

Original article

An online survey among general pediatricians on melatonin use in children with chronic insomnia



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ABSTRACT

Objectives: Although melatonin (MLT) is the molecule most used by pediatricians for sleep problems, scarce evidence exists on its use in healthy pediatric population. The objective of this study was to describe MLT use by Italian pediatricians in healthy children with chronic insomnia.

Study design: A cross-sectional open survey was administered to Italian pediatricians, between June and November 2022, collecting information about their use of MLT in healthy children: age range of patients, dosages used, time of administration, duration of treatment, association with other treatments, perceived efficacy, and side effects. Data were reported as frequencies with their respective 95% confidence intervals. Chi-square statistics assessed significant differences between pediatricians who had training in pediatric sleep and those who did not.

Results: Among 428 respondents, 97.4% of pediatricians used MLT; 87.3% of them prescribed MLT in children aged 1–2 years, 62.1% in 2–5 years and 42.5% in 10–18 years. 84.9% of them suggested to take MLT 30 min before bedtime. 37.9% indicated to continue treatment for one month, 30.2% for 2–3 months. 74.1% of pediatricians usually prescribed MLT 1 mg/day. The most frequent treatment associated with MLT was sleep hygiene (85.4%). Almost all pediatricians found MLT effective in reducing difficulties falling asleep. Only 3.2% of them reported mild side effects.

Conclusions: MLT is widely prescribed by Italian pediatricians, but no consensus exists about its use in typically developing children. There is a need for clear guidelines to optimize the use of MLT in healthy children.

1. Introduction

Sleep disorders are a frequent reason for pediatric consultation [1], being very frequent in children, especially toddlers, in whom the prevalence of bedtime difficulties and night awakenings is estimated to be 20.8% and 23.0% [2]. Symptoms of insomnia or poor sleep must always be assessed by pediatricians. Although simple advice and parental education alone might be effective in many sleep disturbances in childhood, behavioral treatment or a combination of behavioral and pharmacologic treatment is often necessary to treat insomnia in children and adolescents. In the general practice, when behavioral interventions prove to be ineffective, medications and mainly melatonin (MLT) are

frequently prescribed to assist sleep [3,4]. MLT is the most frequent sleep medication used in children and adolescents to treat insomnia [5–8], probably also because of its endogenous origin that makes it perceived as a “natural” sleeping aid by parents and pediatricians [9].

According to a study conducted on Australian pediatricians, 3.7% of all their prescriptions were MLT [10], whereas in Sweden nearly 2% of the pediatric population aged 0–17 years was dispensed at least one prescription of MLT in 2017 [11]. Nevertheless, there are no clinical guidelines on how to prescribe MLT in children [9], also because MLT prescription in childhood is off-label in many countries [12], including Italy, where the only approved treatment with MLT in the pediatric population is the prolonged-release MLT (PRM) for insomnia in children with Autism Spectrum Disorder (ASD) [13]. In Italy, melatonin is not

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Abbreviations

AEs	adverse events
ASD	autism spectrum disorder
CI	confidence intervals
MLT	melatonin
OTC	over the counter
PRM	prolonged-release melatonin
SICuPP	Società Italiana delle Cure Primarie Pediatriche

dispensed by the National health system either in the form of immediate or prolonged release, and its cost is borne entirely by the patient.

Despite the recommendations related to the inconsistent studies on safety, many health professionals consider MLT to be safe, and prescribe it for short-term use for typically developing children [4].

MLT is an endogenously produced indoleamine synthesized by the pineal gland, its secretion is regulated by the suprachiasmatic nucleus in the hypothalamus following a circadian pattern influenced by the alternation of darkness and light [14,15]. It plays a key role in regulating the sleep-wake cycle through its chronobiological effect [15,16]. Differently from children with neurodevelopmental abnormalities, very little data has been published on normal children (mostly school-age or adolescent). Despite the fact that MLT is the molecule most used by pediatricians for sleep problems, there are no specific studies on its use in healthy infants and children. Therefore, further randomized studies of the pharmacokinetics and pharmacodynamics of MLT in otherwise healthy children are needed [17].

The aim of this study was to obtain a panorama of the use of MLT in otherwise healthy infants and children with chronic insomnia by Italian pediatricians, in terms of mode of administration, target population and target sleep disorders.

2. Materials and methods

2.1. Participants

A cross-sectional open survey was administered to a large group of pediatricians affiliated with the SICuPP -Società Italiana delle Cure Primarie Pediatriche - (Italian Primary Care Pediatrics Society), within a limited time window, investigating the use of MLT in their clinical practice. An email invitation was sent to all participants with a link to the online survey based on Google forms, using a single-stage sampling procedure. A reminder email was sent one week after the initial survey invitation, and the survey remained open and accessible from June 8th to November 24th, 2022.

At the time of the survey 1910 pediatricians were affiliated with the SICuPP.

The survey items gathered data with respect to the physician attitudes and behaviors regarding MLT use for sleep problems in infants and children.

There was no monetary or credit compensation for participating in the study. Data collection was anonymous.

The protocol of the study and the procedure, as well as the complete survey, were submitted to the Executive Board of the SICUPP. Few criticisms were raised and corrected, then the final protocol and the survey were approved.

2.2. Measures

A specific questionnaire was arranged for the survey. Pediatricians were asked in which region of Italy they work and whether they had participated in previous formal training in pediatric sleep. The first section collected information about the prevalence of sleep disorders in

their pediatric population. A second section gathered information on the use of MLT: age range of patients, target disorders, dosages used, mode of administration (in terms of timing of administration, duration of treatment and association with other treatments), efficacy and side effects.

For several questions there were fixed options to select. For side effects we listed the more common side effects reported in the literature so that the pediatricians could select them and also add side effects eventually not listed.

The above data were collected using a survey tool with 18 items. The adapted survey instrument was pilot tested by five pediatricians, randomly chosen from the targeted study population, in an effort to establish content validity. Multiple-choice answers were arranged for each question and participants could only choose one of them, with the exception of questions on the therapy in combination with MLT, instrumental examinations in which MLT is used, and disorders targeted by MLT, for which pediatricians could choose more than one answer. Respondents were able to review and change their answers (see Appendix 1).

The survey was intended to be anonymous and all efforts were made to ensure anonymity. The responses to the survey were automatically anonymized and aggregated in a manner neither allowing for the identification of individual respondents nor for the attribution of individual responses to a respondent. The Communications Unit had no access to individual responses and was not able to identify the respondent. Responses in the open-space fields were therefore formulated in such a way that no information permitting identification of the respondent, or another person was introduced. The anonymized and aggregated data will be kept for a maximum period of one year after the closure of the survey.

2.3. Data analysis

Descriptive statistics were applied to characterize sociodemographic variables, such as Italian geographical area of work and prevalence of sleep disturbances in their patients. Data were reported as frequencies and percentages for comparisons between the groups. Frequencies were calculated with their respective 95% confidence intervals (CI).

Chi-square tests were conducted to compare the group of pediatricians who had already attended a training course on pediatric sleep to that of pediatricians who did not, in regard to timing of administration of MLT, duration of treatment and association with other treatments. Fisher's exact test was applied when appropriate.

For all comparisons, p-values less than 0.05 were considered to be statistically significant. Statistical analyses were performed using the SPSS software release 17.0 (SPSS INC, Chicago, Illinois).

2.4. Ethics statement

As the study used routinely collected data that was nonidentifiable and publicly available, ethics approval was not required.

3. Results

A total of 428 pediatricians completed the survey. The response rate was 22.41%.

Of the total sample 417 pediatricians (97.4%) use melatonin in clinical practice, while only 11 pediatricians (2.6%) reported that they did not use MLT and could not complete the questionnaire.

Two-hundred-one of them (48.2%) had attended a training course on pediatric sleep, while 216 (51.8%) had not.

The availability of PRM, approved for insomnia in children with ASD, was known by 39.6% of pediatricians, pediatricians who had previous training in pediatric sleep were significantly more frequent in this group than in those who did not know PRM (chi-square: 20.3; $p < 0.01$).

Pediatricians were asked to report the percentage of children, divided by age groups, experiencing sleep disorders. (See Appendix 1). They reported the age between 6 months and 5 years as the most affected by sleep disorders: 12.9% of pediatricians affirmed that more than 40% of 6 month-to 5-year-old children had sleeping problems. Only 2.2% and 6.6% of clinicians reported sleep disorders in more than 40% of 6 – to 10-year-old and 11- to 16-year-old children.

Other therapies utilized by pediatricians in association with MLT are listed in Table 1. The most frequent therapy associated with MLT was sleep hygiene, very few pediatricians used MLT alone (<4%). No significant difference was found in therapy combination between clinicians who had a previous training in pediatric sleep and those who did not, with the exception of the association of MLT with behavioral therapy that was used more frequently by pediatricians who had a previous training.

The use of MLT to induce sleep in children when performing instrumental examination, like neurophysiology examinations and neuroimaging, was reported by 25.4% of pediatricians, the most frequent use was for inducing sleep during electroencephalography (21.1%), followed by neuroimaging (9.3%) and other neurophysiology examinations (6.2%).

3.1. Mode of administration

A large portion of pediatricians (84.9%) suggested to take MLT 30 min before going to sleep, while 15.1% of them indicated 60 min. No significant difference was found between the group who had training in pediatric sleep and those who did not (chi-square: 0.03; p 0.862) as regards timing of administration.

Among the 417 pediatricians who prescribed MLT, most prescription were for children aged 1–2 years (87.3%) and 2–5 years (62.1%). More than half of them used MLT in children aged 6–12 months (59.0%), and less than a third (26.4%) for infants of 0–6 months; 40.5% used it in children aged 5–10 years and 42.5% in children aged more than 10 years.

When asked to indicate the most frequent age group in which they used MLT, 60.1% of pediatricians the age range between 12 months and 2 years. Only five pediatricians (1.2%) reported to give MLT to children aged 0–6 months (Fig. 1).

As for the duration of treatment, 37.9% of pediatricians indicated to continue MLT treatment for one month, 30.2% for 2–3 months and 22.5% until improvement, only 6.6% declared to continue treatment for more than three months and 2.4% for only one week. The majority of pediatricians (74.1%) usually prescribed MLT 1 mg/day, 61.8% of them to children aged 12 months to 2 years, 17.1% to children of 6–12 months and 12.6% to children aged 2–5 years; 16.5% of pediatricians usually prescribed MLT 2 mg/day and only 9.4% 3 mg/day or more.

3.2. Efficacy

Almost all pediatricians found MLT efficient in reducing difficulties falling asleep, and more than one third of them reported a decrease in night awakenings. Some of them observed an efficacy on daily

Table 1

Pediatricians' use of other therapies in association with melatonin.

Associated treatment	Frequency			Sleep training		No sleep training		χ^2 [2]	p
	N	%	95% confidence interval	N	%	N	%		
None	16	3.8	1.99/5.68	5	2.5	9	4.2	0.905	NS
Sleep hygiene	356	85.4	81.98/88.76	177	88.1	179	82.9	2.245	NS
Behavioral therapy	216	51.8	47.00/56.59	116	57.7	100	46.3	5.434	0.02
Tryptophan	152	36.4	31.83/41.07	78	38.8	74	34.3	0.929	NS
Plant compounds	46	11.0	8.02/14.04	28	13.9	18	8.3	3.323	NS
Dietary treatments	6	1.4	0.30/2.58	12	6.0	8	3.7	1.171	NS
Antihistamines	20	4.8	2.75/6.85	3	1.5	3	1.4	0.008	NS
Atypical antipsychotics	1	0.2	0.00/0.71	1	0.5	0	0.0	–	–

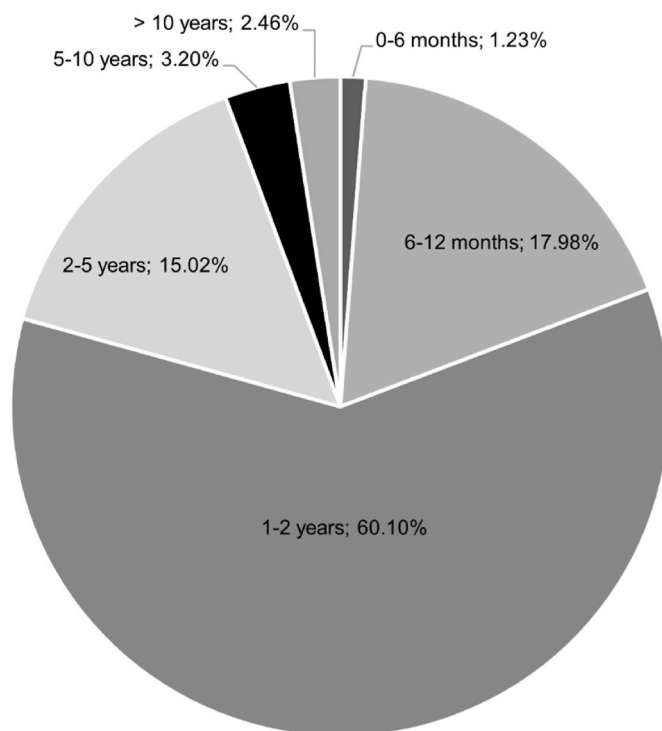


Fig. 1. Age range in which melatonin is most frequently used by pediatricians.

irritability and anxiety (Table 2).

3.3. Side effects

Only 3.2% of pediatricians reported side effects: 1.1% daytime sleepiness, 1.1% hyperactivity/agitation (paradoxical effect), 0.5% headache and 0.5% nightmares.

Table 2

Melatonin efficacy in several sleep disorders.

Sleep disorder	Frequency		
	N	%	95% confidence interval
Difficulties falling asleep	391	93.8	91.44/96.09
Night awakenings	155	37.2	32.53/41.81
Daily irritability	16	3.8	1.99/5.68
Anxiety	12	2.9	1.27/4.48
Headache- episode prevention	4	1.0	0.02/1.89
Movements during sleep	3	0.7	0.00/1.53
Headache- episode treatment	1	0.2	0.00/0.71
Snoring	0	0.0	0.00/0.00

4. Discussion

This study represents the first comprehensive survey on the use of MLT by Italian pediatricians in healthy infants and children. Our research involved typically developing children and the prescription trend by pediatricians and this appears to be the first study reporting on this aspect.

Recent audits focused on the use of MLT in the pediatric population in other countries [18–20]. There is evidence that in the last decades pediatric off-label use of MLT increased in several countries [21–23]. In a study in Norway, MLT prescription in 0- to 17-year-old children increased from 2.06 to 6.80/1000 during the period from 2004 to 2011 [6]. In the same age group, in Sweden, the prevalence of MLT prescription increased from September 1, 1000 in 2006 to 32.36/1000 in 2021 [24], in Denmark from 0.39/1000 in 2008 to 13.91/1000 in 2021 [25]. Whereas in the USA, where MLT is not a prescription medication, its use raised from 0.1% in 2007 to 0.7% in 2012 in 4- to 17-year-old children. A more recent market analysis in the USA reported a growth in the national MLT market in response to the public demand, with sales increasing by approximately 150% between 2016 and 2020 [26]. In England, MLT prescriptions increased from 2.0 to 19.9/1000 between 2008 and 2019, most of them were for children [27]. Another study, aimed at examining trends in prescribing psychotropic medications to children and adolescents in the Australian primary care, reported an increase of MLT prescriptions just over 600% between 2011 and 2018. It is worth mentioning that among 0- to 4-year-olds, MLT was prescribed more frequently than any other psychotropic medication vs. the other age groups [19].

Most of these findings are based on registry-based cohort studies that analyzed the prescriptions of MLT; however, since in most countries MLT may be taken without prescription it is difficult to obtain reliable data on its use.

4.1. MLT use in typically developing children

The majority of studies evaluating MLT use in the pediatric population have been carried out in children with neurodevelopmental disorders or other comorbidities. Only two RCTs recruited typically developing school children and adolescents with sleep onset insomnia and phase delay syndrome [28–32]. The data supporting the use of MLT in the otherwise healthy pediatric population, and mainly infants and toddlers, are very limited and/or non-existent.

However it has been reported that MLT use in healthy children may be indicated as a treatment of occasional sleeplessness, after having ruled out psychiatric pathologies and comorbidities, and having verified sleep hygiene procedures and family education [33]. In a very recent report on MLT prescriptions in adults and children with a psychiatric diagnosis, it was stated that MLT may be an appropriate treatment for typically developing children with insomnia refractory to behavioral interventions [20]. Furthermore, some studies raised the problem of the prescription in children without a specific diagnosis. A large epidemiological study in Denmark reported that a great proportion of younger children aged 5–13 years are prescribed MLT for more than one year after initiation, 20% of them have no clear indication of psychopathology, and their first MLT prescription is authorized by a general practitioner. Furthermore, only half of 0- to 4-year-old MLT users had any indicator of psychopathology [18].

These data raise the issue of the lack of knowledge on the long-term effects of MLT in children and adolescents [12,22,34–37]. Furthermore, the growing popularity and widespread use of MLT imply an increased exposure to this drug and consequently the rising of MLT ingestions among children. In 2020, MLT was the most frequently ingested substance among children in the USA [38] and, according to the Centers for Disease Control and Prevention, the annual number of ingestions increased around 530% from 8337 in 2012 to 52,563 in 2021 [39]. Of these, 83.8% occurred in children aged ≤5 years, most were

unintentional (94.3%) and occurred at home (99.0%), 84.4% were asymptomatic.

4.2. Dosage and timing of administration of MLT

Italian community pediatricians frequently prescribe MLT to treat sleep disorders in children, but practice is not standardized, as in several other countries [23,40,41]. No consensus exists about the dosage and administration time of MLT in typically developing children. Several studies have found a very wide range of doses prescribed (from 0.5 to 18/20/24 mg/day) [7,36,41].

The Canadian Pediatric Society suggests that, following failure of behavior modifications, as well as ruling out any other medical causes of insomnia, trying pharmacologic treatment with MLT seems appropriate in typically developing children with insomnia who have unremarkable medical histories and physical examination findings and who practice good sleep hygiene [42]. According to the Canadian Pediatric Society and other consensus studies, in young people it is recommended to start with a dose of 1–3 mg, when used as a sleep inductor, and a maximum dose at 3 mg in children and 5 mg in adolescents, when used as a chronobiotic in sleep-wake disorders [9,42–44]. There is some evidence that low doses of MLT (1 mg/day or 0.05 mg/kg/day) are still effective in advancing sleep timing and dim light MLT onset in children and adolescents [45,46]. In a Swedish study, MLT mean dose prescribed by physicians for children aged 6–12 years, was 2.17 mg while, among children aged 0–5 years, 76% of all the prescriptions (mainly by pediatricians) were the oral solution of 1 mg/ml [37]. This dosage is consistent with the findings of our study in which the majority of pediatricians (74.1%) usually prescribe 1 mg/day.

Timing of administration plays a critical role in the results of MLT treatment [9]. In our survey, 84.9% of pediatricians suggested to take MLT 30 min before going to sleep, similar to the suggestions reported in another study [17].

4.3. MLT prescriptions in different countries

Some reports showed that MLT is used for a long time; in a Swedish study, a substantial number of children in the Stockholm Region use MLT continuously: after one year, the adherence to MLT was 87% among children aged 6–12 years, 76% among those 0–5 years, and 75% among those aged 13–17 years [37]. Around 40% of pediatricians in our survey indicated that they continue MLT treatment for one month, one third for 2–3 months and almost one out of four until improvement; very few prescribe MLT for only one week.

In a previous Australian survey on management of children sleep disturbances by pediatricians [7], only 27.7% of them prescribed MLT for infants, whereas more than half used MLT in children aged 6–12 months (58.99%), and less than a third (26.38%) for infants of 0–6 months. Moreover, Australian pediatricians tended to use more frequently MLT in adolescents (87.1%) and children (89.1%) than their Italian colleagues seem to do.

In our study, almost all pediatricians found MLT effective in reducing sleep onset latency while only a few of them found MLT effective in reducing the number of night awakenings in children, according to 19 randomized controlled trials, reporting that MLT significantly improved sleep latency, sleep duration, and wake time after sleep onset, but not number of awakenings per night [30].

It is interesting to note that some pediatricians reported improvements in other disorders, such as anxiety or headache, although studies have reported no evidence to support the administration of MLT as a treatment for migraine [47], nor for anxiety [48].

4.4. Unlicensed MLT products and side effects

MLT is regulated differently around the world, with the least amount of regulation placed on over the counter (OTC) dietary supplements. In

Italy there are several unlicensed MLT products, but there is no standard formulation, raising the possibility of variability in both product quality and clinical effect. In practice, variable concentrations of MLT are found in OTC preparations ranging from –83% to +478% of the labelled concentration of MLT content in supplements, also with several contaminants, such as serotonin or tryptophan [49,50].

A review of randomized controlled trials found no evidence of serious adverse events (AEs) associated with exogenous MLT use in the short term. The most common side effects were daytime sleepiness, headache, other sleep-related AEs, dizziness, hypothermia and fatigue; they were mild and tended to resolve spontaneously [9,34,41,51–53]. Accordingly, MLT seems also well tolerated in typically developing children, as reported by the general pediatricians in this study.

5. Limitations

Some limitations of this study should be acknowledged. This was an online cross-sectional survey and the results may reflect selection bias towards respondents who were more prone to approach the sleep issues in their clinical practice. Pediatricians who see many patients may also be more inclined to respond, inflating the estimates of caseload. This survey principally targeted general pediatricians who were affiliated with a specific association and may not reflect the opinion of the whole Italian pediatric community. Although this may be regarded as a limitation, it is worth considering that, probably, only the pediatricians most comfortable with the subject responded to the questionnaire, resulting in an interesting selection bias.

Another limitation is the low response rate. However, this value is in agreement with the general response rates obtained by pediatricians' online survey (29.2%), as reported by study exploring survey response rates among physician specialists [54].

The strength of this study is that we targeted our survey on the use of MLT in typically developing children reporting that the majority of pediatricians use MLT for sleep problems.

6. Conclusions

This study stands out for its meticulous methodology and the specific insights garnered from a survey of Italian pediatricians. Through a cross-sectional open survey conducted between June and November 2022, the research meticulously examined the utilization of melatonin in healthy children with chronic insomnia. The survey encompassed various critical aspects of MLT administration, including patient age, dosages, timing, treatment duration, concurrent therapies, perceived effectiveness, and potential side effects. With a sample size of 428 respondents, the study provides a comprehensive overview of pediatricians' practices. Findings indicate a high prevalence of MLT usage (97.4%) across pediatricians, with varying preferences based on patient age and treatment strategies. The results emphasize the need for standardized guidelines as they reveal a lack of consensus regarding the use of MLT in typically developing children. This research significantly contributes to the literature by illuminating the prevalent use of MLT in this population and highlights the imperative for coherent guidelines to optimize its application.

It is well known that insomnia and sleep related problems decrease quality of life, as well as cognitive performance, in children and adolescents; therefore, it is important to identify the best treatment for this disorder and to increase the knowledge base related to the use of MLT.

To date, only few randomized controlled trials have been conducted on MLT in children with insomnia, with important biases related to the definition of insomnia vs. insomnia complaints [55].

In this study, we have shown that immediate-release MLT is the molecule most used by Italian pediatricians for sleep problems in infants and children; however, this attitude is not based on specific knowledge or indications or guidelines for its use in typically developing children. Italian pediatricians commonly use immediate-release MLT associated

with sleep hygiene measures mainly in the case of sleep-onset insomnia, with a most common dosage of 1 mg and for at least one or two months, considering the positive benefit/risk ratio and the benign safety profile of MLT.

Beside the solid scientific evidence on MLT treatment in children with neurodevelopmental disorders, MLT may also have a role in typically developing children with insomnia. Therefore, there is a need of similar research in order to know the pediatricians' attitude of prescribing melatonin in typically developing children in different countries and or continents.

Future studies should also address the different efficacy of immediate-vs. prolonged-release MLT in healthy children and adolescents, in order to develop clear guidelines and to optimize the management of insomnia in them.

Finally, there is urgent need for consensus recommendations about MLT use, dosage and mode of administration in typically developing infants and children. Although the majority of pediatricians in our and other studies seems to prescribe 1 mg/day of melatonin about 30 min before sleep, there is evidence of a wide range of doses prescribed and timing of administration across different countries.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

Appendix A. Supplementary data

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