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Protocol for targeting insomnia in school-aged children with autism spectrum disorder without intellectual disability: a randomised control trial

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ABSTRACT

Introduction Insomnia affects up to 80% of children with autism spectrum disorder (ASD). Negative consequences of insomnia in ASD include decreased quality of life (QOL), impaired learning and cognition, increased stereotypic and challenging behaviours, and increased parental stress. Cognitive behavioural treatment for childhood insomnia (CBT-CI) is a promising treatment for dealing with insomnia and its negative consequences but has not yet been studied in school-aged children with ASD and comorbid insomnia. Access to healthcare is another challenge for children with ASD, particularly in rural and underserved regions. Previous studies indicate that ASD and insomnia share common arousal-based underpinnings, and we hypothesise that CBT-CI will reduce the hyperarousal associated with insomnia and ASD. This trial will be the first to examine CBT-CI adapted for children with ASD and will provide new information about two different modes of delivery across a variety of primary and secondary child and parent sleep and related outcomes. Knowledge obtained from this trial might allow us to develop new or modify current treatments to better target childhood insomnia and ASD.

Methods and analysis Children (N=180) 6–12 years of age with ASD and insomnia will be recruited from an established autism database, a paediatric clinic and community outreach in the Columbia, MO and surrounding areas. Participants will be randomised to CBT-CI adapted for children with ASD (in-person or remote using computers with cameras) or Sleep Hygiene and Related Education. Participants will be assessed at baseline, post-treatment, 6-month and 12-month follow-ups. The following assessments will be completed regarding the children: objective and subjective sleep, daytime functioning (adaptive functioning, attention, challenging behaviours, anxiety), QOL and physiological arousal (heart rate variability) and parents: objective and subjective sleep, daytime functioning (anxiety, depression, fatigue), QOL, physiological arousal and parental burden/stress.

Ethics and dissemination Ethics approval was obtained in January 2020 from the University of Missouri. Ethics approval was obtained in July 2020 from the US Army Medical Research and Development Command, Office of Research Protections and Human Research Protection Office. All data are expected to be collected by 2024. Full trial results are planned to be published by 2025. Secondary analyses of baseline data will be subsequently published.

Trial registration number NCT04545606; Pre-results.

Strengths and limitations of this study

- ► Four-week cognitive–behavioural therapy for insomnia in children with autism (cognitive behavioural treatment for childhood insomnia, CBT-CI) integrates sleep education, hygiene, stimulus control, positive parenting behaviours, relaxation and cognitive restructuring techniques and will be examined relative to Sleep Hygiene and Related Education (SHARE).
- ► CBT-CI will be conducted in-person and remotely to examine the differences in the two modalities of treatment.
- ► Investigation of the mediating impact of sleep and arousal on child and parent variables will further our understanding of the common arousal-based underpinnings of insomnia and autism.
- ► Six-month and 12-month follow-up will enable examination of persistence of behavioural outcomes of CBT-CI.
- ► Potential limitations include participant attrition at follow-up, which may contribute to selection bias associated with systematic differences between participants completing CBT-CI in-person and remotely, in addition to versus SHARE.

INTRODUCTION

Background

Insomnia (difficulties falling and/or staying asleep as well as daytime dysfunction) impacts up to 80% of children with autism spectrum disorder (ASD)[1] and is associated with decreased quality of life (QOL), exacerbation of core and associated ASD symptoms (increased severity of challenging behaviours, social skill deficits, repetitive behaviours)[2]; reduced parent sleep and increased parenting stress.[3] ASD incidence[4] and prevalence[5] have

increased dramatically in recent decades, with 1 in 54 US children affected.[6] ASD poses significant economic and psychosocial burden to families and communities.[7–9] Improving the health and well-being of children with ASD is a major priority across federal agencies, resulting in the establishment of the Interagency Autism Coordinating Committee.

Cognitive behavioural treatment for childhood insomnia (CBT-CI) which involves stimulus control, sleep consolidation training and strategies for reducing sleep interfering thoughts and worries is a promising treatment for dealing with insomnia and its consequences.[10–14] However, research in school-aged youth with ASD is sparse and consists largely of single-arm studies in children younger than 3 years old.[15] Similarly, research has focused on brief parent-based behavioural sleep education but not clinical interventions for sleep difficulties in children with ASD.[15 16] Thus, our team developed a CBT-CI protocol adapted for children with ASD ages 8–12 and conducted single arm pilots (n=17) in-person and (n=17) remotely that found significant improvements in child and parent sleep and daytime functioning.[13 14]

ASD and insomnia

ASD is a complex neurodevelopmental disorder characterised by impaired social interaction/communication and restricted/repetitive behaviours and interests.[17] The diagnostic features of ASD are impairments in social/communication skills and repetitive behaviours; yet children with ASD also have high rates of medical comorbidites,[17] which often have additional significant detrimental effects.

Insomnia in children involves complaint (child or caregiver) of dissatisfaction with sleep quality or quantity and manifests as one or a combination of the following symptoms: difficulty falling and/or staying asleep (including conditioned difficulty in the absence of caregiver intervention), early morning awakening and inability to return to sleep, an inconsistent or irregular sleep schedule and/or a poor or inconsistent bedtime routine.[17] It can have significant negative effects on learning and attention, QOL and daytime functioning. Importantly, it can also exacerbate symptoms of ASD, leading to increased severity of challenging behaviours, social skill deficits and repetitive behaviours.[2 18 19] Insomnia in children with ASD also affects the entire family, resulting in reduced parental sleep and increased parenting stress.[3 20]

Suggested aetiological factors underlying the high comorbidity of insomnia in ASD include biological abnormalities (eg, timing of melatonin secretion), medical conditions (eg, GI disturbance, epilepsy), anxiety, hyperarousal, medications, cognitive patterns (eg, night-time worrying, fears) and behaviours (eg, poor bedtime routine).[21 22] The communication and behavioural problems associated with ASD may make it difficult for parents to establish consistent bedtime routines and other sleep-promoting behaviours.

Hyperarousal

The Hyperarousal Model of Insomnia[23] assumes increased levels of physiological arousal interfere with falling and/or staying asleep. This model is highly relevant to children with ASD, who are at high risk for arousal dysregulation.[24–26] Emerging research suggests hyperarousal is associated with sleep disruption in children with ASD, showing both higher heart rate (HR) and lower HR variability (HRV) during sleep among children with ASD as compared with those with typical development.[27] In addition, children with ASD show great variability in regulation of the stress hormone, cortisol, with evidence of elevated evening levels.[25 28 29] Regarding arousal-related symptoms, children with ASD often demonstrate anxiety-related night-time behaviours[30] and greater sensitivity to the sleep environment than children with other developmental problems.[31] Further, sensory problems and anxiety are associated with sleep problems in children and adolescents with ASD.[21 32–35]

CBT-CI and sleep

Behavioural treatment (based on learning principles) has been shown to improve sleep in very young children,[36–38] and at least one controlled study indicates it is also efficacious for very young children with ASD.[16] Behavioural sleep interventions are the preferred approach suggested by the Autism Treatment Network (ATN) when treating insomnia in ASD.[39] However, evidence to date consists primarily of case reports or case series and has generally focused on very young children (<3 years). Malow *et al*[15] tested a brief (single 60–90 min session) parent-based behavioural treatment for children with ASD and found sleep latency was reduced by ~20 min on average, while wake time during the night did not improve.

However, CBT-CI may represent a better approach for treating sleep problems in older children with ASD due to the complex nature of sleep problems in school-aged children. In contrast to the brief parental education focus of the behavioural intervention outlined in the ATN pathway, CBT-CI includes a broader variety of behavioural and cognitive techniques and includes both parent(s) and child in multiple treatment sessions. It uses established techniques (ie, stimulus control, limit setting) to target the child's cognitive patterns (eg, anxiety, repetitive thoughts) and behaviours (eg, bedtime electronics) and poor parental limit-setting (eg, inconsistent bedtime routine)[10–12]—all known contributors to insomnia in children with ASD. Also, sleep problems are more complex in older children. Meltzer and Mindell[10] noted in their review of paediatric behavioural sleep interventions (including CBT-CI) that treatment for school-aged children and adolescents often needs to target the physiological arousal associated with emotional stress and anxiety. Because sleep problems at this age are similar to those in adults with insomnia, older children often need CBT that includes techniques that are efficacious in adults (eg, relaxation, cognitive therapy). Despite expert support

for the use of CBT-CI in school-aged children, research examining its efficacy in this age group is limited.

Although sparse, studies that have been done suggest CBT-CI is efficacious in school-aged children. For example, Cortesi *et al*[40] found the addition of a cognitive–behavioural intervention to a melatonin prescription was more effective than melatonin or a cognitive–behavioural intervention alone in a sample of 4–10 years old with ASD. However, methodological rigour is lacking, as the studies have primarily used single-arm designs and have not used physiological screening for obstructive sleep apnoea or other primary sleep disorders—with at least one notable exception. Paine and Gradisar published a CBT-CI randomised controlled trial (RCT) that found significant improvements in sleep in typically developing (TD) school-aged children as a result of a six-session protocol.[41] That trial's use of a waitlist control makes it one of (if not 'the') strongest relative to the single-arm designs of other CBT-CI studies in this age group. Another recent trial lends support to the efficacy of CBT-CI in school-aged children. Specifically, sleep improvements were found following CBT-CI in TD school-aged children.[13 14] Importantly, that federally funded RCT represents key methodological improvements over most existing studies, namely use of an active control group and objective screening for apnoea and other non-insomnia sleep disorders. Similarly, Keogh *et al*[42] conducted a review and meta-analysis of RCTs examining the impact of behavioural sleep interventions among children with ASD and found that although RCTs in this area were scarce (three studies qualified), there is evidence for the effectiveness of behavioural treatments.

Pilot studies

Currently, there are only two pilot studies that have examined CBT-CI (both in person and remote) in school-aged children with ASD. Both were conducted by our team. In a single arm pilot, in-person CBT-CI (n=17) conducted over 8 weeks of treatment improved both objective and subjective child total sleep and total wake time, and decreased reports of child daytime dysfunction (ie, irritability, lethargy and hyperactivity) as well as less reports of ASD symptomology (ie, stereotypy).[13] One month later, objective total sleep time continued to improve, and the amount of inappropriate speech decreased; however, decreases in hyperactivity were not sustained. All other gains were maintained. In addition, parent objective total sleep time, total wake time, sleep-onset latency and sleep efficiency improved, as did subjective sleep onset latency, sleep efficiency, and total wake time. One month later, all gains were maintained and parent fatigue had decreased.

However, 58% of interested families were unable to participate in the in-person pilot due to travel burden. Of those who were able to participate, >50% suggested we offer the treatment remotely. Access to healthcare poses a challenge for children with ASD because they have greater unmet healthcare needs and less access to quality care than children with other special healthcare needs.[43–46] Remote treatment delivery could improve access,[47–54] but has not been tested. Thus, we conducted a remote CBT-CI (n=17) follow-up (FU) single-arm pilot using video conferencing.[14]

The results from the remote pilot indicated that treatment improved objective and subjective sleep-onset latency, total wake time, total sleep time and sleep efficiency as well as reported challenging behaviours (eg, irritability, lethargy and hyperactivity) and ASD behaviours (ie, stereotypy).[14] At 1-month FU, inappropriate speech had improved but hyperactivity increased from post-treatment levels. All other gains were maintained. Parents also experienced improvements in objective and subjective sleep onset latency, total wake time and sleep efficiency, as well as objective total sleep time and fatigue. These gains were sustained at the 1-month FU. Although there were not enough participants to draw definitive conclusions, 70% of children who completed HRV assessments had an increase in root mean squared SD (RMSSD) of normal to normal heartbeat intervals (RMSSD), suggesting their physiological arousal had decreased. Similarly, 60% of children's low frequency/high frequency (LF/HF) ratio decreased after treatment, indicating a decrease in sympathetic predominance, another indicator of improved autonomic nervous system (ANS) regulation.

Parent feedback in both pilots indicated that parents felt their children's sleep difficulties improved early on in the eight-session treatment and suggested shorter treatment length to reduce the burden of treatment.[13 14] Similarly, parents requested the addition of booster sessions to increase engagement throughout the FU periods and to aid in the long-term implementation of treatment strategies.

While the findings from these pilot studies were promising and demonstrated the preliminary efficacy of both in person and remote CBT-CI for improving sleep and daytime functioning in school-aged children with ASD, they warrant further investigation in a larger sample and comparison to active control conditions across a wider range of outcomes. To that end, the current trial improves on the pilots because it uses a more rigorous approach. Specifically, rigour has been increased in the current trial through the use of random assignment of participating families to one of three arms—in-person CBT-CI, remote CBT-CI or Sleep Hygiene and Related Education (SHARE). Parent feedback and results from the pilots indicated that children and parents exhibited rapid improvement in the first four sessions and had maintenance of gains from sessions 5–8. The most relevant modules also were covered during the first four sessions, leaving less relevant material for the latter sessions. Thus, we shortened the trial protocol to four sessions. Our focus on a briefer (four sessions) protocol is important because it minimises child/family burden while optimising treatment efficacy/efficiency. This current trial also increases the number and length of FUs from a single, 1-month FU in our pilot work to two longer FUs (ie, 6 and 12 months), allowing for examination of longer-term maintenance of treatment gains.

Moreover, our examination of arousal in the current study is important given the conceptualised role of physiological hyperarousal in both ASD and insomnia. Additionally, arousal reduction is hypothesised as a key mechanism (in addition to cognitions and behaviours) through which CBT-CI improves sleep. Our exploration of the mediating impact of sleep changes on arousal changes and vice versa will provide novel insights into their relationship and the mechanistic role of arousal in ASD and insomnia. In sum, the proposed trial addresses significant gaps in the literature and the need for effective insomnia treatment in children with ASD.

Current study

Our first specific aim is to examine efficacy and equivalency of primary outcomes. That is to examine the effects of 4 weeks of CBT-CI (in-person and remote) relative to 4 weeks of SHARE on primary child arousal (HRV) and sleep outcomes (objective sleep efficiency measured with actigraphy, bed/waketime variability) as well as parent objective total sleep time immediately following treatment and at 6-month and 12-month FUs. SHARE is a multisession programme based on the behavioural sleep information for children with ASD and insomnia suggested by the ATN.[39] SHARE was chosen as our active control, because we are interested in examining whether the multicomponent cognitive behavioural approach may be more effective in older children. Research has shown the behavioural sleep information in the ATN pathway is effective in younger children with ASD (<3 years), and while we expect SHARE may result in improvements in our trial, we hypothesise the CBT approach may be more effective in older children for the reasons outlined in the Introduction (ie, high prevalence of anxiety, developmental level, etc). Moreover, SHARE was chosen (as opposed to a waitlist), because it controls for non-specific therapeutic factors (alliance), staff attention and seasonal effects. To promote credibility and limit/prevent treatment effects, SHARE includes general sleep/health education of likely interest to families, including sleep hygiene, but does not include other active sleep treatment such as cognitive and behavioural skills training (eg, goal setting, coping skills, cue control, parenting strategies). We hypothesise that compared with SHARE, CBT-CI will decrease arousal and improve sleep after treatment and at 6-month and 12-month FUs. In addition, we hypothesise that both delivery modes will be equally efficacious for improving primary child sleep and arousal outcomes immediately and at 6-month and 12-month FUs.

Our second specific aim is to examine the efficacy and equivalency of secondary outcomes (ie, changes in secondary outcomes) including all other child outcomes (other sleep outcomes, daytime behaviour, QOL) and parent outcomes (sleep, daytime functioning, physiological arousal, caregiver stress). We hypothesise that both delivery methods will improve secondary child and parent outcomes compared with the SHARE at post-treatment and 6-month and 12-month FUs. Moreover, we hypothesise that both delivery modes will be equally efficacious for improving secondary outcomes at post-treatment and 6-month and 12-month FUs.

Our third specific aim is to examine the mediating impact of child sleep and arousal on child and parent daytime functioning and QOL, parent sleep and arousal, and parental stress/burden. We hypothesise CBT-CI will promote improvements in secondary outcomes through reduction in child arousal and improvements in child sleep. We hypothesise that significant improvements in all variables will be evident immediately following treatment (based on our pilot data) and that sustained improvements in child sleep and arousal will mediate sustained improvements in secondary outcomes at 6-month and 12-month FUs.

We hypothesise that ASD and insomnia share common arousal-based underpinnings and that CBT-CI's effectiveness in improving sleep and functioning in this at-risk population is related to its ability to decrease arousal. Hyperarousal and corresponding low HRV are observed in children with ASD.[55] Our pilot work showed that HRV increased following remote (ie, delivered via videoconferencing/telehealth) CBT-CI, indicating improved ANS regulation.[14] In other words, CBT-CI reduced physiological arousal in a sample of children with ASD. The current RCT provides a methodologically rigorous test of the impact of in-person vs remote delivery of CBT-CI in children with ASD on sleep, daytime functioning, QOL, burden (parents only) and arousal. Our examination of treatment delivery formats will provide information about technology's potential to improve outcomes and decrease burden. Finally, this trial provides a unique opportunity to manipulate arousal (through successful treatment of insomnia) and gain new insights into the biological underpinnings of these highly comorbid conditions.

METHODS

Trial design and study setting

Children with ASD and insomnia (6–12 years old), and their parent(s) will be randomly assigned to 4 weeks of in-person CBT-CI, remote CBT-CI or SHARE with 4 bimonthly phone boosters by the randomisation schedule created by the Biostastician. Families will be informed of their random assignment by the Project Coordinator. Participants will be recruited through an existing clinical registry database maintained by the Thompson Center for Autism and Neurodevelopmental Disorders by the participant recruiter (PR). The Thompson Center database includes 1076 children in the target age range of 6–12 years old with ASD and Verbal IQ>70. In addition, approximately 250 new children age into the group every year and new children are diagnosed by the Thompson Center and added to the database every week. Baseline, post-treatment, and 6-month and 12-month follow-ups will measure sleep (objective, subjective) over a period of 2 weeks, daytime functioning, QOL, physiological arousal and caregiver stress. SHARE will be given option

of receiving (at no charge) either in-person or remote CBT-CI after study completion (SC). Graduate therapists/assessors will obtain written informed consent (see patient consent form in online supplemental material 1) from parents and assent from children. Families in all three groups will be compensated US$100 at baseline, post-treatment, and 6-month FU, and US$125 at 12-month FU, plus treatment at no cost. SHARE subjects will be offered CBT-CI (choice of in-person or remote) at no cost following study. All procedures were approved by the University of Missouri Institutional Review Board on 17 January 2020 and the US Army Medical Research and Development Command, Office of Research Protections and Human Research Protection Office on 16 July 2020.

Eligibility criteria

Inclusion criteria are: (1) 6–12 years old, (2) Verbal IQ ≥70, (3) participation of child's parent or legal guardian living in the same house, (4) parent/guardian ability to read and understand English at the fifth grade level, (5) child diagnosed with ASD and insomnia. ASD diagnosis must include previous ASD diagnosis based on DSM criteria and an evaluation using gold-standard diagnostic tools (ie, Autism Diagnostic Observation Schedule and/or Autism Diagnostic Interview-Revised. Insomnia diagnosis requires (1) complaints of difficulties falling asleep, staying asleep or early morning awakening by child report or parent observation for 3+ months, (2) daytime dysfunction (mood, cognitive, social, academic) due to insomnia, (3) baseline diaries and actigraphy indicate >30 min of sleep-onset latency, wake after sleep onset or early morning awakening (time between last awakening and out of bedtime) on 6+ nights.

Exclusion criteria are: (1) parent unable to provide informed consent or child unable to provide assent, (2) unwilling to accept random assignment, (3) participation in another randomised research project, (4) parent unable to complete forms or implement treatment procedures due to cognitive impairment, (5) untreated medical comorbidity, including other sleep disorders (eg, apnoea, epilepsy, gastrointestinal (GI) disease, psychotic disorders, suicidal ideation/intent, (frequent) parasomnias), (6) psychotropic or other medications that alter sleep with the exceptions of stimulants, sleep medications and/or melatonin, (7) stimulants, sleep medications (prescribed or OTC) and/or melatonin within the last 1 month (unless stabilised on medication for 3+ months), (8) participation in non-pharmacological treatment (including CBT) for sleep outside current trial, (9) parent report of inability to undergo Holter Monitoring or actigraphy (eg, extreme sensitivity, behavioural outbursts) and (10) other conditions adversely affecting trial participation.

Randomisation and blinding

Computer randomisation will be done by the team's biostatistician, blocking by age (<9 years, >9 years). Blocking was done by age due to the different developmental abilities associated with children younger and older than 9 years old. Children older than 9 years are more likely to be able to participate in the cognitive component of treatment. We anticipated that any differences due to gender would be controlled for by randomisation, which should ensure equal distribution of gender across the arms (conditions). Descriptive comparisons will also be conducted in baseline characteristics across the three groups, including gender. Gender will also be controlled for in all subsequent analyses. The project coordinator will be given the randomisation schedule by the biostatistician and alert the families and their therapist to their condition. All other study personnel will be blinded to block size. Blocking ensures balance, increases power,[56] and will be accounted for in analyses. Therapist, supervisor and subject blinding to treatment condition is not possible. Instead, therapists and supervisors will be blinded to outcome assessments and subject-completed treatment credibility questionnaires, subjects will be blinded to the therapist-completed treatment improvement expectancy scale, and the outcome assessor will be blinded to treatment condition.

Procedures

Screening

A sleep psychologist will diagnose insomnia and a neurologist will rule out sleep disorders other than insomnia. Procedures will be consistent with ATN Pathway for Insomnia.[39] Screening will be carried out in four stages:

Stage 1: brief screener (~10 min). PR or SC will conduct a brief structured interview to address eligibility criteria and establish probable insomnia diagnosis.

Stage 2: clinical interview (~50 min). An assessor will administer the Children's Sleep Habits Questionnaire.[57] A neurologist-autism specialist/pediatrician-autism specialist will assess child/parent concerns and medical comorbidities (eg, apnoea/other non-insomnia sleep disorders, epilepsy, GI disease) using a questionnaire from the ATN Practice Pathway[39] and clinical judgement. Children with comorbidities will be ineligible until those comorbidities addressed. The neurologist-autism specialist/pediatrician-autism specialist will provide referrals. Children with suspected apnoea or other non-insomnia sleep disorder will be referred to the neurologist.

Stage 3: sleep screening/polysomnography (PSG). A pulmonologist-paediatric sleep specialist will screen for non-insomnia sleep disorders (eg, apnoea, parasomnias (eg, sleepwalking, sleep terrors)). Based on her experience with children with ASD and our pilots (two children excluded for apnoea), we expect ~10% of children to require sleep screening with ~half requiring overnight PSG. Desensitisation will be used if needed. PSG will be modified as needed based on each child's sensitivities (eg, decreased EEG and nasal sensors).

Stage 4: sleep diary (~5 min/day) and actigraphic confirmation of insomnia. Baseline electronic sleep diaries and actigraphy demonstrate >30 min of sleep-onset latency,

wake after sleep onset or early morning awakening on 6+ nights during the 2 weeks. Electronic diaries and actigraphy were used in our pilots; all children met these criteria. Diaries will be collected via Qualtrics with personal web-enabled devices or (if needed) study provided devices. Diaries and actigraphy are recommended for assessment and examination of treatment outcomes in children with ASD.[58–60] Alternate device placement (eg, T-shirt pocket) will offered to those unable to tolerate wearing the actigraph on their wrist.[61]

Interventions

All three arms (remote CBT-CI, in-person CBT-CI, SHARE) include 4 weekly, 50 min individual sessions; and 4 bimonthly, 20 min phone boosters with a therapist (predoctoral graduate students in an APA accredited clinical or school psychology programme at the University of Missouri). In-person CBT-CI will be conducted at the Thompson Center. Remote CBT-CI and SHARE will be conducted from home (families)/from the Thompson Center (therapist). Separate therapist manuals, parent workbooks and child workbooks for each group (in-person CBT-CI, remote CBT-CI, SHARE) have already been developed and tested. Because treatment is individually administered, missed sessions will be rescheduled. Session content for CBT-CI and SHARE are provided in tables 1 and 2, respectively. Project coordinator will serve as the primary contact for families and will contact them if they experience any difficulties in order to increase adherence and retention. She will send the newsletters, birthday cards, provide regular contact/reminder calls and trouble shoot any problems early on. She will also provide periodic contact to invite back anyone who has dropped out and prompt FU of missed appointments. All data will be stored on secured servers for 7 years.

Treatment integrity

Lichstein's[62] three-step method will be used to measure treatment integrity.

Treatment delivery/training

Therapists will use manuals. Practice will begin with mock sessions and then recorded sessions with volunteers. The principal investigator (PI, CM) will score all training sessions. Training will last ~12 weeks until therapists obtain mastery (scoring 100 on each session's Treatment Delivery Score Sheet). Delivery assessment: All sessions will be recorded. Ten per cent will be scored

Table 1 Session content for remote/in-person CBT-CI

Session no	Content
(1) Sleep hygiene and sleep prescription	Sleep hygiene (SH) will be discussed and participants are instructed to adhere to the following rules: (1) avoid caffeine after noon, (2) within 2 hours of bed, avoid exercise/stimulating play, and heavy meals, (3) within 1 hour of bedtime, avoid screen time, (4) use the bed for sleeping only and minimise toys and objects around the bed. The goal of SH is to eliminate sleep-interfering behaviours. The therapist and parents will work together to create a sleep prescription and set regular bed/wake times consistent with Rx.
(2) Bedtime routine and parent management	Patients' sleep prescription will be updated, and they will be instructed to create a bedtime routine to establish consistency and cues to lower arousal and promote sleep. Parents will be taught differential attention to help them attend to the behaviours they want to see their child engage in more.
(3) Cue control and parent management	Patients' sleep prescription will be updated as appropriate. Parents will be taught effective commands, positive attention, to use forced choices and the importance of consistency to help them set bedtime limits.
(4) Cosleeping and parents fading out of room	Patients' sleep prescription will be updated as appropriate. Patient and parents will work to phase the parents out of the room so that the patient can sleep independently.
(5) Circadian education, morning routine and relaxation	Patients' sleep prescription will be updated as appropriate. Therapist and parents will work to create a morning routine for the child, in part using light to facilitate sleep and wakefulness. The child will be taught a 10 min relaxation programme which will be recorded for home use.
(6) Cognitive therapy Basics	Patients' sleep prescription will be updated as appropriate. The child and parent will be taught cognitive therapy basics, such as understanding how thoughts influence feelings. They will be taught to identify thoughts, worries, anger, excitement and fears at bedtime. They will learn to identify somatic manifestations of worry and to log their feelings.
(7) Night-time fears, anxiety and nightmares	Patients' sleep prescription will be updated as appropriate. Therapist and family will discuss the child's night-time worries and address nightmares. The child will be taught nightmare rescripting and other strategies for management bedtime worry/fear (ie, relaxation, having parent check-in on worries, etc).
(8) Booster sessions	In this brief (~20 min) telephone session, techniques from sessions 1–7 will be reviewed. The therapist will encourage continued practice of techniques. Problems will be trouble-shooted.

CBI-CI, cognitive behavioural treatment for childhood insomnia.

Table 2 Session content for share

Session no	Content
(1) Sleep education	Participants are provided sleep education regarding sleep and the brain, mood, behaviour, health and weight.
(2) Sleep architecture and parasomnias	Participants are provided education on sleep stages and cycles, sleep disorders, sleep walking and night terrors, enuresis, and safety precautions regarding sleep.
(3) Physical activity and sleep	Participants are provided education on bedtime routines and how exercise and vigorous play can negatively impact sleep.
(4) Nutrition	Participants are provided with education on how physiology contributes to sleep disordered breathing, risk factors and symptoms of sleep apnoea and nutrition.
(5) Stress	Participants are provided with education on the effects of long-term stress, the connections between sleep and stress, and dreams and nightmares.
(6) Mood	Participants are provided with education mood and feelings and how sleep impacts self-esteem and mood.
(7) Light/dark cycle	Participants are provided with education about the light/dark cycle and the brain clock.
(8) Booster sessions	As in CBT-CI, all training and education covered in previous sessions will be reviewed in a brief (~20 min) telephone call. Continued sleep hygiene practice and education engagement are encouraged. Problems are trouble-shooted.

CBT-CI, cognitive behavioural treatment for childhood insomnia.

by a psychology consultant. A senior psychology consultant will double score initial five treatment and 5% of remaining sessions for reliability. Consultants will inform the PI of scores <95% for supervisory/training purposes. The PI will review 25% and therapists 25% of each other's sessions for ongoing training/supervision. Only consultant reviews will be used to assess fidelity.

Treatment receipt

To ensure treatment comprehension, subjects will be encouraged to ask questions. Workbooks describe and reinforce treatment content. Receipt assessment: Subjects will complete a brief quiz at end of session 2.

Treatment enactment

To ensure home assignments are done, workbooks contain written instructions. Enactment assessment: Subjects will maintain daily electronic diaries and logs.

Treatment credibility and expectancy

At the end of session 2, participants will complete a treatment credibility questionnaire, and the therapists will complete an expectancy for improvement scale. The treatment credibility questionnaire is a 4-item scale assesses the participant reaction to therapist and treatment efficacy, and participants provide ratings of 1 (strongly disagree) to 10 (strongly agree). Higher scores represent better treatment credibility. Participants will complete a Patient Satisfaction and Experience Survey (PSES) at the post-treatment and FU assessments. Reasons for withdrawal will be assessed using a Withdrawal Questionnaire.

Outcomes

A summary of study outcomes is provided in table 3 and a schedule of outcome measures is provided in table 4. Primary actigraphy outcome variables include child bed/waketime variability and sleep efficiency, and parent total sleep time. Primary sleep diary outcome variables include child sleep onset latency (lights-out until sleep onset), total wake time (time awake from lights out until out of bed), total sleep time and sleep efficiency (total sleep time/time in bed x 100%). Primary child HRV arousal outcomes include (RMSSD of N-N intervals), pNN50 (% of N-N intervals >50 ms) and LF/HF ratio (an index of ANS regulation). All other outcome variables as found in table 4 are secondary. Child and parent sleep will be assessed at home (enhancing ecological validity) but arousal will be assessed in clinic.

Study timeline

The study timeline is provided in table 5.

Analytical approach

Power analysis

Power analyses were conducted in two steps. We first determined that the efficacy analyses required 40 people in each of the three groups: CBT-CI remote, CBT-CI in person and SHARE. Next, we determined that the equivalency analyses required 70 people in each CBT-CI group (CBT-CI remote and CBT-CI in person). Thus, a sample of 180 (70 remote CBT-CI, 70 in-person CBT-CI, 40 SHARE) provides adequate power to test efficacy and equivalency for most primary/secondary outcomes (aims 1–2) and our mediation model (aim 3). Given the few rigorous CBT-CI trials in school-aged children, sample size is estimated based on our recent pilot data.

Efficacy (aim 1): Efficacy analyses will be conducted using hierarchical linear modelling (HLM). Our pilots found small-large within-group effect sizes for child sleep/behaviour (0.87–2.22), child arousal (1.23) and parent sleep/fatigue (0.20–2.56).[13 14] These effect sizes

Table 3 Outcome measures

Outcome category	Measure	Primary/secondary	Details
Objective sleep	Daily actigraphy	Primary	Primary variables: child bed/waketime variability and sleep efficiency, and parent total sleep time. All other actigraphy variables are secondary. Child and parent wear actigraphs (Actiwatch 2â, Philips Respironics), watch-like device, that monitors light and gross motor activity. Data analysed using 30 s epochs. Validated algorithm (Actiware-Sleep V.3.3) estimates sleep efficiency and other variables provided by diaries. Combination of diary and actigraphy data estimates bed/waketime variability. Child/parents wear devices 24/7 during each 2-week assessment. Actigraphy assesses outcomes,[70] is well tolerated in paediatric populations[71] and validated against PSG in ages 3–18.[72–74] Our protocol is sensitive to sensory sensitivities associated with ASD and follows recommendations for research with children with ASD[61] including a social story, knowledge quiz and alternate device placement (eg, T-shirt pocket) if child unable to tolerate on wrist.[61] For parents, the total sleep time will be used.
Arousal	Peripheral arousal—heart rate variability (HRV)	Primary	Primary variables: root mean squared SD of N-N intervals, pNN50 (% of N-N intervals >50 ms), and LF/HF ratio (an index of autonomic nervous system regulation). All other HRV variables are secondary. Child Using Holter Monitors, 8 min ECG (first 3 min for acclimation) will be recorded during rest at each assessment (conducted in clinic) using procedures sensitive to the sensory sensitivities associated with ASD. Our 8 min protocol will provide sufficient data for analysis.[75 76] Time domain and frequency domain spectral analysis of short-term HRV performed using Pathfinder (Spacelabs, Seattle, Washington, USA) software. Time domain indices reflect beat-to-beat variability with respect to time. Frequency domain indices reflect underlying rhythms of mechanisms modulating HR. High frequency (0.15–0.4 Hz), low frequency (0.04–0.15 Hz) and very low frequency (below 0.04 Hz) power spectral bands will be examined. Our Holter Monitoring/HRV protocol is sensitive to sensory sensitivities in ASD. For children reluctant to wear electrodes, a social story and positive reinforcement will be used (effective in prior studies).
Subjective sleep	Daily sleep diaries	Primary	Primary: child sleep onset latency (lights-out until sleep onset), total wake time (time awake from lights out until out of bed), total sleep time and sleep efficiency (total sleep time/time in bed × 100%). All other sleep diary variables are secondary. Child (with parent assistance) and parent complete electronic diaries each morning (~5 min) during each 2-week assessment. Electronic diaries tested in our pilots and were not considered burdensome.

Continued

Table 3 Continued

Outcome category	Measure	Primary/secondary	Details
Child daytime functioning	Aberrant behaviour checklist (ABC)	Secondary	ABC is a 58-item parent-report measure of daytime problem behaviours that is psychometrically strong and sensitive to treatment effects in children with ASD.[77]
	Conners' Continuous Performance Test-third Edition (CCPT-3)	Secondary	CCPT-3 is a computerised measure of inattentiveness, impulsivity, sustained attention and vigilance for aged eight and above. Conners' Kiddie CPT will be used for children aged 6 and 7 which provides a comparable measure of the four domains of attention. To account for two different measures in analyses, standardised scores will be used. Both measures are reliable and valid for use in their respective age groups.
	Behaviour Rating Inventory of Executive Function -second Edition (BRIEF-2)	Secondary	BRIEF-2 is an 86-item parent-report measure of day-to-day executive functioning and impairment.
	Child and Adolescent Symptom Inventory-fourth Edition Revised (CASI-4R)	Secondary	A subset of 20 items focused on anxiety from the CASI-4R will be completed by parents. This 20-item scale has been found to be an appropriate outcome measure for children with ASD.[78]
Child quality of life	PedsQL	Secondary	Pediatric Quality of Life (PedsQL) is a 23-item scale measuring children's QOL. It has excellent internal consistency, clinical validity and factor–analytical support.[79] Both child and parent forms will be completed.
Parent daytime functioning	Beck Depression Inventory (BDI-II)	Secondary	BDI-II includes 21 items that measures the severity of depressive symptomatology on a 4-point scale (0-absence of symptoms; 3-severe).[80]
	State-Trait Anxiety Inventory (STAI-Y1)	Secondary	STAI-Y1 includes 20 self-descriptive statements rated according to how the parent generally feels on a 4-point scale(1 (not at all) to 4 (very much so)).[81]
	Fatigue Severity Scale	Secondary	Fatigue Severity Scale includes nine items on severity of fatigue and how fatigue interferes with activities on a 7-point scale (1-strongly disagree; 7-strongly agree).[82]
	Daily fatigue	Secondary	Daily Fatigue rated on electronic diaries (0-none;100-most intense imaginable)
Parent burden/stress	Caregiver Strain Index (CSI)	Secondary	CSI includes 12 items on caregiving impact on well-being.[83]

ASD, autism spectrum disorder; PSG, polysomnography.

Table 4 Schedule of outcome measures

Assessment period	Base	Tx	Post	6-month FU	12-month FUs
Weeks	2	4	2	2	2
Screening, polysomnography if needed, cnsent/assent	X				
Actigraph, Holter Monitor (8 min assessment), ABC, CCPT-3, BRIEF-2, CASI-4R, Peds QL, STAI, BDI-II, CSI	X		X	X	X
Electronic daily diaries	X	X	X	X	X
Tx integrity—delivery and receipt, treatment credibility		X			
Tx integrity—enactment; PSES			X	X	X

ABC, Aberrant Behaviour Checklist; BDI-II, Beck Depression Inventory; BRIEF-2F, Behaviour Rating Inventory of Executive function-2nd edition; CASI-4R, Child and Adolescent Symptom Inventory-4th edition revised; CCPT-3, Conners' Continuous Performance Test-3rd edition; CSI, Caregiver Atrain Index; FU, follow-up; PSES, Patient Satisfaction and Experience Survey; STAI, State-Trait Anxiety Inventory; Tx, treatment.

are consistent with prior sleep trials in older[41] and younger children (0.12–1.75, mostly waitlist or treatment as usual controls).[10] Power was simulated using R statistical software using the above effect sizes, a balanced two-level HLM design and 100 simulated variance–covariance matrices of mixed effects. Given these parameters, a sample size of 135 will have a power of >0.8. Given expected 20%–25% attrition, we will recruit 180 to obtain final sample of 135.

Equivalency (aim 2): Equivalency will be tested using head-to-head analyses. Based on our pilot data, we assumed the true difference was equal to the difference found between treatment arms and used the pooled standard deviation (within-group SD) to calculate the equivalence limits and power for an equivalence tests with 70 people in each group using PASS V.16 software. Since the measurement units of each outcome are different, Cohen's d was calculated for standardisation. With the proposed sample size, an equivalence test of means using two one-sided tests on data from a parallel-group design achieved 80% power at a 5% significance level when Cohen's d ranges from 0.3 to 0.6 and the upper and lower confidence limits are within ±0.5 SD, the width of 1 SD. Thus, the trial will be powered for our primary child sleep outcomes (actigraphic sleep efficiency, bed/waketime variability), parent actigraphic sleep outcomes and some (but not all) of our other secondary outcomes (eg, testing equivalency for child actigraphic total wake time is not feasible, because it would require >500 participants.).

Mediation (aim 3): For the mediation model in aim 3, given that the effect sizes of the mediating paths range from small to large, a sample size of 148 will provide sufficient power (>0.80) to detect the mediation effects.[63] For example, it will have 80% power to detect a 0.14–0.59 (small to large) direct effect of treatment on sleep and a 0.26–0.59 (medium-small to large) indirect effect of treatment on arousal and of arousal on sleep. The PROCESS macro developed by Andrew F. Hayes for SPSS version 27 and SAS version 9.4 will be used to model the complex mediation models with multiple mediators and cross-lagged panels. Sample size calculations were also done in R statistical software for a mediation model with two serial mediators using a Monte Carlo power analysis for indirect effects,[64] assuming a small indirect effect (0.14) of X on Y with correlations between the mediators, independent and dependent variables all set to medium effects (0.39). Using the continuously varying sample size approach of Monte Carlo, ~120 individuals are required to ensure statistical power is at least 80% for detecting the hypothesised indirect effect. Drop-out

Table 5 Study timeline

Project year→	1		2		3		4	
Half →	1	2	1	2	1	2	1	2
(1) Develop manual of operating procedures. Register with ClinicalTrials.gov. Publish trial protocol. Train therapists and assessor.								
(2) Recruit, collect baseline, deliver treatment.								
(3) Collect post-treatment assessment.								
(4) Collect 6 and 12 months follow-up assessments.								
(5) Offer/provide treatment to SHARE participants.								
(6) Final data analysis and dissemination (continues after grant ends); final report.								

SHARE, Sleep Hygiene and Related Education.

rate of 20%–25% expected, so we will recruit a sample of 180.

Evaluations of aims

Tests of hypotheses: All analyses will use intention to treat, and all randomised subjects will be included. Data will be examined to see if it violates the assumptions of HLM (ie, data must be linear and normal, and the assumption of homoscedasticity must be met). If these assumptions are violated, the data will undergo transformation.[65]

Testing of aims 1 and 2: efficacy of CBT-CI

Analysis of change in primary (aim 1) and secondary (aim 2) outcomes will be conducted using a two-level HLM. The first level will be the repeated measure (RM) over time nested within the second level which is person-level data. Group (remote CBT-CI, in-person CBT-CI, SHARE) will capture the between subjects variability, while time (base, post-treatment, 6-month and 12-month FU) will capture within subject variability. Based on a priori hypotheses, separate HLMs will be conducted for each outcome. Planned contrasts will conform to our a priori hypotheses outlined in the Current Study section. We will control for family-wise error using Bonferroni-adjusted p values to protect against type I errors when performing multiple hypotheses tests. The Bonferroni p value correction will be accounted for within each individual construct. That is, it will be accounted for within the actigraphy measures, sleep diary measures and within the different subscales of all of our measures by construct. This correction will be conducted for all outcomes. HLM can be used to compare group means like RM analysis of variance, individual trajectories, between participants and at the individual level. HLM can answer questions such as: Do slopes differ due to treatment or across subjects?, Do specific time points vary among individuals?

Testing of aims 1 and 2: equivalency of interventions

We will compare remote CBT-CI for outcome equality with the 'gold standard' in-person CBT-CI.[64 66] Group means for a variable that exceed the equivalency threshold (ET) will be considered nonequivalent, and those that do not will be considered equivalent (Ho = |μ in-person CBT-CI – μ remote CBT-CI|>ET; H1 = |μ in-person CBT-CI – μ remote CBT-CI|≤ET). This is a novel application of equivalency analyses, so there are no published ET standards for CBT-CI. Thus, we will conduct the analyses two ways—using an ET of ±0.20 μ in-person CBT-CI as recommended for pharmaceutical research and using an ET of ±0.10 μ in-person CBT-CI as recommended for psychological research.[64 67]

Testing of aim 3 (mediation)

To examine relationships between changes in child arousal, sleep, daytime functioning and QOL plus other potential outcome mediators (eg, environmental factors, adherence) and moderators (eg, parent sleep). Analysis of change in outcomes will be evaluated using HLM, with RM over time (base, post-treatment, 6-month and 12-month FU) nested within the person-level data. We will use cross-lagged panel mediation analysis.[68] This will identify unique variance in the mediator and outcome which cannot be explained by other predictors and allow for comparisons between remote CBT-CI, in-person CBT-CI and SHARE. We hypothesise CBT-CI promotes improved sleep through arousal reduction which promotes better daytime functioning and QOL. We also hypothesise improved child sleep and arousal and secondary outcomes lead to reduced arousal in parents and improved sleep, daytime functioning, QOL and burden. Controlling for baseline, prior measurements and autoregressions, CBT-CI-associated sleep and arousal improvements will continue to predict improvements at FU. Mediation effects of sleep and arousal improvements on secondary outcomes at 6 months and 12 months will be estimated. We will also conduct per-protocol analyses for comparison to the planned study aims.

Missing values

HLM can handle missing data at all levels except the highest (level 2 in this case). When collecting measurements from the same people over time, some may not complete the study. With HLM, their information is retained in the prediction model increasing statistical power. We will also examine the impact of missing data values on trial outcomes using several methods. First, drop-out rates will be compared across the treatment groups with χ^2 analyses to assess systematic differences due to treatment. Second, demographic and dependent variables will be examined for their relationship to drop-out. Variables related to drop-out status will be used to impute missing values for use in the analyses described below (via SPSS Missing Values Analysis). We do not anticipate that the single imputation approach will yield markedly different outcomes than a mixed linear models approach or worst-case approach to missing data. Moreover, researchers have suggested that a last observation carried forward approach provides false results and is not recommended.[69] (In addition, we will analyse completers only, as a liberal estimate of treatment efficacy. Finally, comparison of the completers versus imputation analyses will yield an additional estimate of the effect of drop-outs on hypothesis tests.

Patient and public involvement

Patients and public are not involved in any of the following study procedures: development of research questions and outcome measures, participant recruitment, plan for results dissemination, assessment of burden of intervention. Due to parent feedback the current RCT was reduced from eight sessions (as found in the pilot) to four sessions. Every parent will fill out a PSES after post-treatment, 6-month FU and 12-month FU. This questionnaire asks the parents which modules were most/least useful for them, how they felt about the length of the programme, suitability for a child with ASD in this age range, etc. Trial results will be communicated

to participants and the public though peer-reviewed manuscripts.

Ethics and dissemination

All study procedures were approved by the Institutional Review Board at the University of Missouri on 17 January 2020. An independent four-member data safety monitoring board (DSMB) was assembled in September 2020 to oversee the study. Members include those with expertise in autism, childhood insomnia, sleep medicine and CBT. All DSMB members attested that they have no conflicts of interest. The DSMB met once via conference call at the beginning of the study to review the study protocol, manual of operating procedures (MOOP), informed consent form and monitoring plan with emphasis on data integrity and patient safety issues. Following this initial meeting, the DSMB will meet every 6 months to review progress reports prepared by the team biostatistician. Those DSMB reports will include interim statistical analyses. Any changes to these procedures that are recommended by the DSMB will be adopted. The DSMB will review adverse events and monitor study results, focusing on efficacy, recruitment progress, randomisation, compliance, retention, protocol adherence, operating procedures, forms completion, intervention effects, participant safety and minority inclusion. The PI will also submit annual reports to the funding agency.

Results from this trial will be presented at national conferences, including the Associated Professional Sleep Societies (SLEEP) and the National Autism Conference, in the final year of the project. Dissemination will also occur through the submission of a primary article on the outcomes, a second article focusing on equivalency outcomes, a third on arousal biomarkers, and a fourth on an outcome mediation. The treatment materials will be shared electronically and will be widely available to clinicians.

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Contributors All authors made substantial contributions to the concept and design of the study. CM, MM, AFC and NN drafted initial protocol, with input from all authors. CD and AFC drafted statistical analysis plan. CM, MM, DB, KS and ZN drafted screening procedures. DB, KS, BED and ZN drafted referral procedures. CD, MG, NN and AFC conducted initial data processing. CM and MS drafted the manuscript. CM, MS, MG and BED revised the manuscript. All authors reviewed and approved the revised manuscript.

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Disclaimer The study sponsor was not actively responsible or involved in the study design and will have no involvement in collection, management, analysis or interpretation of data. The sponsor will have no involvement in future manuscript preparation and decision to submit for publication. This research was done using previous patient involvement in the pilot study. Patients were invited to comment on the study design and indicated that less sessions were preferable. In response, the current RCT was reduced from 8 sessions (as found in the pilot) to 4 sessions. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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