for each trial.

Linear regression showed significant negative association between age and CSHQ score. In their lifetime, 72% of participants had taken a medication for sleep, most commonly melatonin, clonidine and trazodone. The majority continued these for six months or longer. With these medications, many demonstrated significant improvement in sleep disturbances, with no difference in odds of improvement between medications.

Disturbed sleep was common in this cohort and significantly worse in younger-aged participants. The majority received at least one medication trial for disturbed sleep and each of the most commonly prescribed medication was effective for a substantial percentage of participants. Most participants remained on medication for at least six months, suggesting favorable tolerability.

Key Words: Angelman syndrome, Sleep Disturbance, Melatonin, Clonidine, Trazodone
INTRODUCTION

Angelman syndrome (AS) is a neurogenetic disorder with an estimated prevalence of one in 22,000-56,000 individuals (Oiglane-Shlik et al., 2006; Mertz et al., 2013; Luk & Lo, 2016). AS is characterized by core features which include severe developmental disability, movement or balance disorder, limited expressive verbal ability, and a behavioral phenotype of frequent smiling/sociability. Associated features include comorbid seizure disorder, hyperactivity, aggressive behavior and sleep disturbance (Williams et al., 2006). The disorder is secondary to an absent or dysfunctional maternal ubiquitin-protein ligase E3A gene (UBE3A) (Kishino, Lalande, & Wagstaff, 1997). Haploinsufficiency in the maternal UBE3A leading to AS is known to occur via four potential mechanisms. The most common mechanism, representing about 70% of cases, involves a de novo maternal deletion of the UBE3A. Other subtypes include paternal uniparental disomy, imprinting defects and mutations specifically occurring in the maternally inherited copy of UBE3A (Bird, 2014).

Some estimates have found that as many as 80% of individuals with AS may have challenges with sleep, with those in early childhood most affected (Thibert, Larson, Hsieh, Raby, & Thiele, 2013; Clayton-Smith, 2001). This is significantly higher than the prevalence in neurotypical preschool-aged children, estimated to be about 25% (Sheldon et al., 2005). These sleep disturbances in AS appear to be most prevalent in early development through early childhood (Pelc, Cheron, Boyd, & Dan, 2008); however, sleep problems may persist for many individuals into the teenage years and adulthood (Bruni et al., 2004). Parental reports of sleep disturbance tend to be concentrated in specific domains, with 72% of parents reporting difficulty falling asleep, 66% reporting difficulty staying asleep, and 49% reporting reduced total sleep time (Conant, Thibert, & Thiele, 2009; Larson, Shinnick, Shaaya, Thiele, & Thibert, 2015).
Reduced sleep quality in those with AS has the potential to impact neurocognitive development and learning and contribute to behavioral disturbances. One case series found an association between disturbed sleep and the severity of epilepsy; however, it remains unclear whether poor sleep itself directly worsened the seizure course (Conant, Thibert, & Thiele, 2009). While the impact of sleep disturbance on brain development and cognitive function in individuals with AS requires further investigation, the impact on parent and caregiver wellbeing has been clearly documented. Poor sleep in individuals with AS is implicated in parent/caregiver stress and reduced quality of life (Allen, Kuhn, DeHaai, & Wallace, 2013). Poor sleep may contribute to the finding that parents of children with AS have higher psychological distress compared to parents of children with other rare genetic abnormalities (Griffith et al., 2011).

Proposed etiologies for the high prevalence of sleep disturbance in AS include genetic, medical and behavioral mechanisms. In addition to removing maternal UBE3A, the common deletion causing AS also affects three Gamma-Aminobutyric Acid type A (GABA<sub>A</sub>) receptor subunits: beta-3, alpha-5 and gamma-3 (Minassian et al., 1998). Aberrant functioning in specific GABA<sub>A</sub> receptor subunits may play a role in both seizure course (Lossie et al. 2001) and the disrupted sleep-wake cycle (DeLorey et al., 1998) in individuals with AS. Systematic parent/caregiver interviews have identified co-occurring medical and behavioral issues as contributing factors in the frequent nighttime awakenings seen in AS (Trickett, Heald, & Oliver, 2017).

Despite the high prevalence of sleep disorders in AS, there are a limited number of published treatment studies for disrupted sleep. The potentially multi-factorial nature of sleep problems in AS can make identifying an effective treatment challenging. For example, it may be necessary to obtain a sleep or wake electroencephalogram (EEG) if epileptic activity throughout
the night is suspected. Agitation in response to separation from preferred caregivers may complicate attempts to establish a calming bedtime routine. Incontinence overnight may exacerbate the frequency and duration of mid-nocturnal awakenings.

The current first-line treatment for sleep disturbance in AS is behavioral therapy (Pelc, Cheron, Boyd, & Dan, 2008; Robinson-Shelton & Malow, 2016). However, one study found low usage of such interventions (Didden, Korzilius, Smits, & Curfs, 2004) possibly due to limited availability of and insurance coverage for behavioral specialists. Melatonin has been the most extensively studied pharmacologic treatment for sleep disturbance in AS. A randomized placebo-controlled trial found that melatonin improved several domains of sleep (Braam, Didden, Smits, & Curfs, 2008). Despite these encouraging results, melatonin is not effective for all patients with AS, and there are no other randomized controlled trials examining the safety and efficacy of other agents. Benzodiazepines have been shown to have some effectiveness, but not enough to support their widespread use in individuals with AS (Wheeler, Sacco, & Cabo, 2017). Other sleep medications, including trazodone, are frequently used clinically, but have no published studies in support of their use in AS (Blackmer & Feinstein, 2016). To date, there are no published studies comparing the effectiveness of sleep medications in the AS population.

The purpose of the study was to characterize the sleep habits of a cohort of 50 clinically referred children, adolescents and adults with AS and to retrospectively compare the effectiveness and tolerability of melatonin, clonidine and trazodone, the three most frequently prescribed sleep medications in the study cohort.

**METHODS**

*Editorial Policies and Ethical Considerations*
The study was approved by the Partners Human Research Committee (PHRC) institutional review board. Informed consent was provided by a parent for all subjects; no subjects were capable of providing assent due to impairments in cognitive function and expressive language.

Subjects

Data were obtained from a study aiming to characterize anxiety in subjects with AS funded by the Angelman Syndrome Foundation (ASF). Though participants may have had more problematic behaviors than the general population with AS, they were not selected based on sleep disturbance. Data were collected from children, adolescents and adults with AS and their primary caregivers in a 2-4 hour in-person interview. Subject recruitment information was sent via letters to outpatients at the Massachusetts General Hospital (MGH) Angelman Syndrome Clinic. Study information was also posted to the “Current Research” page on the ASF website. Twenty-three of the 50 subjects were recruited during the 2016 ASF annual meeting. Twenty-seven were recruited from among existing patients seen at the MGH AS Clinic.

Subject inclusion criteria were as follows: 1.) diagnosis of AS by a physician with expertise in the evaluation of patients with neurodevelopmental disorders and confirmed via genetic testing and 2.) availability of one of the subject’s primary caregivers for the interview. Subjects were from 19 different states across the nation as well as Mexico and the United Kingdom. All interviews were conducted between 2016 and 2018. Subjects’ caregivers signed release of information to obtain results of genetic testing. All caregivers interviewed for the study were fluent in English.
Assessment Instruments

The interview consisted of collection of age, gender, and other demographic information as well as a review of developmental and family history. A clinician experienced in care for patients with AS recorded comorbid medical conditions. Finally, standardized rating scales were administered. The severity of subjects’ symptoms specific to AS was measured using the Clinical Global Impressions-Severity scale (CGI-S) by a consistent evaluator for all subjects experienced in the treatment of patients with AS. The CGI-S consists of a single 7-point Likert item, with scores ranging from 1 (“normal, not at all ill”) to 7 (“among the most extremely ill patients”). In the absence of a standardized assessment tool that captures the heterogeneity in areas of impairment due to AS (motor, sleep, speech, neurologic and behavioral), the CGI-S was used to measure the construct of “severity of AS.” There is precedent for use of the CGI-S to capture severity of other heterogeneous neurodevelopmental disorders such as Autism Spectrum Disorder (Klaiman, Huffman, Masaki, & Elliott, 2013). All CGI-S assessments were performed by the same clinician who had expertise in both the use of the CGI-S and clinical care for children, teens and adults with AS. In cases where severity of impairment differed among domains, the evaluator took into account the total amount of support in functioning required as compared to other individuals with AS.

Caregivers were asked to recall details of both the subject’s current medications and previous medication trials including treatment target, dosage, age at which medication was started, duration of treatment, and degree of improvement for each medication (see below). Data for medications targeting sleep or insomnia were of primary interest in the current study. Data on medication use for other treatment targets were incorporated in descriptive and sensitivity analyses. Based on the caregiver’s assessment of improvement in the treatment target for each
medication, the evaluator provided an improvement rating using the Clinical Global Impressions-Improvement scale (CGI-I). The CGI-I is a 7-point Likert item scale, with scores ranging from 1 (“very much improved”) to 7 (“very much worse”).

Caregivers also completed the Child Sleep Habits Questionnaire (CSHQ), an assessment tool used to screen for sleep problems in school-aged (4-10 years) children. The CSHQ is caregiver reported, providing a benefit over other questionnaires that require self-report of sleep habits, which can be limited by cognitive ability. In addition, it has demonstrated validity and reliability in several neurodevelopmental disorders (Goodlin-Jones, Sitnick, Tang, Liu, & Anders, 2008) and has been used to characterize the sleep of individuals with Angelman Syndrome into adolescence (Goldman, Bichell, Surdyka, & Malow, 2012). The tool includes 33 distinct items grouped into 8 subscales: bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night-waking, parasomnias, sleep disordered breathing, and daytime sleepiness. Caregivers indicate frequency of the sleep behavior during a typical week as “usually,” “sometimes” or “rarely” with higher scores indicating worse sleep problems or behaviors and caregivers are asked to rate if certain items are a problem with “yes” or “no” (Owens, Spirito, & McGuinn, 2000). Questions on total sleep time, duration of night awakenings, and time of morning awakening are also included.

Statistical Methods

Demographic and clinical characteristics of the sample were summarized using means, standard deviations, frequencies, and percentages, as appropriate. Sleep habits and use of sleep medications were characterized using means, standard errors, frequencies, and percentages. Sleep habits were tabulated both for the sample as a whole and for subgroups defined by age and
genetic etiology. Medication usage data were tabulated for the full sample and for the three most frequently reported sleep medications. Ninety-five percent confidence intervals (CIs) were computed for percentages reported in the Results using Wilson’s method.

Linear regression using type HC3 robust standard errors (Long & Ervin, 2000) characterized the association between age and caregiver-rated sleep problems as determined by the CSHQ total score. The method of fractional polynomials assessed for evidence of violation of the assumption of a linear association of CSHQ score with age (Royston & Altman, 1994). Ordinal logistic regression compared odds of improvement as rated by the CGI-I between the three medications most frequently used for sleep. Kaplan-Meier survival curves characterized time to discontinuation of the three most common medications, accounting for censoring due to current treatment. Cox proportional hazards regression compared hazard of discontinuation between the three medications. Because some subjects had a history of taking multiple medications for sleep concurrently or sequentially, they contributed more than one observation to sleep medication regression analyses. For this reason, confidence intervals for odds ratios and hazard ratios and associated hypothesis tests used robust standard errors accounting for clustering of observations within subjects. Regression analyses controlled for severity of AS (all models), age of subject when medication was started (ordinal logistic regression and Cox regression models), and mechanism of genetic inheritance (ordinal logistic regression and Cox regression models). Relevant effect size estimates and associated 95% CIs from regression analyses were computed whether or not associations were statistically significant. Post-hoc analyses obtained estimated effect size estimates without adjustment for control covariates and with adjustment for number of concomitant medications, concomitant sleep medication, concomitant anxiety medication, and concomitant seizure medication at start of treatment.
For determining age of first use and duration of use of sleep medications, in cases when caregivers provided a range of possible dates a medication was started or stopped, the date in the middle of the range was imputed. Medication trials for which no dates were provided were excluded from relevant analyses. All statistical tests were two-sided and conducted at the test-wise alpha=0.05 significance level. Due to their small size and our low power to detect clinically meaningful differences, we did not compare subgroups defined by age and genetic etiology using statistical tests. Data analysis was conducted using Stata (version 14), and SAS (version 9.4) statistical software.

RESULTS

Demographics and Clinical Characteristics: The characteristics of the sample are summarized in Table 1. The mean age of the sample was 16.8 years (SD = 9.8 years), with a relatively even distribution of children, adolescents and adults. Participants were generally white (96%) and male (60%), coming from households making over $90,000 (67%). The majority of parents held an advanced graduate or professional degree (50%). All participants had a CGI-S score between 4 and 6, with most having a score of 5 (“markedly ill”) (68%). Participants with a maternal deletion mechanism of inheritance accounted for 68% of the sample. The most commonly reported medical comorbidities were gastrointestinal conditions (90%) and epilepsy (82%).

CSHQ Scores: Specific questions related to known areas of concern in AS (sleep initiation, mid-evening awakening frequency/duration, and early morning awakening) per previous studies (Conant, Thibert, & Thiele, 2009; Larson et al., 2015) are shown in Table 2. Younger participants, including those 12 years and younger and between 13 and 17 years, had a higher
mean CSHQ score (M = 50.3, SEM = 1.8 and M = 51.3, SEM = 1.7, respectively) than those 18 years and older (M = 44.6, SEM = 1.2). This observation was reflected in the results from our linear regression showing a significant inverse association between age and CSHQ score (t(46) = -2.84, p=0.007). Controlling for severity of AS, for every five-year age increase, mean CSHQ score decreased by 1.4 (95% CI -2.3: -0.5) points, corresponding to net improvement on 1-2 of the 33 sleep behaviors assessed on the CSHQ. We found no significant evidence of a non-linear association between age and CSHQ score using the method of fractional polynomials (p=0.79); in other words, the linear model appeared to fit the data reasonably well.

Forty-nine out of 50 caregivers (98%, 95% CI 90%: 100%) reported that one or more sleep habits were a problem, with a mean number of 8.0 (SEM=0.8) sleep habits reported to be problems. Mean number of sleep hours per night was 8.1 hours (SEM = 0.3 hours). Twenty out of 50 participants (40%, 95% CI 28%: 54%) sometimes or rarely fell asleep within 20 minutes of going to bed, with 12 out of 19 caregivers considering this a problem (63%, 95% CI 41%: 81%, one response missing). Thirty-eight out of the 50 participants (76%, 95% CI 63%: 86%) awoke once during the night and 24 out of the 50 participants (48%, 95% CI 35%: 61%) awoke more than once during the night sometimes or usually, with 27 out of 38 caregivers of those waking once (71%, 95% CI 55%: 83%) and 22 out of 24 caregivers of those waking more than once (92%, 95% CI 74%: 98%) considering this a problem. Caregivers of eight participants (16%, 95% CI 8%: 29%) endorsed both “usually fell asleep within twenty minutes” and “rarely woke once or more than once.” Mean duration of nighttime awakenings among the 39 participants who awoke during the night sometimes or more often was 47.7 minutes (SEM = 7.7 minutes). Ten participants (20%, 95% CI 11%, 33%) had a usual time of day to awake earlier than 6:00 am (from 4:00-5:45 am).
Treatments for Sleep Disturbance: Descriptive statistics summarizing medication usage are presented in Table 3. Thirty-six out of 50 participants (72%, 95% CI 58%: 83%) had taken a medication for sleep in their lifetime. The most common medications ever used for sleep included melatonin (20/50 or 40% of participants, 95% CI 28%: 54%), clonidine (17/50 or 34% of participants, 95% CI 22%: 48%), and trazodone (16/50 or 32% of participants, 95% CI 21%: 46%). Of these three medications, the mean age of first usage for melatonin was the lowest (M = 7.4 years, SEM = 1.1 years), with more participants currently taking it (14/50 or 28% of participants, 95% CI 21%: 46%) compared to clonidine or trazodone (10/50 or 20% of participants each, 95% CI 11%: 33%).

Survival curves for time to medication discontinuation by medication are displayed in Figure 1. The majority of subjects continued these medications for six months or more. Using proportional hazards regression, and controlling for AS severity, age of subject at start of medication, and mechanism of inheritance, time to discontinuation did not differ among the three most commonly used medications ($\chi^2 (2)= 0.27, p=0.87$). The estimated hazard ratios comparing hazard of discontinuation for clonidine and trazodone to melatonin were 1.4 (95% CI 0.4: 4.7 clonidine; 95% CI 0.4: 5.1 trazodone). In other words, based on our model, we would estimate that those taking clonidine and trazodone were 40% more likely to stop using their medication at any point during treatment than those taking melatonin.

According to CGI-I ratings, 9 out of 20 participants taking melatonin (45%, 95% CI 26%: 66%), 8 out of 17 participants taking clonidine (47%, 95% CI 26%: 69%), and 10 of 16 participants taking trazodone (63%, 95% CI 39%: 82%) experienced clinically significant improvement (defined as a CGI-I rating $\leq 2$). However, no ratings of “very much improved,”
corresponding to a CGI-I rating of 1, were recorded for the three medications. Using ordinal logistic regression, controlling for AS severity, age of subjects when medication was started, and inheritance mechanism, we found no significant difference in odds of improvement between medications ($\chi^2 (2)=1.17, p=0.56$). Estimated odds ratios comparing improvement on trazodone and clonidine to improvement on melatonin were 1.3 (95% CI 0.3: 5.0) for clonidine and 2.8 (95% CI 0.47: 16.3) for trazodone. In other words, based on our model, those taking clonidine had 30% higher odds of improvement than those taking melatonin, and those taking trazodone had nearly three times the odds of improvement as those taking melatonin. Because of the apparent discrepancy between the high adjusted odds ratio for trazodone and the similar CGI-I ratings distributions among the medications, we refit the model without adjustment for control covariates in a post-hoc analysis. Without adjustment, the estimated odds ratio for trazodone was 1.6 (95% CI 0.4: 6.6), confirming that the addition of control covariates substantially increased the estimated odds ratio for trazodone.

**DISCUSSION**

This study is the first systematic investigation and comparison of sleep medications used in a clinically referred cohort of participants with AS with well characterized sleep problems. The distribution of the sample was representative of the genetic mutations present in the AS population, with about 70% being maternal deletion (Bird, 2014). The sample included a range of both age and severity of illness as measured by the CGI-S.

Selected items from the CSHQ support the conclusion that this sample has a high severity of sleep disturbances. While 16% of participants reportedly “fell asleep within twenty minutes and rarely woke once or more than once,” they may have had sleep problems not captured by the
specific items used. Seventy-eight percent of the sample reported waking up once or more during the night at least sometimes, with 26% waking usually more than once. Of those with night awakenings, the participants spent a mean of 47.7 minutes awake before falling asleep. Furthermore, a relatively large percentage of total participants (20%) had early morning awakenings between 4:00 am and 5:45 am. Mean values for total nightly sleep in the adolescent and younger AS subgroups are below norms for neurotypical individuals in these age groups. Sleep problems identified in this population are consistent with previous reports in individuals with AS (Pelc, Cheron, Boyd, & Dan, 2008) for interrupted sleep, early morning awakening, and decreased total sleep time. It should be noted that abnormalities on the CSHQ do not necessarily translate to formal sleep disorders diagnoses, but rather describe the sleep habits of those studied.

These sleep problems are present despite a high percentage of subjects receiving medications for treatment of disordered sleep (72%). Nevertheless, each of the sleep medications most commonly taken by this study cohort was effective in reducing symptom severity for a substantial percentage of participants. Our results are among the first to suggest that clonidine may be effective in treating sleep disturbance in the AS population, as it has previously shown effectiveness in treating sleep-onset issues with less of an impact on night-time and early morning awakenings in children with developmental disabilities (Ingrassia & Turk, 2005).

The distribution of CGI-I ratings for the three most commonly used medications were fairly similar. Of note, when comparing improvement between trazodone and melatonin the adjusted odds ratio of 2.8 was suggestive of more favorable ratings for trazodone. Post-hoc analyses suggested the difference between the adjusted and unadjusted estimates was driven mainly by the difference in distributions of the age of the participants when the medications were started. In addition, the odds ratio estimate was attenuated after controlling for number of
concomitant medications and concomitant anxiety medication at start of treatment. These differences highlight one of the limitations of our observational study. Participants who took melatonin, which can be taken at young ages and without a prescription, may be different in key ways from participants who took clonidine and trazodone, medications typically prescribed at older ages and perhaps for those with more severe sleep problems, those unresponsive to other medications, or those with comorbid anxiety. Randomized controlled trials are needed to more reliably compare and evaluate the effectiveness of treatments for disturbed sleep in this population and age should be considered in conducting these studies.

Results from the survival analysis demonstrate that most participants stayed on each of the most common medications for at least 6 months. This favorably implicates tolerability of these three medications in the AS population, especially in light of modest improvement. Caregivers and clinicians may be willing to continue treatments with limited effectiveness given a lack of alternative options. More effective treatment for sleep disturbance is imperative for the wellbeing of both the individual with AS and their caregivers. Caregivers of individuals with AS have high reported levels of stress compared to caregivers of those with other rare genetic developmental syndromes (Adams et al., 2018). It is likely that the significant sleep disturbances present in AS contribute to caregiver stress, highlighting the need for more effective interventions.

There was no evidence that melatonin was more effective than the other most commonly used sleep medications in participants with AS, despite it being one of the best supported medications for sleep disturbance in the literature. One randomized placebo-controlled trial of melatonin use in subjects with AS showed positive effects on sleep onset, sleep latency, total sleep time and number of night awakenings (Braam, Didden, Smits, & Curfs, 2008). However, in
light of its favorable safety profile in children with developmental disabilities, the comparable effectiveness of melatonin found in this study can be seen as further support for its first line use as a medication treatment for sleep disorder in AS. Indeed, melatonin had the earliest mean age of first usage (M = 7.4 years old) and greatest number of participants with a lifetime (40%) or current (28%) usage of the medication. Such findings can be interpreted as further evidence for the likely tolerability of melatonin in a mixed age population of subjects with AS.

While only melatonin has been previously studied in a controlled trial in an AS population, clonidine and trazodone are commonly used treatments for sleep disorder in the neurotypical population. Exogenous melatonin is hypothesized to improve sleep via inducing a phase shift of the body’s circadian pacemaker. Meta-analyses of short-term usage of melatonin in populations with developmental disability have suggested mild side effects that were comparable to placebo (reviewed in Hollway & Aman, 2011). Clonidine is a central and peripheral α-adrenergic agonist that acts to inhibit noradrenergic release (Bezchlibnyk-Butler & Jeffries, 2005). Though treatment studies have found good tolerability for clonidine in young populations (Ming, Gordon, Kang, & Wagner, 2008) the potential for constipation, headache, dizziness, fatigue and hypotension should be considered. Trazodone is a serotonin antagonist reuptake inhibitor (Bezchlibnyk-Butler & Jeffries, 2005). Reviews suggest a generally mild side effect profile (reviewed in Hollway & Aman, 2011) though a rare risk for priapism should be considered (Mendelson, 2005). Findings from our study provide important first evidence for effectiveness and tolerability of clonidine and trazodone in patients with AS.

A negative association between severity of disordered sleep and age was found in this study. One interpretation of this finding is that as participants have more years of treatment, sleep issues improve. However, this may also be explained by the finding that the severity of
sleep problems tends to improve with age in AS (Pelc, Cheron, Boyd, & Dan, 200). As such, these findings should encourage clinicians to reevaluate the need for sleep medications as their patients with AS age. Polypharmacy is a common finding in adults with intellectual disabilities (O’Dwyer, Peklar, McCallion, McCarron, & Henman, 2016) and sleep problems represent one area where need may change as patients age. This should especially be considered if medications provide only minimal benefit.

While melatonin, clonidine and trazodone appeared to be well tolerated, continuation of these medications might be at the cost of trying more effective medications with different side effects profiles. Mirtazapine and quetiapine are effective for sleep but can cause appetite increase and associated weight gain. Quetiapine is also associated with extrapyramidal symptoms and can result in tardive dyskinesia. Benzodiazepines and anticholinergic medications can carry a risk for a paradoxical excitatory behavioral response (Du Buske, 1996; Mancuso, Tanzi, & Gabay, 2004). Minimal use of these other potentially beneficial medications may explain the modest nature of improvements seen in this study. This highlights the challenges to the prescribing clinician in treating disordered sleep in patients with AS and emphasizes the need to combine pharmacologic interventions with behavioral treatments.

**LIMITATIONS**

Limitations of the study include the small sample size, the potential for selection bias, the potential for recall bias, and the lack of control for concomitant medications. The small sample size limited our power and made comparing subgroups prohibitive. Confidence limits for our relative risk estimates are wide, and we were not able to rule out clinically meaningful differences among medications. The majority of participants came from well-educated families
in higher socio-economic ranges, and recruitment, in part, was conducted at an annual AS conference, which might have predisposed our study to the selection of families with resources to travel and seek out advanced care. As a result, families of lower socioeconomic status were underrepresented in this sample. As the sample was drawn from a previous study investigating anxiety in Angelman Syndrome, the cohort could be biased towards those with anxiety, which in itself could be contributing to sleep problems. The study was conducted at a tertiary care center, which might attract more severely affected participants with more intractable sleep issues. As such, there might be a low representation of participants who had been previously treated with sleep medications successfully.

While parent report regarding sleep patterns is inferior to methods such as actigraphy or EEG, the high frequency of behavioral dysregulation and difficulty independently initiating and maintaining sleep in this population likely improves the reliability of parent report (Bruni et al., 2004). Caregivers may have been unable to accurately recall improvement on particular medications or their duration of use. Caregivers were not specifically queried as to side effects of medications, limiting our conclusions about tolerability to those inferred from the overall CGI-I score. In addition, since the CGI-I was used without further clarification, improvements in specific sleep domains (sleep latency, frequency of sleep awakenings, etc.) could not be categorized.

Another potential confounding factor was that of the concomitant medications, specifically antiepileptics and medications for anxiety, as well as the total number of sleep medications taken. Sensitivity analyses taking into account these concomitant medications indicated that while they may have effects on odds of improvement or hazard of discontinuation of trazodone, clonidine and melatonin they did not change the lack of significant differences
between these medications. Issues in study design (small number of subjects, large number of concomitant medications, variability in timing of use) limited our ability to more formally account for the effect of concomitant medications in our analyses. Moreover, the high prevalence of certain medical comorbidities (epilepsy and constipation) and low prevalence of others limited our power to conduct analyses into the effect of comorbidities on sleep.

We note, however, that these study design choices were made in the context of the very low prevalence of AS in the population and the associated difficulty in recruiting large and representative samples. Despite its small size, our sample is one of the largest included in a published study of AS to date. Future studies evaluating the effectiveness of treatments for sleep disturbance in AS should take into consideration the age of participants, the number of previous treatments and whether treatments for co-morbid conditions (such as epilepsy) are also being used to address sleep issues. They should also screen for use of behavioral approaches to sleep problems and assess whether adding behavioral interventions increases the effectiveness of medications or reduces the required dosage. They should also consider the impact on sleep from treatments prescribed for indications other than sleep.

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AUTHOR CONTRIBUTION STATEMENT: All authors made substantial contributions to the conception and design of the study, acquisition and interpretation of data, and drafting and revising the manuscript. All authors have given final approval of the version to be published and have agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST: Dr. McDougle, Dr. Ravichandran, Jennifer Mullett and Joseph Pereira have no conflicts of interest to declare. Dr. Keary has received research funding from and has consulted for Ovid Therapeutics.

DATA AVAILABILITY STATEMENT: The data supporting the findings of this report is not available publicly, as it contains information that could compromise the confidentiality of the participants studied.
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FIGURE LEGEND

Figure 1. Kaplan-Meier survival curves showing the proportion of patients remaining on medication by years of use for melatonin (solid line), clonidine (shorter dashed line), and trazodone (longer dashed line). Hash marks indicate censoring times for patients who were taking the medications at the time of the study.