To Sleep or Not To Sleep: A Systematic Review of the Literature of Pharmacological Treatments of Insomnia in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

Jessica R. Barrett, BSc,^{1,2} Derek K. Tracy, MB BCh,^{1,3} and Giovanni Giaroli, MD^{1,4}

Abstract

Objective: This systematic review assessed current evidence on sleep medication for attention-deficit/hyperactivity disorder (ADHD) patients, to establish appropriate guidance for clinicians faced with prescribing such medications.

Methods: Five articles (based on four pharmacological compounds) out of a total 337 were identified as evidence to guide pharmacological treatment of ADHD-related sleep disorders. Data regarding participant characteristics, measures of ADHD diagnosis, measures of sleep, and outcome data were extracted.

Results: Zolpidem and L-theanine both displayed a poor response in reducing sleep latency and increasing total sleep time, however L-theanine did produce an increase in sleep efficiency. Zolpidem produced high levels of side effects, leading to the largest dropout rate of all five studies. Clonidine reduced insomnia; and melatonin also exhibited a positive response, with reduced sleep latency, higher total sleep time, and higher sleep efficiency.

Conclusions: There is a relative paucity of evidence for the pharmacological treatment of ADHD-related sleep disorders; therefore, further research should be conducted to replicate these findings and obtain reliable results.

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a very common childhood behavioral disorder, with ~3–9% of children and 2% of adults impacted worldwide following diagnosis, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) (American Psychiatric Association 1994; National Institute for Health and Clinical Excellence 2008). ADHD is a condition that is not very common on its own, and can present in comorbidity in >69% of patients with other externalizing disorders such as oppositional defiant disorder or conduct disorder; or with internalizing disorders such as depression or anxiety (The MTA Cooperative Group 1999a,b).

Sleep disturbances are also a frequent occurrence in individuals with ADHD, with the resultant sleep deprivation potentially worsening ADHD symptoms and intensifying disruptive behaviors (Wilens et al. 1994). Approximately 28% of medication-free ADHD patients suffer from sleep disturbances such as chronic sleep onset insomnia (CSOI) (Corkum et al. 1999), and overall, 48–

73% of children with ADHD have experienced sleep difficulties in childhood (Greenhill et al. 1983; Allen et al. 1992; Sung et al. 2008) compared with ~10% of healthy controls (Allen et al. 1992). The sleep problems that are most commonly reported in ADHD patients are unwillingness to go to sleep, difficulty falling asleep, recurrent waking, restless sleep, trouble with morning awakening, shorter sleep duration, and sleepiness during the day (Wilens et al. 1994; Prince et al. 1996; Cortese et al. 2009; Lyon et al. 2011), as well as a higher rate of sleep disorders such as restless leg syndrome (RLS), periodic limb movement, and sleep-disordered breathing (Lyon et al. 2011). RLS is a neurological disorder, which is typified by the irresistible need to move the legs, coupled with sensations of discomfort in the limbs, which can be alleviated through movement. These uncomfortable sensations are usually worse in the evenings, nighttime, or at rest. A relationship has been found between RLS and ADHD, and it is posited that RLS may exacerbate or delay the onset of ADHD symptoms, and may also result in a higher incidence of bedtime resistance (Cortese et al. 2005). Because of this relationship, it is assumed that there is

¹Cognition, Schizophrenia, & Imaging Laboratory, Department of Psychosis Studies, the Institute of Psychiatry, King's College, London, United Kingdom.

²South London and Maudsley NHS Foundation Trust, London, United Kingdom.

³Oxleas NHS Foundation Trust, London, United Kingdom.

⁴North East London NHS Foundation Trust, London, United Kingdom.

a shared dopaminergic system dysfunction in both sleep disorders and ADHD (Silvestri et al. 2009); however, it has been found that L-DOPA does improve RLS but not ADHD (England et al. 2011), indicating that the relationship between RLS and ADHD may not be the result of a dopaminergic dysfunction.

We can hypothesize that sleep disturbances in ADHD may be either an adverse effect of pharmacological treatment (Sangal et al. 2006; Faraone et al. 2009; Giblin and Strobel 2011; Huang et al. 2011), an alternative epiphenomenon stemming from core ADHD symptoms (Weiss and Salpekar 2010), a psychiatric comorbidity (Lecendreux and Cortese 2007; Tsai and Huang 2010), or a combination of them. Shorter total sleep time and increased sleep latency are common side effects of stimulant medication (Weiss and Salpekar 2010) because of the pharmacological disruption of dopaminergic and noradrenergic release in the central nervous system (Huang et al. 2011). The importance of noradrenaline as a key neurotransmitter implicated in arousal is discussed in Mitchell and Weinshenker (2010) who note that stimulant medications promote the synaptic release of dopamine and noradrenaline, and to a lesser extent, serotonin, while also blocking their reuptake, thus increasing the synaptic levels of these monoamines, which all play a

role in the arousal pathway. The non-stimulant drug atomoxetine, a selective noradrenaline reuptake inhibitor, acts in a similar way to the stimulant medications, as they are both reuptake inhibitors; however, they block different neurotransmitters in varying proportions. Despite a similar mechanism, atomoxetine's effects on suppressing the sleep states appear to be less profound (Sangal et al. 2006). An optimization of the pharmacological treatment can help the clinician to reduce those sleep difficulties that were the results of side effects of the pharmacological treatment. However, it is also a common experience for the clinician to obtain a positive history of sleeping difficulties in drug-naïve ADHD patients. In some cases, the pharmacological treatment of ADHD core symptoms brings about an amelioration of the sleep alteration, and in some cases, the use of stimulants or non-stimulants is "neutral" to the sleeping difficulties, and an adjunct treatment has to be introduced.

Despite the dearth of evidence for efficacy and safety, and the lack of approval from the United States Food and Drug Administration (FDA) for medications treating insomnia in children, clinicians pragmatically have pharmacologically treated ADHD-related sleep disorders with antihistaminergic medications, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), benzodiazepines,

FIG. 1. Diagram depicting the selection process of articles through literature databases, and the separate stages of exclusion.

TABLE 1. STUDY CRITERIA FOR THE FIVE SELECTED STUDIES ON PHARMACOLOGICAL TREATMENT OF ADHD-RELATED INSOMNIA

Publication	Study design	Participants (n, gender, age)	Recruiting source	Pharmacological treatment	Previous / current treatment	ADHD screening	Sleep screening	Exclusion criteria	Results
Prince et al. (1996)	Systematic retrospective chart review	n = 62 42 children (4–12 years), 20 adolescents (13–17 years), 51 male, 11 female. All participants given pharmacological intervention	Electronic database from specialized pediatric psychopharmacology unit	Clonidine; nighttime doses range 50–800 µg (oral).	42 stimulants 22 tricyclic antidepressants 7 mood stabilizers 3 SSRIs 2 neuroleptics 1 antihistamine (58 for ADHD only)	DSM-III-R; K-SADS-E	Sleep history from parental reports (documented in medical chart) - retrospective	ADHD patients not treated with clonidine for sleep disturbances for ≥ 1 week.	53 patients' (85%) sleep was very much improved, regardless of baseline, medicine-induced, or medicine-exacerbated sleep problems. 19 patients (31%) experienced mild adverse effects.
Van der Heijden et al. (2007)	Randomized double-blind, placebo-controlled trial.	n = 105. Ages 6–12 years. Melatonin (n = 53). Placebo (n = 52).	Sleep disorder outpatient clinic in Gelderse Vallei General Hospital and Kempenhaeghe; magazine adverts, new-spapers, or through The Dutch ADHD Patient Support Center.	Melatonin dosage = 3mg when body weight < 40 kg, 6mg when body weight ≥ 40 kg.	No current treatment. All medication-free for at least 4 weeks prior to enrolment.	Clinical history; Diagnostic Interview Schedule for Children-Parent; CBCL; TRF; DSM-IV.	Clinical history; 1 week 24-hour actigraphy measurement; Dutch Sleep Disorders Questionnaire; Children's Sleep Hygiene Scale.	Total IQ < 80, pervasive developmental disorder, chronic pain, reported hepatic or renal function, epilepsy, previous melatonin use, and the use of stimulants, neuroleptics, benzodiazepines, clonidine, antidepressants, hypnotics, or β-blockers 4 weeks prior to enrolment.	Melatonin advanced sleep onset and DLMO, and increased total sleep time in ADHD and CSOI patients, whereas a delay was seen in placebo group. No effect on ADHD behavior, cognitive performance, or quality of life. No significant adverse effects or discontinuation because of adverse events.
Blumer et al. (2009)	Double-blind, placebo-controlled, parallel-group study.	n = 201 111 children (ages 6–11 years), 90 adolescents (ages 12–17 years). Zolpidem (n = 136). Placebo (n = 65).	Not stated	Zolpidem dosage = 0.25 mg/kg per day (max. 10 mg) orally, 30 minutes before bedtime.	184 stimulants 64 non-hypnotics. 22 clonidine (zolpidem group). 9 drugs that manifest drowsiness (placebo group). 8 antihistamines (placebo group).	DSM-IV-TR; Clinical interviews	Self report of childhood insomnia. Polysomnography, actigraphy	Latency to persistent sleep < 30 minutes. Sleep disturbances caused by physiological effects of drug abuse/misuse. Other sleep disorders. Comorbid major psychiatric disorders (except OCD). History of substance abuse/dependence. Previous adverse effects of zolpidem. Use of pharmacological sleep aids. Current use of rifampicin or serrtraline. Pregnancy.	Zolpidem failed to reduce sleep latency. 7.4% (10 patients) discontinued zolpidem because of mild to moderate psychiatric adverse effects.

(continued)

TABLE 1. (CONTINUED)

<i>Publication</i>	<i>Study design</i>	<i>Participants (n, gender, age)</i>	<i>Recruiting source</i>	<i>Pharmacological treatment</i>	<i>Previous / current treatment</i>	<i>ADHD screening</i>	<i>Sleep screening</i>	<i>Exclusion criteria</i>	<i>Results</i>
Hoeber et al. (2009)	Case-control study (long-term follow up of original RCT (Van der Heijden et al. 2007).	n = 94. Ages 6–12 years at the time of initial study. Males = 70. females = 24. All participants given pharmacological intervention	Previously participated in an RCT on melatonin efficacy.	Melatonin dosage ranged from 0.5 to 10 mg.	Not stated	Not stated	Parental questionnaire	None	Effective in sleep onset problems in 82 cases (87.8%). Eighty patients (85.5%) still using melatonin (mean follow-up time 3.7 years). 8 patients (9%) discontinued melatonin because of improvements in sleep. Three patients (3.1%) discontinued because of adverse effects. Parents of 7 children (7.4%) reported unexpected comorbidity.
Lyon et al. (2011)	Double-blind, placebo-controlled, parallel-group study.	n = 93. Males only. Ages 8–12 years. L-theanine (n = 46). Placebo (n = 47).	Not stated	L-theanine Dosage = 400 mg daily (oral). Two doses, morning and afternoon.	27 stimulants 3 melatonin	DSM-IV-TR	Actigraphy. Pediatric Sleep Questionnaire (completed by parents)	Psychiatric and medical conditions. Learning difficulties. Prior behavior modification program	Improved sleep efficacy and reduced nocturnal motor activity (significant difference). Less nighttime waking (nonsignificant). One minor adverse effect.

ADHD, attention-deficit/hyperactivity disorder; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders 3rd ed. Revised; K-SADS-E, Schedule for Affective Disorders and Schizophrenia for School-Age Children – Epidemiological Version; SSRI, selective serotonin reuptake inhibitor; CBCL, Child Behavior Checklist; TRF, Teachers Report Form; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th ed.; IQ, intelligence quotient; DLMO, dim light melatonin onset; CSOI, chronic sleep onset insomnia; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision; OCD, obsessive-compulsive disorder; RCT, randomized controlled trial.

antipsychotics, serotonin 2 antagonist/reuptake inhibitors (SARI, e.g. trazodone), α -adrenergic agonists, or exogenous melatonin (Wilens et al. 1994; Prince et al. 1996; Owens et al. 2010). Although sleep disorders in ADHD populations are becoming more widely recognized, the safety and efficacy of treatment options are still uncertain and under-studied. There have been two recent reviews on the use of melatonin in treatment of insomnia in ADHD (Bendz and Scates 2010; Miner 2012); however, there have been no previous systematic reviews on the topic of pharmacological interventions in ADHD-related sleep disturbances. With this systematic review, we aim to provide evidence and a guideline to the question posed by clinicians who, after having provided a thorough sleep hygiene psychoeducation program to the patient and the family, started a pharmacological treatment of the core symptoms of ADHD, and optimized the medication, still face the issue of their patient “having trouble sleeping.”

Methods

A systematic literature review was conducted by searching MEDLINE® (via PubMed), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, Embase and Web of Science in order to identify relevant articles published in English from 1983 until April 2013. A final literature search was conducted on April 8, 2013, using the search terms ([sleep AND ADHD] AND [pharmacological AND pharmacology]) for all fields while searching MEDLINE. The following search terms were used for Scopus, CINAHL, PsycINFO, EMBASE and Web of Science: (sleep AND ADHD AND pharmacolog*) in the topic fields of Web of Science, and the abstracts in Scopus, CINAHL, PsycINFO and Embase.

The following inclusion and exclusion criteria were adhered to in the review of articles.

Participants

Studies were included if they focused on a participant population with a diagnosis of ADHD, regardless of age. Studies that involved participants with other comorbid disorders were still included, because of the relative dearth in research.

Interventions

All studies that explored the effect of a purely pharmacological treatment of sleep disorders on ADHD were included. Articles focusing on behavioral interventions for sleep were excluded, along with combination behavioral and pharmacological intervention studies, as the behavioral interventions may have had a confounding effect on the clinical efficacy of the medication.

Outcomes

Studies investigating the efficacy of pharmacological compounds on reducing sleep disturbances in individuals with ADHD were included. Articles were excluded if the selected pharmacological compounds were primarily targeting the ADHD symptomatology as opposed to the sleep disorders associated with ADHD.

Study design

Narrative reviews, open label trials, single case or case series reports, commentaries, letters, and perspective reviews were all excluded, whereas all other study types, including retrospective studies and case-control studies, were included.

Article selection

A total of 337 articles were collected across databases, after the elimination of duplicates. All articles were screened initially via title and abstract searches, and 317 articles were removed for the following reasons: the full text articles were unavailable in English, the topic was unrelated to any of our search term combinations, the study design was inadequate, or the articles were not focused on the pharmacological treatment of sleep disorders in ADHD patients. Full text searches were completed for the remaining 20 articles, and a further 15 were excluded either because of their descriptive review structure, or their lack of specificity to our search criteria, leaving a total of 5 articles selected for review (see Fig. 1 for a graphic representation of study selection). One study, which saw patients receive sleep hygiene prior to melatonin administration (Weiss et al. 2006), was excluded because of the possible confounding effects that sleep hygiene might have on the efficacy of melatonin.

Data were extracted from the Methods and Results sections of each article, which included the study design; participant characteristics (number of participants, age, and gender); recruiting source; pharmacological intervention used and dosage; any previous or current pharmacological, psychological, or behavioral treatment of participants; how the ADHD diagnosis was made or assessed; how sleep was quantified, reported, or assessed both before the intervention and during the intervention; exclusion criteria; and a brief summary of results.

The characteristics extracted from each of the five articles are summarized in Table 1. A meta-analysis was considered; however, because of the heterogeneity of results reported, and the low quantity of papers retrieved, a meta-analysis would have lacked face validity.

Results

Clonidine

One systematic chart review (Prince et al. 1996) was identified among the five selected articles, observing the cases of 62 children and adolescents with ADHD (between 4 and 17 years of age) who had been treated with the α_2 -adrenergic agonist clonidine for sleep disorders in the past. Participants were recruited from a pediatric psychopharmacology unit, and of these participants, 51 were male, and 11 were female, and all participants were administered an oral dose of clonidine at nighttime, with dosages ranging between 50 and 800 μ g. It was found that in 85% of subjects, Clinical Global Impressions-Severity (CGI-S) scores for parents were significantly reduced in comparison with baseline, indicating a reported decrease in insomnia severity. There was a nonsignificant trend for greater improvement in adolescents, and no significant difference for whether clonidine was taken once at bedtime or several times per day. All sleep-disordered subjects with ADHD (baseline, medicine-induced, and medicine-exacerbated) responded similarly well to treatment. Adverse events were observed in 31% of patients, with one patient (1.6%) withdrawing from treatment after becoming depressed, which was resolved following the cessation of clonidine.

Zolpidem

A double blind, placebo-controlled, parallel-group study was retrieved, focusing on the effects of the non-benzodiazepine hypnotic zolpidem on relieving sleep disorders in children and adolescents with ADHD (Blumer et al. 2009). The study observed 201 children and adolescents with ADHD, aged between 6 and 17 years

of age, 136 of whom were administered the oral active drug zolpidem 30 minutes prior to bedtime at a dosage of 0.25 mg/kg/day (up to a maximum of 10 mg), with the remaining 65 participants being administered a placebo. It was observed that zolpidem failed to reduce sleep latency, or increase sleep efficiency (the percentage of the night spent asleep) or total sleep time as observed by polysomnography; however, it significantly increased the subjective Clinical Global Impressions-Improvement (CGI-I) score for subjects and significantly decreased the CGI-S score for both subjects and parents/guardians, indicating greater improvement and less severity in insomnia. Wake time after sleep onset (WASO) also did not differ significantly from baseline after zolpidem treatment. One or more adverse events was experienced in 62.5% of patients treated with zolpidem (dizziness [23.5%], headaches [23.5%], and hallucinations [7.4%]) versus 47.7% of placebo-treated patients, with 7.4% of zolpidem users (10 patients) withdrawing from treatment.

L-theanine

L-theanine (γ glutamylethylamide), a non-protein amino acid, was the pharmacological compound used to investigate treatment of ADHD-related sleep disorders in one double-blind, placebo-controlled, parallel-group study (Lyon et al. 2011). The study consisted of 93 ADHD-diagnosed males, between 8 and 12 years of age, 46 of whom received oral L-theanine at a dose of 400 mg daily (200 mg in the morning, and 200 mg in the afternoon), and 47 of whom were given placebo. It was observed through actigraphy that L-theanine produced no significant difference in sleep latency or total sleep time from baseline levels; however, a significant increase in sleep efficiency was seen, as well as a reduction in nocturnal activity. In addition, WASO did not significantly differ from baseline levels, however a nonsignificant trend toward reduction of WASO was observed with L-theanine. One subject (2.1%) experienced an adverse event with the use of L-theanine, attaining a new facial tic, which ceased following the subject's withdrawal from the study; however, Lyon et al. (2011) noted that the patient had previously exhibited various tics.

Melatonin

Two studies were identified that looked at the effects of melatonin on ameliorating sleep disturbances within ADHD; one randomized, double-blind, placebo-controlled trial (Van der Heijden et al. 2007), and one case-control study (Hoebert et al. 2009), which was a long-term follow-up of melatonin use from the original Van Der Heijden et al. (2007) study. Therefore, the participants used were the same for both studies, with the exception of a minor variation in sample size caused by loss in follow-up and poor response rate to questionnaires in the Hoebert et al. (2009) study.

The initial Van Der Heijden et al. (2007) study investigated 105 children with ADHD-related sleep disorders, between 6 and 12 years of age, 53 of whom were given melatonin (at a dose of 3 mg at a body weight <40 kg, or 6 mg at a body weight $\geq$ 40 kg, in the evening), with the remaining 52 given a placebo. All children were recruited through a sleep disorder outpatient clinic, or through magazine and newspaper advertisements or the Dutch ADHD patient support center. It was observed that melatonin significantly decreased sleep latency from baseline in contrast to placebo, and increased total sleep time, whereas the placebo drug decreased total sleep time. A significant increase in sleep efficiency and reductions in nocturnal activity were also seen. Additionally, a significant increase in sleep onset (compared with a delayed sleep onset by

placebo) was observed, as well as a significant reduction in reports of difficulty in falling asleep, and significant amelioration of core ADHD problems reported by parents. Ten children (18.9%) experienced adverse events such as headaches (5.7%), hyperactivity (5.7%), dizziness (3.8%), and abdominal pain (3.8%), but no patients withdrew from treatment.

The case-control study by Hoebert et al. (2009) observed 94 participants of the initial sample, as all participants of the Van Der Heijden et al. (2007) study were offered melatonin after the conclusion of the trials. The majority of children were still using melatonin at follow-up $\sim$ 3.7 years later (85.5%), 61 of whom were taking melatonin daily (64.9%). Melatonin was discontinued in 22 patients (23.4%), 8 (8.5%) of whom discontinued because of complete improvement of sleep disorder and 3 (3.2%) of whom discontinued because of adverse events such as excessive perspiration, dizziness, visual disturbances, headaches, nausea, daytime laziness, abdominal pain, and excessive morning sedation. All of these adverse events were resolved following withdrawal from the study. Adverse events were experienced in 20.2% of children, such as dizziness (4.3%), bed wetting (3.2%), sleep maintenance insomnia (3.2%), headache (2.1%), nausea (2.1%), skin pigment changes (2.1%), nightmares (2.1%), visual disturbances (2.1%), excessive morning sedation (2.1%), constipation (1.1%), excessive perspiration (1.1%), decreased mood (1.1%), daytime laziness (1.1%), and change in behavior (1.1%). Of patients' parents, 7.4% considered melatonin responsible for a previously unnoticed comorbidity in their children, such as pertussis, pneumonia, adverse reaction to general anesthesia, celiac disease, and food allergy, Osgood-Schlatter disease, viral eye infection, and visual disturbances for which there was no cause.

It should be noted that none of the pharmacological interventions significantly exacerbated or alleviated ADHD symptoms.

Discussion

The data collated in this review highlight the variability in efficacy of pharmacological compounds used in the treatment of sleep disorders in individuals with ADHD. Although subjective measurements, such as CGI scales, tend to indicate an overall improvement in insomnia following treatment with the active drugs, this does not always correspond with the objective data collected by polysomnography or actigraphy; this is the case in the use of zolpidem. Similarly Lyon et al. (2011) indicate that subjective parental reports did not correlate with objective measures in their administration of L-theanine. Furthermore, whereas the subjective reports denoted that zolpidem might improve the clinical presentation of insomnia and reduce the severity of insomnia, the actigraphic evidence displayed a failure to alter sleep latency, sleep duration, and sleep efficiency, as well as an abundantly high incidence of adverse events. The difficulty with parental self-report tends to be a general lack of awareness of baseline sleep disturbances, and, therefore, an uncertainty in the changes in sleep disturbances after treatment with the active drug. This highlights a methodological limitation within the studies that purely relied on parental subjective outcomes, such as the case-control study of melatonin (Hoebert et al. 2009) and the case review study on clonidine (Prince et al. 1996). Further research should be conducted to replicate these results, and to obtain more empirical evidence of efficacy of treatment.

Methodologies across studies are generally inconsistent, primarily with the heterogeneous study samples. Females were somewhat under-represented in these samples, especially in the L-theanine study (Lyon et al. 2011), in which only males were

studied; however, it is not an unfeasible representation of the general population, as ADHD is three times more common in males than in females (Cohen-Zion and Ancoli-Israel 2004; Lyon et al. 2011). Similarly, with the exception of the randomized controlled trial (RCT) on melatonin (Van der Heijden et al. 2007), there was large variation in the previous or current medication use among patients, which might have led to a confounding effect in the measure of efficacy of the pharmacological intervention. Furthermore, the exclusion criteria varied between studies, with some articles excluding comorbid psychiatric disorders or learning difficulties, whereas others did not. Comorbid psychiatric disorders may also confound the measure of efficacy of the pharmacological interventions; however, excluding these disorders, especially learning difficulties, might render the sample population unrepresentative of the general population, as comorbidity is very common within ADHD patients.

Methodological critiques for each article are described as follows. As the Prince et al. (1996) clonidine article was a retrospective systematic chart review, many of the variables were very difficult to control; for example, the initial screening for the ADHD diagnoses were conducted by different clinicians, as was the prescription of clonidine, thus resulting in such variable dosages. Additionally, there were a large number of individuals taking other medication concurrently, which might have led to confounding results of the efficacy of clonidine. Finally, the measurements of sleep were purely derived from parental self-report, rather than the child's self-report, or objective measures such as actigraphy; therefore, the observation of change in sleep might not have been reliable.

The zolpidem article (Blumer et al. 2009) used a combination of objective and subjective measures to obtain a rich overview of the efficacy of zolpidem in ADHD-related sleep disorders; however, it failed to control for the possibility that other medications being taken by the participants at the time of study might have had confounding effects on the outcome of zolpidem, or might display interaction effects with zolpidem.

The L-theanine study (Lyon et al. 2011) used a combination of objective actigraphic measures to observe change in sleep, as well as subjective parental report measures, which provides a full report on the sleep patterns of participants; however, the study did fail to control for the other medications that individuals were taking at the time of study, such as the three individuals taking melatonin, which is sleep promoting, and, therefore, may have confounding effects on the results of L-theanine efficacy. This study also only looked at the effects of L-theanine on males with ADHD; therefore, as previously mentioned, the results might not generalize to the female ADHD population in the same way.

Methodology was very rigorous in the initial melatonin study by Van der Heijden et al. (2007), ensuring that there was a set time that the melatonin was administered for all participants, excluding any participants who had taken any other medications 4 weeks prior to enrolment, thus guaranteeing that there were not confounding effects of other medications, and utilizing both objective actigraphy data and subjective measurement tools to observe change in sleep. However, by eliminating confounding effects of other medications, these findings may not be generalizable to the ADHD population who are being treated with stimulant or non-stimulant medication. The case-control study (Hoebert et al. 2009) was, however, not as rigorously controlled as a longitudinal study might be expected to be; therefore, there were a few limitations with the follow-up. The data were derived from parental self-report; however, the parents were not interviewed systematically. It was hard to generalize the results to the effect of the drug as there was no placebo arm of the

study, and in the parental interviews, there were no questions about medications being concurrently used. Despite this, the sample size was large, and the prior RCT (Van der Heijden et al. 2007) was extremely carefully controlled.

Our systematic review does not allow us to explore if sleep disorders in ADHD stem from the disorder itself or are a highly prevalent co-morbidity; furthermore, it does not allow us to ascertain if ADHD-related sleep disorders respond differently to pharmacological treatment than do sleep disorders without ADHD. Finally, our search methodology has several limitations; we only selected articles in the English Language (language selection bias), and we did not search the "gray literature" or unpublished papers, which can potentially lead to a tendency to find mainly positive findings (publication biases). Conclusively, our search excluded all case studies, case series, or open label studies, which could have carried important information but that we excluded for lack because of scientific rigor in the methodology.

Conclusions

In conclusion, there is a relative paucity of evidence that meets high levels of scientific rigor in regard to the treatment of ADHD-related sleep disturbances, and a certain disparity in results caused by methodological differences in sleep measure outcomes (subjective vs. objective). Further research needs to be conducted to reproduce these results, in order to observe a more reliable result of each medication on the effects of ADHD-related insomnia; however, from this modest amount of evidence, we can conclude that zolpidem and L-theanine were not effective in the treatment of the primary sleep disorder characteristics, sleep latency and total sleep time, among other secondary characteristics, and that, additionally, zolpidem had a high rate of adverse events. These indications suggest that medications that agonize the α_1 subunit of the GABAA brain receptor might not be effective in treating the sleep disturbances of ADHD patients in the same way that they treat these disorders in healthy adults. Clonidine reduced the parents' subjective reports of severity of insomnia, indicating that the α_2 -adrenergic agonist may play a role in reduction of noradrenaline release in the wake pathways of ADHD patients, as they do in healthy controls. Alternatively, melatonin treatment seems to have positive effects on all primary sleep disorder characteristics, including sleep efficiency, and the majority of all secondary characteristics, such as nocturnal activity, sleep onset, and WASO.

In our opinion, given the absence of strong evidence in any pharmacological treatment for insomnia in ADHD, clinicians should prioritize sleep hygiene education and optimization of the current treatment with stimulants or non-stimulants for ADHD.

Clinical Significance

This article indicates the paucity of evidence for pharmacological treatment of sleep disorders in ADHD, thus acting as a warning to clinicians who are prescribing medications for ADHD-related sleep disorders. We highlight the medications that may not be effective in treating these sleep disorders and advise clinicians that in the absence of adequate levels of evidence, priority should be given to sleep hygiene education and optimizing the stimulant or non-stimulant treatment of ADHD.

Disclosures

Dr Giaroli has received honoraria for serving on a speaker's bureau for Eli Lilly, FlynnPharma, and Janssen. He has also

received reimbursement for travel expenses and conference attendance from Eli Lilly, FlynnPharma, and Shire. Dr Tracy has received honoraria from Eli Lilly and Roche UK for educational talks. Dr. Barrett has no competing financial interests.

References

- Allen RP, Singer HS, Brown JE, Salam MM: Sleep disorders in Tourette syndrome: A primary or unrelated problem? *Pediatr Neurol* 8:275–280, 1992.
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.
- Bendz LM, Scates AC: Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. *Ann Pharmacother* 44:185–191, 2010.
- Blumer JL, Findling RL, Shih WJ, Soubrane C, Reed MD: Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention-deficit/hyperactivity disorder in children 6 to 17 years of age. *Pediatrics* 123:e770–776, 2009.
- Cohen-Zion M, Ancoli-Israel S: Sleep in children with attention-deficit hyperactivity disorder (ADHD): A review of naturalistic and stimulant intervention studies. *Sleep Med Rev* 8:379–402, 2004.
- Corkum P, Moldofsky H, Hogg-Johnson S, Humphries T, Tannock R: Sleep problems in children with attention-deficit/hyperactivity disorder: Impact of subtype, comorbidity, and stimulant medication. *J Am Acad Child Adolesc Psychiatry* 38:1285–1293, 1999.
- Cortese S, Faraone SV, Konofal E, Lecendreux M: Sleep in children with attention-deficit/hyperactivity disorder: Meta-analysis of subjective and objective studies. *J Am Acad Child Adolesc Psychiatry* 48:894–908, 2009.
- Cortese S, Konofal E, Lecendreux M, Arnulf I, Mouren MC, Darra F, Dalla Bernardina B: Restless legs syndrome and attention-deficit/hyperactivity disorder: A review of the literature. *Sleep* 28:1007–1013, 2005.
- England SJ, Picchietti DL, Couvadelli BV, Fisher BC, Siddiqui F, Wagner ML, Walters AS: L-dopa improves restless legs syndrome and periodic limb movements in sleep but not attention-deficit-hyperactivity disorder in a double-blind trial in children. *Sleep Med* 12:471–477, 2011.
- Faraone SV, Glatt SJ, Bukstein OG, Lopez FA, Arnold LE, Findling RL: Effects of once-daily oral and transdermal methylphenidate on sleep behavior of children with ADHD. *J Atten Disord* 12:308–315, 2009.
- Giblin JM, Strobel AL: Effect of lisdexamfetamine dimesylate on sleep in children with ADHD. *J Atten Disord* 15:491–498, 2011.
- Greenhill L, Puig-Antich J, Goetz R, Hanlon C, Davies M: Sleep architecture and REM sleep measures in prepubertal children with attention deficit disorder with hyperactivity. *Sleep* 6:91–101, 1983.
- Hoebert M, Van der Heijden KB, Van Geijlswijk IM, Smits MG: Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *J Pineal Res* 47:1–7, 2009.
- Huang YS, Tsai MH, Guilleminault C: Pharmacological treatment of ADHD and the short and long term effects on sleep. *Curr Pharm Design* 17:1450–1458, 2011.
- Lecendreux M, Cortese S: Sleep problems associated with ADHD: A review of current therapeutic options and recommendations for the future. *Expert Rev Neurother* 7:1799–1806, 2007.
- Lyon MR, Kapoor MP, Juneja LR: The effects of L-theanine (Suntheanine®) on objective sleep quality in boys with attention deficit hyperactivity disorder (ADHD): A randomized, double-blind, placebo-controlled clinical trial. *Alternative Med Rev* 16:348–354, 2011.
- Miner PJ: Melatonin for Insomnia in Children With ADHD. *Advances for NPs & Pas*; 2012. Available at <http://nurse-practitioners-and-physician-assistants.advanceweb.com/Features/Articles/Melatonin-for-Insomnia-in-Children-With-ADHD.aspx> Accessed February 6, 2013
- Mitchell HA, Weinshenker D: Good night and good luck: Nor-epinephrine in sleep pharmacology. *Biochem Pharmacol* 79:801–809, 2010.
- MTA Cooperative Group: A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 56:1073–1086, 1999a.
- MTA Cooperative Group: Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: The Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder. *Arch Gen Psychiatry* 56:1088–1096, 1999b.
- National Institute for Health and Clinical Excellence: Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults. CG72. London: NICE; 2008.
- Owens JA, Rosen CL, Mindell JA, Kirchner HL: Use of pharmacotherapy for insomnia in child psychiatry practice: A national survey. *Sleep Med* 11:692–700, 2010.
- Prince JB, Wilens TE, Biederman J, Spencer TJ, Wozniak JR: Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder: A systematic chart review of 62 cases. *J Am Acad Child Adolesc Psychiatry* 35:599–605, 1996.
- Sangal RB, Owens J, Allen AJ, Sutton V, Schuh K, Kelsey D: Effects of atomoxetine and methylphenidate on sleep in children with ADHD. *Sleep* 29: 1573–1585, 2006.
- Silvestri R, Gagliano A, Aricò I, Calarese T, Cedro C, Bruni O, Condurso R, Germanò R, Gervasi G, Siracusano R, Vita G, Bramanti P. (2009). Sleep disorders in children with Attention-Deficit/Hyperactivity Disorder (ADHD) recorded overnight by video-polysomnography. *Sleep Med* 10:1132–1138, 2009.
- Sung V, Hiscock H, Sciberras E, Efron D: Sleep problems in children with attention-deficit/hyperactivity disorder: Prevalence and the effect on the child and family. *Arch Pediatr Adolesc Med* 162:336–342, 2008.
- Tsai MH, Huang YS: Attention-deficit/hyperactivity disorder and sleep disorders in children. *Med Clin N Am* 94:615–632, 2010.
- Van der Heijden KB, Smits MG, Van Someren EJW, Ridderinkhof KR, Gunning WB: Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry* 46:233–241, 2007.
- Weiss MD, Salpekar J: Sleep problems in the child with attention-deficit hyperactivity disorder: defining aetiology and appropriate treatments. *CNS Drugs* 24:811–828, 2010.
- Weiss MD, Wasdell MB, Bomben MM, Rea KJ, Freeman RD: Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. *J Am Acad Child Adolesc Psychiatry* 45:512–519, 2006.
- Wilens TE, Biederman J, Spencer T: Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 33:424–426, 1994.

Address correspondence to:

Giovanni Giaroli, MD

North East London NHS Foundation Trust

Loxford Hall

Loxford Lane

Ilford IG1 2PL

United Kingdom

E-mail: Giovanni.Giaroli@nelft.nhs.uk