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CONCOMITANT USE OF STIMULANTS FOR ADHD AND SEDATIVE-HYPNOTICS

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ADHD	Attention-deficit/hyperactivity disorder
AE(s)	Adverse event(s)
CADDRA	Canadian ADHD Resource Alliance
CGI(-I or -S)	Clinical Global Impression(-Improvement or -Severity)
CNS	Central nervous system
CRSD	Circadian rhythm sleep disorder
DSHEA	Dietary Supplement Health and Education Act
DSM-4(-TR)	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (Text Revision)
DSM-5(-TR)	Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, (Text Revision)
DRRC	Drug Regimen Review Center
DUR	Drug utilization review
ESS	Epworth Sleepiness Scale
FDA	US Food and Drug Administration
FFS	Fee-for-service
GABA	Gamma-aminobutyric acid
GMPs	Good Manufacturing Practices
ICD-10	International Classification of Diseases, Tenth Revision
ITT	Intention-to-treat
LPS	Latency to persistent sleep
NAASO	Number of awakenings after sleep onset
NICE	National Institute for Health and Care Excellence
MAT	Medication-assisted treatment
MINI	Mini International Neuropsychiatric Interview
MRA(s)	Melatonin receptor agonist(s)
ODT(s)	Orally disintegrating tablet(s)
OR	Odds ratio
RCT(s)	Randomized controlled trial(s)
SR(s)	Systematic review(s)
TCA(s)	Tricyclic antidepressant(s)
TST	Total sleep time
US	United States
WASO	Wake time after sleep onset

1.0 INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) and insomnia represent two prevalent yet distinct medical conditions that often coexist,[1] presenting healthcare providers with intricate treatment challenges. ADHD is characterized by symptoms of hyperactivity, inattention, and/or impulsiveness, and affects individuals across the lifespan.[1-3] Insomnia is characterized as difficulty initiating and/or maintaining sleep, or experiencing poor sleep quality despite conducive sleep conditions, resulting in symptoms during waking hours (eg, irritability, fatigue).[4-6] Insomnia can be either chronic (symptoms occurring ≥3 times a week for ≥3 months) or short-term,[7] whereas ADHD is usually a chronic, lifelong condition that requires ongoing treatment.[3] Among those with ADHD, an estimated 73% of pediatric patients and 67% of adults have comorbid insomnia.[2] The relationship between ADHD and sleep disturbances is complex and likely multifactorial; ADHD symptomatology and certain medications may exacerbate sleep issues, while disrupted or insufficient sleep can aggravate ADHD-related symptoms.[1,8]

Central nervous system (CNS) stimulants, including methylphenidate, amphetamine, dextroamphetamine, lisdexamfetamine, methamphetamine, and dexmethylphenidate are approved by the United States (US) Food and Drug Administration (FDA) for the treatment of ADHD; some are also approved for other indications (eg, narcolepsy, binge eating disorder).[9] Pharmacologic agents FDA-approved for the treatment of insomnia belong to several drug classes such as benzodiazepines (eg, estazolam), non-benzodiazepine benzodiazepine receptor agonists or z-drugs (eg, zolpidem), and orexin receptor antagonists (eg, lemborexant), among others.[10]

The primary objective of this report is to evaluate the potential risks of concomitant use of ADHD stimulants and agents approved for insomnia (benzodiazepine or non-benzodiazepine, non-barbiturate sedative-hypnotics), and to formulate clinical considerations with respect to concurrent use of these drug classes. FDA safety communications from 2010 to present were reviewed regarding the use of ADHD stimulants or reviewed sedative-hypnotics in general (applicable to patients using these products as monotherapy or concomitantly), as were utilization data in the Utah Medicaid fee-for-service (FFS) population regarding the use of reviewed ADHD stimulants and sedative-hypnotics. Due to time constraints, this report did not exhaustively search for all primary studies that have potentially evaluated the effectiveness/safety of treating insomnia with approved sedative-hypnotics in patients with ADHD using stimulants.

2.0 METHODS

Although additionally approved for other indications, this report focused on the use of CNS stimulants in the treatment of ADHD, and benzodiazepines approved for insomnia; this report also includes non-benzodiazepine, non-barbiturate sedative-hypnotics approved for insomnia.

For drug-specific information, we primarily reviewed drug compendia databases, Lexidrug and DynaMed, with the latter sourcing drug monograph information from Micromedex. Information from drug compendia was supplemented by product prescribing information (ie, package inserts) for the reviewed sedative-hypnotics, obtained from the drug sponsors' website, Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm), or DailyMed (https://dailymed.nlm.nih.gov/dailymed/).

For clinical practice guidelines that possibly addressed the management of sleep disorders in patients with ADHD, published within the past 5 years (2019−2024), we reviewed previously completed Drug Regimen Review Center (DRRC) reports, and searched the following major medical organizations' websites:

- American Academy of Pediatrics (AAP): https://www.aap.org/
- Canadian ADHD Resource Alliance (CADDRA): https://www.caddra.ca/
- National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/

To evaluate the potential risk of concomitant use of ADHD stimulants with benzodiazepines or non-benzodiazepine, non-barbiturate sedative-hypnotics, or any pertinent safety issues within these drug classes, we reviewed FDA drug safety communications published from 2010 (earliest year of publication on the FDA's website) onward; FDA drug safety communications can be accessed at: https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications.

Due to the lack of guidance on the concomitant use of ADHD stimulants with sedative-hypnotics from reviewed guidelines, we performed a literature search in two bibliographic databases (Ovid-Medline and Epistemonikos) for recent (2019−2024) systematic or expert reviews, using free-text terms and controlled vocabulary. A modified CADTH filter for guidelines was used in Ovid-Medline,[11] whereas a website-embedded filter for systematic reviews (SRs) was used in Epistemonikos. For complete details on the search strategies, please see **Appendix A**. Additionally, reference lists of resources were also screened for relevant studies.

For patients in the Utah Medicaid FFS population with an ADHD diagnosis (according to International Classification of Diseases, Tenth Revision [ICD-10] code **F90.X**) during the latest 18-month period (November 2022 through April 2024), we report the patient distribution based on age and sedative-hypnotic filled for the subgroup of patients who filled a reviewed sedative-hypnotic within 30 days of an ADHD stimulant, based on pharmacy outpatient claims, from May 2023 through April 2024.

3.0 BACKGROUND

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, Text Revision,* (DSM-5-TR) defines ADHD as symptoms of inattention and/or hyperactivity or impulsivity which are present for at least 6 months, resulting in impaired functioning or development in more than one setting (eg, home, school, work).[12] Symptoms of inattention may include drifting off task, inability to complete instructions or tasks, and difficulty maintaining concentration. Hyperactivity symptoms may include inappropriate running, restlessness, or excessive fidgeting, tapping, or talkativeness. Impulsivity refers to spontaneous actions taken without forethought, potentially posing self-harm, such as running into the street without regard for safety. Impulsive behaviors may be observed as social intrusiveness, such as frequent interruptions or intruding on others' conversations. Notably, although the onset of ADHD typically occurs during childhood, these symptoms tend to deviate from the standard normative behavior for that particular age and developmental stage. Based on the presenting symptoms, ADHD can be classified into 3 subtypes: (1) predominantly inattentive symptoms, (2) predominantly hyperactive/impulsive symptoms, or (3) combination of both inattentive and hyperactive/impulsive symptoms.[12] According to CDC data from a 2016−2019 national survey, the estimated number of children 3−17 years of age ever diagnosed with ADHD was 6 million (9.8%) in the US,[13] and modestly lower in Utah (9.3%).[14] Notably, an

estimated two thirds of patients with childhood ADHD will continue to experience symptoms into adulthood.[15]

Sleep disturbances are common in patients with ADHD, with an estimated 73% of pediatric patients and 67% of adults with ADHD also suffering from insomnia.[2] The occurrence of insomnia varies depending on the subtype of ADHD; patients who have predominately hyperactive and/or impulsive symptoms are more likely to experience insomnia.[16] Regardless of the ADHD subtype, inadequate amounts of sleep can negatively impact the patient's quality of life and academic/work performance, and may cause fatigue or cognition impairment (eg, difficulties with concentrating, learning, or memory) during waking hours, which may resemble or worsen ADHD-related symptoms.[1,2,17,18] Because ADHD stimulants may impact sleep patterns, potentially causing delays in falling asleep or difficulties maintaining sleep, insomnia may be caused or exacerbated by the use of these medications[*].[1,3] **Importantly, the impact of ADHD stimulants on sleep varies significantly between individuals, with some patients experiencing improved sleep,**[17,19] **and between agents, depending on the pharmacokinetic profile.**[1]

Unlike the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-4), the DSM-5 has shifted its focus away from potential causal attributions related to comorbidities and acknowledges "…bidirectional and interactive effects between sleep disorders and coexisting medical and psychiatric illnesses.." (page 1100).[20] While providers should continue to manage comorbid conditions that may contribute to sleep disorders, the DSM-5 acknowledges that there can still be underlying insomnia even with appropriately treated contributing conditions, which warrants management/treatment of the sleep disorder. Rather than solely focusing on the potentially contributing condition, both coexisting conditions (eg, mental health condition and comorbid insomnia) should be treated.[20]

The administration timing of ADHD stimulants and sedative-hypnotics should be considered when determining appropriateness as they are intended to be administered at distinct times during the day. ADHD medication taken in the morning (eg, with short- and long-acting agents) and potentially in the afternoon (for short-acting agents) are expected to wear off around bedtime based on the duration of action (as shown in **Table 1**). Thus, rather than taking another dose of a stimulant in the evening to control ADHD symptoms, which could have sleep-altering effects for some individuals, providing a sedative-hypnotic seems reasonable for a patient who failed ADHD-guideline recommended treatments for sleep disturbances, including behavioral interventions and/or stimulant adjustments (ie, changing the dosage, administration timing, or formulation; see **Section 4.0**).

3.1 Characteristics of ADHD stimulants

ADHD stimulants modulate the catecholaminergic system, increasing norepinephrine and dopamine in synaptic clefts, which is associated with improved ADHD symptoms.[3]

Mono-ingredient products are available containing active agents that are either amphetamine- (amphetamine, dextroamphetamine, lisdexamfetamine, or methamphetamine) or methylphenidate-based (dexmethylphenidate or methylphenidate).[9,21] Combination products include varying strengths of

[*] Notably, sleep issues in patients with attention-deficit/hyperactivity disorder (ADHD) may also be exacerbated by or manifest due to other factors, such as poor sleep hygiene or psychiatric comorbidities (eg, anxiety, post-traumatic stress disorder, depression).

mixed salts of amphetamine and dextroamphetamine, or serdexmethylphenidate with dexmethylphenidate.[22] ADHD stimulant preparations are either short-acting (immediate-release) or long-acting (extended-release), with the duration of effect typically ranging from 3 to 6 hours for short-acting preparations or up to 16 hours for long-acting preparations.[23] Usually long-acting agents are taken once a day in the morning, and short-acting agents are taken 1 to 3 times daily.[21,24]

Most of the reviewed ADHD stimulants listed in **Table 1** are approved for use in pediatric patients at least 6 years of age. Additionally, some short-acting amphetamine-containing products (eg, Evekeo, ProCentra, Zenzedi) are approved in younger children aged 3 to 5 years.[25-27] Some products are also approved for the treatment of ADHD in adults.[22] A subset of ADHD stimulants are also approved for the treatment of narcolepsy in patients ≥6 years of age,[25-28] exogenous obesity in patients ≥12 years of age (Evekeo),[25] and binge eating disorder in adults (Vyvanse).[29] Notably, all ADHD stimulants are Schedule II controlled substances, which is reserved for medications with high abuse potential that can possibly lead to physical or psychological dependence.[30]

Table 1 provides an overview of the ADHD stimulants reviewed in this report, including their corresponding FDA indications, administration frequency, and duration of action, organized by duration of action (short- or long-acting) and chemical structure/class (amphetamines or methylphenidates).

Table 1. Overview of Central Nervous System Stimulants FDA-approved for the Treatment of Attention-deficit/Hyperactivity Disorder[9,21,22,31,32a]

Product (brand name)	Administration frequency	FDA-approved indication(s) (ages for use)	Duration of action
Short-acting amphetamine-containing products			
Amphetamine sulfate oral tablet (Evekeo)[25]	Once or twice daily	• ADHD (children ages ≥3 years only) • Narcolepsy (patients ages ≥6 years) • Exogenous obesity (patients ages ≥12 years)	4–6 hours
Amphetamine sulfate ODT (Evekeo ODT)[25]	Once or twice daily	• ADHD (children ages 6–17 years)	4–6 hours
Dextroamphetamine sulfate oral solution (ProCentra)[26]	Once or twice daily	• ADHD (children ages 3–16 years) • Narcolepsy (patients ages ≥6 years)	4–6 hours
Dextroamphetamine sulfate oral tablet (Zenzedi)[26]			
Generic dextroamphetamine + amphetamine oral tablet (Adderall)[27]	Once or twice daily	• ADHD (children ages 3–17 years) • Narcolepsy (patients ages ≥6 years)	4–6 hours
Methamphetamine oral tablet (Desoxyn)[33]	Once or twice daily	• ADHD (children ages ≥6 years only)	NR
Long-acting amphetamine-containing products			
Amphetamine ER ODT (Adzenys XR ODT)[34]	Once daily in the morning	• ADHD (patients ages ≥6 years)	10–12 hours
Amphetamine ER oral suspension or ER oral chewable tablet (Dyanavel XR)[34]	Once daily in the morning	• ADHD (patients ages ≥6 years)	10–12 hours
Dextroamphetamine sulfate ER oral capsule (Dexedrine Spansule)[26]	Once or twice daily	• ADHD (children ages 6–16 years) • Narcolepsy (patients ages ≥6 years)	5–8 hours
Dextroamphetamine ER transdermal patch (Xelstrym)[35]	Apply 2 hours before needed effect and remove 9 hours after applying	• ADHD (patients ages ≥6 years)	12 hours (if worn for 9 hours)
Dextroamphetamine + amphetamine ER oral capsule (Adderall XR)[27]	Once daily in the morning	• ADHD (patients ages ≥6 years)	10–12 hours
Dextroamphetamine + amphetamine ER oral capsule (Mydayis)[27]	Once daily in the morning	• ADHD (patients ages ≥13 years)	12–16 hours

[a] *For complete details, please refer to the drug-specific prescribing information (ie, package insert).*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; ER, extended-release; FDA, US Food and Drug Administration; NR, not reported; ODT, oral disintegrating tablet; US, United States

Table 1. Overview of Central Nervous System Stimulants FDA-approved for the Treatment of Attention-deficit/Hyperactivity Disorder[9,21,22,31,32a]

Product (brand name)	Administration frequency	FDA-approved indication(s) (ages for use)	Duration of action
Lisdexamfetamine oral capsule or chewable tablet (Vyvanse)[29]	Once daily in the morning	• ADHD (patients ages ≥6 years) • Moderate to severe binge eating disorder (adults only)	10–12 hours
Short-acting methylphenidate-containing products			
Dexmethylphenidate oral tablet (Focalin)[36]	Twice daily	• ADHD (children ages ≥6 years only)	3–5 hours
Methylphenidate hydrochloride oral chewable tablet or oral solution (Methylin)[28]	Two or three times daily	• ADHD (patients ages ≥6 years) • Narcolepsy (patients ages ≥6 years)	3–5 hours
Methylphenidate hydrochloride oral tablet (Ritalin)[28]	Two or three times daily	• ADHD (patients ages ≥6 years) • Narcolepsy (patients ages ≥6 years)	3–5 hours
Long-acting methylphenidate-containing products			
Dexmethylphenidate ER oral capsule (Focalin XR)[36]	Once daily in the morning	• ADHD (patients ages ≥6 years)	9–12 hours
Methylphenidate hydrochloride ER oral capsule (Aptensio XR)[28]	Once daily in the morning	• ADHD (patients ages ≥6 years)	Up to 16 hours
Methylphenidate hydrochloride ER oral tablet (Concerta)[28]	Once daily in the morning	• ADHD (patients ages ≥6 years)	10–12 hours
Methylphenidate ER ODT (Cotempla XR-ODT)[37]	Once daily in the morning	• ADHD (children ages 6–17 years)	10–12 hours
Methylphenidate ER transdermal patch (Daytrana)[37]	Apply 2 hours before needed effect and remove 9 hours after applying	• ADHD (children ages 6–17 years)	12 hours (if worn for 9 hours)
Methylphenidate hydrochloride ER oral capsule (Jornay PM)[28]	Once daily in the *evening*	• ADHD (patients ages ≥6 years)	NR
Methylphenidate hydrochloride ER oral capsule (Metadate CD)[28]	Once daily in the morning	• ADHD (patients ages ≥6 years)	10–12 hours

[a] *For complete details, please refer to the drug-specific prescribing information (ie, package insert).*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; ER, extended-release; FDA, US Food and Drug Administration; NR, not reported; ODT, oral disintegrating tablet; US, United States

Table 1. Overview of Central Nervous System Stimulants FDA-approved for the Treatment of Attention-deficit/Hyperactivity Disorder[9,21,22,31,32a]

Product (brand name)	**Administration frequency**	**FDA-approved indication(s) (ages for use)**	**Duration of action**
Methylphenidate hydrochloride ER oral chewable tablet (QuilliChew ER)[28]	Once daily in the morning	• ADHD (patients ages ≥6 years)	10–12 hours
Methylphenidate hydrochloride ER oral powder for suspension (Quillivant XR)[38]	Once daily in the morning	• ADHD (patients ages ≥6 years)	10–12 hours
Methylphenidate hydrochloride ER oral tablet (Relexxii)[28]	Once daily in the morning	• ADHD (patients ages ≥6 years)	12 hours
Methylphenidate hydrochloride ER oral capsule (Ritalin LA)[28]	Once daily in the morning	• ADHD (children ages 6–12 years)	8–10 hours
Dexmethylphenidate + serdexmethylphenidate oral capsule (Azstarys)[39]	Once daily in the morning	• ADHD (patients ages ≥6 years)	10–12 hours

[a] *For complete details, please refer to the drug-specific prescribing information (ie, package insert).*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; ER, extended-release; FDA, US Food and Drug Administration; NR, not reported; ODT, oral disintegrating tablet; US, United States

3.2 Characteristics of benzodiazepine and non-benzodiazepine sedative-hypnotics

There are 5 benzodiazepine sedative-hypnotics FDA-approved for the treatment of insomnia: estazolam, flurazepam, quazepam, triazolam, and temazepam.[40] Non-benzodiazepine, non-barbiturate sedative-hypnotics approved for the treatment of sleep-onset insomnia or sleep-maintenance insomnia include the z-drugs, eszopiclone, zolpidem, and zaleplon; the orexin receptor antagonists, suvorexant, lemborexant, and daridorexant; the melatonin receptor agonist (MRA), ramelteon; and the tricyclic antidepressant (TCA) and histamine receptor antagonist, doxepin (low-dose; 3 mg and 6 mg tablet only).[10] A key aspect related to the pharmacokinetic properties that differentiates sedative-hypnotics is their approved use, either for sleep-onset insomnia (for rapid onset agents) and/or sleep-maintenance insomnia (for agents with longer duration of action). Thus, not all products are indicated for sleep-maintenance insomnia, and not all products are indicated for sleep-onset insomnia. Patients are restricted to the agents that are approved for their specific type of insomnia disorder. All reviewed sedative-hypnotics for insomnia are indicated in the adult population. The melatonin agonist, tasimelteon is approved for non-24-hour sleep-wake disorder in adults, and for nighttime sleep disturbances in Smith-Magenis syndrome in patients as young as 3 years of age.[41,42] Although not yet approved for insomnia, there have been clinical trials evaluating tasimelteon (specifically Hetlioz) for this indication.[43] **Table 2** summarizes the FDA-approved indications for the reviewed sedative-hypnotics, according to insomnia subtype.

Benzodiazepines enhance the binding of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS, to the GABA-A subtype receptor, resulting in calming, sedative, and anti-anxiety effects.[44,45] Likewise, the z-drugs exert a sedative effect through interaction with GABA-A receptors.[9] Relative to benzodiazepines, zolpidem and zaleplon exhibit greater selectivity for the alpha-1 subunit, and eszopiclone has potentially higher affinity for alpha-1 and alpha-2 subunits.[9] Doxepin likely induces its sedative properties by antagonizing histamine-1 receptors.[9,10] Ramelteon, with its strong affinity for melatonin receptors MT1 and MT2, activates a pathway involved in regulating circadian rhythms. Orexin receptor antagonists block orexin receptors (OX1R and OX2R), inhibiting the binding of wake-prompting neuropeptides (orexin A and B) to orexin receptors, thereby suppressing wakefulness.[9,10]

Table 2. FDA Indications for Reviewed Sedative-Hypnotics, According to Insomnia Subtype

Active ingredient	Labeled indication			
	Sleep-onset insomnia	Sleep-maintenance insomnia	Unspecified insomnia	Other
Doxepin (low-dose)[46]		✓		
Ramelteon[47]	✓			
Suvorexant[48]	✓	✓		
Lemborexant[49]	✓	✓		
Daridorexant[50]	✓	✓		
Triazolam[51]			✓	
Temazepam[52]			✓	
Estazolam[53]				✓ frequent nighttime awakening, trouble falling asleep, and/or premature morning awakenings
Flurazepam[54]				
Quazepam[55]				
Eszopiclone[56]	✓	✓		
Zaleplon[57]	✓			
Zolpidem[58-60]	✓ for Ambien, Ambien CR, Edluar	✓ for Ambien CR		
Tasimelteon[61]				✓ Non-24 hour sleep wake disorder and nighttime sleep disturbances in SMS

Abbreviations: FDA, US Food and Drug Administration; SMS, Smith-Magenis Syndrome; US, United States

Sedative-hypnotics listed in **Table 3** are available as oral formulations (tablet or capsule),[62-74] with zolpidem also available as an extended-release tablet or sublingual tablet[†],[75,76] and tasimelteon as an oral suspension.[41,42,69] Sedative-hypnotics approved for insomnia are usually taken once a day, before or at bedtime. Except for doxepin, ramelteon, and tasimelteon, which are non-controlled substances, all others have a low risk of dependence and abuse, and therefore, are classified as Schedule IV controlled substances.[30,40] **Table 3** provides an overview of certain pharmacokinetic characteristics of benzodiazepine and non-benzodiazepine sedative-hypnotics reviewed in this report, including onset, half-life, and duration of action, organized by drug class.

[†] Intermezzo (zolpidem sublingual tablet) and Zolpimist (zolpidem metered oral spray) have been discontinued in the US.

Table 3. Overview of Sedative-Hypnotics FDA-approved for the Treatment of Insomnia, and Tasimelteon[9,10,45] [a]

Generic name (brand name)	Administration frequency	Onset	Half-life	Duration of action
Benzodiazepines				
Short-acting benzodiazepine(s)				
Triazolam oral tablet (Halcion)[51,62,77,78]	Once daily before bedtime	15–30 minutes	1.5–5.5 hours	Short
Intermediate-acting benzodiazepine(s)				
Estazolam oral tablet (generic only)[63,78,79]	Once daily at bedtime	15–60 minutes	10–24 hours	Intermediate
Temazepam oral capsule (Restoril)[52,64,78,80]	Once daily before bedtime	45–60 minutes	3.5–18.4 hours	Intermediate
Long-acting benzodiazepine(s)				
Flurazepam oral capsule (generic only)[65,78,81]	Once daily at bedtime	30–60 minutes	• Parent: 2.3 hours • Active metabolite: 74–160 hours	Long
Quazepam oral tablet (Doral)[55,66,78,82]	Once daily at bedtime	30 minutes	• Parent: 39 hours • Active metabolite: 73 hours	Long
Non-benzodiazepine, non-barbiturate hypnotics				
Benzodiazepine receptor agonist(s) (z-drugs)				
Eszopiclone oral tablet (Lunesta)[56,67,78,83]	Once daily immediately before bedtime[b]	15–30 minutes	6 hours	Intermediate
Zaleplon oral capsule (Sonata)[57,68,78,84]	Once daily immediately before bedtime or after going to bed with difficulty falling asleep	<30 minutes	1 hour	Ultrashort
Zolpidem oral tablet (Ambien)[59,69,78,85]	Once daily immediately before bedtime[b]	30 minutes	2.5 hours	Short
Zolpidem ER oral tablet (Ambien CR)[60,69,78,85]	Once daily immediately before bedtime[b]	30 minutes	2.8 hours	Short
Zolpidem sublingual tablet (Edluar)[58,69,78,85]	Once daily immediately before bedtime[b]	30 minutes	2.65–2.85 hours	Short
Orexin receptor antagonist(s)				
Suvorexant oral tablet (Belsomra)[48,70,78,86]	Once daily within 30 minutes of bedtime[b]	30 minutes	12 hours	NR
Lemborexant oral tablet (Dayvigo)[49,71,78,87]	Once daily immediately before bedtime[b]	<30 minutes	17–19 hours	NR
Daridorexant oral tablet (Quviviq)[50,72,78,88]	Once daily within 30 minutes of bedtime[b]	<30 minutes	8 hours	NR

[a] *For complete details, please refer to the drug-specific prescribing information (ie, package insert).*

[b] *Patients should plan to have at least 7–8 hours of sleep before anticipated wake-up time.*

Abbreviations: ER, extended-release; FDA, US Food and Drug Administration; NR, not reported; US, United States

Table 3. Overview of Sedative-Hypnotics FDA-approved for the Treatment of Insomnia, and Tasimelteon[9,10,45] [a]

Generic name (brand name)	Administration frequency	Onset	Half-life	Duration of action
Melatonin receptor agonist(s)				
Ramelteon oral tablet (Rozerem)[47,73,78,89]	Once daily within 30 minutes of bedtime	15–30 minutes	• Parent: 1–2.6 hours • Active metabolite: 2–5 hours	Short
Tasimelteon oral capsule (Hetlioz)[41,42,61]	Once daily 1 hour before bedtime at the same time every day	Weeks to months	• Parent: 1.3 hours • Active metabolite: 1.3–3.7 hours	NR
Tasimelteon oral suspension (Hetlioz LQ)[41,42,61]	Once daily 1 hour before bedtime at the same time every day	Weeks to months	• Parent: 1.3 hours • Active metabolite: 1.3–3.7 hours	NR
Tricyclic antidepressant(s) and histamine receptor antagonist(s)				
Doxepin oral tablet (Silenor)[46,74,78,90]	Once daily within 30 minutes of bedtime	30 minutes	• Parent: 15 hours • Active metabolite: 31–51 hours	Long

[a] *For complete details, please refer to the drug-specific prescribing information (ie, package insert).*

[b] *Patients should plan to have at least 7–8 hours of sleep before anticipated wake-up time.*

Abbreviations: ER, extended-release; FDA, US Food and Drug Administration; NR, not reported; US, United States

4.0 RECOMMENDATIONS FOR MANAGING INSOMNIA IN PATIENTS WITH ADHD

The following subsections provide treatment recommendations from guidelines and expert opinion about managing comorbid insomnia, or more generally sleep disturbances, in patients with ADHD.

4.1 Guideline recommendations

We reviewed 3 ADHD guidelines, one each from CADDRA (2020),[3] AAP (2019),[91] and NICE (2018, updated 2019), for recommendations on the management of sleep problems in patients with ADHD.[92] Additionally, we reviewed an accompanying AAP treatment algorithm that supplements the AAP clinical practice guideline,[18] and a 2019 European consensus statement.[93] Overall, clinical practice guidelines and the European consensus statement emphasize establishing appropriate sleep hygiene practices, and in applicable patients, modifying the patient's ADHD stimulant dosage, administration timing, or formulation as an initial approach to managing sleep problems in patients with ADHD, rather than initiating pharmacologic therapy for insomnia.[3,18,91-93] None of the reviewed ADHD management guidelines or the 2019 European consensus statement address the use of prescription pharmacologic agents approved for insomnia (eg, benzodiazepines, non-benzodiazepine sedative-hypnotics) as a treatment option in patients with ADHD and insomnia, potentially because this is beyond their intended scope; nonetheless, several acknowledge the common co-occurrence of insomnia with ADHD.[3,18,91-93]

The 2019 AAP guideline, which is specific to children and adolescents with ADHD, mentions that patients with ADHD commonly have comorbid conditions, including but not limited to, learning disabilities, disruptive behavior, mood disorders, seizures, autism spectrum disorder, and *sleep disorders*.[91] Generally, when ADHD coexists with another condition, especially a psychiatric comorbidity, the more debilitating condition should be treated first[3,93]; exceptions that should be treated before ADHD include psychosis, substance use disorder, bipolar disorder, severe mood disorders, and suicidal ideation, as these conditions may complicate ADHD treatment.[3] AAP (2019) strongly recommends providers to screen for comorbid conditions when evaluating a child or adolescent for ADHD.[91] The supplemental treatment algorithm elaborates this point by mentioning all children and adolescents should be comprehensively screened for primary sleep disorders, including evaluation of associated risk factors, during the initial assessment for ADHD.[18] If the findings indicate the likelihood of a sleep disorder, the provider should conduct a thorough sleep history, including evaluating the patient's sleep environment, bedtime routine, sleep onset duration, overall sleep duration, number of nighttime awakenings, time of awakening, and the patient's condition upon waking. Patients with ADHD may experience sleep issues, including insomnia, for several reasons, as outlined below[18]:

- Poor sleep hygiene (eg, inconsistent sleep schedule, lack of bedtime routine, caffeine consumption)
- ADHD medication (both stimulants and non-stimulants) effects on sleep patterns, which include direct effects (eg, delayed sleep onset, reduced sleep duration, increased time to fall asleep) and indirect effects (eg, inadequate management of ADHD symptoms in the evening, rebound symptoms or medication withdrawal)
- Comorbid mental health conditions (eg, mood disorders, anxiety)

- Circadian-based phase delay in sleep-wake patterns, leading to prolong sleep initiation and challenges in awakening at the appropriate time (ie, primary sleep disorder)
- An inherent sleep deficiency associated with ADHD may contribute to sleep issues in this patient population. For example, untreated children with ADHD, absent of comorbid mood or anxiety conditions, exhibit significantly higher bedtime resistance, encounter more problems with sleep initiation, and experience more frequent nocturnal awakenings compared to "typically developing children in control groups". Moreover, some children with ADHD, with or without a primary sleep disorder, experience daytime sleepiness.

While completely distinguishing between primary sleep disturbances and symptoms of ADHD may not be feasible as they are often coexisting, it is nonetheless prudent to consider sleep disturbances in the treatment plan for affected patients.[3,18] Clinical judgement plays a crucial role in determining whether sleep-related symptoms stem from, or are influenced by, another disorder, before starting and during treatment.[3] When determining whether sleep problems warrant an insomnia diagnosis or are ADHD-treatment related, several factors merit consideration[18]:

- The duration of action of ADHD stimulants is an important consideration for patients who are taking these medication and who experience sleep problems.[9] Monitoring and adjusting the dosage and timing of these stimulants (and/or caffeine intake, if needed) can improve the patient's sleep duration, onset, and quality. Notably, the duration of effect for a specific medication can vary among patients, and for some, may deviate from the duration indicated in product prescribing information.[3]
- Emphasizing appropriate sleep hygiene practices (eg, going to bed at the same time and place, waking up at the same time) by adjusting behavior before and at bedtime, and education on sleep optimization[93] can improve sleep and reduce related negative consequences.

NICE provides a more general recommendation to simply monitor sleep pattern changes (eg, using a sleep diary) and make adjustments to the patient's medication regimen, as appropriate.[92]

The 2020 CADDRA guideline recommends behavioral interventions as first-line treatment for children, adolescents, and adults with ADHD who experience sleep problems in general.[3] Guideline authors mention that there is limited evidence regarding the pharmacological management of sleep disturbances in patients with ADHD.[3] However, an observational study and a long-term follow-up study,[94,95] as cited by the CADDRA guideline, have demonstrated melatonin (an over-the-counter sleep aid in the US)[96] as potentially effective for alleviating sleep problems in patients with ADHD, especially children.[3] According to the 2019 European consensus statement for adults with ADHD,[93] melatonin has demonstrated improved sleep onset and sleep duration compared to placebo in children with ADHD and chronic insomnia.[97] Additionally, clinical experience suggests efficacy with melatonin at night in combination with light therapy in the morning for adults with ADHD and insomnia.[93,98]

Specifically for stimulant-induced insomnia, CADDRA (2020) suggests that providers may consider switching to a shorter acting stimulant or adjusting the timing of stimulant administration to the earliest possible time in the morning.[3] Notably, sleep disturbances may also be caused by end-of-dose rebound symptoms when the therapeutic effect of the ADHD medication wears off. In this case, providers may consider switching from an immediate-release to a longer acting agent or administering an additional lower dose of a short-acting stimulant before the rebound symptoms regularly occur.[3] In the general

management of ADHD, some guidelines tend to prefer long-acting stimulants over short-acting stimulants as first-line pharmacologic treatment due to avoidance or better tolerability of rebound symptoms, lower abuse potential, and improved patient compliance (reduced need for multiple daily dosages).[3,93]

Regarding general guidance for any combination pharmacologic therapy (ie, for treatment of ADHD such as adding an agent to treat rebound symptoms or differing mechanism of action, or to address coexisting disorders [eg, sleep, anxiety]), the 2020 CADDRA guideline suggest providers query a drug interaction database for potential drug-drug interactions, and determine whether the combined agents could produce additive effects that might require cautious monitoring or even preclude their concomitant use.[3]

Table 4 summarizes the treatment recommendations from reviewed guidelines and the European consensus statement for managing sleep disturbances in patients with ADHD.

Table 4. Guideline Recommendations for the Management of Insomnia in Patients with Attention-deficit/Hyperactivity Disorder

Professional organization and guideline Publication year	Key guidance points[a]
Canadian ADHD Resource Alliance (CADDRA) Canadian ADHD Practice Guidelines, Edition 4.1; 2020[3]	Target population for recommendations: children, adolescents, and adults with ADHD • Sleep problems may exacerbate ADHD symptoms, therefore treatment of sleep issues can improve ADHD symptomology. • First-line treatment for insomnia or sleep disturbances: behavioral interventions. • Melatonin may be a pharmacologic treatment option for insomnia or sleep disturbances in general . ○ Limited evidence regarding the pharmacological management of sleep disturbances in patients with ADHD. • For stimulant-induced insomnia, may consider switching to a shorter acting stimulant or adjusting the stimulant administration to as soon as possible in the morning. • Generally, when prescribing any combination pharmacologic therapy (ie, for treatment of ADHD or to address coexisting disorders), providers should query a drug interaction database for potential drug-drug interactions, and determine whether the combined agents could produce additive effects that might require cautious monitoring or even preclude their concomitant use.
American Academy of Pediatrics (AAP) Clinical practice guideline for the diagnosis, evaluation, and treatment of ADHD in children and adolescents; 2019[18,91 b]	Target population for recommendations: children and adolescents with ADHD • All children and adolescents should be comprehensively screened for primary sleep disorders, including evaluation of associated risk factors, during the initial assessment for ADHD. If a sleep disorder is suspected, the provider should conduct a thorough sleep history. • Sleep issues may arise due to insufficient sleep hygiene (eg, lack of a bedtime routine, inconsistent sleep schedule), comorbid mental health conditions (eg, anxiety), or ADHD medication effects. • Implementing behavioral changes before and at bedtime can enhance sleep and reduce related negative consequences. • Sleep quality, onset, and duration can be influenced by CNS stimulant or regular caffeine use. Adjusting the dosage and timing of these substances can cause improved sleep outcomes.

[a] *Reviewed guidelines did not make guidance points at the level of formal graded recommendations with level of evidence ratings, except possibly the NICE guideline that included the statement as part of a list of recommendations.*

[b] *Because the 2019 American Academy of Pediatrics (AAP) guideline did not specifically address the treatment of stimulant- or ADHD-related insomnia, extracted information is reported from the AAP supplemental process of care algorithm.*

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; CADDRA, Canadian ADHD Resource Alliance; CNS, central nervous system; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; NDAL, Neurodevelopmental Disorders Across the Lifespan; NICE, National Institute for Health and Care Excellence

Table 4. Guideline Recommendations for the Management of Insomnia in Patients with Attention-deficit/Hyperactivity Disorder

Professional organization and guideline Publication year	Key guidance points[a]
National Institute for Health and Care Excellence (NICE) ADHD: diagnosis and management; 2018 (updated 2019)[92]	Target population for recommendations: children, adolescents, and adults with ADHD • Monitor sleep pattern changes (eg, using a sleep diary), and make necessary medication adjustments, as appropriate.
European Network Adult ADHD (ENAA), Neurodevelopmental Disorders Across the Lifespan (NDAL), European Psychiatric Association (EPA) Updated European consensus statement on diagnosis and treatment of adult ADHD; 2019[93]	Target population for recommendations: adults with ADHD • Careful adjustment of CNS stimulant dosages, in addition to psychoeducation focused on optimizing sleep, can enhance sleep quality. • Compared to placebo, melatonin has demonstrated improvements in sleep onset and sleep duration in children with ADHD and chronic insomnia. • In adults with ADHD and insomnia, clinical experience suggests efficacy with melatonin at night in combination with light therapy in the morning. • When treating insomnia, treatment should prioritize educating patients on good sleep hygiene practices and appropriately adjusting the stimulant or non-stimulant ADHD medication.

[a] *Reviewed guidelines did not make guidance points at the level of formal graded recommendations with level of evidence ratings, except possibly the NICE guideline that included the statement as part of a list of recommendations.*

[b] *Because the 2019 American Academy of Pediatrics (AAP) guideline did not specifically address the treatment of stimulant- or ADHD-related insomnia, extracted information is reported from the AAP supplemental process of care algorithm.*

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; CADDRA, Canadian ADHD Resource Alliance; CNS, central nervous system; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; NDAL, Neurodevelopmental Disorders Across the Lifespan; NICE, National Institute for Health and Care Excellence

4.2 Expert opinion recommendations

Overall, there is a paucity of evidence available on the use of benzodiazepines or other prescription sedative-hypnotics (eg, z-drugs, orexin receptor antagonists) for the management of insomnia in patients with ADHD. Therefore, experts tend to suggest adding sedative-hypnotics as a later-line option for refractory cases in children, and presumably adults, with ADHD.[1,99] For most children with ADHD, behavioral interventions are effective in alleviating sleep difficulties, even among those prescribed ADHD stimulants.[96] Nevertheless, some patients may continue to exhibit sleep disturbances (or may not have access to such evidence-based behavioral interventions), highlighting the need for other treatment modalities.[96]

According to expert opinion, behavioral interventions, such as ensuring appropriate sleep hygiene and a consistent sleep/wake routine, are first-line treatment for children and adolescents experiencing stimulant-induced or exacerbated insomnia.[96,99] Other initial inventions include optimizing ADHD medications to improve sleep, such as switching to a non-stimulant (eg, atomoxetine, guanfacine), or changing the formulation or adjusting the dosage of the ADHD stimulant. Patients taking higher dosages of ADHD stimulants frequently suffer from insomnia.[96,99] Usually adverse effects from ADHD medications can be mitigated by modifying the causative medication dosage and/or administration timing.[96] Therefore, providers should establish a baseline history of sleep issues before starting ADHD treatment, and then regularly assess sleep as part of ongoing ADHD management.[99]

For patients experiencing rebound symptoms, adding a small dose of a short-acting stimulant in the afternoon or early evening can be beneficial for some patients.[99] Notably, certain patients (eg, those with a pre-existing sleep problem) may be more predisposed to experiencing sleep disturbances when taking ADHD stimulants.[99]

If patients continue to experience insomnia that does not improve with behavioral interventions and ADHD medication optimization, a trial of melatonin can be considered, given 30−60 minutes prior to bedtime.[96,99] Melatonin dosages range from 1−6 mg depending on patient response; dosages exceeding 6 mg are rarely required.[96,99] Melatonin tends to be recommended over other medications for insomnia, especially in children, because of the more robust evidence supporting its use in children,[97,100] and the favorable side effect profile.[96] However, patients should receive guidance regarding the quality of melatonin products, as they are available over-the-counter and commonly plagued with quality concerns (see **Section 4.3**).[96] Because there is limited evidence for use of other sedative-hypnotics, especially in children,[96] the decision to use these medications should be carefully evaluated between the provider and patient/caregiver, typically after exhausting all other options.[99]

Recommendations from UpToDate, an evidence-based information resource for healthcare professionals, for the management of sleep issues are specific to children and adolescents with ADHD.[1] Similar to guideline recommendations, authors advise nonpharmacologic interventions, such as establishing healthy sleep habits, behavioral changes, and/or setting a regular sleep/wake schedule as an initial treatment approach for sleep issues in children and adolescents with ADHD. As a secondary step, adjustment of the patient's ADHD medication regimen can be considered, with individualized medication decisions based on the patient's current ADHD regimen, primary sleep complaint, and response. For patients with sleep-onset insomnia, switching to a short-acting stimulant from a long-

acting stimulant may be an option if the issue is not related to the long-acting product wearing off too soon (ie, ADHD symptom rebound effect) — as long-acting products may wear off before or around bedtime. An immediate-release stimulant may be preferred in patients who are more sensitive to alerting effects. Similar to the aforementioned recommendations in previous sections,[3,99] authors note that adding a dose of an immediate-release stimulant in the afternoon may improve sleep-onset insomnia as a result of rebound effects.[1] If adjusting stimulant therapy proves ineffective in treating the patient's insomnia, switching to a non-stimulant (eg, atomoxetine, clonidine, guanfacine) is an option.[1] **If all of the previously described steps fail and the patient continues to experience insomnia, adding a pharmacologic hypnotic (eg, melatonin, zolpidem, eszopiclone) can be considered.**[1] Although most sleep-promoting agents have not been formally evaluated in the pediatric population in general, there is some evidence that suggests z-drugs (eg, zolpidem, eszopiclone) have a lack of efficacy for the treatment of ADHD-related pediatric insomnia and are associated with potential adverse effects (see **Section 5.2**).[1,101-103]

4.3 Melatonin: product quality concerns

Although some reviewed guidelines and experts tend to prefer melatonin for the treatment of insomnia in patients with ADHD, especially children,[3,93] there are potential product quality and safety concerns regarding its use. In the US, melatonin is marketed as an over-the-counter dietary supplement under the 1994 Dietary Supplement Health and Education Act (DSHEA).[104] Unlike FDA-approved prescription medications, dietary supplements are not subject to stringent federal regulations, which could otherwise reliably ensure consistent product quality and safety.[104] Although manufacturers of dietary supplements must adhere to Good Manufacturing Practices (GMPs), a 2013 report showed most manufacturers do not (posing quality/purity issues), potentially due to the higher associated costs.[10]

Independent third-party laboratories, such as US Pharmacopeia and ConsumerLab.com, offer testing services to assess the quality (but not safety or efficacy) of dietary supplements.[104] These companies provide certification seals (USP and CL, respectively) to indicate to the consumer that the manufacturer complies with certain quality standards (eg, contains label-specified ingredients and amounts, does not contain certain contaminants).[10] However, the consistency of third-party testing varies, including differences in the frequency of batch testing, transparency of methods, and scope of tested impurities.[104]

5.0 EVIDENCE FROM RCTS ON THE USE OF PRESCRIPTION SEDATIVE-HYPNOTICS FOR ADHD-RELATED INSOMNIA

From our literature searches, we identified 2 recently published reviews of controlled clinical trials (Larsson et al) or "prospective studies" (Surman et al) that focused on the treatment of sleep in patients with ADHD.[105,106] The target population age varied between these reviews: Larsson et al (2023) focused on children and adolescents,[105] and Surman et al (2021) focused on adults.[106] Surman et al identified 1 small cross-over randomized controlled trial (RCT) evaluating the efficacy and safety of ramelteon in adults with ADHD-related insomnia,[106,107] while Larsson et al identified 2 pediatric RCTs evaluating the efficacy and safety of either eszopiclone or zolpidem in children and adolescents with ADHD-related insomnia.[101,102,105] **Table 5** provides an overview of the patient population, interventions, and comparisons for each of these trials.

In patients crossing over from placebo to ramelteon 8 mg, circadian timing appeared improved, however, when both cross-over groups were considered overall, ramelteon did not significantly improve most measured sleep parameters (eg, sleep timing, sleep latency, total sleep time [TST]).[107] Moreover significantly worsened sleep fragmentation and Epworth Sleepiness Scale (ESS) scores were observed among adults with ADHD and insomnia. The included population (N=36) had a mix of sleep disorders as classified according to the older DSM-4 diagnostic manual: primary insomnia, or a delayed sleep phase type of circadian rhythm sleep disorder (CRSD).[107] Included patients with primary insomnia were not further distinguished as having sleep-onset insomnia and/or sleep-maintenance insomnia (a factor that could bias results). Thus, results from this small study may or may not be generalizable to a population with sleep-onset insomnia as currently classified by DSM-5. Ramelteon is approved for sleep-onset insomnia.[47] Regarding the effect on sleep onset, carryover effects are very probable in this study as evident by the opposite effect in each individual cross-over group: the group that took ramelteon first, then crossed over to placebo, did show a trend of improved sleep onset, whereas the group that received placebo first, then switched to ramelteon, had a trend of worsened sleep onset with ramelteon.

In the pediatric studies, zolpidem 0.25 mg/kg and high- and low-dose eszopiclone (either 2 mg or 3 mg, or 1 mg or 2 mg, respectively, depending on age) failed to significantly improve latency to persistent sleep (LPS; primary outcome in both trials) from baseline to week 4 (for zolpidem) or week 12 (for eszopiclone) compared to placebo.[101,102] However, significant improvements in subjective measures resulted with zolpidem, with respect to Clinical Global Impression-Improvement (CGI-I) pediatric and caregiver scores.[101] In the eszopiclone study, although not significant, the change in sleep onset was numerically improved with either low- or high-dose eszopiclone compared to placebo.[102] Reasons for not finding an favorable objective response with active treatment are unclear, but potential factors may include the studied population having ADHD with comorbid insomnia, rather than insomnia alone.[102]

Notably, none of these studies compared outcomes by subgroup of ADHD pharmacologic treatment status, so efficacy and safety profile of these agents specifically among patients who received ADHD stimulants is unclear. The safety profile observed in the ramelteon study was consistent with expected adverse events (AEs) in the general adult population: drowsiness was the most common AE reported with ramelteon in patients with ADHD (likely managed with ADHD stimulants).[107] While dizziness and headache were common with zolpidem in the pediatric study (as in adult studies of the general population), hallucinations were also more frequent with zolpidem than placebo (7.4% vs 0%, respectively) and occurred at a rate possibly higher than that in the general adult population (<1% in clinical trials).[59,101] For eszopiclone, headache, dysgeusia, and dizziness occurred more often with high-dose eszopiclone versus placebo in the pediatric RCT,[102] which is consistent with the common AEs observed in the general adult population.[56]

Additional evidence may exist evaluating the use of prescription sedative-hypnotics in children and/or adults with ADHD-related insomnia, as our search focused only on review-level evidence published within the past 5 years. However, because Larsson et al performed a systematic search for pediatric trials, we can be reasonably confident that we identified relevant controlled pediatric trials published between their search date of 2005 to April 2021.[105] We are also aware of a 2024 review in patients with ADHD and sleep disturbances, which identified the same 3 aforementioned RCTs as Larsson et al and Surman et al, and no additional relevant studies.[108]

Table 5. Study Design Overview of Reviewed RCTs in Patients with ADHD-related Insomnia Treated with Ramelteon, Zolpidem, or Eszopiclone

Study design (publication year)	Total study duration: length of treatment	Intervention and comparator	Population	Use of ADHD or sleep medications
Adult studies				
Randomized, double-blind, placebo-controlled cross-over trial (2011)[107]	8 weeks total[a]: 2 weeks on treatment	• Ramelteon 8 mg daily • Placebo	• Adults (19–65 years of age); N=36 total; 32 analyzed • Primary diagnosis of ADHD according to **DSM-4-TR criteria**, and confirmed by ADHD rating scale and MINI assessments • Initial insomnia diagnosis per **DSM-4 criteria**, either primary insomnia or the delayed sleep phase type of circadian rhythm sleep disorder	• Unclear; in a subset of trial participants with complete actigraphy data (n=24), 13 (54%) were treated with an ADHD stimulant daily in the morning.[109]
Pediatric studies				

Multicenter, double-blind, placebo-controlled RCT (2009)[101]	8 weeks total:
	6 weeks on treatment
		• Zolpidem 0.25 mg/kg daily (max: 10 mg daily)
		• Placebo
			• Children (6–11 years of age) and adolescents (12–17 years of age); N=201 for zolpidem; N=486 for eszopiclone
			• Diagnosed with ADHD (according to **DSM-4[-TR] criteria**)
			  ○ Established on ADHD treatment for a minimum of 1 month prior to study enrollment
			• Complaints of insomnia[b]
			  ○ LPS >30 minutes
			  ○ Insomnia not due to direct effects of abuse or misuse of prescribed medications
				• Participants had to be established on all chronic therapies, including ADHD treatment, for a minimum of 1 month prior to study enrollment
				• ADHD stimulants were the most commonly reported ADHD pharmacologic treatment in the zolpidem (N=136) and placebo (N=65) groups.
				  ○ 123 participants (90.4%) reported using ADHD stimulants in the zolpidem group
				  ○ 61 participants (93.8%) reported using ADHD stimulants in the placebo group
				• 41 participants (30.1%) in the zolpidem group and 23 participants (35.4%) in the placebo group reported using a nonhypnotic medication for sleep
				  ○ Clonidine (16.2%) was most frequently reported in the zolpidem group
				  ○ Medications that caused drowsiness as an adverse effect (13.8%) and antihistamines (12.3%) were most frequently reported in the placebo group

Multicenter, double-blind, placebo-controlled RCT (2014)[102]	12 weeks total: 12 weeks on treatment	• High-dose eszopiclone (2 mg for children, 3 mg for adolescents) • Low-dose eszopiclone (1 mg for children, 2 mg for adolescents) • Placebo		• Participants had to be established on all chronic therapies, including ADHD treatment, for a minimum of 1 month prior to study enrollment • Participants could not use OTC sleep aids, energy drinks, herbal products, and sympathomimetics • In the overall cohort, 65.8% of participants were using an ADHD stimulant ○ Across all treatment groups, the most commonly reported ADHD medication was methylphenidate (ranged from 21.2% to 30.7%), followed by lisdexamfetamine (ranged from 14.9% to 19.6%), then dextroamphetamine/amphetamine (ranged from 15.7% to 16.8%)

[a] *Due to the cross-over design, the 8-week trial included 2 weeks of treatment with ramelteon or placebo, followed by a 2-week washout period, and then 2 weeks of the alternative treatment.*

[b] *Insomnia was defined as trouble initiating or maintaining sleep despite sufficient time and opportunity for rest.*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DSM-4(-TR), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (Text Revision); OTC, over-the-counter; LPS, latency to persistent sleep; MINI, Mini International Neuropsychiatric Interview; RCT(s), randomized controlled trial(s)

5.1 Ramelteon in adults with ADHD-related insomnia

An 8-week randomized, double-blind, placebo-controlled cross-over trial (in 2011) evaluated the use of ramelteon 8 mg in adults (19−65 years of age) with ADHD, diagnosed according to DSM-4-TR criteria, and confirmed by ADHD rating scale and Mini International Neuropsychiatric Interview (MINI) assessments.[107] Additionally, per DSM-4-TR, participants had a diagnosis of primary insomnia or delayed sleep phase type of CRSD, which is characterized by difficulty falling asleep like sleep-onset insomnia, but it is a distinct sleep disorder from insomnia according to the newer DSM-5 criteria. Excluded participants were those with high scores on the Hamilton Depression Scale and Hamilton Anxiety Scale; psychiatric conditions (eg, bipolar disorder, psychosis, untreated depression, severe anxiety disorder) or other active sleep disorders that may contribute to insomnia symptoms; and unstable medical conditions. Due to the cross-over design, eligible participants were randomized to initially receive either ramelteon 8 mg or matching placebo for 2 weeks, followed by a 2-week washout period, and then crossed over to receive the other treatment for 2 weeks. Outcomes of interest included objective sleep measures (eg, TST, sleep efficiency, sleep fragmentation) and subjective sleep measures (eg, ESS, ADHD rating scale).[107]

Overall, 36 adults were enrolled in the study, with the greatest proportion being between 19 and 30 years of age.[107] A similar proportion of men (52.8%) and women (47.2%) were included in the study. Of these participants, 12 participants (33.3%) had primary insomnia, 21 participants (58.3%) had delayed sleep phase type of CRSD, and 3 participants (8.3%) met criteria for other disrupted sleep wake cycle disorders (eg, irregular sleep-wake pattern) — these 3 participants had their data excluded from the statistical analysis. Additionally, 4 participants withdrew from the study, resulting in 32 participants completing both treatment phases.[107] The proportion of included participants taking ADHD stimulants in the total population is unclear,[107] but a subgroup analysis of participants with complete actigraphy outcomes data noted that 13 of 24 participants (54%) were on a routine ADHD stimulant morning regimen.[109] While participants were instructed to administer study medication between 8 PM to 9 PM or 30 minutes prior to desired sleep time, the actual time of administration was highly variable (ranging from 6 PM to 12:40 AM, and averaging 10 PM),[107] which could have affected study outcomes.

Participants crossing over from placebo to ramelteon 8 mg daily had a significantly earlier mid-sleep time (ie, time point between sleep start and end time which reflects circadian timing), by approximately 45 minutes, compared to treatment with placebo[‡].[107] Although a relationship was observed between the magnitude of sleep phase advance and the timing of ramelteon administration relative to sleep start time, it did not achieve significance, with the highest effectiveness observed when ramelteon was administered 1.5 hours prior to bed. For objective sleep timing measures (ie, sleep start and end time, and circadian amplitude), no significant differences between groups were observed, but ramelteon 8 mg trended toward an earlier sleep start time compared to placebo, regardless of treatment order. Additionally, no significant differences between ramelteon 8 mg and placebo were found for other sleep

[‡] This outcome was only calculated for the second treatment group (placebo-then-active group) in the trial because the first group (active-then-placebo) had 1 month of timing between baseline actigraphy data and the active drug making timing comparisons unreliable due to possible differences in factors affecting circadian rhythm.

parameters such as sleep latency, sleep efficiency, and TST. Regarding the effect on sleep onset, the group that took ramelteon first, then crossed over to placebo, did show a trend of improved sleep onset, whereas the group that received placebo first, then switched to ramelteon, had a trend of worsened sleep onset with ramelteon. Notably, compared to placebo, ramelteon 8 mg significantly increased sleep fragmentation (19.9 vs 22.1, respectively) and ESS scores (6.1 vs 8.9, respectively), with the percentage of participants exhibiting excessive sleepiness (with a score over 10; generally the threshold to diagnose excessive sleepiness) more than doubling during ramelteon treatment compared to placebo.[107]

All AEs that occurred during the study period were mild.[107] Drowsiness was the most frequently reported AE across active (number of complaints: 2), placebo (number of complaints: 3), and washout (number of complaints: 4) periods. No participants withdrew from the study due to AEs.[107]

5.2 Z-drugs in pediatric patients with ADHD-related insomnia

Both pediatric RCTs (2009 and 2014) were double-blind, placebo-controlled, parallel group trials among children (6−11 years of age) and adolescents (12−17 years of age) diagnosed with ADHD according to DSM-4(-TR) criteria, and suffering from insomnia, defined as trouble initiating or maintaining sleep despite sufficient time and opportunity for rest.[101,102] Enrolled participants in either study were required to have a LPS >30 minutes, and for the eszopiclone RCT only, > 45 minutes of wake time after sleep onset (WASO) as measured by polysomnography, and insomnia not due to direct effects of abuse or misuse of prescribed medications.[101,102] In addition, the eszopiclone RCT also required participants to have functional impairment while awake due to sleep issues.[102] Participants in both RCTs were established on all chronic therapies, including ADHD treatment for a minimum of 1 month prior to study enrollment.[101,102] In both studies, excluded participants were those with another primary sleep condition, a major psychiatric condition (eg, bipolar disorder, history of psychosis, major depression, conduct disorder), recent history of substance abuse and/or dependence, or prior AEs with the study medication (ie, zolpidem, or eszopiclone or zopiclone).[101,102] Additional exclusion criteria unique to the zolpidem RCT included the use of rifampicin, sertraline, or pharmacological sleep aids that the patient declined to cease.[101] The primary efficacy outcome in both trials was reduction in LPS from baseline to a predetermine timepoint (ie, at week 4 for the zolpidem RCT or at week 12 for the eszopiclone RCT) as measured by polysomnography.[101,102] Additional details for each of these trials are discussed below.

5.2.1 Zolpidem in pediatric patients with ADHD-related insomnia

An 8-week, double-blind, placebo-controlled RCT randomized eligible participants (N=201) in a 2:1 ratio to either zolpidem 0.25 mg/kg daily (maximum: 10 mg daily) or matching placebo, each administered 30 minutes prior to bedtime.[101] As previously mentioned, the primary outcome was the change in LPS from baseline to week 4, either measured between weeks 3 and 4 or weeks 4 and 6, which could introduce bias if the timing of measurements was inconsistent between treatment groups. Secondary efficacy outcomes included CGI-I scores, CGI-Severity (CGI-S) scores,[§] and polysomnographic and actigraphy assessments.[101]

[§] Clinical Global Impression-Improvement (CGI-I) and CGI-Severity (CGI-S) scores range from 1 to 7; a higher CGI-I score indicates greater improvement, whereas a higher CGI-S score indicates greater insomnia severity.

Baseline demographics were similar across treatment groups, with the mean duration from the insomnia diagnosis being about 5 years, and approximately 30% of participants with a history of using behavioral therapies for insomnia. Baseline sleep measures were comparable between treatment groups (eg, LPS, WASO), including insomnia severity as measured by CGI-S scores. In both treatment groups, stimulants were the predominant medication used for ADHD treatment, with 90.4% of zolpidem-treated participants and 93.8% of placebo-treated participants reporting stimulant use (exact agents are not reported). Additionally, 41 participants (30.1%) in the zolpidem group and 23 participants (35.4%) in the placebo group reported using nonhypnotic medications (eg, clonidine, antihistamines) for sleep.[101] Participants were required to have discontinued pharmacologic sleep aids to participate in the trial, so it is unclear if use of these sedating medications occurred prior to or during the trial.

For the primary outcome, there was no significant difference between zolpidem 0.25 mg/kg and placebo in the baseline-adjusted least square mean change in LPS at week 4.[101] Additionally, no significant difference was observed between treatment groups in the baseline-adjusted least square mean changes for sleep efficiency, proportion of WASO or number of awakenings after sleep onset (NAASO), and TST at week 4.

With respect to CGI-I child/adolescent scores, zolpidem showed a significant difference from placebo at weeks 4 and 8 in the entire cohort, including among the subgroup of adolescents but not for children. Authors hypothesized that the subgroup differences in CGI-scores (ie, significance in adolescents and not children) could be due to: a) underdosing in children due to rapid zolpidem metabolism, b) differences in insomnia pathophysiology, and/or c) age-dependent differences in sensitivity of the outcome instrument. For child/adolescent and parent/caregiver CGI-S scores, zolpidem demonstrated a significant difference from placebo at week 4, with zolpidem showing greater improvements in insomnia severity.[101] **Table 6** provides an overview of select findings from this study.

Among all treated participants, 85 zolpidem-treated participants (62.5%) and 31 placebo-treated participants (47.7%) experienced at least 1 AE during the study.[101] The most common AEs, occurring more frequently with zolpidem than placebo, were dizziness, headache, and hallucinations. Although most AEs were mild to moderate in severity, 10 participants in the zolpidem arm discontinued treatment due to AEs, most often hallucinations; no participants discontinued treatment due to AEs in the placebo group. No deaths occurred during the study.[101]

CGI scoring was conducted by the investigator based on interviews with the child/adolescent and the parent/caregiver.

Table 6. Select Results from the Zolpidem RCT in Pediatric Patients with ADHD and Comorbid Insomnia[101]

Efficacy outcome **Number of participants analyzed in each group**	**Least square mean ± SE (95% CI)**			
	Zolpidem	**Placebo**	**SS difference of zolpidem vs placebo**	**P-value**
Change in LPS from baseline to week 4 – **primary outcome**[a]	−20.28 minutes ± NR	−21.27 minutes ± NR	Nonsignificant	NR
Secondary outcome – CGI scores: zolpidem (n=126); placebo (n=60)[b]				
• Change in child/adolescent CGI-S score from baseline to week 4	−2.21 ± 0.13	−1.57 ± 0.19	−0.64 ± 0.23 (−1.09 to −0.19)	<0.05
• Change in parent/caregiver CGI-S score from baseline to week 4	−2.22 ± 0.13	−1.67 ± 0.19	−0.55 ± 0.23 (−1.01 to −0.09)	<0.05
• Change in child/adolescent CGI-I score from baseline to **week 4**[c]	5.80 ± 0.11	5.30 ± 0.17	0.40 ± 0.20 (0.05 to 0.85)	<0.05
○ Subgroup analysis:				
▪ Zolpidem (n=65); placebo (n=34): Children (aged 6–11 years)	5.60 ± 0.16	5.50 ± 0.22	Nonsignificant	0.79
▪ Zolpidem (n=61); placebo (n=26): Adolescents (aged 12–17 years)	6.00 ± 0.16	5.20 ± 0.25	0.80 ± NR (0.24 to 1.42)	<0.05
• Change in parent/caregiver CGI-I score from baseline to week 4[c]	5.70 ± 0.12	5.40 ± 0.17	Nonsignificant	0.07
• Change in child/adolescent CGI-I score from baseline to **week 8**: zolpidem (n=123); placebo (n=56)	5.70 ± 0.12	5.30 ± 0.17	0.4 ± NR (0.03 to 0.86)	<0.05
○ Subgroup analysis:				
▪ Zolpidem (n=63); placebo (n=32): Children (aged 6–11 years)	5.30 ± 0.16	5.80 ± 0.23	Nonsignificant	0.12
▪ Zolpidem (n=60); placebo (n=24): Adolescents (aged 12–17 years)	6.10 ± 0.17	4.70 ± 0.26	1.30 ± NR (0.70 to 1.93)	<0.001
Secondary outcome – polysomnography assessments[d] (%): zolpidem (n=124); placebo (n=60)				
• Change in proportion of WASO from baseline to week 4	0.63 ± 0.94	1.29 ± 1.35	Nonsignificant	0.68
• Change in proportion of NAASO from baseline to week 4	0.13 ± 0.22	−0.21 ± 0.32	Nonsignificant	0.38
• Change in proportion of sleep efficiency from baseline to week 4	1.66 ± 1.33	1.16 ± 1.92	Nonsignificant	0.83
Secondary outcome – actigraphy assessments (min): zolpidem (n=107); placebo (n=49)				
• Change in TST from baseline to week 4	0.43 ± 7.9	−2.33 ± 11.8	Nonsignificant	0.84

[a] *The number of participants analyzed from each treatment group for the primary outcome is unclear, but appears to be the number of participants randomized to each group (ie, 136 participants in the zolpidem group and 65 participants in the placebo group).*

[b] *This is the number of participants included in the analysis from each treatment group for CGI scores, unless otherwise noted (ie, subgroup analysis)*

[c] *"The CGI-I involves an evaluation with respect to baseline; therefore, this value is presented as an actual value rather than a statistical changes from the baseline value." (page e774)*

[d] *To calculate the proportion of WASO and NAASO, and sleep efficiency, the polysomnography findings for each metric were adjusted by the duration of time spent in bed, which varied based on age.*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; LPS, latency to persistent sleep; NAASO, number of awakenings after sleep onset; NR, not reported; RCT, randomized controlled trial; SE, standard error; SS, statistically significant; TST, total sleep time; WASO, wake time after sleep onset

5.2.2 Eszopiclone in pediatric patients with ADHD-related insomnia

A 12-week, placebo-controlled RCT randomized eligible participants (N=486) in a 1:1:1 ratio to either low-dose eszopiclone (1 mg for children 6−11 years of age, 2 mg for adolescents 12−17 years of age), high-dose eszopiclone (2 mg for children 6−11 years of age, 3 mg for adolescents 12−17 years of age), or placebo, each taken by mouth at bedtime.[102] Baseline demographics were similar across treatment groups, with approximately 53% aged 6−11 years and about 46% aged 12−17 years. Overall, 65.8% of participants were using a stimulant approved for ADHD, with methylphenidate being the most common. The primary outcome was the change in LPS from baseline to week 12, as measured by polysomnography. Key secondary outcomes were the change from baseline to week 12 for polysomnography-measured WASO, parent/caregiver and child/adolescent CGI-I scores, and Conners' ADHD rating scale. A 2-week single-blind, washout, follow-up period assessed treatment discontinuation and rebound effects among the intention-to-treat (ITT) population, defined as those who received at least one dose of the study treatment in a single-blinded fashion.[102]

Compared to placebo, neither low- or high-dose eszopiclone significantly improved LPS from baseline to week 12.[102] However, a numerical reduction in LPS was achieved with both low- and high-dose eszopiclone, resulting in a least square mean difference of 7.33 and 2.21 for low-dose and high-dose eszopiclone, respectively, versus placebo. Nonetheless, because the primary outcome was not statistically significant, all key secondary outcomes (ie, WASO, and CGI-I and Conners' ADHD scores) were considered nonsignificant regardless of the p-value based on the hierarchical statistical approach used by the study investigators.[102] **Table 7** provides an overview of select results from this study.

Regarding safety, 61.0% of participants in the high-dose eszopiclone group, 59.5% of participants in the low-dose eszopiclone group, and 46.0% of participants in the placebo group experienced at least 1 treatment-emergent AE during the double-blind period of the trial.[102] The most common AEs among eszopiclone recipients were headache, dysgeusia, and dizziness, which occurred more frequently in patients in the high-dose group relative to other treatment groups. Rates of AEs were generally consistent across age ranges, except for dysgeusia, which was reported numerically more often among adolescents. The severity of most AEs was mild to moderate; however, 2 participants in the high-dose eszopiclone group, aged 6−11 years of age, experienced serious AEs, with both events deemed to be unrelated to eszopiclone: 1 participant experienced next-day sedation, and the other had respiratory distress. AEs resulted in study discontinuation for 5 participants (3.1%) receiving high-dose eszopiclone, 4 participants (2.5%) receiving low-dose eszopiclone, and 3 participants (1.9%) receiving placebo. No deaths were reported during the study. During the 2-week, single-blind follow-up, there no notable safety concerns or discrepancies between treatment groups regarding rebound or discontinuation effects.[102]

5.2.2.1 Open-label, follow-up, extension safety study

The safety of eszopiclone was further evaluated in the 12-month, open-label extension study among participants who completed the placebo-controlled RCT (n=55) and participants with no prior exposure to eszopiclone (n=249), of whom approximately 76% were receiving an ADHD stimulant.[102] Overall, 121 participants (39.8%) completed the 12 months of treatment, either with eszopiclone 2 mg (for children aged 6−11 years) or 3 mg (for adolescents aged 12−17 years), with the median duration of eszopiclone

exposure of 184 days. Reported AEs during the 12-month open-label study were similar to the double-blind period of the 12-week RCT among eszopiclone-treated participants, with the most common AEs for eszopiclone being headache (21.5%), dysgeusia (13.9%), and dizziness (9.9%). Rates of AEs were consistent across age groups, except for numerically increased occurrences among adolescents for headache, dysgeusia, and nasopharyngitis. Thirty-four participants (11.2%) experienced AEs that resulted in study discontinuation; reasons for discontinuation included dizziness (4 participants), hallucinations (5 participants), and suicidal ideation (2 participants). One death occurred during the study period, and was deemed to be unrelated to eszopiclone.[102]

Table 7. Select Results from the Eszopiclone RCT in Pediatric Patients with ADHD and Comorbid Insomnia[102]

Efficacy outcome	Least square mean ± SE				
	High-dose eszopiclone (n=160) (2 mg for children, 3 mg for adolescents)	**Low-dose eszopiclone (n=162)** (1 mg for children, 2 mg for adolescents)	**Placebo (n=160)**	**Difference of high-dose eszopiclone vs placebo; statistical significance**[a]	**Difference of low-dose eszopiclone vs placebo; statistical significance**[a]
Change in LPS from baseline to week 12 (minute) – **primary outcome**	−18.3 ± 3.9	−23.4 ± 3.9	−25.7 ± 3.9	7.33; nonsignificant	2.21; nonsignificant
Key secondary outcomes:					
• Change in WASO from baseline to week 12 (minute)	−23.4 ± 3.4	−16.8 ± 3.4	−17.3 ± 3.4	−6.04; nonsignificant	0.55; nonsignificant
• Change in parent/caregiver CGI-I score[b] from baseline to week 12	2.3 ± 0.1	2.6 ± 0.1	2.7 ± 0.1	−0.4; nonsignificant	−0.2; nonsignificant
• Change in child/adolescent CGI-I score[b] from baseline to week 12	2.3 ± 0.1	2.5 ± 0.1	2.7 ± 0.1	−0.4; nonsignificant	−0.2; nonsignificant
• Change in Conners' ADHD score (inattention)	−8.8 ± 1.0	−5.8 ± 1.0	−7.1 ± 1.0	−1.7; nonsignificant	1.3; nonsignificant

[a] *Because the high- or low-dose eszopiclone did not significantly differ from placebo for the primary outcome, all key secondary outcomes were considered nonsignificant, regardless of the p-value.*

[b] *"The CGI-I involves an evaluation with respect to baseline, and the value is therefore presented as an absolute value rather than as the least square mean change from the baseline value." (page e1099)*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CGI-I, Clinical Global Impression-Improvement; LPS, latency to persistent sleep; RCT, randomized controlled trial; SE, standard error; WASO, wake time after sleep onset

6.0 RISKS OF ADHD STIMULANTS AND SEDATIVE-HYPNOTICS

We did not find any FDA drug safety communications or labeled warnings specific to concomitant use of ADHD stimulants with the reviewed sedative-hypnotics. Nonetheless, these medications carry potential serious risks that are applicable to any patient using these drug classes in general. In the absence of such warnings, this section focuses on the *individual drug class* risks, according to FDA safety communications, and Lexidrug (for ADHD stimulants) or product prescribing information (for sedative-hypnotics).

6.1 FDA safety communications

From 2010 to 2024 (as of present), there have been no FDA drug safety communications addressing potential risks associated with concomitant use of ADHD stimulants with medications approved for insomnia (eg, benzodiazepines, z-drugs).[110] Nevertheless, during this period, the FDA has issued 12 warnings related to specific drug classes of interest: 5 for ADHD stimulants, 3 for benzodiazepines, and 4 for z-drugs. No safety communications were found for the other insomnia medications reviewed in this report.

Safety warnings for both ADHD stimulants and benzodiazepines addressed their addiction and abuse potential. Unique safety concerns for ADHD stimulants included potential cardiovascular risks and specifically for methylphenidate products, risk of priapism or permanent skin color loss (with the patch formulation only). Unique safety concerns for benzodiazepines included risks associated with combined opioid use or agents used in medication-assisted treatment (MAT) for opioid addiction and dependence (ie, methadone, buprenorphine). Unique safety concerns for z-drugs included the potential risk of next-morning impairment and complex sleep behaviors (eg, sleep walking, sleep driving).

Table 8 provides an overview of the FDA drug safety communications issued from 2010 onward for the ADHD stimulants, benzodiazepines, and z-drugs, focusing on FDA guidance for healthcare providers and patients. Additional information for each of these safety announcements are discussed in the following subsections.

Table 8. Summary of FDA Drug Safety Communications for ADHD Stimulants and Agents FDA-Approved for Insomnia from 2010–2024

FDA drug safety communication (date of issuance)	Drug class/agents in safety warning	Key points of the FDA safety communication[a]
FDA safety communications regarding ADHD stimulants		
Safety review update of medications used to treat ADHD in children and young adults (November 2011)[111]	• ADHD stimulants: methylphenidate, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, amphetamine (mixed salts), methamphetamine • Non-stimulants: atomoxetine, pemoline (no longer marketed)	Update to the public that a recent study (at the time) found no association between the use of certain ADHD medications and an increased risk of serious adverse cardiovascular events (ie, myocardial infarction, sudden cardiac death, stroke) in children and young adults using ADHD medications. Despite the neutral effect observed, the FDA advised the following: • Avoid using stimulants and atomoxetine in patients with serious heart issues, or in those whom increases in blood pressure or heart rate would pose concern. • Monitor blood pressure or heart rate occasionally in patients treated with ADHD medications (eg, stimulants). • Patients should adhere to their prescribed ADHD medication regimen, as directed by their healthcare provider.
Safety review update of medications used to treat ADHD in adults (December 2011)[112]	• ADHD stimulants: methylphenidate, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, amphetamine (mixed salts), methamphetamine • Non-stimulants: atomoxetine, pemoline (no longer marketed)	Update to a cardiovascular safety review on medications used for ADHD, with a recent study (at the time) finding no significant increased risk of serious cardiovascular events (ie, myocardial infarction, sudden cardiac death, or stroke) in adults using ADHD medications compared to non-users. Despite the neutral effect observed, the FDA advised the following: • Avoid using stimulants and atomoxetine in patients with serious heart issues, or in those whom increases in blood pressure or heart rate would pose concern. • Monitor blood pressure or heart rate occasionally in patients treated with ADHD medications (eg, stimulants). • Patients should adhere to their prescribed ADHD medication regimen, as directed by their healthcare provider.
FDA warns of rare risk of long-lasting erections in males taking methylphenidate ADHD medications and has approved label changes (December 2013)[113]	• Methylphenidate products: methylphenidate hydrochloride, methylphenidate, dexmethylphenidate hydrochloride	The drug labels and medication guides for methylphenidate products were updated to include information about the potential for priapism. • Rarely, methylphenidate products may induce priapism in males of all ages. Failure to promptly treat priapism may result in permanent penile injury. • If priapism or any erection persists for >4 hours, patients should seek immediate medical attention. • All male patients treated with methylphenidate products and their caregivers should be counseled on recognizing the signs and symptoms of priapism, emphasizing the importance of seeking immediate medical intervention if such symptoms occur.
FDA reporting permanent skin color changes associated with use of Daytrana patch (methylphenidate transdermal system) for treating ADHD (June 2015)[114]	• Methylphenidate patch (Daytrana)	FDA warns about the potential for permanent skin color loss (known as chemical leukoderma) associated with the use of the methylphenidate patch (Daytrana), added as a labeled warning in the product prescribing information. • Patients and/or caregivers should monitor for the emergence of lighter skin areas, especially beneath the area where the patch was applied, and promptly inform their healthcare provider if any skin color changes occur. • If skin color changes occur, healthcare providers should consider alternative treatment options.
FDA update to warnings to improve safe use of prescription stimulants used to treat ADHD and other conditions (May 2023)[24]	• ADHD stimulants (eg, amphetamine, dextroamphetamine, methylphenidate)	To ensure prescribing information about addiction, abuse, and misuse were consistent across the entire drug class, the FDA in 2023 updated the labeled black box warnings and other product labeling sections for all prescription ADHD stimulants. The misuse and abuse (also referred to as nonmedical use) of CNS stimulants can lead to overdose and death, with increased risk associated with higher dosages or non-approved administration methods such as snorting or injecting. • Prescribers should evaluate the patient's risk for misuse, abuse, and addiction prior to prescribing a CNS stimulant. • Healthcare providers should educate patients and caregivers about the risks of abuse, misuse, and addiction associated with CNS stimulant use, and appropriate storage and disposal of unused or expired medications. • Patients should be instructed to not share their prescribed stimulant with anyone else for whom it was not prescribed. • Prescribers should regularly monitor for symptoms and signs of abuse, misuse, and addiction during CNS stimulant use.

[a] *This table provides a summary of the FDA safety communications pertaining to ADHD stimulants, benzodiazepines, and z-drugs spanning from 2010 to 2024 (as of present), focusing on FDA guidance for healthcare providers and patients. For information on the data supporting the rationale behind the FDA drug safety communication, please refer to the corresponding FDA drug safety communication.*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; FDA, US Food and Drug Administration; MAT, medication-assisted treatment; US, United States

Table 8. Summary of FDA Drug Safety Communications for ADHD Stimulants and Agents FDA-Approved for Insomnia from 2010–2024

FDA drug safety communication (date of issuance)	Drug class/agents in safety warning	Key points of the FDA safety communication[a]
FDA safety communications regarding benzodiazepines		
FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning (August 2016)[115]	• Benzodiazepines, including those approved for sleep (ie, quazepam, temazepam, triazolam, estazolam, flurazepam) • Opioids (eg, codeine, fentanyl, morphine, oxycodone) • Other hypnotic CNS depressants (eg, eszopiclone, ramelteon, suvorexant, zaleplon, zolpidem) • Other CNS depressants such as muscle relaxants (eg, baclofen, carisoprodol) and antipsychotics (eg, aripiprazole, lurasidone, olanzapine)	FDA identified significant risks, including respiratory depression and death, associated with the concomitant use of opioids with benzodiazepines or other CNS depressants. To mitigate these risks and reduce the combination use of opioids with benzodiazepines or other CNS depressants, the FDA added boxed warnings to the labeling of benzodiazepines, in addition to opioids for pain and opioid-containing cough medications. FDA advised the following: • Healthcare providers should restrict co-prescribing opioid analgesics with benzodiazepines or other CNS depressants solely to patients for whom other therapeutic options are insufficient. If co-prescribing these medications is necessary, healthcare providers should strive to use the lowest effective dose and duration of each medication. • Patients and caregivers should be informed about the potential risks of respiratory depression and sedation, including any related signs and/or symptoms. • Prescribers should avoid prescribing opioid cough medications to patients concurrently using benzodiazepines or other CNS depressants. • Patients on opioids and benzodiazepines or other CNS depressants, including alcohol, and their caregivers, should promptly seek medical attention if they, or those under their care, exhibit symptoms such as unusual dizziness, extreme drowsiness, breathing difficulties, or unresponsiveness.
FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks (September 2017)[116]	• Benzodiazepines, including those approved for sleep (ie, quazepam, temazepam, triazolam, estazolam, flurazepam) • MAT drugs (ie, buprenorphine ± naloxone, methadone) • Other hypnotic CNS depressants (eg, eszopiclone, ramelteon, suvorexant, zaleplon, zolpidem) • Other CNS depressants such as muscle relaxants (eg, baclofen, carisoprodol) and antipsychotics (eg, aripiprazole, lurasidone, olanzapine)	FDA advised against withholding buprenorphine and methadone from patients using benzodiazepines or other CNS depressants due to the harm of untreated opioid addiction potentially outweighing the increased risk of potentially serious adverse effects. The FDA required inclusion of this information in the prescribing information for buprenorphine and methadone, including recommendations for minimizing concurrent use of MAT drugs with benzodiazepines. FDA advised the following: • Healthcare providers should implement measures and precautions, along with formulating a treatment strategy, when combining buprenorphine or methadone with benzodiazepines or other CNS depressants. ○ Patients should be counseled about the serious risks (eg, overdose, death) associated with combing CNS depressants, whether prescribed or illicit, with buprenorphine or methadone. ○ A plan should be developed to manage the use of benzodiazepines or other CNS depressants when initiating MAT, including tapering the benzodiazepine or CNS depressant to discontinuation, if feasible. ○ Confirming the diagnosis if a patient is prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, and considering alternative treatment options for these conditions. ○ Perform urine or blood screening to monitor for illicit substances, as appropriate. • Patients undergoing MAT should adhere to their prescribed medication regimen, and should refrain from using benzodiazepines or other CNS depressants with buprenorphine or methadone, as their combined use increases the risk of adverse effects, including overdose and death.
FDA requiring boxed warning update to improve safe use of benzodiazepine drug class (September 2020)[117]	• Benzodiazepines, including those approved for sleep (ie, quazepam, temazepam, triazolam, estazolam, flurazepam)	The FDA updated the black boxed warning for all benzodiazepines to include risks of abuse, addiction, physical dependence, and withdrawal symptoms (eg, seizures) due to abrupt cessation or dose reduction. • Healthcare providers should evaluate the patient's condition, concurrent medications, and the risk of abuse, misuse, and addiction to determine if the benefits of prescribing a benzodiazepine outweigh the risks. • When prescribing benzodiazepines, either alone or in combination with other medications, the lowest effective dosage and duration of each medication should be used. ○ Special attention is warranted when co-prescribing benzodiazepines with opioids or other CNS depressants due to the potential for serious adverse effects (eg, respiratory depression); patients should be instructed to promptly seek medical attention if they experience respiratory or other serious symptoms (see August 2016 benzodiazepine FDA safety communication). • Providers should regularly monitor patients for signs and symptoms of abuse, misuse, or addiction during benzodiazepine use, and promptly provide or refer the patient for early substance abuse treatment if a substance use disorder is suspected, as appropriate. • Providers should gradually taper benzodiazepines to decrease the dosage or discontinue the agent, tailoring the tapering regimen to each patient's individual needs while providing continual monitoring and support to prevent severe withdrawal effects.

[a] *This table provides a summary of the FDA safety communications pertaining to ADHD stimulants, benzodiazepines, and z-drugs spanning from 2010 to 2024 (as of present), focusing on FDA guidance for healthcare providers and patients. For information on the data supporting the rationale behind the FDA drug safety communication, please refer to the corresponding FDA drug safety communication.*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; FDA, US Food and Drug Administration; MAT, medication-assisted treatment; US, United States

Table 8. Summary of FDA Drug Safety Communications for ADHD Stimulants and Agents FDA-Approved for Insomnia from 2010–2024

FDA drug safety communication (date of issuance)	Drug class/agents in safety warning	Key points of the FDA safety communication[a]
FDA safety communications regarding z-drugs		
Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended starting doses for certain drugs containing zolpidem (January 2013)[118] *Note that updated information for this safety concern is provided in the FDA communication from* ***May 2013***	• Zolpidem products: Ambien, Ambien CR, Edluar, and Zolpimist	Safety announcement regarding the risk of next-day impairment (decreased mental alertness the morning after use) with certain zolpidem products (ie, Ambien, Ambien CR, Edluar, and Zolpimist; does not apply to Intermezzo) approved for use at bedtime, recommending a reduction in the zolpidem dosage due to recent findings indicating potentially elevated morning drug levels that could impair alertness-related activities (eg, driving). • FDA advises healthcare providers to warn all patients, regardless of sex, using zolpidem products about the potential risk of impaired mental alertness the next morning following administration, especially for tasks such as driving. ○ Data suggests extended-release formulations (Ambien CR) pose the greatest risk for next-morning impairment ○ Women are potentially more susceptible to this risk than men due to slower rates of zolpidem elimination • FDA has recommended manufacturers change the recommended starting doses of zolpidem for women, reducing the dosage of immediate-release products (Ambien, Edluar, and Zolpimist) from 10 mg to 5 mg, and the extended-release product (Ambien CR) from 12.5 mg to 6.25 mg. Additionally, for men, providers are encouraged to consider prescribing lower starting doses of zolpidem (5 mg for immediate-release and 6.25 mg for extended-release).
FDA approves new starting doses for certain zolpidem products (May 2013)[119]	• Zolpidem products: Ambien, Ambien CR, and Edluar	Notification to the public that the FDA approved new initial dosing recommendations for certain immediate- and extended-release zolpidem products due to the risk of next-morning impairment, which was added as a labeled warning/precaution for Ambien CR. • For immediate-release zolpidem products (ie, Ambien and Edluar), the recommended initial dosage was reduced to 5 mg for women and either 5 mg or 10 mg for men, whereas for the extended-release product (Ambien CR), the recommended initial dose was reduced to 6.25 mg for women and either 6.25 mg or 12.5 mg for men. • If lower dosages (5 mg for Ambien and Edluar, and 6.25 mg for Ambien CR) are ineffective, the dosage may be increased to 10 mg for Ambien and Edluar and 12.5 mg for Ambien CR (regardless of sex); however, caution is advised as higher dosages may elevate the risk of next-morning impairment. • Caution patients using extended-release zolpidem (Ambien CR) at doses of either 6.25 mg or 12.5 mg against driving or participating in tasks that require full mental alertness the day following administration due to potential residual drug levels, resulting in impairment of such activities.
FDA warns of next-day impairment with sleep aid Lunesta (eszopiclone) and lowers recommended starting dose (May 2014)[120]	• Eszopiclone	Eszopiclone (Lunesta) can lead to next-day impairment, prompting a reduction in the recommended starting dose from 2 mg to 1 mg at bedtime for both men and women. • Patients prescribed the 1 mg dose may consider escalating to 2 mg or 3 mg if clinically appropriate, though higher doses pose an elevated risk of next-day impairment. • Healthcare providers should adhere to the updated dosing when starting eszopiclone, while patients should maintain their prescribed dose and consult their healthcare provider for personalized dose adjustments.
FDA adds boxed warning for risk of serious injuries caused by sleep walking with certain prescription insomnia medicines (April 2019)[121]	• Eszopiclone, zaleplon, and zolpidem	FDA safety announcement about rare, but serious, injuries due to complex sleep behaviors (eg, sleep walking, sleep driving) in patients exposed to eszopiclone, zaleplon, or zolpidem. The FDA required the addition of the risk of complex sleep behaviors to the black box warning for each of these agents, and added a contraindication to the product labeling of eszopiclone, zaleplon, and zolpidem to avoid use in patients with a history of complex sleep behavior while taking any of these agents. • Patients prescribed eszopiclone, zaleplon, or zolpidem should be counseled about the potential for rare, but serious, adverse effects, including serious injuries or death from complex sleep behaviors, and should be instructed to discontinue the medication if such behaviors occur. ○ Complex sleep behaviors have occurred at the lowest recommended doses, and after an initial dose or continued use in patients with or without a history of such behaviors.

[a] *This table provides a summary of the FDA safety communications pertaining to ADHD stimulants, benzodiazepines, and z-drugs spanning from 2010 to 2024 (as of present), focusing on FDA guidance for healthcare providers and patients. For information on the data supporting the rationale behind the FDA drug safety communication, please refer to the corresponding FDA drug safety communication.*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; FDA, US Food and Drug Administration; MAT, medication-assisted treatment; US, United States

6.1.1 Addiction and abuse potential of ADHD stimulants and benzodiazepines

Recent FDA safety warnings focus on the potential for addiction and abuse of ADHD stimulants and benzodiazepines.[24,117] The FDA updated the black box warnings for all ADHD stimulants in 2023 and all benzodiazepines in 2020, to highlight their abuse and addiction potential, in addition to the risk of misuse with ADHD stimulants, and potential withdrawal upon abrupt discontinuation or dosage reduction with benzodiazepines. The FDA advises prescribers to evaluate the patient's risk of misuse, abuse, and addiction before prescribing either an ADHD stimulant or benzodiazepine, ensuring that the potential benefits outweigh the risks.[24,117] If benzodiazepines are used, either alone or in combination with other medications, the lowest effective dose and duration of each medication should be employed.[117] Prescribers should regularly monitor for symptoms and signs of abuse, misuse, and addiction (eg, refills are requested sooner than needed) during treatment with either of these drug classes,[24,117] and promptly provide or refer the patient for early substance abuse treatment if a substance use disorder is suspected, as appropriate.[117]

Patients misusing or abusing ADHD stimulants (ie, nonmedical use), especially through non-oral routes (eg, injecting, snorting), have an increased risk of developing substance use disorder compared to those who are using the medication as prescribed by their healthcare provider.[24] Therefore, providers are encouraged to counsel patients against sharing their stimulants with those for whom it was not prescribed, and to use the medication as directed.[24]

6.1.2 Unique safety concerns for ADHD stimulants: cardiovascular effects

In 2011, the FDA released 2 drug safety communications focused on the cardiovascular safety of ADHD medications in both children and adults.[111,112] These safety announcements described 3 separate retrospective cohort studies: 1 involving children and young adults aged 2−24,[122] and 2 involving adults aged 25−64 years.[111,112,123] The cohort study among children and young adults included 1,200,438 participants and 373,677 person-years of current ADHD medication exposure,[111,122] and the 2 adult studies included a total of 150,359 current ADHD medication users, with 107,322 person-years of current ADHD medication exposure.[112,123] All of these studies demonstrated no increased risk of serious adverse cardiovascular events (ie, myocardial infarction, stroke, sudden cardiac death) among patients currently treated with ADHD medications, including stimulants, compared to those not exposed to ADHD medications.[111,112,122,123] Furthermore, comparisons between former or past users of ADHD medications and current ADHD medication users found no significant increased risk of cardiovascular events in studies exclusively among children and adults.[111,112,122,123] Therefore, FDA guidance for ADHD medications remained unchanged. Despite the neutral risk observed, providers were encouraged to avoid stimulants (and atomoxetine, a non-stimulant for ADHD) in patients with serious heart issues, or in those whom increases in blood pressure or heart rate would pose concern; and to continue monitoring blood pressure or heart rate occasionally in patients treated with ADHD medications.[111,112]

6.1.2.1 Unique safety concerns for methylphenidate products: priapism and permanent skin color loss

In 2013, the FDA issued a safety announcement that methylphenidate products (eg, Concerta, Daytrana, Ritalin) may induce priapism in males of all ages.[113] If priapism or any erection persists for >4 hours, patients should seek immediate medical attention as permanent damage may occur if left untreated. Therefore, all male patients treated with methylphenidate products and their caregivers should be counseled on recognizing the signs and symptoms of priapism, emphasizing the importance of seeking immediate medical intervention if such symptoms occur.[113]

In 2015, an FDA announcement specifically for the methylphenidate patch (Daytrana) was released to warn patients and providers of the potential risk of permanent skin color loss, referred to as chemical leukoderma, which was added as a new warning to the product labeling.[114] Patients and/or caregivers should monitor for the emergence of lighter skin areas, especially beneath the area where the patch was applied, and promptly inform their healthcare provider if any skin color changes occur. If skin color changes occur, healthcare providers should consider alternative treatment options.[114]

6.1.3 Unique safety concerns for benzodiazepines: combination use with opioids and medications for opioid addiction

Due to increases in the co-prescribing of concomitant benzodiazepines with opioid analgesics and their associated potential harms, the FDA added a black box warning to the labeling of benzodiazepines and opioid analgesics and opioid-containing cough preparations in 2016 to discourage combination use of benzodiazepines or other CNS depressants (eg, alcohol, muscle relaxants) with opioids.[115] Although the FDA's review focused on opioid analgesics, the FDA anticipated similar risks associated with the concurrent use of opioid-containing cough medications and benzodiazepines or other CNS depressants, and therefore, extended the black box warning to include opioid cough preparations.[115]

Because of the potential for serious harm, the FDA advised providers to restrict co-prescribing opioid analgesics with benzodiazepines or other CNS depressants solely to patients for whom other therapeutic options are insufficient, and to avoid prescribing opioid cough medications to patients using benzodiazepines or other CNS depressants.[115] If co-prescribing an opioid analgesic with benzodiazepines or other CNS depressants is necessary, providers should strive to use the lowest effective dose and duration of each medication. Patients and caregivers should be informed about the potential risks of respiratory depression and sedation, including any related signs and/or symptoms, and promptly seek medical attention if any unusual symptoms occur (eg, extreme drowsiness, breathing difficulties, respiratory depression, unresponsiveness).[115]

6.1.3.1 Combination use of benzodiazepines with buprenorphine- or methadone-based MAT

Although the combined use of benzodiazepines or other CNS depressants with buprenorphine or methadone are associated with potentially serious risks (eg, death, overdose), the FDA, in 2017, advised against withholding buprenorphine or methadone from patients undergoing MAT who were also taking benzodiazepines or other CNS depressants due to the harm of untreated opioid addiction potentially outweighing the increased risks.[116] If combining buprenorphine or methadone with benzodiazepines or

other CNS depressants is required, providers should implement measures and precautions, along with formulating a treatment strategy, which may include counseling patients about associated risks, confirming the diagnosis if a patient is prescribed benzodiazepines or other CNS depressants for anxiety or insomnia and considering alternative treatment options for these conditions, and tapering the benzodiazepine or CNS depressant to discontinuation, if feasible. Additional considerations may include urine or blood screening to monitor for illicit substances, as appropriate, and facilitating care coordination between other providers to ensure they are aware of the patient's MAT therapy.[116]

6.1.4 Unique safety concerns for z-drugs: next-morning impairment

An initial safety announcement released in January 2013 addressed lowering the recommended starting dose of certain zolpidem products (ie, Ambien, Ambien CR, Edluar, Zolpimist) due to the risk of next-morning impairment (decreased mental alertness the morning after use).[118] In May 2013, the FDA approved the updated labeled starting dose recommendations for Ambien, Ambien CR, and Edluar.[119] For immediate-release zolpidem products (ie, Ambien and Edluar), the recommended initial dosage was reduced from 10 mg to 5 mg for women and either 5 mg or 10 mg for men, whereas for the extended-release product (Ambien CR), the recommended initial dose was reduced from 12.5 mg to 6.25 mg for women and either 6.25 mg or 12.5 mg for men.[118,119] If lower dosages are ineffective, the dosage may be increased to 10 mg for Ambien and Edluar and 12.5 mg for Ambien CR, regardless of sex.[119]

The recommended initial dose of eszopiclone was reduced from 2 mg to 1 mg for both men and women in 2014.[120] Patients prescribed the 1 mg dose may consider escalating to 2 mg or 3 mg if clinically appropriate, though higher doses pose an elevated risk of next-day impairment. In general, providers should prescribe, and patients should adhere to, the lowest effective dose required to manage the patient's insomnia symptoms to mitigate the potential for mental impairment.[120]

In 2019, the FDA required the addition of a black box warning for z-drugs regarding the risk of rare, but serious, injuries due to complex sleep behaviors (ie, engaging in activities without remembrance or not fully awake) in patients exposed to eszopiclone, zaleplon, or zolpidem.[121] Additionally, a contraindication was added to the product labeling of z-drugs to avoid use in patients with a history of complex sleep behavior while taking any of these agents. Providers should counsel patients prescribed z-drugs about the risk of complex sleep behaviors, and to discontinue the medication if such behaviors occur.[121]

6.2 Warnings and precautions

Table 9 summarizes select drug class warnings (warnings listed for ≥3 agents) for ADHD stimulants, as indexed in Lexidrug, and the reviewed sedative-hypnotics, according to product prescribing information. **Notably, this is not a comprehensive list**; please refer to the specific package insert for additional warnings/precautions.

Table 9. Select Drug Class Warnings for ADHD Stimulants and Reviewed Sedative-Hypnotics, According to Lexidrug or Product Prescribing Information [9,10 a]

Drug class warning	ADHD stimulants[124-131]								Benzodiazepines[51-55]					Z-drugs[56-60]			ORAs[48-50]			MRAs[47,61]		Other[46]
	AMP	DEXTRO	DEX	AMP + DEXTRO	LIS	METHA	METHY	SER + DEX	EST	FLU	QUA	TEM	TRI	ESZ	ZAL	ZOL	DAR	LEM	SUV	RAM	TAS	Low-dose DOX[c]
Abuse, misuse, and addiction	X (BBW)								X (BBW)													
Risks from concomitant use with opioids									X (BBW)													
Dependence and withdrawal reactions									X (BBW)													
Avoid use in patients with cardiovascular disease (eg, structural cardiac abnormalities)	X	X	X	X	X	X	X	X														
May exacerbate tics or Tourette syndrome	X	X	X	X	X	X	X	X														
Hypertension/tachycardia	X					X		X														
CNS effects impairing mental alertness	X	X		X	X	X																
Peripheral vasculopathy	X	X	X	X	X	X	X	X														
Visual disturbances	X	X	X	X	X	X	X															
Serotonin syndrome	X	X				X																
Growth suppression and weight loss in pediatric patients	X	X	X			X		X														
Psychiatric adverse reactions (eg, psychosis, mania)	X	X	X	X	X	X	X	X														
Cognitive and behavioral abnormalities (eg, aggression, amnesia)									X	X	X	X	X	X	X	X				X		X
Next-day impairment and CNS depression									X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypersensitivity reactions									X	X	X	X	X	X	X	X				X		
Complex sleep behaviors (eg, sleep driving)									X	X	X	X	X	X (BBW)			X	X	X	X		X
Withdrawal symptoms									X (BBW)					X	X	X						
Avoid or use caution (depending on agent) in patients with compromised respiratory function (eg, sleep apnea) or depression									X	X	X[b]	X	X	X	X	X	X	X	X	X		X
Sleep paralysis, disturbing hallucinations, and cataplexy-like symptoms																	X	X	X			
If insomnia persists longer than 7 to 10 days with drug therapy, evaluate for a comorbid diagnoses									X	X	X	X	X	X	X	X	X	X	X	X		X

[a] Note this table is not comprehensive for all warnings/precautions; information was extracted for select warnings that were common across the drug class (warnings listed for ≥3 agents) as indexed in Lexidrug (for ADHD stimulants) or product prescribing information (for sedative-hypnotics). For drug classes that included fewer than 3 agents (ie, MRAs), select warnings that were common with other sedative-hypnotics in general were extracted. For additional information, please refer to the product-specific prescribing information (ie, package insert).

[b] Quazepam is contraindicated in patients with chronic pulmonary insufficiency, or those with suspected or established sleep apnea.

[c] Low-dose doxepin (3 mg or 6 mg tablet) was included in the table to visualize the warnings and precautions of this agent to other reviewed sedative-hypnotics.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; BBW, black box warning; CNS, central nervous system; DAR, daridorexant; DEX, dexmethylphenidate; DEXTRO, dextroamphetamine; DOX, doxepin; EST, Estazolam; ESZ, eszopiclone; FDA, US Food and Drug Administration; FLU, flurazepam; LEM, lemborexant; LIS, lisdexamfetamine; METHA, methamphetamine; METHY, methylphenidate; MRAs, melatonin receptor agonists; ORAs, orexin receptor antagonists; QUA, quazepam; RAM, ramelteon; SER, serdexmethylphenidate; SUV, suvorexant; TAS, tasimelteon; TEM, temazepam; TRI, triazolam; US, United States; ZAL, zaleplon; ZOL, zolpidem

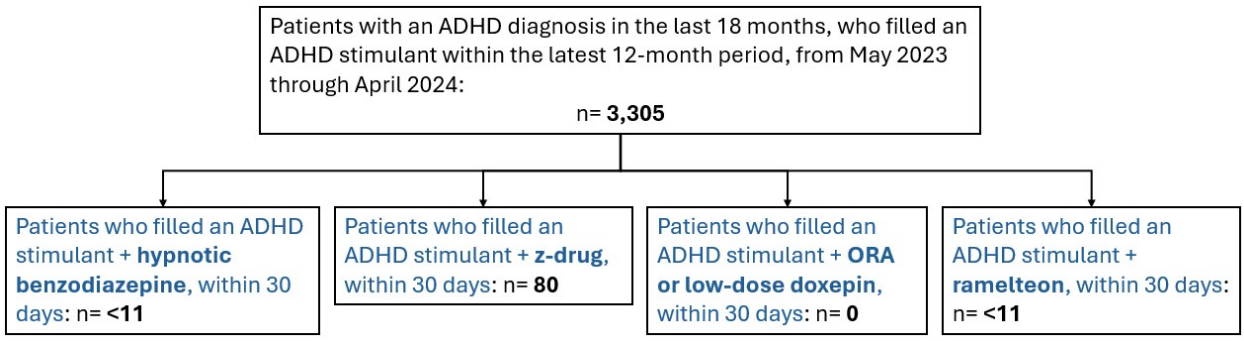
7.0 DRUG INTERACTIONS

According to the Lexidrug interaction database, there was only one identified interaction between ADHD stimulants and the reviewed sedative-hypnotics: amphetamines (eg, amphetamine, dextroamphetamine, lisdexamfetamine, methamphetamine) or methylphenidates (eg, dexmethylphenidate, methylphenidate) with TCAs (eg, doxepin).[132,133] TCAs may potentiate the cardiovascular side effects of amphetamines, whereas amphetamines and methylphenidates may enhance the serotonergic effects of TCAs, potentially precipitating serotonin syndrome and/or toxicity. Patients should be monitored for cardiovascular symptoms (eg, increased blood pressure, tachycardia) when amphetamines, including amphetamine, dextroamphetamine, lisdexamfetamine, and methamphetamine, are used in combination with doxepin, including low-dose, or other TCAs. Additionally, patients using amphetamines or methylphenidates with TCAs should also be monitored for symptoms of serotonin syndrome and/or toxicity (eg, clonus, tremor, alterations in mental status). Notably, patients with additional risk factors (eg, higher drug doses) may be more prone to experiencing serotonergic toxicities.[132,133]

8.0 UTAH MEDICAID FEE-FOR-SERVICE (FFS) PHARMACY UTILIZATION DATA

We identified 3,305 patients with a diagnosis of ADHD (ICD-10 diagnosis code of F90.X; occurring in their record between November 2022 through April 2024) who filled an outpatient pharmacy claim for an ADHD stimulant during the most recent 12-month period, from May 2023 through April 2024 (ie, observation period). Of these 3,305 patients, about 3% filled a sedative-hypnotic within 30 days after an ADHD stimulant fill — which we infer to as concomitant use (ie, concomitant cohort). Patients in this concomitant ADHD stimulant/sedative-hypnotic cohort were nearly all adults. The most common sedative-hypnotic drug class filled was z-drugs. No orexin receptor antagonists (ie, lemborexant, daridorexant, suvorexant) were filled, nor tasimelteon or low-dose doxepin. Except temazepam, there were no fills for other hypnotic benzodiazepines. **Figure 1** shows the Utah Medicaid FFS cohort of interest (ie, patients with ADHD) that filled a sedative-hypnotic within 30 days after filling an ADHD stimulant during the 1 year observation period, and shows the distribution of patients according to the sedative-hypnotic drug class filled.

Figure 1. Utah Medicaid FFS Patient Cohort with ADHD Diagnosis and Distribution According to Sedative-Hypnotic Drug Class[a]



[a] *Fills for a sedative-hypnotic of interest occurred within 30 days after an ADHD stimulant claim from March 2023 through April 2024. During the 12-month observation period (May 2023 through April 2024),* ***3,215*** *patients had an ADHD diagnosis and filled an ADHD stimulant, but did not fill a sedative-hypnotic of interest within 30 days after an ADHD stimulant fill.*

Abbreivations: ADHD, attention-deficit/hyperactivity disorder; ORA, orexin receptor antagonist

Based on unique patient counts, the most common sedative-hypnotic filled during this period was zolpidem (of any formulation; 66 adults), followed by eszopiclone (13 adults). **Table 10** shows the patient distribution of the concomitant cohort, based on patient age and type of sedative-hypnotic.

Notably, ADHD stimulant utilization trends may be impacted by the shortage of immediate-release formulations of amphetamine mixed salts, which has been ongoing since 2022.[134] The current shortage is due to a multitude of factors, including increasing demand coupled with supply chain issues (eg, inadequate manufacturer production) which has forced some patients off their usual medication regimen. Patients may have switched to alternative therapies including extended-release amphetamine mixed salt products or non-stimulant medications.[134,135]

For feasibility/time-restriction purposes, our assessment does not characterize the specific formulations of ADHD stimulants filled (eg, long-acting versus short-acting products). In order to capture possible concomitant use, we choose a timeframe for the occurrence of sedative-hypnotic fills of up to 30 days after an ADHD stimulant claim; however, prescription fills may not exactly represent concomitant use because fills may not always match actual usage.

Table 10. Patient Distribution Among Those Who Filled an ADHD Stimulant + Sedative-Hypnotic, Based on Patient Age and Sedative-Hypnotic[a]

Sedative-hypnotic	Number of unique patients, stratified by age (years)		
	0 to <15	15 to <18	≥18
Benzodiazepines[b]			
Estazolam	0	0	0
Flurazepam	0	0	0
Quazepam	0	0	0
Temazepam	0	0	<11
Triazolam	0	0	0
Z-drugs			
Eszopiclone	0	0	13
Zaleplon	0	0	<11
Zolpidem (of any formulation)	0	<11	66
Orexin receptor antagonists			
Daridorexant	0	0	0
Lemborexant	0	0	0
Suvorexant	0	0	0
Melatonin receptor agonists			
Ramelteon	0	0	<11
Tasimelteon[c]	0	0	0
Other			
Low-dose doxepin	0	0	0

[a] Fills for a sedative-hypnotic of interest occurred within 30 days after an ADHD stimulant claim from March 2023 through April 2024.

[b] While the listed benzodiazepines are FDA-approved for insomnia, utilization could potentially reflect use for other indications (eg, anxiety, seizures).

[c] Tasimelteon is FDA-approved for non-24 hour sleep wake disorder and nighttime sleep disturbances in Smith-Magenis Syndrome

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, US Food and Drug Administration; US, United States

9.0 CONSIDERATIONS FOR USING ADHD STIMULANTS WITH SEDATIVE-HYPNOTICS

Currently, Utah Medicaid does not require a prior authorization (PA) and has no restrictions regarding concomitant use of an amphetamine- or methylphenidate-containing stimulant with a sedative-hypnotic.[136]

Because reviewed guidelines and experts tend to emphasize sleep hygiene and/or adjusting the existing ADHD stimulant dosage, administration timing, or formulation in patients with ADHD and comorbid insomnia, if not previously tried,[1,3,18,91-93,96,99] it may be reasonable to consider performing educational outreach and/or retrospective drug utilization review (DUR) to providers of patients co-managed with an ADHD stimulant and a sedative-hypnotic to ensure these steps have been tried, if possible. Notably, for some patients, modifications of an ADHD stimulant may be more difficult due to shortages, particularly those on immediate-release formulations of amphetamine mixed salts.[134] However, in the general management of ADHD, guidelines tend to prefer long-acting stimulants over short-acting stimulants as first-line pharmacologic treatment due to avoidance or better tolerability of rebound symptoms, lower abuse potential, and improved patient compliance (eg, reduced need for multiple daily dosages).[3,93]

May consider performing educational outreach and/or retrospective DUR to providers of patients who are continuously filling prescriptions for both an ADHD stimulant and a sedative-hypnotic to garner attention to the provider of potential modifications to therapy, if appropriate and not previously tried. The intention of this intervention is not to deny medication access to patients who need combination therapy, but to prompt a risk-benefit discussion between the patient and provider if not yet considered, and to encourage alternative options for insomnia, as appropriate/available. Although we did not identify any definite risks from concomitant use of ADHD stimulants with any of the reviewed sedative-hypnotics in patients with ADHD, medications within these drug classes still carry potential risks that are applicable to any patient using these drug classes in general. Providers could be encouraged to:

1. Monitor for potential signs or symptoms of abuse, misuse, or addiction in patients treated with any of these drug classes, alone or together: ADHD stimulants, benzodiazepines, z-drugs, and orexin receptor antagonists, as these are all controlled substances, which carry abuse potential.[30]
2. Establish a baseline history of sleep issues before starting ADHD treatment, and then regularly assess sleep as part of ongoing ADHD management.[99]
3. For the treatment of insomnia in patients with ADHD, providers should be encouraged to:
    a. Use behavioral interventions (eg, appropriate sleep hygiene and a consistent sleep/wake routine) and/or
    b. Distinguish between patients with ADHD stimulant-exacerbated insomnia and patients experiencing a rebound effect (ie, ADHD symptoms return after loss of stimulant effect, potentially causing insomnia). Patients with stimulant-exacerbated insomnia may have the ADHD stimulant formulation, administration timing, or dosage modified to improve sleep, or they may try switching to a non-stimulant (eg, atomoxetine, guanfacine) before trying pharmacological options for insomnia.[3,18,91-93,96,99] Patients who experience rebound effects would not require a downward dosage or off-titration of ADHD stimulants; rather, they could try

adding a lower dose of a short-acting stimulant before the rebound symptoms regularly occur, or changing the formulation to extend the effect of their ADHD stimulant into bedtime to curtail ADHD symptoms.[3]

c. If the patient continues to experience insomnia despite the aforementioned approaches, a pharmacologic agent for insomnia can be used.[3,96,99]
    i. Melatonin is often suggested as the initial medication to try, especially in children,[3,93] because there is some supportive evidence in a controlled setting with a pharmaceutical-grade formulation in children,[97,100] and it tends to have a favorable side effect profile.[96] Yet, in the US, melatonin is unregulated as strictly as prescription products because it is available over-the-counter as a dietary supplement, presenting potential quality/purity concerns.[104] Moreover, to our knowledge, this is not a product covered for Medicaid patients.
    ii. There is limited evidence to guide the use of pharmacologic agents for insomnia in adults with ADHD. In the only RCT we are aware of in adults with ADHD[**] and mixed sleep disorders (primary insomnia or a delayed phase CRSD),[107] the safety profile of ramelteon was similar to the general adult population according to product labeling.[47]

10.0 SUMMARY

Sleep disturbances are common in patients with attention-deficit/hyperactivity disorder (ADHD), with more than 50% of pediatric and adult patients with ADHD suffering from insomnia.[2] The negative impact of inadequate amounts of sleep may be even more severe for those with ADHD than the general population, affecting quality of life, academic/work performance, and cognition, as well as exacerbating ADHD-related symptoms (eg, hyperactivity, inattention, and/or impulsiveness).[1,2,17,18] Because ADHD stimulants may impact sleep patterns, favorably or unfavorably depending on the patient,[1,3,17] there are multiple approaches that can be taken to ameliorate sleep issues in patients with ADHD. Modifications to the ADHD stimulant dosing, administration timing, or formulation may be tried, to either decrease exposure at bedtime for patients experiencing an over-stimulating effect, or to increase exposure in those experiencing a rebound of ADHD symptoms at bedtime as their stimulant wears off.[3,18,91-93] For insomnia that persists despite trying these approaches, it would be appropriate to initiate an indicated pharmacological treatment, rather than to leave the insomnia unmanaged.[1,99]

ADHD stimulant preparations are either short-acting (immediate-release) or long-acting (extended-release). Short-acting agents can be taken 1 to 3 times daily, with the duration of effect typically ranging from 3 to 6 hours; long-acting agents are usually taken once a day in the morning, with an effect duration up to 16 hours.[21,24] **Table 1** of the report shows the general duration of action of the reviewed ADHD stimulants.

Sedative-hypnotics approved for sleep-onset insomnia and/or sleep-maintenance insomnia consist of several drug classes/agents:

- Benzodiazepines: estazolam, flurazepam, quazepam, triazolam, and temazepam
- Non-benzodiazepine benzodiazepine receptor agonists (z-drugs): eszopiclone, zolpidem, and zaleplon

[**] Authors implied some patients were receiving stimulants but did not report details about stimulant use.

- Orexin receptor antagonists: suvorexant, lemborexant, and daridorexant
- Melatonin receptor agonist (MRA): ramelteon
- Tricyclic antidepressant and histamine receptor antagonist: doxepin (low-dose; 3 mg and 6 mg tablet only)

Mechanism of action differs among sedative-hypnotic drug classes,[40] and the onset and duration of action may vary between agents within the same class. Related to the pharmacokinetic profile, these medications are either indicated for sleep-onset insomnia and/or sleep-maintenance insomnia (see **Table 2**). Sedative-hypnotics approved for insomnia are usually taken once a day, before or at bedtime.

Overall, there is a paucity of evidence for the use of pharmacological agents (other than melatonin) for the treatment of insomnia in patients with ADHD, thereby making it difficult to conclude any potential risks from concomitant use of ADHD stimulants and sedative-hypnotics. ADHD clinical practice guidelines recognize the need for treatment of frequently co-occurring insomnia and encourage sleep hygiene and/or ADHD stimulant adjustment (ie, changing the dose, timing, or formulation) as first-line management strategies.[3,18,91-93] Although ADHD guidelines do not explicitly address the use of pharmacological agents for sleep (other than melatonin), experts tend to suggest adding pharmacological sedative-hypnotics as a later-line option for refractory cases in children, and presumably adults, with ADHD.[1,99] The decision to use these medications, particularly in children, should be carefully evaluated between the provider and patient/caregiver, typically after exhausting all other options.[99] Although melatonin tends to be recommended over other medications for insomnia, especially in children, because of the more robust evidence supporting its use in children[97,100] and the favorable side effect profile,[96] there are potential product quality/safety concerns related to its status as an over-the-counter dietary supplement in the US, which is not regulated to the same extent as prescription products that would otherwise better guarantee product purity/quality.[104]

According to identified reviews, studies evaluating the safety of sedative-hypnotics in patients on ADHD stimulants is limited.[105,106] From these reviews, we found 3 randomized controlled trials (RCTs) examining the use of sedative-hypnotics (ramelteon, zolpidem, or eszopiclone) for insomnia among patients with ADHD.[101,102,107]

The 1 study we identified in adults with ADHD (N=36) evaluated the effect of ramelteon in a cross-over study.[107] Included participants had mixed sleep disorders: primary insomnia or a delayed sleep phase type of circadian rhythm sleep disorder (CRSD). The safety profile of ramelteon in patients with ADHD was similar to the general adult population: adverse events (AEs) were mild, with drowsiness being the most frequently reported AE.[107]

The 2 pediatric RCTs evaluated either eszopiclone (N=486) or zolpidem (N=201) versus placebo in children and adolescents with ADHD-related insomnia.[101,102] The most common AEs, occurring more frequently with zolpidem than placebo, were dizziness, headache, and hallucinations.[101] Although most AEs were mild to moderate in severity, 10 participants in the zolpidem arm discontinued treatment due to AEs, most often hallucinations.[101] In the eszopiclone RCT, the most common AEs among eszopiclone-treated participants were headache, dysgeusia, and dizziness, which occurred more frequently in patients in the high-dose group relative to other treatment groups.[102] The severity of most AEs was mild to moderate. Reported AEs during the 12-month open-label study among participants who completed

the placebo-controlled RCT (n=55), as well as participants with no prior exposure to eszopiclone (n=249) were similar to the double-blind period of the 12-week RCT among eszopiclone-treated participants, with the most common AEs for eszopiclone being headache, dysgeusia, and dizziness.[102] Notably, these studies did not break down safety results by stimulant usage (ie, comparing outcomes in patients with versus without stimulant use), so it is uncertain whether there are safety differences dependent upon stimulant usage in patients with ADHD. These 2 pediatric RCTs that studied zolpidem or eszopiclone included a high proportion of patients who were receiving stimulants (>90% and 65.8%, respectively),[101,102] suggesting results may be generalized to stimulant-treated patients with ADHD; whereas, the proportion of adults receiving ramelteon in the adult trial is unclear.[107] Refer to **Section 5.0** for a summary of the efficacy outcomes and limitations of these studies.

We did not identify any FDA drug safety communications (from 2010 to present) or labeled warnings specific to concomitant use of ADHD stimulants with the reviewed sedative-hypnotics. In lieu of such warnings, we reviewed all warnings in general for any patients taking these agents, regardless of concomitant use (see **Section 6.0**). Drug interaction software by Lexidrug reported only 1 interaction between doxepin and methylphenidate- or amphetamine-containing stimulants that requires monitoring for toxicity: doxepin may potentiate amphetamine-associated cardiovascular risks, and concurrent use of doxepin and methylphenidate could result in serotonin syndrome.[132,133] Notably, these potential interactions might be based upon use of higher-dose doxepin, and not the low-dose doxepin used as a sedative-hypnotic. Medications within these drug classes carry potential risks that are applicable to any patient. With respect to black box warnings, all ADHD stimulants carry the risk of abuse, misuse, and addiction; benzodiazepines also carry this risk, in addition to potential risks from concomitant use with opioids (eg, respiratory depression), dependence, and withdrawal reactions with abrupt discontinuation or dosage reduction; and z-drugs carry the potential risk of complex sleep behaviors (eg, sleep driving, sleep walking).[51-60,124-131]

We identified 3,305 Utah Medicaid fee-for-service (FFS) patients with a diagnosis of ADHD and an outpatient pharmacy claim for an ADHD stimulant during the observation period from May 2023 through April 2024. Of these 3,305 patients, about 3% filled a sedative-hypnotic within 30 days after an ADHD stimulant fill (ie, concomitant cohort). Nearly all patients in the concomitant cohort were adults, and zolpidem (of any formulation) was the most common sedative-hypnotic filled during the observation period, based on unique patient counts (see **Table 10**).

To ensure the appropriate use of an ADHD stimulant in combination with a sedative-hypnotic among the Utah Medicaid FFS population, Utah Medicaid may consider performing educational outreach or retrospective drug utilization review to providers of patients who continuously fill prescriptions for both an ADHD stimulant and a sedative-hypnotic so the provider can offer potential modifications to therapy, if appropriate.

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APPENDIX A: LITERATURE SEARCHES

Epistemonikos Search for Systematic Reviews, Conducted May 8, 2024

(title:(insomnia* OR sleep) OR abstract:(insomnia* OR sleep)) AND (title:("attention deficit" OR "attention-deficit" OR hyperkin* OR hyperactiv* OR ADHD OR HKD OR ADDH OR AD/HD OR ADD-H) OR abstract:("attention deficit" OR "attention-deficit" OR hyperkin* OR hyperactiv* OR ADHD OR HKD OR ADDH OR AD/HD OR ADD-H))

- Results limited to within the last 5 years (ie, 2019–2024): **127**

Ovid-Medline Search for Expert Reviews, Conducted May 10, 2024

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <May 09, 2024>

#	Searches	Results
1	*Attention Deficit Disorder with Hyperactivity/ or *"Attention Deficit and Disruptive Behavior Disorders"/	31960
2	*Child Behavior Disorders/ or *Conduct Disorder/ or *Hyperkinesis/	20018
3	((attention* or hyperactiv* or hyperkin*) adj2 (defic* or dysfunc* or disorder*)).ti,kw,kf.	20164
4	(ADDH or ADHD or "AD/HD" or ADD-H or HKD).ti,kw,kf.	17356
5	1 or 2 or 3 or 4	57360
6	"Hypnotics and Sedatives"/ or "Sleep Initiation and Maintenance Disorders"/	48973
7	(insomnia* or sleep*).ti,ab,kw,kf.	261776
8	6 or 7	290478
9	5 and 8	2393
10	"review".pt. or (expert adj2 opinion*).ti,ab. or (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab. or algorithms/	3691775
11	exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or exp treatment guidelines/ or Clinical Decision Rules/	435716
12	(guideline or practice guideline or consensus development conference).pt.	48046
13	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf.	50189
14	(standards or guideline or guidelines).ti,kf. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf. or consensus*.ab. /freq=2	245963

#	Searches	Results
15	(guideline* or standards or consensus* or recommendat*).au.	9
16	10 or 11 or 12 or 13 or 14 or 15	4176414
17	9 and 16	393
18	limit 17 to yr="2019 -Current"	**124**