Medications

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Case Vignette

Melody, a 7-year-old girl with the known diagnosis of Smith-Magenis syndrome was referred for disrupted sleep. Following diagnosis at 14 months when she first presented with developmental delay, the initial treating child neurologist and parents worked diligently to entrain the sleep schedule and used melatonin since age 3. At presentation, bedtime was 8:30 PM with sleep latency under 15 min and only a single brief awakening before sleep offset at approximately 5 AM on an extended-release preparation of 3 mg melatonin given 30 min prior to lights out. However, her parents would frequently find Melody's light on at night. She would take daily brief "power naps" lasting 15–20 min in addition to occasional longer naps of 1–2 h that were equally restful and did not interfere with nighttime sleep. Polysomnography showed decreased rapid eye movement (REM) stage sleep and confirmed an early morning final arousal; there was no apnea or periodic limb movements (PLMS). New episodes of awakening with stiffness, tongue deviation, and right-sided posturing led to an overnight video EEG which did not reveal epileptiform activity but did not capture events of concern. Over the ensuing months, there were no further similar arousals. Behavioral challenges included hyperactivity, skin picking, and tantrums which persisted despite multimodal therapies in a self-contained special education class. Acebutolol was added at age 9 to her extended-release melatonin; this led to increased alertness during the day. For the first time, she needed to be awakened in the morning for school. While medication improved her chronobiologic disorder, she continued to have severe behavioral dysregulation which only worsened as she approached puberty. Sleep and behavioral issues deteriorated despite treatment with fluoxetine. Repeat polysomnography at age 12 now showed an elevated PLM index of 12 events per hour. Serum ferritin of <10 mcg/L was likely explained by heavy menstrual bleeding. Treatment with iron and birth control pills to control menstruation improved symptoms.

Introduction

Considering all of the challenges of raising a child with developmental disabilities, parents may have earned a pass if they try almost anything to encourage or enforce good sleep patterns. Physicians, therapists, and the blogosphere, as well as common sense, assure them that a good night's sleep is essential for optimal functioning, and it is clear to them that their child with a developmental disability is neither sleeping well nor functioning optimally. Parents also know that with their own sleep deprivation comes increased irritability and more anxiety, which they cannot afford. What to do? Even though there are few parents who want to expose their child to any medication, exhausted and desperate ones will try almost anything deemed safe and effective by "experts," whether based on strong clinical studies, limited evidence, or just anecdotal endorsement. This chapter will review the scientific basis, where it exists, for medication for sleep in this population. It will also outline the known safety and efficacy for both formulary and over-the-counter medications commonly used to promote smooth sleep initiation and maintain efficient sleep consolidation in children, especially those with developmental disorders. It must be acknowledged at the outset that few if any of these approaches are Food and Drug Administration (FDA) approved for the purpose of supporting sleep. Because many pediatric pharmacotherapies of

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all sorts are not FDA approved for use in children, pediatric clinicians have long been familiar with this problem and comfortable enough weighing the data and outlining to families the pros and cons of off-label administration until more complete data become available.

Organizing a discussion of sleep disturbances in children with developmental disabilities is a major conundrum. While there are instances in which a particular clinical problem is highly associated with a specific disease state (e.g., sleep-disordered breathing and Down syndrome or chronobiologic disturbance in Smith-Magenis syndrome), the issues under discussion should not be limited to a recitation of genetic conditions – and not all children with these disorders are affected to the same degree. But it is equally important that a discussion of medications to treat a syndrome like periodic limb movement disorder (PLMD) emphasizes the association with attention-deficit/hyperactivity disorder (ADHD) in a book about children with developmental disabilities. This is true even if PLMD is not unique to ADHD, nor necessarily a major contribution to disability for many affected children with ADHD, or even true in the majority of children with the neurobehavioral syndrome. Indeed, none of the sleep-related challenges in children within the broad spectrum of developmental disabilities are unique to the presenting disorder. Therefore, the chapter will focus on medications commonly used for disorders of initiating and maintaining sleep, parasomnias, and their daytime consequence of excessive sleepiness – which is also rarely encountered as an independent symptom of its own. It will also try to provide an overview of the known effects on sleep for medications commonly used for other purposes in children with epilepsy, autism, and ADHD.

Before initiating a discussion of medications, it is important to remember that pharmacologic treatment should never be the goal but, rather, a temporary mechanism to achieve relief of symptoms. If a family comes for a consultation with a chief complaint that they need a medication (for any clinical problem), it is tempting to immediately eject them from the office. While that has never occurred in this clinician's practice, I do explain that it is the clinical concern that should be the chief complaint – which must then be put it into context and followed by a careful history and full examination, followed sometimes by laboratory studies where indicated – before a differential diagnosis can be developed. Only then can we discuss the strategies to address the problem, and only if medication is a reasonable option can we talk about the risks and benefits of drug treatment with specific goals and plans on how to monitor its outcome as part of a comprehensive plan.

Treatment of Insomnia

The lack of approved medications by the FDA has never stopped clinicians who treat children from prescribing medications or recommending nonprescription drugs. In one survey, more than 75% of primary care pediatricians surveyed recommended nonprescription medications for pediatric insomnia and greater than 50% had prescribed a medication specifically for sleep. After children with transitory indications such as acute pain and travel, the most common stated indication for usage was in children with developmental disabilities [1]. A survey of child and adolescent psychiatrists confirmed the common use of prescription or nonprescription medications for sleep among children with a variety of psychiatric disorders including developmental disabilities such as ADHD, autism spectrum disorder, and intellectual disability [2]. Antihistamines were the nonprescription medications most commonly recommended for treatment of insomnia in children, and alpha-agonists (especially clonidine) were the medications most frequently prescribed.

In 2004 the National Sleep Foundation in collaboration with Best Practice Project Management, Inc. convened a conference to evaluate the role of pharmacologic management of pediatric insomnia; results were reported in *Pediatrics* in 2006 [3]. While the discussion extended to all children, there was a specific focus on vulnerable populations, highlighting developmental disabilities, particularly neuropsychiatric disorders including ADHD, autism, epilepsy, and Tourette syndrome. The conference did not review evidence for specific drugs but rather outlined the problem, made recommendations for the design of clinical trials including ethical considerations when dealing with children, and discussed the priorities for future research. They pointed to autism spectrum disorders as having one of the highest priorities due to its prevalence, chronicity, and frequent lack of responsiveness to behavioral sleep approaches. Children with ADHD were also identified as another high priority group also due to the high prevalence and evidence that this group is the most likely receive off-label hypnotic therapy.

Another group of experts, many of them the same, had previously met under the auspices of the American Academy of Sleep Medicine in 2003 with representation from the American Academy of Pediatrics and the Food and Drug Administration; results were published in the Journal of Clinical Sleep Medicine in 2005 [4]. From the outset it was stated that any discussion of drug management must be prefaced by reinforcing the primary role of good sleep hygiene, with pharmacologic intervention largely considered adjunctive. The panel went on to describe the "ideal" hypnotic as one with high oral bioavailability, predictable kinetics, quick onset of action, and rapid metabolism – but sufficiently long to allow once nightly dosing without producing residual daytime sedation. This ideal drug would also have no effect on normal sleep architecture as well as no rebound, tolerance, or withdrawal with few side effects and no drug-drug interactions. Finally, this medication should be available in convenient doses and multiple formulations, including palatable liquids. It was concluded that in the absence of such a drug,

rational treatment must rely on the best match between clinical circumstances and the particular properties of the available medications. Again, the panel emphasized that medication should never be the first nor the sole strategy and should be used in the context of a comprehensive treatment program, except for very self-limited circumstances such as travel. Other important points included the fact that sleep problems in infants and young children are almost always related to asynchrony between the child's sleep development and parental expectations, so that medication is rarely, if ever, indicated. Adolescents should be screened for substance abuse and pregnancy prior to initiation of therapy since many recreational substances have synergistic properties when combined with hypnotics, and hypnotics are potentially harmful to developing fetuses. All patients need to be screened for concurrent use of over-the-counter remedies since some contain similar ingredients under different brand names, and there are also potential drug-drug interactions. Medications should be prescribed only for short-term usage (i.e., without refills) unless there is reassessment of target symptoms and evaluation of patient adherence with both the behavioral as well as pharmacologic plan.

As with the later panel, the experts noted that sleep disturbances were a prominent part of the lives of many children. Across a variety of neuropsychiatric and medical conditions, they emphasized contributions of family stress, caregiver interactions, peer relations, medical needs, sedating or activating medications, physical challenges, and psychiatric comorbidities. They pointed to common situations such as pain or abnormal motor activity that could cause insomnia. At the same time, they recognized that children with developmental disabilities were prone to the same emotional, behavioral, medical, and circadian sleep disorders as typically developing children, so that more common causes of insomnia also need to be primary considerations even in this vulnerable population.

Still, children with neurologic disorders and specific genetic, psychiatric, or behavioral syndromes can be predisposed to particular types of insomnia. Total blindness is associated with free-running circadian disorder. Smith-Magenis syndrome includes a disruption of normal circadian melatonin release leading to poorly organized sleep patterns. Williams syndrome appears to have a higher incidence of periodic limb movement disorder. Rett syndrome has prolonged sleep latency and fragmented sleep. Children with ADHD often have sleep onset and maintenance insomnia which can correlate with obstructive apnea, periodic limb movement syndrome, or stimulant medication rebound. As previously stated, none of these associations are diagnostic nor are all children with proven genetic conditions as listed above affected. However, at the very least, it helps families (and clinicians) to have an increased level of suspicion and to recognize early if there are symptoms of sleep disorder, in order that a full evaluation must address this common association. It is worth reiterating that those with developmental disabilities are not immune to the common disorders that affect neuro-typical children; evidence from systematic reviews suggests that most pediatric sleep problems respond well to behavioral treatments, and these should be tried first before embarking on a course of medication [5].

Medications Commonly Used to Treat Insomnia

Melatonin Receptor Agonists

Melatonin

Although not a prescription drug and widely available even in supermarkets, there have been more placebo-controlled trials for melatonin in the treatment of pediatric insomnia than there have been for any sleep-promoting drug licensed by the FDA. Its use was first popularized in the 1990s in children with intellectual disability, and it has been a mainstay of treatment for pediatric clinicians, not only for children with ADHD and autism spectrum disorders but for typically developing children as well.

Melatonin, also discussed in Chapter 31, has relatively short-acting sleep-promoting properties, with a half-life of approximately 1 h. This makes it much more effective in treating initial insomnia than sleep maintenance insomnia or terminal insomnia. It is best administered approximately 30 min before lights out, and it works best when timed with normal circadian rhythms; therefore, it should be used in the evening and not at other times of day. Appropriate dosing of this exogenous hormone therapy is hard to gauge, not only because it is unclear how much is absorbed, but ready access to unregulated distribution without FDA oversight means that there is little quality control; outside analysis has shown that some pills contain far less or none of the active ingredient. Melatonin is thought to be sedating in dosages of 1 mg or more; the most commonly available form may be a 3 mg tablet, although many formulations and doses are available. Most research studies have used doses of 2.5–10 mg when treating initial insomnia, but doses as low as 0.5 mg have been clinically effective, and as high as 15 mg have proven safe without evidence of significant adverse events in children with severe neurodevelopmental disabilities [6].

There have been few adverse effects from melatonin except for occasional reports of enuresis, depression, and excessive daytime somnolence. A single small series reported as a letter to the editor raised the specter of increased seizures in children with profound developmental delay and epilepsy, but this has never been replicated, and the actual report is sketchy without mention of concomitant medications, EEG confirmation, or even precise dose of melatonin [7].

Melatonin has been widely studied in a variety of neurodevelopmental disorders for more than two decades [8]. These studies have mostly described small populations and have been open label without confirmation by measurements of the hormone or its metabolites. Increasingly, there have been more rigorous investigations in various populations. A study endorsing melatonin's safety and efficacy was performed in medication-free children with ADHD and sleep difficulties using a placebo-controlled, double-blind model with outcome measures that included actigraphy and salivary melatonin levels [9].

There is a randomized, double-blind, placebo-controlled crossover study of children with autism spectrum disorder and/or fragile X syndrome whose parents reported significant sleep disturbance. While the study supported the efficacy and tolerability of melatonin treatment, the design had structural flaws, and there was considerable data loss and poor compliance in some participants [10]. More recent studies looking at salivary melatonin and urinary metabolites of this hormone demonstrated the feasibility of the approach, but at this time the high interindividual variability of diurnal melatonin concentrations challenges clinical application [11].

There are some unique situations in which melatonin can be directly therapeutic. Melatonin can be extremely effective for children with total blindness who have a free-running cycle which typically progressively delays their sleep-wake schedule over time, leading to periods of severe dissonance between their need to sleep and the environmental expectations. It can be very frustrating for a child to be up all night and unable to stay awake at school; melatonin can be used to help entrain their circadian rhythms as demonstrated in adults [12]. Another condition is Smith-Magenis syndrome, in which children have a major sleep disturbance with a phase shift of the circadian rhythm of melatonin and a paradoxical diurnal secretion of the hormone. In one study, treatment with melatonin at night (6 mg) followed by the beta-adrenergic antagonist acebutolol (dosed at 10 mg/kg) in the morning significantly improved sleep onset, reduced nocturnal awakenings, increased sleep duration, and delayed sleep offset in the morning [13]. While there have been no double-blind controlled trials in the disorder, melatonin, with adjunctive acebutolol if necessary, has become widely accepted and standard of care [14].

While most research reports of melatonin usage have studied the immediate release preparation, there are also extended-release formulations, including one which is approved for marketing in the European Union. In one study of the long-term effectiveness and safety, 88 children with severe neurodevelopmental disorders including Smith-Magenis syndrome, autism, Rett syndrome, tuberous sclerosis, intellectual disability, and other disorders were studied over 6–72 months. Within 3 months, subjects showed a significant reduction in sleep latency and nocturnal awakenings, increase in sleep duration, and a dramatic improvement in sleep quality reported by 90% of parents, without serious adverse events or treatment-related comorbidities. Still, the study was limited by the open-label design and had no objective measures of sleep such as polysomnography or actigraphy and there was absence of a placebo control group [15]. Subsequently, a much larger study employing similar rigorous structure confirmed the value of the extended-release preparation of melatonin. In this recent report on 125 children and adolescents with autistic spectrum disorder and Smith-Magenis syndrome (SMS), they only enrolled those whose sleep failed to improve on behavioral intervention. This trial included sleep measures using a validated caregivers' sleep and nap diary and a composite sleep disturbance index. After 13 weeks of double-blind treatment, participants slept on average 58 min longer at night with extended-release melatonin compared to 9 min on placebo. Sleep latency decreased by 40 min on average versus 12.5 min with placebo [16].

Ramelteon

Ramelteon is a melatonin receptor agonist, the first of its class, approved for use in adults in the treatment of insomnia. Its package insert lists no restriction on duration of use. Selective binding to melatonin receptors promotes sleep and helps to maintain a normal sleep-wake cycle. Although the half-life is only 1–2.5 h, there is an active metabolite. There is one available pill (8 mg) which is FDA approved for adults only, and off-label use in children may require smaller doses. Common side effects include dizziness, nausea, daytime somnolence, and fatigue. The only commonly expected drug-drug interaction is with fluvoxamine, since that medication inhibits CYP1A2. This is the same pathway for ramelteon's metabolism, so concurrent use can lead to dramatic increases in ramelteon levels. While not approved for children, there is at least one small report describing its effectiveness in children with autism [17].

Antihistamines

Diphenhydramine

Of all medications provided to children with difficulty in settling, diphenhydramine is one of the most popular, yet the scientific basis for its use is among the weakest. This competitive H1 histamine receptor blocker has multiple effects on the central and peripheral nervous systems including sedative and hypnotic, as well as antiallergic, antiemetic, and antitussive properties. It is rapidly absorbed from the gastrointestinal (GI) tract with peak levels within 2 h; the drug affects a wide range of physiologic functions including arousal, cognition, and memory through interactions with H1 receptors in the posterior hypothalamus. Diphenhydramine

has been evaluated in both adults and children, and it produces a decrease in sleep latency and the number of awakenings with an average duration of effect lasting 4–6 h. Dose is generally up to 1 mg/kg with a maximum of 50 mg. When it was studied in infants aged 6–15 months whose parents reported frequent night awakenings, the trial had to be stopped early because it was ineffective: only 1 of 22 children on active drug improved compared with 3 of 22 who received placebo [18]. Even when apparently effective, use of this drug often leads to tolerance, with need for increasing doses and consequent increase in side effects [19]. Safety issues with this popular over-the-counter approach are often not discussed, but overdoses are not uncommon. Anticholinergic side effects include blurred vision, dry mouth, constipation, urinary retention, tachycardia, pupillary dilatation, constipation and urinary retention, dystonia, and confusion. More severe adverse reactions can include stupor, anxiety, and visual hallucinations with rare cardiac rhythm disorders and seizures. There have even been rare lethal consequences, including one report from accidental overdosage [20].

Hydroxyzine

This piperazine antihistamine is a prescription drug which exerts its sedative effects like diphenhydramine through H1 receptor blocking properties with minimal effects on sleep architecture. Although there are multiple reports on the use of the drug for anxiety disorders, there are no direct studies that address its use for sleep promotion. However, it has been compared with chloral hydrate (see below) as a sedative for use in procedures such as EEG [21]. These authors, based in Turkey where both drugs are still commonly employed routinely as sedatives, demonstrated that both drugs worked equally well in promoting rapid sleep onset. General dosing recommendation for use as a hypnotic or anxiolytic is 0.5–1 mg/kg/dose.

Chloral Hydrate

While chloral hydrate has lost its popularity in the United States as a sedative and hypnotic, it is still widely available around the world. In the past, its apparently benign safety profile with significant sleep promotion and little respiratory or cardiovascular toxicity made it one of the most common medications for insomnia given to children. It is rapidly absorbed from the GI tract and converted to trichloroethanol which is a powerful central nervous system (CNS) depressant with a half-life of 8–12 h in children and adults and significantly longer in infants and children. Even though typical therapeutic doses of 20–50 mg/kg/dose usually have little adverse effect, children with obstructive apnea, white matter disease, and brain stem disorders are at particular risk for respiratory compromise. Overdoses can lead to respiratory depression, stupor, and coma as well as cardiovascular instability [22].

Clonidine

The only FDA-approved indication for this alpha-2-adrenergic agonist for developmental disabilities is ADHD in children, and it is approved only in an extended-release preparation. Notwithstanding this bureaucratic limitation, clonidine was still the second most commonly used medication for treating sleep difficulties (after antihistamines) according to a large survey of 800 pediatricians in four states across the United States [23]. A recent review of the use of clonidine in the pediatric population focused on its use in children with various developmental disabilities [24]. Furthermore, clonidine was the most widely used medication to treat insomnia according to a survey of child and adolescent psychiatrists [25].

Clonidine was first marketed for the control of hypertension, and it is still occasionally used for that purpose. From its first use, it manifested the common side effect of sedation, and early studies demonstrated that it was associated with relatively normal sleep architecture except for REM suppression. Its serum half-life is long (6–24 h), but its peak effects for sleep generally last only 2–4 h. Side effects include hypotension, bradycardia, and anticholinergic properties such as dry mouth. Sudden discontinuation can lead to rebound hypertension and REM rebound. Most clinicians start with 0.05 mg at any age and increase in 0.05 mg increments, although there is no clear recommended hypnotic dose. A small case series gives examples of the value of clonidine in children with a variety of developmental disorders [26]. The drug has also been studied in children with autism with two-thirds of patients having a positive response at 0.1 mg in an open-label retrospective review [27].

The frequent coexistence of sleep problems in children with ADHD led to its off-label popularity as a treatment, as well as the finding that adrenergic drugs showed efficacy in treatment of ADHD long before regulatory approval of an extended-release clonidine for this indication [28]. Caution is advised in this population because there have been reports of serious cardiovascular side effects when clonidine is co-administered with stimulants [29, 30].

Benzodiazepines

There is a long history of various benzodiazepines being used for adults and children with insomnia and parasomnias. The reputed mechanism is through activation of GABA-A receptors which can lead both to drowsiness and reduced

anxiety. Despite decreased arousability, people taking benzodiazepines show a reduction in deep non-REM (stage N3 or slow wave) sleep. The two most commonly prescribed benzodiazepines for children are clonazepam and diazepam, both of which are among those in this class with the longest half-lives. Clonazepam is a far more effective chronic antiepileptic medication than diazepam, and it can be used for both seizure control and sleep promotion. Both drugs can be effective in treating non-REM parasomnias, including night terrors and sleepwalking. Other benzodiazepines are rarely used, mostly because of extremely long half-lives (flunazepam) or, conversely, such short half-lives that rebound arousals in the middle of the night are common (temazepam, estazolam, and triazolam). Among the concerns about using this class of drugs is the effect of muscle relaxation in children with obstructive and central sleep apnea. This class of medications should be avoided in children with sleep-disordered breathing because they blunt the arousal response to hypoxemia and can thus worsen apnea.

Non-benzodiazepine Hypnotics

There have been few studies of the use of non-benzodiazepine hypnotics in children, none of which are approved for use in individuals below 18 years old. They are widely used for insomnia in adults and not infrequently prescribed off-label to children. These drugs include zolpidem (Ambien), eszopiclone (Lunesta), and zaleplon (Sonata). This class of drugs is an improvement on benzodiazepine hypnotics because they allow normal sleep architecture and have a lower incidence of rebound effects when abruptly stopped. Still, they are not intended for nightly use lasting more than a few days. All of these drugs have a similarly rapid onset of action with significantly shortened sleep latency, but zaleplon has the shortest half-life (1 h) and typically only helps sleep-onset insomnia. Even zolpidem, with a half-life of 2.5 h, may allow for continued arousals at night, but an extended-release preparation is now available which can provide all-night coverage. Since many children with insomnia have sleep-onset difficulties only, it may be clinically acceptable to add a brief course of a non-benzodiazepine hypnotic to a behavioral regimen for an adolescent with a condition like delayed sleep-phase syndrome; however, this is more likely to run the risk of morning sedation or of rebound insomnia when the drug is stopped. Since there is evidence that tolerance to the drug does not occur even after 6 months of nightly exposure, eszopiclone has been FDA approved for long-term use in adults [31].

There is limited pharmacokinetic information about the use of zolpidem in children ranging in age from 2 to 18 years which showed efficacy and tolerability. Based on a single pediatric pharmacokinetic study, the recommended pediatric dose is 0.25 mg/kg with a maximum dose of 20 mg [32]. A placebo-controlled double-blind study of children with insomnia and ADHD found no effect: there was no improvement in sleep latency between the active compound and placebo, but there were more complaints of dizziness, headache, and hallucinations with zolpidem [33]. Eszopiclone has a longer half-life of 6 h, but there are no studies that describe its safety or efficacy in children.

Sedating Antidepressants

Trazodone (Desyrel) and mirtazapine (Remeron) are occasionally used to achieve sleep. Both are atypical antidepressants which are often sedating even at doses lower than typically used for the FDA-indicated symptom, but neither is approved for any purpose in children or adolescents. Trazodone is a serotonin 5-HT_2 receptor antagonist that promotes sleep by inhibiting uptake of serotonin and blocking histamine receptors. Mirtazapine is a histamine H1-receptor antagonist which reduces sleep latency and increases sleep duration without significant effects on REM. Both can lead to daytime sedation. The common side effects of trazodone are dizziness, vision changes, constipation, and dry mouth; rare complications can include exacerbation of seizures, cardiac arrhythmias, hypotension, and priapism. The most common side effect of mirtazapine is weight gain. Dizziness, constipation, and dry mouth are also frequently seen.

Other antidepressants including paroxetine (Paxil), amitriptyline (Elavil), and imipramine (Tofranil) may also have sedating properties. Although paroxetine is among the most sedating of the SSRIs, it should be avoided in children and adolescents because of the risk of suicidality. The use of antidepressants for sleep difficulties complicating mood disorders requires careful consideration of the type of sleep problem from insomnia to daytime sleepiness or co-existing primary sleep disorder such as obstructive apnea or PLMS. It is not uncommon for sleep difficulties to respond to effective treatment of the primary mood disorder, and at other times treating the sleep problem can significantly improve mood symptoms. In addition to mood disorders, these medications are commonly used for migraine prophylaxis (amitriptyline) and uncommonly for ADHD (imipramine).

Neuroleptics

The use of atypical neuroleptics including risperidone and aripiprazole has been approved to treat aggression in children with autism. Randomized controlled trials noted adverse events including drowsiness and somnolence, and in fact, these were the most commonly noted side effects occurring in twice as many subjects in the risperidone arm compared to placebo (24% vs 12%) in one pivotal study [34]. Typical and atypical antipsychotic drugs are also used off-label for similar behavioral problems in children with other

developmental disabilities. Since there is often a calming effect in addition to sedation in some that allows children to settle more effectively, some clinicians have tried these drugs to help with sleep in children. However, there is no evidence on safety or efficacy in the neurologically typical child and only anecdotal information about its effect on sleep in autism. Risperidone has been shown to increase non-REM sleep (both N2 and N3) and to suppress REM sleep [35]. While these medications may help children to fall asleep and the known effects on sleep architecture are favorable, their routine use is strongly discouraged since there is little on the safety and tolerability for short-term use as well as the long-term risks for gynecomastia, tardive dyskinesia, and other unknown consequences. It is also important to recognize the risk of weight gain with this class of medication which could significantly worsen any underlying sleep apnea.

Herbal Supplements

There is widespread usage of complementary sleep aids which are generally believed to have an acceptable safety profile, but none have been studied in children, and the data are generally weak in adults. A review of the available evidence for the sleep-promoting qualities of herbal supplements was carried out by the American Academy of Sleep Medicine in 2004. Although there were few randomized placebo-controlled studies, rigorous scientific data supporting safety and benefit were lacking for the majority of nutritional supplements. Available studies were limited by small studies with inadequate design, no objective measurements, and lack of statistical analysis [36]. There was no evidence for chamomile or St. John's wort. Limited, conflicting studies showed possible value for the short-term use of valerian. This plant derivative was studied in children with intellectual disability in a randomized double-blind, placebo-controlled fashion, with positive results, but the total n was only 5 [37]. The AASM review cited the significant potential risks associated with Jamaican dogwood, kava kava, alcohol, and L-tryptophan. Although L-tryptophan was quite popular at one point, it is no longer available following cases of eosinophilic myalgia syndrome attributed to contamination during the manufacturing process. Proponents of complementary and alternative medications have recommended herbal supplements such as lavender applied as aromatherapy, but they have never been systematically studied [38].

Treatment of Excessive Daytime Sleepiness

As important as the caveat about not treating insomnia with a pharmacologic approach before comprehensive investigation of the causes and initial behavioral management, it is even more urgent applied to daytime somnolence in the patient population with developmental disabilities. One should never treat a symptom like sleepiness with medication until it is clear whether the child is getting adequate amount and quality of nocturnal sleep, whether there is a sedating medication, or if the child is sleepy as a consequence of post-ictal lethargy or unrecognized seizures. Daydreaming or emotional withdrawal from the environment can be interpreted as sleepiness. Physically limited children may be so under-stimulated at times as to fall asleep during the day, a problem that can be further compounded by misinterpretation since they may not sleep well at night resulting from their total daily sleep requirement being partially met by daytime sleep such that their nighttime sleep is fragmented. Perhaps the most common cause beyond inadequate amount of nocturnal sleep – an epidemic problem affecting more than half of US adolescents and a third of younger children – one must consider primary sleep disturbances such as obstructive apnea and periodic limb movement disorder [39]. Only after all of these are first addressed is it reasonable to consider if medications may be necessary to supplement behavioral approaches, such as with narcolepsy. Please see also Chapter 8 for additional discussion, especially as regards treatment of narcolepsy.

Modafinil

This non-stimulant alerting agent has become the first-line approach for excessive daytime sleepiness associated with narcolepsy because of its safety and side effect profile [40]. Its mechanism of action appears to be different from methylphenidate or amphetamines, and it is hypothesized that it works on hypothalamic wake-promoting centers. Well-controlled trials in adults with narcolepsy have demonstrated improvements in wakefulness and objective measures of sleepiness in narcoleptic individuals. The half-life of 10–12 h allows for once- or twice-daily administration (usually morning and noon) at doses of 200–400 mg. Experience has demonstrated very low abuse potential or rebound increase in sleepiness. While still off-label in children, there are reports in children with narcolepsy demonstrating effectiveness [41]. Armodafinil, the R-enantiomer of the parent compound, has a longer half-life and can enhance wakefulness with a single daily administration at doses of 150–250 mg daily.

Stimulants

Methylphenidate and amphetamine preparations have largely been supplanted by modafinil for the treatment of daytime sleepiness in narcolepsy due to its better safety profile. The non-stimulant results in much less irritability, anxiety, tachycardia, increased blood pressure, appetite suppression, and nocturnal sleep disturbance. However, many of these negative

attributes were described when the only available preparations were short-acting. Longer-acting, smoother delivery systems such as various proprietary extended-release forms of methylphenidate (e.g., Concerta, Daytrana, and Quillivant XR), dexmethylphenidate (e.g., Focalin XR), and lisdexamfetamine dimesylate (e.g., Vyvanse) can generally provide the same degree of wakefulness as modafinil with minimal side effects. Pharmacologic treatment in general is well outlined in a review from the American Academy of Sleep Medicine [42].

Kleine-Levin Syndrome

In discussing neurologic disorders producing daytime somnolence, it is important to highlight this rare sleep disorder which primarily affects adolescents. It is characterized by episodes of severe hypersomnia, cognitive impairment, apathy, and psychiatric disturbance. Most have specific feelings of derealization and eating disturbances with a large minority expressing hypersexuality, compulsions, and depressed mood. Treatment has been mainly symptomatic with stimulants, neuroleptics, or antidepressants, but these rarely help. Only lithium had a higher reported response rate for preventing relapses in one very large review [43]. In a more recent review, carbamazepine, valproate, and other anti-epileptic drugs were still favored by many clinicians [44].

Treatment of Restless Leg Syndrome and Periodic Limb Movement in Sleep

The distinction between restless legs syndrome (RLS) and periodic movements in sleep (PLMS) is discussed elsewhere in Chapter 10, but it should be noted that the distinction is often difficult in children, who are typically unable to describe the subjective discomfort that defines RLS. It is common to rely on evidence of associated PLMS to support suspicion of RLS in children. Either or both related conditions can disturb consolidated night sleep and lead to daytime sleep deprivation that can cause sleepiness; they can also mimic or contribute to symptoms of ADHD.

Medications Used to Treat RLS and PLMS

Iron Supplementation

Iron depletion as defined by low serum ferritin can lead to both RLS and PLMS. The mechanism appears to be the local deficiency of iron necessary as a cofactor for tyrosine hydroxylase, the first step in dopamine synthesis. It took time for this to be appreciated, since there is a wide range of serum ferritin levels in the unaffected population, but clinical improvement is often seen in symptomatic individuals whose ferritin is less than 50 mcg/ml – even those who are normocythemic – when given iron supplementation [45, 46]. The usual dose is 3 mg/kg/day of elemental iron divided twice daily in non-anemic individuals with a goal to bring serum ferritin up to 50 mcg/ml [47].

The relationship between developmental disabilities and sleep problems may have subtler and poorly understood connections. For example, children with autism often have restricted diets and gastrointestinal symptoms in addition to sleep onset as well as sleep maintenance insomnia. Whether due to narrow food choices or malabsorption, children with these problems would be at risk for iron deficiency. Although anemia is uncommon in this population, at least one group has looked at ferritin levels and found a remarkable incidence of insufficient dietary iron intake, particularly in preschool children, with extremely low ferritin levels (mean 15.7 mcg/L) at baseline. Treatment over 8 weeks increased mean ferritin levels significantly and improved restless sleep [48]. Unfortunately, the methodology was limited, and did not include objective measures to monitor PLMS by polysomnography, and it is unclear whether sleep questionnaires could adequately identify the presence of restless legs or periodic limb movements in this population. The study was limited in scope, both in sample size, duration of treatment (inadequate to bring ferritin levels above 50), and objective outcome measures, but it is very provocative and suggests further lines of research.

Selective Dopamine Agonists

Drugs such as pramipexole (Mirapex), ropinirole (Requip), and pergolide (Permax) have become the standard treatment for adults with RLS and PLMS. They are more powerful and require lower doses than direct dopamine precursors such as L-dopa. Well-designed studies have only been carried out in adults, and there is little evidence base in children and adolescents beyond case reports. If these drugs are used, it makes sense to follow the guidelines for adults, start with the lowest possible dose, and make gradual changes no more than weekly in order to find the lowest effective dose and avoid unnecessary side effects. As with other treatments for sleep disorders, there are no FDA-approved medications for pediatrics. However, experience has been summarized in a recent comprehensive review article [46].

Treatment of Parasomnias

Parasomnias, discussed in detail in Chapter 7, are abrupt events that disrupt the sleep-wake interface – either during entry into sleep, within sleep, or during arousal from sleep. They can be frightening both to children and caregivers and may be confused with other paroxysmal phenomena includ-

ing seizures and panic attacks. While most common in preschool aged children, they tend to occur infrequently, and it is unusual to have more than one event per night or on a daily basis. It is believed that there is a genetic predisposition which allows activation of subcortical central pattern generators to respond to external (e.g., ambient noise) or internal (e.g., reflux, fever, epilepsy, PLMS, apnea) stimuli, leading to the instability of the arousal mechanisms resulting in behaviors from somniloquy to full pavor nocturnus or night terrors. Children with developmental disabilities may have many reasons for immaturity of their sleep-wake system in addition to being prone to the very disorders just listed that can trigger disruption and parasomnias. Since parents are already concerned about their children's neurodevelopmental status, it is not hard to imagine why they might leap to the conclusion that such nocturnal arousals have a more serious basis such as seizure. According to one study, disruptive parasomnias in children should trigger an evaluation for a precipitating cause. In a large case series of 84 children with sleep terrors, 58% had sleep-disordered breathing, and partial arousals disappeared with treatment [49]. The pathophysiology and differential diagnosis of parasomnias are discussed in more detail elsewhere. This section will only discuss the treatment of non-REM parasomnias, which are the most common. It should be noted that all pharmacologic approaches to parasomnias are off-label since there are no approved agents for any of these disorders.

Treatment of infrequent sleep disruption caused by sleepwalking, confusional arousals, and sleep terrors obviously requires understanding, support, and environmental protection to avoid injury. However, infrequent events typically do not need to be treated. Parents are usually reassured that events can be minimized by avoiding sleep deprivation with a regular schedule including adequate nap time and by the fact that most toddlers will outgrow their tendency to experience parasomnias. In cases where parasomnias are frequent or atypical events or additional reassurance is needed, full polysomnography with 16-channel EEG is recommended to clarify the (unlikely) differential which includes seizure disorder, apnea, or PLMS.

Medications Commonly Used to Treat Non-REM Parasomnias

Benzodiazepines

There have not been any formal studies of benzodiazepines or other medication treatments in non-REM parasomnias, but expert consensus suggests pharmacologic treatment if no specific treatable triggers can be found and the events are problematic. This includes low-dose benzodiazepines at bedtime, such as clonazepam at doses ranging 0.125–0.5 mg. Potential side effects such as drooling and paradoxical hyperactivity may be particularly troublesome for children with neurodevelopmental disabilities [50].

The mechanism of action is believed to be based on benzodiazepines' GABAergic effect. This can improve the situation by reducing the depth of N3 sleep from which non-REM parasomnias arise and by decreasing arousability. It is important to first be sure that one is not missing a secondary form of parasomnia due to obstructive sleep apnea, since decreasing arousability could lead to longer events with more profound desaturations. It is also important to choose medications with optimum durations of action, since a drug with too long of a half-life can lead to morning sedation or irritability and a drug with too short of a half-life can delay undesired events until later in the night without actually eliminating them. Clonazepam probably has the best track record [51]. Its time-to-peak action is 1–3 h, which coincides with the usual timing of non-REM parasomnias, and duration of action is typically 6–8 h in children and up to 12 h in adults, even though the half-life of the drug is typically longer than 24 h. In recent years, clonazepam has become more convenient, with oral dissolving tablets in sizes ranging from as small as 0.125 mg to as large as 2 mg. Some clinicians find comparable efficacy with diazepam in doses from 2.5 to 10 mg. It is often too long acting for adolescents, but more rapid metabolism in younger children makes it a reasonable option without causing a hangover effect. Although not available as a dissolvable tablet, it has the advantage of being available as a suspension for children unable to swallow pills.

Other Medications

There are case reports of other drugs being effective for non-REM parasomnias. Paroxetine was effective in an adult with a 30-year history of night terrors, although most pediatric clinicians would avoid this drug in children due to its higher rate of suicidal ideation compared to other SSRIs [52]. Another isolated case report described remarkable improvement with trazadone in a 7-year-old child with sleep terrors [53].

Chronobiologic Disorders

Although these neurologic disorders will be discussed in Chapter 9, it is worth mentioning the challenges presented by children with congenital blindness and Smith-Magenis syndrome. The former may not be able to form a sleep-wake cycle due to lack of input to the hypothalamic centers. The latter was already briefly discussed in the section on melatonin treatment due to its inverted pattern of melatonin secretion leading to a characteristic circadian sleep disorder in addition to dysmorphic features, developmental delays, and behavioral difficulties. The disrupted sleep pat-

tern can be so severe that it is what first brings children with Smith-Magenis syndrome to medical attention [14].

Treatment with nightly melatonin with a morning beta-adrenergic blocker, when necessary, has proven to be effective to control sleep schedule in many children, with beneficial secondary effects on behavior as well [54]. Melatonin was given in doses up to 15 mg at night, and acebutolol 10 mg/kg was given in the morning. This led to more organized, stable sleep architecture with improved N3 and REM sleep percentages as well as elimination of daytime naps, marked reduction in tantrums, and generally improved behavior. Other specific disorders with melatonin secretion abnormalities have also been studied: for example, Angelman syndrome has been shown to have low-peak melatonin levels in addition to a phase delay in nocturnal melatonin release [55].

Conclusions

While sleep disorders in children with neurological disorders are even more common than in the general population, there is still a lack of comfort with their management voiced by many pediatricians, neurologists, and developmental specialists. This is partly due to the minimal training in sleep medicine many receive during training. In addition, many well-meaning clinicians are intimidated by the dearth of well-designed trials to demonstrate safety and efficacy leading to the lack of FDA approval of drugs for children. Reliance on adult data and anecdotal experience are often inadequate. Without a clear evidence base and the absence of FDA-approved medications for specific sleep disorders in children, it is no wonder that pediatric generalists and specialists are reluctant to recommend drugs and unsurprising that parents and caregivers wind up using over-the-counter preparations and complementary-alternative approaches that have even less scientific credibility. However, as a society, we are coupled with the twin epidemics of obesity (leading to increased prevalence of sleep-disordered breathing) and inadequate sleep (attributed to factors from lifestyle choices to school hours and excessive light exposure at night). Therefore, it is incumbent on all involved in the care of children to advocate for improved knowledge of sleep as well as more effective treatments.

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