Sleep Medicine Reviews 63 (2022) 101613

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Sleep as an outcome measure in ADHD randomized controlled trials: A scoping review

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ARTICLE INFO

Article history:
Received 6 December 2021
Received in revised form
31 January 2022
Accepted 14 February 2022
Available online 23 February 2022

Keywords:
Neurodevelopmental disorders
Mental health disorders
Insomnia
Medications
Stimulants

SUMMARY

Sleep disturbances are highly prevalent among children with ADHD. Yet, diagnostic and treatment regimens are primarily focused on daytime symptomatology. The goals of this scoping review are to 1) identify interventional ADHD RCTs that have used sleep as an outcome measure, 2) describe and assess the validity of tools utilized to measure sleep-specific outcomes.

40/71 RCTs used sleep as a primary outcome. Actigraphy (n = 18) and sleep log/diary (n = 16) were the most common tools to measure sleep, followed by Children's Sleep Habits Questionnaire (n = 13), and polysomnography (n = 10). Sleep was a secondary outcome in 31 RCTs. Polysomnography and actigraphy used a heterogeneous spectrum of sleep-related variables and technical algorithms, respectively. 19/23 sleep questionnaires were validated covering a spectrum of sleep-related domains.

Despite the intrinsic nature of sleep disturbances in ADHD, the number of RCTs measuring sleep-specific outcomes is limited and tools to measure outcomes are not standardized. Given the potential adverse effects of ADHD medications on sleep, sleep should be included as a core outcome measure in future clinical trials.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder, affecting 7.2% of children and adolescents under the age of 18 and 2.6% of adults, globally [1,2]. However, it must be noted that the prevalence of ADHD may differ between jurisdictions, for example, in the United States, the prevalence of ADHD for both children and adults is, on average, higher than global figures (11% of children, 4.4% of adults [3]). The clinical features of ADHD are diverse and can be categorized into predominantly inattentive, predominantly hyperactive/impulsive, or combined presentations. Not only, however, does ADHD affect daytime functioning, but also nighttime behaviours - mainly, the amount and quality of sleep [4].

Currently, the diagnosis and treatment of ADHD is based on daytime symptomatology. Over the last three decades, however, an increasing number of studies have implicated sleep as an intrinsic feature of ADHD. Sleep disorders that have been implicated in ADHD include restless legs syndrome (RLS), periodic limb movements in sleep (PLMS), circadian rhythm sleep disorders (CRSD) [5], and alterations in sleep efficiency and latency [6]. There is also a strong interconnection between sleep and ADHD daytime symptoms. Disturbed sleep can exacerbate existing ADHD symptoms and may even mimic symptoms of ADHD [5] in children with primary sleep disorders. According to the American Academy of Pediatrics, sleep disorders should be excluded in all patients with ADHD [7]. Moreover, the recent description of ADHD sleep phenotypes [8] and ADHD-related sleep disorders [9,10] have helped to solidify new perspectives for approaching sleep problems, integrate existing

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https://doi.org/10.1016/j.smrv.2022.101613
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Abbreviations

AASM	American Academy of Sleep Medicine
ADHD	attention Deficit Hyperactivity disorder
ASD	Autism Spectrum Disorder
ASHQ	Adolescent Sleep Habits Questionnaire
CRSD	Circadian Rhythm Sleep Disorders
CSHQ	Children's Sleep Habits Questionnaire
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELIT	Evaluation List Insomnia Therapy
ER	Extended Release
ESS	Epworth Sleepiness Scale
FSI	Fatigue Symptom Inventory
HSDQ	Holland Sleep Disorders Questionnaire
IRLSS	International Restless Legs Severity Scale
JHRLSS	Johns Hopkins Restless Legs Severity Scale
MAS	Mixed Amphetamine Salts
MPH	Methylphenidate
MTS	Methylphenidate Transdermal System
NOS	Not Otherwise Specified
OROS	osmotic release oral system
PCQ	Physical Complaints Questionnaire
PDSS	Pediatric Daytime Sleepiness Scale
PLMS	periodic limb movements in sleep
PSERS	Pittsburgh Side Effects Rating Scale
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
PSQ	Pediatric Sleep Questionnaire
PSS	Pictorial Sleepiness Scale
RCT	Randomized Controlled Trial
RLS	Restless Legs Syndrome
TDSS	Teacher Daytime Sleepiness Scale
TEAE	Treatment Emergent Adverse Event
USA	United States of America
WASM-IRLSSG	World Association of Sleep Medicine-International Restless Legs Syndrome Study Group

evidence, and offer new treatment options for children and adolescents with ADHD.

Given the implications of disturbed sleep on the functioning of children with ADHD, it is vital that interventions aimed at ameliorating the daytime symptoms of ADHD (e.g., hyperactivity, restlessness) are not inadvertently worsening sleep. For example, a frequent adverse effect of methylphenidate (MPH), the most commonly prescribed first line pharmacological treatment for ADHD, is sleep disturbance. A meta-analysis of 185 randomized controlled trials (RCTs) found that treatment with MPH conferred a 60% greater chance of suffering from trouble sleeping/sleep problems [11]. Adverse effects on sleep may even be precipitated by inappropriate medication timing and/or dosing, which are largely dependent on the specific needs of the individual being treated.

With the purpose of providing an extensive overview of the current knowledge, a scoping review approach was agreed upon by the team. The important role of sleep in ADHD warrants an exploration into how sleep has been assessed in interventional studies. Therefore, we performed a scoping literature review that aims to investigate the extent and quality in which sleep has been considered and incorporated as an outcome measure in ADHD interventional RCTs. Our goals were: 1) to identify interventional RCTs that have assessed sleep as an outcome measure in patients with ADHD, 2) review the types of tools utilized as sleep-specific outcome measures; 3) to assess the validity and applicability of tools used to capture sleep.

Methods

The protocol for this scoping review has been registered with Open Science Framework and can be accessed at https://osf.io/vwrpt/. This scoping review was carried out in accordance with the PRISMA-Scr checklist (Table S1) and follows the methodological framework outlined by Arksey and O'Malley [12] which includes the following steps:

Identifying the research question

Primary: Of the interventional ADHD RCTs that include sleep as a primary or secondary outcome measure, 1) What kind of tools were used to assess sleep? 2) What were the variables measured and protocols used by technical tools such as polysomnography (PSG) and actigraphy? 3) Were the sleep questionnaires validated? 4) What kinds of sleep domains were covered by these questionnaires? Secondary: What were the characteristics of these RCTs (demographics, design), and what were the interventions tested.

Identifying relevant studies

The search strategy was developed based on preliminary searches and discussions with the team and a librarian. The search terms included variations of the terms ADHD and sleep - the detailed search strategy is outlined in Table 1. The following databases were searched in June, 2020 with no date restrictions: CINAHL (via EBSCOhost), Embase (via OVID), Medline (via OVID), and PsycINFO (via EBSCOhost). Citation chaining was also utilized to identify additional relevant studies, which may not have been captured by the search strategy. Lastly, we searched clinical trial registries to capture additional grey literature.

Study selection

Covidence was used to facilitate the selection process. Following de-duplication, two reviewers (SM & TZ) independently assessed the search results, first by title and abstract reading, followed by full text readings. If the title nor abstract contained sufficient information to make a decision, the full text article was reviewed. A third reviewer was involved to handle potential discrepancies between reviewers one and two.

Inclusion criteria

Studies were included if 1) Subjects in the testing group of studies were diagnosed with ADHD according to DSM, ICD, or other validated criteria; 2) Sleep is used as a primary or secondary outcome measure (including post-hoc and secondary analyses). Primary outcome measure was defined as "…the planned outcome measure that is the most important for evaluating the effect of an intervention/treatment". Secondary outcome measure was defined as "… a planned outcome measure that is not as important as the primary outcome measure for evaluating the effect of an intervention but is still of interest" [13]; 3) Sleep assessment tool/instrument is described/outlined; 4) Has a study design of

Table 1
Search strategy.

Database	ADHD	Sleep	RCT Filter
CINAHL (via EBSCOhost)	(MH "Attention Deficit Hyperactivity Disorder") OR attention deficit N2 disorder* OR attention deficit N4 hyperactiv* OR ADHD	(MH "Fatigue") OR (MH "Insomnia") OR (MH "Sleepiness") OR (MH "Sleep") OR sleep* OR somnolence OR fatigue OR insomnia	Cochrane Handbook Version 6 (3.6.3, p 65–66)[a]
Embase (via OVID)	attention deficit disorder/OR attention deficit adj2 disorder*.mp. OR attention deficit adj4 hyperactiv*.mp. OR ADHD.mp.	sleep/OR somnolence/OR fatigue/OR insomnia/OR sleep*.mp. OR somnolence.mp. OR fatigue.mp. OR insomnia.mp.	Cochrane Handbook Version 6 (3.6.2, p 64–65)[a]
Medline (via OVID)	Attention Deficit Disorder with Hyperactivity/OR attention deficit adj2 disorder*.mp. OR attention deficit adj4 hyperactiv*.mp. OR ADHD.mp.	fatigue/OR sleepiness/OR "Sleep initiation and maintenance disorders"/ OR Sleep/OR fatigue.mp. OR insomnia.mp. OR sleep*.mp. OR somnolence.mp.	Cochrane Handbook Version 6 (3.6.1 p63; *sensitivity- and precision-maximizing version*)[a]
PsycINFO (via EBSCOhost)	DE "Attention Deficit Disorder with Hyperactivity" OR DE "Attention Deficit Disorder" OR "Attention deficit N2 Disorder*" OR "Attention deficit N4 hyperactiv*"	DE "Fatigue" OR DE "Insomnia" OR DE "Sleepiness" OR DE "Sleep" OR fatigue OR insomnia OR sleep* OR somnolence	Adapted from Watson & Richardson[b] DE "Treatment Effectiveness Evaluation" OR DE "Treatment Outcomes" OR DE "Psychotherapeutic Outcomes" OR DE "Side Effects (Treatment)" OR DE "Treatment Compliance" OR DE "Treatment Duration" OR DE "Treatment Refusal" OR DE "Treatment Termination" OR DE "Treatment Withholding" OR DE "Placebo" OR "Followup Studies" OR placebo* OR random* OR "comparative stud*" OR clinical N3 trial* OR research N3 design OR evaluat* N3 stud* OR prospectiv* N3 stud* OR (singl* OR doubl* OR trebl* OR tripl*) N3 (blind* OR mask*)

[a] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.
[b] Watson RJ, Richardson PH. Identifying randomized controlled trials of cognitive therapy for depression: comparing the efficiency of Embase, Medline and PsycINFO bibliographic databases. Br J Med Psychol. 1999 Dec; 72 (Pt 4):535-4.

randomized controlled trial as is defined by the Cochrane Handbook [14]. Studies that outlined control group(s) in their abstract but did not explicitly mention randomization of some appropriate form as defined by the Cochrane Handbook were full text screened separately to verify if the study did meet the RCT requirement for inclusion. Importantly, we included RCTs that target, not only ADHD symptoms, but also sleep symptoms/disorders (e.g., insomnia).

Exclusion criteria

Studies were excluded if 1) The full text was not available online; 2) The study was a published protocol, not including results; 3) The study is a systematic or scoping review of RCTs; 4) The study did not carry out a therapeutic intervention aimed at ameliorating the symptoms of ADHD or sleep (e.g., applying conditions such as sleep restriction to observe the effects on ADHD symptoms); 5) There was no description of how sleep was measured; 6) Sleep disturbance or sleep-related conditions were included only as a treatment emergent adverse event (TEAE).

Charting the data

Two reviewers (SM and TZ) were involved in extracting data from the included studies using the data collection sheet (Table S2). Prior to formal data extraction, SM and TZ practiced using the data collection sheet to ensure continuity and accuracy. Extracted data was organized in an Excel Sheet. A third and fourth reviewer (SS and OI) were involved to oversee the data collection process.

Collating, summarizing, and reporting results

Descriptive statistics were used in the quantitative analysis of the collected data. A descriptive, qualitative analysis was carried out by two reviewers (SM and TZ) in conjunction with senior members of the team (SS and OI).

We analyzed the included RCTs according to the following criteria:

1. Demographic Information
   - 1.1. Age, medical diagnoses (i.e., ADHD, ASD, comorbidities), ADHD diagnostic criteria
   - 1.2. Date and location of RCTs
   - 1.3. Primary or secondary data analyses with secondary data analysis being defined as 'the analysis of data collected by others' [15].
2. Intervention
   - 2.1 Pharmacological: medication, timing, dosing regimen
   - 2.2. Non-pharmacological: type
   - 2.3. Target symptoms: ADHD or sleep
3. Sleep outcome measure
   - 3.1 Sleep as a primary outcome measure
     Note: secondary analysis papers that were focused on the analysis of a sleep outcome measure could be classified as "sleep as a primary outcome measure", even if the original publication had a different primary outcome (e.g., ADHD symptoms).
   - 3.2 Sleep as a secondary outcome measure
4. Quality assessment: Jadad scale [16] (described in Table S3)

Description and validation of sleep-specific outcome measures:

1. Technical tools

   1.1 Technical protocols
   1.2 Outcome variables measures

2. Questionnaires

   2.1 Analysis of validation studies was done using the framework of Sen & Spruyt [17], and the validity definitions were taken from Spruyt et al. [18]. For the purposes of our review, where questionnaires had been validated with more than one validation study, we reviewed only the first published study. Where a validation study could not be identified in the literature, we referred to the original RCT for any validation studies that were referenced for the respective questionnaire.
   2.2 Sleep domains covered by questionnaires

Results

After removal of duplicates, 2265 records were screened. After title/abstract and full text screening, 71 RCTs meeting the inclusion criteria were identified and included in this scoping review (Fig. 1).

Demographic Information

There were a total of 52 pediatric studies (Age Range: 2–18 years; n = 5644) and 19 adult studies (Age Range: 18–66 years; $n = 3475$). A detailed breakdown is shown in Table S3.

Date and location

Most of the studies ($n = 47$) were published in the last decade between 2010 and 2019. seven were published in 2020; 15 between 2000 and 2009; two between 1990 and 1999. The location of studies was distributed across four continents, with the majority coming from North America (United States of America (USA): $n = 43$; Canada: $n = 11$; Puerto Rico: $n = 1$). eight were conducted in Europe (Netherlands: $n = 5$; Finland: $n = 1$; Germany: $n = 1$; Sweden: $n = 1$); six in Iran; five in Australia.

Secondary analyses

Included in the 71 RCTs are three secondary analyses [19–21]. Owens et al. [19] analyzed sleep as an exploratory endpoint in two individual studies [22,23], neither of which were included in this review because no sleep-specific outcome measure was used. Instead, these two studies included insomnia as a sleep-related TEAE. Surman et al. [21] analyzed two studies [24,25] that were both included as individual studies in this scoping review. Ricketts et al. [20] analyzed data from the Multimodal Treatment of ADHD Study, which was not included in our scoping review.

In addition, there were six pairs of studies that shared the same study population. Five pairs consisted of an initial RCT [24,26–29] followed by a secondary analysis [30–34]. One pair of studies consisted of an initial RCT [35], and a subsequent investigation carried out with additional data collection to assess the long-term effects of the intervention using the same population [36].

ADHD diagnosis

ADHD was the primary diagnosis in 69/71 RCTs. In two RCTs, participants had a primary diagnosis of ASD (including Asperger's syndrome and pervasive developmental disorder) and exhibited ADHD-like symptoms [37,38]. DSM-IV was the most widely used diagnostic criteria for ADHD, followed by DSM5 and DSM III. 12 RCTs did not specify if DSM was used in the diagnosis of ADHD.

Intervention

53 RCTs used pharmacological interventions, the majority (n = 43) of which were aimed at the amelioration of ADHD symptoms, while a small number of interventions (n = 9) [34,39–46] were used for sleep disturbances, including insomnia and RLS. One pharmacological study targeted both ADHD and sleep symptoms [29] (Fig. 2).

15 RCTs used non-pharmacological interventions. Five of which were targeting ADHD symptoms [47–51], two targeting sleep symptoms [52,53], and eight targeting both ADHD and sleep symptoms [35,36,54–59].

Three RCTs used a combination of pharmacological and non-pharmacological interventions, two targeting ADHD symptoms [20,37] and one targeting sleep symptoms [60] (Fig. 2).

Medications for the treatment of ADHD symptoms

45/71 RCTs used medication for the treatment of ADHD symptoms, including two that used both pharmacological and non-pharmacological interventions (Fig. 2). The most common pharmacological intervention for ADHD was MPH (n = 18 [19,27,28,31,33,61–73]), followed by amphetamines (n = 10 [21,24,25,32,74–79]), guanfacine (n = 7 [26,30,38,80–83]), dasotraline (n = 2 [84,85]), atomoxetine (n = 1 [86]), modafinil (n = 1 [87]), novel AMPA receptor positive allosteric modulator (Org 26575 & 25676) (n = 1 [88]), and novel $\alpha_2\beta_2$ neuronal nicotinic receptor partial agonist (ABT-089; Pozanicline) (n = 1 [89]). Two studies employed more than one medication group (MPH and atomoxetine, n = 1 [90]; MPH and amphetamines, n = 1 [91]).

Of the MPH studies, four used osmotic release oral system (OROS) MPH, seven used MPH-multiple layer release (MRL)/extended release (ER)/PRC-063 (brand name Aptensio XR® specified in 2/7, Biphentin® specified in 3/7, Foquest®/Adhansia XR® specified in 1/7, no brand specified in 1/7), three used MPH-immediate release (IR; brand specified as Ritalin in 2/3), two used methylphenidate transdermal system (MTS), and four used MPH not otherwise specified (NOS). Of the amphetamine studies, four used lisdexamfetamine (brand specified as Vyvanse in 2/4), six used triple bead mixed amphetamine salts (MAS; Mydayis; specified as SHP465 in 3/6), one used dextroamphetamine/levoamphetamine (Adderall). Guanfacine ER was used in all guanfacine studies. The remainder of the ADHD medication RCTs used only one form of their respective medication (Table 2a).

In two RCTs, which tested a combination of pharmacological and non-pharmacological interventions, atomoxetine [37] and MPH [20] were used as pharmacological intervention, while parent training and behavioural therapy were used as non-pharmacological interventions, respectively (Table 2b).

Medications for the treatment of sleep

10/71 RCTs used medication for the treatment of sleep, including one which used both pharmacological and non-pharmacological interventions (Fig. 2). The most common pharmacological interventions for sleep were melatonin (n = 1 [46]), zolpidem (n = 1 [39]), eszopiclone (n = 1 [45]), carbidopa/l-DOPA (n = 1 [34]), l-theanine (n = 1 [41]), and cyproheptadine (n = 1 [42]. Two RCTs used a combination of melatonin and methylphenidate [43,44] (Table 2c). One RCT was targeting both ADHD and sleep symptoms using carbidopa/L-DOPA [29] (Table 2d). One

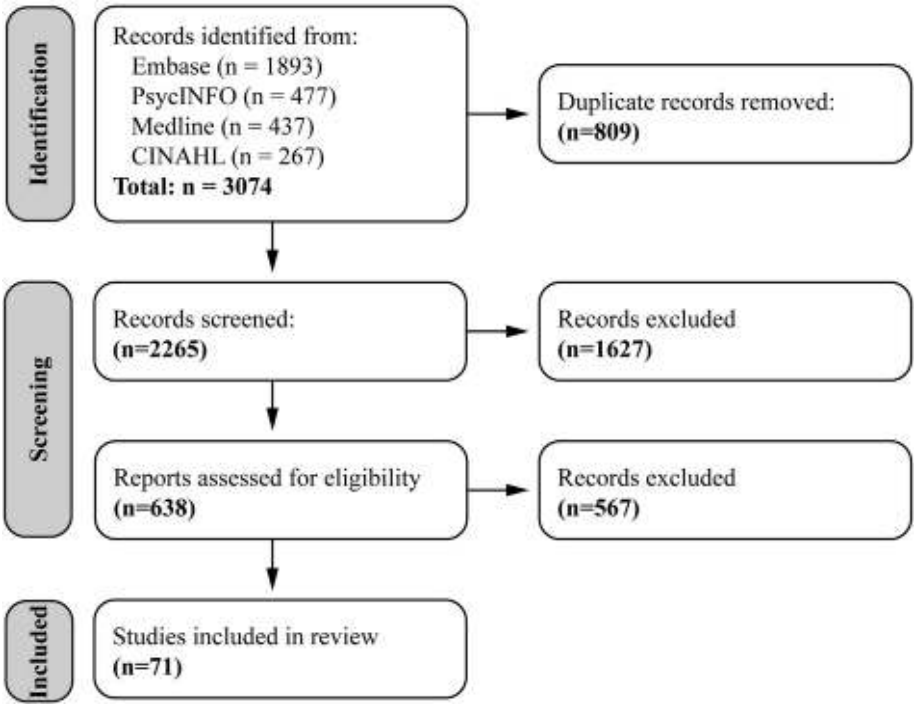

Fig. 1. Study selection. Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. doi: 10.1136/bmj.n71. The PRISMA Statement and the PRISMA Explanation and Elaboration document are distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

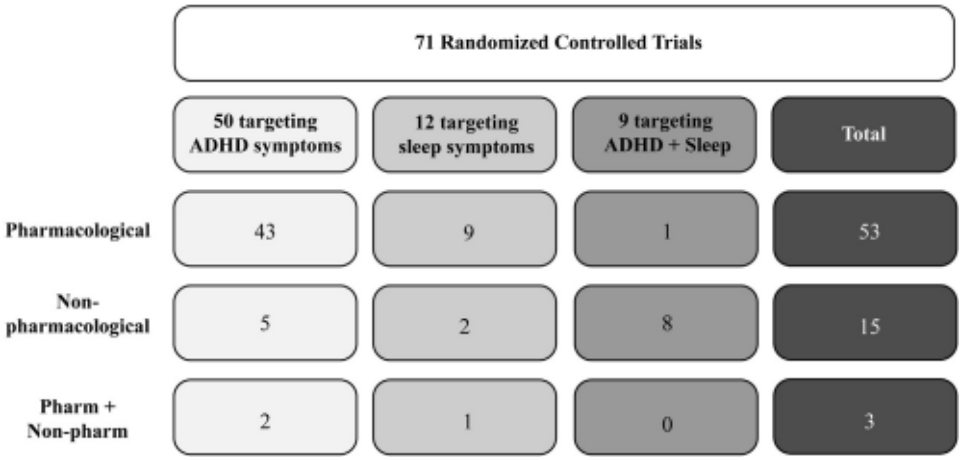

Fig. 2. Breakdown of included RCTs according to treatment target and modality.

RCT used melatonin in addition to a non-pharmacological sleep hygiene intervention [60] (Table 2e).

Medication timing

The timing for all ADHD and sleep medications is presented in Table 2a–e.

Non-pharmacological interventions

The most commonly employed non-pharmacological interventions were behavioural therapy/parent training. For the treatment of ADHD, several novel interventions, including trigeminal nerve stimulation [50], slow oscillating transcranial direct current [51], and neurofeedback [47,49] were used. All non-pharmacological interventions are listed in Table 3.

Tools utilized as sleep-specific outcome measure

Tools used in studies evaluating sleep as a primary outcome

40/71 RCTs used sleep as a primary outcome. Of these 40 RCTs, actigraphy was the most commonly employed (n = 18), followed by sleep log/diary (n = 16), Children's Sleep Habits Questionnaire (CSHQ; n = 13), and polysomnography (PSG) (n = 10). Solleveld et al. [69] utilized the greatest number of sleep outcome measures (n = 6), including actigraphy, sleep log/diary, Epworth Sleepiness Scale (ESS), Evaluation List Insomnia Therapy (ELIT), Holland Sleep Disorders Questionnaire (HSDQ), and Johns Hopkins RLS Severity Scale (JHRLSS). Five RCTs used both actigraphy and PSG, while 18 used neither actigraphy nor PSG. Of those 18 RCTs, 11 had used only one sleep outcome measure (Fig. 3a). Kent et al. [66] used a sleep

Table 2a

Medications for the treatment of ADHD. Numbers in brackets (e.g., (#)) represent studies that were secondary analyses of already included studies in this review. Populations of crossover studies were not included in the breakdown of treatment (*T*) and controls (*C*). Additionally, for studies that used the same study population, the number of participants were only counted *once*. Mid-day not spec. includes those studies which used the term 'noon'. MPH: methylphenidate; ER: extended release; OROS: osmotic release oral system; IR: immediate release; NOS: not otherwise specified; MLR: multi-layer extended release; MTS: methylphenidate transdermal system; OD: once daily; BD: twice daily; TD: three times daily; QD: four times daily; MAS: mixed amphetamine salts; LDX: lisdexamfetamine; Org 26575 & 25676: Novel AMPA Receptor Positive Allosteric Modulator; ABT-089: Novel $\alpha_4\beta_2$ neuronal nicotinic receptor partial agonist.

Medication	Studies (N)	Timing of Medication								Participants
		0700–1000	1100–1400	1500–1800	1900-bed	AM not spec.	Mid-day not spec.	PM not spec.	Not spec.	
Methylphenidate	**18**									1720 650 T/391C
OD	**8**	**3**				**2**			**3**	
ER/MLR-MPH/PRC-063	5	1				2			2	
OROS-MPH	2	2								
MTS	2	2								
MPH-NOS	1								1	
BD	**3**	**1**		**1**		**1**	**1**		**1**	
MPH-IR	1	1		1						
MPH-NOS	2					1	1		1	
TD	**4**	**4**	**3**	**4**			**1**			
MPH-IR	3	3	3	3						
MPH-NOS	1	1		1			1			
QD	**1**				**1**				**1**	
MPH-NOS	1				1				1	
5x/d	**1**				**1**				**1**	
MPH-NOS	1				1				1	
Not specified	**4**									
OROS-MPH	2									
ER-MPH	2									
Amphetamines	**9 (+1)**									1549 1125 T/413C
OD	**8**	**4**				**2**			**3**	
LDX	2								2	
Triple-bead MAS/SHP465	5	3				1			1	
Adderall	1									
Not specified	**1**	**1**								
LDX	1								1	
Guanfacine	**7**									950 641 T/283C
OD	**5**	**1**				**4**		**2**		
Guanfacine ER	5	1				4		2		
BD	**1**				**1**	**1**				
Guanfacine ER	1				1	1				
Not specified	**1**									
Guanfacine ER	1									
Dasotraline	**2**									673 447 T/226C
OD	**2**					**1**		**1**		
Atomoxetine	**1**									445 220 T/225C
BD	**1**								**1**	
Modafinil	**1**									338 264 T/74C
OD						**1**				
Methylphenidate + amphetamines	**1**									37 (crossover)
OD	**1**					**1**				
ER d-MPH & ER MAS	1					1				
Methylphenidate + atomoxetine	**1**									85 (crossover)
BD (atomoxetine)	**1**	**1**		**1**						
TD (MPH)	**1**	**1**		**1**			**1**			
MPH-NOS	1	1		1			1			
Org 26575 & 25676	**1**									64 (crossover)
BD	**1**								**1**	
(ABT-089)	**1**									387 (crossover)
QD	**1**								**1**	

Table 2b
Pharmacological + non-pharmacological interventions for the treatment of ADHD. Populations of crossover studies were not included in the breakdown of treatment (*T*) and controls (*C*). Additionally, for studies that used the same study population, the number of participants were only counted *once*. Mid-day not spec. includes those studies which used the term 'noon'. BD: twice daily; MPH: methylphenidate; NOS: not otherwise specified; TD: three times daily.

Medication	Studies (N)	Timing of Medication								Participants
		0700–1000	1100–1400	1500–1800	1900-bed	AM not spec.	Mid-day not spec.	PM not spec.	Not spec.	
Atomoxetine + parent training	**1**									54 41 T/13C
BD	1								1	
MPH + behavioural therapy	**1**									576 431 T/143C
TD	1					1	1	1		
MPH-NOS	1					1	1	1		

Table 2c
Medications for the treatment of sleep. Populations of crossover studies were not included in the breakdown of treatment (*T*) and controls (*C*). Additionally, for studies that used the same study population, the number of participants were only counted *once*. Mid-day not spec. includes those studies which used the term 'noon'. OD: once daily; QD: four times daily.

Medication	Studies (N)	Timing of Medication								Participants
		0700–1000	1100–1400	1500–1800	1900-bed	AM not spec.	Mid-day not spec.	PM not spec.	Not spec.	
Melatonin	**1**									105 53 T/52C
OD	1				1					
Melatonin + Ritalin	**2**									50 26 T/24C
Not specified	2									
Zolpidem	**1**									201 136 T/65C
OD	1				1					
Eszopiclone	**1**									483 323 T/160C
OD	1				1					
L-DOPA/carbidopa	**1**									18 10 T/8C
QD	1					1	1	1		
Ramelteon	**1**									36 (crossover)
OD	1				1					
L-theanine	**1**									93 46 T/47C
QD	1					1		1		
Cyproheptadine	**1**									40 20 T/20C
BD	1					1		1		

Table 2d
Medications for the treatment of sleep & ADHD. Populations of crossover studies were not included in the breakdown of treatment (T) and controls (C). Additionally, for studies that used the same study population, the number of participants were only counted *once*. Mid-day not spec. includes those studies which used the term 'noon'. QD: four times daily.

Medication	Studies (N)	Timing of Medication								Participants
		0700–1000	1100–1400	1500–1800	1900-bed	AM not spec.	Mid-day not spec.	PM not spec.	Not spec.	
L-DOPA/carbidopa	**1**									29 15 T/14C
QD	1					1	1	1		

Table 2e
Pharmacological + non-pharmacological interventions for the treatment of sleep. Populations of crossover studies were not included in the breakdown of treatment (T) and controls (C). Additionally, for studies that used the same study population, the number of participants were only counted *once*. Mid-day not spec. includes those studies which used the term 'noon'. OD: once daily.

Medication	Studies (N)	Timing of Medication							Participants
		0700–1000	1100–1400	1500–1800	1900-bed	AM not spec.	PM not spec.	Not spec.	
Melatonin + sleep hygiene	**1**								19 (crossover)
OD	1				1				

Table 3
Non-pharmacological interventions used for the treatment of 1) sleep, 2) ADHD, and 3) sleep & ADHD. C: control group, N: number of participants, T: treatment group.

Treatment	Studies (*N*)	Participants
Treatment of Sleep		
Behavioural therapy/parent training	2	*N* = 116 (59 T/57C)
Treatment of ADHD		
Neurofeedback	2	*N* = 68 (33 T/35C)
Behavioural therapy/parent training	1	*N* = 51 (26 T/25C)
Slow oscillating transcranial direct current	1	*N* = 14 (crossover)
Trigeminal nerve stimulation	1	*N* = 62 (32 T/30C)
Treatment of Sleep & ADHD		
Behavioural therapy/parent training	6	*N* = 733 (367 T/366C)
Elimination diet	1	*N* = 24 (13 T/11C)
Cognitive skills tasks	1	*N* = 20 (10 T/10C)

log as the sole tool for assessing sleep (Jadad score = 3). Notably, this was the oldest RCT included in this scoping review and the sleep diary was recorded by nursing staff.

Tools used in studies evaluating sleep as a secondary outcome

31 RCTs used sleep as a secondary outcome, including post-hoc analyses. Of these 31 RCTs, the most commonly employed tool was the Pittsburgh Sleep Quality Index (PSQI; n = 14), followed by CSHQ (n = 6), Pediatric Daytime Sleepiness Scale (PDSS; n = 3), ESS (n = 3), and actigraphy (n = 3). Goodman et al. [65] utilized the greatest number of sleep outcome measures (n = 3), including actigraphy. No study in this category used PSG (Fig. 3b).

Methodology and validation of questionnaire-based sleep outcome measures

23 questionnaires were identified, the majority of which were sleep-specific. Although we included two RCTs [20,61] that did not use a sleep specific tool (Pittsburgh Side Effects Rating Scale, Achenbach Child Behaviour Checklist), these RCTs were still included because in that context, the aforementioned tools had explicitly been used to assess sleep. Two questionnaires, ELIT and Physical Complaints Questionnaire (PCQ) were originally published in Dutch, and as a result were not analyzed in our review.

Four questionnaires did not have any accompanying validation study and were resultantly deemed non-validated (Pittsburgh Side Effects Rating Scale, Sleep Hygiene 7-item measure, UAB Insomnia Questionnaire, Sleep Problem Prevalence). The Pittsburgh Side Effects Rating Scale, Sleep Hygiene 7-item measure, and UAB Insomnia questionnaire were each used as the primary outcome measure used by one RCT, respectively (Fig. 3a). Two RCTs used self-validated questionnaires; Mehri et al. [53] translated the CSHQ into Persian, whilst Mohammadi et al. [43] translated the SDSC into Persian. The self-validated questionnaires were not considered separate from their original among the total number identified, since they were conducted for the purpose of the specific RCT and not for widespread usage.

Table S4 outlines each questionnaire and the accompanying first published validation study. The majority of validation studies consisted of populations from the United States of America (USA) (n = 8 [92–99]). Australian [100], Dutch [101], Italian [102], and South African [103] populations were included in one validation study each. The International Restless Legs Severity Scale validation study consisted of adult populations from the USA, Germany, Ireland, Italy, Spain, and Sweden [104]. The psychometric properties of each validation study were analyzed according to Sen & Spruyt [17] and Spruyt et al. [18]. Criterion validity was the most common (n = 11 studies [94–96,99,100,103–108]), followed by construct validity (n = 5 studies [93,99,101,104,106]), concurrent validity (n = 1 study [104]), and discriminative validity (n = 1 study [104]). 13 validation studies carried out reliability analyses, which included internal, test-retest, and inter-rater reliability (Table S4).

Nine sleep domains were identified in the questionnaires, these are: 1) amount of sleep, 2) routines, 3) daytime, 4) bedtime/transitions, 5) nighttime, 6) arousal disorders, 7) movement disorders, 8) breathing, and 9) sleep hyperhidrosis (Fig. 4). The Pediatric Sleep Questionnaire (PSQ) was the only questionnaire to capture all nine domains. The CSHQ, SDSC, HSDQ, and Adolescent Sleep Habits Questionnaire (ASHQ) included eight domains, respectively. The ESS, PDSS, Teacher Daytime Sleepiness Scale (TDSS), Pictorial Sleepiness Scale (PSS), and Fatigue Symptom Inventory (FSI) only captured the daytime domain (e.g., excessive daytime sleepiness), whereas the JHRLSS and International Restless Legs Scale (IRLSS) only captured movement disorders. All sleep questionnaires and the accompanying sleep domains are shown in Fig. 4.

Methodology and validity of technical tools (PSG and actigraphy)

10/71 RCTs used PSG to collect and evaluate data used for primary outcome measures. No RCT that had used sleep as a secondary outcome measure, or had employed non-pharmacological interventions, used PSG. Of the 10 studies that used PSG, seven were conducted in the USA [29,34,39,45,75,82,90] and three were conducted in Canada [64,67,71]. Notably, none of the included RCTs that used PSG were conducted outside of North America.

Two RCTs specified the use of the Sandman Polysomnography System for their PSG device [67,82], one RCT specified the use of SD32+ digital amplifiers along with Sandman Elite Software Version 9.3 [64], and the remaining seven did not specify (Fig. S1). The data collection schedule for PSG was outlined in all but one RCT [45]. In general, measurements were taken at baseline, at each study visit if applicable, and at termination or the end of periods corresponding to the study's treatment conditions (placebo, different drug dosages, etc) (Fig. S1). One RCT collected a "week" of PSG data for an unspecified number of nights during baseline, and one night at each subsequent data collection period (one PSG x four weeks) [67], while one RCT did not specify the number of nights [45]. For the analysis of PSG-collected data, five RCTs scored based on the American Academy of Sleep Medicine (AASM) Manual Version 2.0 [34,64,67,71,82], and five RCTs did not specify

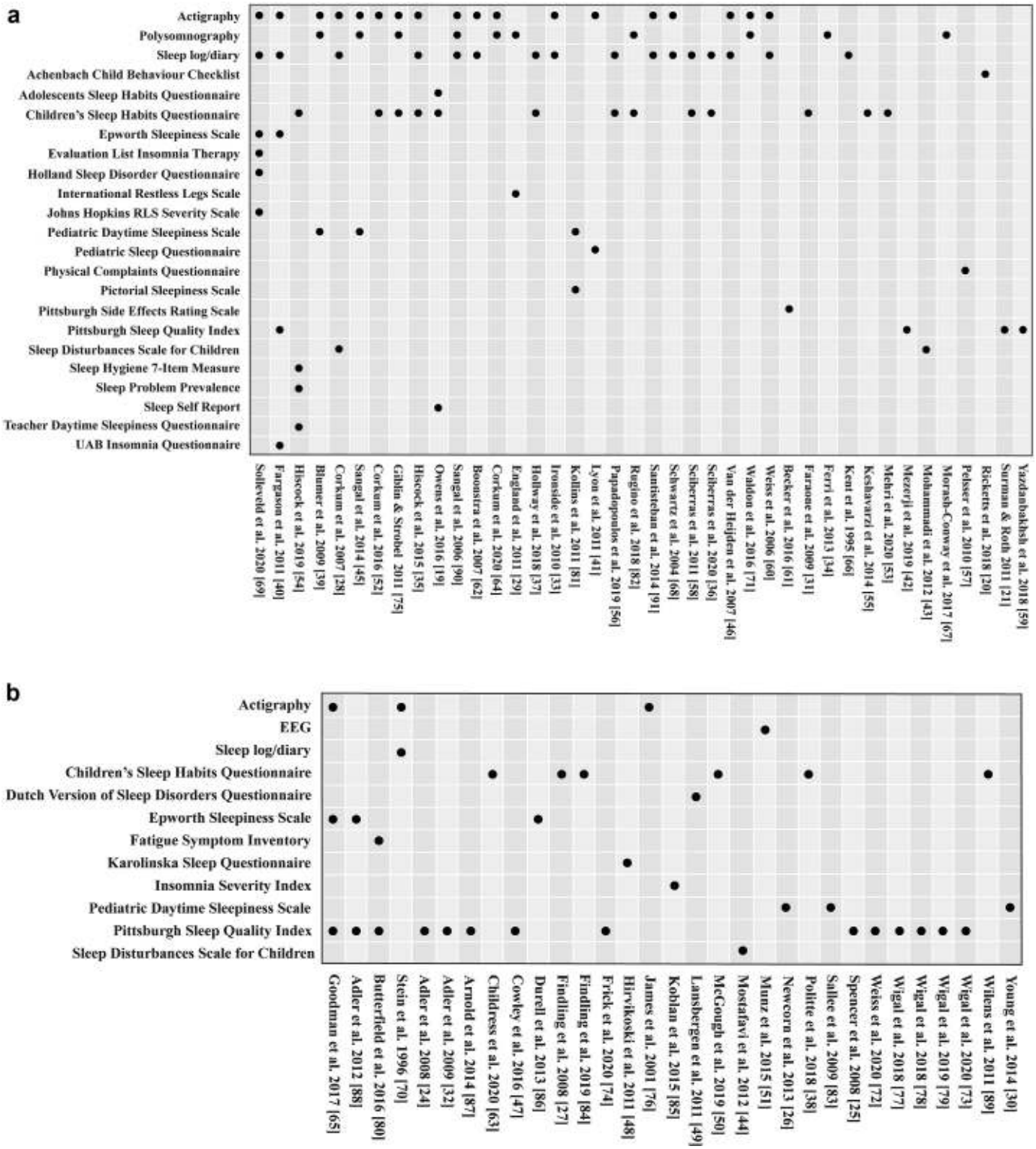

Fig. 3. a. Sleep specific tools used as outcome measures in RCTs that used sleep as a primary outcome measure. **b.** Sleep specific tools used as outcome measures in RCTs that used sleep as a secondary outcome measure.

[29,39,45,75,90]. One RCT used criteria by the World Association of Sleep Medicine-International Restless Legs Syndrome Study Group (WASM-IRLSSG) and AASM [34] (Fig. S1).

The most commonly reported PSG variable was sleep efficiency (n = 7), followed by total sleep time (n = 6) and wake after sleep onset (n = 5) (Fig. 5). Only one RCT that utilized PSG reported apnea/hypopnea events [82]. Ferri et al. [34] reported the greatest number of variables, a large percentage of which pertain to limb movements (i.e., periodic limb movements in sleep, isolated leg movements).

21/71 RCTs used actigraphy. Of these studies, nine were conducted in the USA, eight in Canada, three in the Netherlands, and one in Australia.

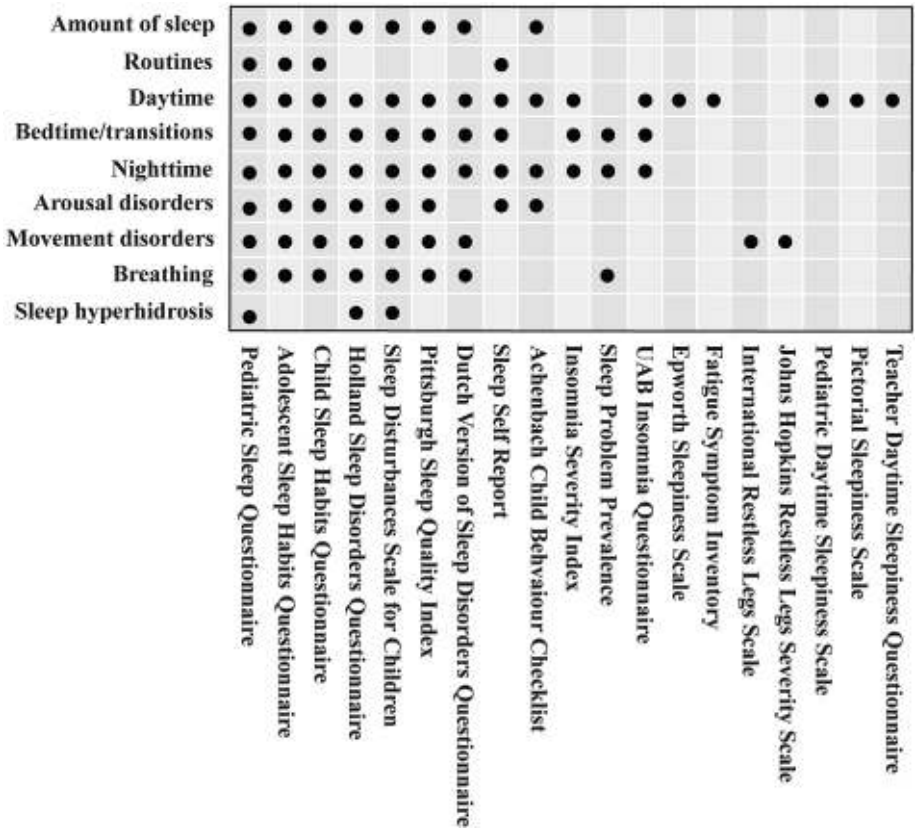

Fig. 4. Sleep domains measured by the sleep-specific questionnaires identified in the 71 included RCTs. Four questionnaires (Pittsburgh Side Effect Rating Scale, Evaluation List Insomnia Therapy, Physical Complaints Questionnaire, and Sleep Hygiene 7-item Measure) could not be located in full, and thus we were not able to assess their domains.

For the 18 RCTs that used actigraphy to collect and evaluate data for primary outcome measures, 13 specified the model of actigraph. In these studies, several different devices were used: Basic Mini-Motionloggers (n = 2), Actiwatch Activity Monitoring System (n = 2), Actiwatch (n = 2), Micro Mini-Motionloggers (n = 2), Actiwatch AW-64 Actigraphy System (n = 1), Actiwatch 2 (n = 1), Actiwatch AW4 (n = 1), Micro-Mini Octagonal Basic Motionlogger Actigraph (n = 1), and an unspecified AW64 Series wrist device (n = 1) (Fig. 6).

Actigraphy data was collected at a variety of different time points as specified by each study's data collection schedule. The duration of the actigraph worn also varied depending on the RCT. A more detailed breakdown of this information is presented in Fig. 6. For the analysis of actigraphy-derived data, 13 RCTs specified the algorithm used. The most commonly employed algorithm was the Action-W2 Software (n = 4), followed by Actiwatch Sleep Analysis Software Version 1.19 (n = 1), a combination of Actiware-Sleep Version 5.04 Sleep Scoring Software and Clocklab Analysis Software (n = 1), Actiware Sleep Software (n = 1), Actiware Sleep 3.4 (n = 1), AW64 Series Sleep Software (n = 1), a combination of Actiwatch Sleep Analysis 5.0 Software and MATLAB employing the Oakley Algorithm (n = 1), an Actiwatch Scoring Algorithm developed by Kushida et al. [109] (n = 1), and Action-W Software Version 2.6 (n = 1). One RCT specified that actigraph-collected data was submitted for data processing, citing Ambulatory Monitoring Inc (Fig. 6).

Three RCTs used actigraphy to collect and evaluate data for secondary outcome measures, all of which were conducted in the United States. Of these studies, only one RCT specified the actigraph used, which was the Actiwatch-Spectrum. Moreover, only one RCT specified the algorithm employed for actigraphy-related data analysis, which was the Actiwatch Sleep Software.

Effect of intervention on sleep outcome

50 RCTs were targeting ADHD symptoms, the majority of which were using pharmacological treatments such as stimulants (Fig. 2). Of these, an adverse effect on sleep was seen in 19/50 RCTs. All 19 RCTs were using a pharmacological treatment modality (MPH n = 11; Amphetamines n = 7; Atomoxetine n = 2; Guanfacine n = 2; Dasotraline n = 1). PSG and/or actigraphy used in 10/19, while questionnaires/scales were used in 9/19 RCTs. Sleep and sleep plus ADHD were targeted in 12 and nine RCTs, respectively. No adverse effects on sleep were seen in these groups of included RCTs.

Quality assessment of RCTs: Jadad score

Jadad scores are presented in Table S3.

Discussion

Given the increasing amount of evidence to suggest that sleep disturbances are intrinsic to the ADHD clinical phenotype, the aim of this scoping review was to identify ADHD RCTs that used sleep as a primary or secondary outcome measure.

Only a minor fraction of the 2265 articles screened met our inclusion criteria. The scarce use of sleep as an outcome measure in RCTs may be explained by the limited acknowledgement of sleep as an intrinsic characteristic of ADHD. The heterogeneity of protocols and tools used to measure sleep-related outcomes supports this notion. Both technical tools such as PSG or actigraphy, and questionnaires/scales or sleep diary protocols were used in various combinations. 18/40 of the RCTs that used sleep as a primary

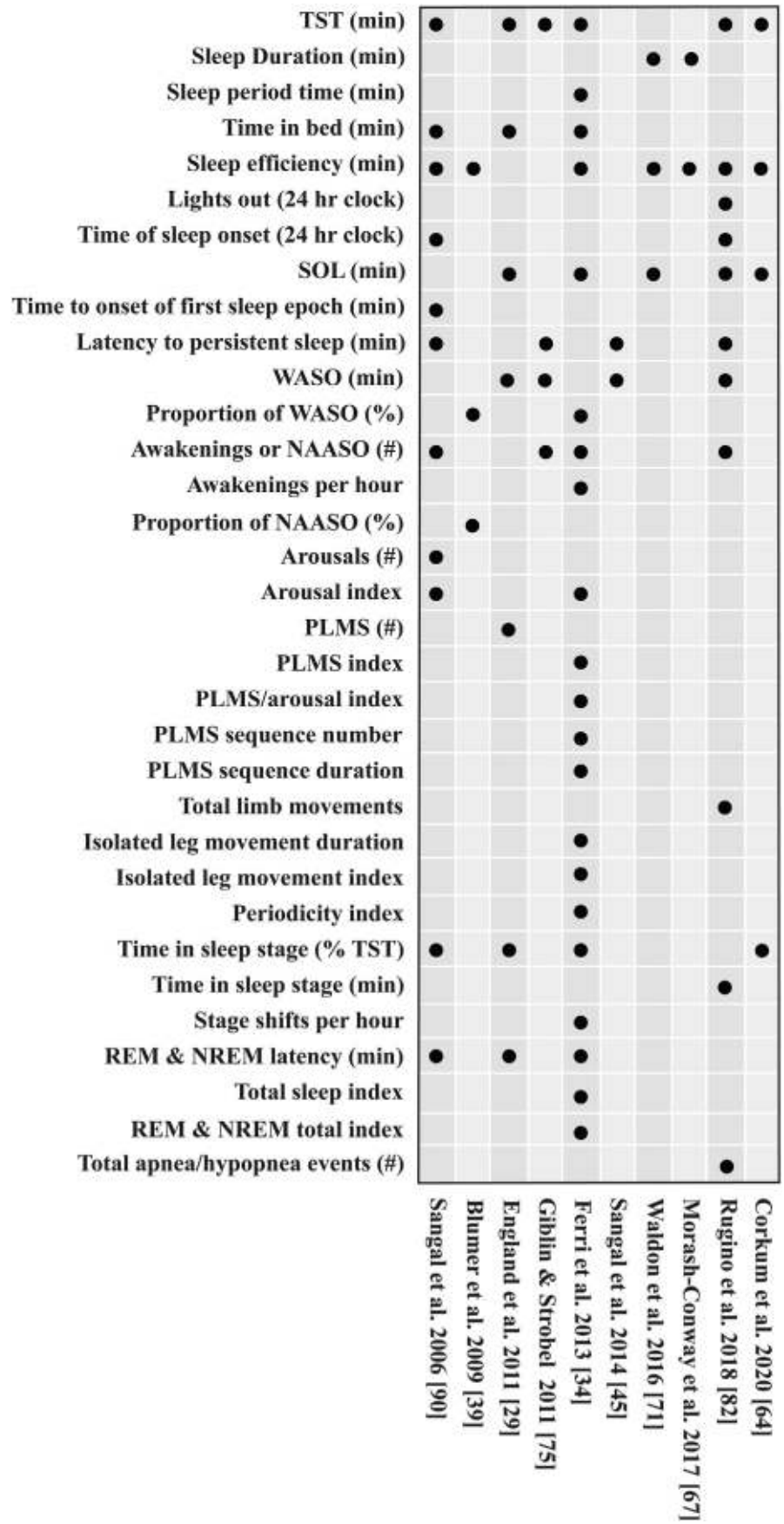

Fig. 5. Variables measured using PSG in the included RCTs. NAASO: number of awakenings after sleep onset, NREM: non rapid eye movement sleep, PLMS: periodic limb movements in sleep, REM: rapid eye movement sleep, SOL: sleep onset latency, TST: total sleep time, WASO: wake after sleep onset.

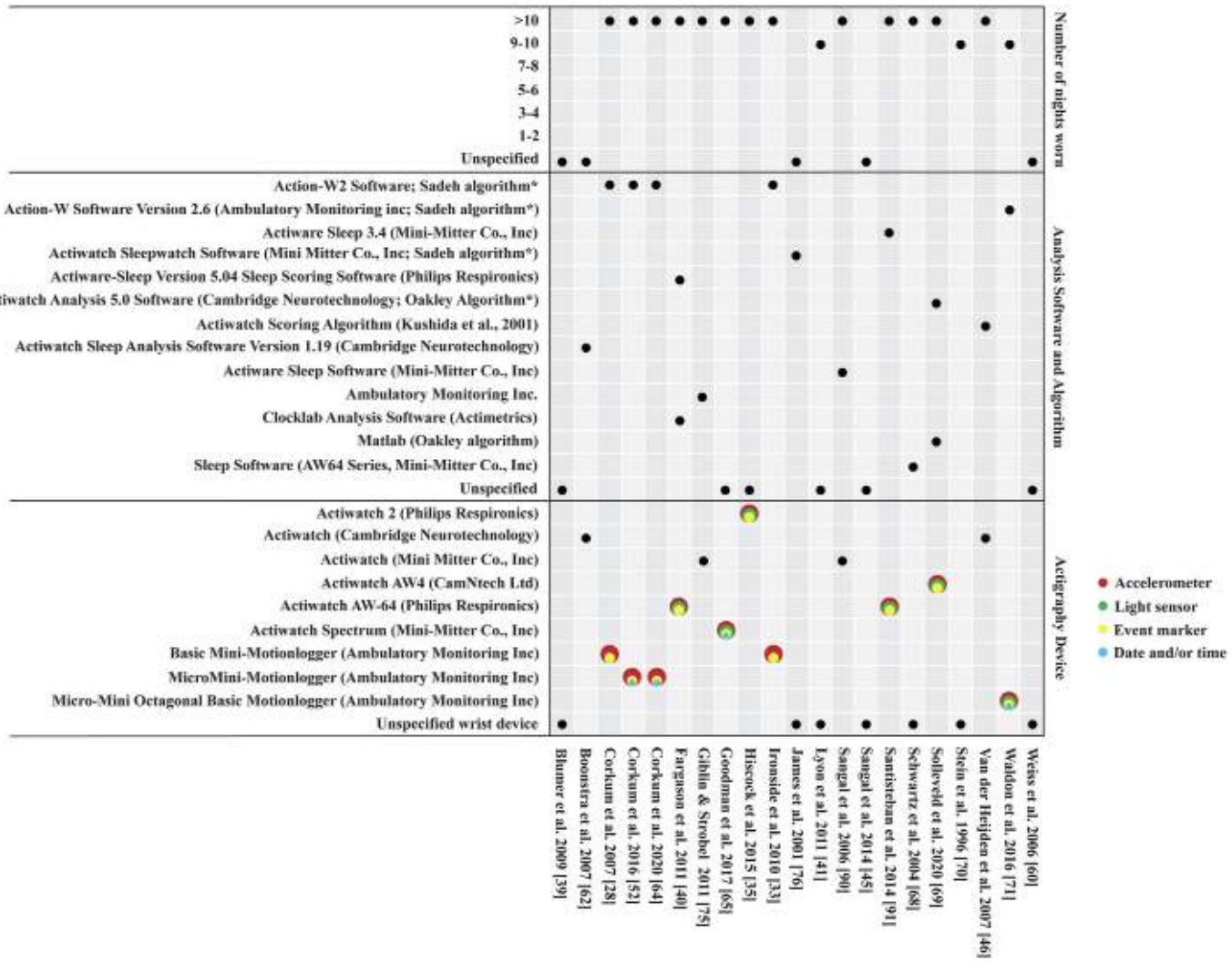

Fig. 6. Included RCTs that utilized actigraphy as a sleep tool. *Sadeh A, Aldster J, Urbach D, & Lavie P. Actigraphically based automatic bedtime sleep-wake scoring: Validity and clinical applications. Journal of Ambulatory Monitoring 1989; 2, 209–216.

outcome measure utilized either actigraphy or PSG in addition to a questionnaire/scale or sleep diary, four used PSG and/or actigraphy only, and 18 used questionnaires/scales only (Fig. 3a).

PSG and actigraphy as technical sleep assessment tools

Although PSG was used quite commonly to measure sleep as a primary outcome (10/40 RCTs), the PSG endpoints varied considerably between studies (Fig. 5). PSG has long been regarded as the 'gold standard' for measuring sleep. However, it is associated with certain challenges that may limit its use in clinical practice. While PSG is able to capture a variety of important information (including respiratory, cardiac, and EEG monitoring), that information is usually only captured over a single night and in a sleep laboratory - a foreign environment that may hinder sleep [110]. This may be particularly relevant for children with neurodevelopmental disorders including ADHD and ASD, who are often sensitive to changes in routine and environment and thus may require a second night to obtain an accurate assessment.

Given these challenges, at-home monitoring systems such as actigraphy have been recommended by the American Academy of Sleep Medicine for assessment of certain sleep disorders (e.g., insomnia, circadian rhythm sleep disorders) in pediatric patients [111]. Unfortunately, actigraphy solely measures movements of the non-dominant arm, and therefore may miss PLMS [111]. In addition, cost and access to research-grade actigraphy devices may be a barrier to accessing this type of technology. In a recent study by Chinoy et al. [112] consumer sleep-tracking devices including smart watches that utilize similar accelerometer technology to that found in research-grade actigraphy were found to have high sensitivity with low-medium specificity. Therefore, the increasing availability of high-quality consumer devices might ease the access to research-grade actigraphy in the future [112].

Sleep questionnaires and sleep diaries

Sleep questionnaires were used in the vast majority of studies. In those 40 RCTs that used sleep as a primary outcome measure, sleep questionnaires were used in 18 studies in combination with PSG/actigraphy and in another 18 studies without. Of the 23 questionnaires identified, the most commonly employed questionnaires were the CSHQ, PSQI, and ESS. These questionnaires are well-known across the world and have been validated for use in numerous populations, whereas for four questionnaires (Pittsburgh Side Effects

Rating Scale (PSERS), Sleep Hygiene 7-item measure, UAB Insomnia Questionnaire, Sleep Problem Prevalence) we could not find any published validation study. Interestingly, two of these non-validated questionnaires (Sleep Problem Prevalence and Sleep Hygiene 7-item measure) were used in the same RCT, with the Sleep Problem Prevalence used as the primary outcome measure [54]. And while the majority of these non-validated questionnaires were used in combination with additional validated questionnaires and/or PSG/actigraphy, the PSERS, which is not a sleep specific tool, was used as the sole sleep tool in one of the MPH studies [61]. Questionnaires were also heterogeneous in terms of sleep domains covered. While the PSQ, CSHQ, SDSC, HSDQ, and ASHQ covered most domains (Fig. 4), questionnaires such as the ESS, PDSS, PSS, and FSI are symptom specific, and the JHRLSS and IRLSS are disorder-specific.

Sleep diaries have long been touted as an important aspect of subjective sleep assessment corresponding well to sleep and wake times [113,114]. Sleep diary/log was used in the majority of included RCTs (16/40 RCTs with sleep as a primary outcome) as an adjunct measure. Only one RCT [66] used sleep diary as the only measure for sleep. Given the limitations of a sleep diary in accurately identifying certain domains of sleep disturbance (sleep diaries tend to be an inaccurate measure of wake after sleep onset), it is recommended that this tool be used as an adjunct to other validated questionnaires and/or actigraphy.

In recent years, questions have been raised about the involvement of children in research. The National Institutes of Health recommends involvement of children in research as a key factor to evoke meaningful patient outcomes [115]. Currently available sleep diaries are usually filled out by the parent/caregiver (depending on the age of the child/adolescent), or in some circumstances, by clinical staff [66]. In our scoping review, only two RCTs involved children in filling out the sleep diary [69,90], highlighting the need for increased involvement of children in ADHD RCTs [116].

ADHD medications - dosing and timing regimens

Given the current evidence showing that sleep disturbance is a common side effect of certain ADHD medications [11,117], we felt it important to also review the medication dosing regimens and timing used in the included RCTs. For MPH, four RCTs did not specify dosing regimen (e.g., once-daily, twice-daily) and an additional five RCTs did not specify timing of the medication (e.g., 08:00). This lack of information is concerning, particularly for MPH, which has numerous different formulations that have unique pharmacokinetic and pharmacodynamic properties which can be used to meet unique needs of certain individuals [118]. While standardized recommendations for the timing and dosage of MPH and ITS various formulations are lacking, structured behavioral observations [119,120] or a computational modeling tool for MPH drug regimens, such as the one developed by Bonnefois et al. [121,122] could enable the selection of an individualized medication regimen, ultimately introducing the concept of personalized care for children and adolescents with ADHD.

Limitations

Our methodological approach looked only at the first published validation study. Therefore, it is likely that additional validation studies (e.g., validated in different languages or populations, such as pediatrics i.e., the ESS, validated for use in children by Janssen et al. [123]) for these tools have been carried out and have not been captured in our scoping review. Additionally, two sleep tools (ELIT and PCQ) were not published in English, and thus no validation studies could be obtained. Moreover, this methodological approach meant that we did not look at the validation of questionnaires in specific age groups (e.g., children and adolescents). For example, the PSQI [124] and IRLSS have not been validated for use in children, despite being classified as validated questionnaires in our scoping review. An additional review of age group-dependent questionnaire validation is needed to close this knowledge gap.

Furthermore, the RCTs included in this review were carried out across nine different countries with various linguistic and cultural peculiarities. While the analysis of questionnaires in specific cultural settings is out of the scope of this review, we would like to highlight the importance of cultural norms in the connotation of sleep [125,126], and that terms used in questionnaires may have different meanings in different languages [127]. For example, two RCTs [43,53] carried out in Iran used self-validated (translated to Persian) versions of the SDSC and CSHQ, respectively; the CSHQ was originally validated in American children, whilst the SDSC was validated in Italian children. Therefore, even validated questionnaires have limitations unless they are designed and validated for the specific population in which it will be used [128].

An important aspect in the assessment of questionnaires is user-friendliness and accessibility. Scoring systems, such as the one developed by Klingman et al. [129], which assessed three domains (comprehensiveness, brevity, and psychometric soundness) may be useful in the evaluation of sleep questionnaires for clinical practice. However, as was highlighted by Ibanez et al., sleep questionnaires are highly heterogeneous [130] - some with a more general approach to sleep versus those that are targeting specific sleep disturbances or disorders. Finally, given that our focus was primarily on study methodology, we did not conduct an in-depth analysis of the effects of each intervention on sleep. However, this is the subject of a secondary review.

Harmonization of sleep-specific outcome measures

Our scoping review has shown that in the context of ADHD, there is no consensus on how sleep should be assessed, including which tools would be most suitable for this population. Core outcome sets that are specific for ADHD-related sleep problems as well as tools that reliably measure these outcomes need to be developed by expert groups. Harmonization is needed to make results comparable in future studies.

At this stage of the discussion, in our opinion, the assessment of sleep in ADHD should include, at a minimum, tools that have the ability to capture each of the following sleep phenotypes resembling: narcolepsy, periodic limb movements, epilepsy, delayed sleep phase syndrome, and obstructive sleep apnea [8], which allows for a more thorough clinical assessment of the affected individuals. Methodological validation, appropriateness for ADHD-related sleep disturbances, cultural appropriateness, user friendliness, and patient participation are major criteria for the choice of assessment tools. However, with an emerging understanding of the relationships between ADHD and sleep, a broader approach will be necessary in the future. The use of an explorative mixed methodology that incorporates patient goals [131] and concerns [132], structured reporting with diaries and logs, and observations, as is recommended by the IRLSSG pediatric consensus [119,120] may support the collection of more in-depth, personalized data; though the feasibility of such an approach in individuals with ADHD exceeds the scope of this review.

Conclusions

Sleep is integral to the ADHD clinical phenotype, and the repercussions of disturbed sleep can be felt, not only by the child/adolescent, but also by the family and/or caregivers. Despite this, only a small proportion of interventional ADHD RCTs utilized sleep

as a primary or secondary outcome measure. Questionnaires were widely used to evaluate sleep disturbances, but some of them have not yet been validated. The tools identified in our review are heterogeneous in nature, each developed to target a particular aspect of disturbed sleep and may not accurately capture the array of sleep disturbances experienced by individuals with ADHD. This situation highlights the need for a consensus statement by an expert group harmonizing core outcome sets and THE most appropriate assessment tools.

Practice points

1. Sleep is an intrinsic feature of ADHD, but is not adequately assessed as an outcome measure in interventional ADHD RCTs.
2. Both symptoms/sleep domains captured, and type of validation should be considered when choosing tools for future research studies.

Research agenda

To optimize the investigation of sleep in ADHD, we recommend the development of:

1. A battery of tools capable of capturing the wide range of sleep disturbances experienced by individuals with ADHD.
2. A core set of standardized, validated sleep-related outcome measures for ADHD to be employed in future RCTs investigating therapies for ADHD.

Conflicts of interest

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

Acknowledgments

To BC Children's Hospital Research Institute, for their generous ongoing support of our research, as well as the Summer Studentship awarded to SM in 2020. To Helen Brown, Librarian, University of British Columbia, for her guidance in protocol and search strategy development.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101613.

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