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Interventions to improve sleep for individuals with Angelman syndrome: A systematic review

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ABSTRACT

Objective: The aim of the review was to synthesise the literature on the types and effectiveness of interventions to improve sleep for individuals with Angelman Syndrome (AS).
Method: Four databases were searched using predetermined search terms. Data extraction was performed on studies to examine (a) participant characteristics (b) study design (c) intervention procedures (d) intervention duration (e) dependent (outcome)variables. Intervention outcomes were categorised as positive, negative or and certainty of evidence as a measure of quality was reported for each study.
Results: Ten studies, including 54 participants with AS, met the inclusion criteria. Included studies comprised of both single subject designs (n = 3) and group-based designs (n = 7). Pharmacological interventions (n = 8) were the most commonly used followed by combined pharmacological and behavioral treatment (n = 1) or behavioral interventions as a single intervention (n = 1). Pharmacological interventions demonstrated both positive (n = 2) and mixed outcomes (n = 6) and were categorised at a suggestive level of evidence. Behavioral interventions as a sole intervention (n = 1) and as a combined intervention (with pharmacological intervention; n = 1) were found to have positive outcomes and was also categorised at a suggestive level of evidence.
Conclusion: This review found provisional evidence but weak evidence for the effectiveness of behavioral interventions, and mixed outcomes for the effectiveness of Melatonin for the treatment of sleep problems in AS. All 10 studies only achieved a suggestive level of certainty, therefore, further high-quality research is needed to evaluate interventions for the treatment of sleep problems in this population.

What this paper adds

This paper is unique in that it provides a detailed exploration and analysis of interventions for sleep problems in individuals with AS. This paper extends on a recent review by Spruyt, Braam, and Curfs (2018)). Spruyt and colleagues undertook a review and meta-analysis of sleep problems in individuals with AS. That review included 10 studies and while sleep treatment was one variable listed amongst their study characteristics, they did not analyse the effectiveness of interventions and excluded some studies included in the current review. Therefore, the current paper adds to the literature by providing detailed descriptions of the interventions for sleep problem in individuals with AS and compares the outcomes of the interventions as well as the strength (or quality) of the evidence.

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1. Introduction

Angelman Syndrome (AS) is a neuro-genetic disorder characterized by intellectual disability, sleep disturbance, seizures and a happy demeanour. Abnormal sleep-wake cycles are extremely common within AS, affecting 20–80 % of individuals (Williams et al., 2006). These sleep problems manifest as difficulties with initiating and maintaining sleep and irregular sleep patterns (Spruyt et al., 2018). The most frequent sleep disturbances reported for AS are reduced sleep duration, increased sleep latency and a disrupted sleep architecture (such as frequent night-time awakenings) and somnolence (Pelc, Cheron, Boyd, & Dan, 2008; Spruyt et al., 2018). A comparison of sleep disorders in AS with an age-matched sample of peers without intellectual disabilities, revealed that individuals with AS presented with a higher rate of sleep disturbances than the control group, across varying topographies (Bruni et al., 2004). Identical sleep disturbance rates and topographies have been reported across individuals with AS ranging from 2 years 3 months to 26 years 2 months (Bruni et al., 2004), suggesting that without intervention, sleeping difficulties persist throughout the lifespan.

Combating sleep disturbances is important for both individuals with sleep problems and for their caregivers. Sleeping problems can have both physical and psychological implications including; caregiver distress, fatigue, anxiety and impaired social functioning (Didden & Sigafoos, 2001; Griffith et al., 2011). Goldman, Bichell, Surdyka, and Malow (2012) found an association between variability in sleep duration and parental stress, and between prolonged sleep latency in children and parental insomnia and daytime sleepiness. Additionally, children may exhibit disruptive daytime behaviors such as lack of energy and daytime somnolence following sleep disturbance (Bruni et al., 2004). Therefore, improving sleep quality may alleviate some of these challenges for parents or caregivers. It is noteworthy that medication prescriptions are provided in 81 % of children's visits to paediatricians, family physicians and psychiatrists for sleep problems (Stojanovski, Rasu, Balkrishnan, & Nahata, 2007). However, behavioral treatments for children's sleep problems have been shown to be more efficacious than medication, both in short-term and longer-term studies (Ramchandani, Wiggs, Webb, & Stores, 2000). Extinction, graduated extinction (Kuhn & Elliott, 2003) and parental education have been reported as well-established treatments (Kuhn & Elliott, 2003; Mindell, 1999). In addition, positive bedtime routines (Mindell, 1999) and extinction with parental presence (Kuhn & Elliott, 2003) were reported as promising interventions, and scheduled awakenings as probably efficacious according to Chambless criteria (Chambless et al., 1998; Kuhn & Elliott, 2003; Mindell, 1999). The Chambless criteria aims to identify if a treatment has met predetermined criteria to be identified as a treatment which is regarded as "probably efficacious" or as a "well established" treatment (Chambless et al., 1998). However, these reviews were undertaken within the typically developing population, therefore, the findings cannot be generalized to the populations with neurodevelopmental disabilities.

Rossignol and Frye (2011) conducted a meta-analysis and systematic review of melatonin administration for sleeping disturbances in autistic spectrum disorder (ASD) and found that melatonin administration was associated with improved sleep parameters, improved daytime behaviors and minimal side effects. However, inconsistent methods were applied throughout studies, including variously using objective and subjective outcome measures that cannot be compared. Additionally, none of these studies compared the effectiveness of melatonin to other treatments. While there has been no systematic evaluation of the management of sleep problems in AS to date, the literature suggests that the focus of primary studies has been on medical interventions, predominantly through the administration of melatonin (Braam, Didden, Smits, & Curfs, 2008; Zhdanova, Wurtman, & Wagstaff, 1999). Although behavioral interventions are the most frequently used procedures for sleep disturbance in the typically developing population, only a very limited number of behavioral studies have addressed sleep problems for individuals with AS (Esbensen & Schwichtenberg, 2016). This may reflect assumptions regarding an underlying biological cause for sleeping difficulties in AS. Suggested biological causes include circadian rhythm disorders (Goldman et al., 2012; Braam, Didden et al., 2008; Braam, Smits, Didden, & Curfs, 2008) and the occurrence of nocturnal seizures (Goldman et al., 2012; Clayton-Smith, 1993). As melatonin is effective in improving circadian rhythm disorders and has been linked to the reduction of seizures in some studies (Jain & Besag, 2013), pharmacological treatments may be considered most relevant.

The current systematic review aimed to investigate interventions used for improving sleep in children and adults with AS using both group and single-subject designs and comparing behavioral and pharmacological treatments. The effects of treatments on the primary outcomes sleep disturbances (e.g. sleep latency, frequency of night-time awakenings, total sleep time duration) were analyzed.

2. Method

2.1. Search procedures

Searches were conducted in four electronic databases: Web of Science Core Collection Database, Science Direct, Psychology and Behavioral Sciences Collection, and Scopus. In all four databases the key search terms were applied, see Table 1.

Table 1
Search terms used across the four electronic databases.

List 1	List 2
Sleep Disturbance	Angelman Syndrome
Sleeping intervention	Happy puppet
Medication	Developmental disabil*
Melatonin	

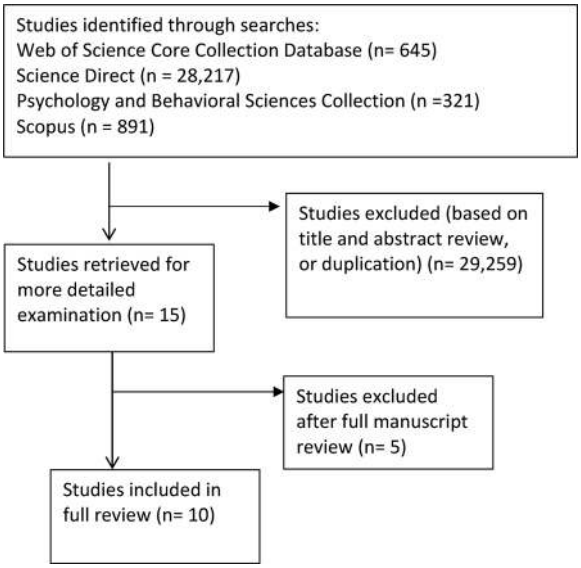

Fig. 1. Flowchart of included and excluded studies.

Titles and abstracts were reviewed according to the inclusion criteria. The studies which met inclusion criteria were compiled into a reference list. The search was limited to peer-reviewed studies written in English, prior to and including 2016. Searches were performed during January and February 2017. Scoping searches were carried out in June 2019 to determine if there any additional research articles were published in the intervening period. See Fig. 1 for flowchart of procedure.

2.2. Inclusion and exclusion criteria

Included: Studies that used at least one participant with AS and implemented an intervention to improve sleeping disturbance were included. Case studies were included to ensure that all interventions pertaining to AS were included, as this is a limited sample. Relevant studies were only included if they were in the English language. Excluded: Studies that looked at other elements of sleep disturbance other than treatments, such as prevalence rates, sleep links to parental stress, genetic pathways or epilepsy were excluded. Studies that did not evaluate an intervention were excluded from the review. Studies that only examined assessment tools such as questionnaires or polysomnography for assessing types of sleep disturbance were excluded from the review. Systematic reviews, meta-analyses and literature reviews were excluded from the review (e.g. Hoban, 2000). Studies that indicated a dropout of participants, but did not specify which participants this applied to, were excluded (e.g. Moss, Gordon, & O'Connell, 2014). Studies that grouped together results from a range of clinical populations but did not present results specifically for participants with AS were excluded from the review (e.g. Dhondt, Verloo, Verhelst, & Van Coster, 2013).

2.3. Data extraction

Each study from the systematic search was assessed for inclusion criteria. Studies selected for inclusion in this review were summarized in terms of (a) participant characteristics (b) design (c) intervention procedures (d) duration (e) dependent variables (f) intervention outcomes and (g) certainty of evidence (quality indicator). Intervention outcomes were summarized as positive, negative or mixed Positive results were classified as an improvement in all dependent variables from a visual analysis of data in single-case experimental designs or a statistically significant improvement for a group on all dependent variables in between-group designs. Negative results were classified as no improvement in any dependent variable from a visual analysis of data in single-case experimental designs or as no statistically significant improvement within a group on any dependent variable in a between-group design. Mixed results were classified as improvement in some participants or dependent variables (but not all) following visual analysis of data within single-case experimental designs or as statistically significant improvements in some dependent variables of a group (but not all) in a between-group design.

Certainty of evidence was described as "suggestive", "preponderant" or "conclusive" (Schlosser, 2009; Simeonsson & Bailey, 1991; Smith, 1981) in order to evaluate studies in light of the methodological quality of evidence across the reviewed studies. Suggestive evidence was the lowest level of certainty. Studies in this category might have an intervention only or AB designs but did not involve a true experimental design (e.g. group design with random assignment, an ABAB design, or a multiple baseline design). Preponderant was the second level of certainty of evidence. Studies in this level had the following four characteristics: (a) experimental design (b) adequate interobserver agreement (c) operationally defined dependent variables and (d) sufficient detail to enable replication in subsequent studies. Studies at the preponderant level were in some way limited in their ability to control for alternative explanations for treatment effects. Studies at the conclusive level, however, could control for alternative explanations of treatment effects, contained all the components of lower levels and contained a measure of treatment fidelity.

2.4. Reliability of search procedures

Inter-observer agreement was conducted on all aspects of the searches to ensure all the appropriate studies had been included. Agreement between raters was defined as both raters having identified the same article for inclusion or exclusion, and if both raters agreed that the information represented in the data extraction table was an accurate representation of the study. Disagreement was defined as one rater including or excluding an article, or disagreeing with the description of a study. Inter-observer agreement was calculated by dividing the number of agreements by agreements plus disagreements and multiplying by 100.

The first and the third author conducted the searches independently using the search terms and databases and screened the results for inclusion criteria and each produced a list of studies that should be considered for inclusion. Reliability of database searches was calculated by the percentage of articles identified by both raters. A combined total of 15 articles were identified at this stage, and the percentage of agreement was 67 % (10 articles appear across both lists). Complete copies of all 15 studies being considered for inclusion were acquired, the first, the second and fourth author independently applied the inclusion and exclusion criteria to these 15 studies.

To ensure the inclusion and exclusion criteria were applied accurately, each author compiled a list of the studies selected and this was compared across co-authors. Agreement on whether a study should be included or excluded was 91 %. The disputed article was then discussed by co-authors until 100 % agreement was obtained. After a final list of 10 studies was agreed upon, information from each study was extracted by the first author to develop a summary table.

To guarantee accuracy of information, the second author used a checklist to evaluate inter-coder agreement on the extraction of data. This checklist consisted of six questions; (a) is this an accurate description of participants? (b) Is this an accurate description of design? (c) Is this an accurate description of the intervention procedure and duration? (d) Is this an accurate description of the dependent variables? (e) Is this an accurate description of the outcomes? (f) Is this an accurate description of the certainty of evidence? This approach provided inter-coder agreement on data extraction and analysis. There were 60 items on which there could be agreement or disagreement. The level of agreement was 92 %. This process was repeated until 100 % agreement on the accuracy of the summaries was achieved. The resulting summaries are presented in Table 2.

3. Results

The systematic search procedures and application of the inclusion criteria resulted in the inclusion of 10 studies in this review.

Table 2 summarizes: (a) participant characteristics, (b) design, (c) intervention procedures (d) duration (e) dependent variables (f) intervention outcomes and (g) certainty of evidence for the 10 included articles.

3.1. Participant characteristics

The 10 included articles included 54 individuals with Angelman syndrome. Of these 54 participants, 12 were male (22 %) and 20 were female (37 %), with a further 22 (40 %) participants whose sex was not reported. Participants ranged in age from 2 to 27 years, with a mean of 7 years. In addition to Angelman syndrome, 8 were also diagnosed with chronic insomnia, 1 participant was diagnosed with epilepsy, insomnia and central sleep apnea and 15 were diagnosed with circadian rhythm sleep disorders (CRSD). For the purpose of including all studies with Angelman syndrome, some studies which grouped results together with various diagnoses have been included, without the possibility to isolate the separate effects on the participants with Angelman syndrome.

3.2. Design

Included studies contain single subject designs (n = 3) and group-based designs (n = 7). Single subject designs include a multiple baseline design, an observational study and a case study. Group-based designs include randomized placebo-controlled designs, quasi-experimental designs, open uncontrolled designs and a double-blind cross-over placebo-controlled trial. A test for maintenance was included using follow-up phases in 7 studies.

3.3. Intervention procedures and duration

Pharmacological interventions were the most commonly used treatments (n = 8; 80 %). A combined pharmacological and behavioral treatment was conducted in 1 study (10 %) and behavioral interventions as a single intervention was conducted in 1 study (10 %). The intensity of treatment ranged from 6 days to 44.8 weeks (M = 28.4 weeks). Medication utilised within pharmacological studies included 25 mg of diphenhydramine hydrochloride and melatonin ranging from 0.3 mg to 10 mg.

3.4. Dependent (outcome) variables

Dependent variables were varied and included; independent sleep onset, sleep latency, total sleep time, disruptive behavior, sleep efficiency, non-sleep behavior problems, wake up time, number of awakenings, size of improvement, adverse effects, serum melatonin levels, diurnal sleep time, sleep quality, sleep onset and sleep offset times, daytime napping occurrence, mood changes, arousal index, REM sleep, non REM sleep, respiratory disturbance index, number of movements per hour during total sleep time, lowest oxygen saturation associated with central event, early arousal, duration of night awakenings, sleep habits, sleep duration by day, sleep duration by night.

Table 2
Summary of Included Studies.

Citation	Participant characteristic	Design	Intervention Procedures (IP) and Duration (D)	Dependent variables	Outcomes and Certainty of evidence (CoE)
Behavioral Intervention					
Allen et al. (2013)	3 females & 2 males; all with AS; age range: 2–11 years	Multiple baseline design across participants	*IP:* Behavioral intervention including a sleep compatible environment, sleep schedule, and recommendations for parent-child interactions. Treatment recommendations were provided via video telehealth/phone contact in health clinics by the research team. Weekly contact with project co-ordinator via phone and email. Available to contact at any time. *D:* 8-21 weeks of intervention	Independent Sleep onset, sleep efficiency, sleep latency, sleep duration.	*Outcome:* positive. All five participants showed increases in independent sleep onset. Outcomes were maintained at 1- and 3-month follow up for 4 of the five participants. *CoE:* suggestive, due to insufficient detail regarding which procedures were used per participant (e.g. ignoring or "excuse –Me-Drill") and TF was subjective. NR.
Combined Intervention					
Summers et al. (1992).	1 male with AS; aged 9 years	Case Study	*IP:* Combined behavioral (scheduled bedtime, sleep restriction by day, fluid restriction in evening, returned to bed) and pharmacological treatments (25 mg of diphenhydramine hydrochloride, approximately 0.5 mg/kg) administered one hour before bed. *D:* 49 days (31 days of combined treatment, 18 days of behavioral treatment).	Sleep duration by day and sleep duration by night.	*Outcome:* positive. The participant was found to have increased duration of sleep at night and decrease sleeping by day following combined treatment. Slight decreases in night time sleep were noted following the removal of medication and at follow up. However, no increases in day time sleep duration were found. *CoE:* suggestive, due to non-experimental design and TF was NR.
Pharmacological Treatment					
Braam et al. (2008a)	4 individuals with AS allocated to the melatonin condition. The total sample of 51 participants ranged in age from 2 to 78 years	Randomized controlled study (placebo vs. treatment)	*IP:* Pharmacological (Melatonin 2.5-5 mg) administered at 6-7pm, or placebo. *D:* 4 weeks of treatment (Melatonin or placebo).	Sleep latency, sleep onset time, wake up time, total sleep duration, number of night wakes, duration of night wakes, Measures were also taken on salivary melatonin concentrations, number of epileptic seizures, adverse reactions of melatonin.	*Outcome:* mixed. Statistical significance was found for some but not all dependent variables. Sleep latency decreased, sleep onset time advanced, total sleep time increased. The mean number and duration of night time awakenings decreased. There was no significant changes in lights out time, number of nights with night waking and sleep offset time compared to baseline. *Results prohibit interpretation of outcomes for individual with AS separately. *CoE:* suggestive, IOA was NR on sleep diaries completed by parents, TF was NR (efforts were taken to record compliance (e.g. the number of tablets returned were compared with number of tablets prescribed). Randomisation did not account for age, gender or developmental stage. Results prohibit interpretation of outcomes for individuals with AS separately.

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Table 2 (*continued*)

Citation	Participant characteristic	Design	Intervention Procedures (IP) and Duration (D)	Dependent variables	Outcomes and Certainty of evidence (CoE)
Braam et al. (2008b)	8 children with AS with chronic insomnia	Randomized placebo-controlled study	*IP:* Pharmacological (Melatonin 2.5-5 mg), or placebo. *D:* 8 weeks: treatment group received 4 weeks of Melatonin, followed by 4 weeks of Melatonin. The control group received 4-week placebo-controlled phase followed by 4 weeks open melatonin treatment	Sleep onset, sleep latency, total sleep time duration, number of nights with wakes.	*Outcome:* positive, significant changes were noted for sleep onset, sleep latency, total sleep time and number of night wakes. After 4 weeks some patients displayed a reduction in therapeutic gains. CoE: suggestive, due to non-experimental design (e.g. the study used a series of case studies with an AB design with no baseline), IOA was NR, TF was NR. Age of participants was not provided, and dependent variables were not defined.
Coppola et al. (2004)	1 participant with AS, the total sample of 25 participants ranged in age from: 3.6–26 years (M = 10.5)	Double-blind cross-over placebo-controlled trial	*IP:* Pharmacological (fast release Melatonin 3-9 mg administered at noctorual bedtime). *D:* 8 weeks: 4 weeks fast –release melatonin or placebo, 1 week cross over period, followed by 4 weeks of all administered melatonin. A 2- month open label phase followed the study.	Sleep latency, night sleep total duration, diurnal sleep time, frequency of night awakenings, early arousal.	*Outcome:* mixed, results were reported for all participants collectively. Results found significant treatment effects for sleep latency, but not for night wakes or diurnal sleep time. ***The findings report that the participant with AS improved on melatonin 9 mg, worsened when Melatonin was discontinued and recovered when melatonin was restored. *CoE:* suggestive due to TF was NR, IOA was NR on sleep diaries completed by parents, dependent variables were not defined.
De Leersnyder et al. (2011)	4 females and 1 male with AS (mean age = 7years). 83 other participants with autism, blindness, bourneville syndrome, encephalopathy, mental retardation, rett syndrome, delayed sleep-phased syndrome, smith-magenis syndrome	Pre-test and post-test design (no control group)	*IP:* Pharmacological (prolonged release Melatonin 2-6 mg, depending on weight), all AS participants received prolonged release Melatonin 6 mg. *I:* 6-72 months treatment duration, mean duration for AS participants = 44.8 months. Data was analyzed at 3- month follow up.	Sleep onset and offset times, sleep duration, sleep latency, sleep quality, number of awakenings, daytime napping.	*Outcome:* mixed: statistical significance found for sleep offset times, sleep duration, sleep latency, sleep quality, number of awakenings, daytime napping but not for sleep onset time. *Results prohibit interpretation of outcomes for individuals with AS separately. *CoE:* suggestive, due to non-experimental design and TF was NR.
Jain et al. (2014)	1 male with AS with epilepsy, insomnia & central sleep apnea, aged 9 years	Case study	*IP:* Pharmacological (sustained-release Melatonin 3 mg administered 30 minutes prior to bedtime). *D:* 1 month of intervention.	Total sleep time, sleep efficiency, sleep latency, wakefulness after sleep onset, arousal index, non-rapid eye movement sleep, rapid eye movement sleep, respiratory disturbance index, lowest oxygen saturation associated with central events	*Outcome:* mixed, from polysomonography results after intervention improvements were noted for total sleep duration, Sleep efficiency and sleep latency. But an increase as noted in wakefulness after sleep onset. TF was NR. *CoE:* suggestive, non-experimental design, no baseline data.

(*continued on next page*)

Table 2 (*continued*)

Citation	Participant characteristic	Design	Intervention Procedures (IP) and Duration (D)	Dependent variables	Outcomes and Certainty of evidence (CoE)
Ross et al. (2002)	1 male 7 years with AS who presented with night awakenings, 48 other diagnoses including epilepsy, cerebral palsy and developmental delay	Pre-test and post-test design (no control group)	*IP:* Pharmacological (Melatonin 2.5 – 10 mg), AS participants received Melatonin 2.5 mg. *D:* Not specified	Total sleep time, night time sleep, duration of interruptions in sleep, and time at onset of sleep, number of night awakenings	*Outcome:* mixed, data was returned and interpretable for analysis for 28 participants. Improvements were seen in total sleep time, night time sleep, duration of interruptions in sleep, and time at onset of sleep. Improvements were not statistical significance for night awakenings. *Results prohibit interpretation of outcomes for individual with AS separately, other than indicating a benefit from treatment. *CoE:* suggestive, due to non-experimental design, TF was NR, IOA was NR on sleep diaries completed by parents
Takaesu et al. (2012)	6 participants with AS and CRDS (4 females and 2 males) given the melatonin treatment; age range 7–26 years. 15 individuals with AS (8 females and 7 males) took part in the sleep-wake cycle analysis; age range = 6–27 years; 8 participants were diagnosed with CRSD.	Pre-test and post-test design	*IP:* Pharmacological (Melatonin 1 mg between 18:00 and 19:00). *D:* 3 months of taking daily melatonin dose between 18:00 and 19:00	Total sleep time duration, frequency of daytime sleep episodes and nocturnal sleep, peak serum melatonin levels	*Outcome:* mixed, nocturnal sleep patterns improved for 4 of the 6 patients with AS and CRDS. *CoE:* suggestive, due to non-experimental design, insufficient detail was provided which precludes replication (e.g. details for the controls group used for analysis, dependent variables, sleep logs), and TF was NR.
Zhdanova et al. (1999)	9 females and 4 males with AS; age range: 2–10 years	Pre-test and post-test design (no control group)	IP: Pharmacological (Melatonin 0.3 mg, administered 30minutes-1 hour prior to bedtime). *D:* 6 days of melatonin intervention	Time of sleep onset and time of awakenings (total sleep period), Time of lights out to sleep onset (Sleep latency), number of movements per hour during melatonin levels	*Outcome:* Positive, total sleep period increased significantly following melatonin treatment. Nocturnal motor activity reduced for 11 of the 13 participants (statistically significant decrease). Sleep latency was not analyzed due to absence of objective data on time of lights out. *CoE:* suggestive, due to non-experimental design, missing data therefore analysis was conducted on 4 consecutive days of baseline and treatments periods, IOA was NR (sleep diaries pertain to periods when Actigraphs were not worn), TF was NR.

AS – Angelman Syndrome; IOA – Interobserver agreement; TF – Treatment fidelity; NR – not reported; CRSD - circadian rhythm sleep disorders.

3.5. Intervention outcomes and certainty of evidence

Treatment fidelity was observed in only one of the studies (10 %) and was subjective as it involved weekly contact with the study co-ordinators, but no direct measurement (Allen, Kuhn, DeHaai, & Wallace, 2013). Interobserver agreement was utilised in one study using objective an measure (i.e. an actigraphy) alongside a subjective measure (i.e. sleep diary) to compare accuracy of results (Summers et al., 1992). Compliance with treatment was reported for one study (Braam, Didden et al., 2008) by comparing the number of tablets returned versus the number of tablets that had been provided at the start of the intervention.

Behavioral interventions in the study of Allen et al. (2013) demonstrated a 100 % success rate, with all participants achieving positive outcomes (n = 5). This study was rated as providing a suggestive level of certainty. These interventions also contained social validity measures to investigate treatment acceptability and customer satisfaction. A functional relationship was demonstrated using a withdrawal and subsequent reinstatement of treatment. However, the intervention utilised for each participant was not specified, which does not provide the opportunity for future replication. Furthermore, treatment fidelity measures were subjective (phone call conversations between therapists and parents implementing the procedures) with no direct observation utilized. A combined behavioral and pharmacological intervention was shown to achieve a positive outcome for the participant in a single case study (Summers et al., 1992). Due to the absence of an experimental design and lack of treatment fidelity procedures, this study was rated at a suggestive level of certainty.

Pharmacological interventions demonstrated varied outcomes of success. Positive outcomes were reported for two (25 %) of the pharmacological studies (Braam, Smits et al., 2008; Zhdanova et al., 1999). Braam, Smits et al. (2008) reported significant changes for sleep onset, sleep latency, total sleep time and number of night wakes across all participants. However, this study did not report the precise success rate or statistical significance of change on dependent variables and did not provide an experimental design, treatment fidelity procedures or interobserver agreement. Zhdanova et al. (1999) reported a high success rate, with 92 % of participants improving following the administration of a 0.3 mg dose of melatonin, with reported social validity as parents reported more appropriate waking times. However, Zhdanova et al. (1999) did not provide an experimental design, treatment fidelity, interobserver agreemnt, and did not complete data analysis on sleep latency due to missing data. Therefore, both of these studies were rated at suggestive levels of certainty.

Mixed outcomes were reported for the majority (75 %) of the pharmacological studies, at suggestive levels of certainty (Braam, Didden et al., 2008; Coppola et al., 2004; De Leersnyder, Zisapel, & Laudon, 2011; Jain, Arthur, & Simakajornboon, 2014; Ross, Davies, & Whitehouse, 2002; Takaesu, Komada, & Inoue, 2012). Of these, 83 % did not provide treatment fidelity procedures (Braam, Didden et al., 2008; Coppola et al., 2004; De Leersnyder et al., 2011; Ross et al., 2002; Takaesu et al., 2012), interobserver agreement was not reported for 50 % of these studies (Braam, Didden et al., 2008; Coppola et al., 2004; Ross et al., 2002), an experimental design was not applied to 67 % of these studies (De Leersnyder et al., 2011; Jain et al., 2014; Ross et al., 2002; Takaesu et al., 2012), and dependent variables were not operationally defined in 33 % of these studies (Coppola et al., 2004; Takaesu et al., 2012). Additionally one study provided anecdotal parental reports of improvement and did not include a baseline measure (Jain et al., 2014), one study provided insufficient details on sleep logs and control groups for replication (Takaesu et al., 2012), and one study did not separate results for the participant with AS versus those with other diagnoses, and randomisation did not account for age, gender or developmental stage (Braam, Didden et al., 2008).

Takaesu et al. (2012) reported a 66.7 % success rate among participants. Similarly, Braam, Didden et al. (2008) reported a 62.5 % success rate among participants, with mixed results as all sleep onset times and number of wakes per night did not meet statistical significance. However, these results were socially valid as parents reported fewer disturbances to siblings and to parental sleep cycles due to the 30 min earlier sleeping time and reduced frequency of night awakenings. In addition, parents reported participants' behavior was easier to manage, with more attentive daytime behaviors and less daytime sleepiness. Furthermore, parents were asked to rate the size of improvement following the study; 5 participants indicated a strong improvement; however, one of these participants was removed from the study following the open melatonin phase when night awakenings increased. Two participants reported moderate improvements. Subsequently, parents of 1 of these participants were not satisfied with the degree of improvement and removed the individual. Unchanged behavior reported for another participant resulted in their removal from the study by parents. Jain et al. (2014) completed a case study with one 9-year old boy with AS and reported gradual improvements in arousals, awakenings and total sleep time which increased to 5 − 6 hours, following the use of sustained-release melatonin. However, an increase in wakefulness after sleep was also reported.

The studies conducted by Coppola et al. (2004); De Leersnyder et al. (2011), and Ross et al. (2002) must be examined with caution as the sample of participants included individuals with AS but did not analyse the effects of the intervention separately for each population. Coppola et al. (2004) reported a success rate of 72 % amongst participants and stated that the participant with AS improved consistently on high doses of melatonin (9 mg/day). The results of this study were mixed as melatonin treatment did not significantly modify the number of nocturnal awakenings. The results were socially valid as parents reported improved familial environments, improved behaviors and better dispositions for rehabilitative treatment. De Leersnyder et al. (2011) reported a 90 % success rate amongst participants; however, sleep onset time did not reach statistical significance. Parents additionally reported less fatigue, less stress and fewer depressive signs amongst their family members. Ross et al. (2002) reported a success rate of 69.4 % amongst participants but the frequency of night awakenings did not reach statistical significance.

4. Discussion

The largest number of studies to examine interventions for sleep in individuals with AS have been pharmacological interventions. The eight studies had variable findings, with two studies (Braam, Smits et al., 2008; Zhdanova et al., 1999) noting positive findings

and 6 studies reporting mixed results across participants or dependent variables (Braam, Didden et al., 2008; Coppola et al., 2004; De Leersnyder et al., 2011; Jain et al., 2014; Ross et al., 2002; Takaesu et al., 2012). Despite positive findings for two of the studies, they had limitations: Braam, Smits et al. (2008) found that after 4 weeks some patients displayed a reduction in therapeutic gains and Zhdanova et al. (1999) only reported data on one variable (total sleep period). Within that study it was noted that data on sleep latency was not analyzed due to absence of objective data.

Of the six pharmacological studies which had mixed results, some reported variable responding between participants (Takaesu et al., 2012) or across variables (i.e. Braam, Didden et al., 2008). Takaesu et al. (2012) found that 2 of the 6 participants reported non-effective treatment outcomes. Braam, Didden et al. (2008) and Coppola et al. (2004) reported statistically significant improvements for sleep latency when comparing melatonin treatment to placebo. With the exception of a case study, nocturnal awakening was not found to reduce consistently, or to a statistically significant degree, with melatonin (Braam, Didden et al., 2008; Coppola et al., 2004; Jain et al., 2014). Of note, within the case study, results were based on anecdotal parental reports, precluding any objective analysis of the level of change observed (Jain et al., 2014). Furthermore, 2 participants were withdrawn from one study, 1 due to increases in night awakenings, which suggests reduced effects of melatonin in reducing night awakenings (Braam, Didden et al., 2008). Therefore, the implementation of more objective measures are necessary in sleep interventions in order to determine the level of change in dependent variables.

The review found that behavioral interventions have been used in isolation (Allen et al., 2013) or combined with pharmacological intervention (Summers et al., 1992) to improve the sleep of individuals with AS. All participants who took part in a behavioral intervention or a behavioral intervention combined with pharmacological interventions were found to have positive results and these studies were rated as providing a suggestive level of certainty. Summers et al. (1992) found that the combined intervention led to increased duration of sleep at night and decreased sleeping by day. Following the removal of medication (i.e. behavioral intervention only) there was a slight decrease in night-time sleep, however, there was no increase in day-time sleep. More research is required into behavioral interventions as a potential treatment for sleep difficulties in AS.

Across all 10 studies it is noteworthy that only a suggestive level of certainty was achieved. One common factor was that none of the studies reported adequate treatment fidelity. Allen et al. (2013) did attempt to gather treatment fidelity data but this was subjective and was based on weekly contact with a project co-ordinator via phone. Furthermore, five of the ten studies did not report interobserver agreement (Braam, Didden et al., 2008; Braam, Smits et al., 2008; Coppola et al., 2004; Ross et al., 2002; Zhdanova et al., 1999). The lack of treatment fidelity and interobserver agreement across the studies highlights the challenge of undertaking rigorous research in applied settings which involve interventions applied at night within the privacy of a family's home. In addition, a large number of studies had non-experimental designs (Summers et al., 1992; De Leersnyder et al., 2011; Jain et al., 2014; Ross et al., 2002; Takaesu et al., 2012; Zhdanova et al., 1999). Given the challenges associated with recruiting large samples of individuals with AS for studies, the experimental rigor of research in this area could be improved through the use of single subject designs (i.e. multiple baseline design) such as that used by Allen et al. (2013).

4.1. Clinical implications and future research

While behavioral interventions were the only method to provide consistent positive effects, there are only two studies conducted using this type of therapy and so the evidence in this regard is extremely limited. Further studies are urgently required to evaluate these methods in more detail. More rigorous experimental designs, the use of interobserver agreement and treatment fidelity indicators would further strengthen the certainty of evidence of these treatment procedures. To date, both pharmacological and behavioral interventions have predominantly been implemented by parents. Further studies could investigate whether any improvements in sleep outcomes generalizes to other settings, for instance, in the homes of other relatives, or in hospitals. Overall, future behavioral treatment research should aim to enhance the quality of studies by pre-registering treatment protocols, using treatment manuals, improving the experimental methodologies used, fidelity checking and reporting findings for specific populations where various clinical groups are studied together. See Fig. 2 for critical features of studies required to enhance the quality of sleep research in AS.

The eight pharmacological interventions consisted of melatonin administration with doses ranging from 0.3 mg to 10 mg, and studies using 25 mg of diphenhydramine hydrochloride. Interestingly, of the interventions with the lowest level of melatonin administration demonstrated positive outcomes (Zhdanova et al., 1999), whereas studies administering higher levels of melatonin demonstrated mixed outcomes (Coppola et al., 2004; Ross et al., 2002). This may suggest a placebo effect of melatonin, as one would expect higher doses to result in more effective treatment outcomes. It would appear that the administration of different doses of melatonin for differing heights and weights of participants was not considered. However, two studies varied melatonin dosage by administering a lower dose (2.5 mg) to participants under age 6 and a higher dose (5 mg) to participants older than 6 years (Braam, Didden et al., 2008, 2008b). These two studies were found to have mixed and positive results indicating that further studies should continue to investigate the optimal doses of melatonin administration.

To date, diphenhydramine hydrochloride has only been used in one study (Summers et al., 1992) a case study using one participant. Within this case study diphenhydramine hydrochloride was not evaluated in isolation. A combined treatment of diphenhydramine hydrochloride and behavioral interventions was found to be effective at across 31 days at increasing the duration of sleep at night and decrease sleeping by day. Summers et al. (1992) reported that behavioral intervention on its own showed evidence of continued sleep improvements following discontinuation of diphenhydramine hydrochloride, however, based on existing research no conclusions on the sole effects of diphenhydramine hydrochloride on the treatment of sleep in AS can be drawn. Future studies should consider use of ABAC designs to evaluate the relative effectiveness of behavioral and pharmacological interventions separately, as well as in combination.

1. Experimental design (e.g. group design with random assignment, an ABAB design, or a multiple baseline design)
2. Inter Observer Agreement
3. Operationally defined dependent variables and independent variables.
4. Sufficient detail to enable replication in future studies
5. Control for alternative treatment effects
6. Include a measure of treatment fidelity
7. Description of participants with Angelman syndrome (gender, age, number of the participants included)
8. A breakdown of results for each population (e.g. outcomes for AS, ASD etc)
9. Data on maintenance and generalizability

Fig. 2. Critical features of future studies to improve the quality of sleep research.

The main limitation of this review is the inclusion of 3 studies, which contained mixed populations (but contained at least one participant with AS). In two of these three studies, the individual data for the participant(s) with AS was not possible to ascertain so results must be interpreted with caution. Further limitations include a lack of control groups in some studies; therefore, the strongest evidence should be attributed to the studies which included a control group or demonstrated experimental control through the use of single subject design.

4.2. Conclusion

The current review provides preliminary but weak evidence for the use of behavioral interventions and/or combined interventions (including both behavioral and pharmacological interventions) for alleviating sleep disturbances in AS. The current review found that Melatonin was the most commonly evaluated interventions for the treatment of sleep problems in individuals with AS however the findings are inconclusive with only two studies reporting positive outcomes and six reporting mixed outcomes. This review highlights the dearth of high-quality research in the evaluation of sleep interventions for the treatment of sleep problems for individuals with AS will all 10 studies only achieving a suggestive level of certainty. Therefore, further high-quality research is needed in all of the intervention domains.

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