

Melatonin treatment for sleep disorders in children with neurodevelopmental disorders: an observational study

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The study aim was to quantify melatonin-associated improvement in sleep by means of a parent-completed sleep diary during routine outpatient activity. An investigation into sleep disturbance was made at neurology outpatient appointments. Those parents who identified a problem were asked to complete a sleep diary, after which treatment was initiated. The first week of the diary was completed before treatment, the second when established on the maximum dose of melatonin required. Forty-nine patients (26 males, 23 females) aged from one to 13 years, were treated between 1997 and 1998: 28 of these returned interpretable diaries. In a further 18 patients, an assessment could be made of the usefulness of the treatment. Patients were fairly typical of those attending a tertiary centre, the most common primary diagnosis being epilepsy ($n=26$). Only seven patients were visually impaired. Of the 46 patients who were assessed, 34 showed an improvement. No adverse effects were attributed to the treatment.

Sleep disorders in children are common (Zuckerman et al. 1987) and a major source of stress for the whole family. In severe instances they may lead to breakdown in family functioning. In children with neurodevelopmental disabilities, the prevalence may be as high as 80% (Bartlett et al. 1985, Quine 1991).

Disorders such as blindness, learning disability,* cerebral palsy, autism, head injury, and CNS disease can all diminish the ability to perceive and interpret a variety of cues for synchronizing sleep with the environment. Melatonin is an indoleamine hormone (Lerner et al. 1958) synthesized and secreted by the pineal gland mainly at night.

Photic information from the retina is transmitted to the pineal gland through the suprachiasmatic nucleus of the hypothalamus and the sympathetic nervous system. During daylight hours, the retinal photoreceptor cells are hyperpolarized, which ultimately inhibits secretion of melatonin. At the onset of darkness, the retinal photoreceptors release noradrenaline, the retino-hypothalamic-pineal system is activated, and the synthesis of melatonin is increased.

Oral doses of one to five milligrams of melatonin result in serum melatonin concentrations that are ten to one hundred times higher than the usual night-time peak within one hour of ingestion, followed by a decline to baseline values in four to eight hours. Low oral doses (0.1 to 0.3 mg) given in the daytime result in peak serum concentrations that are within the normal night time range.

The dose-dependent physiological effects of the hormone (e.g. hypothermia, increased sleepiness, and decreased alertness) have not yet been fully evaluated in people who have been taking large doses for prolonged periods. Decreased serum luteinizing hormone concentrations and increased serum prolactin concentrations have been reported after the administration of pharmacological doses of melatonin in individuals without sleeping disorders (Bojkowski et al. 1987, Sadeh 1997). It has been suggested that melatonin may inhibit the hypothalamic-pituitary-gonadal axis (Brzezinski 1997).

Attenburrow and colleagues (1996) found that some patients with insomnia had decreased evening melatonin secretion. Wurtman and Zhdanova (1995) describe the effects of melatonin in a physiological dose (0.3 mg) in elderly people with insomnia. Melatonin greatly reduced nocturnal movements, latency to sleep onset, awakenings per night, and subjective sleep quality. It did not increase morning sleepiness and had no effect on core body temperature.

In a placebo-controlled, double blind study, Jan and colleagues (1994) examined the effects of melatonin on children with neurological and/or visual disabilities. The starting dose was 2.5 mg and maintenance doses ranged from 2.5 mg to 10 mg. Thirteen of fifteen children showed improvement in sleep. The parents of the other two children continued melatonin treatment because of improvements in behaviour. No adverse events were noted.

Most investigators have found neutral or beneficial effects on seizure control in patients with epilepsy (Jan et al. 1994, Espezel et al. 1996, Jan and O'Donnell 1996, Jan et al. 1999). Sheldon (1998), however, reported increased seizures in four of six children with severe neurologically disabling conditions.

Encouraged by the results of Jan and colleagues and by

*UK usage. North American usage: mental retardation.

the possibility of significantly improving the quality of life of our patients and their families, we decided to audit the effects of melatonin on sleep in paediatric neurology outpatients by

means of a parent-completed sleep diary. Some of our experience has previously been published in a letter to this journal (Ross et al. 1999).

Table I: Characteristics of patients whose carers returned interpretable sleep diaries (n=28)

Patient	Age	Sex	Visual impairment	Primary diagnosis	Sleep problem	Benefit	Dose, mg	Carers' comments
1	11	M	N	Epilepsy with aphasia	Settling/frequent waking	Y	2.5	Very dramatic
2	2	M	Y	Cerebral palsy ^a	Low requirement	Y	2.5	
3	7	M	N	Angelman's ^a	Night waking	Y	2.5	Brilliant
4	4	F	N	Epilepsy	Difficulty settling	Y	2.5-5	
5	9	F	N	Epilepsy	Settling/frequent waking	Y	5	Brilliant
6	11	F	N	Epilepsy	Settling/frequent waking	Y	10	
7	1	F	Y	TB meningitis	Low requirement	Y	5	Brilliant
8	7	F	N	Epilepsy	Night waking	Y	5	
9	7	M	N	Epilepsy/ADD	Settling/night waking	Y	2.5	Brilliant
10	6	F	Y	Non-specific leukodystrophy ^a	Night waking	Y	7.5	
11	8	F	N	Epilepsy	Frequent waking	Y	5	Brilliant
12	3	M	N	Down syndrome	Fragmented sleep	Y	2.5-5	
13	9	M	N	Developmental delay	Low requirement	N		Brilliant
14	7	F	N	Learning difficulties ^a	Fragmented sleep	N	7.5	
15	2	F	Y	PEHO-like syndrome ^a	Early waking	N		Brilliant
16	3	M	N	Non-specific leukodystrophy ^a	Fragmented sleep	N		
17	2	M	N	Hunter's disease	Night waking	N	7.5	Brilliant
18	8	M	N	Epilepsy	Low requirement	Y	7.5	
19	3	M	N	Epilepsy	Low requirement	Y	5	Brilliant
20	3	M	N	Cerebral palsy ^a	Fragmented sleep	Y	5	
21	6	M	N	Epilepsy	Difficulty settling	Y	2.5	Brilliant
22	1	M	Y	Ohtahara's syndrome	Delayed-sleep phase	Y	5	
23	2	F	N	Turner's syndrome	Settling/low requirement	Y	5	Brilliant
24	9	M	N	Epilepsy	Settling/frequent waking	Y	10	
25	9	M	N	Epilepsy	Settling/frequent waking	N		Brilliant
26	7	F	Y	Optic glioma	Prolonged night waking	Y	5	
27	2	F	N	Epilepsy	Frequent waking	Y	5	Brilliant
28	8	F	N	Migraine	Difficulty settling	N	7.5	

^aEpilepsy as a secondary diagnosis. PEHO, progressive encephalopathy with oedema, hysarrhythmia and optic atrophy.

Table II: Characteristics of patients without returned diaries (n=18)

Patient	Age	Sex	Visual impairment	Primary diagnosis	Sleep problem	Benefit	Dose, mg	Carers' comments
32	5	M	N	Epilepsy		Y		Seizures improved
33	13	F	N	Epilepsy		Y		
34	10	M	N	Epilepsy	Low requirement	Y	5	Seizures improved
35	8	M	N	San Filippo ^a	Delayed-sleep phase	Y	5	
36	7	M	N	Developmental delay		Y	2.5	Seizures improved
37	8	F	N	Epilepsy	Settling/agitation	Y	2.5	
38	10	M	N	Lennox-Gastaut ^a	Difficulty settling	Y	2.5-5	Seizures improved
39	3	M	N	Lennox-Gastaut ^a		Y	2.5	
40	2	M	N	Infantile spasms ^a		Y	2.5	Seizures improved
41	9	F	N	Developmental delay ^a		Y		
42	4	F	N	San Filippo ^a	Fragmented sleep	Y	10	Seizures improved
43	7	F	N	Epilepsy		N		
44	10	M	N	Epilepsy		N		Seizures improved
45	1	M	N	Epilepsy		N		
46	7	M	N	Learning difficulties	Frequent waking	N	10	Seizures improved
47	3	F	N	Epilepsy		N		
48	7	M	N	Brain tumour ^a	Settling/low requirement	Y	7.5	Seizures improved
49	8	F	N	Epilepsy	Difficulty settling	Y	5	

^aEpilepsy as a secondary diagnosis.

Method

Enquiries into sleep disturbance were made at paediatric neurology outpatient appointments. Treatment with melatonin was offered to carers with an explanation that this is an unlicensed drug with a theoretical risk of delayed puberty, but which literature suggests may be a useful and safe treatment (Espezel et al. 1996, Jan et al. 1997). Formal ethical approval was not sought because the study was conducted

during regular outpatient treatment.

Those parents or carers who identified a sleep problem (see Table I) were shown how to complete a sleep diary. The first week of the diary was completed before melatonin was commenced, and the second week when on the maximum melatonin dose for age. For those not returning completed sleep diaries the case notes were reviewed to clarify the sleep problem and assess response to treatment. Where there was no mention of melatonin therapy, it was assumed that melatonin treatment would not be helpful.

Melatonin 2.5 mg and 5 mg capsules were dispensed from the Birmingham Children’s Hospital pharmacy. The product used (Penn Pharmaceuticals, Gwent, UK) is entirely synthetically produced, thus there was no risk of acquiring prion disease from this treatment. Children under 5 years of age were started on 2.5 mg and those 5 years or more started on 5 mg. This was increased by 2.5 mg at intervals of three days up to a maximum dose of 7.5 mg (if less than two years of age) or 10 mg. Parents were advised that a further dose of up to 5 mg could be given if their child initially settled to sleep but later awoke.

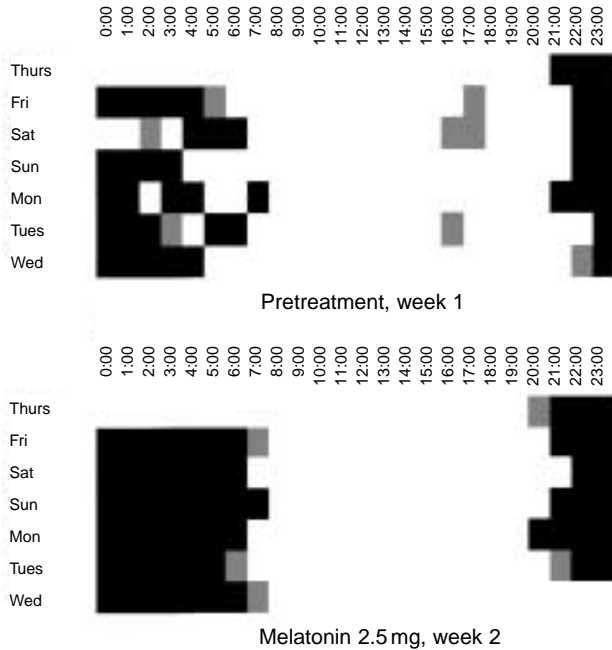


Figure 1: Patient 1, difficulty settling and frequent waking.

Table III: Responses to melatonin treatment by type of sleep disturbance

<i>Sleep problem</i>	<i>Beneficial</i>	<i>Not beneficial</i>
Fragmented sleep	3	2
Difficulty settling	12	2
Low requirement	7	1
Awakening	11	4
Delayed-sleep phase	2	9

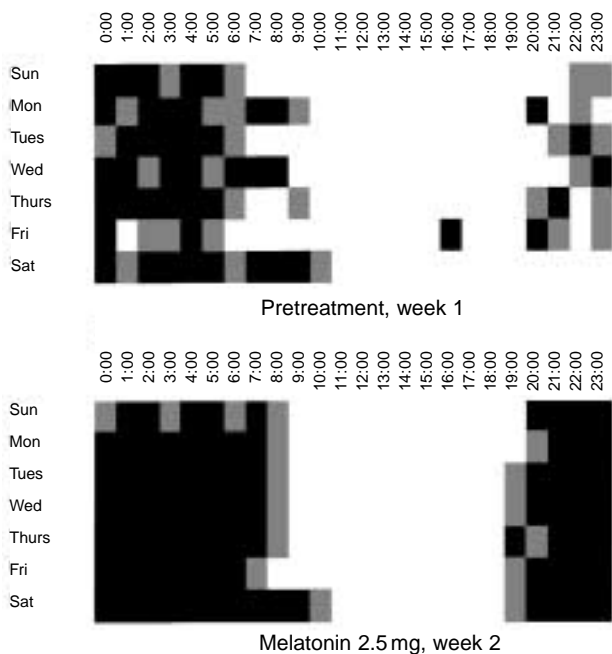


Figure 2: Patient 9, difficulty settling and night waking.

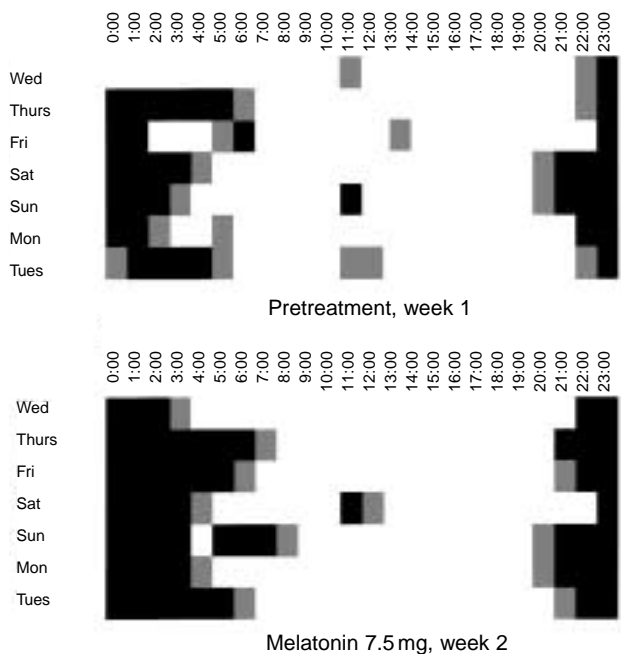


Figure 3: Patient 18, low sleep requirement.

PATIENTS

Forty-nine patients (26 males, 23 females) received melatonin from the hospital pharmacy between 1997 and 1998 aged from one to 13 years. They suffered from a mixture of sleep disorders (Table I) in addition to underlying developmental or neurological disorder (see Tables I and II). This group of children can prove particularly difficult to diagnose using standard international criteria (the International Classification of Sleep Disorders). We chose to categorize them by symptom type rather than seeking to describe them by diagnostic category of the International Classification of Sleep Disorders. Of the 49 patients, seven children were visually impaired. Twenty-six children had epilepsy. Thirty one diaries were returned, of these twenty eight could be interpreted. The salient character-

istics of these patients and their parents' assessment of effects of melatonin are summarized in Table I.

Eighteen diaries were not returned (Table II). Three uninterpretable diaries were returned, (patients 29, 30 and 31). All diaries were analyzed using the Wilcoxon signed ranks test, for matched pairs within patient comparison.

Results

Representative examples of five sleep diaries are shown (Figures 1 to 5). The upper section of each Figure is the diary completed pretreatment and the lower section during treatment. Black boxes represent sleep for the whole hour, grey boxes represent sleep for part of the hour. The diaries run from midnight to midnight.

Table IV: Quantitative analysis of sleep parameters before and on treatment with melatonin

	Median (range), hours/week	Median difference (95% confidence interval)	p
Sleep time			
Pretreatment	54 (13.5–86.5)	8.7	<0.0005
Posttreatment	65.5 (18–99.5)	(5.5–12.75)	
Night time sleep			
Pretreatment	53 (8.5–74)	10	<0.0005
Posttreatment	64 (13–87.5)	(6–14.2)	
Duration of interruptions			
Pretreatment	9 (0–35.7)	–2.75	0.03
Posttreatment	5 (0–35)	(–6.25–0)	
Number of interruptions			
Pretreatment	7 (0–23)	–1.5	0.097
Posttreatment	3.5 (0–26)	(–3.5–0.5)	
Time fell asleep (24h clock)			
Pretreatment	22:06 (19:00–03:06)	–1.1	0.001
Posttreatment	21:24 (18:06–00:54)	(–1.67– –0.5)	

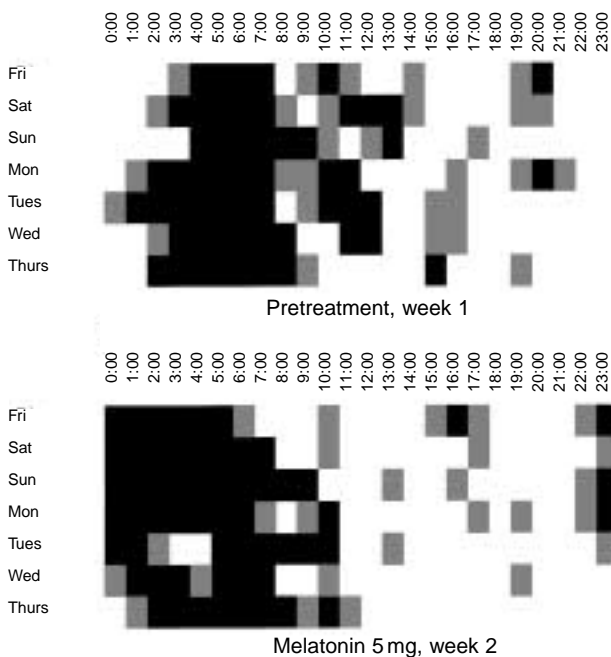


Figure 4: Patient 22, delayed sleep-phase.

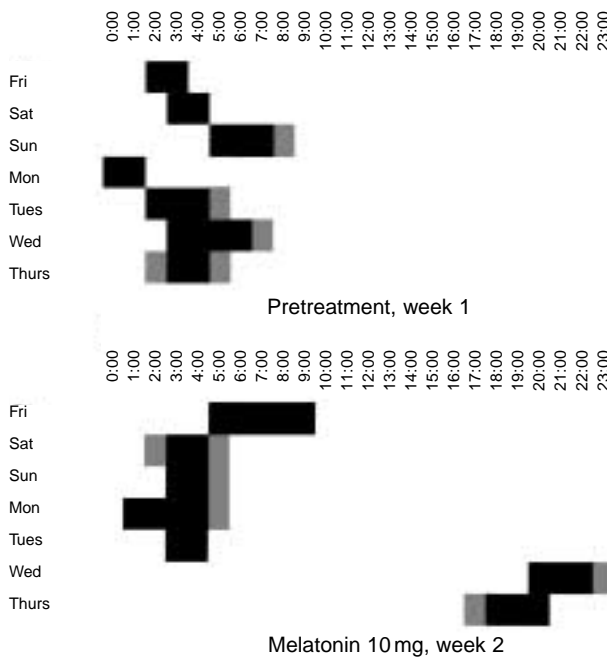


Figure 5: Patient 13, low sleep requirement.

Parents and carers reported five main categories of sleep disturbance: difficulty settling to sleep, low sleep requirement, night waking, fragmented sleep, and delayed onset of sleep. More than one category of sleep disturbance was exhibited in nine patients. In 10 patients, it was not possible to ascertain from the case notes what the sleep problem was. As can be seen from Table III, the categories of disordered sleep most likely to benefit from melatonin treatment in this series were difficulty settling to sleep and low sleep requirement.

STATISTICAL ANALYSIS OF RETURNED DIARIES

Quantitative data abstracted from returned sleep diaries are shown in Table IV. Improvements were seen in total sleep time, night time sleep, duration of interruptions in sleep, and time at onset of sleep. All of these parameters reached statistical significance ($p < 0.05$).

There were fewer interruptions of sleep on melatonin treatment but this did not reach statistical significance, estimated median difference -1.50 ($p = 0.097$).

Twenty six of the 46 patients whose parents' responses could be assessed had epilepsy. Most had epilepsy which was difficult to treat and had learning and/or behavioural difficulties: this reflected the severity of disease which is seen in the clinic population of a tertiary referral centre. Most of these children (21 of 26) showed a good response to melatonin treatment: of the 26 patients with epilepsy, 15 returned diaries of whom 14 noted that there had been an improvement. Total sleep time (in these 15) changed from 54.8 hours per week (range 13.5 to 86.5) pretreatment to mean 67.5 hours per week (range 18 to 99.5) while on melatonin treatment. None of those with interpretable diaries reported a worsening of seizure frequency or severity. Three parents reported an improvement in seizure frequency whilst taking melatonin. Numbers were too small to comment on other disease group responses.

There was no sex difference in response to melatonin treatment. Seven of the 49 patients had visual impairment, of these an assessment of response to melatonin treatment could be made in six: five of these patients derived benefit from melatonin. Of the 42 patients without visual impairment, an assessment of response to melatonin could be made in 40: 29 experienced improvements in sleep.

Mann-Whitney U tests on the pre- to post-changes and analysis of covariance (ANOVA) methods were used to look at the question of whether the melatonin effects observed in the sleep diaries were associated with characteristics such as age, sex, diagnostic group (epilepsy or other diagnosis), and visual impairment. There was no evidence of any of the factors being associated with changes in response to melatonin.

Discussion

This observational study is not a clinical trial of efficacy, instead we treated patients from a general paediatric neurology clinic and analyzed parents' recordings of sleep behaviour on and off treatment. Evidence that melatonin can ameliorate disorders of sleep in neurologically impaired children is persuasive (Jan et al. 1994, Jan et al. 1999) because multiple studies in different age groups have shown that melatonin improves sleep and there is a plausible biological explanation for this. This study recorded systematically and prospectively what happened to unselected, consecutive children treated at a UK paediatric neurology department.

Thirty four of forty six patients with sleep disturbance attending a paediatric neurology department who could be assessed, derived benefit from oral melatonin as shown by analysis of diaries and parents' reports. Improvements were seen in similar proportions in those who failed to return a sleep diary. More conservatively 34 out of 49 prescribed melatonin derived benefit on an 'intention to treat' basis. Most children did not have a sleep problem typical of a disturbance of circadian rhythm. No adverse effects were attributed to the treatment. Benefit was usually obvious within a few days of starting treatment.

The effectiveness of melatonin therapy in improving sleep in children with neurological difficulties has been previously reported, however, in this report the majority of patients (42/49) did not have visual impairment.

The 95% confidence interval for a serious adverse effect in our population, given that none was observed, is 0–7.3%. In the largest published series (Jan and O'Donnell 1996), no serious adverse events were noted in 100 treated patients, giving a 95% confidence interval of 0–3.6%.

We do not recommend melatonin as a first line treatment for pre-pubertal children with sleep problems. As has been found in the community based studies quoted, sleep problems are very common in young children and most settle with conventional sleep hygiene advice and the use of behavioural interventions, based on an assessment of likely causative factors (Bartlett et al. 1985, Zuckerman et al. 1987, Quine 1991). Furthermore, there is a theoretical risk that long term melatonin treatment may delay pubertal development in some children (Brzezinski 1997).

However, neurologically or developmentally impaired patients are not typical of the wider population, and there are good biological reasons for them to be at risk of developing intractable and severe sleep disturbances. (For a recent review see Stores and Wiggs 2001).

We are currently collaborating in setting up a multicentre, randomized cross-over double-blind placebo controlled trial of melatonin treatment for sleep disorders in children with developmental disorders and learning difficulties who have not responded to advice on bedtime routine, sleep hygiene, and simple behavioural measures.

Conclusion

This study provides further evidence for the safety and tolerability of melatonin. Evidence for efficacy has previously been reported in a double-blind, placebo controlled trial by Jan, and colleagues (1994) and this observational study of its use in unselected paediatric neurology outpatients is compatible with the published series that showed 69 to 74% of patients showing clinically significant improvement in sleep with melatonin.

With the information currently available, oral melatonin appears to be safe and well tolerated in paediatric neurology outpatients and is an effective treatment for sleep disorders in about 75% of these patients. As with all newer treatments, adverse effects may be recognized in time as more children and their families are offered this therapy.

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Headache in Childhood (Open meeting)

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Child Head Injury, Recovery, Development and Outcome (Closed meeting)

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