**TREATMENT OF CHRONIC INSOMNIA IN CHILDREN AND ADOLESCENTS WITH NEURODEVELOPMENTAL DISABILITIES**

SHORT RUNNING TITLE: **Treatment of insomnia in NDD**

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**ABSTRACT**

Sleep disturbances, and especially insomnia, represent a common problem in children with neurodevelopmental disabilities. Effective pharmacologic interventions are needed to improve sleep and quality of life especially when behavioral therapy alone is insufficient. Unfortunately, there are no approved sleep medications by the United States Food and Drug Administration or European Medicines Agency for pediatric insomnia and most of the medications are prescribed off-label. Antihistamine agents, such as hydroxyzine or diphenhydramine, are the most widely prescribed sedatives in the pediatric practice. Melatonin is also commonly used and, apparently, is the safest choice for children with developmental disabilities. Benzodiazepines are not recommended in children and should only be used for transient insomnia, especially if daytime anxiety is present. Zolpidem, zaleplon, eszopiclone are selective benzodiazepines binding preferentially to GABA type A receptor complexes but only few studies have been carried out in children and adolescents. Alpha-agonists such as clonidine are used in child psychiatry to improve sleep onset latency, especially in ADHD subjects. Tricyclic antidepressants are used in adults with insomnia due to their sedating properties, but are not recommended in children because of their safety profile. Trazodone and mirtazapine hold promise but require further studies. Well-controlled studies employing both objective polysomnography and subjective sleep measures are needed to determine the efficacy and safety of the currently prescribed pediatric sleep medicines.

**KEYWORDS:** Sleep disorders; insomnia; neurodevelopmental disorders; drug effects

**INTRODUCTION**

Sleep disorders in children with Neurodevelopmental disabilities (NDDs), represented by difficulty in falling asleep, night awakenings, and reduced sleep duration, are among the most common parental complaints to health care professionals, with prevalence of 86%.(Robinson-Shelton & Malow, 2016). In children with NDDs sleep disturbances impact on cognitive and emotional development, aggravating the functional impairment associated with these conditions(van de Wouw, Evenhuis, & Echteld, 2012) but affect also the entire family environment disrupting the siblings and marital relationships and increasing the levels of stress.(S. E. Goldman, Bichell, Surdyka, & Malow, 2012)

The pathophysiology of sleep disorders in children with NDDs is multifactorial: in some patients problematic sleep is a phenotypic characteristic of a particular disorder or genetic condition and the knowledge of the distinctive features of sleep disorders in patients with NDDs is crucial for their effective treatment.(Grigg-Damberger & Ralls, 2013) In other cases, sleep disorders represent a main comorbidity: a meta-analysis(Cortese, Faraone, Konofal, & Lecendreux, 2009) on sleep in ADHD found that children or their parents reported bedtime resistance, sleep-onset difficulties, night awakenings, difficulties with morning awakening, sleep breathing problems, and daytime sleepiness significantly more often than healthy controls. Moreover, sleep disorders might be aggravated by common issues linked to NDDs (such as sensory and motor deficits, psychopathological disturbances, respiratory disorders, epilepsy, and mental retardation) all contributing to the developmental delay.

Sleep problems could be specific in different syndromes (i.e. sleep apnea in Down or Prader-Willi syndromes) but the sleep complaints in children with NDDs are mainly represented by difficulty in settling at night (51%) and nocturnal awakenings (67%)(Quine, 1991) Fragmented sleep throughout the day and night determines daytime sleepiness and irregular sleep schedule that may lead to a free-running rhythm or to a complete reversal of the night-day cycle.(Okawa MSH., n.d.).

The are no US Food and Drug Administration (FDA) approved medications to treat insomnia in pediatric patients including those with NDDs, and therefore most of the drugs are prescribed off-label.

In this review, we will describe the current clinical evidence for the treatment of chronic insomnia in children and adolescents with NDDs.

**METHODS:**

**Search strategy and results from each database**

To ensure high levels of methodological adequacy as recommended by the Cochrane group (Higgins JPT & Green S, 2011) and avoid the inevitable bias caused by dependence on investigators agreeing to provide data from unpublished studies, we did not search for unpublished data. We excluded non peer-reviewed references (e.g., conference proceedings) since we considered peer-review process as essential to the quality of the publication. We retained all types of study designs.

We searched the following electronic databases: PubMed, Ovid (including PsycINFO, Ovid MEDLINE®, and Embase), Web of Knowledge (Web of Science, Biological abstracts, BIOSIS, FSTA). The specific search terms and syntax for each database are reported in the Supplemental Material. The search was finalized on February 12nd, 2017. No language limitations were applied, to avoid biases due to language restrictions. References list of pertinent reviews/systematic reviews were screened to reduce the likelihood of missing any relevant publication. Two authors (MA and SC) independently and blindly performed the search and screening of papers against eligibility criteria. Any disagreement between the two authors was resolved by consensus.

**NON-PHARMACOLOGICAL TREATMENT**

Prevention is the best treatment for insomnia of childhood but, unfortunately, most parents request an evaluation when the disorder has become chronic. Although we will focus on drug treatment, we should emphasize that when there is a decision to start a pharmacologic intervention, behavioral interventions should be always associated.(Jan et al., 2008); good sleep practices and behavioral interventions are the first recommended treatments for pediatric insomnia in either healthy or NDD children. (Honaker & Meltzer, 2014)

The first line of treatment is the promotion of better sleep habits that need to be modified and adapted to these children, are often somewhat challenging to implement, and should be associated with other behavioral interventions using a gradual approach (gradual withdrawal, gradual extinction, fading etc.), rather than an abrupt change (e.g. extinction techniques), that may be easier and more acceptable for parents as well as being more appropriate for some children with special needs. The choice of one particular form of behavioral intervention rather than another should be guided by the parent preferences(Wiggs & France, 2000) and like in typically developing children, there is no evidence that one approach is more effective than another.(Angriman, Caravale, Novelli, Ferri, & Bruni, 2015)

A systematic review of behavioral treatments for insomnia reported that moderate-to-low level of evidence supports behavioral interventions in adolescents and in children with NDDs. This review showed only two studies involving behavioral interventions for sleep problems for children with special needs that met the inclusion criteria. One study included children with autism spectrum disorders (Adkins et al., 2012) whereas the other focused on children with Down syndrome.(Stores & Stores, 2004). An older study showed that bedtime fading resulted successful to advance the bedtimes in a sample of 3 patients with Rett’s syndrome. This treatment resulted in more regular sleep patterns for the girls by increasing appropriate nighttime sleep, reducing inappropriate daytime sleep and reducing problematic nighttime behaviors (e.g., night wakings.)(Piazza, Fisher, & Moser, 1991)

There were no significant effects for any of the four sleep outcome measures(Meltzer & Mindell, 2014) but sleep hygiene education was associated with improvement in daytime behaviors, pediatric quality of life, and sense of competence in parents.

More studies are needed to identify factors that may predict treatment success and to tailor behavioral interventions for young children based on the child (e.g., temperament, age), parental, and environmental factors and on the underlying disease.

However, the involvement of parents as agents for changing problematic sleep behaviors is fundamental; in this way, the consistent application of cognitive behavioral techniques can be effective in improving quality of life and well-being for patients and caregivers. (Grigg-Damberger & Ralls, 2013) (Jan et al., 2008).

 Allen et al.(Allen, Kuhn, DeHaai, & Wallace, 2013) evaluated the effectiveness of a behavioral treatment package to reduce chronic sleep problems in 5 children (2-11 years of age) affected from Angelman Syndrome. The treatment package targeted the sleep environment, the sleep-wake schedule, and parent-child interactions during sleep times. Changes in disruptive bedtime behaviors and in sleep onset were found to be statistically significant.

Training group of parents in behavioural approaches to manage sleep problems represents a novel behavioral approach: the article from Stuttard et al. (Stuttard, Beresford, Clarke, Beecham, & Curtis, 2015) reports the findings from a preliminary evaluation of a group-delivered intervention routinely delivered by a Child and Adolescent Mental Health Service Learning Disability team in England: parents (n = 23) of children with intellectual disabilities were recruited and the follow up was of 6 months. No parent dropped out and statistically significant improvements in night wakings, parent-set goals and parents' sense of efficacy were observed.

Table 1 reports non-pharmacological approaches to insomnia in children with NDDs.

**Table 1. Behavioral strategies for insomnia in children with neurodevelopmental disabilities**

|  |
| --- |
| Adjust sleeping environment |
| * Dark, quiet, non-stimulating
 |
| * Turn off electronic devices
 |
| * Develop a constant bedtime routine
 |
| * Promote self-soothing skills that allow the child to manage nocturnal awakenings
 |
| * Put to bed and get them up at the same time every day
 |
|  |
| In case of difficulties falling asleep: |
| * + Avoid naps 4 hours before bedtime
	+ Apply bedtime fading (delay bedtime closer to the child target bedtime of about 30 minutes; then move bedtime earlier)
 |
| * + Favor light exposure when the child gets up and reduce photic stimulation at evening, to reinforce circadian alignment
 |
| * + Apply graduated extinction for the child disruptive bedtime behaviors
 |
|  |
| In case of frequent nocturnal awakenings:* + *Extinction with parental presence*: The parent remains in the room during extinction, acting as a reassurance for the child but providing little interaction
	+ *Graduate extinction*: ignore negative behaviors (i.e., crying) for a given amount of time before checking on the child. The parent gradually increases the amount of time between crying and parental response. Parents provide reassurance through their presence for short durations and with minimal interaction
 |

(adapted from Grigg-Damberger & Ralls, 2013)

An interesting non pharmacological approach refers to bed materials and accessories: Gringras et al. (Paul Gringras et al., 2014) assessed the effectiveness of a weighted-blanket intervention in treating severe sleep problems in children with autism spectrum disorder with a randomized, placebo-controlled crossover design; the use of a weighted blanket did not help children with ASD sleep for a longer period of time, fall asleep significantly faster, or wake less often, but resulted well tolerated from the entire family.

More recently, Frazier et al. (Frazier et al., 2017) in a preliminary, randomized study investigated the tolerability and the efficacy of a novel mattress technology - the Sound-To-Sleep (STS) system - in the treatment of sleep problems in , 45 children, ages 2.5 to 12.9 years children with autism. A good compliance to this technology was observed and parent-diary outcomes indicated improvements in falling asleep and reduced daytime challenging behavior. Actigraphy-derived sleep parameters indicated improved sleep duration and sleep efficiency.

**PHARMACOLOGICAL TREATMENT**

In children and adolescents with NDDs, behavioral techniques may be difficult to implement and may take weeks or months to show benefits, therefore sleep-promoting agents while continuing behavioral intervention should be recommended.

Causes of sleep problems in children with NDDs are often complex and multifactorial: sleep difficulties may be related to co-occurring medical conditions (eg, epilepsy or gastroesophageal reflux) or poor sleep hygiene or behavioral insomnia of childhood that can be challenging to identify in a child with NDDs and be exacerbated by communication challenges. Providers may not have received training, or have the time, to implement behavioral interventions for sleep. Parent-based education and behavioral interventions are the first line of treatment for insomnia, unless symptom severity necessitating early pharmacotherapy is present.

Children who do not respond to behavioral interventions could be candidates for pharmacological treatment of insomnia that should always be considered in combination with behavioral treatment.(Angriman et al., 2015)(Pelayo & Yuen, 2012)

Due to the lack of controlled studies, there are no sleep medications approved by the FDA or European Medicines Agency (EMA) for pediatric insomnia in general and in children with NDDs. The most used off-label medications are: sedating antihistamines (e.g., diphenhydramine and hydroxyzine), melatonin, benzodiazepines, α-2–receptor agonists (e.g., clonidine), pyrimidine derivatives (e.g., zaleplon and zolpidem), antipsychotics (e.g. risperidone and quetiapine), and sedating antidepressants (e.g., trazodone and mirtazapine).(Pelayo & Yuen, 2012), but little data exist on their efficacy for the treatment of insomnia in children.(Mindell et al., 2006).

It should be taken into account that drugs could be initially useful for parent and child relief and in general it is better not to wait a long time to treat insomnia, implementing an immediate brief drug trial rather than act later on a chronic insomnia that has already lasted for several months or years (Pelayo and Dubik, 2008). Especially in infants and children, chronic insomnia can lead to maternal depression, family dysfunction and impaired social functioning but also can affect child’s physical and mental health. Due to these serious implications for both individuals and society, it is essential to treat insomnia either through education of parents, teachers and other caregivers but also with an effective drug treatment, when the insomnia lead to a disruption of family life, child’s and parents’ health.

A recent Australian survey on pharmacological management of insomnia in children reported that the most commonly prescribed medications for poor sleep initiation were melatonin (89.1%), clonidine (48%) and antihistamines (29%). Most pediatricians (82%) reported also using behavioral strategies for sleep disturbances, most commonly anxiety relaxation techniques (75%) for poor sleep initiation and graduated extinction (i.e. “controlled crying”, 52%) for disrupted overnight sleep.Paediatricians most commonly prescribed for children with autism (85.2%), developmental delay (76.2%), ADHD (54.5%), behavioral disorders (42.6%), visual impairment (40.6%), and anxiety disorders (25.7%). However, over half of the paediatricians (54.5%) prescribed for typically developing children. (Heussler et al., 2013)

In children with NDDs or psychiatric disturbances different surveys confirmed that drugs are commonly prescribed off-label (Bruni et al., 2004)

A survey by Owens et al.,(Owens, Rosen, Mindell, & Kirchner, 2010) showed that more than one-third of 1,273 child psychiatrists treated insomnia with medication at least half of the time in patients with ADHD, ASD, and with mental retardation/developmental disabilities (MR/DD). Moreover, they reported to treat 17% of preschoolers and at least one-quarter of school-aged and adolescent patients. Overall, 96% of psychiatrists recommended at least one medication in a typical month, and 88% recommended an over-the-counter medication.

In general, psychiatrists were more likely to use herbal preparations in children with anxiety or mood disorders than in children with NDDs or ADHD; melatonin was recommended by more than one-third of them (39%) although it is unclear whether it was being used primarily at bedtime for its mild hypnotic effects or as a chronobiotic. The physicians recommended for sleep disorders (mainly insomnia) nonprescription antihistamines in 69% of cases and α agonists in 67% of children with MR/DD. Trazodone was the second most frequently prescribed medication for children with MR/DD (66%) while sedating antidepressants were used in 75.5% of MR cases. Atypical antipsychotics were used by more than half of the psychiatrists in children with MR/DD (52%) and benzodiazepines were used in 21.6% of cases of MR/DD. Tricyclic antidepressants were also used for children in these diagnostic groups (25.5%).

We have to consider that this situation could be specific for the USA, however similar results have been replicated also in other countries (Heussler et al. 2013; Bruni et al., 2004)

Three recent registry study examined the prescription habits of pediatricians toward sleep disorders in developmental disabilities. Efron et al.(Efron, Lycett, & Sciberras, 2014) described sleep medication use in a sample of 257 school-aged children with ADHD and of these 57 (22%) were taking sleep medication (melatonin 14% and clonidine 9%). Sleep medication use was associated with combined-type ADHD and ADHD medication use. The presence of co-occurring internalizing and externalizing co-morbidities was also associated with sleep medication use in ad hoc analyses.

A recent study in autism spectrum disorders showed that medications for sleep were prescribed in 46% of 4- to 10-year-olds of children affected from autism and sleep difficulties. The most common medication used for sleep was melatonin followed by α-agonists, with a variety of other medications taken for sleep (anticonvulsants, antidepressants, atypical antipsychotics, and benzodiazepines). Children taking medications for sleep had worse daytime behavior and pediatric quality of life than children not taking sleep medications. (Malow et al., 2016)

Another recent research (Bock, Roach-Fox, Seabrook, Rieder, & Matsui, 2016) found that the most common circumstances and sleep problems for which OTCM or RXM were recommended were mood disorders, developmental delay and attention deficit hyperactivity disorder (ADHD) (56, 40, and 39%, respectively), and insomnia, bedtime struggles/delayed sleep onset and circadian rhythm disorders (52, 48, and 28%, respectively). A total of 30% recommended OTCM or RXM to otherwise healthy children with sleep problems. Melatonin (73%), OTC antihistamines (41%), antidepressants (37%), and benzodiazepines (29%) were the most commonly recommended OTCM and RXM, respectively.

Before beginning a drug treatment in children with NDDs, different aspects should be taken into account: commonly these children are taking other drugs (mainly sedatives, antiepileptics, etc.) and the eventual interactions should be considered cautiously, previous sleep medications or homeopathic or OTC preparations, finally the age of the child and his/her clinical history. Treatment goals must be established with the parents and, if possible, with the patient and should be realistic, clearly defined, and measurable. The immediate goal of treatment will usually be to alleviate or improve*,* rather than to completely eliminate*,* sleep problems.

When a drug has been administered, abrupt discontinuation should be avoided and the treatment should be carefully monitored since there is a natural inclination of the parents to give the lowest dose.(Pelayo & Dubik, 2008)

The choice of the drug, in view of the lack of scientific evidence, should be guided by an accurate evaluation of the main complaint (i.e. difficulty falling asleep, night awakenings, phase advance or delay, nocturnal hyperactivity, mid-night awakening, etc.) but also a correct family history can be useful.

The three greatest unmet clinical needs in the treatment of insomnia are residual daytime sedation, tolerance and addiction potential and improvement in sleep maintenance.

Table 2 reports the most commonly used pharmacologic agents for insomnia in children with NDDs.

The following section is devoted to describe the drugs and off-label compounds commonly used in chronic insomnia of children with NDDs.

**Melatonin**

Melatonin (N-acetyl-5-methoxytryptamine) is a chronobiotic agent involved in the regulation of the sleep–wake cycle. In older children and adults, its production and secretion begin in the evening and peak during the night between 2:00 and 4:00 AM and are inhibited by light.(Kennaway, 2000)

A nationwide study showed that hypnotic drug use in 0- to 17-year-old patients increased during the period 2004-2011, from 8.9 to 12.3/1000, mainly owing to the doubling of melatonin use that was dispensed in the highest annual amount among all hypnotic drugs. (Hartz, Furu, Bratlid, Handal, & Skurtveit, 2012)

Approximately 56% of pediatricians prescribed melatonin for sleep onset insomnia (89.1%), delayed sleep phase (66.3%), and nighttime awakenings (30.7%). It is also prescribed in children with autism (85.2%), NDDs (76.2%), ADHD (54.5%), behavioral disorders (42.6%), visual impairment (40.6%), anxiety disorders (25.7%), and typically developing (54.5%).(Heussler et al., 2013)

Systematic reviews and meta-analyses of placebo-controlled, randomized controlled trials (RCTs) in children with NDDs, especially autism, have demonstrated that exogenous melatonin improves sleep, either by reducing the time taken to fall asleep (sleep-onset latency) or by increasing total sleep time, or both.(Phillips & Appleton, 2004),(Wiebe Braam et al., 2009)

A large clinical trial confirmed the efficacy of melatonin in the treatment of sleep impairment in children with NDDs, using different doses, ranging from 0.5 to 12 mg; the main effects of melatonin were reduced sleep latency (from 102 to 55 minutes in 12 weeks) and increased total sleep time (40 minutes).(Appleton et al., 2012) A placebo-controlled study in 146 children (age 3−15 years) with intellectual disability showed similar results*.*(P. Gringras et al., 2012)

A randomized, placebo-controlled, double-blind, crossover trial of controlled-release melatonin 5−15 mg 20−30 minutes before bedtime in 50 children with NNDs and delayed sleep phase syndrome showed again a great efficacy in decreasing sleep latency (p<0.01) and a non-significant improvement of total nighttime sleep by 31 min. Melatonin was well tolerated but some side effects emerged (seizures, infection, gastrointestinal illness, and agitation).(Wasdell et al., 2008)

Different studies showed that melatonin (with doses of 1–10 mg given 30–60 min before bedtime) alone or in combination with cognitive-behavioral therapy is effective in insomnia of children with ASD.(Cortesi, Giannotti, Sebastiani, Panunzi, & Valente, 2012),(Suzanne E. Goldman et al., 2014) or with Angelman syndrome.(Wiebe Braam, Didden, Smits, & Curfs, 2008) ; (Andersen, Kaczmarska, McGrew, & Malow, 2008) In nine girls with Rett syndrome (MLT dosage 2.5 to 7.5 mg) the actigraphic evaluation showed that sleep-onset latency was significantly decreased while the number of nighttime awakenings was not affected, and the mean total sleep time increased.(McArthur & Budden, 1998)

A typical syndrome with inverted circadian rhythm of melatonin is the Smith-Magenis syndrome. The most efficacious treatment is a combination of acebutolol, a b1-adrenergic antagonist, given in the morning that decreases daytime plasma melatonin levels during the day and exogenous melatonin at night to replace normal peak endogenous melatonin.(De Leersnyder et al., 2001)

Melatonin has been also effective in children with ADHD with delayed sleep phase syndrome (DSPS) and insomnia at a dosage of about 5 mg.(Van der Heijden, Smits, Van Someren, & Gunning, 2005),(Van der Heijden, Smits, Van Someren, Ridderinkhof, & Gunning, 2007),(Smits et al., 2003),(Weiss, Wasdell, Bomben, Rea, & Freeman, 2006)

A systematic review of the literature found that melatonin given in doses 3 to 6 mg/night significantly reduced sleep onset latency and increased total sleep duration, but did not impact on daytime ADHD core symptoms.(Cortese et al., 2013). A recent randomized controlled trial found a reduction in mean sleep latency in ADHD patients treated with methylphenidate and melatonin 3 to 6 mg. (Mohammadi et al., 2012)

In some patients with NDDs, the loss of efficacy of melatonin treatment after an initial good response is a major problem possibly caused by slow metabolism because of decreased activity of the CYP1A2 enzyme. (W. Braam et al., 2013) This may result in increasing daily melatonin levels. Consequently, melatonin levels accumulate and after some time the circadian melatonin rhythm is lost. This loss of circadian rhythm might explain why exogenous melatonin loses its effectiveness.(W. Braam et al., 2010).

There is now a greater understanding that low doses (0.5 mg) can be effective for some children, with diminishing benefit with doses exceeding 6 mg. Unlike traditional hypnotics such as chloral hydrate and the benzodiazepines, melatonin does not affect sleep architecture.(Bruni et al., 2014)

A single study reported that melatonin for treatment of chronic sleep onset insomnia in children is effective in a dosage of 0.05 mg/kg given at least 1 to 2 h before desired bedtime.(van Geijlswijk, van der Heijden, Egberts, Korzilius, & Smits, 2010)

Headaches, confusion, dizziness, cough and rashes have been reported, but these common symptoms are likely to be coincidental or caused by impurities in the unregulated formulations of melatonin. Previous reports of poor seizure control, poor asthma control and adverse endocrinological problems during puberty have not been confirmed. Both systematic reviews and meta-analyses of RCTs suggest that there are no significant adverse side effects associated with the use of melatonin.

Unanswered clinical questions include whether slow-release preparations are superior to immediate-release in increasing total sleep time, and whether a more rational and optimal prescription of melatonin might be achieved by measuring salivary melatonin before its use.

**Ramelteon**

Ramelteon is a synthetic melatonin receptor agonist with high affinity for the MT1 and MT2 receptors, is approved by the FDA for use in adults. Only few case reports have been published in children with NDDs reporting in general a low level of efficacy on night awakenings.(Stigler, Posey, & McDougle, 2006),(Asano, Ishitobi, Kosaka, Hiratani, & Wada, 2014),(Miyamoto et al., 2013)

**Antihistamines**

Histamine is a wake-promoting neurotransmitter, and inactivation or suppression in various animal models has led to sedation and disrupted wakefulness patterns.(Mignot, Taheri, & Nishino, 2002)

First generation antihistamines are lipid soluble and pass through the blood-brain-barrier; they bind to H1 receptors in the CNS and have minimal effects on sleep architecture.

Ethanolamines (such as diphenhydramine) have potent sedative effects as do piperazine derivatives (such as hydroxyzine).

Diphenhydramine is the most commonly used and is a competitive H1-histamine receptor blocker. Peak blood and tissue levels are achieved within 2 h of ingestion. The recommended dosage for adults is 25 to 50 mg, whereas in children the effective dose is 0.5 mg/kg up to 25 mg. Hydroxyzine is effective at 0.5 mg/kg in children.12

Although antihistamines are the most prescribed or obtained over-the-counter agents for pediatric insomnia(Schnoes, Kuhn, Workman, & Ellis, 2006) randomized controlled data in children are lacking. A study showed a significant decrease in sleep latency time and number of awakenings(Russo, Gururaj, & Allen, 1976) while another study in infants showed inefficacy compared to placebo.(Merenstein, Diener-West, Halbower, Krist, & Rubin, 2006)

Other antihistaminines have been used: trimeprazine was used in 22 children with night awakenings showing a moderate improvement;(France, Blampied, & Wilkinson, 1999) niaprazine (1 mg/kg in a single dose at bedtime) showed a decrease of sleep onset latency and an increase of sleep duration(Ottaviano, Giannotti, & Cortesi, 1991) even if compared with benzodiazepines.(Montanari, Schiaulini, Covre, Steffan, & Furlanut, 1992)

No studies are available on the efficacy of antihistamines in children with NDDs.

The most common adverse reaction to antihistamines at therapeutic doses is impaired consciousness. With overdose, adverse effects are predominately anticholinergic, including fever, mydriasis, blurred vision, dry mouth, constipation, urinary retention, tachycardia, dystonia, and confusion. There are some reports on toxicity of diphenhydramine with catatonic stupor, anxiety, visual hallucinations and, more rarely, respiratory insufficiency and seizures,(Dinndorf, McCabe, & Frierdich, 1998) with fatal toxicity in 5 infants 6-12 weeks old.(Baker et al., 2003) Hydroxyzine seems to be safer and no fatal cases have been reported.(Magera, Betlach, Sweatt, & Derrick, 1981)

Finally, tolerance can develop quickly and some children can experience dramatic and paradoxical overarousal.(P. Gringras, 2008)

**Clonidine**

Clonidine is a central and peripheral α-adrenergic agonist that acts on presynaptic neurons and inhibits noradrenergic release and transmission, approved by the FDA for the treatment of hypertension. Due to its sedative effects, clonidine is commonly prescribed as a sleep aid in children, but there are no well-controlled studies available.(Nguyen, Tharani, Rahmani, & Shapiro, 2014)

It is hypothesized that clonidine produces sedation via decrease in norepinephrine via negative feedback by agonism of the α2-adrenergic receptors at the level of the locus coeruleus, which would increase REM sleep. Administration of low doses of clonidine (range 0.025–0.05 mg) has little effect on sleep and can either increase or decrease the duration of REM sleep. At medium-to-high doses (0.1–0.3 mg), clonidine appears to have postsynaptic activity on the α2-adrenergic receptors, which results in decrease of acetylcholine, increasing REM latency, stage 2 sleep, and slow-wave sleep.(Delbarre & Schmitt, 1971)

The most commonly reported side effects of clonidine include drowsiness, transient sedation, headache, dizziness, fatigue, somnolence, insomnia, hypotension, and bradycardia.

Ingrassia and Turk,(Ingrassia & Turk, 2005) in a retrospective chart review found clonidine to be an effective therapeutic intervention for alleviating sleep disturbances in six children with NDDs, aged 6-14 years a t a dose of 0.05 – 0.1 mg at bedtime. No relevant side effects were reported.

In a retrospective review, 19 children with ASD were treated with oral clonidine at 50 μg with a slow titration up to 100 μg, 30 minutes before bedtime, reporting reduced sleep latency and nocturnal awakenings. Adverse effects were skin irritation with transdermal administration, and daytime drowsiness with administration of tablets. (Ming, Gordon, Kang, & Wagner, 2008)

Moreover, Hollway et al.(Hollway & Aman, 2011) in a comprehensive literature search, showed that clonidine was effective on sleep disturbances in children with comorbid ASD and other NDDs at doses ranging from 0.05 to 0.225 mg/day.

In children who are taking concomitant CNS-depressing agents and in individuals with hemodynamic instability or cardiac pathology, the use of clonidine should be accurately monitored.(Spiller et al., 2005)

**Benzodiazepines: Clonazepam**

Benzodiazepines bind to the benzodiazepine subunit of the GABA chloride receptor complex, facilitating the action of the inhibitory neurotransmitter GABA. These hypnotics have long been the first choice treatment for insomnia in adults, but they raise concerns about cognitive impairment, rebound insomnia, and the potential risk for dependence. These concerns and little evidence-based data availability in the pediatric population, contribute to limit their use in children.(Owens, 2011) Short term or as-needed administration is the most frequent suggested treatment.

In 5 children aged 1.5 to 10 years with Williams syndrome, clonazepam 0.25–0.75 mg at bedtime, determined an immediate improvement in nighttime awakenings and daytime behaviors in four of the five patients that persisted at 3-6 months follow-up.(Arens et al., 1998) An effect on REM sleep behavior disorder in a child with autism has been reported.(Thirumalai, Shubin, & Robinson, 2002)

From the available data, clonazepam may represent a treatment option in children with arousal disorders (parasomnias) or PLMD/RLS, but future trials focused on objective sleep measures and safety issues are needed.

**Non-benzodiazepine sedative-hypnotics**

They represent non-benzodiazepine receptor agonists (NBzRAs) that binds preferentially to GABAA receptor complexes containing α1 subunits; they have minimal effects on sleep architecture with a slight increase slow-wave sleep.(Zisapel, 2012)

There are very few studies conducted in children. One study reported children with ADHD and insomnia aged 6-11 years or 12-17 years receiving treatment with zolpidem at 0.25 mg/kg per day (max 10 mg/day) vs. placebo reported a mean change in latency to persistent sleep at week 4 that did not differ between zolpidem and placebo groups. No next-day residual effects of treatment and no rebound phenomena occurred after treatment discontinuation.(Blumer, Findling, Shih, Soubrane, & Reed, 2009) Eszopiclone has been administered in 371 children aged 6–17 years with a diagnosis of ADHD and sleep disturbances but failed to show a benefit over placebo; dose-dependent adverse events were reported in 46–61% of patients.(Sangal, Blumer, Lankford, Grinnell, & Huang, 2014) The most frequent adverse events (>5%) were dizziness and headache68 but also disinhibition and hallucinations have been reported.(Liskow & Pikalov, 2004)

**Gabapentin**

FDA approved gabapentin for treatment of partial seizures in 1993. It was originally designed as a precursor of γ-amino butyric acid (GABA) that easily enters the blood–brain barrier, and increases brain synaptic GABA. It has been approved for the treatment of neuropathic pain and RLS in addition to its original purpose as an anticonvulsant medication. However, its precise pharmacological mechanism in humans remains unknown. In addition to its demonstrated efficacy in these indications, patient-reported sleep assessments among a variety of clinical conditions suggest that gabapentin has beneficial effects on sleep. The improvement of sleep might be mediated by the increase in slow-wave sleep and the decrease of WASO.(Rosenberg et al., 2014)

In a recent case series, gabapentin was found to be a safe and a well-tolerated treatment for sleep-onset and sleep maintenance insomnia in 23 children, 87% of whom had NDDs. With gabapentin initiated at an average dose of 5 mg/kg (range 3–7.5 mg/kg) 30–45 minutes before bedtime, with titration to a maximum dose of 15 mg/kg (range 6–15 mg/ kg), 78% of children showed improvement in sleep (as reported by parents). Furthermore, this beneficial response was noted at doses of 5 to 15 mg/kg orally at bedtime, much lower than the recommended dose to treat epileptic seizures (40 mg/kg divided three times daily). Side effects in a few cases included agitated nighttime awakenings and difficulty falling asleep.(Robinson & Malow, 2013)

**Antidepressants**

Tricyclic and atypical antidepressants (mirtazapine, nefazodone, and trazodone), are used in clinical practice to treat insomnia in adult and pediatric populations. Their effects on sleep is mediated by an action on different neurotransmitters, such as serotonin, histamine and acetylcholine, involved in sleep regulation.

*Tricyclic antidepressants*

Tricyclic antidepressants (amitriptyline, trimipramine, and doxepin) determine a reduction of REM and slow-wave sleep and have been used to treat insomnia. Either amitriptyline or trimipramine have been demonstrated to have sedative effects in adults.(Holmberg, 1988),(Ware, Brown, Moorad, Pittard, & Cobert, 1989),(Riemann et al., 2002)

There are no data supporting the use of amitriptyline or trimipramine in children with NDDs; however, amitriptyline is commonly used in children with NDDs beginning with a very low dose (5 mg) and then increasing it until the desired effect is achieved, but it should not exceed 50 mg.

Doxepin in adults (3-6 mg), determines improvements in sleep maintenance and early morning awakenings; when used in children with pruritus, it determined central nervous system depression.(Zell-Kanter, Toerne, Spiegel, & Negrusz, 2000)

Side effects of tricyclics include anxiety and agitation, anticholinergic effects (e.g., blurred vision, dry mouth, urinary retention, orthostatic hypotension), cardiotoxicity and worsening of RLS symptoms.

*Mirtazapine*

Mirtazapine is an α2-adrenergic, 5-HT receptor agonist with a high degree of sedation at low doses.(Younus & Labellarte, 2002) It has been shown to decrease sleep-onset latency, increase sleep duration, and reduce wake after sleep onset (WASO), with relatively little effect on REM sleep.(Wichniak, Wierzbicka, & Jernajczyk, 2012)

There is a single open-label study in autistic children and children with other forms of pervasive developmental disorders, which suggests some efficacy for insomnia.(Posey, Guenin, Kohn, Swiezy, & McDougle, 2001)

*Trazodone*

Trazodone is one of the most sedating antidepressants and the most widely studied of antidepressants in terms of sleep in adults. It is the most commonly prescribed insomnia medication for children with mood and anxiety disorders in a survey of child and adolescent psychiatrists(Owens et al., 2010)

Its action is mediated by the 5-HT2A/C antagonism and inhibition of postsynaptic binding of serotonin and blocking of histamine receptors.

Recent empirical evidence suggest that trazodone may interact with the melatonin system: Giannaccini et al. (Giannaccini et al., 2016) measured clinical and melatonin parameters before and after 1 month of therapy with trazodone in insomniac mood-depressed patients. Patients with refractory depressed-mood and insomnia improved after treatment and responsive patients excreted more urinary 6-hydroxy-melatonin sulfate than before treatment, reflecting an enhanced nighttime production of the pineal hormone in these subjects and suggesting an interaction between trazodone and melatonin system. Based on this data, the Authors support the role of melatonin as a biological indicator of pro-hypnotic and antidepressant benefits of trazodone.

Trazodone suppresses REM sleep and increases slow-wave sleep, which may prove to have beneficial effects in memory function of children who are challenged intellectually and who struggle to generalize and maintain adaptive skills of daily living.

As reported above, it is commonly used to manage insomnia in clinical practice. However, only very few studies have been conducted in children and adolescents. Anecdotal reports show the efficacy of trazodone mainly in mid-night and terminal insomnia.

Trazodone has been used for insomnia in 17 children with opsoclonus-myoclonus syndrome.(Pranzatelli et al., 2005) The starting dose of 25 mg was increased to a maximum of 100 or 150 mg depending on age. The effects on sleep were not dose dependent and low dosages were effective for insomnia.

The most commonly reported side effects are dry mouth, nausea, vomiting, drowsiness, dizziness/light-headedness, headache, and morning hangover. Less common or rare side effects are hypotension, tachycardia, serotonin syndrome and priapism.(Bossini et al., 2015) It is not commonly indicated in Rett syndrome for the risk of QT interval prolongation. It should be noted that, since the doses of trazodone for insomnia are lower than those used for depression, the incidence of side effects is also lower.

**Chloral hydrate**

Chloral hydrate is indicated for nighttime sedation in children since it was initially considered a safe agent in infants and young children at dosages of 25–100 mg/kg/day. However, respiratory depression and hepatotoxicity have been reported after administration of chloral hydrate.(Biban, Baraldi, Pettennazzo, Filippone, & Zacchello, 1993)

For these reasons it should be avoided or at least carefully controlled in children with NDDs at risk for OSA.(Sheldon, 2001)

It may cause gastric distress, nausea, and vomiting, drowsiness, dizziness, malaise, and fatigue. Children may experience idiosyncratic reactions characterized by confusion, disorientation, and paranoia. Used chronically, chloral hydrate is habit forming and associated with tolerance. (Glaze, 2004)

**Atypical antipsychotics**

Atypical antipsychotics such as risperidone, quetiapine, aripiprazole, and olanzapine are typically used off-label in children with psychiatric or developmental disorders.(Masi et al., 2009),(Capone, Goyal, Grados, Smith, & Kammann, 2008) Risperidone and olanzapine have been prescribed for sleep disturbances in children, but no studies are available evaluating their safety and effectiveness. (Schnoes et al., 2006),(Hollway & Aman, 2011),(Meltzer, Mindell, Owens, & Byars, 2007)

Tolerability profile of these medications can be tricky: excessive weight gain may exacerbate any sleep-disordered breathing present in the child; metabolic effects like hyperglycemia or hyperprolactinemia may be unsafe in certain clinical conditions (i.e. Down Syndrome or Prader-Willy Syndrome).

Atypical antipsychotics (e.g., risperidone, aripiprazole) should be considered to treat a comorbid condition (i.e. aggressive, self-injurious behaviors in children with ASD) and they might help to relief from insomnia when dosed at bedtime.

A small randomized, and placebo-controlled study of quetiapine (25 mg — a relatively low dose) in adults, showed a statistically non-significant trend toward improvement in total sleep time and reduced sleep latency.(Tassniyom, Paholpak, Tassniyom, & Kiewyoo, 2010)

 There is a single open-label trial involving 11 children with ASD who did demonstrate a reduction in sleep disturbance.(Golubchik, Sever, & Weizman, 2011)

Without more definitive data, the use of neuroleptics for insomnia in children is generally not recommended.

**Tryptophan / 5-hydroxytryptophan (5-HTP)**

Tryptophan is a precursor of serotonin and melatonin widely used in the 80s for the treatment of sleep disorders and headache prophylaxis. It does not have opioid-like effects and does not limit cognitive performance or inhibit arousal from sleep.(Lieberman, Kane, & Reife, 1985) In the literature, several positive effects on sleep have been reported: improvement of sleep latency and decrease of arousals.(Schneider-Helmert & Spinweber, 1986),(Hartmann & Spinweber, 1979)

One study with L-Tryptophan at different dosages (250 mg, 1 g and 3 g) in adults showed improvement in sleep latency, a reduction in WASO, with a moderate effect on quality of sleep. None of the papers reported systematic information regarding adverse effects associated with tryptophan.(Hudson, Hudson, Hecht, & MacKenzie, 2005),(Hartmann, Lindsley, & Spinweber, 1983),(Spinweber, 1986)

5-HTP is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of serotonin. It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. The effects of 5-HTP on sleep structure are conflicting: increase or decrease of REM and increase of SWS.(Meolie et al., 2005)

The exact mechanism of action of the sedative effects of 5-HTP is not completely clear and it is not sure that it is mediated only by conversion in serotonin. Serotonin (5-HT) should not be considered either wake-promoting or SWS-promoting, the effect of 5-HT on sleep-wake behavior would depend upon the activation of the serotonergic system (systemic administration of low vs. high doses of the precursor 5-HTP), and the time at which the activation occurs (light vs. dark period of the light-dark cycle).(Imeri, Mancia, Bianchi, & Opp, 2000) It has been hypothesized that the 5-hydroxytryptophan-related increase of SWS during the dark period depends upon the synthesis or release of as yet to be identified sleep-promoting factors.(Monti, 2011)

Very limited data are available on the effects of 5-HTP on insomnia symptoms and none in children with NDDs.

**Iron**

Iron is a co-factor for tyrosine hydroxylase, the enzyme responsible for catalyzing the conversion of the amino acid L-tyrosine to dopamine.

Iron deficiency anemia in infancy was reported to be associated with higher motor activity during sleep, shorter night sleep duration and higher frequency of night waking(Kordas et al., 2008) andsupplemental iron was associated with longer sleep duration.(Kordas et al., 2009)

In some cases, night awakenings starting in the first year of life might be an early sign of restless leg syndrome.(Kotagal & Silber, 2004),(Picchietti & Stevens, 2008)

Because iron deficiency is common in children, measuring the ferritin level is reasonable. Different reports showed a relation between low serum ferritin levels and insomnia associated with sleep hyperkinesia (i.e. RLS or PLMs) in children with ADHD or ASD.(Abou-Khadra, Amin, Shaker, & Rabah, 2013),(Cortese, Konofal, Bernardina, Mouren, & Lecendreux, 2009),(Dosman et al., 2007)

A recent review showed an increased incidence of periodic limb movements of sleep (42%) compared with controls (8%) in 53 pediatric patients with ASD with low serum ferritin level (below 35 ng/ml); sleep fragmentation and poor sleep efficiency were associated with lower median ferritin level.(Youssef, Singh, Huntington, Becker, & Kothare, 2013)

In 102 children (68 with ASD, 18 typically developing, and 16 with developmental delay) there was an increase of PLMs,(Lane et al., 2015) but serum ferritin level was not significantly correlated to any sleep parameter.

Iron supplementation (6 mg/kg/day of elemental iron) in 33 children with ASD showed an improvement of restless sleep score but no relation was found with serum ferritin concentrations.(Dosman et al., 2007)

When poor sleep is reported in children with ADHD or NDDs, serum ferritin levels should be monitored and questions on restless sleep should be asked. If ferritin levels are less than 50 mcg per L, 1–2 mg/kg/day of elemental iron (up to 6 mg/ kg/day of elemental iron) should be administered.(Abou-Khadra et al., 2013),(Cortese, Konofal, et al., 2009)*.* Parents should be asked for a personal and family history of hemochromatosis.

**Vitamin D**

Clinical research on the relation between vitamin D and sleep is ongoing, and a few studies have been published on the role of vitamin D metabolism and sleep disorders. Preliminary data suggest the possibility that altered vitamin D metabolism could play an important role in the presentation and severity of sleep disorders.(McCarty, Chesson, Jain, & Marino, 2014)

Low vitamin D concentrations may impact sleep quality via increased pain, myopathy, immune dysregulation, and cardiovascular disease.

The few published studies suggest vitamin D supplementation may improve sleep quality; especially in patients with neurologic complaints who also have evidence of abnormal sleep. Most patients have improvement in neurologic symptoms and sleep but only by maintaining a narrow range of 25(OH) vitamin D3 blood levels of 60–80 ng/ml.(Gominak & Stumpf, 2012)

Vitamin D is related to dopamine metabolism; it could be useful to investigate vitamin levels in association with iron parameters in children with NDDs and insomnia associated with motor hyperactivity during sleep.

**Orexin antagonists**

Recently, orexin neuropeptides have been identified as regulators of the sleep/wakefulness transition and documented to aid an initial transitory effect towards wakefulness by activating cholinergic/monoaminergic neural pathways of the ascending arousal system.(Chow & Cao, 2016)

Orexin hold an important role in the wakefulness promoting ascending arousal system by having an excitatory effect on almost every wake promoting neuronal group of reticular ascending system (RAS) and represent the critical modulators of the sleep wake cycle homeostasis.

The orexin receptor antagonists can be classified on the basis of receptor binding affinities, either as Selective Orexin Receptor Antagonists (SORAs; i.e. selective for OX1 or OX2 receptors) or Dual Orexin Receptor Antagonists (DORAs; i.e. compound with spread binding capacity to OX1 and OX2).(Kumar, Chanana, & Choudhary, 2016) It was hypothesized that antagonizing both orexin receptors would elicit the most powerful sleep-promoting effects.(Morairty et al., 2012)

Currently, the most widely debated DORA molecules (almorexant and suvorexant) administered to healthy volunteers and patients with insomnia, effectively reduced the number of awakenings and sleep latency while increasing total sleep time.(Kumar et al., 2016)

The most frequent dose dependent adverse effects are mild somnolence, headaches, dizziness and abnormal dreams.(Bennett, Bray, & Neville, 2014)

The major route of metabolism for almorexant and suvorexant is CYP3A. Suvorexant is the most widely studied and concomitant use with CYP3A Inhibitors is not recommended since the effects could be increased about 2-3 folds (e.g., ketoconazole, itraconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, ciprofloxacin, diltiazem, erythromycin fluconazole, grapefruit juice, verapamil). On the other hand strong CYP3A Inducers can substantially decrease almorexant and suvorexant exposure (e.g., rifampin, carbamazepine, phenytoin).(Kishi, Matsunaga, & Iwata, 2015)

This category of compounds might be promising for children with NDDs since they act on a different neurotransmitter system with less interactions with other drugs commonly used in these children.

Randomized controlled trials are needed to assess both the short- and long-term effects of these medications, as well as their efficacy in comorbid diseases that affect sleep architecture.

RECOMMENDATIONS FOR FUTURE RESEARCH

The treatment of insomnia in special populations is a field that still needs to be explored. It is extremely important to improve sleep quality and quantity in children with NDDs since this would lead to improve insomnia related daytime impairments involving not only the child but the entire family. A better quality of sleep could ameliorate daytime behavior and even cognitive development and for sure will lead to an improvement of sleep related psychological distress in the family.

The medical approach should consider medical and psychiatric contributing factors, primary sleep disorders and maladaptive behaviors related to sleep. The correct treatment should follow a specific scheme: behavioral treatment strategies through the parents, circadian rhythm regulation and pharmacological treatment.

Use of medications for pediatric insomnia should be diagnostically driven, and should be implemented in conjunction with empirically-based behavioral treatment strategies and adequate sleep hygiene

Future studies should address a number of shortcomings identified in our review. First, It is imperative to perform new studies to identify objective and specific outcome indicators that could give measures of wake time after sleep onset (WASO), sleep onset latency (SOL), number of awakenings, sleep time or sleep efficiency. Use of actigraphy should be an integrative part of any studies in this field and also integrate information from multiple informants (e.g. parents, teachers, therapists, etc.) Second, we need to understand whether treatments are more effective in certain subgroups, in relation to specific comorbidities (i.e. RLS in children with ADHD or respiratory disturbances in Rett’s syndrome). Third, randomized controlled trials on larger sample of children with NDDs comparing the different drugs with double blind studies should be carried out possibly extended in longitudinal studies to evaluate how symptoms of insomnia changed with the development.

Fourth, studies should be devoted to identify specific doses of all agents that may be required in younger children, and the potential for side-effects and drug-drug interactions.

Fifth, an important step of future studies would be to analyze in details how sleep improvement through specific drugs could improve the cognitive outcomes in specific populations in the interplay with the cognitive- behavioral therapy.

Finally, there is a need to investigate the long-term effectiveness of the different drugs analyzing the possible effects of tolerance and the eventual lack of efficacy over time of specific drugs (i.e. benzodiazepines).

**CONCLUSIONS**

Insomnia in children with NDDs, associated with the other neurobehavioral comorbidities, affects the quality of life of both children and families, is associated with poorer developmental outcome, and contributes to worsen behavioral disturbances.

Despite the widespread use of pharmacological treatment, the lack of well designed, controlled studies concerning the efficacy, tolerability, dosage, and safety profile of hypnotic medications in children raise the need of further research in this field of sleep medicine.

The lack of research in this area is detrimental for children and their families and well conducted trials should be performed based on the physiopathology of the disorders evaluating also the presence of other comorbid sleep disorders and choose the correct drugs not based only on their sedative or anxiolytic effects.

Future researches will hopefully lead to a development of a drug with proved efficacy and suitable safety profile that will allow a better health and quality of life of children and adolescents with NDDs and their families.

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