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# Original Article

# Pharmacological and non-pharmacological management of sleep disturbance in children: An Australian Paediatric Research Network survey

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#### ABSTRACT

Background: Australian paediatricians use a wide variety of practices when managing sleep disturbances in children, including use of melatonin and behavioral strategies. However, practice patterns around the use of strategies, dosing, and how the patient populations managed, are unknown. Results could inform guidelines for the management of child sleep disturbances.

Objective: We aimed to document management practices by Australian general paediatricians for paediatric sleep disturbances through an online survey sent to members of the Australian Paediatric Research Network (APRN) who are recruited from the Royal Australasian College of Physicians.

Results: 181 (49%) of 373 eligible paediatricians responded, with 101 prescribing melatonin. The most commonly prescribed medications for poor sleep initiation were melatonin (89.1%), clonidine (48%) and antihistamines (29%). Melatonin doses ranged from 0.5 mg to 12 mg and duration of treatment was as long as 200 weeks. Less than half of the paediatricians were aware of any potential melatonin side effects. Most paediatricians (82%) reported 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.

Conclusions: Australian paediatricians use both pharmacological and non-pharmacological treatments for paediatric sleep disturbances. Melatonin is the most commonly prescribed medication, but wide variation in its prescribing suggests a lack of knowledge of recommended dosages and effectiveness. Given the prevalence and variation in prescribing, there is an urgent need to develop clear guidance for paediatricians managing children with sleep disturbance.

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# 1. Introduction

Sleep disturbances are among the most frequent concerns managed by paediatricians. Up to 40% of typically developing children experience difficulty in initiating and maintaining sleep [1], rising to 40-80% in children with developmental disorders, attentiondeficit/hyperactivity disorder, depression and anxiety [2,3]. Sleep

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sleep apnoea) or behavioral (e.g. limit setting disorder, sleep onset association, insomnia) [4]. Inadequate sleep has detrimental effects on the neurobehavioral

disturbances in children can be organic in nature (e.g. obstructive

and cognitive development of the child [5] as well as on family members and family dynamics [6]. Sleep-deprived children tend to have poorer memory and attention, increased emotional lability, and poorer impulse control [6,7]. Parents often suffer from psychological distress [3,6]. Insufficient sleep in parents is associated with increased maternal health problems including maternal depression, higher family stress, and parental conflict [6,7]. Paediatric sleep disorders can be overlooked, as they often present with hyperactivity and irritability, rather than daytime sleepiness [8]. This may be

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related to a lack of physician knowledge about paediatric sleep problems and their management [9].

Several studies have demonstrated improvement in behavioral paediatric sleep disorders with management strategies including unmodified/graduated extinction, bedtime routines, scheduled awakenings, and parent education [10]. In contrast, a variety of medications including antihistamines, antidepressants, benzodiazepines, alphaagonists, melatonin, and herbal preparations have been prescribed for paediatric sleep disorders despite a relative paucity of clinical evidence for their effectiveness [4]. Two national surveys from the United States have highlighted the dangers of their widespread use without well-designed studies regarding the efficacy, dosing, and safety of these medications in children [9,11].

Melatonin is currently recommended by many practitioners as a "natural sleeping aid" due to its endogenous origin. Initially identified by Lerner et al. in the late 1950s [12], melatonin was named for its ability to aggregate melanin granules (mela-) and after its precursor, serotonin (-tonin) [13]. Although primarily synthesized by the pineal gland under the regulation of the suprachiasmatic nucleus of hypothalamus, melatonin is also produced by the retina and gastrointestinal tract [14,15]. This functionally diverse hormone is most commonly noted for its control of the human sleepwake cycle via the circadian rhythm of its production. A number of studies have demonstrated promising results for treatment of sleep disorders co-morbid with medical, psychiatric, or developmental disorders [16]. In a more recent meta-analysis of five randomized double-blinded, placebo-control trials. Rossignol and Frye demonstrated significant improvement in sleep onset latency times and sleep duration in autistic spectrum disorders with melatonin use [16]. A meta-analysis from the Netherlands showed that melatonin significantly decreases sleep latency by a mean of 34 minutes and increases sleep duration by 50 minutes in intellectually disabled individuals [17]. However, Buscemi et al. found that melatonin is not as effective in treating secondary sleep disorders [18].

Melatonin use has been reported in the paediatric population since 1991 and has generally been regarded as safe, despite the lack of rigorous clinical trials assessing its safety. Rossignol and Frve revealed no adverse effects with short-term use. Long-term effects have been minimally investigated and there is a theoretical risk of hypothalamic-gonadal axis suppression based on studies demonstrating higher melatonin secretion in males with hypogonadotropic hypogonadism and delayed puberty [19,20]. However, these concerns were not borne out in a recent paper evaluating puberty in 51 adolescents with a mean melatonin usage of 3.1 years [21]. Other reported adverse events include increased seizure activity and frequency, hyperactivity, agitation, worsening sleep, nightmares, and constipation [22]. Many of these side effects have subsequently been attributed to other substances mixed with melatonin preparations in commercial formulations varying in dosage, purity, and efficacy [4,23]. Furthermore, studies on melatonin have different dosages demonstrating efficacy, which has translated into varying prescribing practices by paediatricians and psychiatrists [22,24,25].

A recent audit of Australian compounding pharmacies demonstrated that, in a total of 1463 prescriptions dispensed over a two week period, the median age of people was 12 years. The most common prescribers were paediatricians (43%) and the most common reason was for attention deficit hyperactivity disorder (ADHD). Given the extraordinarily high number of apparent prescriptions being written by paediatricians, we aimed to document Australian paediatricians' management of child sleep disturbances, including the use of medications and behavioral strategies. We hypothesized that most paediatricians use a range of behavioral strategies for behavioral sleep disturbances and that the medication use including melatonin would be reserved for children with comorbid problems such as, ADHD and autism.

#### 2. Methods

#### 2.1. Design

The Australian Paediatric Research Network (APRN) facilitates multi-site research in secondary care paediatric outpatient settings [26]. In early 2010, we invited members to answer questions on melatonin and other medication use as part of the annual APRN multi-topic survey (included as Supporting information). Ethics approval was not required because paediatricians, not patients, provided data.

#### 2.2. Participants

APRN members were recruited from the 1006 general paediatricians registered in 2007 with the Royal Australasian College of Physicians [27]. All Australian states and territories are proportionally represented and APRN members and non-members are broadly similar other than minor differences in age, gender and practice location [27,28]. Members eligible for the 2010 multi-topic survey were all 373 registered members.

# 2.3. Multi-topic survey

In late 2009, we invited members to submit survey topics to the APRN Steering Group. Each of the five proposed topics was developed into a two-page survey by a team of interested paediatricians. Following the two page survey, these were streamlined and combined into a single web-based survey Monkey questionnaire, distributed via four emails at approximately weekly intervals spanning March–April 2010.

The melatonin use questions (see Supporting information) were pupose-designed by four authors with clinical expertise in sleep (HH, KW, MD, HH) to examine two areas. Area 1 comprised nine questions about prescribing melatonin and included: youngest and oldest age prescribed, disturbance prescribed for ("difficulty falling asleep", "night waking", "delayed sleep phase", "obstructive sleep apnoea", plus "other"), diagnostic conditions (seven options, e.g. "normally developing", "developmental delay", "autism"), dosage, length of prescription, review schedule and paediatrician knowledge of side effects. Area 2, comprise of two seven-item questions examining paediatricians' management of sleep disturbances (specifically, the four conditions identified above) using behavioral sleep management techniques (e.g. "relaxation techniques", "controlled crying") and other medications (e.g. "selective serotonin reuptake inhibitors", "antihistamines"). Items were coded "yes" if marked.

The paediatrician characteristics used to describe the sample (age, gender, working hours, involvement in research and the location, type and postal code of the paediatrician's primary practice) were obtained from the APRN database. The practice postal code provides an indicator of the social disadvantage of the practice locality via its Socio-Economic Indexes For Areas (SEIFA) Disadvantage Index Value [29]. SEIFA values are standardized scores by geographic area compiled from 2006 census data to numerically summarize the social and economic conditions of Australia (national mean 1000, SD 100; higher values represent greater advantage). We categorized SEIFA into tertiles to represent high, medium and low socioeconomic disadvantage.

# 2.4. Statistical analysis

We use proportions to describe and Pearson chi-square tests to compare: responders and non-responders for (a) the entire multitopic survey and (b) by melatonin use (yes versus. no); the medications and behavioral strategies that paediatricians use to manage

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child sleep, and paediatricians' knowledge of side effects. We describe the dosages using means (standard deviations (SD)). We used Stata 11.1 for all analyses.

#### 3. Results

# 3.1. Responder characteristics (Table 1)

180/371 (48%) of paediatricians completed the survey, of whom 101 (56%) prescribed melatonin. Responders differed from non-responders in that they were more likely to be female and work fulltime. Compared with paediatricians who did not prescribe melatonin, those that did, were more likely to be working in metropolitan settings and not in private practice. The most frequent reasons for not prescribing were "not part of my practice or patient load" (n = 12); "lack of knowledge or experience to prescribe" (n = 5); and "insufficient evidence for the efficacy or safety of melatonin" (n = 4).

# 3.2. Melatonin for specific sleep conditions and populations

Among the 101 paediatricians who had prescribed melatonin, most had done so for children (89.1%) and adolescents (87.1%), with less than a third (27.7%) for infants. The youngest patient prescribed melatonin by any given paediatrician ranged from 6 months to 14 years of age, with an average of 4 years and 1 month.

Paediatricians reported prescribing melatonin for the following sleep disturbances: difficult sleep initiation (89.1%), delayed sleep phase (66.3%), and nighttime wakings (30.7%). 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.

### 3.3. Melatonin: dosages, duration, and follow-up of treatment

Infant dosage ranged from 0.5–3.5 mg with a mean (SD) of 2.1 mg (1.0); child dosage ranged from 1–10 mg with a mean (SD) of 3.5 mg (1.5) and adolescent dosage ranged from 2–12 mg with a mean (SD) of 5.3 mg (2.4). Maximum prescribing doses were 5 mgs (infants), 10 mgs (children) and 18 mgs (adolescents) with a wide range. The most common reported starting dose was 3 mgs (30% in infants, 51% in children and 44% in adolescents).

Duration of treatment ranged from 0 to 200 weeks, with an average of 16.5 weeks (SD 26.3 weeks. The time to first follow-up visit ranged from 2 to 26 weeks, with an average of 6.2 (SD 3.8) weeks.

# 3.4. Melatonin: awareness of side effects

Fewer than half (45.5%) of the respondents who had prescribed melatonin were aware of its reported side effects. Of these, the most common side effects that paediatricians knew about were daytime somnolence (n = 14%, 30.4%); increased risk of seizures (n = 13%, 28.3%); mood disturbance and headaches (both n = 9%, 19.6%).

# 3.5. Non-pharmacological and pharmacological treatment of sleep-related disturbances (Table 2)

Most paediatricians (82.4%) reported using behavioral strategies for sleep-related conditions. Poor sleep initiation was most frequently managed by anxiety relaxation techniques (74.5%), limit setting (58.4%), and changing bed/wakeup times (47.5%). Sleep delay was managed by changing bed/wakeup times (59.4%), anxiety relaxation techniques (38.6%), and limit setting (28.7%). Disrupted overnight sleep was most commonly managed by graduated extinction (i.e. "controlled crying" (51.5%), limit setting (40.6%), and anxiety relaxation techniques (32.7%). Appropriately,

Table 1
Characteristics (%) comparing (a) responders versus non-responders and (b) comparing responders who did versus did not prescribe melatonin.

Characteristic	Whole sample ( $N = 371$ )			Melatonin prescribers ( $N = 181$ )		
	Non-responders N = 191	Responders N = 180	р	Yes N = 101	No <i>N</i> = 79	р
Paediatrician						
Male	58.1	48.3	0.06	51.5	44.3	0.3
Age (years)						
25-34	4.8	2.2		2.0	2.5	
35-44	42.9	34.3	0.1	33.7	35.4	0.9
45-54	32.3	35.0		34.7	35.4	
55-64	18.5	24.4		26.7	21.5	
65+	1.6	3.9		3.0	5.1	
Works part-time	71.8	39.4	< 0.001	34.7	45.6	0.1
Involved in research	52.5	45.8	0.1	39.6	51.9	0.1
Main practice						
Location						
Metropolitan	70.1	70.6		61.4	82.3	
Regional	24.3	25.6	0.7	32.7	16.5	0.007
Rural	5.7	3.9		5.9	1.3	
Туре						
Academic	21.0	18.9	0.6	19.8	17.7	0.7
Community Health	3.9	10.6	0.01	8.9	12.7	0.4
Private practice	39.8	42.2	0.6	54.5	26.6	< 0.001
Public Hospital	80.1	79.4	0.9	83.2	74.7	0.2
Other	0	8.3	< 0.001	9.9	6.3	0.4
SEIFA Disadvantage						
High	29.8	36.8		42.6	29.2	
Medium	33.9	33.1	0.3	28.7	38.9	0.2
Low	36.3	30.1		28.7	31.9	

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**Table 2**Proportions of paediatricians (95% confidence intervals (CIs)) who use behavioral and pharmacological approaches to manage specific sleep disturbances.

Approach	Sleep disturbance, % (CI)						
	Sleep initiation	Sleep delay	Disrupted overnight sleep	OSA <sup>a</sup>			
Behavioural							
Anxiety relaxation techniques	74.5 (65.6-82.9)	38.6 (29.0-48.3)	32.7 (23.4-42.0)	3.0 (0-7.3)			
Controlled crying	39.6 (30.0-49.3)	10.9 (4.7-17.1)	51.5 (41.6-61.4)	1.0 (-1.0-3.0)			
Limit setting	58.4 (48.6-68.2)	28.7 (19.7-37.7)	40.5 (30.9-50.3)	1.0 (-1.0-3.0)			
Camping out	20.8 (12.7-28.8)	5.0 (1.0-9.3)	17.8 (10.2-25.4)	1.0 (-1.0-3.0)			
Changing bedtime/wakeup time	47.5 (37.6-57.4)	59.4 (49.7-69.1)	15.8 (8.6-23.1)	1.0 (-1.0-3.0)			
Other strategies	45.5 (35.7-55.4)	17.8 (10.2-25.4)	29.7 (20.6-38.8)	11.9 (5.5-18.3)			
None	2.0 (-0.1-4.7)	6.9 (1.9-12.0)	6.9 (1.8-12.0)	71.3 (62.3-80.3)			
Pharmacological							
Melatonin <sup>b</sup>	89.1 (82.9-95.3)	66.3 (57.0-75.7)	30.7 (21.5-39.8)	0			
SSRI/SNRI	4.0 (0-7.8)	3.0 (0-6.3)	3.0 (0-6.3)	0			
Vallergan/phenergan	28.7 (19.7-3.8)	8.9 (3.3-14.6)	17.8 (10.2-25.4)	0			
Clonidine	47.5 (37.6-57.4)	17.8 (10.2-25.4)	6.9 (1.8–12.0)	0			
Benzodiazepine	2.0 (-1.0 - 4.7)	2.0(-1.0-4.7)	4.0 (0-7.8)	0			
Antiepileptics/neuroleptics	3.0 (0-6.3)	0	3.0 (0-6.3)	0			
Other medications	20.8 (12.7-28.8)	13.9 (7.0-20.7)	9.9 (4.0-15.8)	19.8 (11.9-27.7)			
None	19.8 (11.8–27.7)	33.7 (24.3-43.0)	44.6 (34.7–54.4)	55.4 (45.6-65.3)			

OSA = Obstructive sleep apnoea.

behavioral strategies played little in managing obstructive sleep apnoea (OSA).

After melatonin, the most commonly prescribed medications were clonidine (prescribed by 47.5% primarily for problems with sleep initiation) and anti-histamines such as phenergan (promethazine, prescribed by 28.7% for problems with sleep initiation). The medication used in OSA was limited; paediatricians preferred to refer children to an ENT specialist (n = 6), prescribe nasal steroids (n = 5) or investigate the apnoea before prescribing (n = 2).

## 4. Discussion

# 4.1. Principal findings

This is the first survey of Australian paediatricians' management of child sleep disturbances. Most paediatricians used behavioral management strategies and just over half reported prescribing melatonin. Most paediatricians used behavioral techniques in an appropriate way, e.g. they managed poor sleep initiation by anxiety relaxation techniques (74.5%), limit setting (58.4%), and changing bed/wakeup times (47.5%) and sleep delay by changing bed/wakeup times (59.4%). However, for both sleep problem areas, use of medication was more common than use of behavioral strategies, contrary to current recommendations [10].

Paediatricians prescribed melatonin over a wide age range (from 6 months to 25 years) and for a variety of sleep disturbances. Fewer than half were aware of the side effects for melatonin. Medication use overall was common (reported by 80% of paediatricians) and 47% of paediatricians prescribed clonidine to manage problems with sleep initiation. A wide range of different dosages were used indicating a lack of certainty about dosing regimes. This high use of medication may reflect the underlying complexity of sleep disturbances in the setting of comorbid developmental and mental health conditions managed by paediatricians.

# 4.2. Interpretation in light of existing studies

Our findings mimic those of older US and UK surveys of paediatricians' management of sleep disturbances. In a 2003 US survey, 75% of community-based paediatricians had recommended nonprescription medication for insomnia (including melatonin and antihistamines) and more than 50% had prescribed medications including  $\alpha$ -agonists that were prescribed by 31% [9]. Similar findings occurred in a 2002 survey of 222 US paediatricians where 45% had prescribed an  $\alpha$ -agonist [30]. Melatonin has been available over the counter in the US for some time. However, in contrast to our study, US paediatricians were less likely to recommend melatonin for initial insomnia in typically developing children (23% [9] versus. 55%, respectively). This may reflect greater concerns that have since emerged with respect to the effect of poor sleep on a child's daytime functioning, and/or evidence of effectiveness from double-blind placebo-controlled trials and thus, increased willingness of Australian paediatricians to prescribe. It may also reflect parent trial of melatonin prior to consulting a US physician, given that melatonin was available over the counter in the US at that time, but is not currently so in Australia.

In a 2005 survey of community paediatricians working in the UK, 98% had prescribed melatonin with doses of 0.5-24 mg. Most had used behavioral strategies (87%) prior to melatonin and 22% had trialed other medication prior to the use of melatonin [22]. This is comparable to our study where 80% of paediatricians reported using behavioral strategies, but we did not determine the timing of this. However, Australian paediatricians were more likely to prescribe clonidine for poor sleep initiation (48%) than UK paediatricians (22%). This may reflect a higher proportion of children with ADHD in our sample compared with the UK study (i.e. 52% versus. 44%, respectively). Groups of children treated were otherwise similar with autism being the most common group treated for their sleep disorders in our study and the UK [22]. We could not find any more recent surveys of paediatrician's practice with respect to management of sleep problems. A recent audit of melatonin prescribing through compounding pharmacies in Australia; however, revealed that paediatricians were the most common prescribers (43% of 227 audit forms), typically prescribing for insomnia in children with ADHD (24.2%) [31].

# 4.3. Study limitations

Our study has some limitations. First, the multi-topic survey response fraction was 49%, but this is considerably better than the US and UK response fractions of 25%, 27% and 15% [8,22,30]. Comparable data for Australian general paediatricians are not available, although the most recent Royal Australasian College of Physicians

b Other conditions (e.g. jetlag/travel, chronic fatigue, movement disorders, night terrors, sedation for EEG) = 8.9%.

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workforce survey (2008, 22% paediatricians response) describes a group with a similar gender distribution, but fewer working parttime [28]. Second, we had no objective measures of pediatric practice, but the recent two week national prospective audit of 18 compounding pharmacies in Australia estimated that a total of 1463 prescriptions for melatonin were dispensed with paediatricians being the most common prescribers [31]. While we collected information about dosage, we did not collect details such as, timing of administration and use of concurrent management strategies. Doing so, may have provided more evidence for educational requirements of general paediatricians who see children with sleep difficulties. In this survey, the most common reason for melatonin prescribing was to help with sleep in children with ADHD. This is not surprising given that the most common condition managed by Australian paediatricians is ADHD [32]. Melatonin use in typically developing children was less common (57%). At the time of the survey there was very little evidence for the use of melatonin in the typically developing population. The wide variety in dosing and approaches suggests a clear need for more evidence around prescribing and use of melatonin, particularly in typically developing children.

We did not evaluate the incidence of reported adverse effects, but rather clinician awareness of potential adverse effects. The UK study found that 18% of clinicians reported adverse effects and this clearly needs to be investigated further within Australia as a limited number of our clinicians reported awareness of these potential effects.

#### 4.4. Clinical and research implications

This study highlights the wide variety of practice by Australian paediatricians when prescribing melatonin and other medications; it may reflect a lack of knowledge of the evidence for prescribing for children of varying ages and populations. A number of reviews have summarized the evidence for pharmacological and non-pharmacological treatment of paediatric insomnia in typically developing children [4] and in children with visual impairment [33]. autism [34.35], and ADHD [36]. Australian paediatricians may benefit from the guidelines for the treatment of sleep disorders in children, in particular the prescribing of melatonin, based on these reviews. Further training around the classification and subsequent management of behavioral sleep difficulties may also be required. This may include online training with clinical decision flowcharts to maximize reach for rural paediatricians. The Australasian Sleep Association is planning to develop such training packages for pediatric sleep disorders.

# 4.5. Unanswered questions and future research

Future research should focus on longitudinal studies of melatonin use to document the true incidence of adverse events, the interaction of exogenous melatonin on a variety of body systems including endogenous melatonin production, and impact of dosaging and duration of therapy on sleep difficulties in the typically developing population. Finally, rigorous controlled trials of pharmacological and non-pharmacological interventions in special populations commonly managed by APRN paediatricians (e.g. autism, ADHD) are needed.

# **Conflict of Interest**

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2012.09.023.

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