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Adult Attention-Deficit/Hyperactivity Disorder (ADHD) and Insomnia: an Update of the Literature

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Abstract
Purpose of Review Insomnia is diagnosed when there is dissatisfaction with sleep quantity or quality. It has a prevalence in the general population ranging from 31 to 56%. Insomnia has previously been associated with adult attention-deficit/hyperactivity disorder (ADHD). In this review, we address three topics: (1) the cross-sectional relationship between ADHD and insomnia in adulthood, (2) the longitudinal relationship between ADHD and insomnia, and (3) insomnia as a side effect of pharmacological treatments for adult ADHD.
Recent Findings Three cross-sectional, clinical, and population studies report a prevalence of insomnia in ADHD adults ranging from 43 to 80%. Longitudinal evidence for a link between childhood-onset ADHD and insomnia at later age is mixed, with one study confirming and another study not supporting such a longitudinal association. In randomized, placebo-controlled trials, insomnia is reported significantly more often in the treatment arm than in the placebo arm. In varying percentages of trial participants, insomnia is a treatment-emergent adverse effect in triple-bead mixed amphetamine salts (40–45%), dasotraline (35–45%), lisdexamfetamine (10–19%), and extended-release methylphenidate (11%). Ten to seventeen percent of subjects in placebo-controlled trials of atomoxetine report insomnia, possibly related to poor metabolizer status. The mechanisms explaining the relationship between ADHD and sleep problems are incompletely understood, but both genetic and non-shared environmental influences may be involved.
Summary Adults with ADHD should be assessed for insomnia, which is frequently comorbid, and both conditions should be treated.

Keywords Adult attention-deficit/hyperactivity disorder · Sleep · Insomnia · Psychostimulants

This article is part of the Topical Collection on *Attention-Deficit Disorder*

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Introduction

In the general population, the prevalence of insomnia symptoms ranges from 31% in Western Europe to 56% in the USA [1]. It is the most common sleep disorder in the general population, but almost half of people affected receive no treatment for insomnia [1, 2]. Following DSM 5, insomnia is diagnosed when there is dissatisfaction with sleep quantity or quality, difficulty initiating or maintaining sleep, and early morning waking, for at least three nights per week over a period of at least 3 months [3]. The DSM 5 no longer distinguishes between primary and secondary insomnia [3]. In this broader conception, insomnia is considered a disorder that requires independent clinical study.

Adult attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder marked by inattentiveness, impulsivity, with or without hyperactivity [3, 4]. For 60% of children with ADHD, the disorder persists into adulthood [5], where the cross-national estimated prevalence of ADHD is 2.8% [6]. In 2012, Yoon et al. published a clinical review of sleep disorders in children and adults with ADHD, and stressed that the literature was scant [7•]. No longitudinal studies were included in

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this review. Seven studies among adults with ADHD using both self-reports and objective methods to assess insomnia symptoms were discussed. The three studies using self-reports showed an increased prevalence of insomnia in adult ADHD [8–10]; however, one of these was referenced as another study by the same author [11]. Four of the listed studies using objective methods to measure insomnia showed mixed results. Two actigraphy studies found decreased sleep quality and insomnia symptoms in adults with ADHD [12, 13]. One polysomnographic study showed sleep disturbance [14], but another did not [15]. Yet, both of the polysomnographic studies showed increased nocturnal motor activity in the ADHD patients [14, 15]. These preliminary studies in adult populations suggest that there is an association between adult ADHD and insomnia. While the review acknowledged insomnia in children with ADHD, the authors commented, "it is currently not known whether there are similar sleep problems in adults (with ADHD)" [7•].

Four years later, a systematic literature review by Instanes et al. (2016) on adult ADHD and comorbid somatic disease classified the relationship between adult ADHD and sleep disorders as well-established [16•]. Some new studies showing an increased prevalence of insomnia in clinical and non-clinical samples of adults with ADHD were included [17–19]. However, certain fundamental questions about ADHD and insomnia that were raised by Yoon et al., Instanes et al., and Hvolby (2015) cannot be fully answered [7•, 16•, 20•]. For example, what is the role of pharmacological treatments in the relationship between ADHD and insomnia?

This current review summarizes recent findings of cross-sectional and randomized controlled studies exploring the relationship between insomnia and adult ADHD. For the first time, we also review longitudinal studies. We note that other sleep disorders, i.e., circadian rhythm disorders, sleep apnea, hypersomnia, and restless legs, are also associated with adult ADHD [16•] and may result in secondary insomnia. However, we do not review studies of these sleep disorders. We have retrieved key English language papers from Medline, Embase, and Psychnet searches, published since the review by Yoon et al. in 2012. These fall into the following three categories:

1. The cross-sectional relationship between ADHD and insomnia in adults (defined as 18 years or over)
2. The longitudinal relationship between ADHD and insomnia
3. Insomnia associated with pharmacological treatments for ADHD

These subjects together will give more insight into the nature of the relationship between insomnia and ADHD.

Findings From Cross-Sectional Studies

In a chart review, Fisher et al. (2014) investigated sleep problems in ADHD across the lifespan (N = 1828, of which n = 1163 adults) [21•]. This study distinguished between two ADHD categories: inattentive ADHD and "ADHDplus" (patients with hyperactive/impulsive ADHD symptoms and a documented secondary sleep or affective disorder requiring medication). No patients were assessed while on ADHD medication. Insomnia symptoms were found to be present in ADHD, regardless of sex, age, or ADHD subtype. There was no significant difference in insomnia symptoms between adult ADHD patients with and without other comorbid sleep disorders. In 80% of adults with ADHD, unrefreshing sleep, trouble falling asleep, frequent nighttime awakenings, insufficient sleep, excessive sleep, and nighttime restlessness were reported. These problems were also significant variables affecting neuropsychological test performance. Sleep complaints were reported significantly *more* often in adults (80%) than in children or adolescents, where they occurred in 74 and 41%, respectively [21•]. Sleep-onset insomnia (SOI, or difficulty falling asleep at the desired bedtime) and sleep maintenance problems were particularly significant difficulties in the ADHD adults. Several other studies have confirmed an association between SOI and adult ADHD [10, 14, 22].

A recently published, large Norwegian study by Brevik et al. (2017) compared the prevalence of self-reported insomnia symptoms in adult ADHD patients (n = 268) to that in a population-based control group (n = 202) [23•]. Where information was available, the prevalence of insomnia was compared in two ADHD subtypes (inattentive n = 54 and combined n = 81); for the rest, subtype was not specified. Even though adult ADHD is a highly comorbid condition, no formal exclusion criteria for comorbidities were applied to either group. Insomnia symptoms occurred in 67% of the adult ADHD patients, compared to 29% of controls. They were more common in the combined subtype (80%) compared to the inattentive subtype (56%) [23•].

Investigating women in a nationally representative Canadian population study (aged 20–39 years, N = 3908), Fuller-Thompson et al. (2016) found self-reported ADHD in 2.6% (n = 107) [24•]. Significant insomnia symptoms were present in 43% of those with self-reported ADHD compared to 12.2% in those without ADHD. When the association between ADHD and insomnia was analyzed after correcting for age, race, education, and income, the risk for insomnia was found to be five times greater in women with self-reported ADHD, compared to those without ADHD (OR = 5.08). However, it should be noted that Fuller-Thompson et al. did not report on concurrent or previous (stimulant) medication use nor correct for affective disorder. Both of these may have accounted for the increased risk of insomnia. Indeed, the women who reported ADHD also had significantly more

lifetime affective disorders than those without ADHD [24•]. Similarly, Brevik et al. applied no formal exclusion criteria for comorbid disorders, which may have influenced the associations with insomnia [23•].

Comorbid mental disorders tend to increase the prevalence of insomnia, both in population studies and clinical samples. This was shown in a Dutch general population study, where insomnia was common in those with current and remitted mental disorders [25]. In another study in adult ADHD patients, depressive symptoms increased the risk for insomnia [9]. Other factors associated with adult ADHD, such as substance use [26] or family history of affective disorder, also increase the risk for insomnia [25, 27•]. These cross-sectional findings are summarized in Table 1.

The Longitudinal Relationship Between ADHD and Insomnia

A limitation of cross-sectional studies is that they cannot explain causal relationships. Both ADHD and insomnia are heterogeneous disorders, and the relationship between them is complex. Only longitudinal studies can illustrate how childhood events may affect outcomes later in life. While they cannot truly indicate causality, they may give closer insight into possible causality. In addition, longitudinal studies give a better indication on how long-lasting associations truly are, as cross-sectional associations may be more subject to report-bias (e.g., ADHD patients reporting more negative about sleep patterns) and reflecting short-term associations. Two recent studies have investigated how the early trajectory of ADHD and its age-of-onset affect insomnia in adulthood [27•, 28•].

In a large longitudinal twin study ($N = 2232$), Gregory et al. (2017) investigated whether children diagnosed with ADHD were likely to have poor sleep quality later in life [28•]. ADHD was determined in childhood (at 5, 7, 10, and 12 years) from mother and teacher reports, using the DSM-IV criteria and Rutter Child Scales. At age 18, an ADHD diagnosis over the past year was made using the DSM-5 criteria in a structured interview. At age 18, sleep disturbance over the past month was ascertained using the Pittsburgh Sleep Quality Index (PSQI), derived as the sum of overall sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. A PSQI global score > 5 is considered to be the cutoff indicating insomnia [29].

A total of 8.1% of the total sample had the ADHD diagnosis at age 18 ($n = 166$). Of these, 67.5% ($n = 112$) did not meet criteria for ADHD during childhood and were considered late-onset ADHD. The remaining 21.9% ($n = 54$) met diagnostic criteria in both in childhood and at age 18 and were therefore classified as having persistent ADHD. The study went on to examine the associations between insomnia at age 18 and childhood-onset ADHD that remitted childhood-onset ADHD that persisted and late-onset ADHD, respectively. Only persistent ADHD (diagnosed in childhood and present at age 18), or late-onset ADHD (diagnosed at 18 years only), was associated with insomnia at age 18. However, childhood ADHD that had remitted by age 18 showed *no* increased risk for insomnia in early adulthood.

From this study, it appears that longitudinally, the presence of insomnia in early adulthood is associated with the course of ADHD. Only where ADHD symptoms are concurrent, does insomnia appear to occur. These associations remained significant after adjusting for many potential confounders such as maternal insomnia, a diagnosis of depression, generalized anxiety, alcohol dependence, cannabis dependence or conduct disorder in young adulthood, the presence of young children at home, and taking ADHD medication.

Contrary to the approach of Gregory et al., Goldman-Mellor et al. (2014) examined whether childhood ADHD predicted insomnia in adulthood in a longitudinal study from Dunedin, New Zealand [27•]. They investigated whether a childhood history of mental health problems and family psychiatric history predicted insomnia at age 38 years. At this age, rates of insomnia are high [27•]. A cohort of 1037 children was followed from birth through to their fourth decade. Subjects were examined and interviewed 12 times prospectively, with a 95% retention rate. During childhood (5–11 years), hyperactive and inattentive behavior was determined from parents and teachers using the Rutter Child Scales. During adolescence (11–15 years), ADHD was examined using DSM-III criteria. At the 38-year assessment, insomnia (in the last month) and psychiatric diagnoses (affective disorders/alcohol/drug dependence) were diagnosed over the last 12 months according to DSM-IV criteria and the Diagnostic Interview Schedule, respectively.

One fifth of the participants were diagnosed with insomnia at age 38. At this age, insomnia was highly comorbid with psychiatric disorders. Those with family histories of depression or anxiety, and lifelong affective disorders beginning in childhood, were at a uniquely high risk of developing insomnia in adulthood. In contrast, unlike the associations reported by Gregory et al. [28•], no significant association was found between childhood hyperactive and inattentive behavior (5–11 years) and insomnia at age 38. Furthermore, neither conduct disorder nor ADHD during adolescence (11–15 years) increased the risk for insomnia in adulthood.

However, this study differs from that of Gregory et al. in that neither the presence of ADHD in adulthood nor a possible onset of ADHD after 15 years was reported. Therefore, the question of whether late-onset ADHD or ADHD persisting into adulthood was linked to insomnia at age 38 cannot be answered. An interesting finding from another publication from the Dunedin study could explain the apparent lack of association between ADHD symptoms in childhood and insomnia at 38 years. Moffitt et al. (2015) reported that in the

Table 1 Recent (2014–2017) cross-sectional and longitudinal studies of the association between insomnia symptoms and ADHD

Study	Classification (sample size)	Age of population in years, range (mean)	Female, %	ADHD medication status	ADHD instrument	Sleep instrument	Major findings	Strengths (S) and/or weaknesses (W)
Cross-sectional studies								
Fisher et al. 2014 [21•]	Adults ≥ 18 year (n = 1163) ADHDplus[a] (n = 286) ADHD-I[b] (877)	9–80 (38) (35)	 38 61	All subjects tested when not on medication	Clinical diagnosis by neuropsychologist: Personal Problems Checklist for Adults Personal History Checklist for Adults Patient Behavior Checklist for ADHD Adults	Personal History Checklist for Adults[c] Patient Behavior Checklist for ADHD Adults	Insomnia symptoms in 80% of ADHD adults, regardless of sex, age, or ADHD subtype Insomnia symptoms negatively affected neuropsychological tests of attention	S: Large sample size, comprehensive neuropsychological testing, group with comorbid affective disorders identified W: Study sample from a single clinic No control group Studied over 20 years when diagnostic criteria may have changed
Fuller-Thompson et al. 2016 [24•]	ADHD (n = 107) No ADHD (3801)	20–39	100	No information	Self-report of a previous diagnosis of ADHD	Insomnia measured using a recoded variable to the question: "How often do you have trouble going to sleep or staying asleep?"	The risk for insomnia in those with self-reported ADHD was 43% compared to 12.2% in those without ADHD	S: Nationally representative, comprehensive profile of women W: No information about medication use Reliance on self-report for ADHD diagnosis No correction for comorbid affective disorders
Brevik et al. 2017 [23•]	Adult ADHD Patients (n = 268) Controls (n = 202)	18–74 (38) (37)	60 63	Methylphenidate (n = 69) Amphetamine (n = 12) Atomoxetine (n = 3)[d] Off medication (n = 36)	DSM-IV Adult ADHD Self-Rating Scale	Bergen Insomnia Scale	Insomnia symptoms occurred in 67% of ADHD, compared to 29% of controls Insomnia symptoms occurred in 66% of patients on current stimulant treatment and in 72% of patients off treatment	S. Large, clinically validated sample of adult ADHD patients and representative population controls W. Definition of insomnia may not have differentiated patients with delayed sleep phase disorder Comorbid disorders may have influenced the risk of insomnia
Longitudinal studies								
Goldman-Mellor et al. 2014 [27•]	No insomnia (n = 761) Insomnia (n = 186)	5–38	53	No information	Childhood hyperactive and inattentive behavior: Rutter Child Scales Adolescence: DSM-III	DSM-IV	No significant association between childhood hyperactive and inattentive behavior or ADHD during adolescence and insomnia at age 38	S: Longitudinal study, corrected for multiple psychiatric disorders W: ADHD at age 38 years not reported

Table 1 (continued)

Study	Classification (sample size)	Age of population in years, range (mean)	Female, %	ADHD medication status	ADHD instrument	Sleep instrument	Major findings	Strengths (S) and/or weaknesses (W)
Gregory et al. 2017 [28•]	Childhood ADHD (n = 247) ADHD age 18 (n = 166)	5–18	51	Sensitivity analyses excluding subjects on current ADHD medication did not affect the associations	Childhood ADHD: DSM-IV ADHD age 18: DSM 5	Pittsburgh Sleep Quality Index	Only persistent ADHD (diagnosed in childhood and present at age 18), or late-onset ADHD (diagnosed at 18 years only), were associated with insomnia at age 18	S: Longitudinal study, corrected for wide range of possible confounders W: No information collected about sleep quality in childhood, possible limitations of twin design

[a] ADHD plus: ADHD and a documented secondary disorder (depression or anxiety requiring medication, but not bipolar or major depression, sleep apnea, narcolepsy, circadian rhythm disorders, concerns of mild impact to the brain, or behavioral disorder) thought to have affected neuropsychological test performance

[b] ADHD-I Inattentive subtype

[c] Items from the Personal History Checklist for Adults included problems of unrefreshing sleep, trouble getting to sleep, waking up a lot at night, not getting enough sleep, sleeping too much, and restlessness

[d] The 3 patients on ATX were included in the group on current stimulant treatment

same cohort, the groups with childhood ADHD and adult ADHD were virtually non-overlapping: 90% of adult ADHD cases lacked a history of childhood ADHD [30]. Further analysis of this cohort would determine whether age of onset of ADHD was independently associated with insomnia in adulthood, and whether the 10% with persistent ADHD from childhood to adulthood had a greater risk of insomnia at age 38. This analysis however has so far not been reported. The longitudinal studies referred to here are reported in Table 1.

While the mechanisms for the relationship between ADHD and sleep problems are not understood, Hvolby (2015) proposes several possible scenarios that may explain this finding [20•]. Perhaps ADHD and sleep problems are comorbid disorders which interact? Where ADHD is present, insomnia occurs—and vice versa—with reciprocal causation. Poor sleep may worsen ADHD symptoms, as sleep regulates cognitive and emotional brain processes [31, 32]. Symptoms associated with insomnia may also present as ADHD [20•]. Secondly, sleep problems may be intrinsic to ADHD; therefore, insomnia symptoms are part of the ADHD presentation. Symptoms of ADHD such as inattention, difficulty with planning, or nocturnal motricity may lead directly to poor sleep hygiene and insomnia [20•, 33]. Difficulty in organizing tasks and procrastination may delay bedtime. In this scenario, ADHD and insomnia in young adulthood may have a shared neuropathological origin [20•]. In a recent genome-wide association study, strong positive genetic correlations were found between insomnia, anxiety/depressive symptoms, and major depression [34•]. This suggests that insomnia in adult ADHD is often comorbid with depressive symptoms. Interestingly, there was no correlation between the genes found for insomnia and self-reported ADHD symptoms. The top genetic association in this study was found between insomnia and restless legs syndrome (RLS), which is also associated with ADHD [16•]. RLS is a neurological disorder where patients experience an unpleasant sensation in the limbs and feet, combined with an urge to move to relieve the discomfort. It is associated with initial insomnia and poor sleep quality controls [16•]. The population prevalence is wide-ranging, from 3 to 34% [16•]. In small studies, the prevalence of RLS has been shown to be elevated in persons with ADHD compared with controls, and ADHD was more common in patients with RLS compared to controls [16•]. While more research is needed to clarify this association, the relationship between ADHD and insomnia may be mediated through RLS.

Environmental influences on insomnia in ADHD are also relevant, as found by Gregory et al. [28•]. In their twin study, individual differences in ADHD and sleep quality were explained by genetic and non-shared environmental factors, with moderate genetic overlap. In young adulthood, genes explained 55% of the association between ADHD symptoms and sleep quality, and non-shared environmental influences explained 45%. These environmental influences may include

(maternal) exposure to neurotoxins, alcohol, drugs, and mobile telephones, which may all impact on sleep and ADHD [28•, 35]. Marital conflict and inconsistent parenting styles are family environmental processes that may play a role in ADHD through the dopamine system, which is believed to be dysregulated in ADHD. A study showed that the tandem repeat insertion allele of the dopamine receptor D4 gene increased susceptibility to ADHD in the context of marital conflict [36].

Insomnia Associated With Pharmacological Treatment for ADHD

Another factor complicating the relationship between ADHD and insomnia is that pharmacological treatments of ADHD may cause, worsen [33], or improve insomnia symptoms [10, 13, 14, 37]. However, it is important to acknowledge that even non-medicated adults with ADHD experience insomnia symptoms [9, 10, 13, 14, 17, 18, 21, 22]. In the Norwegian cross-sectional study referred to above, Brevik et al. found that ADHD patients currently using stimulant medication ($n = 94$) had significantly *lower* insomnia scores than patients without stimulant treatment ($n = 34$). Treatment included methylphenidate ($n = 69$), amphetamines ($n = 12$), the non-stimulant atomoxetine (ATX, $n = 3$), or a combination ($n = 7$). No further information about the dosing or pharmacological agents was given. Insomnia symptoms occurred in 66% of patients currently on stimulants compared to 72% in those off treatment [23•]. These findings could indicate that ADHD medication may be helping patients with managing their insomnia. However, as the authors note, those off medication may also have chosen to stop because of insomnia [23•]. So, interpretation is difficult, and one would require placebo-controlled interventions to evaluate truly whether ADHD medication impacts on insomnia. In this section, we review recent findings concerning the association between insomnia and the stimulants (methylphenidates and amphetamines), non-stimulants (ATX), and an antidepressant, bupropion. The studies reviewed are included in Table 2.

Stimulants

Extended-release formulations of the stimulants were developed to reduce multiple daily dosing and adverse effects [42]. They include compounds under investigation such as the multi-layer, extended-release methylphenidate (PRC-063) and dasotraline, a novel inhibitor of dopamine and norepinephrine reuptake. The triple-bead formulation of mixed amphetamine salts (triple-bead MAS) is awaiting registration in adults. Osmotic controlled-release oral delivery system methylphenidate (OROS-MPH), extended-release mixed amphetamine salts, and lisdexamfetamine dimesylate (LDX) are already licensed and in clinical use in several countries. Possibly because of their neurotransmitter action, stimulants are wake-promoting in most people. Methylphenidate has $\alpha 2$ and dopamine D1 receptor actions and increases norepinephrine and dopamine in the prefrontal cortex. Amphetamine is believed to compete with endogenous monoamines for transport into nerve terminals [43•]. Stimulants may be associated with increased difficulty in falling asleep, longer sleep-onset latency, and overall shorter duration of sleep, as extensively reviewed by Stein et al. [44]. While insomnia is a common treatment-emergent adverse event (TEAE), there is inter-individual variability in response to these medications [43•].

In several recently published, placebo-controlled studies of the extended-release stimulants, the TEAE insomnia occurred significantly more frequently in the treatment arm (11–45%) than in the placebo arm (4–16%) [38•, 39•, 40•]. Medications and dosages used in these studies were triple-bead MAS (dosage 25, 50, or 75 mg once daily, $N = 412$) [38•], dasotraline (dosage 4 or 8 mg once daily, $N = 341$) [39•], and extended-release methylphenidate (PRC-063, dosage 25–100 mg, once daily, $N = 59$) [40•]. Insomnia was listed as the most frequently reported TEAE for triple-bead MAS and dasotraline [38•, 39•]. In the triple-bead MAS study (2017), insomnia occurred in 41% on active treatment, as opposed to 12.5% on placebo. There was no dose-response relationship between active drug and insomnia. This was a forced-dose trial, meaning that the entire randomized group moved through a series of rising doses, allowing for comparisons. This high rate of insomnia might have been lower with a slower upward titration, as is habitual in clinical practice [38•]. In the fixed-dose trial of dasotraline (2015), insomnia occurred in 35% (4 mg/day dose), in 45% (8 mg/day dose), and in 15.5% in the placebo group. There was a dose-response relationship between active drug and insomnia in this study. The high percentage with insomnia may have been related to the fixed-dose methodology, where patients were initiated on dasotraline 4 or 8 mg once daily, without titration [39•].

Somewhat lower rates for insomnia were reported in a systematic review of LDX by Coghill et al. (2014). In short-term trials, insomnia occurred in 10–19% of those on LDX (dosage 30, 50, or 70 mg) and in 4–5% of those on placebo [45•]. Insomnia was reported even less frequently in a (smaller) randomized, double-blind, placebo-controlled, cross-over of trial of extended-release methylphenidate (PRC-063, 2016) [40•]. During the initial open-label, dose optimization phase ($n = 59$), insomnia occurred in 31% (doses 25-100 mg). During the subsequent 2-week, double-blind phase, insomnia was reported in 11% of the treatment group and in 4% of the placebo group ($n = 53$, doses 45–100 mg). The authors suggest that this lower rate of insomnia in the blinded period was related to a decrease of adverse effects as the trial continued, and as the doses were optimized. Sleep efficiency (the ratio of hours of sleep to hours spent in bed) was poorer on PRC-063 than in the placebo arm. There were no differences observed between extended-release methylphenidate (PRC-063) and

Table 2 Recent evidence (2014–2017) for a relationship between ADHD treatment and insomnia in cross-sectional, open-label trials, or randomized double-blind, placebo-controlled ADHD treatment studies

Study	Classification	Duration (weeks)	ADHD medication daily dosage (sample size)	Age of population, years (mean)	Sex (female,%)	Sleep instrument	Insomnia (%)[a]
Brevik et al. 2017 [23•]	Cross-sectional study comparing medicated ADHD vs. non-medicated ADHD	N/A	Stimulants[b] (n = 94) Off medication (n = 36)	18–74 (34) (37)	66 64	Bergen Insomnia Scale	Medicated ADHD: 66.3 Non-medicated ADHD: 72.2
Frick et al. 2017 [38•]	Randomized double-blind, placebo-controlled, forced-dose trial of triple-bead MAS	6	25 mg (n = 104) 50 mg (n = 101) 75 mg (102) placebo (n = 104)	(38) (37) (38) (36)	50 35 47 46	Pittsburgh Sleep Quality Index	25 mg: 40 50 mg: 40 75 mg: 45 placebo: 13
Koblan et al. 2015 [39•]	Randomized, placebo-controlled, fixed-dose trial of dasotraline	4	4 mg (n = 114) 8 mg (n = 107) placebo (n = 110)	34 36 34	44 40 40	Insomnia Severity Index	4 mg: 35 8 mg: 45 placebo: 16
Wigal et al. 2016 [40•]	Randomized, double-blind, placebo-controlled cross-over of extended-release methylphenidate (PRC-063)	7–9	Dose optimization phase 25 mg–100 mg (n = 59) Double-blind phase cross-over 45–100 mg (n = 53) placebo (n = 53)	32	64	Pittsburgh Sleep Quality Index	Dose optimization phase (PRC-063) 25mg–100mg: 31 Double-blind phase (PRC-063): 11 Placebo: 4
Fijal et al. 2015 [41•]	Open-label comparison of safety and tolerability of atomoxetine among the different CYP2D6[c] metabolizer groups	12	40–100 mg Poor metabolizers (n = 117) Non-poor metabolizers (n = 1819)	34 33	43 41	Spontaneously reported treatment-emergent adverse events	Poor metabolizers: 15 Non-poor metabolizers: 8

[a] Percentage with insomnia in each of the trials

[b] Stimulants: methylphenidate (n = 69), amphetamines (n = 12), non-stimulant ATX (n = 3), or combination (n = 7)

[c] Triple-bead MAS: triple-bead formulation mixed amphetamine salts, CYP2D6: cytochrome P450 2D6

placebo for four other items on the PSQI (sleep latency, sleep disturbance, needs medications to sleep, or daytime dysfunction) [40•]. These results are promising, but larger trials are needed to confirm the lower incidence of insomnia. As noted by Childress (2017), extended-release methylphenidate (PRC-063) has efficacy for up to 16 h after dosing, so it will be important to monitor sleep in future research [43•].

When self-reported sleep quality at the start and end of the trial with extended-release methylphenidate (PRC-063) was compared, an interesting finding emerged. Neither the overall sleep quality nor the PSQI global score showed any significant difference between the treatment and placebo groups [40•]. By the end of the triple-bead MAS trial, sleep quality had improved in the active group by the trial end, based on PSQI score [38•]. Similarly, during the 2-week randomized, blinded phase of the dasotraline trial, there was no significant difference in PSQI score or overall sleep quality between the active and placebo groups [39•]. Findings were similar in the LDX trials reviewed, where available data from all studies indicated no overall worsening of sleep quality in adults, as measured by the PSQI [45•].

The reports of insomnia in both the treatment and placebo arms of all mentioned studies on long-acting stimulants, and an overall sleep quality which improved by trial end in some studies, implies that adult patients with ADHD may begin with poor sleep. These findings were confirmed in a post hoc analysis of two large placebo-controlled trials of amphetamines (triple-bead MAS and LDX). Insomnia was reported in similar proportions in both the active and placebo groups [37]. Some long-acting stimulants, such as triple-bead MAS, the extended-release methylphenidate (PRC-063), and LDX, may not worsen overall sleep quality for the duration of the trial [38•, 40•, 45•]. Moreover, a group with ADHD may exist for whom insomnia *improves* with treatment

[37, 38•]. On the other hand, the PSQI which measured insomnia in these trials also measures daily function. One would expect this to improve with treatment for ADHD. Hence, the improvement in overall sleep quality as reflected by the PSQI may reflect daytime improvement rather than a lessening of insomnia. In addition, the onset of insomnia is determined by the drug formulation, the length of the trial, the timing of dosing, and whether maximum doses are fixed, forced, or titrated upwards.

Non-stimulants

Insomnia has been reported in studies of the non-stimulant, ATX [46], but it is less common compared to studies of the long-acting stimulants [47, 48]. A lower incidence of insomnia may be related to differences in pharmacology, as ATX inhibits the presynaptic norepinephrine transporter and may have less dopaminergic action than the stimulants [43•]. Walker et al. (2015) reviewed studies of ATX published from 1998 to 2014 and concluded that insomnia was mostly non-serious, occurred early and resolved during treatment. Interestingly, insomnia was reported was more frequently with twice daily dosing (17%) than with once daily dosing (10%) [49].

ATX is predominantly metabolized by cytochrome P450 2D6 (CYP2D6), which is encoded by the highly polymorphic CYP2D6 gene [41•]. Genetic polymorphisms are important determinants of CYP2D6 enzymatic activity, which results in variability in the metabolism of ATX. Individuals can be categorized into four metabolizer groups: ultrarapid, extensive, intermediate, and poor. The plasma half-life of ATX is approximately four times longer in poor metabolizers, who experience more frequent adverse events than the other groups, significantly more insomnia. A 12-week, open-label study confirmed an increased incidence of insomnia in the poor metabolizer group, compared to the other three groups [41•]. This genetic polymorphism may help explain the heterogeneity in the association between atomoxetine and insomnia, particularly with twice daily dosing and in poor metabolizers.

De Oliveira et al. (2017) conducted a systematic review of the safety profiles of several ADHD treatments [48]. Ten studies were included in a mixed treatment comparison, allowing for the comparison of more than two interventions, even when these were not directly compared in the literature. The findings concerning the ranking of treatments in terms of their probability to provoke insomnia are unclear, as the text of this paper contradicts the results depicted in the figure. According to the figure, when ATX, bupropion, extended-release mixed amphetamine salts, and placebo were compared, extended-release mixed amphetamine salts had the highest probability to provoke insomnia (79% of probability). The safest option (after placebo) was bupropion (29% of probability). Ideally, all available treatments should be compared to give comprehensive results.

Conclusions

Based on cross-sectional studies, in clinical and population samples, insomnia is associated with adult ADHD in 43–80% [21•, 23•, 24•], regardless of pharmacological treatment for ADHD [23•]. Longitudinal studies give conflicting results. In one, the persistence of ADHD into early adulthood was strongly associated with insomnia symptoms at age 18 [28•]. In a second, there was no association between childhood or adolescent ADHD and insomnia at age 38 [27•]. Future longitudinal studies are necessary and should consider age-of-onset and the persistence of ADHD symptoms, which appear to be relevant. Certainly, there is a strong association between affective disorders and insomnia in adulthood [25, 27•, 34•]. Therefore, when studying insomnia in adult ADHD, it is important to correct for affective disorders, which also disturb sleep. The strong genetic correlation between insomnia and anxiety/depressive symptoms and major depression was recently shown in a genome-wide association study [34•]. Furthermore, while there was no correlation between the genes found for insomnia and self-reported ADHD symptoms, those for insomnia and RLS *were* strongly correlated. Therefore, the relationship between ADHD and insomnia may be mediated through RLS. Environmental influences may include (maternal) exposure to neurotoxins, alcohol, drugs, and child self-blame for marital conflict [35, 36]. In the twin study, environmental influences explained 45% of the association between ADHD and sleep quality [28•].

There are some important caveats to consider. Firstly, while an association between adult ADHD and poor sleep quality has been reported in the population-based studies, causality cannot be inferred. The questions remain, how does ADHD in adulthood lead to poor sleep and does poor sleep lead to ADHD symptoms? Furthermore, results from population-based studies may not be applicable in the clinical setting; hence, both settings should be investigated. Secondly, the improvements in sleep quality reported in trials of pharmacological treatments may be related to improvements in daytime functioning. Thirdly, the pharmacological trials had different sizes and designs, which may also have affected the frequency of insomnia. ADHD treatments may also remedy comorbid conditions (such as depression), with the result that sleep improves.

Treatment Recommendations

Many adults with ADHD have disturbed sleep patterns. For these patients, restoration of healthy sleep may be one of the treatment goals. Sleep quality should be evaluated before and

during treatment. Any changes should be carefully tracked. Psychoeducation, sleep hygiene interventions, and cognitive behavioral therapy may minimize the adverse effects of insomnia in adults with ADHD [50]. Extended-release stimulants are frequently associated with insomnia in adult ADHD, but this adverse event should not present a barrier to treatment. There is much individual variation in response to the pharmacological treatments of ADHD. In the trials reviewed, extended-release methylphenidate (PRC-063) showed the least insomnia (11%) [40•]. From the systematic review of LDX, rates of insomnia were higher (10–19%) [45•]. Insomnia appeared to be most frequent in triple-bead MAS and dasotraline (40–45%) [38•, 39•]. The frequency of insomnia with ATX is relatively low (10–17%) [48] and may be related to poor metabolizer status [41•]. For many patients, insomnia exists before any treatment starts. For others, overall sleep quality may improve with extended-release stimulants [37, 38•]. If treatment-emergent insomnia is intolerable with extended-release stimulants, it may be beneficial to switch to another agent. Adjunctive agents such as melatonin and or light therapy may also be considered to manage insomnia if non-pharmacological methods fail [51]. Clinicians treating ADHD should evaluate sleep quality and insomnia symptoms using standardized instruments, prior to starting treatment.

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Compliance with Ethical Standards

Conflict of Interest Dora Wynchank served on the advisory boards of Janssen BV; and until 2014, Novartis and Eli Lilly until 2014.

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