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GUIDELINE RECOMMENDATIONS REGARDING PHAMACOLOGIC TREATMENT FOR PEDIATRIC INSOMNIA

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ABBREVIATIONS

AACAP, American Academy of Child and Adolescent Psychiatry

AAN, American Academy of Neurology

AAP, American Academy of Pediatrics

AASM, American Academy of Sleep Medicine

ADHD, Attention Deficit Hyperactivity Disorder

ASD, Autism Spectrum Disorder

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)

CADTH, Canada's Drug and Health Technology Agency

CBT, cognitive-behavioral therapy

CPS, Canadian Paediatric Society

FCBHS, Florida Center for Behavior Health Improvement and Solutions

FDA, Food and Drug Administration

ICSD-3, International Classification of Sleep Disorders-3rd edition

PSG, polysomnography

SSRIs, selective serotonin reuptake inhibitors

NICE, National Institute for Health and Care Excellence

NREM, non-REM

RCT, randomized controlled trial

REM, rapid eye movement phase of sleep

TST, total sleep time

1.0 INTRODUCTION

Pediatric insomnia is described by the National Sleep Foundation as "repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age appropriate time and opportunity for sleep and results in some form of daytime functional impairment for the child and/or family."[1] Between 15% to 25% of the pediatric population experiences difficulties initiating or maintaining sleep according to the Canadian Paediatric Society;[2] however, the percentage of these cases requiring clinical intervention for chronic insomnia is unclear. In 2016, sleep medicine experts outlined recommended sleep durations for children that support healthy development, optimal mental and physical health, and benefits to quality of life.[3] Recurrent, insufficient sleep that falls short of the recommended optimal sleep durations is associated with attention difficulties, behavior disturbances, learning problems, and increased risk of accidents, injuries, cardiovascular and metabolic disorders (eg, hypertension, obesity, and diabetes mellitus), poor academic performance, and depression in the pediatric population.[3,4] Moreover, inadequate sleep in teenagers is associated with severe psychologic burden manifesting as higher rates of self-harm, suicidal thoughts, and suicide attempts.[3]

Although non-pharmacological interventions aiming to correct potentially modifiable aggravating or perpetuating factors are usually the first-line approach for the management of insomnia in children, there may be some patients for whom such approaches do not fully resolve ongoing insomnia. Thus, there is a need for pharmacologic interventions to help relieve the burdens and detrimental effects of insomnia.

This report will review clinical practice guidelines that address pharmacologic management of *pediatric insomnia* as a general topic, or insomnia in the context of pediatric Attention Deficit Hyperactivity Disorder (ADHD) or Autism Spectrum Disorder (ASD), which are subpopulations with a high burden of sleep disruption. While there are many other subpopulations with high burdens of insomnia (eg, epilepsy,[5] cerebral palsy,[6] Angelman syndrome Rett syndrome, Williams syndrome, and Smith-Magenis syndrome[7]) versus healthy counterparts, guidelines for insomnia pharmacotherapy in other pediatric subpopulations were not found. This review also provides information regarding recommendations for behavioral treatment relative to the initiation of pharmacotherapy. Sleep inducing drugs may be used in other sleep disorders aside from insomnia, but the scope of this report does not include other distinct conditions that can also occur in pediatric patients (eg, parasomnias, periodic leg movement disorder, restless leg syndrome, REM Behavior Disorder, or Intrinsic Circadian Rhythm Sleep-Wake Disorders such as Delayed Sleep-Wake Phase Disorder, Non-24-Hour Sleep-Wake Rhythm Disorder, and Irregular Sleep-Wake Rhythm Disorder); nor will this report cover the management of obstructive sleep apnea or other sleep-disordered breathing conditions where sleep disruption can also occur.

2.0 METHODS

To identify pertinent clinical guidance statements for the pharmacologic management of pediatric insomnia, websites of the following medical associations were searched (searched in February 2022):

- American Academy of Sleep Medicine: https://aasm.org/clinical-resources/practice-standards/practice-guidelines/
- American Academy of Neurology: https://www.aan.com/Guidelines/Home/Search
- American Academy of Child and Adolescent Psychiatry: https://www.aacap.org/

- The College of Psychiatric and Neurologic Pharmacists list of treatment guidelines for sleep-wake disorders: https://cpnp.org/guideline/external/sleep
- Florida Center for Behavioral Health Improvements and Solutions (FCBHS): https://floridabhcenter.org/

We also searched OvidMedline for clinical guidelines (using a CADTH-derived filter for guidelines)[8] addressing the management of pediatric insomnia. Position statements on the Choosing Wisely website (https://www.choosingwisely.org/clinician-lists/) were searched using the key words, insomnia or sleep. Epistemonikos and the Cochrane Database were searched for recent systematic reviews regarding pharmacotherapy for pediatric insomnia. Other databases that provide citations of medical society clinical guidelines were also searched including ECRI Guidelines Trust (https://guidelines.ecri.org/) and UptoDate. **Appendix A** provides the search strings used in these databases. **Appendix B** provides a list of guidelines and consensus statements that have been incorporated into this review.

3.0 BACKGROUND

There are no FDA-approved therapies for pediatric insomnia that results in negative effects on daytime function and quality of life; although, this does not mean that there is an absence of treatment need. There is growing recognition of insomnia symptoms among pediatric patients, particularly in populations with high burdens of sleep disruption such as those with ADHD, ASD, or epilepsy.[4,5,9-13] Sleep problems are also common among other disorders such as depression, anxiety, bipolar disorder, among others.[14,15,16,17*] In fact, sleep disruption is considered a core symptom of ADHD and is integrated into the diagnosis criteria for depression and anxiety.[18-20] While co-occurring conditions should be considered in the workup of patients with insomnia symptoms, the diagnosis of insomnia can be established and treated supplementary to co-morbidities, particularly when "…insomnia is especially prominent or unexpectedly prolonged, and is the focus of clinical evaluation and treatment."[21]

Sleep-medicine experts have changed the structure of insomnia diagnosis. Diagnosis manuals have moved away from using primary and secondary insomnia classifications because this likely contributed to inadequate treatment— due to the misassumption that treatment of a potential contributing condition is sufficient to resolve the insomnia condition. Authors describe that "Beyond the clearly important management of comorbid disorders such as major depression or chronic pain, treatment approaches to chronic insomnia are essentially the same (ie, cognitivebehavioral and/or pharmacologic), regardless of the presence or type of comorbidity."[21] The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) separates insomnia disorder from other distinct sleep disorders (hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep disorders, non-REM sleep arousal disorders, nightmare disorder, REM sleep behavior disorder, restless legs syndrome, and substance- or medication-induced sleep disorder). Different from DSM-4, the DSM-5 has shifted focus away from potential causal attributions related to comorbidities and acknowledges "…the reality that patients in psychiatric and general medical practice frequently have sleep disorders

* Conditions that commonly present with sleep problems: gastroesophageal reflux disease (GERD), developmental disorders, Down syndrome, Prader-Willi syndrome, Smith-Magenis syndrome, Tourette disorder, nocturnal asthma, atopic dermatitis, depressive disorders, anxiety disorders, mania, neuromuscular disorders, nocturnal seizures, chronic fatigue syndrome, headache disorders, traumatic brain injury, blindness, low serum ferritin, chronic otitis

that warrant an independent clinical condition."[22] Though clinicians should still specify comorbid conditions present that may be contributing, the DSM-5 calls for treating both the comorbid disorder *and* insomnia and acknowledges that there can still be residual and/or underlying insomnia which should be addressed despite the management of other co-occurring conditions.[22]

Similarly, the International Classification of Sleep Disorders-3rd edition (ICSD-3) distinguishes insomnia separate from other sleep disorders (eg, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders[†], parasomnias, sleep-related movement disorders, other sleep disorders).[21] The ICSD-3 describes insomnia disorder as trouble initiating or maintaining sleep, and in children can manifest as resistance toward appropriate bedtime schedules and/or difficulty sleeping without parent or caregiver intervention.[21,23,24] In addition, the patient or caregiver reports that these symptoms are (a) associated with daytime consequences (eg, fatigue, cognitive impairment [inattention, impaired concentration or memory], impaired social, family, or academic performance, mood disturbance/irritability, proneness to errors/accidents/reduced motivation), (b) not attributable to environmental circumstances or inadequate opportunity to sleep, and (c) not better explained by another sleep disorder.[23] Insomnia is classified as chronic by ICSD-3 when symptoms are persistent, occurring at least 3 times a week for at least 3 months. Symptoms that do not meet this threshold are referred to as short-term insomnia. Factors leading to perpetuation of insomnia may include "…anxiety about sleep, maladaptive sleep habits and the possibility of an underlying vulnerability in sleep-regulating mechanisms," or persistence of pain-inflicting disorders.[25] A similar definition for insomnia, first proposed in 2006 by the National Sleep Foundation, specific for the pediatric population is "…repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age appropriate time and opportunity for sleep and results in some form of daytime functional impairment for the child and/or family."[1]

Behavioral-related sleep problems are a common parent-reported complaint of young children where problematic bedtime resistance may be referred to by the parent as "bedtime problems" or "nightwakings." These type of sleep problems have also been referred to as *behavioral insomnia of childhood* and categorized into the following: a) *sleep-onset association type* in which the child requires/demands certain conditions of caregivers (ie, cuddling) before they fall asleep or return to sleep upon midnight waking; and b) *limit-setting type* in which the child stalls or refuses to go to sleep and perpetuated by the caregiver's ineffective limit-setting actions/habits.[2] **Behavioral/educational management** is typically the approach for symptom resolution; however, such strategies have been explored primarily for children <5 years of age.[26,27] Additionally, experts described that ADHD and ASD pediatric populations "…tend to have more severe or chronic sleep problems that may not respond to behavioral interventions alone."[28] Systematic review authors have found moderate-quality evidence supporting behavioral-only interventions (ie, without cognitive therapy) for pediatric insomnia management in young children (ie, 5 years old or younger), and few low-quality studies for school-aged children, adolescents, and special needs groups (ASD and Down syndrome).[29]

[†] Chronic insomnia may be confused with delayed sleep-wake phase disorder (DSWPD) which is a circadian rhythm disorder. In insomnia, the patient has difficulty falling asleep or staying asleep regardless of the desired bedtime, whereas patients with DSWPD can initiate sleep adequately when allowed to go to sleep at their circadian-driven bedtime.[22]

With additional complexity vs. behavioral-only interventions, **cognitive behavioral therapy (CBT)** for insomnia aims to modify cognitive processing/patterns (with mindfulness and relaxation components) in addition to modification of behavioral factors (eg, sleep education/hygiene/routine).[30] Therapy is tailored based on patient-specific challenges considering social, cultural, and maturational factors that impact sleep patterns.[30] Typically, CBT incorporates motivational interviewing techniques facilitated by clinical psychologists. There is variability, however, in the age at which a pediatric patient is capable of undergoing cognitive therapy (may vary between 6 to 9 years old)[31] as they may not be mature enough to engage in challenging and restructuring of thoughts. Moreover, if there are neurological/intellectual deficits, the strategy of modifying cognition may not be as feasible.

Studies on CBT for pediatric insomnia are mainly in adolescent populations, and there is insufficient evidence in many pertinent subpopulations (ie, patients with multiple sclerosis-related insomnia[32], school-aged children with ASD[33], young school-aged children). A 2017 systematic review stated that due to the limited evidence from heterogeneous RCTs with small sample sizes and with risk of bias issues, "...it is not possible to make firm conclusions about the efficacy of adolescent cognitive behavioral sleep interventions."[34] The literature so far serves as positive preliminary evidence suggesting that CBT may help improve sleep duration, onset, and efficiency in adolescents which should be confirmed by high-quality RCTs.[34] Individual circumstances/maturity/cognitive function must be considered to determine whether behavioral intervention or CBT is the best option for a given patient. Authors describe that "If the adolescent suffers solely from a biological predisposition for a severe delayed sleep phase, the application of CBT-I as the first line of treatment is not recommended," perhaps since CBT is not expected to be able to modify the underlying issue.[31]

3.1 Insomnia in ADHD and ASD

Insomnia, difficulty going to sleep, or restless sleep are common symptoms in pediatric patients with ADHD and ASD.[13,19,35] In ADHD, insomnia may occur in patients as a result of the ADHD condition itself,[19,35] (ie, a core symptom of ADHD, such as inability to turn thoughts off at bedtime), a symptom as a result of comorbid disorders (ie, anxiety, ASD, depression, epilepsy, restless leg syndrome, circadian rhythm disorder, mood disorder, etc), a side effect of stimulant medication, a co-morbidity on its own, or a combination of these.[13,19,36] Insomnia as a core symptom can present at the outset of the diagnosis of ADHD while untreated with stimulant medication and can persist as a core symptom even while on ADHD medication. While treatment of ADHD with ADHD medication can improve sleep for some patients, the use of ADHD medication may not completely resolve sleep problems so an adjunctive treatment for insomnia may be needed.[37]

The majority of pediatric patients with ADHD have at least one comorbidity and nearly half have multiple co-morbidities often including anxiety, depression, bipolar disorder, post-traumatic stress disorder, developmental conditions (eg, intellectual disorder, ASD), disruptive behavior disorders, or physical conditions such as sleep apnea or Tourette syndrome. Thus, patients should be screened for suspected comorbid conditions.[19,38-40] Furthermore, some patients may have altered circadian rhythms, which can result in delayed-phase sleep disorder and other types of circadian disorders.[4,39] Guidelines recommend for sleep to be monitored in patients taking ADHD medications and that sleep problems should be screened and regularly addressed in the treatment plan.[36,41]

Disruption in sleep, either as a sleep onset or sleep maintenance problem, is reported to affect 50% to 80% of children with ASD. Adolescents with ASD appear more likely to have shorter sleep durations, daytime sleepiness, and delayed sleep onset, whereas younger children with ASD are likely to have bedtime resistance, parasomnias, and night-waking.[42] The Autism Treatment Network has described that in typically-developing children, the primary cause of insomnia is usually behavioral related; however, in ASD, the root of insomnia is multifactorial as core symptoms of ASD (social deficits and restricted/repetitive behaviors) can influence sleep tendencies and behaviors, and can be compounded by additional psychiatric/neurologic comorbidities, and/or medication-related adverse effects from agents used to treat autism symptoms or comorbidities.[43,44] Comorbidities are common among children with ASD, often including seizures, sleep disturbances, ADHD, and mood disorders. Additionally, about 30% of patients with ASD have intellectual disability.[13] Sleep disturbances *may be a core symptom* of ASD, and/or related to psychiatric comorbidities, neurobiological alterations, genetic mutations, and disrupted sleep architecture.[42] Moreover sleep disturbances can exacerbate problematic daytime behaviors.[42]

The assessment/workup of the sleep disturbance should consider possible environmental factors (eg, household noises, stimulating electronics) and comorbid medical conditions or other sleep disorders that might disrupt sleep (eg, gastroesophageal reflux, obstructive sleep apnea, restless leg syndrome, seizures, asthma, allergies, eczema, or enuresis); and a consistent bedtime routine should be established.[13,45] A report by the American Academy of Pediatrics (AAP) describes that "Restless sleep and night awakenings would suggest a need for laboratory evaluation for ferritin and other indicators of iron sufficiency to determine if low iron stores might be present," as low iron stores may be associated with restless leg syndrome and insomnia.[6,13] The bedtime routine and caregiver response to nighttime awakenings should be reviewed to determine possible behavioral approaches for implementation. The impact of sleep loss on the child's and caregiver's health and daily functioning should be considered when determining the need to start and/or escalate therapy.[46]

3.2 Sleep schedules and assessment

The normal durations of REM and NREM vary with age, but start to transition during adolescent years to align more closely with adult sleep architecture; yet, there can still be considerable individual variability in sleep architecture and what is considered as sufficient restful sleep. During adolescents, puberty onset is associated with later sleep onset and wake times (ie, referred to as phase delay).[47] In adolescent years, an increase in independence and social engagement can influence the tendency to develop sleep debt during the week. Sleeping-in on weekends, in attempt to compensate for sleep debt does not recoup the benefits of regular restful sleep and can contribute to circadian disruption.[47]

Following a systematic review of the literature, experts of the American Academy of Sleep Medicine (AASM) recommended the following sleep durations in a 24 hours period, *on a regular basis*, to support healthy development (learning/behavior), optimal health (both mental and physical), and quality of life:[3]

- for infants 4 to 12 months of age, 12 to 16 hours;
- for children ages 1 to 2 years, 11 to 14 hours;
- for children ages 3 to 5 years, 10 to 13 hours;
- for children ages 6 to 12 years, 9 to 12 hours; and
- for teenagers 13 to 18 years of age, 8 to 10 hours

On a societal level, the American Thoracic Society has recommended that school start times for adolescents should be delayed (eg, shifted from 8:00 to 8:30) "…to align with the physiological circadian propensity of this age group." They also suggest that health care providers and the general public should receive a greater level of education on sleep hygiene to enable more impactful encouragement of healthy sleep habits and prioritization of regular sleep time.[47]

There are many sleep screening questionnaires that can be used to identify, characterize, and assess sleep disturbance in children and adolescents. The 2012 guideline by the Autism Treatment Network lists examples of questionnaire tools[‡].[44] Additionally, the foundation provides a clinical Toolkit for sleep behavioral interventions and tips for good sleep hygiene targeted to the ASD population. In a guidance report for the management of ASD and intellectual developmental disorders by Florida Center for Behavioral Health Improvements and Solutions (FCBHS), the group notes screening options such as the BEARS Sleep Screening Algorithm (for ages 2 to 18 years of age) and the Children's Sleep Habits Questionnaire (appropriate for ages 4 to 12 years of age), in addition to the use of sleep diaries.[48] An example of a sleep diary for children can be found at www.sleepforkids.org/pdf/SleepDiary.pdf (by the National Sleep Foundation). As in adults, no routine laboratory studies are necessary for the evaluation of pediatric chronic insomnia but select tests may be indicated based on clinical suspicion of certain disorders.[49,50]

- **Polysomnography (PSG)**: PSG evaluation is not required for the diagnosis of chronic insomnia.[51-53] It is indicated in certain situations, for example, for suspected parasomnias with atypical features or injury, sleep related epilepsy, sleep apnea, sleep-related movement disorders such as periodic leg movements, if behavioral/pharmacologic treatment fails and/or if the diagnosis is uncertain.[51,52] It is unclear that PSG is helpful in the evaluation of "some primary sleep disorders, such as sleep-related rhythmic disorders and circadian rhythm disorders," nor has it been validated or well-studied in patients with sleep problems related to pain, cancer, juvenile fibromyalgia, depression, trauma, or traumatic, brain injury.[52] However, based on the clinician's judgment such evaluation could be employed in these circumstances.[52]
- **Actigraphy** is used when there is clinical suspicion of irregular sleep–wake schedules or circadian rhythm disorders. A *weak* recommendation is given for use of this tool for assessing quantitative sleep parameters in adults.[23]

[‡] The guideline lists the following examples in their table 2: Children's Sleep Habits Questionnaire (CSHQ), Children's Sleep Habits Questionnaire in Toddlers and Preschool Children, Sleep Disturbance Scale for Children, Family Inventory of Sleep Habits, Behavioral Evaluation of Disorders of Sleep Scale, BEARS (acronym stands for **B**edtime problems, **E**xcessive daytime sleepiness, **A**wakenings during the night, **R**egularity and duration of sleep, **S**noring), and Adolescent Sleep Wake Scale.

4.0 GUIDELINE RECOMMENDATIONS

> *"It is important to treat insomnia because the condition causes decreased quality of life, is associated with impaired functioning in many areas, and leads to increased risk of depression, anxiety and possibly diabetes and cardiovascular disorders"*[9,§]

The **American Academy of Sleep Medicine (AASM)** described that childhood insomnia is often related to poor sleep hygiene practices.[54] Bedtime resistance and nighttime awakenings in infants, toddlers, and preschoolers often involve predisposing, precipitating, and perpetuating factors and involves complex interaction of environmental, biological, and neurodevelopmental factors.[55]

The initial management of pediatric sleep problems should usually begin with educating the parent/child about establishing good sleep hygiene/routines/sleep schedules. Not only should this be employed for younger children,"… behavior interventions are also effective and long-lasting for insomnia in school- or teen-aged children with other medical, psychological, or neurodevelopmental disorders."[54] Similarly, behavioral intervention is recommended as the first approach by other expert organizations including the British Association for Psychopharmacology, the Canadian Paediatric Society (CPS), and the Florida Center for Behavior Health Improvement and Solutions Group (FCBHS).[2,9,53] The CPS proposes **establishing good sleep hygiene behaviors** consisting of the following:[2,56]

- Consistent routine of regular bedtime and morning wake time
- Age-appropriate number of hours in bed
- Dark and quiet sleep space
- Avoiding hunger, eating, caffeine and nicotine prior to bedtime
- Employing relaxation techniques before bed (eg, including reading)
- Avoidance of television, computers and video games 1 hour before bedtime

The Canadian guideline describes that the limit-setting type of behavioral insomnia frequently responds to optimization of sleep hygiene; whereas the sleep-onset association type of behavioral insomnia may require additional behavioral interventions.[2] Guidelines highlight that behavioral therapies such as unmodified, graduated extinction; positive routines; and bedtime fading are generally appropriate for children aged ≤5 years;[4,55] whereas older children and adolescents may respond to cognitive-behavioral therapy (CBT) which is mostly adapted from the approach established in adults.[4]

- Cognitive behavior therapy (CBT) "…involves elements of sleep restriction, stimulus control, sleep hygiene education, and cognitive therapy and may include relaxation techniques."[47] Yet, in 2015 the American Thoracic Society described that providers trained in CBT are scarce and insurance coverage for such service is limited; thus, in the real-world, this treatment is probably inaccessible for many.[47]
- Unmodified extinction is where parents set a bedtime and wake-up time and ignore protest behavior that occurs after the bedtime and before the wake-up time. In graduated extinction, parents ignore bedtime resistance for specified periods and then respond without reinforcing the resistant behavior (eg, brief verbal reassurance). The objective is to reduce/eliminate parental attention that reinforces the bedtime protest (crying/screaming) of the child.[55]

§ This statement by the British Association for Psychopharmacology is graded as a category A recommendations, which means that it is directly based on category I evidence [eg, randomized controlled trial(s)]

- Positive routines: parents develop and strictly adhere to regular pre-bed relaxation rituals (eg, enjoyable calming activities) to establish a positive behavior/habits to foster sleep onset. [55]
- Bedtime fading: parents put their child to bed close to the time the child begins to fall asleep[55]

Nonetheless authors acknowledge some cases will have an insufficient response or be refractory to this approach and may benefit from pharmacological treatment.[39] According to AASM, educational and behavior interventions may not fully attenuate sleep problems, particularly in some children with considerable developmental delays, cognitive impairment, or other medical/psychiatric disorders. Such patients not responding to behavioral or educational interventions may benefit from judicious use of sleep-promoting medications (ie, with close monitoring for efficacy and side effects).[54]

Melatonin is generally the first-line *agent* recommended across the board for children with insomnia, including those with intellectual disorders, ASD, or ADHD-related insomnia.[2,9,53] The FCBHS includes **clonidine** and **diphenhydramine** as secondary treatment options for pediatric insomnia, despite that evidence is very limited for diphenhydramine (see section 5.4) and observational-based for clonidine (see section 5.2). The FCBHS guidance places remaining off-label drugs (eg, z-drug hypnotics, orexin inhibitors, antidepressants, benzodiazepines, ramelteon) into a 'not recommended' category that we interpret as not recommended for routine use or for the majority of patients. Furthermore, the FCBHS recommends that if a sleep medication is administered, it should be used cautiously, on a short-term basis, and patients should be monitored for side effects.[48,53] A 2017 Spanish consensus statement advised that clonidine and other non-routine use agents (eg, zolpidem, benzodiazepines) should only be used for pediatric insomnia "…following a thorough evaluation by a specialised unit;" whereas the group recommends melatonin (first-line) and first generation antihistamines (diphenhydramine or hydroxyzine) at the primary-care level.[6]

Table 1 summarizes recommendations from the FCBHS for the treatment of insomnia disorder which are provided in a step-wise approach (ie, Level 1 of therapy, Level 2 of therapy, etc). The group has an additional guideline for the ASD or intellectual disability subpopulations, as further described in the following section (4.1) and in Table 2. Noteworthy differences in the step-wise approaches for insomnia between the 2 guidelines is that the latter guideline for ASD or intellectual disability does not list diphenhydramine an option, and it includes a Level 4 step, which is not represented in the general population guideline. Level 4 incorporates/recommends a specialist consultation (eg, pediatric sleep specialist, child and adolescent psychiatrist, pediatric neurologist, or developmental pediatrician), especially if trials of melatonin (Level 2) or clonidine (Level 3) are unsuccessful. However, it is not delineated whether the group supports the specialist's clinical decision-making regarding off-label prescribing of insomnia medications on a case-by-case basis, beyond the medications (melatonin, clonidine) recommended as options for use by general prescribers.

Table 1. Recommendations from the Florida Center for Behavior Health Improvement and Solutions

2018, Insomnia Disorder Medication Guidelines for Children and Adolescents[53]

- Comprehensive assessment of pediatric patients with sleep complaints includes the following: assessment of sleep practices (eg, electronic or caffeine uses, daytime napping); primary sleep disorders (eg, obstructive sleep apnea, restless leg syndrome, circadian rhythm disorders); medical, psychiatric, and neurodevelopmental co-morbidities; concomitant medications; caregiver role, presentation (sleep onset or maintenance problem).
- The BEARS sleep screening algorithm can be used to screen for major sleep disorders in patients 2-18 years.

Treatment Approach

Level 1: Psychosocial/non-pharmacologic interventions

- Educate patient/caregiver about sleep regulation, appropriate and healthy sleep practices
- Behavioral Interventions
  - Healthy sleep practices: implementing regular sleep schedule and bedtime routine, stimulus control, avoidance of electronic devices/caffeine, age-appropriate napping, sleep restriction
  - Caregiver-based, behavioral education/therapy for younger children: sleep training, bedtime fading, bedtime pass
  - Cognitive behavioral therapy for insomnia for older children and adolescents, plus stimulus control and sleep restriction

Level 2: Melatonin

- Melatonin (pharmaceutical grade preferred, if available), 30 to 60 minutes prior to the desired bedtime.
  - For children 2 years and older, start at 0.5 to 1 mg nightly and may titrate to 3mg if needed
  - For adolescents, start at 1 to 3 mg nightly and may titrate to 9-10mg if needed

Level 3: Pharmacotherapy

- Pharmacotherapy should only be considered for short-term use
- Pharmacotherapy *with* behavioral treatment may be appropriate for (a) short-term crisis intervention, (b) insomnia with comorbid high risk psychiatric or neurodevelopmental conditions, or (c) insomnia that exacerbates psychiatric and/or medical conditions.
- Recommend clonidine 0.05–0.3 mg nightly
  - "Evidence exists supporting the use of clonidine in certain clinical populations with comorbid insomnia (neurodevelopmental disorders and ADHD)."
- Diphenhydramine: 12.5–50 mg nightly, can be considered for short-term situational or occasional use in younger children, especially those with comorbid atopic disease.

Level 4

- Apply appropriate psychotropic medications for patients with psychiatric comorbidities

Not Recommended

- The panel *recommends against* medication as the first or sole treatment strategy; or the use of a sedating psychotropic medication in the absence of another psychiatric disorder.
- There is insufficient evidence, experience, and/or unacceptable risk/benefit profile to warrant a recommendation for use of other insomnia agents (eg amitriptyline, benzodiazepines, doxepin, doxylamine, eszopiclone, ramelteon, suvorexant, zolpidem). The format of the authors' table infers that these medications are generally not recommended.

4.1 Recommendations for insomnia management in the context of ASD

A 2020 guideline has been published by the American Academy of Neurology (AAN) specific for the ASD population.** Overall, there was minimal evidence found to guide the treatment of insomnia or disrupted sleep in ASD. The guideline recommends for clinicians to ensure potential contributing co-morbid conditions have been addressed, and that consideration is made for modification of medications among the patient's regimen that may affect sleep where possible. Despite the lack of robust evidence for parental education and behavioral therapy for sleep problems in ASD, the recommended first-line approach is the implementation of behavioral interventions (eg, CBT, education, sleep training) either as monotherapy or added concomitantly to insomnia medication (pharmaceuticals or nutraceuticals), depending on individual circumstances. This recommendation is similar to an earlier 2011 practice pathway published by the Autism Treatment Network where authors advise that behavioral treatment is first-line, but "…if an educational (behavioral) approach does not seem feasible, or the intensity of symptoms has reached a crisis point, the use of pharmacologic treatment is considered."[57] The AAN described that "Core or co-occurring ASD symptoms such as intellectual disability, sensory integration deficits, ritualistic or self-injurious behaviors, poor communication skills, and limited responsiveness to social cues can interfere with sleep training and exacerbate or prolong sleep problems."[4] Thus, additional approaches such as pharmacotherapy may be necessary.

Regarding specific pharmacotherapy, the 2020 AAN guideline recommends offering melatonin if behavioral strategies are insufficient, as there is RCT supportive evidence for melatonin in patients who were non-responders to behavioral therapy. Following evidence synthesis, authors concluded that **melatonin alone** is *probably effective* for improving bedtime resistance, sleep onset latency, sleep continuity, and total sleep time; while **CBT alone** was concluded as *possibly effective* (with less confidence in effect versus a rating of *probably effective*) for sleep attributes of latency, continuity, and total sleep time. The combination of **melatonin+CBT**, is concluded as *probably effective* for these sleep attributes. Providing a parent educational pamphlet about how to foster good sleep hygiene was rated as *possibly effective* only for sleep continuity, and there is otherwise insufficient evidence or evidence of no benefit for other outcomes.[4] A peer review of the ANN guideline by the American Academy of Sleep Medicine notes a limitation of this guideline is that that it lacks guidance for managing real-world "sleep crises" (ie, severe sleeplessness disruption that affects child and family functioning) which typically can occur in children with greater ASD disabilities/symptoms—especially with psychiatric comorbidities present— and where additional therapy options to promote sleep may be needed.[58]

Several other expert groups also recommend considering melatonin as the first-line pharmacotherapy for improving sleep in children with ASD such as the American Academy of Pediatrics, a British expert group, and the FCBHS.[9,13,48] If melatonin is insufficient, clonidine is recommended by the FCBHS (and mentioned as an option by other guidelines[13], especially for those with co-morbid ADHD[56]).

If patients fail or are inappropriate for melatonin or clonidine, the FCBHS recommends a specialist consultation (eg, pediatric sleep specialist, child and adolescent psychiatrist, pediatric neurologist, or

** The guideline contains a disclaimer, which among the statements includes that the information it is not meant to be used to make mandates of any particular course of medical care, should not be used as a substitute for independent professional judgement on the patient-specific factors -- as the information does not account for all patient specific scenarios or individual variation among patients.

developmental pediatrician). Yet, it is unclear which medications the group views as acceptable if prescribed by a specialist. Overall, the group appears to support pharmacotherapy when symptoms result in significant daytime impairments in child and/or caregiver functioning and if behavioral interventions alone are insufficient or are unable to be implemented; and *recommends against* pharmacotherapy as the initial or sole treatment strategy, or the use of a sedating psychotropic medication in the absence of other psychiatric disorders.[48] **Table 2** includes guideline recommendations for the management of sleep problems in the ASD population.

Table 2. Recommendations for Insomnia Management in Autism Spectrum Disorder

2020, American Academy of Neurology Recommendations for the Management of Insomnia and Sleep Disrupted Sleep Behavior in Pediatric Patients with Autism Spectrum Disorder[4]
• Assess for coexisting conditions and concomitant medications that possibly may be contributing to sleep disturbance (Level B). o Patients should receive appropriate treatment for their coexisting condition(s) and medications that are potentially contributing to sleep problems should be assessed to determine whether they can be stopped or adjusted • Parents/guardians should be counseled regarding strategies for improved sleep habits, with **behavioral strategies** as a first-line treatment approach *either alone or in combination with pharmacologic or nutraceutical approaches*, depending on individual circumstances. o Certain strategies suggested include unmodified extinction, graduated extinction, positive routines, or bedtime fading; although, authors acknowledge that there is not robust evidence for these approaches in patients with ASD. o Cognitive behavioral therapy • Clinicians *should* offer **melatonin** to children and adolescents with ASD with sleep disturbances or dysregulation if behavioral strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed; a high-purity pharmaceutical grade of melatonin should be used when available ▪ Initiate melatonin at a low dose (1–3 mg/d), 30–60 minutes before bedtime, and titrate to effect, not exceeding 10 mg/d ▪ Council patient (as appropriate) and their parents regarding potential adverse events and the lack of long-term safety data • There is no supportive evidence for the routine use of weighted blankets or specialized mattress technology for improving disrupted sleep; however no serious adverse events are associated with this approach • All recommendations expressed in the bullets above are graded Level B which uses the verb 'should' but "…the requirements are less stringent but are still associated with confidence in the rationale and a favorable benefit–risk profile." • As part of the disclaimer of this publication, authors state that their work "…should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care"
2020 American Academy of Pediatrics, Clinical Report[13]
o Disordered sleep is associated with challenging daytime behaviors in children with ASD; addressing one may help with the other. o Empirical support exists for the effectiveness of parent education and behavioral interventions for children with ASD and sleep disturbances. ▪ Behavior interventions aim to establish bedtime routines and expectations that the child sleeps in their own bed. o No medication is currently approved by the US Food and Drug Administration for the treatment of insomnia in children with or without ASD.

- For sleep onset issue, consider **melatonin** at doses from 1 to 6 mg; for sleep maintenance problem consider long-acting melatonin if available.
  - Adverse effects are uncommon but may include nightmares.
- Any medication tried for sleep problems should be started at a low dose and monitored for adverse effects.
  - Agents such as clonidine and diphenhydramine have been used for sleep onset problems or night-waking in children, but supportive evidence is very limited.

2019 Florida Center for Behavior Health Improvement and Solutions: Sleep Disturbance in the Context of ASD and Intellectual Disability[48]

- Comprehensive assessment of pediatric patients with sleep complaints includes the following: assessment of sleep hygiene/practices (eg, electronic use, lack of regular routines, napping); primary sleep disorders (eg, OSA, restless leg syndrome, circadian rhythm disorders); medical disorders (eg, sleep apnea, night terrors, seizures, pain, low serum ferritin); psychiatric disorders (eg, anxiety); neurodevelopmental co-morbidities; concomitant medications (eg, stimulants, SSRIs); caregiver role, presentation (sleep onset or maintenance problem).
- Consider comorbid chronic sleep loss and primary sleep disorders as potential contributors to psychiatric symptoms.
- Sleep screening tools mentioned in the guideline are the BEARS sleep screening algorithm for patients 2-18 years, and the Children's Sleep Habits Questionnaire (CSHQ) for ages 4 to 12 years, along with sleep diaries

Treatment Approach

Level 1: Psychosocial/non-pharmacological intervention and treatment of comorbidities

- Educate patient/caregiver about sleep regulation, appropriate and healthy sleep practices. The panel refers to the Sleep toolkit resource of Autism Speaks Autism Treatment Network (ATN)
- Behavioral Interventions: despite limited evidence for effectiveness of behavioral interventions in this population, it is recommended that caregivers/providers develop a sleep plan that incorporates behavioral intervention such as the following:
  - Graduated extinction, which focuses on eliminating caregiver reinforcement of inappropriate bedtime behavior and promoting positive reinforcement of adaptive sleep behavior
  - Sleep training, bedtime fading, bedtime pass, and nightlight
  - Stimulus control, sleep restriction
- Caregiver-based, behavioral education/therapy for younger children
- Healthy sleep practices: regular sleep schedule, avoid nighttime screens, limit caffeine, age appropriate napping
- Treat psychiatric comorbidities with appropriate psychotropic medications

Level 2: Melatonin

- Melatonin (pharmaceutical grade preferred, if available), up to 2 hours prior to bedtime
  - Initiate at 0.5 to 1 mg nightly and may titrate to 3mg in children or 10 mg in adolescents if needed; there is no data for melatonin use in children under 2 years of age.
  - Variable responses may occur due to lack of uniformity in manufacture of over-the-counter (OTC) products
  - Better response is generally expected if melatonin treatment is combined with behavioral interventions; and melatonin is noted as most helpful for sleep onset

Level 3: Clonidine

- Pharmacotherapy should only be considered for <u>short-term use</u> if:
  - Symptoms result in significant daytime impairments in child and/or caregiver functioning
  - If behavioral interventions alone are insufficient or are unable to be implemented

- Pharmacotherapy *with* behavioral treatment may be appropriate for (a) short-term crisis intervention, (b) insomnia with comorbid high risk psychiatric or neurodevelopmental conditions (eg, ADHD, MDD, or ASD), or (c) insomnia that exacerbates psychiatric and/or medical conditions.
- Recommend **clonidine** 0.05–0.3 mg at bedtime: begin at 0.05mg to 0.1mg and if no response after 1 week, may titrate upward by 0.05mg-0.1mg increments as tolerated to response, up to a maximum of 0.3mg per night.
  - Clonidine is most helpful for sleep onset problems and may not help sleep maintenance; patients may develop tolerance and nocturnal awakenings
  - Monitor blood pressure and heart rate; avoid abrupt discontinuation

Level 4: Specialist Consultation

- Consult with a specialist (pediatric sleep specialist, child and adolescent psychiatrist, pediatric neurologist, or developmental pediatrician)

The panel ***recommends against*** medication as the first or sole treatment strategy; or the use of a sedating psychotropic medication in the absence of other psychiatric disorder. No recommendation for use of other insomnia agents (eg amitriptyline, benzodiazepines, doxepin, doxylamine, eszopiclone, ramelteon, suvorexant, zolpidem) is provided since the authors found insufficient clinical pediatric use or experience/evidence, and/or unacceptable risk/benefit ratios. Note that diphenhydramine is not included or recommended in this guideline, unlike their guideline for general pediatric insomnia.

2019 Canadian Paediatric Society, Guidance Report[56]

Sleep disturbances

- Counsel caregiver to improve sleep hygiene and reinforce behavioral techniques (possibly in collaboration with a behavioral therapist, and possibly combined with melatonin therapy).
  - Avoid screen devices 1 hour before bedtime
- **Melatonin**, when combined with appropriate sleep hygiene and behavioral modification strategies, appears to be effective in reducing sleep onset times and increasing sleep duration, but may not reduce nocturnal or early waking
  - Side effects may include difficulty waking, daytime sleepiness, or enuresis.

Possible comorbidities and typical pharmacotherapies that may be considered

- Irritability and aggression in children with ASD (5 years of age and older): risperidone or aripiprazole
- Anxiety: SSRIs such as fluoxetine or sertraline
- ADHD: methylphenidate or another stimulant medication. Atomoxetine or alpha-2 adrenergic receptor agonists (eg, clonidine or long-acting guanfacine) are alternatives, when combined with parent training in ADHD behavioral management
- Depression: antidepressants, typically SSRIs

2012 Practice Pathway by the Autism Treatment Network (ATN) for the Identification, Evaluation, and Management of Insomnia in Children and Adolescents With Autism Spectrum Disorders[44]

Background Information about the publication

- Best practices, **based on expert consensus**, for overarching approach to insomnia. This is a collaborative work of the ATN in association with the National Initiative for Children's Healthcare Quality (NICHQ)
- The pathway was published following implementation/testing at 4 ATN sites and was consolidated following a systematic literature review and grading of evidence based on studies in children with neurodevelopmental disabilities.
- "The pathway is not intended to serve as the sole source of guidance in the evaluation of insomnia in children who have ASD or to replace clinical judgment, and it may not provide the only appropriate approach to this challenge."

Main practice points

A. All children with ASD should be screened for insomnia
B. The evaluation of insomnia should include attention to medical contributors that can affect sleep (including neurologic conditions and other sleep disorders that contribute to insomnia).
C. Educational/behavioral interventions are the *first line*, after excluding medical contributors (based on preliminary data or inference from data in typically developing children). However, if an educational (behavioral) approach does not seem feasible, or the intensity of symptoms has reached a crisis point, the use of pharmacologic treatment is considered.
    - Examples of behavioral treatments commonly used are modification strategies (eg, extinction of inappropriate bedtime behaviors, positive reinforcement of adaptive sleep behavior) which are often paired with sleep hygiene instructions. Although behavioral interventions are effective in typically developing children, there is limited evidence (eg, 2 small non-controlled studies) in the ASD population.
    - Alternative therapy: massage and aromatherapy have been studied, however, the graded studies did not lead to statistically significant improvements in sleep
    - Pharmacologic treatments: there is limited evidence on medications for insomnia management in this population; however the most evidence exists for the use of **melatonin**. Benefits have been shown in several small randomized controlled trials (RCTs), and a positive safety profile is suggested by these RCTs and other case-series; though larger studies would be helpful to confirm the benefits/risk of melatonin.
        - "Other pharmacologic interventions such as risperidone, secretin, L-carnitine, niaprazine, mirtazapine, and clonidine, as well as multivitamins and iron, have limited evidence supporting their use in treating insomnia in ASD."
D. Providers should ensure timely follow-up and monitor progress/resolution of insomnia

Checklist for carrying out the practice pathway

Assessment
- New Patients: 1) sleep questionnaires should be used such as the Children's Sleep Habits Questionnaire; the guideline provides a list of example questionnaire that can be used; 2) assess parent/provider concerns; 3) assess for medical contributors if needed; 4) assess family willingness to use the Sleep Toolkit
- Follow-up: 1) employ the Children's Sleep Habits Questionnaire; 2) ask family whether insomnia has resolved; 3) assess the use of the Sleep Toolkit

Treatment
- New Patients: 1) treat medical contributors and consult or refer if needed; 2) counsel family; 3) discuss healthy sleep habits and consider sleep medications
- Follow-up: 1) consider sleep medications and medication management; 2) re-introduce Sleep Toolkit; 3) have discussion with parents

Follow up
- New Patients: arrange timely follow-up
- Follow-up: arrange follow-up where needed **and refer patients with unresolved insomnia to a sleep specialist**

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor

4.2 Recommendations for insomnia management in the context of ADHD

Guidelines on the management of ADHD address insomnia briefly, and generally according to the following themes: (a) insomnia as a core symptom of ADHD with breakthrough symptoms due to ADHD medication wearing-off too early, (b) insomnia as a result of an arousal side effect of the medication lasting too long into the bedtime, or (c) insomnia as symptom manifestation of unmanaged co-morbidity. However, we must also consider that insomnia can be diagnosed and treated on its own if other conditions are managed to the best of their ability, as experts acknowledge that insomnia symptoms can still persist despite treatment of ADHD or other potentially contributing disorders.[37] The underlying root of insomnia can be very different and multifaceted in each person, so the approach must be individualized. Ultimately, the treatment of sleep problems can help improve ADHD as well.[19]

Even in the context of ADHD, the management of sleep problems should incorporate promotion of positive and consistent sleep hygiene practices and routines,[19,39] as there is some evidence in pediatric patients with ADHD showing that promotion of good sleep hygiene and behavioral sleep management plans are helpful for managing ADHD-related sleep problems.[19,59] Pharmacologic approaches such as adding melatonin and/or incorporating clonidine into the medication regimen may be considered if behavioral interventions alone are insufficient,[19] and after considering the influence of other possible factors discussed below.

4.2.1 Wearing-off effect

A wearing-off effect of ADHD medication should be considered especially if negative symptoms (ie, rebound ADHD symptoms that may include insomnia) are experienced at the time when the ADHD medication would be expected to wear off based on the mediation's expected duration of action.[19] In other words, insomnia symptoms can be due to the ADHD-medication effect wearing off too soon, causing breakthrough core ADHD symptoms such as sleep problems. Long acting or extended release ADHD stimulants vary in duration of action, and can be as short as 6 hours for certain products (eg, Metadate CD, Ritalin LA) typically dosed once daily in the morning.[60] Thus, if there is a suspected wearing-off effect, practitioners may try tailoring the dose and/or timing of medication, or switch to a different formulation with a longer duration of action. Additionally, a short-acting, add-on medication can be used in the afternoon. For example, if a patient is experiencing a wearing off effect while on a long-acting stimulant taken once daily *in the morning*, the dose could be divided and taken 30 minutes apart to make the effect last longer; **or** a lower dose of a short-acting ADHD medication can be overlapped at the tail end of the effect from the long-acting stimulant.[19] Combination treatment including adding "…an ADHD agent with a different mechanism, a short acting ADHD agent to cover uncovered portions of the day, or an agent to address concurrent mood, sleep, or anxiety disorders" may be employed to address patient-specific symptoms or co-occurring disorders as described by the Canadian guideline.[19] The British Association for Psychopharmacology guideline for ADHD management also recognizes the strategy of dose tailoring, using a short-acting medication when the extended release agent is wearing off.[61]

4.2.2 Side-effect from ADHD stimulant medication

Some patients may experience an arousal effect from the stimulant lasting into bedtime and thus causing insomnia. If the duration of action is expected to be lasting too long, initiating the medication as

early as possible in the morning or using a shorter-acting formulation can be considered.[19] Other regimen modifications such as reducing the last dose of the day or switching to shorter-acting formulation for the P.M. dose can also be considered.

Atomoxetine is known to have a less negative impact on sleep compared to traditional stimulants, and can be helpful for patients with co-occurring ADHD and anxiety or tics if the impact from stimulants are difficult to manage.[19,62] Atomoxetine has also been found to significantly induce somnolence as a side effect.[63] The European ADHD Guidelines Group notes that atomoxetine can be given in the evening as a potential substitute for the patient's stimulant medication (or P.M. dose) to manage sleep-onset delay that the provider suspects to be caused by stimulant medication, especially when attempts to modify the stimulant regimen have been tried (alternative formulation, dose, and/or timing).[62] The NICE guideline for ADHD treatment recommends consideration of atomoxetine or guanfacine in patients 5 years and older who cannot tolerate side effects of first-line or second-line ADHD agents, methylphenidate and lisdexamfetamine, respectively.[64]

- Atomoxetine must be used with caution or avoided in (a) combination with oral or intravenous beta-2 agonists, (b) in CYP2D6 poor metabolizers, or (c) patients with peripheral vasculopathy including Raynaud's phenomenon. Patients should be monitored for possible side effects including priapism, urinary retention, liver injury, blunting of growth, and peripheral vasculopathy.[19]

Clonidine has a sedating side-effect[63] that can also be advantageously used to manage insomnia. Clonidine is approved, as the extended release tablet, for the treatment of ADHD as monotherapy or adjunctive to stimulants, but is considered a third-line agent for the treatment of ADHD.[19] This is because supportive evidence for the efficacy of ADHD-symptom management is strongest for stimulant medications, and stronger for atomoxetine and guanfacine compared to clonidine.[40] However in the context of sleep-disturbance, the FCBHS recommends clonidine as a pharmacologic option for the management of sleep disturbances, but secondarily to melatonin and implementation of behavioral interventions.[48,53] The Canadian guideline recommends for clonidine to be used in the context of a psychiatry specialist.[19]

The American Academy of Child and Adolescent Psychiatry (2007) described that after trials of various stimulants, if one particular stimulant is more efficacious for a patient's ADHD symptoms yet produces a troublesome side effect, an adjunctive pharmacotherapy can be considered. Authors further describe that "Low doses of clonidine, trazodone, or an antihistamine are often helpful for stimulant-induced insomnia;" however, this may be based on expert opinion since no citations of studies or evaluation of evidence is provided with this comment in the guideline.[65]

Table 3 consolidates recommendations by the European ADHD Guidelines Group with further elaborations for the management of sleep problems in the context of ADHD medication side effects.

Table 3. Guidance on the Management of Adverse Effects of ADHD Medications

2013 Update of the European ADHD Guidelines Group (EAGG) 2011 Guideline on Management of ADHD Medication Side Effects[62]

- Updated literature through June 2012
- The precise nature/strength of the association of sleep disturbances with stimulant medication need to be established: "There is no extensive evidence for differential effects on sleep of different classes or formulations."
- Patients with ADHD should be screened for possible sleep disturbances using clinical interview, or sleep questionnaires and sleep diaries prior to initiation of pharmacological treatment and at each follow-up visit.

The management of sleep problems during treatment with ADHD drugs should include*:

(i) Monitoring

- Sleep problems should be screened for prior to starting ADHD medications so that providers can recognize when sleep problems are an ADHD symptom, and in order to "….avoid ascribing sleep disturbance to medication when, in fact, it is due to ADHD per se."
- Inquiry of sleep problems should occur during the baseline and at follow-up visits assessing bedtime resistance, sleep-onset difficulty, night awakenings, difficulty with morning awakenings, sleep-breathing disorder and daytime sleepiness.
- If possible use of sleep questionnaires are encouraged such as the Children's Sleep Habits Questionnaire (CHSQ) and sleep diaries
- Since ADHD and restless legs syndrome (RLS) may be associated with one another, authors recommend to screen for RLS using the Allen et al, 2003
- Polysomnography is indicated upon suspicion of a sleep-breathing disorder, episodic nocturnal phenomena, limb movements and unexplained excessive daytime sleepiness

(ii) Consider if it is possible to stop the ADHD medication

(iii) Implement sleep hygiene; for example:

- Stimulus control (dim light prior to bedtime, bed used for sleep only, avoid TV, screens or bright light when close to bedtime, avoid eating near or at bedtime, avoid use of telephones, radios, music once in bed)
- adjusting bed time to the estimated sleep onset
- avoidance of caffeine
- allow child to get up for a short period of time if unable to sleep
- avoid co-sleeping

(iv) If behavioral measures are insufficient and it is not convenient or appropriate to stop ADHD medication, review and treat possible causes of sleep problems:

(a) screen for restless leg syndrome, periodic leg movements of sleep, and iron deficiency

(b) If there is a wearing-off effect of the stimulant: add small doses of short-acting psychostimulants in the evening

(c) If the likely cause is persistent stimulant action, consider reducing the P.M. dose, using an alternative class or formulation, or employing **atomoxetine** for cases of sleep-onset delay. Authors describe that atomoxetine is more commonly reported to have somnolence as a side-effect rather than insomnia; thus, this medication can be given in the evening as a potential substitute for the patient's stimulant medication (or PM dose).

(v) Consider adding **melatonin**

Information in the text implies that melatonin can be used to help manage possible stimulant side effects or for sleep problems that are a core ADHD symptom. Authors explain that melatonin may be considered in scenarios when patients/practitioners/families who do not want to change the medication class or agent.

Table 3. Guidance on the Management of Adverse Effects of ADHD Medications

- **Clonidine**: authors describe that observational and limited RCT evidence of clonidine used as monotherapy or in combination with methylphenidate for the treatment of ADHD was associated with significantly more somnolence than placebo. Thus, clonidine has been used to attempt to improve sleep onset issues in ADHD; however; no RCTs have been designed to assess whether clonidine improves sleep latency in the context of psychostimulant-induced insomnia. The guideline authors do not provide a recommendation for clonidine other than that it may be used to manage tics in ADHD patients after other dose adjustment measures have failed (based on expert opinion).
- No other sedating medications are mentioned (eg, diphenhydramine, zolpidem)

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; EAGG, European ADHD Guidelines Group; RCT, randomized controlled trial; RSL, restless legs syndrome

Notes

**The recommendation for add-on melatonin or switch to atomoxetine for the management of sleep-onset delay are both Grade A (ie, based on well conducted meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias); the remainder recommendations are per expert opinion*

4.2.3 Possible co-morbid conditions that can manifest with sleep disruption

Since sleep disruption can be related to **co-occurring anxiety**, the 2018 Canadian Guideline on ADHD management points out that "a general rule of thumb is to treat the most impairing condition first."[19] However, the effect from stimulants should also be considered. Stimulants can increase anxiety, particularly at their initiation or up-titration; so, slower titration schedules should be considered (or dose reductions) with co-occurring anxiety. Atomoxetine, which is known to have less negative effect on sleep compared to ADHD stimulants, may be helpful for patients with co-occurring ADHD and anxiety if the impact from stimulants on anxiety are difficult to manage.[19,36]

Co-occurring depression can manifest with sleep-onset disruption or restlessness.[19] As previously mentioned, it is recommended for the most impairing condition to be addressed first, followed by additive therapy for the next condition if needed. However, if the depressive symptom is due to bipolar disorder, treatment should follow clinical recommendations for bipolar management. Otherwise, antidepressants (eg, bupropion, selective serotonin reuptake inhibitor [SSRIs]) may be used in combination with stimulants to manage major depressive disorder with ADHD. However, close monitoring and if required, dose adjustments, must be considered regarding possible drug interactions involving fluoxetine or paroxetine (CYP2D6 inhibitors) when combined with the amphetamine-based stimulants or atomoxetine (CYP2D6 substrates).[19]

It should also be considered that SSRIs (particularly sertraline and fluoxetine) may precipitate sleep disturbances by suppression of REM sleep or secondary to motor restlessness (eg, akathisia) or agitation side effects.[66,46,67] Akathisia can be managed with a beta-blocker or benzodiazepine.[68] Several guidelines on the management of depression, including one for pediatric patients, have noted the therapeutic utility of trazodone and mirtazapine for depression with insomnia, due to their sedation side effect.[16,69] The 2007 American Academy of Child and Adolescent Psychiatry guideline for the management of pediatric depression stated that these two agents, trazodone and mirtazapine, are "…mainly used as adjunctive and transient treatments for insomnia."[69]

5.0 RECOMMENDATIONS FOR USE, SYSTEMATIC REVIEW, AND SAFETY INFORMATION CONSOLIDATED BY MEDICATION

Agents may be used off-label to fill the treatment gap in pediatric insomnia for which there are no FDA approved prescription medications. As background information, **Appendix C** summarizes the indication for each non-benzodiazepine, non-barbiturate hypnotic approved for adult insomnia. Indications vary according to the insomnia problem (ie, sleep initiation versus maintenance issue) and are specific to the drug formulation. The following sections summarize information (eg, guideline recommendations, efficacy and safety information from systematic reviews) for the following select medications or drug classes: melatonin, alpha-2 receptor agonists (clonidine and guanfacine), z-drugs (zolpidem and eszopiclone), and antihistamines. A consistent theme among guidelines and expert position statements is the support for melatonin to be considered as an option for pediatric sleep disturbances especially when behavioral interventions are not sufficient on their own.

Per guidance from an expert of pediatric psychiatry and sleep medicine, regarding the duration of pharmacotherapy, "…the goal of limiting drug exposure should be balanced by ensuring adequate duration of therapy to allow behavioral interventions to be successfully implemented."[46] Abrupt discontinuation of sleep medication should be avoided, otherwise this can result in "rebound insomnia" or other sleep problems.[46]

5.1 Melatonin

A. Recommendations for Use

Two expert consensus statements focused on the role of melatonin for use in pediatric sleep disorders: one published in 2018 by the Canadian Peadiatric Society and another, in 2015, by international experts in pediatric neurology or psychiatry. Recommendations provided for melatonin were as follows:

- The Canadian Peadiatric Society considered melatonin to be safe and effective for sleep disorders in children and adolescents, but should usually be considered after sleep hygiene intervention.[2]
- The international expert consensus statement expressed that melatonin should be considered for children with sleep onset problems or difficulty waking up in the morning at conventional times.[70]

Other clinical guidelines or guidance statements, previously mentioned in earlier sections of this report, supporting consideration of melatonin for pediatric insomnia are listed as follows:

- For pediatric insomnia in general, the FCBHS recommends melatonin as an initial medication option prior to the trial of diphenhydramine or prescription pharmacotherapies, but only after behavioral/education interventions have been implemented.[53]
- Guidelines for the management of pediatric ADHD: The 2013 European guideline recommended that melatonin can be considered to help manage possible stimulant-induced insomnia **or** for sleep problems that are a core symptom of ADHD (grade A recommendation). Authors also explained that melatonin may be considered in scenarios when patients/practitioners/families do not want to change the ADHD medication class or agent when it is most effective for other ADHD symptoms.[62] A 2019 British consensus statement recommends that melatonin can also improve sleep in children with ADHD who are not on stimulant medication.[9]

- Guidelines for the management of pediatric ASD:
  - The American Academy of Neurology (2020) recommends offering melatonin to children and adolescents with ASD and sleep disturbances or dysregulation if behavioral strategies have not been helpful, and when contributing coexisting conditions and medication side effects have been addressed.[4] Melatonin alone and the combination of melatonin/CBT were therapy options concluded as *probably effective* for improving bedtime resistance, sleep onset latency, sleep continuity, and total sleep time; while CBT alone was concluded as *possibly effective* (with less confidence in effect versus a rating of *probably effective*) for sleep attributes of latency, continuity, and total sleep time.[4]
  - The American Academy of Pediatrics (2020) recommends considering melatonin for sleep onset problems.[13]
  - The Canadian Peadiatric Society (2019) advised that melatonin, when combined with appropriate sleep hygiene and behavioral intervention, appears effective for reducing sleep onset times and increasing sleep duration[56]
  - The 2019 British consensus statement recommends that melatonin can improve sleep in children with ASD.[9]

Information from expert consensus statements with the primary focus on melatonin for pediatric sleep disorders is consolidated into **Table 4**.

Table 4. Practice Points and Expert Consensus Statements on the Use of Melatonin for Pediatric Insomnia

Canadian Peadiatric Society, 2018 Practice Point for the Use of Melatonin in Pediatric Patients with Sleep Disorders [2]
o Pharmacological therapy for sleep problems can be considered after a trial of sleep hygiene intervention. o Despite the limitations of studies supporting the use of melatonin (small study population, short-term studies), melatonin is considered safe and effective for short-term use for the management of insomnia in children (as young as 2 years of age), and side effects appear to be mild and self-limited.[71] ▪ The formulation chosen should be tailored to the sleep problem (ie, short-acting forms for sleep initiation insomnia, and long-acting forms for sleep maintenance insomnia). ▪ Authors cite supportive RCT evidence in studies with ADHD or ASD populations, in addition to idiopathic childhood sleep onset insomnia (of delayed sleep phase type or sleep-onset association type) without obvious contributing comorbidity. ▪ In a long-term follow-up study of 3.7 years in children with ADHD taking melatonin, there were no significant safety concerns, but the discontinuation of melatonin did usually result in relapse of sleep-onset insomnia and need to resume melatonin treatment.[71]

Table 4. Practice Points and Expert Consensus Statements on the Use of Melatonin for Pediatric Insomnia

International Expert Consensus Statement Regarding the Role of Melatonin In Pediatric Neurology, 2015 [70]

- International experts in pediatric neurology published consensus recommendations for the use of melatonin for pediatric sleep disorders following a systematic review of the literature. The general recommendations listed below should be tailored to each individual. Supportive studies varied based on the dose, timing, and modalities of administered melatonin.

Recommendation

- *Melatonin should be considered for children with sleep onset problems or difficulty waking up in the morning at conventional times*
- *There is a strong argument for determining dim light melatonin onset (DLMO, typically assessed by a saliva test), not only for an optimal diagnosis, but also for optimal timing/dosage of melatonin treatment for patients with chronic insomnia*
  - The best evidence for efficacy of melatonin is for sleep onset insomnia and delayed sleep phase syndrome. Many children with developmental disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder and intellectual disability have sleep disturbance and can benefit from melatonin treatment.
  - Melatonin decreases sleep onset latency and increases total sleep time but does not decrease night awakenings.
    - *When used as a chronobiotic* (ie, to adjust circadian clock), it is most effective when administered 2–3 h before measured DLMO, or 3-4 hours before actual sleep onset time if DLMO cannot be measured.
      - ✓ Start with a low dose of 0.2-0.5 mg melatonin (immediate release); may increase by 0.2-0.5 mg every week as needed (maximum of 3 mg for children <40kg; maximum of 5 mg for adolescents). If no response after 1 week, increase dose by 1 mg every week until effect appears.
    - *If used as sleep inducer*, administer 30 min before bedtime, starting with 1-3mg
    - Treatment duration should be tailored to the specific patient in relation to the peculiar neurodevelopmental disabilities but in general should be not less than 1 month
    - Slow melatonin metabolism can lead to high residual levels in the daytime; the loss of variation in melatonin plasma levels between day and night can cause loss of efficacy at night. Lowering the dosage may improve this issue when slow metabolism of melatonin is suspected.
    - Melatonin is primarily metabolized by CYP1A2 and CYP2C19; thus inhibitors of CYP1A2 (eg, tricyclic antidepressants, fluvoxamine, cimetidine, oral contraceptives) may increase melatonin exposure, whereas inducers (eg, carbamazepine, esomeprazole, omeprazole) can decrease exposure
  - Stopping successful treatment too early (ie, 4 weeks after initiation) may result in recurrence of symptoms
    - Stop melatonin treatment once a year during one week (preferably in summer) after a normal sleep cycle is established. Withdrawal of treatment can also be considered right before puberty or shortly after.

Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; DMLO, dim light melatonin onset; RCTs, randomized controlled trials

B. Systematic Review Information, Melatonin

Three systematic review meta-analyses (SRMA) published within the last 4 years were identified containing RCT evidence for melatonin in pediatric patients with sleep disturbances.[72-74] Two of these SRMAs focused on patients with neurodisabilities or neurodevelopmental disoder,[73,74] while the other included patients with or without co-morbid conditions.[72] Doses of melatonin in included RCTs were anywhere from 0.1 and 10 mg but most were within the range of 2 mg to 6 mg per evening. The SRMA findings suggest melatonin can be helpful for improving the time to sleep onset and total sleep time in pediatric patients based on low to moderate quality of evidence. There is a range of various disorders across included RCTs, several with mixed neurodisability populations including but not limited to ADHD, ASD, fragile X syndrome, Rett syndrome, cerebral palsy, visual impairment, intellectual disability, and epilepsy.[72-74]

- Wei et al (2020) SRMA included 7 RCTs comparing melatonin with placebo for sleep onset insomnia in pediatric patients with or without comorbid disease. Based on low to moderate quality evidence, short-term melatonin treatment resulted in significant improvements in sleep onset time and total sleep time (TST). There was no significant difference in drop-out rates related to treatment-related adverse event for melatonin vs. placebo. Although migraine and generalized epilepsy (reported 4 months after melatonin treatment) were reported in 2 cases, due to the low rate, a causal effect (vs. confounder comorbidity or coincidence) is unclear.[72]
- Parker et al (2019) SRMA included 13 RCTs of melatonin for children with sleep disturbances and neurodisabilities. Based on mostly poor quality evidence (RCTs with high or unclear risk of bias), compared to placebo, melatonin treatment significantly improved diary-reported TST and sleep onset; and actigraphy-measured TST and sleep onset. The single RCT with low risk of bias showed significant improvements in TST and sleep onset. Authors concluded that there is evidence of benefit for melatonin compared with placebo for improving TST and sleep onset, but the clinical significance to the well-being of the patient/family in specific groups of children and the duration of benefit remain uncertain. Although the effect estimate tended to favor melatonin for reducing the number of night awakenings, the difference was not significant. Melatonin appeared well-tolerated vs. placebo.[73]
- Abdelgadir et al (2018) included 11 RCTs of melatonin in pediatric patients with sleep/neurodevelopmental disorders. Melatonin appeared safe and effective for improving TST and sleep onset latency compared with placebo. Although the effect estimate tended to favor melatonin for reducing the frequency of nocturnal awakenings, the difference was not significant. The evidence base is limited due to study heterogeneity and inconsistency but overall was judged to be of moderate quality evidence. Melatonin appeared well tolerated vs. placebo as rates of treatment-related adverse events were not different from placebo in individual studies; however there was not enough data available to allow meta-analysis on this outcome.[74]
- Regarding ramelteon, an approved melatonin receptor agonist for adult insomnia, reviews mention only pediatric case series available. Positive effects/tolerability without daytime sedation have been observed in these case series.[75] A 2019 SR did not locate any RCTs available for ramelteon in the pediatric population.[76]

C. Safety, Melatonin

The overall impression of melatonin's safety profile, as described by the 2 expert position statements focusing on melatonin, is that side effects appear mild and self-limited, and melatonin is not known to be associated with serious adverse effects.[2,70] Furthermore, the international expert consensus statement describes that animal models and limited human data do not indicate an association with melatonin and seizures but instead that melatonin *might* decrease them. Animal models showed neuroprotective effects of melatonin; thus melatonin is under study for ameliorating neuronal damage related to birth asphyxia. Since it has been used at high dosages in infants without side effects, authors expect that it is safe for use as young as 6 months of age.[70] The FCBHS guideline describes that long-term observational studies out to 4 years did not show major adverse events in a variety of pediatric populations. Although there have been concerns of possible effects on pubertal development, based on animal studies, this effect has yet to be demonstrated in humans with long-term use.[53] The impact of potential drug interactions should be considered: CYP inducers can affect melatonin efficacy, as melatonin is primarily metabolized by CYP1A2 and CYP2C19, and inhibitors can affect tolerability.

Product quality: In the US, melatonin is a dietary supplement marketable under the 1994 Dietary Supplement Health and Education Act (DSHEA). Melatonin is a prescription-only product in other countries. For example, it is approved in Europe (as the product Slenyto) for the treatment of pediatric insomnia in patients 2 to 18 yours old who have ASD or Smith-Magenis syndrome.[77,78] In contrast to FDA-approved prescription drugs, US dietary supplements are not subject to federal regulations that may otherwise more reliably ensure product quality and safety. DSHEA permitted for dietary supplements that were on the market prior to 1994 to bypass FDA review for confirmation of safety and effectiveness.[79] Although manufacturers are required to meet rules for Good Manufacturing Practices (GMPs), many may not comply with the standards and can operate as-is until cited (or sued) by the FDA which has limited resources for inspections and enforcement.[80,81] Independent, third-party laboratories offer testing services in an effort to vet the quality (but not safety/efficacy) of dietary supplements. Though the list is not meant to be exhaustive, examples of companies that test the strength, certain purity aspects, and disintegration of supplements includes US Pharmacopeia (USP) and ConsumerLab.com which provide their unique seals (USP and CL, respectively) to certain product labels determined to meet GMPs. However, third-party testing companies may vary with respect to the frequency of batches tested, transparency of methods and thresholds used, scope of impurities actually tested for, etc.[82] Furthermore, it is not clear that companies currently test for serotonin, a possible impurity described as a specific concern among melatonin over-the-counter products.[78,83,84]

5.2 Alpha-2 receptor agonists (clonidine and guanfacine)

The extended release formulation of clonidine and guanfacine are approved for treating ADHD in the US; whereas the immediate release formulations of these agents are approved for the treatment of hypertension. Clonidine and guanfacine are known to have side effects of fatigue, somnolence, and/or sedation.[63,85] A meta-analysis (2014) supports this association, showing that alpha-2 antagonists (clonidine, clonidine XR and guanfacine XR) used for the treatment of ADHD as monotherapy or add-on therapy were associated with significantly higher risk of somnolence relative to placebo in RCTs.[85] Thus, alpha-2 antagonists are sometimes employed to use their somnolence side-effect as an advantage for managing sleep disturbance related to ADHD.

A. Recommendations for Use

- For pediatric insomnia in general, the FCBHS guidance recommends clonidine as a pharmacologic option secondarily to melatonin and implementation of behavioral/education interventions.[53] Authors do not mention guanfacine for insomnia (reason unknown). Refer to Table 1 for further information from this guideline. Though their recommendation wording is not specific to a subpopulation, the text specifies that clonidine has been studied in the context of insomnia related to neurodevelopmental disorders and ADHD.[53] In their separate guidance statement for pediatric sleep disturbance related to ASD or intellectual disabilities, authors also include clonidine as an option (refer to Table 2).[48]
- NICE 2018 ADHD guideline recommends consideration of guanfacine or atomoxetine in patients 5 years and older if they cannot tolerate side effects of methylphenidate or lisdexamfetamine.[64] The NICE guideline also recommends consultation with a tertiary ADHD specialty service prior to initiation of clonidine for sleep disturbance in children with ADHD.[64]
- The 2018 Canadian guideline recommends clonidine as a 3rd line option in ADHD, used in the context of a psychiatry specialist.[19] Guanfacine is a second-line option for the management of ADHD.[19]
- In the 2007 guideline by the American Academy of Child and Adolescent Psychiatry authors described a general consensus among clinicians that clonidine can be helpful as adjunctive therapy to treat tics or stimulant-induced insomnia rather than as a primary treatment for ADHD; however, a graded formal recommendation for this approach was lacking.[65]

B. Systematic Review Information

A 2017 systematic review (Anand[75] et al) summarized studies regarding medications used to treat behavioral insomnia in children with ADHD. Only 2 case series (both rated low quality of evidence) suggested **clonidine** treatment was associated with sleep symptom improvement (eg, based on Clinical Global Assessment of Sleep Severity) in patients with ADHD-related sleep disturbances who were taking a variety of ADHD medications.[86] Similarly, authors of a 2013 guidance statement (Cortese et al) described that observational evidence has suggested that clonidine induces a greater somnolence effect vs. placebo when used as monotherapy or in combination with methylphenidate for the treatment of ADHD. Thus, clonidine has been used to attempt to improve sleep-onset problems in ADHD; however; no RCTs have been designed to assess whether clonidine improves sleep latency in the context of psychostimulant-induced insomnia or for pediatric insomnia in general.[62,76]

The 2017 systematic review by Anand et al also identified 1 RCT (rated good quality) where **guanfacine** was compared to placebo in children with ADHD-related sleep problems who were not yet receiving ADHD medications. Guanfacine treatment was not significantly different from placebo for sleep onset (trend favored placebo) or for night awakening frequency, and was actually significantly worse than placebo for total sleep time.[86] The guidance statement by Cortese et al, briefly suggests that a nonpsychostimulant medication (eg, guanfacine, atomoxetine, clonidine) can be considered for substitution of a traditional stimulant if the patient's sleep disturbance is due to a side effect of the stimulant.[62]

C. Safety, Alpha-2 receptor agonists

Precautions for use of alpha-2 agonists include hepatic or renal insufficiency. Patients should be monitored for the following adverse effects including hypotension, bradycardia, syncope, elevated blood pressure and heart rate upon abrupt discontinuation. Precautions should be taken (monitoring or avoidance if possible) in patients with underlying conditions and/or who are taking other medications that increase the risk of a prolonged QTc interval. Since this medication should not be abruptly discontinued, due to rebound hypertension, it is not ideal for patients who are not adherent to its daily administration.[19]

5.3 Z-drugs (zolpidem and eszopiclone)

Guidelines specific to the pediatric population either do not mention z-drugs or do not recommend the use of z-drugs for routine use. The FCBHS describes that pharmacotherapy should not be used as the initial treatment strategy and if pharmacotherapy is used, it should not be the sole treatment strategy, as behavioral and educational interventions should be implemented. Based on the FCBHS algorithm in patients with ASD or intellectual disability, if the routine approaches (eg, education/behavioral, melatonin, clonidine) are insufficient then specialist consultation should be sought (eg, pediatric sleep specialist, child and adolescent psychiatrist, pediatric neurologist, or developmental pediatrician). Perhaps under this setting other off-label, non-routine-use pharmacotherapies may be determined as medically necessary by the specialist on a case-by-case basis; however, the FCBHS guidance does not elaborate further about the specialists' realm of additional medications and places z-drugs in a 'not-recommended' category that we interpret to mean for the majority of patients or for routine use.[48] Further information from RCTs as reported in systematic reviews is included below for zolpidem and eszopiclone to more fully explore the potential utility of these medications as a last line option.

A. Systematic Review Information

Based on the 2017 systematic review regarding potential treatments for ADHD-associated sleep disturbance (Anand et al[86]), the z-drugs, zolpidem and eszopiclone, have not demonstrated significant improvement in any *objectively*-measured sleep parameter when compared with placebo; however, in the single zolpidem RCT, *subjective* measures (eg, clinical global improvement scores) were significantly improved with zolpidem treatment vs. placebo. Review authors advised for clinicians to discuss the limitations of available evidence with the patient and the family and plan for short-term treatment should a trial with a pharmacological intervention be agreed upon. Only 1 RCT for eszopiclone and zolpidem each are reported among SRs for pediatric patients with ADHD-related sleep onset problems as follows:[37,86]

- The zolpidem study, a double-blind RCT (Blumer et al 2009), was rated as good-quality evidence by systematic review authors. The effect of zolpidem 0.25 mg/kg per day oral solution (maximum of 10 mg/day) was assessed in 136 patients, 6 to 17 years of age with ADHD-associated sleep latency insomnia who were on stable ADHD medication.[87] While no significant effect difference was found for sleep onset (ie, latency to persistent sleep [LPS]) versus placebo at week 4 (primary endpoint), scores for subjective measures of Clinical Global Impression-Improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S) were significantly improved in the zolpidem arm compared to placebo at week 4. In subgroup analysis, the difference was maintained only for the 12 to 17-year-old age group but not for the 6 to 11-year-old age group. Authors postulated, based on pediatric

pharmacokinetic data with zolpidem[88], since younger patients clear zolpidem more quickly, the same mg/kg dose may not be therapeutically effective across each age group. Additional theories regarding the underpinnings of zolpidem efficacy variation with respect to age were also provided and altogether require further research.[87]

- The single eszopiclone RCT (Sangal et al 2014) was rated as high quality. No significant differences were found for low or high dose eszopiclone (1 or 2 mg in children aged 6-11 years; 2 or 3 mg in children ages 12-17 years) versus placebo for the change from baseline to week 12 on polysomnography-measured LPS or for secondary subjective measures on sleep onset, TST, and number of nighttime awakenings.[86,89]

B. Safety, Zolpidem and Eszopiclone

Package inserts for both eszopiclone and zolpidem cite the results of the pediatric RCTs described above. In these pediatric studies for ADHD-related insomnia, the most common pediatric adverse events reported were as follows:

- For zolpidem**:** dizziness (23.5% for zolpidem vs. 1.5% placebo), headache (12.5% vs. 9.2%), and hallucinations (observed only in the zolpidem arm at 7%).[90]
- For eszopiclone: dysgeusia (9% with eszopiclone vs. 1% with placebo), dizziness (6% vs. 2%), hallucinations (2% vs. 0%) and suicidal ideation (0.3% vs. 0%).[91]

Labeled warnings for eszopiclone and zolpidem include the following, in brief:[91,92]

a. The z-drugs have a **black box warning** regarding complex sleep behaviors that have been reported while using these agents including sleep-walking, sleep-driving, sleep eating, and engaging in other activities while not fully awake. This adverse effect has been observed at recommended doses, with or without the concomitant CNS-depressants. Due to potential serious injury of self or others, these agents are contraindicated in patients with a history of such behavior while on previously receiving one of these medications.
b. Eszopiclone and zolpidem have CNS-depressive effects including respiratory depression, and can cause next-day impairment in alertness and motor coordination. In order to minimize next-day risks, these medications should be taken at least 7-8 hours before the patient plans to wake-up for the day. Risks increase with higher dosages and when used with other CNS depressants. Consider dose adjustments of the z-drug and/or other concomitant CNS depressants if administered close together such that the physiologic effects of each drug are expected to overlap. Precautious use is advised in patients who have respiratory impairments particularly in those with sleep apnea or myasthenia gravis since these hypnotics can decrease respiratory drive.
c. Re-evaluate for comorbid diagnoses if insomnia symptoms do not improve after 7 to 10 days of eszopiclone or zolpidem use: "…failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated."[91]
d. Psychiatric/neurologic disruptions (in addition to complex sleep behaviors highlighted above):
    - Abnormal thinking and behavioral changes have been reported including decreased inhibition, bizarre behavior, agitation, and depersonalization while taking these agents.
    - Worsening of depression or suicidal thinking may occur while taking these agents.
e. Withdrawal symptoms can occur with abrupt discontinuation of the medication

f. Rare reports of severe anaphylactic/anaphylactoid reactions have been reported with these agents
g. Avoid zolpidem use in severe hepatic impairment and consider dose adjustment for mild/moderate hepatic impairment. Consider eszopiclone dose adjustments, especially in patients with severe hepatic impairment.
h. Cytochrome P450 (CYP) interactions: CYP3A4 is a major metabolic pathway for eszopiclone and zolpidem; thus, potent inhibitors and inducers are expected in increase and decrease exposure, respectively. In adults on potent CYP3A4 inhibitors, no more than 2 mg/evening of eszopiclone is recommended. Consideration for lower dosage is recommended for zolpidem in the context of potent CYP3A4 inhibitors.

5.4 Antihistamines

A. Recommendations for Use

- For pediatric insomnia in general, the FCBHS guidance includes diphenhydramine as a medication option, listed secondarily to a trial of melatonin and implementation of behavioral/education interventions.[53] Authors describe that diphenhydramine 12.5–50 mg nightly, can be considered for short-term situational or occasional use in younger children, especially those with comorbid atopic disease. However, this group does not include this medication (or any other antihistamine) for insomnia in ASD or intellectual disability populations.[48]
- Expert guidance from UptoDate also note that antihistamines (particularly first-generation antihistamines) can be considered for pediatric insomnia for "…short-term situational or occasional use in younger children, especially those with comorbid atopic disease."[46] Authors describe that widespread clinical experience, particularly with diphenhydramine and hydroxyzine, has indicated a positive tolerability profile with these agents in children; however, there is mixed empirical evidence for their efficacy, and tolerance to their effects can develop.[46]

B. Review Information

Among a 2019 SR and information in UptoDate, only 2 small RCTs with diphenhydramine are reported altogether for pediatric sleep problems.[46,76] One of these was a 2 week cross-over study with 50 patients aged 2 to 12 years old with a mix of sleep disorders. Results suggested that diphenhydramine 1 mg/kg can significantly improve subjective sleep latency and night awakenings.[93] The other small RCT study in infants 6 to 15-months of age focused on night awakenings and found that diphenhydramine (taken up to a week) was no better than a placebo for reducing night awakenings.[94]

C. Safety

Safety and tolerability concerns with antihistamines include anticholinergic side effects(eg, dry mouth, constipation, urinary retention, blurred vision), residual morning sleepiness ("hangover") and possible additive effects with other drugs that have anticholinergic characteristics.[46] Paradoxical excitation or hyperactivity are also mentioned as possible side effects of diphenhydramine; however, among the RCTs cited in the FCBHS or review articles where diphenhydramine was used for either nighttime awakenings

or nocturnal cough disturbance in pediatric patients, the rate of paradoxical excitation was either similar to the placebo group,[94,95] or such side effect was not reported.[93]

5.5 Orexin inhibitors

Based on systematic review information[76] and clinicaltrials.gov, there do not yet appear to be completed RCTs of orexin inhibitors for the treatment of pediatric insomnia.[76] There is a single registered prospective observational study for lemborexant that includes pediatric use,[96] and we are aware of an observational study in adolescents treated with suvorexant.[97] Clinical guidelines do not include recommendations for the use of these agents in the pediatric population at this time due to insufficient evidence.

Adverse event(s) reported in 5% or more of adult patients taking suvorexant, and at least twice the rate in the placebo group was somnolence only. Labeled warnings for less common but serious adverse events that are possible with orexin inhibitors include the following in brief:[98-100]

- Orexin inhibitors may cause next-day impairments in alertness and motor coordination
- Orexin inhibitors have CNS depressant effects. Caution should be exercised when used with other CNS depressants as effects can be additive (consider dosage reductions). Effects on respiratory function should be considered along with caution exercised (or avoidance) in patients with respiratory compromise.
- Possible worsening of depression and suicidal ideation: in adult clinical trials, a dose-dependent increase in suicidal ideation (assessed by questionnaire) was observed patients taking suvorexant or lemborexant.
- Complex sleep behaviors (eg, sleep-walking, sleep-driving) have been reported with hypnotics such as orexin inhibitors.
- Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms may occur with the use of orexin inhibitors.
- If insomnia persists after 7 to 10 days despite the use of these hypnotic therapies, reevaluate the patient for a potentially insufficiently treated psychiatric or medical condition.
- Daridoexant, lemborexant, and suvorexant are metabolized by CYP3A (eg, 3A4 and/or 3A5): concomitant use of these agents with strong CYP3A inhibitors is not recommended (eg, azole antifungals, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan). Dose recommendations for adults are in place if on moderate CYP3A inhibitors; see package inserts for further information.

6.0 UTAH MEDICIAD PHARMACY UTILIZATION DATA

Pediatric pharmacy claims (for patients <18 years of age) were queried among the Fee-for-service (FFS) population over a 1 year period, from April 2021 through March 2022, for non-benzodiazepine prescription hypnotics: daridorexant, doxepin 3 mg or 6 mg, eszopiclone, lemborexant, ramelteon, suvorexant, zaleplon, and zolpidem. These agents are approved for the treatment of adult insomnia, either for sleep onset and/or sleep maintenance type; see **Appendix C** for more information on the FDA-indication for each agent. Despite the possible need for treatment, no medications are FDA-approved for insomnia in pediatric patients.

Altogether, there were 5 unique pediatric patients who received any of these medications. There were 12 pediatric claims total, consisting of either eszopiclone, ramelteon, suvorexant or zolpidem; and the patient age range was 12-17 years old. No pediatric claims were found for daridorexant, doxepin 3 or 6mg, lemborexant, or zaleplon; or for any patient under 12 years of age.

i. Of the 5 patients, the majority were 17 years of age
ii. Patients often had multiple complex co-morbidities. Pooled diagnosis codes among these patients included conditions such as epilepsy, intellectual/developmental disorder, sleep disorder/insomnia, ADHD, conduct disorder, Rett's Syndrome, Schizophrenia/Bipolar disorder, suicidality, cerebral palsy, and anxiety.
iii. Several patients were prescribed the insomnia medication by a pediatric and/or neurology/psychiatry specialist.
iv. With respect to claims for ramelteon and suvorexant, these medications were prescribed by specialists of psychiatry/neurology or child/adolescent psychiatry. Suvorexant was used as a last-line pharmacotherapy following trial of other therapies. ICD10 coding and medication records do suggest co-morbidities were being managed/treated and that patients had multiple neurodevelopmental disorders.

Table 5. Fee-for-Service Pediatric Utilization, April 2021-March 2022

Product	Claim Count	Patient Count
Doxepin 3 or 6 mg tablet	0	0
Eszopiclone 1 mg or 3 mg tablet	<5	<5
Ramelteon 8 mg tablet	<5	<5
Belsomra (suvorexant) 10 mg tablet	<5	<5
Zolpidem tartrate 10 mg or 5 mg tablet	6	<5
Total Unique Patients		**5**

7.0 SUMMARY

Recurrent, insufficient sleep that falls short of optimal sleep durations is associated with attention/concentration difficulties, emotional and behavioral dysregulation, learning/memory impairments, and increased risk of accidents, injuries, cardiovascular and metabolic disorders (eg, hypertension, obesity, and diabetes mellitus), poor academic performance, and depression in the pediatric population.[3,4,19] Moreover, inadequate sleep in teenagers is associated with severe psychologic burden manifesting as higher rates of self-harm, suicidal thoughts, and suicide attempts.[3]

Guidelines by medical associations that we identified for the management of pediatric insomnia were primarily oriented to address insomnia related to ADHD or ASD. We located few guidance statements for pediatric insomnia in general, non-specific to co-occurring disorders, including a guidance report by the Florida Center for Behavioral Health Improvements and Solutions (FBCHS, sponsored by the Florida Agency for Health Care Administration [ie, Florida Medicaid]) and a consensus statement by pediatric neurology/psychiatry experts in Spain.[53,101] Guidelines on the management of ADHD address insomnia according to the following themes: (a) insomnia as a core symptom of ADHD with breakthrough symptoms due to ADHD medication *wearing-off* too early, (b) insomnia as a result of the medication arousal effect lasting too long into the bedtime, or (c) insomnia as a symptom manifestation of an unmanaged co-morbidity (see section 4.2 of report). Insomnia can be diagnosed and treated on its own if other conditions are managed to the best of their ability, as experts acknowledge that insomnia symptoms can still persist despite treatment of ADHD or treatment of other comorbidities.[37] Ultimately, the treatment of sleep problems can help improve ADHD behavioral symptoms.[19] The Autism Treatment Network described that in ASD, the root of insomnia is multifactorial as the core symptoms of ASD (social deficits and restricted/repetitive behaviors) can influence sleep tendencies and behaviors; and can also be compounded by additional psychiatric/neurologic comorbidities, and/or medication-related adverse effects from agents used to treat autism symptoms or comorbidities.[43,44] Comorbidities are common among children with ASD, often including seizures, sleep disturbances, ADHD, and mood disorders; and about 30% of patients with ASD have intellectual disability.[13] Sleep disturbances *may be a core symptom* of ASD, and/or related to neurobiological alterations, genetic mutations, and disrupted sleep architecture.[42] Moreover, sleep shortages can exacerbate problematic daytime behaviors.[42]

Behavior approaches (ie, education and optimization of sleep hygiene/routines) and/or cognitive behavioral therapy (CBT, generally for older children >5 years of age) are usually the recommended first-line approach for pediatric insomnia management.[4,44,48,53,54,56] Yet, there is limited or insufficient insurance coverage for CBT and a scarcity of providers trained in CBT, as described by the American Thoracic Society.[47] Additionally, some patients may have an insufficient response or may be refractory to behavioral approaches.[39] The American Academy of Sleep Medicine (AASM) notes that educational and behavioral interventions may not fully attenuate sleep problems, particularly in children with considerable developmental delays, cognitive impairment, or other medical/psychiatric disorders. Such patients may benefit from judicious use of sleep-promoting medications (ie, with close monitoring for efficacy and side effects).[54]

There is consistent support among guidelines and expert position statements for the consideration of melatonin as an option for pediatric sleep disturbances, especially when other approaches such as behavioral/educational interventions or modifications/management of other medications/conditions where possible are not sufficient on their own. We located 9 key guidelines or position statements that included melatonin as a recommended option for pediatric insomnia (see page 19 of the report for the

list and recommendations). The 2018 Canadian guideline cites supportive RCT evidence in studies with ADHD or ASD populations, in addition to idiopathic childhood sleep onset insomnia (of delayed sleep phase type or sleep-onset association type) without an obvious contributing comorbidity; yet, there are a limited number of RCTs in total.[2] The overall impression of the safety profile described by the 2 expert statements focusing on melatonin is that side effects appear mild and self-limited and that melatonin is not known to be associated with serious adverse effects.[2,70] The FBCHS guidance report describes that long-term studies out to 4 years did not show major adverse events in a variety of pediatric populations. The impact of potential drug interactions should be considered: CYP inducers can affect melatonin efficacy since melatonin is primarily metabolized by CYP1A2 and CYP2C19, and inhibitors can affect tolerability. Refer to page 23 regarding further information about melatonin including general product quality concerns.

The FBCHS recommends diphenhydramine (secondarily to melatonin) as an option for pediatric insomnia; however, in their separate statement for the management of populations with ASD and/or intellectually disability, diphenhydramine is not included for insomnia management related to these conditions.[48,53] The Spanish consensus statement was the only other guideline including first-generation antihistamines (diphenhydramine and hydroxyzine) as options for pediatric insomnia.[6] Although there are very few supportive RCTs for diphenhydramine for pediatric insomnia (perhaps insufficient to make firm conclusions)[76], clinical experience (anecdotal evidence) suggests that first-generation antihistamines may be helpful for pediatric insomnia, along with having a positive tolerability profile, based on information from UptoDate.[46]

Alpha 2 receptor agonists (clonidine or guanfacine) are associated with somnolence and/or sedation as a significant side effect;[63,85] thus, they are mentioned among guidelines as a useful substitutive or adjunctive therapy for the management of insomnia related to ADHD (either for insomnia as a core symptom or as a side effect from traditional stimulant medications). For pediatric insomnia in general and for patients with ASD or intellectual disability, the FBCHS guidance has clonidine as a pharmacologic option, secondary to melatonin and implementation of behavioral/educational interventions; authors do not mention guanfacine for insomnia.[53] Medical association guidelines that address the management of ASD note the limited evidence for clonidine in ASD but do not go as far to recommend for or against its use in this population.[4,13,44] Clonidine has observational-level evidence for insomnia outcomes primarily in the context of insomnia related to neurodevelopmental disorders.[53,62,76]

Conclusion: Many guidelines recommend melatonin as an option for the management of pediatric insomnia, especially for insomnia related to ADHD and ASD. Beyond melatonin, diphenhydramine, and clonidine, there are not firm recommendations provided for sedative prescription medications due to limited/insufficient evidence in the pediatric population. Thus, if patients fail CBT, melatonin, and potentially other limited options (eg, clonidine or diphenhydramine where appropriate), then a specialist consultation should be considered to determine the next approach. Guidelines do not provide guidance beyond agents that may be used in the primary care setting. The FBCHS appears to support short-term use of pharmacotherapy when symptoms result in significant daytime impairments in function for the child and/or caregiver and if behavioral interventions alone are insufficient or are unable to be implemented. Additionally, this group recommends against pharmacotherapy as the initial or sole treatment strategy.[48]

As there are no FDA-approved medications for pediatric insomnia, off-label prescribing of agents may be considered (perhaps through prior authorization) on a case-by-case basis, by or in consultation with a

specialist (eg, pediatric sleep specialist, child and adolescent psychiatrist, pediatric neurologist, or developmental pediatrician). A potential caveat is the scenario in which a patient/provider do not have access to a specialist (depending on how narrow the definition of a specialist is, and depending on shortages of such specialist services in the patient's geographical area). It should be considered that the persistence of insomnia may depend on whether contributing or related conditions (eg, neurological, inflammatory, traumatic) are temporary or chronic conditions, as changes in the sleep regulating brainstem and hypothalamic nuclei can coincide among conditions.[32] Thus, it is possible for the therapeutic need to persist beyond short-term with potentially contributing/coinciding conditions that are chronic (eg, epilepsy, traumatic brain injury, cancer, multiple sclerosis, etc).

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APPENDIX A - LITERATURE SEARCHES

Epistemonikos (https://www.epistemonikos.org/en/)

- ((insomnia OR sleep-disorder* or sleep-disturbance*) AND (adolescent* OR child* OR pediatric*)) [Title or Abstract]
  - limited to Systematic Reviews in last 5 years (2/23/2022 102 results)
- (title:(title:(adolescent* OR child* OR pediatric*) AND title:(insomnia OR sleep*) AND (title:(clonidine OR diphenhydramine OR melatonin) OR abstract:(clonidine OR diphenhydramine OR melatonin))) OR abstract:(title:(adolescent* OR child* OR pediatric*) AND title:(insomnia OR sleep*) AND (title:(clonidine OR diphenhydramine OR melatonin) OR abstract:(clonidine OR diphenhydramine OR melatonin))))
  - limited to last 10 years (28 results 2/5/22)

Cochrane Systematic Reviews Database

- (insomnia or sleep):ti (40 Cochrane Systematic Reviews [CSRs])
- (clonidine or diphenhydramine or doxepin or zolpidem):ti,ab,kw (51 CSRs, 2/25)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 25, 2022>

1 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/ (416301)

2 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (46644)

3 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw. (40420)

4 (standards or guideline or guidelines).ti,kf,kw. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf,kw. or consensus*.ab. /freq=2 (210699)

5 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (23790)

6 recommendat*.ti,kf,kw. or guideline recommendation*.ab. (52452)

7 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw. (72354)

8 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw. (11614)

9 (guideline* or standards or consensus* or recommendat*).au. (546)

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (687018)

11 exp *"Sleep Initiation and Maintenance Disorders"/ (11546)

12 (insomnia or sleep-dis*).ti. or exp *"Sleep Initiation and Maintenance Disorders"/ (23630)

13 exp *Pediatrics/ or exp *adolescent/ or exp *child/ or (pediatric* or child* or adolescen*).ti,ab. (1841193)

14 10 and 12 and 13 (80)

15 exp *Central Nervous System Stimulants/ae and (ADHD or attention-def*).ti. (339)

16 ((stimulant* or attention-def* or ADHD) and (side-effect* or adverse-effect* or insomnia or (sleep-dis* or sleep-prob*))).ti. (291)

17 (15 or 16) and 10 (28)

18 14 or 17 (105)

19 (15 or 16) and manag*.ti. (23)

20 18 or 19 (122)

Choosing Wisely Website

Search Recommendations:

- ‘sleep’ (19 results)
- ‘insomnia’ (6 results)

ECRI Guidelines Trust Website (https://guidelines.ecri.org/)

- ‘insomnia’ (18 results)
- ‘sleep’ AND (limit to AGE to Newborn, Infant, Child or Adolescent) AND (limit INTERVENTION to Management or Treatment) (34 results)

APPENDIX B – LIST OF GUIDELINES AND EXPERT POSITION STATEMENTS

1. 2018 – 2019 Insomnia Disorder Medication Guidelines for Children and Adolescents from the Florida Center for Behavior Health Improvement and Solutions (FCBHS)[53]
2. 2019 British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders[9]
3. 2017 Spanish Expert Consensus Statement[6]
4. Canadian Paediatric Society: Practice point on melatonin for the management of sleep disorders in children and adolescents (2012, updated 2018, reaffirmed 2021)[2]
5. 2015 International Expert Consensus Statement (Burni et al): Current role of melatonin in pediatric neurology – Clinical recommendations[70]
6. 2018 National Institute for Health and Care Excellence: ADHD Guideline[64]
7. 2018 Canadian ADHD Resource Alliance (CADDRA): ADHD Practice Guidelines[19]
8. 2013 International Expert Review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents[62]
9. 2020 American Academy of Neurology (AAN): Practice guideline – Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder[4]
10. 2020 American Academy of Pediatrics: Identification, Evaluation, and Management of Children With Autism Spectrum Disorder (2020)[13]
11. 2019 FCBHS guideline for managing ASD/intellectual disability[48]
12. 2019 Canadian Paediatric Society: Post-diagnostic management and follow-up care for autism spectrum disorder[56]
13. 2012 Autism Treatment Network (ATN): A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders[44]

Additional screened guidelines that were not found to have guidance on managing pediatric insomnia

- 2020 American Psychiatric Association Practice Guideline for the Treatment of Schizophrenia[102]
- 2019 American Academy of Pediatrics: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents[40]
- 2019, VA/DoD, “Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea
- 2017, AASM, Clinical Practice Guidelines for the Pharmacologic Treatment of Chronic Insomnia in Adults
- 2017 European guideline for the diagnosis and treatment of insomnia
- 2016 Practice Guideline for Chronic Insomnia in Adults from the American College of Physicians

APPENDIX C – ADDITIONAL BACKGROUND INFORMATION

The following is a list of agents that are recommended for consideration (versus no treatment) by the 2017 American Academy of Sleep Medicine guideline for the treatment of chronic insomnia in adults, arranged according to the type of insomnia problem.[103] The agents that have an FDA-indication for that respective insomnia problem are also indicated in the list. Some of the orexin inhibitors were approved after the writing of this guideline (eg, daridorexant and lemborexant).

A. Sleep Onset Insomnia

- AASM guideline recommends consideration of eszopiclone, ramelteon, temazepam, triazolam, zaleplon, zolpidem
- Agents with FDA indication in adults for the respective insomnia issue: daridorexant, eszopiclone, lemborexant, ramelteon, suvorexant, temazepam, triazolam, zaleplon, zolpidem

B. Sleep Maintenance Insomnia

- AASM guideline: doxepin, eszopiclone, suvorexant, zolpidem
- FDA indication in adults: daridorexant, doxepin, estazolam, eszopiclone, lemborexant, suvorexant, zolpidem CR

C. Midnight awakening with difficulty returning to sleep

- Not specifically addressed in the AASM guideline
- FDA indication in adults: Intermezzo (zolpidem IR)