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CLINICAL REVIEW

Systematic review of the effectiveness of behaviorally-based interventions for sleep problems in people with rare genetic neurodevelopmental disorders

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SUMMARY

Sleep problems are prevalent in people with rare genetic neurodevelopmental disorders (RGND) and, in some cases, RGNDs are associated with specific forms of sleep disturbance that appear relatively unique. Although a notable amount of research has focused on behavioral intervention for sleep problems in people with higher incidence developmental disorders, research focused on potentially modifiable learning and environmental factors for people with RGND has received less attention. This review summarizes empirical evidence from studies providing behavioral interventions for sleep problems in RGND. A systematic search identified nine studies for inclusion. Studies were coded to extract data on participant characteristics, intervention components, dependent variables, research rigor and intervention effects. Study rigor was then evaluated using an established criteria and effects were classified as positive, neutral or mixed. Seven of the nine studies demonstrated positive treatment effects and two mixed results. In most studies, treatment consisted of multiple intervention components and were implemented by parents in the home. However, only three studies met criteria for an adequate level of rigor, thus greatly limiting certainty of conclusions. This review identifies current intervention practices and potential foci for future research.

Introduction

Rare genetic neurodevelopmental disorders (RGND) are a group of syndromes characterized by an abnormal structure and number of chromosomes [1]. A disorder is considered 'rare' if it affects <1/2000 of the general population [2]. Examples of RGND include Angelman syndrome (AS), Prader–Willi syndrome (PWS), Fragile X syndrome (FXS), Rett syndrome (RTT), Williams syndrome, and Smith-Magenis syndrome (SMS). People with RGNDs experience phenotypic physiological, intellectual, and developmental impairments that often severely affect development, behavior and sleep [1].

Sleep problems are prevalent in RGND with 30%–90% of people with AS, RTT, SMS, FXS, and PWS experiencing problems [3–8]. The type of sleep problem experienced varies and can include sleep onset delay (SOD), frequent and prolonged night-wakings (NWs) and early morning awakenings as well as parasomnias (e.g., bruxism, sleep terrors) and sleep disordered breathing [3–10]. In some cases, the topography of the sleep problem appears to be relatively unique to a specific RGND. For example, children with RTT present with NWs that are uniquely characterized by laughing or screaming [3,11]. Similarly, people with PWS, RTT and Williams syndrome exhibit higher rates of excessive daytime sleepiness that may offset desirable nighttime sleep routines [3,6,12–14]. If untreated, sleep disturbances tend to persist and occasion significant adverse short-

Abbreviations: AS, Angelman syndrome; ASD, Autism Spectrum Disorder; FXS, Fragile X syndrome; NWs, Night-wakings; PWS, Prader–Willi syndrome; RGND, Rare genetic neurodevelopmental disorders; RTT, Rett syndrome; SMS, Smith-Magenis syndrome; SOD, Sleep onset delay.

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and long-term effects on learning, behavior, and cognitive development [5,15]. Further, child sleep problems may negatively affect family well-being, quality of life, and physical and mental health [16–18].

Sleep patterns and sleep architecture in people with RGND can differ from those of typically developing individuals [5]. Generally, the sleep problems observed in individuals with developmental disabilities seem underpinned by a complex interaction between biopsychosocial variables (e.g., differences in melatonin secretion) as well as behavioral variables (e.g., skill deficits, contingent parental interactions) [19]. However, for people with RGND, research has focused more on biological etiologies than on behavioral variables. For individuals with RGND, previous research suggests that differences in sleep architecture and impaired melatonin secretion -which can result in circadian rhythm disturbances-may underlie most sleep problems [20–23] but very little is known about other contextual and behavioral (operant) influences. Further, sleep problems in individuals with RGND are also more likely to be exacerbated by co-existing medical conditions that impact sleep [e.g., sleep apnea and nocturnal seizure activity; 20]. Overall, the profile of sleep problems experienced by people with RGND appears to differ substantially from that of the typically developing population and those with other higher-incidence disabilities (e.g., ASD, ADHD).

Given the possibility of interactions between biopsychosocial variables, co-occurring medical complexity and unique topographies of sleep problems, treatment approaches effective with other populations may not be appropriate or effective for individuals with RGND [3]. Consistent with the purported biological etiology of sleep problems in people with RGND, sleep problems in this population are most commonly treated pharmacologically [8,24,25]. Although there is notable evidence to support medication to improve sleep [26,27], medication may be expensive, sometimes requires difficult to obtain prescriptions and may be precluded by concern for side effects and interactions with other medication [28]. Further, sole reliance on medication may displace opportunities to learn behaviors that promote healthy sleep (e.g., relaxation techniques, sleep hygiene). Finally, although medication is effective for some forms of sleep problems, it is often ineffective for other forms. For example, melatonin often successfully treats SOD but typically fails to address problems with NWs [27]. Therefore, identifying other treatment options is desirable and the extent to which sleep problems associated with RGND may be amenable to behavioral or biobehavioral treatments should be considered [3,23].

Previous reviews have addressed the effectiveness of behavioral interventions for sleep problems in individuals with higher incident developmental disabilities (e.g., ASD) and reported that behavioral approaches are effective [29–31]. However, previous reviews have not included participants with RGND and, given the differences between RGND and other developmental disabilities [3], results of reviews focused on the treatment of sleep in other developmental disabilities should not be assumed to generalize to RGND [6,17,32]. Therefore, there is a critical need to identify empirical evidence pertaining to sleep intervention for RGND such that effective methods might be collated and evaluated. This current review focuses on people with RGND and excludes disorders that are degenerative or proliferative or that result from environmental causes or infection. Overall, this review has three aims: 1) to identify, code and evaluate studies that use behavioral interventions to address sleep problems in children with RGND; 2) to identify the best supported behavioral intervention approaches in an effort to inform practice; and 3) to elucidate gaps in the research literature in an effort to direct foci of future research.

Methods

This systematic review and the preparation of this manuscript was undertaken in accordance with the PRISMA guidelines [33,34].

Search procedures

Internet searching, online posting in the PedSleep forum, and consultation with medical professionals was used to compile an initial list of RGNDs (i.e., RTT, FXS, AS, SMS, Cri-du-chat syndrome, Williams syndrome, Sotos syndrome, DiGeorge syndrome/22q11.2 deletion syndrome, Turner syndrome, septo-optic dysplasia, agenesis of the corpus callosum, and PWS). Degenerative or proliferative developmental disabilities as well as disabilities that result from environmental causes or infection and those not associated with intellectual or developmental delays (e.g., epilepsy, spina bifida) were excluded from this list.

A search of electronic databases PsycINFO, Education Resources Information Centre (ERIC), Education Research Complete, and PubMed, was initially conducted in December 2017 by the sixth and seventh authors. An updated search was conducted in March 2019 but revealed no additional manuscripts that met the inclusion criteria. Initially, the search terms 'sleep' + 'treatment' were combined with the syndrome labels. This search yielded few returns and was subsequently expanded to include only the terms 'sleep' + the names of each listed RGND individually. Next, the search terms 'sleep' + 'treatment' + 'developmental disabilities' were used and the participant characteristics sections of the resulting articles was screened to identify papers to further consider for inclusion. Ancestry searches were conducted for articles that were identified via database searches. Then, a search of Google Scholar was conducted using the aforementioned search terms as key words. A summary of the systematic search procedures is presented in Fig. 1.

Inclusion and exclusion criteria

Given the paucity of research on treatment for sleep problems in individuals with RGND, this review did not restrict consideration to a particular research design. As such, case studies and single-case design research was included, along with double-blinded, placebo-controlled experimental designs. To be included, an article had to meet the following criteria: 1) published in an academic, peer-reviewed, English language journal; 2) involve at least one participant with a RGND; 3) utilize behavioral treatment [35]; and 4) report quantitative data on sleep outcomes or data that were contemporaneous with treatment (e.g., frequency and duration of NWs throughout baseline and treatment phases). Studies were excluded if treatment consisted of medical or surgical procedures (e.g., tonsillectomy). Studies in which participants were on existing medications without change throughout treatment could still be included; however, studies that manipulated medication type or dosage as the primary treatment were excluded. Owing to the scarcity of research, no restriction was placed on the date of publication. The first and sixth author screened each article resulting from the search procedures to determine whether inclusion criteria were met. There were 127 articles identified and screened of which nine met inclusion criteria. There was consensus (i.e., 100% inter-rated agreement) between authors on the inclusion and exclusion of studies.

Data extraction

Coding of variables

Each article was summarized according to: 1) participants, including number, gender, age, diagnoses, comorbidities; 2)

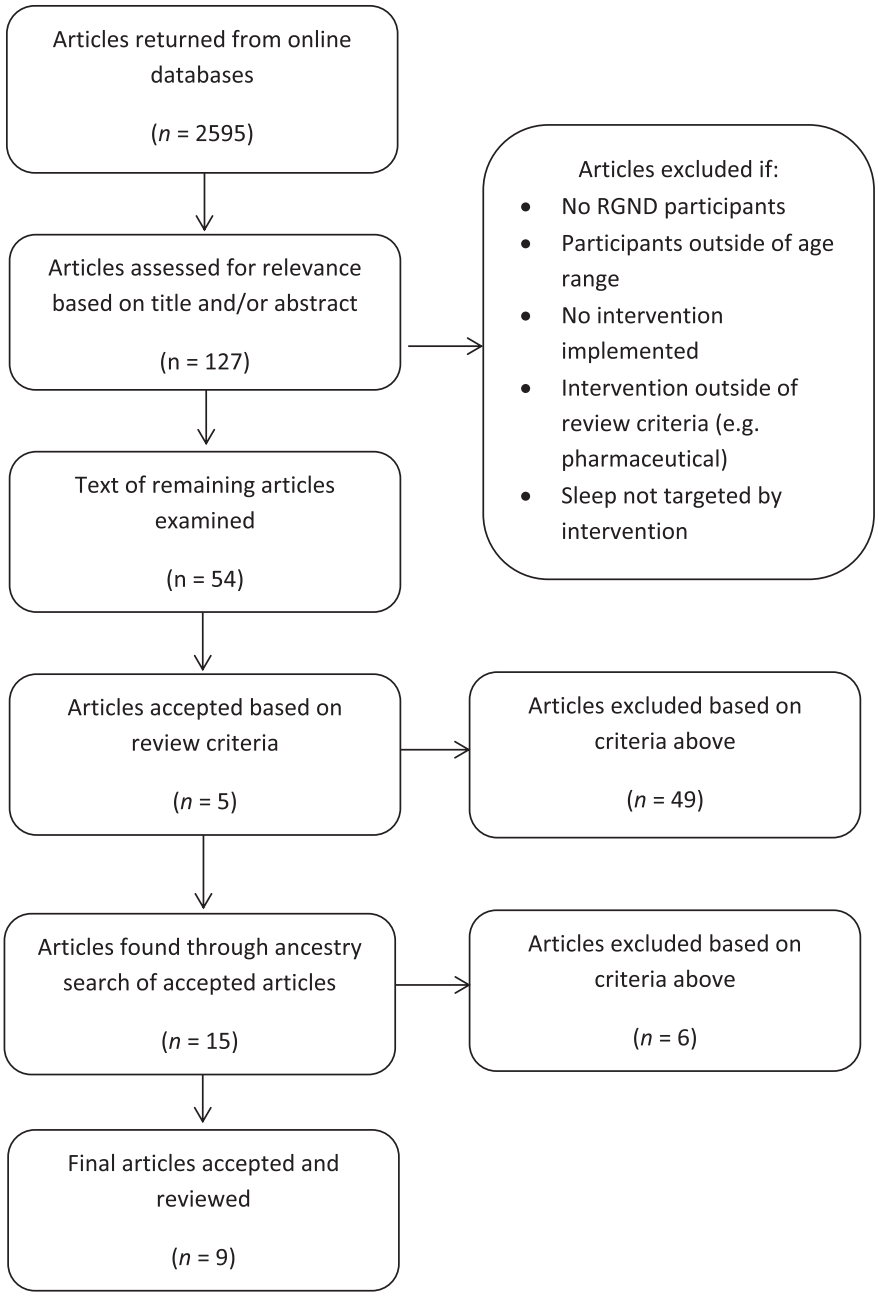

Fig. 1. Flowchart of search procedures and included studies.

reported sleep problems; 3) study design and follow-up; 4) intervention characteristics, including the intervention agent, setting and dosage; 5) dependent variables, data collection procedures, results and measures of treatment acceptability; and 6) evaluation of study rigor and treatment outcomes. Upon completion of the table, the first and second authors checked the accuracy of these summaries, and the evaluation of quality indicators and overall study rigor.

Study rigor

Individual study research rigor was evaluated using the criteria outlined by Reichow, Volkmar, and Cicchetti [36]. These criteria are used readily in reviews of interventions for children with ASD [33,37,38] and were therefore considered appropriate for use with other developmental disabilities. Further, Reichow et al.'s rigor metric provides criteria for both group designs and single-case research design (SCRD) studies. Each study was evaluated against primary and secondary quality indicators. Primary quality indicators included whether the study clearly described participant characteristics; operationalization and replicability of independent and dependent variables and baseline conditions; and the level of experimental control (SCRD), use of statistical analyses and adequate power (group design studies). Secondary quality indicators for SCRD included, reported measures of interobserver agreement (IOA), treatment fidelity and follow-up data, blind rating of sleep outcomes, and social validity. Additionally, secondary indicators for between group designs also included random assignment of participants, attrition, and effect sizes. Based on these criteria, research strength was classified as 'strong', 'adequate' or 'weak'. Studies determined to be strong in methodological rigor

received high quality ratings on each primary indicator and evidenced at least three (SCRD) or four (between groups design) secondary indicators. Studies were assigned ratings of adequate if they received quality ratings on at least four primary quality indicators and evidenced at least two secondary quality indicators. Studies determined to have weak rigor received less than four high quality ratings on primary quality indicators or evidenced fewer than two secondary indicators.

In alignment with the evaluation criteria used by Mulloy et al. [39], treatment effects were also classified according to whether they were 'positive', 'neutral', or 'mixed'. A treatment was deemed to have positive effects if a statistically significant improvement was reported in between-groups designs, or if all participants demonstrated a reduction in sleep problems in SCRD studies. Neutral effects refers to studies in which no statistically significant improvements were reported in between-groups designs or no change in sleep was noted for any participants, in SCRD studies. Mixed evidence was defined as those studies in which improvement was reported for some of the participants or if outcomes improved on some dependent variables, but not all. No studies reported a worsening of conditions.

Results

A summary of the study participants; sleep problem/s; study design; intervention characteristics; dependent variables; data collection procedures and results; study rigor and treatment effects is presented in Table 1.

Participants

Collectively, prior to attrition, the nine studies included 121 participants. Sample sizes ranged from one to 66 participants ($M = 13.44$) per study. RGND represented in the corpus of included studies included AS (4 studies), PWS (2 studies), FXS (2 studies) and Wolf Hirschhorn syndrome, RTT, SMS, and Triple X syndrome (1 study each). Participants ranged in age from two to 14 yrs old. Gender was reported for 95 participants and 36% were female. Comorbid seizure disorders were noted to affect children in four studies, and sleep apnea was a presenting factor for a child with PWS in one study [40].

Type of sleep disturbance

In all cases, treatment focused on insomnias. Specifically, this included SOD, bedtime resistance, frequent and prolonged NWs, curtain calls (e.g., bids for parental attention), unwanted co-sleeping and early morning wakings. For four children (one with PWS, two with RTT, and one with AS) the sleep problems also included excessive daytime sleepiness [41–43] and for three children night-time crying and screaming were targeted (one with RTT, one with WHS, and one with PWS) [41,42,44]. In two cases, children were receiving medication to treat the sleep problem [43,45]. This included diphenhydramine hydrochloride [43], though it is unclear in the Weiskop, Richdale and Matthews [45], study which medication directly targeted sleep problems.

Research design

Four of the nine studies used a non-experimental AB design. Three studies evaluated treatment effects using a single-case multiple baseline across participants design [42,45,46]. Interventions were evaluated using a between-groups design in two studies. Specifically, Piazza, Fisher, and Sherer [40] used a randomized pre-test/post-test two arm design in which participants were randomly assigned to one of two treatment conditions and Montgomery, Stores, and Wiggs [47] used a randomized controlled trial (RCT) three-arm design with a cross-over control group.

Intervention characteristics

Sleep hygiene modifications

In six studies, modifications or recommended modifications to sleep hygiene practices were included as a component of intervention [45–48]. This involved ensuring a sleep-conducive environment was established (e.g., dark room or minimal light), an appropriate temperature, and absence of auditory or visual stimulation [46] and establishing a consistent and calming bedtime routine [41,44,45,48]. Sleep hygiene modifications were always implemented as part of a multi-component intervention.

Bedtime scheduling and bedtime fading

In seven studies, intervention involved some form of modification to the sleep-wake schedule as a component of intervention. In four studies, this involved establishing a consistent sleep-wake time [40,44,46,48]. In three studies, a bedtime fading or bedtime fading with response-cost procedure was used [40,42,46]. This procedure was implemented to ensure that each child was sufficiently tired when put to bed, to reduce SOD [40,42,46]. This was typically calculated by averaging sleep onset time during baseline and then adding 30 min to this time. Bedtime was then incrementally bought earlier in 30-min intervals [40,42,46]. In two studies, the bedtime fading procedure was combined with a response-cost component [40,42]. In these studies, the response-cost procedure involved the child being removed from their bed and kept awake for 60 min if sleep onset or a night-waking exceeded 15 min. After the 1-h period, the child was returned to bed. Of note, Piazza et al. [40] compared a bedtime scheduling procedure with a faded bedtime with response-cost procedure and found that sleep among children who received the faded bedtime with response-cost procedure improved significantly more than those in the bedtime scheduling group.

Extinction or modified extinction procedures

Many studies used an extinction procedure in which sleep interfering behaviors were ignored for some [41] or all of the participants [44,46,48] or a modified version that allowed some contingent responding to the child's behavior [46]. In the two studies that used group parent training, parents were provided with information about extinction and/or modifying their responses to their child [45,47].

Reinforcement

In four studies, reinforcement schedules were established wherein children were reinforced contingent on night-time sleep [41,44,46,48]. Reinforcers were typically provided for the child upon waking in the morning [41,44,48], though in one case, it was provided in the form of social attention and physical presence during the sleep onset period for demonstrating sleep compatible behaviors [46]. In the two studies that used group parent training, parents were also provided with information about reinforcement procedures and/or the role of reinforcement [45,47].

Differential reinforcement and desensitization

In the study conducted by Didden et al. [41], where a functional behavioral assessment indicated anxiety was found to be contributing to the sleep problem, the child was subjected to a desensitization procedure in combination with differential reinforcement of appropriate bedtime behavior. These strategies were implemented across successive nights, involving 19 intervention steps, where sleeping through the night with a sleep onset of less than 15-mins,

Table 1
Summary of research investigating behaviorally-based treatments for sleep disturbance in children with RGND.

Author(s)	N Participants; Gender; Age; Diagnoses; Comorbidities	Sleep problem/s	Design; Follow-up	Intervention characteristics	Dependent variables; Data collection procedures; Results	Study rigor and treatment effects
Allen et al. (2013)	3F, 2M, 2–11 y (M = 5.6 y) with AS & seizure disorder.	Bedtime resistance SOD, NW, and CS.	MBL across participant design. *F/up:* 1 & 3 mo post-treatment.	*Setting:* Home *Agent:* Parent *Dosage:* 6–8 wks min. *Int.* modification of sleep environment & sleep schedule; bedtime fading; EXT; Sr sleep compatible behavior.	*Parent-reported daily sleep diaries*: Sig. decrease in DBC replicated following withdrawal for two participants. Sig. increase in ISO for all participants. *Actigraphy (weekly + 1 and* 3 mo *post-treatment):* Average increase in TST of 30mins/24hr. Improvement in SE. WASO unchanged. ACSHQ: Reduction in sleep problems *F/up:* Improvements maintained. *AARP:* Parents rated highly acceptable.	*Rigor:* Adequate *Treatment outcomes:* Mixed
Bramble (1997)	N = 15 (2:1 M to F), 3.5–12 y (M = 7.2 y). 9/15 with known etiology + single cases of AS + SMS. Comorbid physical conditions (e.g., epilepsy and blindness).	SOD, NW, CS.	Pre-test/post-test AB design. *F/up:* 4 and 18 mo post intervention	*Setting:* Home *Agent:* Parents *Dosage:* 2 wks *Int:* sleep hygiene, EXT, consistent sleep time, and reinforcement.	*Parent-reported daily sleep diaries:* Reduction in SOD from BL (M = 58.6 min, SD = 24.6min), to treatment (M = 15.8, SD = 7.8). 59% reduction in freq. NWs. *VAS and HBS (2 sleep items):* Sig. decrease in parent- and author rated sleep problem severity scores. *F/up:* Improvements maintained. Participant with SMS re-developed settling difficulties. CS eliminated for 10/11 children.	*Rigor:* Weak *Treatment outcome:* Positive
Curfs et al. (1999)	1F, 6 y, with Wolf-Hirschhorn syndrome and Seizure disorder	SOD and NW, including frequent crying.	Case study: AB design. *F/up:* 3 mo post-treatment.	*Setting:* Home *Agent:* Parent *Dosage:* 114 nights *Int:* EXT, reinforcement.	*Parent-reported daily sleep diaries*: Reduction in mean duration of night-time disruptions (BL = 116.03; treatment = 26.17). Freq. night-time disruptions reduced to 0. *F/up:* Improvements maintained.	*Rigor:* Weak *Treatment outcome:* Positive
Didden et al. (1998)	6 M, 2–7 y (M = 3.8 y). Various DD including 1 with PWS and 1 with FXS.	Bedtime resistance, SOD, NWs, and EDS. Child with FXS - bedtime fear + CS.	ABC, AB and B only design. *F/up*: 3–6 mo post-treatment.	*Setting:* Home *Agent:* Parent *Dosage:* Unclear *Int:* EXT, reinforcement. Desensitization (bedtime fear): 19 step procedure - differential reinforcement of appropriate bed-time behavior	*Parent-reported daily sleep diaries (duration of target behavior or partial interval recording in min):* Decrease in mean duration of sleep interfering behavior and mean duration of intervals with disruptive behavior across participants. *Bedtime fear*: completed all 19 steps (sleeping alone in own bed without fear). *F/up:* gains maintained	*Rigor*: Weak *Treatment outcome:* Positive
Montgomery et al. (2004)	24 F, 42 M, 2–8 y with various DD, including 2 children with AS, one child with WS, one child with triple X syndrome. four participants with comorbid epilepsy.	NW and SOD	RCT, three arm design with crossover control group. *Group 1*: Info. via booklet *Group 2*: Info. face to face *Group 3 (Control group):* no intervention + re-randomized into treatment F/up: 6 mo post-treatment.	*Setting:* Home *Agent:* Parents *Dosage:* 6 wks *Int:* Info. delivered about responding to sleep problems (e.g., normal sleep; monitoring behavior; good sleep habits; techniques for changings undesirable sleep behaviors).	*Parent reported sleep diaries (recorded for 2 wks before each assessment + 1 wk at F/up):* Both treatment groups had sig. lower mean CSDS (total score on each sleep problem) post-treatment compared to control group. Treatment effects similar regardless of delivery method. *Parental eval. of response to treatment:* 15/20 in Group 1 saw at least a 50% reduction in sleep issues. 15/22 saw a reduction in Group 2. 0/24 saw a reduction in the Control group. F/up: gains maintained	*Rigor:* Adequate *Treatment outcome:* Positive (both treatment groups)
Piazza et al. (1991)	3 F, 4–8 y (M = 6.7 y) with RS.	SOD, CCs, EDS, NWs (including SIB and screaming)..	Multiple BL across participants design. *F/up*: recorded for one child, timing unspecified.	*Setting:* Inpatient unit (2/3); home (1/3). *Agent:* Clinician (2/3); parent (1/3). *Dosage:* Unclear *Int:* FBRC (removal from bed and kept awake).	*Clinicians:* 24 h momentary time sampling (30 min intervals) in/out of bed; asleep/awake, SOD, duration of NWs. *Parental time-sampling:* until 12am, followed by two scheduled checks 2am and 4am. Increase in average percentage of appropriate sleep (during defined sleep periods) for all participants (Case 1: 87%–90%, Case 2: 69%–75%, Case 3: 81%–92%). Reduction in freq. and duration of NW for affected participants (Child 2: 1 h to 0.6 h, Child 3: 1.8 h–0.5 h). Reduction in daytime sleepiness (Case 1: 12%–2%, Case 3: 15%–7.2%). Reduction in SOD for affected participant (Case 1; 1:25 h–0.6 h). *F/up:* Gains maintained when recorded.	*Rigor:* Weak *Treatment outcome:* Positive

Piazza et al. (1997)	N = 14, 4–14 y (M = 7.8y) with various DD; 1 with PWS and sleep apnea	*Sleep problems*: NWs, early waking and SOD. .	Randomized, pre-test post-test, two arm design.	*Setting:* Inpatient unit *Agent:* Clinician *Dosage:* average of 8 wks (ceased upon patient discharge). *Int Procedure 1*: FBRC treatment (incl. child with PWS). *Procedure 2:* Bedtime scheduling	Procedures as described by Piazza et al. (1991). Sig. decrease in mean disturbed sleep hours across treatments. Procedure one mean decrease (1:44 h −0:53 h) sig. greater than the procedure two mean decrease (1.37–1:10 h). Participant with PWS early waking and NWs reduced to near zero following treatment.	*Rigor:* Weak *Treatment outcome:* Positive (both treatments)
Summers et al. (1992)	1 M, 9y with AS and seizure activity.	NWs, EDS, SWSD (disorganized type). Prior use of diphenhydramine hydrochloride (Benadryl) to aid sleep.	Quasi-experimental, interrupted time-series, single-case design. Phase 1: BL; Phase 2: behavior therapy + pharmacology; Phase 3: behavior therapy alone *F/up*: 45 d.	*Setting:* Inpatient unit + home *Agent:* Clinician + parent *Dosage:* Unclear *Int: Phase 2:* Elimination of daytime naps, consistent bedtime; remained in bed during NWs; 25 mg of diphenhydramine hydrochloride Phase 3: As above (sans medication). *F/up:* Behavioral treatment at home. Medication as required.	*Clinician:* Whole interval recordings (if asleep for entirety of 15 min period). *Parent recordings*: method unclear. Mean hours of night sleep sign, increased from BL (M = 1.9 h, SD = 1.4) to treatment (M = 8.3 h, SD = 1.1). Decrease in mean hours of night sleep in Phase 3 (M = 7.8 h, SD = 1.3). Mean hours of day sleep sign. less than BL across treatments. No sign. difference in mean hours of day sleep between combined phase (M = 0.08, SD = 0.21) and behavior therapy phase, (M = 0.7 h). *F/up:* Anecdotal report of 7–8 h of sleep per night and only one early waking, during one week period.	*Rigor:* Weak *Treatment outcome:* Positive
Weiskop et al. (2005)	10M, 3F, 1.1–9.1 y, (M = 5.1 y). *Study 1:* N = 6 with ASD and Asperger's. *Study 2:* N = 7 with FXS. one child medicated for sleep problem.	Sleep settling, bed-time refusal, NW, CS, or EMW.	Concurrent multiple BL across participants design *F/up*: 3 mo post-treatment	*Setting:* Home *Agent:* Parent *Dosage:* min. 7 wks *Int:* 3, weekly individual parent-training sessions. Taught behavioral interventions (e.g., set bedtime and routine, reinforcement, EXT, visual schedule).	*Parent-recorded daily sleep diaries:* Weekly reduction in average pre-sleep disturbances, established independent sleep onset for affected participants. Reduction in average SOD for 6/10 participants. Reduction in frequency of NWs for 7/8 children. Elimination of CS for affected participants (6/6). Average night-time sleep duration varied. *GAS*: increase in goal achievement from BL *F/up:* Gains maintained across dimensions for some but not all affected participants.	*Rigor:* Adequate *Treatment outcome:* Mixed

AARP = *Abbreviated Acceptability Rating Profile*, ACSHQ = Abbreviated Children's Sleep Habits Questionnaire, AS = Angelman Syndrome, BL = Baseline, CS = Co-sleeping, CSDS = Composite Sleep Disturbance Scores, DBC = Disruptive Behavior Composite (mean disturbances per night), DD = Developmental Disabilities, DVs = Dependent Variables, EDS = Excessive Daytime Sleepiness, EMW = Early Morning Waking, EXT = Extinction, FBRC = Faded-bedtime with response-cost, FXS = Fragile X Syndrome, F/up = Follow-up, GAS = Goal Achievement Scale, HBS = Handicaps, Behaviors and Skills Scale, IOA = Interobserver Agreement, ISO = Independent Sleep Onset (weekly percentage), M = Mean, NW = Night Wakings, RCT = Randomized Controlled Trial, RS = Rett syndrome, SD = Standard Deviation, SE = Sleep Efficiency, SMS = Smith-Magenis syndrome, SOD = Sleep Onset Delay, Sr = Reinforcement, SWSD = Sleep-wake Schedule Disorder, TST = Total Sleep Time, VAS = Visual Analog Scale, WASO = Wake After Sleep Onset, WS = Williams syndrome.

was gradually increased across the 19 stages using edible and social reinforcement.

Parent training/psychoeducation procedure alone

In one study [47], the focus was on investigating the effectiveness of behaviorally-based treatment delivered face-to-face (one 90-min session) versus via a booklet. In that study, participants were assigned to one of two treatment groups or a control group. In both treatment groups, the following behavioral techniques were addressed: sleep hygiene, extinction with modifications, and reinforcement [47]. Weiskop et al. [45], also used parent training procedures in which parents attended three, weekly, individual parent-training sessions where they were taught about the effects of antecedents and consequences on children's behavior, extinction techniques, reinforcement, and sleep hygiene. Parents were supported to determine goals for their child and set a regular bedtime and bedtime routine, in addition to other behavioral strategies (e.g., the use of reinforcement and extinction) [45].

Setting and intervention agent

Interventions were predominantly implemented in the family home by the parents ($n = 6$) [41,44–48]. The three exceptions to this involved implementation of treatment by clinicians in in-patient units [40] or some variation of implementation in home and in-patient settings [42]. For example, in one study treatment was implemented in the in-patient unit, with in-home implementation and follow-up data collected by the parent [43]. Similarly, in another study the intervention was implemented in the home with the parent as the intervention agent for one of three participants, while intervention was conducted in an in-patient setting by clinicians for other participants [42]. Across studies, intervention lasted from two weeks to 114 d ($M = 53$ nights).

Dependent variable data collection procedures

Five studies relied on parent-reported sleep diaries as the primary measure of sleep and sleep treatment outcomes [41,44,45,47,48]. In two cases, this was combined with an additional subjective rating [46,48]. Four studies also used a momentary time-sampling, partial or whole interval recording procedure [40–43] to measure sleep for some or all participants. Only one study used actigraphy to measure sleep outcomes [46].

Dependent variables that were assessed included asleep/awake, time of morning waking, frequency and duration of night-wakings, early morning wakings, duration of sleep interfering behavior, mean nightly disturbances, SOD, and independent sleep onset. Actigraphy was also used in one study as a measure of total sleep time (TST), wake after sleep onset (WASO) and sleep efficiency (SE) [46]. At times this information was used to calculate a percentage of appropriate sleep during defined sleep periods and inappropriate sleep occurring outside of that defined period [40,42]. In order to measure the effectiveness of the desensitization procedure, Didden et al. [41], recorded the number of steps in the hierarchy that were completed each night. Finally, Weiskop et al. [45], also used the Goal Achievement Scale to measure parent-reported achievement of treatment goals.

Study findings

Treatment effects

Seven studies (77.8%) reported positive treatment outcomes [40–44,48] and two studies reported mixed results [45,46]. In one study [47], treatment outcomes were positive based on group statistical analysis (i.e., both treatment groups had significantly lower composite sleep disturbance scores post-treatment, when compared to control group). However, in that study, individual parental evaluation of responses indicated that most -but not all-parents reported a reduction in sleep problems and therefore the result was classified as mixed. Mixed treatment outcomes were also reported in a multi-component intervention study as sleep improved on all dependent variables except WASO [46].

In almost all of the studies, intervention consisted of multiple treatment components. As a result, it is difficult to determine the effects of isolated treatment components. Common components to effective treatments included modification to sleep hygiene, extinction or modified extinction, and reinforcement. Interventions that consisted of only a single component (e.g., bedtime fading with a response-cost) also resulted in a reduction in sleep problems.

Follow-up

All but one study [40] assessed the maintenance of treatment gains by recording follow-up data for some or all participants. Follow-up data was recorded one to 18 mo following treatment and was typically recorded for seven to 14 d, the exception being Summers et al. [43], wherein parental follow-up data was collected for a 45-d period. For two studies, short- and long-term follow-up data were collected [46,48]. For seven out of eight studies, treatment gains were maintained or improved at follow-up [41,42,44–48]. For one study, sleep outcomes deteriorated [43] when compared to the combined behavioral plus pharmacological treatment condition.

Study rigor

Study design rigor was evaluated for each of the nine included studies. No study was considered ‘strong’, three studies met criteria of ‘adequate’ strength, and six studies were rated as being ‘weak’. In regard to primary quality indicators, all nine studies received high quality ratings for independent variables (e.g., treatment was described in replicable detail) and comparison conditions (group design studies only) and most studies met relevant criteria to receive a high rating on dependent variables (e.g., dependent variables were operationally defined and logically aligned with treatment outcomes). By contrast, several single case studies failed to demonstrate experimental control due to absence of replication (e.g., AB design studies) or due to insufficient statistical power in group designs. Issues with baseline conditions (i.e., instability of baseline data), visual analysis (unstable trends and overlapping data points), and participants (e.g., failure to report standardized test scores) resulted in a number of SCRD studies receiving ratings of ‘weak’. In regard to secondary indicators, an absence of IOA, treatment fidelity data, and blind rating negatively impacted upon the research rigor in both single-case and group design studies. By contrast, maintenance data were frequently recorded ($n = 8$) and the social validity of the research was generally high ($n = 6$). Of the studies that reported positive treatment outcomes, six were rated as being weak, whilst only one had adequate strength. The two studies reporting mixed outcomes, met criteria of adequate strength. A summary of ratings is presented in Table 1.

Discussion

This review sought to investigate the effectiveness of behavioral interventions for sleep problems in children and adolescents with RGND. Nine studies were identified that provided intervention to children with FXS, RTT, PWS, SMS, AS, Triple X syndrome, and Wolf-Hirschorn syndrome. Of these

studies, seven demonstrated positive treatment effects and two were mixed. In most studies, treatments (including the content of parent education programmes) consisted of multiple behavioral components, including extinction, reinforcement and/or modifications to both sleep hygiene practices and the sleep/wake schedule. However, in three studies EXT and reinforcement and bedtime fading (with or without a response-cost) used in isolation was sufficient to result in a reduction in sleep problems. Treatment was most often implemented in the home by parents; suggesting behavioral-focused strategies may be effective in improving sleep in this population. However, caution is warranted because only three studies met criteria for an adequate level of rigor and no study was considered to provide a strong demonstration of effects. Across studies, the most common limitations associated with research procedures were an absence of IOA, treatment fidelity and blind ratings, as well as issues associated with experimental control (e.g., limited replications of effects in SCRD).

The results of these studies considered in tandem with the research rigor ratings [36], highlight some of the unique challenges associated with sleep research and presents opportunities for future research to replicate and extend promising findings. Because behaviorally-based interventions for sleep disturbance are implemented overnight by parents in the home, collection of IOA and treatment fidelity data by a second observer/researcher may be considered overly intrusive by some families. Further, collecting video recordings in a person's bedroom raises a number of ethical and privacy considerations presenting obstacles to many criteria strong research procedures (e.g., direct observation, blind rating and treatment fidelity). Issues associated with experimental control were also identified in this review and may be difficult to overcome. For example, working with children with rare developmental disabilities precludes conducting larger *N* single-case design studies (e.g., multiple baseline across participants) or RCTs with sufficient power. The heterogeneity of behavioral phenotypes and the topography of sleep problems within and across developmental disabilities, can also necessitate the use of individualized treatments, wherein data can only be reported in Case study or AB design format. Thus, drawing conclusions about treatment effects for specific disorders requires multiple replications of treatment effects across participants, contributing toward the corpus of collective research in this area.

Current practice and future research

The findings of this review foreground many important practical recommendations and suggest directions for future research in this area. First, the treatments that have been evaluated have many of the same components that have been found to be successful with other populations. For example, reinforcement, extinction, modification of sleep environment and establishing a healthy sleep routine were among the most common approaches used and each of these components have been used with success in treating sleep problems in other populations [29–31]. Therefore, the findings of this review suggest that the differences in presentation and potential differences in etiology of sleep problem may not require unique treatment approaches. Although future research remains warranted, that research should perhaps emphasize further replication and extension of the behavioral approach that has been effective with other populations.

Second, conducting future intervention research that has the potential for increased certainty of evidence (i.e., improved rigor), may initially require studies designed to evaluate the veracity of various data sources, accuracy of alternative data collection methods and other similar research design procedure and protocol modifications. If sleep science is to be advanced, researchers must identify and utilize technologies that provide an accurate, cost-effective and objective in home assessment of sleep. For example, using Bluetooth or smartphone technologies, pressure sensitive bed foils, and polysomnography systems that integrate wireless data transmission, such as those being introduced for use with patients with obstructive sleep apnea [49]. Research should also make greater use of video analysis and actigraphy as a means of data collection. Although privacy issues must be carefully considered with input from families, the analysis of video recordings could be used to triangulate parent-reported sleep diary data and gather information about adherence to the treatment protocol, thus providing a measure of IOA and treatment fidelity. Dual parent recordings of treatment checklists which outline each treatment step may also offer a low-tech, efficient alternative for recording treatment fidelity. The use of video recording could also enhance the accuracy of assessment and treatment data as it allows for the detection of non-signaled awakenings and other behaviors occurring in the bedroom that parents might not otherwise know about.

Third, given the heterogeneity of RGND, future research should endeavor to provide additional information about the participant characteristics (e.g., standardized assessment outcomes), and any information about variables contributing toward the sleep problem (e.g., nocturnal seizure disorders, obstructive sleep apnea), or previous treatments that may have been tried (e.g., melatonin). More extensive reporting of individual characteristics and assessment information can allow more precise conclusions to be drawn regarding the effects of behavioral intervention and whether this may interact with the underlying etiology of sleep problems or atypicalities that are so frequently observed in children with RGND (e.g., nocturnal seizure activity and sleep apnea) and/or whether the effectiveness of interventions may be mediated by other characteristics (e.g., cognitive ability). In the existing research, the presence of medical co-morbidities such as seizure disorders did not appear to affect the treatment outcome. However, it is the view of the study authors that medical complexities and contra-indicators for behavioral treatment are carefully assessed among a multi-disciplinary team prior to commencing treatment.

Finally, although a large-scale RCT investigation in this area would likely be prohibitively complex, rigorously designed single-case non-concurrent multiple baseline or alternating treatment design studies with the capability of demonstrating multiple replications of treatment effects could add to the existing corpus of research. Additionally, given both the plethora of evidence to support the use of pharmacological interventions for sleep problems in children with RGND [26,27] but also the limitations of such approaches, future research may undertake to evaluate the relative combined efficacy of combined pharmacological and behavioral interventions.

Despite challenges, additional research in the treatment of sleep problems in people with RGND is necessary and the studies reviewed here suggest it would be fruitful. Consigning a child and their parents to the chronic consequences of prolonged sleep deprivation because a condition is rare, complex to treat or viewed as the inevitable outcome of genetic abnormalities is undesirable and underpins the importance of further research in this area. Given 1) the effectiveness of behaviorally-based interventions for sleep problems in children with higher incidence developmental disorders and a similar combination of biopsychosocial variables [29,30]; 2) the promising effects and high social validity of those behaviorally-based interventions in this review; and 3) considerable

potential to benefit children and their families, further research into the effectiveness of behavioral treatments for children with RGND is warranted.

Practice points

1. There is **a paucity of** evidence of the positive effects of behavioral treatments for sleep problems in children and young people with RGND, including extinction, reinforcement, and modification of sleep hygiene and sleep-wake schedules.
2. Parent-implemented, home-based, behavioral interventions can be effective in those with RGND
3. Small group parental psychoeducation may be an effective and efficient means of delivering information about behavioral interventions for children with RGND
4. Rigorous assessment of the variables that underpin the sleep problem for individual children may help to inform the type of intervention strategies selected

Research agenda

1. Research on this topic faces numerous challenges related to the heterogeneity and rarity of the population, the heterogeneity of sleep presentations, as well as the inaccessibility of the target behaviors
2. The use of rigorously designed experimental single-case research studies (e.g., non-concurrent multiple baseline or alternating treatment designs) may provide a viable alternative to large scale RCTs, while also being responsive to the heterogeneity of the participants.
3. Future research should utilize the potential of technological advances (e.g., Bluetooth technology, wireless sensors) actigraphy and video recording as an objective measure of sleep outcomes that also permits triangulation of sleep diaries for IOA purposes.
4. Efforts to establish blind ratings, IOA, and treatment fidelity would greatly increase the rigor of behavioral sleep research.
5. Including details of participant characteristics may lead to more precise conclusions about the applicability of techniques to individuals and/or medical comorbidities or complexities that may be contra-indicators for behavioral intervention.
6. Further investigations are recommended into the effectiveness of behavioral interventions for sleep problems in adults with RGND

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

References

[1] Davis AS, Hoover KL, Mion AM. Understanding and treating children and adolescents with neurodevelopmental disorders. In: Butcher JN, Kendall PC, editors. APA handbook of psychopathology: child and adolescent psychopathology. Washington, DC, US: American Psychological Association; 2018. p. 279–315.
[2] European Commission, (n.d.). Rare diseases: Commission activities in the area of Rare diseases. Retrieved April, 2019, from http://ec.europa.eu/research/health/index.cfm?pg=area&areaname=rare.
[3] Young D, Nagarajan L, de Klerk N, Jacoby P, Ellaway C, Leonard H. Sleep problems in Rett syndrome. Brain Dev 2007;29:609–16. https://doi.org/10.1016/j.braindev.2007.04.001.
[4] Dykens EM, Kasari C. Maladaptive behaviour in children with Prader-Willi syndrome, Down syndrome, and nonspecific mental retardation. Am J Ment Retard 1998;102:228–37.
[5] Kronk R, Bishop EE, Raspa M, Bickel JO, Mandel DA, Bailey DJ. Prevalence, nature, and correlates of sleep problems among children with Fragile X syndrome based on a large scale parent survey. Sleep J Sleep Sleep Dis Res 2010;33:679–87. https://doi.org/10.1093/sleep/33.5.679.
*[6] Richdale A, Cotton S, Hibbit K. Sleep and behaviour problems in the Prader–Willi syndrome: a questionnaire study. J Intellect Disabil Res 1999;43:380–92.
[7] Summers JA, Allison DB, Lynch PS, Sandler L. Behaviour problems in AS. J Intellect Disabil Res 1995;39:97–106.
[8] Wong K, Leonard H, Jacoby P, Ellaway C, Downs J. The trajectories of sleep disturbances in Rett syndrome. J Sleep Res 2015;24:223–33.
[9] Bruni O, Ferri R, D'Agostino G, Miano S, Roccella M, Elia M. Sleep disturbances in Angelman syndrome: a questionnaire study. Brain Dev 2004;26:233–40. https://doi.org/10.1016/S0387-7604(03)00160-8.
[10] Miano S, Bruni O, Elia M, Musumeci A, Verrillo E, Ferri R. Sleep breathing and periodic leg movement pattern in Angelman Syndrome: a polysomnographic study. Clin Neurophysiol 2005;116:2685–92.
[11] Hagberg B. Rett syndrome: long-term clinical follow-up experiences over four decades. J Child Neurol 2005;20:722–7.
[12] Annaz D, Hill C, Holley S, Karmiloff-Smith A. Characterization of sleep problems in children with Williams syndrome. Res Dev Disabil 2011;32:164–9.
[13] Cassidy SB, McKillop JA, Morgan WJ. Sleep disorders in Prader-Willi syndrome. Dysm Clin Gen 1990;4:13–7.
[14] Helbing-Zwanenburg B, Kamphusien HAC, Mourtazaev MS. The origin of excessive daytime sleepiness in the Prader-Willi syndrome. J Intellect Disabil Res 1993;37:533–41.
[15] Colten HR, Altevogt BM, editors. Sleep disorders and sleep deprivation: an unmet public health problem. Institute of medicine (US) Committee on sleep medicine and research. Washington (DC): The National Academies Press; 2006.
[16] Chu J, Richdale AL. Sleep quality and psychological wellbeing in mothers of children with developmental disabilities. Res Dev Disabil 2009;30:1512–22.
[17] Cotton S, Richdale A. Sleep patterns and behavior in typically developing children and children with autism, Down syndrome, Prader-Willi syndrome and intellectual disability. Res Autism Spectr Disord 2010;4:490–500.
[18] McDougall A, Kerr AM, Espie CA. Sleep disturbance in children with Rett syndrome: a qualitative investigation of the parental experience. J Appl Res Intellect Disabil 2005;18:201–15.
[19] Richdale AL. Autism and other developmental disabilities. In: Wolfson AR, Montgomery-Downs H, editors. The oxford handbook of infant, child, and adolescent sleep and behavior. Oxford, UK: Oxford University Press; 2013. p. 471–94.
[20] Mann-Dosier LBM, Vaughn BV, Fan Z. Sleep disorders in childhood neurogenetic disorders. Children 2017;4:82. http://doi.org/10.3390/children4090082.
[21] Potocki L, Glaze D, Tan DX, Park SS, Kashork CD, Shaffer LG, et al. Circadian rhythm abnormalities of melatonin in Smith-Magenis syndrome. J Med Genet 2000;37:428–33.
[22] Spruyt K, Braam W, Smits M, Curfs LM. Sleep complaints and the 24-h melatonin level in individuals with Smith–Magenis syndrome: assessment for effective intervention. CNS Neurosci Ther 2016;22:928–35. https://doi.org/10.1111/cns.12653.
[23] Takaesu Y, Komada Y, Inoue Y. Melatonin profile and its relation to circadian rhythm sleep disorders in Angelman syndrome patients. Sleep Med 2012;13:1164–70. https://doi.org/10.1016/j.sleep.2012.06.015.
[24] Bailey DJ, Raspa M, Bishop E, Olmsted M, Mallya UG, Berry-Kravis E. Medication utilization for targeted symptoms in children and adults with fragile X syndrome: US survey. J Dev Behav Pediatr 2012;33:62–9.
[25] Braam W, Didden R, Smits MG, Curfs LG. Melatonin for chronic insomnia in Angelman syndrome: a randomized placebo-controlled trial. J Child Neurol 2008;23:649–54. https://doi.org/10.1177/0883073808314153.
[26] Gringas P, Nir T, Breddy J, Frydman-Marom A, Findling RL. Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2017;56:948–57.
[27] Bruni O, Alonso-Alconada D, Besag F, Biran V, Braam W, Cortese S, et al. Current role of melatonin in pediatric neurology: clinical recommendations. Eur J Paediatr Neurol 2014;12:1–12.
[28] Bramble D. Consumer opinion concerning the treatment of a common sleep problem. Child Care Health Dev 1996;22:355–66. https://doi.org/10.1111/j.1365.2214.1996.tb00438.x.
[29] Rigney G, Ali NS, Corkum PV, Brown CA, Constantin E, Godbout R, et al. A systematic review to explore the feasibility of a behavioural sleep

* The most important references are denoted by an asterisk.

intervention for insomnia in children with neurodevelopmental disorders: a transdiagnostic approach. Sleep Med Rev 2018;41:244–54.
[30] Turner KS, Johnson CR. Behavioral interventions to address sleep disturbances in children with autism spectrum disorders: a review. Top Early Child Spec Educ 2012;33:144–52.
[31] Vriend JL, Corkum PV, Moon EC, Smith IM. Behavioral interventions for sleep problems in children with autism spectrum disorders: current findings and future directions. J Pediatr Psychol 2011;36:1017–29. https://doi.org/10.1093/jpepsy/jsr044.
[32] Stores G. Annotation: sleep studies in children with a mental handicap. J Child Psychol Psychiatry 1992;33:1303–17.
[33] Ledbetter-Cho K, Lang R, Watkins L, O'Reilly M, Zamora C. Systematic review of collateral effects of focused interventions for children with autism spectrum disorder. Autism Dev Lang Impair 2017;2:1–22.
[34] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;7. https://doi.org/10.1371/journal.pmed.1000097.
[35] Cooper JD, Heron TE, Heward WL. Applied behavior analysis. Columbus, OH: Merrill; 2007.
[36] Reichow B, Volkmar FR, Cicchetti DV. Development of the evaluative method for evaluating and determining evidence-based practices in autism. J Autism Dev Disord 2008;38:1311–9. https://doi.org/10.1007/s10803-007-0517-7.
[37] Alresheed F, Machalicek W, Sandford A, Bano C. Academic and related skills interventions for autism: a 20-year systematic review of single case research. Rev J Autism Dev Disord 2018. https://doi.org/10.1007/s40489-018-0141-9.
[38] Whalon KJ, Conroy MA, Martinez JR, Werch BL. School-based peer-related social competence interventions for children with autism spectrum disorder: a meta-analysis and descriptive review of single case research design studies. J Autism Dev Disord 2015;45:1513–31. https://doi.org/10.1007/s10803-015-2373-1.
[39] Mulloy A, Lang R, O'Reilly M, Sigafoos J, Lancioni G, Rispoli M. Gluten-free and casein-free diets in the treatment of autism spectrum disorders: a systematic review. Res Autism Spectr Disord 2010;4:328–39. https://doi.org/10.1016/j.rasd.2009.10.008.
*[40] Piazza CC, Fisher WW, Sherer M. Treatment of multiple sleep problems in children with developmental disabilities: faded bedtime with response cost versus bedtime scheduling. Dev Med Child Neurol 1997;39:414–8.
*[41] Didden R, Curfs LG, Sikkema SE, de Moor J. Functional assessment and treatment of sleeping problems with developmentally disabled children: six case studies. J Behav Ther Exp Psychiatry 1998;29:85–97. https://doi.org/10.1016/S0005-7916(97)00038-4.
*[42] Piazza CC, Fisher W, Moser H. Behavioural treatment of sleep dysfunction in patients with the Rett syndrome. Brain Dev 1991;13:232–7.
[43] Summers JA, Lynch PS, Harris JC, Burke JC, Allison DB, Sandler L. A combined behavioral/pharmacological treatment of sleep-wake schedule disorder in Angelman syndrome. J Dev Behav Pediatr 1992;13:284–7. https://doi.org/10.1097/00004703-199208000-00009.
*[44] Curfs LM, Didden R, Sikkema SP, De Die-Smulders CE. Management of sleeping problems in Wolf-Hirschhorn syndrome: a case study. J Genet Couns 1999;10:345–50.
*[45] Weiskop S, Richdale A, Matthews J. Behavioural treatment to reduce sleep problems in children with autism or fragile X syndrome. Dev Med Child Neurol 2005;47:94–104.
*[46] Allen KD, Kuhn BR, Dehaai KA, Wallace DP. Evaluation of a behavioral treatment package to reduce sleep problems in children with Angelman syndrome. Res Dev Disabil 2013;34:676–86.
*[47] Montgomery P, Stores G, Wiggs L. The relative efficacy of two brief treatments for sleep problems in young learning disabled (mentally retarded) children: a randomised controlled trial. Arch Dis Child 2004;89:125–30.
*[48] Bramble D. Rapid-acting treatment for a common sleep problem. Dev Med Child Neurol 1996;39:543–7.
[49] Penzel T, Schobel C, Fietze I. New technologies to assess sleep apnea: wearables, smart phones, and accessories. F1000 Res 2018;7:413. https://doi.org/10.12688/f1000research.13010.1.