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Melatonin use in managing insomnia in children with autism and other neurogenetic disorders - An assessment by the international pediatric sleep association (IPSA)

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A B S T R A C T

Though it is widely prescribed for improving sleep of children with autism and other neurogenetic disorders, there is a need for practical guidance to clinicians on the use of melatonin for managing insomnia in this population. Because data were either lacking or inconclusive, a task force was established by the International Pediatric Sleep Association (IPSA) to examine the literature based on clinical trials from 2012 onwards. A summary of evidence pertaining to melatonin's utility and potential side effects, practice-related caveats, and insights for use are published herewith.

1. Introduction

Melatonin prescriptions for children and adolescents have increased globally to a substantial degree over the last decade. It is now the most commonly prescribed drug to treat insomnia in children and adolescents with or without neurodevelopmental disorders (NDDs [1]). There is also increasing discussion on social media and amongst parents about melatonin use in children, including concerns about possible delay in pubertal development - a recent survey of 2754 X (Twitter) posts on sleep aids in children found that melatonin was the most frequently discussed option (60 %), followed by weighted blankets and essential oils [2]. A questionnaire survey of parents of 212 children of 1–13.9 years age found that among the 131/212 subjects who had been provided melatonin in the previous 30 days, 51 % had exhibited bedtime resistance and 46 % had trouble falling asleep [3]. Further, in about half of the 212 children, the parents had initiated melatonin use on their own, and had been encouraged by a friend or family member in an additional fourth. Given the potential for harm from lack of physician

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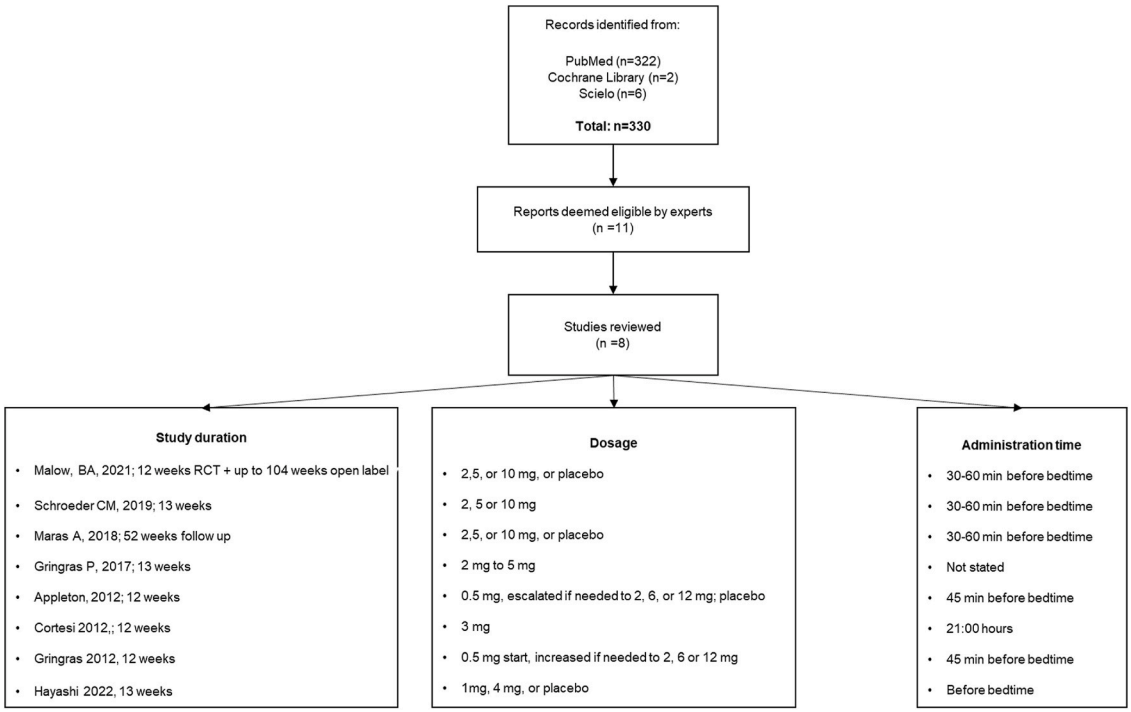

Fig. 1. Flowchart showing study selection, and dosage and administration details.

input in this approach, and to provide providers scientifically-based guidance on the use of melatonin, the development of this expert review and commentary was recommended by (IPSA). Its scope covers the use of melatonin in children and adolescents with autism and neurogenetic disorders (Smith Magenis syndrome, Angelman syndrome, Rett syndrome, tuberous sclerosis complex) who have insomnia. The operational definition of insomnia is persistent difficulty with sleep initiation, duration, or consolidation that occurs despite adequate opportunity and circumstances for sleep and results in concern, dissatisfaction, or perceived daytime impairment, such as fatigue, decreased mood or irritability, general malaise, or cognitive impairment (ICSD-3-TR). Further impetus for creating this expert opinion paper is the adverse downstream effect of disrupted sleep on neurocognitive and psychosocial functioning in a population of vulnerable children whose brain function already is of concern [4]. Consequently, a task force of experts from IPSA proceeded to develop this supporting evidence specifically for relevance and applicability to pediatric sleep medicine.

2. Geographic regions included in this assessment process

In order to take into consideration the unique features of medical practice in various countries and to synthesize recommendations that were regionally relevant, an international panel of experts from Asia, Australia, South America, Central America, Europe and North America was gathered. No information on melatonin use was available for Africa, based on literature search.

3. Methods

The following databases were searched– PubMed (www.ncbi.nlm.nih.gov/pubmed/), the Cochrane Library (www.cochranelibrary.com) and Scielo Database (http://www.scielo.org/). A literature search for clinical trials was conducted using these databases while applying the following Medical Subject Headings (MeSH): melatonin combined with autism, children, pediatric, insomnia, neurodevelopmental disorders, and sleep difficulties. Clinical trials focused on ADHD were excluded because the pathophysiology may differ. Other exclusion criteria applied were use of melatonin in the sleep laboratory, epilepsy or neurophysiology units, circadian rhythm sleep-wake disorders, and provision for sleep induction in the clinical setting. Studies had to be published between 2012 and 2022 on children aged ≤18 years, and had to be prospective, clinical trials. Studies were required to be written in English, Italian, Spanish or French to be included. Each publication was reviewed by two sleep experts for meeting inclusion criteria (Fig. 1). Towards the end of the project, pearling was carried out for publications that might have been otherwise missed.

This supporting evidence primarily targets melatonin use in this type of pediatric population as an independent objective, only related with diagnosis of insomnia.

The domains studied and primary and secondary outcome measures are summarized in Table 1. They includes evidence for the use of melatonin including citation, publication year, type of study, population, number of patients, intervention (melatonin dosage, type, administration time), and effect on study endpoints.

4. Summary of the use of melatonin in the studies selected

Initially, ten studies were identified. An 11th study was identified during the process of finalizing the report. Three of 11 were excluded – one due to the indication of insomnia in typically developing children, and two being meta-analyses on published data prior to 2012, leaving eight clinical trials in autism or neurogenetic disorders that were published between 2012 and 2022 (Table 1). Other than autism, diagnoses included as neurogenetic disorders were Smith Magenis syndrome, Angelman syndrome, tuberous sclerosis complex and Rett syndrome.

Participants were age two years or older ([5–7], Gringras et al 2021, [9–12]). Six of 8 studies were randomized, placebo-controlled, while 2/8 were open label, placebo-controlled. They comprised a total of 1027 children. They were between 2 and 17.5 years, with two-thirds being male. Due to overlap in the publications [5–7], the possibility of some subjects having been counted more than once cannot be excluded. Subjects were randomized to placebo or melatonin; 5/8 used long acting formulations including a controlled-release formulation in 1/5 and 4/5 using pediatric prolonged release melatonin (PedPRM) that is available

Table 1
Study procedures, target symptoms and outcome measures.

Authors, year	Clinical trial				Melatonin use				Sample	Target symptoms of insomnia	Outcome measure child			Outcome measure parent			Adverse effects
	Open label	Placebo-controlled	randomized	blinding	duration	type	dosage	administration			diary	questionnaire	actigraphy	diary	questionnaire	actigraphy	
Malow BA, et al., 2021 [5]	✓	✓	✓	double	12 weeks RCT + up to 104 weeks open label	PedPRM	2, 5, or 10 mg/day		n = 80; 2–17.5 years 74.% male ASD, NGD	SOL, TST, NOA, LSE and quality of sleep	sleep and nap	CSDI			PSQI, WHO-5		✓
Study results	Improvements in child sleep disturbance and caregiver satisfaction with child sleep patterns, quality of sleep, and quality of life were maintained throughout the 104-week treatment period																
Adverse effects details	Fatigue (6.3 %), somnolence (6.3 %), and mood swings (4.2 %)																
Remarks	No impact on height, weight, BMI, Tanner staging, during follow up																
Schroeder CM, 2019 [6]		✓	✓	double	13 weeks follow up	PedPRM	2, 5 or 10 mg/day		n = 125; 2–17.5 years; 73.6 % male NGD, SMS	SOL, TST		SDQ			PSQI, WHO-5, ESS, CSDI		✓
Study results	Significant improvement in externalizing but not internalizing behavior, caregivers' quality of life also improved																
Adverse effects details	Somnolence 28.3 %																
Remarks	Same pool of subjects as in [5]																
Maras A, et al., 2018 [7]	✓	✓			52 weeks follow up	PedPRM	2, 5, or 10 mg/day		n = 95; age 2–17.5 years; 74.7 % male ASD, NGD	SL, TST, NOA, LSE	SND				PSQI, WHO-5, ESS, CSDI		✓
Study results	Subjects slept (mean) 62.08 min longer, fell asleep 48.6 min faster; had 89.1 min longer uninterrupted sleep episodes; less nightly awakenings (>50 % decrease) and better sleep quality compared with baseline.																
Adverse effects details	Fatigue (18.9 %), vomiting (17.9 %), somnolence 16.8 %, cough 13.7 %, mood swings 13.7 %																
Remarks	Same pool of subjects as in Ref. [5]. PSQI global and WHO-5 improved significantly																
Gringras P, et al., 2017 [8]		✓	✓	double	13 weeks	PedPRM	2 mg escalated to 5 mg		n = 125; age 2–17.5 years 73.6 % male ASD, NGD	TST	SND	CSDI					✓
Study results	TST 57 min longer SL decreased by 39.6 min																
Adverse effects details	Somnolence (11,7 %), Mood swings (1,7 %)																
Remarks	41 percent of patients on PedPRM had significantly improved sleep on 2 mg dose by end of 3 weeks; PedPRM was equally effective in those with or without ADHD comorbidity																
Appleton R, et al., 2012 [9]	✓	✓	✓	double	12 weeks	Melatonin (Alliance Pharmaceuticals)	0.5 mg (start) up to 2 mg, 6 mg and 12 mg		n = 110; 3–15 years 66 % male NDD		✓ SND	CSHQ, PedsQL, ESS, ABC	✓		ESS; PedsQL Family Impact Module		✓
Study results	With melatonin slept average 23 min more than placebo; melatonin reduced SOL by mean 45 min																
Adverse effects details	Coughing 31.4 %, mood swings 22.9 %, vomiting 21.4 %, increased excitability 18.6 %,																
Remarks	Behavioral intervention provided to all for 4–6 weeks prior to study enrollment																
Cortesi F, et al., 2012 [10]		✓	✓		12 weeks	Controlled-release melatonin	3 mg	9 p.m.	n = 160; ASD age 4–10 80 % male 4 study		✓	CSHQ	✓				✓

(*continued on next page*)

Table 1 (*continued*)

Authors, year	Clinical trial				Melatonin use				Sample	Target symptoms of insomnia	Outcome measure child			Outcome measure parent			Adverse effects
	Open label	Placebo-controlled	randomized	blinding	duration	type	dosage	administration			diary	questionnaire	actigraphy	diary	questionnaire	actigraphy	
									groups- CR Mel + CBT, CR Mel, CBT, Placebo								
Study results					Better treatment response in the group CBT + melatonin												
Adverse effects details					No adverse effects were reported by guardians/children in this trial												
Remarks					Baseline and combination group outperformed others, with fewer dropouts and greater # of responders												
Gringras P, et al., 2012 [11]	✓	✓		double	12 weeks	immediate release	Start with 0.5 mg and increased up to 2 mg, 6 mg, and 12 mg	45 min before bedtime	n = 146 age 3-15 66.5 % male NDD		✓		✓				✓
Study results					Melatonin increased TST by ± 22.4 min measured by sleep diaries (n = 110) and ±13.3 measured by actigraphy (n = 59). It reduced SOL measured by sleep diaries (±37.5 min) and actigraphy (±45.3 min), most effective for children with the longest sleep latency; associated with earlier waking times than placebo (±29.9 min).												
Adverse effects details					Coughing (31,4 %), Mood swings (22,9 %), Vomiting (21,4 %), Increased excitability (18,6 %), Rash (15,7 %), somnolence (12,9 %)												
Remarks					Measures of child behavior and quality of life tended to favor melatonin but were not significant												
Hayashi M, et al., 2022 [12]	✓	✓				Melatonin granules (Nobel Pharma Co.)	1 mg/4 mg or placebo	45 min before bedtime	n = 186; age 6-15 61.7 % male ASD 1 mg = 65 4 mg n = 65 Placebo n = 66		SOL measured by electronic sleep diary						✓
Study results					SOL was reduced significantly during randomization phase by 5 min in placebo, 22 min in 1 mg dose, and 28 min in 4 mg dose groups												
Adverse effects details					Withdrawal/discontinuation of melatonin associated with deterioration of irritability and aberrant behaviors requiring hospitalization; n = 2												
Remarks					Subjects below age 6 or above 15 years not included. TST did not change because an unspecified number of subjects had concurrent DSPD												

OBS: All patients aged >2 years. RCT = randomized clinical trial; NDD = neurodevelopmental disorders; ASD = autism spectrum disorders; NGD = neurogenetic disorder (Smith Magenis syndrome/Rett syndrome/ Angelman syndrome/tuberous sclerosis complex); PEDPRM = pediatric-appropriate prolonged-release melatonin; ESS = Epworth Sleepiness Scale; PSQI= Pittsburgh Sleep Quality Index; CSDI= Composite Sleep Disturbance Index; SDQ = strengths and difficulties questionnaire; CSHQ =Children's Sleep Habits Questionnaire; PedsQL = Pediatric Quality of Life Inventory Family Impact Module; ABC = Aberrant Behavior Checklist; CBT = cognitive behavioral therapy; TST = total sleep time; SOL = sleep onset latency; SL = sleep latency; NOA = number of awakenings; LSE = duration of uninterrupted sleep; SE = sleep efficiency; DLMO = dim light melatonin onset.

mainly in Europe; 3/8 used immediate release melatonin. The nightly dose ranged from 0.5 mg to 12 mg.

Sleep diaries were used across all 8 studies to estimate sleep duration; commonly used sleep questionnaires such as the Children's Sleep Habits Questionnaire (1/8) and the Epworth Sleepiness Scale (2/8) were also used. Additional measures used were questionnaires like the Composite Sleep Disturbance Index (2/8) and the Strengths and Difficulties Questionnaire (1/8) for assessing child sleep and emotional/behavioral problems, respectively. Further, for assessing parental sleep quality and mental health, the Pittsburgh Sleep Quality Index (PSQI) in 3/8 and the World Health Organization Well-Being Index (WHO-5) in 3/8 were used.

Sleep was assessed objectively by actigraphy in 4/8 studies for sleep latency, total sleep time and sleep efficiency. The follow-up period in the studies was 12–104 weeks.

5. Response to the use of melatonin

Different outcome measures were used in different studies (sleep diaries in 8/8, 6 types of sleep questionnaires, 2 types of parental well-being questionnaires, and actigraphy). These varied measures applied across a small data set limited the ability of the task force in drawing precise conclusions.

Sleep diaries indicated that melatonin improved sleep in all studies. Based on either the Sleep and Nap diary (SND) or actigraphy, initial SOL decreased in all 8 studies by 28–45 min. With regard to total sleep time (TST) based on SND or actigraphy, there was an increase in 6/8 studies that ranged from 22.4 to 57 min, no change in 1 of 8 and unextractable data in another 1 of 8 studies. In the study with no change [12], the authors speculate that coexisting delayed sleep phase disorder may have played a role in limiting an increase of TST. Sleep diaries showed a dose-response in the Hayashi et al. study (2022) – when melatonin was administered 45 min before bedtime the SOL was reduced by 5 min on placebo, by 22 min on the 1 mg dose of melatonin, and by 28 min on the 4 mg dose.

With the slightly more precise tool of actigraphy that was used in 4/8 studies, the analysis showed: a baseline SOL of 85.84–126.8 min (median 106.27 min); at week 12, 3.69–68.4 min (median 51.05 min); and in studies expressing as a difference (decrease) of 25–45.34 min (median 35.17 min) [9,7,10,11]. Melatonin also significantly increased total sleep time over placebo in these 4 of 8 studies, at baseline: 414–434.2 min (median 424.1 min); at week 12, 449.9–505.81 min (median 477.86 min); and in studies expressing as a difference (increase) of 7.23–13.3 min (median 10.27 min) [8–11]. In one study there was no change in sleep efficiency [9].

A concomitant improvement in the child's behavior was noted on a composite sleep disturbance index in the study by Malow et al [5]. In the study by Schroeder et al [6], there was improvement on externalizing behaviors, but not in internalizing behaviors.

Cortesi et al [10] combined melatonin with cognitive behavioral therapy. Using this combination approach at the 12-week assessment, more children met an acceptable norm of SOL of less than 30 min, or SOL reduction by 50 %, and improved sleep efficiency $\geq$85 % than in the melatonin-alone group, in the CBT-alone group, or in the placebo-alone group. This suggests a better treatment response, at least in the short term. Three of 8 studies [5–7] showed improved parental sleep quality following administration of melatonin to the child. Caution is needed in making further assumptions on these issues due to the overlap of study subjects in Refs. [5–7].

In the longest study of 106 weeks [5], sexual development and growth parameters were systematically assessed. At week 106, the mean change from baseline (due to physiologic maturation) for pubic hair, breast and genital development were similar in both the melatonin and placebo groups. There was no delay in development of puberty in the melatonin-treated group.

Co-existing epilepsy was present in 16/80 subjects in the Malow et al [5] study and in 16/110 subjects in the Appleton et al [9]. Seizure diaries were maintained in these studies. The results were inconclusive for the seizure disorder improving, worsening or remaining unaltered during the clinical trial.

6. Adverse effects

Seven of eight studies (87.5 %) reported side effects. The most common short-term adverse effects were fatigue, vomiting, somnolence, cough, mood swings, increased excitability, headaches, and rash. Adverse effects were not related to a specific formulation of melatonin. In the study of Maras et al [7], three adverse events were considered "serious'' according to standard regulatory definitions, during weeks 13–52 of the study. They included (one case each) aggression, oppositional defiant disorder and constipation. All of these events were considered "not related'' to the study medication by review of the physician investigator, and none led to study drug discontinuation. In the study of Hayashi et al., 2/196 children had a serious adverse event of behavioral deterioration upon abrupt discontinuation of melatonin requiring hospitalization.

7. Insights brought by the panel

To start with, the potential risks associated with melatonin use in children with autism and specified neurogenetic disorders must be balanced against potential harm related to persistently disordered sleep in this special population.

7.1. Metabolic and genetic factors

Melatonin is primarily metabolized by cytochromes CYP1A2 and CYP2C19; inhibitors of CYP1A2 such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), and H-2 blockers may increase daytime circulating melatonin concentrations leading to side effects of fatigue and somnolence, and blunt the diurnal fluctuation in melatonin levels, thereby reducing efficacy of melatonin for sleep induction over the long term (Bruni et al., 2014). There may be genetic factors in autism that affect melatonin biosynthesis. In Smith Magenis syndrome, while the etiology is related to a deletion at chromosome 17p11.2, we do not as yet know why the melatonin release pattern becomes inverted [9].

7.2. Potential contamination

The indiscriminate use of melatonin as an over-the- counter sleep-promoting agent for insomnia without excluding other specific conditions such as restless legs syndrome or restless sleep disorder due to iron deficiency, is to be discouraged. There is a risk that the child may not be receiving melatonin alone - in a study of 31 over-the-counter melatonin supplements that were analyzed by ultraperformance liquid chromatography, serotonin was identified as a contaminant in 8/31 [13]. In another study using the same analytic method, cannabidiol was found as a contaminant from 1 of 25 brands [14].

7.3. Risk of bias

Sleep diary information in the included literature was compiled by the parents – consequently there is a possibility of biases in the sleep diary data, though actigraphy may have partially mitigated some of the bias in 4/8 studies. Even actigraphy though is not without limitations such as: *a.* inability to distinguish quiet wakefulness from sleep without movement, *b.* inability to distinguish excessive movement in sleep from wakefulness, or *c.* dependence on the caretaker to mark "lights out" time and sleep offset time.

7.4. Medication obtaining patterns and bioequivalence

Many melatonin formulations are available in various regions of the world, and there is variation in how they can be accessed [15]. Some melatonin products are licensed, requiring prescriptions, while others are over the counter [15]. In a study of 30 brands of melatonin "gummies," analyzed by high performance liquid chromatography (HPLC), the actual quantity of melatonin varied from 74 % to 347 % of the labeled quantity [14]. In another HPLC study [13], the melatonin content in 31 preparations ranged from −83 % to + 478 % of the labeled content. This variability in content of melatonin across various preparations carries a huge potential risk for adverse effects. It may be a high bar to cross, but when possible, pharmaceutical grade melatonin should be used.

7.5. Prolonged use

While available data reported few or non-serious adverse effects of melatonin use during up to 104 weeks of managing insomnia in children with autism and other NDDs [5], one needs to be cautious in continuous use of melatonin and provide periodic clinical reassessment - this is just part of good clinical practice. More studies are required for assessing its long-term safety from the standpoint of growth and sexual development.

7.6. Other considerations

Melatonin administration combined with behavioral sleep interventions is an effective treatment for insomnia in children with autism and other NDDs [10].

The dose of melatonin was variable, between 2 and 12 mg, hence individualization with the lowest possible dose is called for. Due to the possibility of a dose-response pattern, periodic adjustment in the dose may be required - in the prescribing observatory for mental health (POMH) survey of the United Kingdom, when the dose of melatonin was increased from 5 mg to 10 mg, there was an additional increase in total sleep time by mean 16.6 min ($n = 19$) and an additional reduction in SOL by mean of 24.7 min ($n = 19$; $p = 0.006$) on the sleep and nap diary [16].

While children who receive melatonin for the treatment of insomnia may experience adverse events, the extent to which these lead to long-term consequences (when treatment is for more than 2 years) remains uncertain [17].

Evidence reviewed by the task force could not determine the efficacy of prolonged-release melatonin over immediate-release melatonin. Clinical trials should use pharmaceutical grades of melatonin preparation. Global harmonization of the formulation, dose, time of administration is also needed, keeping in mind differences in practices and countries.

Most studies applied melatonin within an hour of sleep onset, which would be generally 2–3 hours after DLMO, however, DLMO was not a factor that was taken into consideration in organizing these studies [18].

● RECOMMENDATIONS

1. Melatonin use in children with autism and certain neurogenetic syndromes (Smith Magenis syndrome, Rett syndrome, Angelman syndrome, and tuberous sclerosis complex) for insomnia should be undertaken **only** under medical supervision.
2. Clinicians **should** consider prescribing melatonin to children with autism and neurogenetic syndromes with comorbid chronic insomnia if behavioral strategies alone have not been effective or only partially effective, and coexisting medical conditions and concomitant medications such as anti-epileptic drugs (e.g., felbamate) that might worsen sleep have been addressed. This recommendation is also supported by practice guidelines on this topic from the American Academy of Neurology [19]. When possible, for optimum response, behavioral therapy **should** be considered as an option in conjunction with melatonin.
3. Before prescribing melatonin, other disorders that might interfere with sleep initiation or maintenance such as restless legs syndrome, restless sleep disorder, obstructive sleep apnea **should** be excluded or, if present, appropriately managed.
4. The initial sleep assessment **should** address key domains of sleep such as the amount of sleep, bedtime routines, daytime behaviors, bedtime transitions, night-time movements, breathing in sleep and excessive sweating. Cultural diversity and family expectations combined with the response to prior (unsuccessful) approaches also need to be factored in.
5. Due to lack of data for insomnia in children with autism or NDDs <2 years of age, melatonin **should** only be used with caution in this age group, and after consultation with a pediatric sleep specialist.
6. Dosage recommendations **should** be conservative, starting with the lowest dose, escalated only gradually if indicated, and up to a maximum of 10 mg.
7. Clinicians **should** advise patients and families regarding the potential adverse effects of melatonin use and the lack of long-term safety data.
8. The administration of melatonin for sleep induction as a hypnotic in autism and the neurogenetic disorders mentioned in this report is recommended around 30–60 min before the desired bedtime. This time is after peak of dim-light melatonin onset (DLMO), which generally occurs 2–3 h prior to sleep [18].
9. We recommend that clinicians periodically reevaluate the need for continued use of melatonin, and check that no adverse effects have developed. More long-term data need to be gathered on adverse effects.
10. Given the above recommendation parents should be cautious, and remain informed about the use of melatonin.

8. Limitations

Included neurogenetic disorders were Smith Magenis syndrome, Rett syndrome and Angelman syndrome and tuberous sclerosis complex. It is not known whether the findings apply to other neurogenetic disorders as well.

ADHD was excluded from consideration due to the possible difference in pathophysiology from autism. Further, studies reviewed had not controlled for comorbidities like obstructive sleep apnea, periodic limb movement disorder, restless legs syndrome, anxiety or gastroesophageal reflux. These comorbidities could have also impacted sleep regulation.

There was an overlap in study subjects in three studies [5,6,11], which might have affected validity of some of the results.

Three different formulations of melatonin - melatonin, melatonin-controlled release and melatonin prolonged release were used, which may have impacted the validity of some of the results.

Assessment tools varied - while sleep diaries were used as the primary outcome measure in the study subjects, actigraphy was also utilized in 4/8 studies; sleep onset latency and total sleep time are likely to differ when measured by these modalities.

A conflict-of-interest statement was not provided for the Appleton [8] study. Two of the eight studies were industry sponsored.

9. Summary

This was an expert opinion obtained by convening a panel of pediatric sleep specialists to discuss the use of melatonin in children with autism and certain neurogenetic disorders, age 2–17.5 years, derived from 8 clinical trials that had been published between 2012 and 2022, with total number of subjects being 1027. Melatonin, when administered in a hypnotic dose (2–10 mg) prior to bedtime helped participants fall asleep more quickly and prolonged their nocturnal sleep. Most

studies of administration of melatonin were of short duration, lasting weeks. Side effects were mild, generally consisting of daytime somnolence, fatigue, vomiting, and increased excitability. In one study of 106 weeks, there was no adverse effect on somatic growth or sexual maturation [5]. Cognitive behavioral therapy was used as an adjunct to melatonin in one study, with beneficial results. There should be periodic reassessment of the need for continuing melatonin therapy beyond a few months. Before instituting melatonin therapy in this population, other sleep pathologies such as restless legs syndrome that require alternative management strategies should be excluded. Due to lack of safety and efficacy data, melatonin should be used only with great caution in children below the age of 2 years.

10. Future directions

Clinical trials may need to consider which type of formulation, i.e. immediate release versus prolonged release is more appropriate for insomnia in a specific population, along with including subjective and objective measures of sleep, body weight, efficacy of combining cognitive behavioral therapy with melatonin, and impact on quality of life.

We speculate that early recognition of neurogenetic disorders that are associated with faulty melatonin secretion patterns, such as Smith Magenis syndrome, may lead to early intervention with melatonin supplementation to promote better sleep in this population. The role of melatonin in sleep initiation and sleep maintenance difficulties of infants, which remains unstudied, will be hopefully investigated further.

As proposed by Skrzelowski et al [15], at least in North America, it is important that safety data for over-the-counter preparations be reported by providers and caregivers to the governmental registry at https://www.Safetyreporting.hhs.gov.

CRediT authorship contribution statement

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Declaration of competing interest

I do not have any conflict of interests to disclose regarding this work. Members of the task force have submitted their disclosures separately to the office of the World Sleep Society.

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