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Therapeutic Options for Melatonin Use in Children

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Abstract

The reviews of the somnogenic effect of melatonin seem controversial. The studies differ widely from each other with respect to the dosage (from 0.1 mg to 10 000 mg) and time of administration (day or night). The effectiveness of melatonin depends on a number of factors, including dose, individual sensitivity and the time of administration. Numerous studies in children report that melatonin may be beneficial for sleep. Long-term and well-designed studies of the effect of melatonin in children are needed.

Key words: Melatonin – Sleep

Basic Physiology

Melatonin is a time-keeping hormone. It is secreted only in the dark and provides a time-of-day cue. Its secretion follows one of hundreds of circadian rhythms of bodily functions controlled by the suprachiasmatic nuclei (SCN) of the hypothalamus. Light and melatonin serve as complementary functions, with light providing a daytime signal and melatonin a night-time signal. The phase-response curve of melatonin and light are about 12 hours out of phase with each other.

Melatonin (*N*-acetyl-5-methoxytryptamine) is a small lipid-soluble indolamine molecule[1,2]. It can easily cross most membrane barriers. It is produced mainly by the pineal gland, but is also secreted in the retina, gastrointestinal tract, skin, lacrimal glands and, possibly, other tissues. However, in these tissues the actions of melatonin appear to be restricted only to the local areas.

In the pineal gland, melatonin is synthesised by the pinealocytes. Tryptophan is converted to serotonin, then to *N*-acetylserotonin and finally to melatonin. Norepinephrine mainly initiates the production through adrenergic receptors of the pinealocytes. Arylakylamine *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase are the enzymes responsible for the day–night rhythm of melatonin production.

Pineal melatonin secretion depends on light being transmitted to the retina, which, through the retinohypothalamic tract, influences the function of the suprachiasmatic nucleus (SCN), the anterior hypothalamic region, the paraventricular nucleus and the lateral hypothalamus area. The exact molecular mechanisms involved in the retinal–SCN communication are still unclear. However, the light–dark cycles affect the activity of the SCN, which is responsible for the production of melatonin in the pineal gland. Additional input from the brain also influences melatonin production.

Melatonin and Sleep

Melatonin regulates the sleep–wake cycle. Arendt reports that melatonin reduces jet lag symptoms[3] and helps people with delayed sleep phase syndrome. It can normalise the sleep–wake cycle in blind people[4–6]. Besides the time-dependent phase-shifting effect, melatonin has a somnogenic effect. It is unclear how this works.

Table 1. The efficacy of melatonin in sleep disorders following night-time administration					
Authors	**Year**	**Dose**	**Time to sleep onset**	**Time to onset of stage 2 sleep**	**Total sleep time**
Cramer *et al.*[13]	1974	High	↓		
James *et al.*[15]	1987, 1990	Low	No effect		No effect
McFarlane *et al.*[14]	1991	High			↑
Ellis *et al.*[16]	1996	Low	No effect		
Tzischinsky & Lavie[19]	1994	Low	↓		↑
Zhdanova & Wurtman[8]	1997	Low	↓	↑	
Ferini-Stambi *et al.*[18]	1993	High	No effect		
Waldhauser *et al.*[17]	1990	High	No effect		

↑ = increased; ↓ = decreased

Table 2. The efficacy of melatonin in sleep disorders following daytime administration							
Authors	**Year**	**Dose**	**Time**	**Subjective sleepiness**	**Time to sleep onset**	**Sleep efficiency**	**Total sleep time**
Lieberman *et al.*[20]	1984	High	Day	↑			
Nickelsen *et al.*[21]	1989	High	Night	↑			
			Day	↑			
Dollins *et al.*[22]	1993	High	Day	↑			
		Low	Day	↑			
Vollrath *et al.*[23]	1981	Low	Day			↓	
Cajochen *et al.*[12]	1996	Low	Day	↑			
			Night	↑			
Nave *et al.*[24,26]	1995, 1996	Low	Day		↓		↑
			Night		↓		↑
Reid *et al.*[25]	1996	Low	Day		↓	↑	
Dollins *et al.*[10]	1994	Low	Day	↑	↓		↑
Hughes & Badia[27]	1997	High	Day		↓		↑
		Low	Day		↓		↑

↑ = increased; ↓ = decreased

However, some studies of exogenous melatonin have given inconsistent results. Mendelssohn[7] questioned the effect of exogenous melatonin. His literature review on the efficacy of melatonin as a hypnotic agent looking at placebo-controlled studies concluded that there was no evidence that melatonin administration improved sleep in insomniacs. On the other hand, Zhdanova and Wurtman's[8] review of numerous studies during the past four decades suggested a hypnotic effect of exogenous melatonin in humans. The majority of studies (Tables 1 and 2) show a substantial increase in circulating melatonin levels, associated with sedation, shortening of latency to sleep, increased sleep efficiency and propensity for, or increased, total sleep time.

These studies of the somnogenic effect of melatonin gave inconsistent results, but they differed widely with respect to subjects (healthy adults or insomniacs), the dosage (from 0.1 mg to 10 000 mg), the route of administration (intravenous, nasal or oral routes) and the time of administration (day or night). The effectiveness of any biologically active molecule will depend on a number of factors including dose, individual sensitivity and the time of administration.

Melatonin: Inter-individual Differences in Sensitivity

Individual differences in sensitivity are reflected both in a different time interval for the sleep-promoting effect to occur and in a different degree of effect[9]. A wide range of doses (from physiological concentration to a thousand-fold greater than normal) have been used. Individual variations in the response might also be related to variations in circulating levels induced. Zhdanova and Wurtman[8] found that in young people an 0.3 mg dose of melatonin induced serum levels of the hormone ranging from 142 pg/ml to 205 pg/ml. In older people the same dose induced a wider range from 76 pg/ml to 423 pg/ml. Some people absorb less melatonin or metabolise it faster.

Dose

The endogenous circulating melatonin concentrations typically do not exceed 200 pg/ml. Initially high pharmacological doses were tested, inducing several-fold concentrations of melatonin over those that occur normally. There was no clear dose dependency of effect. However, when melatonin doses under 1 mg were used, the dose dependency of the sleep-promoting effect was shown[8,10]. A dose of 0.1 mg was less potent than one of 0.3 mg.

Melatonin: Time of Administration

Lavie[11] suggested that the time of administration appeared to be the most crucial factor with respect to melatonin's sleep-inducing effects. Although this is controversial, Zhdanova and Wurtman[8] and Cajochen *et al.*[12] suggest an effect of melatonin independent of the time of administration (from 1200 h to 2100 h).

Lavie[11] expected night and daytime administration to have different results for two reasons. Endogenous melatonin is exclusively secreted during the night. When melatonin is administered at night, after the rise of its endogenous secretion, it is superimposed on previously elevated levels. Therefore daytime and night-time administrations result in different plasma concentrations. The second reason is because the main outcome in studies is an increase in sleepiness. The effect of night-time administration is bounded by the endogenous increase in nocturnal sleepiness.

Night-time Administration of High Doses of Melatonin Induces Sleep

In relation to night-time administration of melatonin, some studies have provided evidence that only high doses (> 50 mg) have sleep-inducing effects. Cramer *et al.*[13] injected a high dose of 50 mg of melatonin during the day and night. At 2130 h the injection decreased *sleep latency*. MacFarlane *et al.*[14] treated 13 insomniacs with injections of melatonin at night in a blind placebo-controlled trial. The *high* dose (75 mg) increased sleep time but the *low* dose did not have the same effect.

James *et al.*[15] administered low doses (1 mg or 5 mg) of melatonin or placebo in a double-blind, crossover design to 10 normal subjects at 2245 h. The only effect was a *prolongation* of REM latency. There was *no effect* on sleep latency, total sleep and sleep duration. Ellis *et al.*[16] did *not* observe any melatonin effect on sleep quality in insomniacs. Waldhauser *et al.*[17] administered 80 mg to young normal sleepers at 2100 h and reported *no significant changes* in sleep quality. Ferini-Strambi *et al.*[18], who administered 100 mg melatonin alone and in combination with triazolam to normal volunteers, reported *no significant changes* in sleep latency, total sleep time or sleep efficiency.

Although the above studies showed little to no effect of melatonin administration at night-time, a few studies have shown some sleep-inducing effects. Tzischinsky and Lavie[19] administered a low dose (5 mg) of melatonin to normal volunteers at 1700 h, 1900 h and 2100 h and reported *decreased* sleep latency and *increased* total sleep. Zhdanova and Wurtman[8] administered 0.3 mg and 1 mg of melatonin to 12 normal volunteer at 2100 h and reported *shortened* latencies to sleep onset and stage two.

In some studies only high doses had sleep-inducing effects. In some, low doses were somnogenic too, while others showed no effect at all of melatonin on sleep.

Daytime Administration of Melatonin Induces Sleep with Both High and Low Doses

The result of studies in which melatonin was administered during the day produced far more consistent results for both high and low dosages. Lieberman *et al.*[20] administered a high dose of 80 mg of melatonin or placebo at 1200 h, 1300 h and 1400 h. Melatonin altered performance in a manner similar to hypnotic drugs. Nickelsen *et al.*[21] gave 50 mg in a double-blind, placebo-controlled study at 0900 h or 1900 h for 7 days. There was a *significant* effect on self-rated sleepiness for the morning administration. Dollins *et al.*[22] administered 10 mg, 20 mg, 40 mg or 80 mg of melatonin at 1145 h and reported that all dosages *increased* the scores on the Stanford Sleepiness Scale as well as feelings of fatigue.

Table 3. Treatment of melatonin in children: case reports or small studies of five or less children

Author	Year	No. of subjects	Age (years)	Diag-nosis	Dose (mg)	Duration of treatment	Response	Sleep effected	Adverse events
Palm *et al.*[28]	1991	1	9	B&DD	0.5		Good	P	
Dahlitz *et al.*[29]	1991	1	14	DD	5	4 w	Good	P, I	None
Tzischinsky *et al.*[30]	1992	1	18	B	5	> 3 w	Good	P	None
Tomoda *et al.*[32]	1994	1	18	D	5	4 w	Good	P, I	None
Jan *et al.*[33]	1994	4	5.5–13	B&DD	2.5–10		Mod. (3/4)	P	
Nagtegaal *et al.*[34]	1994	1	12	–	5		Good	I	
Lapierre & Dumont[35]	1995	1	5	B&DD	5		Good	P	
Etzioni *et al.*[36]	1996	1	14	DD	3	> 2 w	Good	E	None
Robertson & Tanguay[42]	1997	1	10	PD	6–12	15 m	Good	P, E	None
Horrigan & Barnhill[43]	1997	1	17	DD	3	> 3 m	Good	E, I	None
Tanaka *et al.*[44]	1997	1	9	DD	5	2 w	Good	E	None
Pillar *et al.*[52]	1998	1	13	DD	3	4 w	Good	P	None
Miyamoto *et al.*[54]	1999	2	4, 10	DD	3–5	2 y–3 y	Good	P, I	None
Jan *et al.*[55]	1999	3	2–6	DD	3–5	3 y–4 y	Good	I	None
Hatonen *et al.*[59]	1999	5		DD	2.5–5	3 w	Mod. (3/5)	E	None

Study
CR = case report
DBP = double-blind placebo
PC = placebo controlled

Diagnosis
B = blind
PD = psychiatric disorder
DD = developmental delay

Duration of treatment
w = week
m = month
y = year

Effect on sleep
I = induces sleep onset
P = shifts phases of sleep
E = improves sleep efficiency/quality

Similar effects were reported for daytime administration of much lower dosages. Vollrath *et al.*[23] administered 1.7 mg of melatonin as a nasal spray to normal young adults at 0900 h and reported that within 40–120 minutes post-administration *nine out of the ten fell asleep*. Only one fell asleep with placebo.

Significant sleepiness following administration of 5 mg of melatonin at 1300 h or 1800 h was reported by Cajochen *et al.*[12]. Sleepiness appeared 40–90 minutes after administration, the effects on the EEG appearing almost immediately.

Zhdanova and Wurtman[8] administered either 0.1 mg or 0.3 mg of melatonin at 1800 h, 2000 h or 2100 h in a double-blind crossover study. Both doses at all times *decreased* latency to sleep onset and stage 2 sleep. Nave *et al.*[24] investigated the effects of 3 mg of melatonin administered at 1200 h on sleep propensity monitored polysomnographically. Melatonin significantly *decreased* latency to sleep, *increased* the amount of total sleep and *decreased* core body temperature. Reid *et al.*[25] performed a similar study. Five milligrams of melatonin was administered at 1400 h and sleep propensity was measured with a modified version of the Multiple Sleep Latency Test. Melatonin significantly *decreased* the latency to sleep stages 1 and 2, starting 1 h after administration. Sleep propensity was *higher*.

Dollins *et al.*[10] tested the effects of 0.1 mg, 0.3 mg, 1 mg or 10 mg of melatonin in comparison to placebo at 1145 h in healthy men. They reported that the 0.3 mg, 1 mg and 10 mg significantly *increased* subjective sleepiness and *decreased* sleep latency while *increasing* sleep duration. The dose of 0.1 mg was less potent that a dose of 0.3 mg or higher doses. This confirms that melatonin has a *dose-dependency sleep-promoting effect*. Nave *et al.*[24] administered 3 mg, 6 mg or placebo at 1800 h. Both dosages of melatonin significantly *decreased* sleep latency and *increased* total sleep time. Hughes and Badia[27] administered 1 mg, 10 mg and 40 mg of melatonin at 1200 h. All dosages significantly *shortened* sleep latency, and the 10 mg and 40 mg dosages *increased* total sleep time.

Studies of the Use of Melatonin in Children

Melatonin has been used to treat sleep disorders since the early 1990s. In 1991 Palm *et al.*[28] described the first melatonin treatment of a blind child with multiple disabilities, who had a fragmented sleep pattern. Subsequently numerous studies have been published on the use of melatonin in paediatric sleep–wake cycle disorders (Tables 3 and 4). However, there have been very few well-designed controlled and long-term studies[1].

Most of these children were neurologically impaired with or without visual problems. Ages ranged from 0.5 years to 18 years. The dose ranged from 2 mg to 10 mg at nocturnal bedtime. None of the authors noted significant adverse side-effects even though some children had used melatonin for 5–7 years. Few studies of melatonin treatment

Table 4. Treatment of melatonin in children: studies of more than five children

Author	Year	Study	No. of subjects	Age (years)	Diagnosis	Dose (mg)	Duration of treatment	Response	Sleep effected	Adverse events
Jan *et al.*[31]	1994	P	15	0.5–14	B, DD	2.5–5	Months	Moderate (12/15)	P	None
Jan and O'Donnell[37]	1996	U	100	0.3–21	PD, B, DD	2.5–10	Approx. 3 m	Mod (82%)	P	None
Zhdanova *et al.*[38]	1996	U	12		Healthy	0.3–1	1 dose	Good	I	None
Camfield *et al.*[39]	1996	P	6	3–13	B, DD	0.5–1	EOW (10 w)	Poor (3/6)	E	None
Masters[40]	1996	U	20		PD	3–6	1 w–13 w	Good	P	None
Palm *et al.*[41]	1997	U	8	3–23	B, DD	0.5–4	6 m–6 y	Good (7/8)	P	None
Schmitt-Mechelke[45]	1997	U	36	1–16	B, DD	2–10		Good (94%)		
Ross *et al.*[46]	1997	U	16	3–13	DD, BD	2.5–10	Months	Poor (44%)	E	None
Hung *et al.*[47]	1998	U	37	1–19	B, DD	2–10		Good (86%)		
Jan *et al.*[48] (Vancouver study)	1998	U	90	0.3–21	B, DD	2.5–20		Good (87%)		
Jan *et al.*[48] (Edmonton study)	1998	P	16	3.5–15	B, DD	2.5–10		Mod. (79%)		
Wassmer *et al.*[53]	1998	U	12	3–16	DD, PD, BD	2.5–5	1 dose	Good (11/12)	I, P	None
Ross *et al.*[50]	1998	U	43	1–13	DD, BD, B	2.5–10	Months	Mod. (77%)	I, E, P	None
McArthur & Budden[51]	1998	P	9	4–17	DD	2.5–7.5	4 w	Good	I, E	None
Wassmer *et al.*[55]	1999	U	25	2–17	PD, BD, DD	2.5–5	1 dose	Good (80%)	I	None
O'Callaghan *et al.*[56]	1999	P	7	2–28	DD	5	2 w	Good (6/7)	I	None
Zhdanova *et al.*[57]	1999	U	13	2–10	DD	0.3	5 days	Good	E	None
Okawa *et al.*[58]	1999	U	20	14–18	Healthy	?	?	Poor (2/20)	P, I	None

Study
U = uncontrolled clinical trial
P = involved use of placebo

Diagnosis
B = blind
PD = psychiatric disorder
DD = developmental delay
BD = behaviour difficulties

Duration of treatment
w = week
m = month
y = year
EOW = every other week

Effect on sleep
I = induces sleep onset
P = shifts phases of sleep
E = improves sleep efficiency/quality

of non-circadian sleep disorders have been published. In most studies melatonin was beneficial for sleep. Few studies have been published reporting the contrary (possibly because of reporting bias).

The Birmingham Experience

The Neurology Department at Birmingham Children's Hospital has been using melatonin since early 1997. We have used it in children to treat sleep disorders and instead of sedation for investigations requiring sleep. We assessed the usefulness of melatonin for sleep disorders in 43 children, following informed consent, by means of parent-completed sleep diaries before and during treatment[50]. All of the children had some neurological disability and 24 had epilepsy. The sleep disorders varied from difficulty settling (12), delayed sleep phase (2), to disturbed (10), and fragmented sleep (3), or a combination of sleep disorders. Melatonin was given as a fast-released preparation before bedtime, starting at 2.5 mg or 5 mg. The dose was increased by 2.5 mg at intervals of three days up to a maximum of 10 mg. Thirty-three of 43 children (77%) experienced improvement in sleep.

We have studied the somnogenic effect of melatonin and its use for investigations, particularly sleep EEGs. In a pilot study[49] we found that combining partial sleep deprivation with melatonin increased the efficacy of the sleep EEGs without detracting from the usefulness of the EEG. Twelve patients aged 3–12 years were studied, following informed consent. Instead of the usual sleep-deprived EEG, the children were partially sleep deprived and were given melatonin (2.5 mg or 5 mg) just before the EEG recording. Eleven of 12 children (92%) fell asleep during the EEG recording after being given melatonin. Sleep onset was within 20–60 minutes. No adverse effects were noted.

In a second study[53] we compared sleep induced by melatonin to sleep induced by sleep deprivation. Thirty children underwent a melatonin-induced sleep EEG. Depending on their age they were administered 2.5 mg or 5 mg of melatonin just before the EEG recording. Thirty of 50 children (matched for age and sex), who had a sleep-deprived EEG in the same period, were used as the control group. Data were collected from the detailed request form, a parent questionnaire with a sleep diary and a telephone interview following the EEG. No significant difference was found between the two groups for age, sex and the prevalence of learning and behavioural difficulties. Sleep was obtained in 80% of both groups. The children in the melatonin group fell asleep within 21 minutes ($\pm$ 2.2, 95% CI). The sleep-deprived group fell asleep within 34 minutes ($\pm$ 7.4, 95% CI, $p < 0.013$). Melatonin was acceptable and not associated with any adverse events, and was preferred by those parents who had previously experienced a sleep-deprived EEG.

Conclusions

Melatonin's effect on sleep in adults is inconsistent, but the studies differ with respect to subjects, dosage and the time of administration. There seems to be a consensus that melatonin may be useful in the treatment of paediatric sleep disorders. Jan *et al.*[1] pointed out the dearth of larger placebo-controlled trials of melatonin use in children. We are currently setting up a double-blind placebo-controlled trial along with colleagues in other hospitals in the United Kingdom, and hope to add to the increasing information about this exciting treatment.

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