

Melatonin treatment of sleep–wake cycle disorders in children and adolescents

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Lerner, a dermatologist who isolated melatonin (MLT) in 1959, was the first to report on its hypnotic properties¹, and was also the first to self-administer this hormone. Later, in 1971, Anton-Tay and coworkers injected MLT into volunteers who quickly fell asleep². In adults, MLT treatment appears to have beneficial effects in those who have sleep disorders due to delayed sleep onset^{3–6}, shift work^{7–9}, and jet lag^{10–13}. MLT can enhance adaptation to forced phase shift in simulated shift-work and jet-lag conditions. However, better controlled, long-term studies are still required. MLT may also benefit certain types of adult insomnia^{13–24}.

In 1991, Palm and colleagues described the first MLT treatment of a blind child with multiple disabilities who had a free-running, fragmented sleep pattern²⁵. Subsequently, numerous articles have been published on the use of MLT in paediatric sleep–wake cycle disorders (Table I)^{3,25–46}. Most of these children were neurologically impaired, with or without visual loss. Formal studies on MLT treatment of non-circadian sleep disorders have not been published but for these patients MLT appears to be mostly ineffective³³. None of the authors has noted significant adverse side effects, even though some of their subjects have been receiving MLT for 5 to 7 years^{33,37}. In most instances the oral dose ranged from 2 to 10 mg at nocturnal bedtime. The fast-release, not the delayed-release, form was used in all studies. Some researchers have studied the endogenous MLT secretion in their subjects. There have been very few well-designed, controlled, and long-term studies, which may be due to the extreme difficulties of researching the population of patients with multiple disabilities. However, there is a consensus among researchers that MLT is beneficial in the treatment of paediatric sleep–wake cycle disorders⁴⁷ but most studies present only preliminary results. Furthermore, it is often not clear why certain children respond well to treatment while others less so, or not at all.

Sleep problems are common in the general population. Interest in the sleep-inducing properties of MLT as well as its

various other potential uses has recently surged. Exaggerated claims have been made, while many members of the medical profession responded with scepticism and mistrust⁴⁸.

Most governments have made it illegal to sell MLT 'over the counter' but prescriptions can still be written by physicians, with special permission from government agencies, on a named-patient basis. In the United States MLT, as a nutritional supplement, has been widely available in health-food stores since 1993. Although there are reputable sources of MLT, investigators for the Medical Letter found unidentified impurities in six products (Medical Letter 37: 111–112, 1995). Due to the fact that MLT patenting cannot be protected⁴⁹, the costs of regulatory requirements are high and the price of over-the-counter tablets is low, major drug companies have shown little interest in this drug in view of the limited profits to be made after gaining approval. This is why governments should provide funds for the clinical development of MLT.

Pharmacokinetics of melatonin

MLT or N-acetyl-5-methoxytryptamine is a small lipid-soluble indoleamine molecule which can easily cross most membrane barriers. It is produced mainly by the pineal gland and for this reason MLT is referred to as the 'pineal hormone'. It is also secreted independently in small amounts in the retina^{50–52}, the gastrointestinal tract⁵³, the skin⁵⁴, the lacrimal glands⁵⁵, and most likely in other tissues⁵⁶. However, in these tissues the actions of MLT appear to be restricted only to the local areas. Various foods also contain MLT and add to the blood levels^{57,58}.

In the pineal gland, MLT is synthesized by the pinealocytes. Tryptophan is converted to serotonin, then to N-acetylserotonin, and finally to MLT. The neurotransmitter norepinephrine is primarily responsible for initiating the production of this hormone through the adrenergic receptors of the pinealocytes, although the pinealocyte membranes contain additional receptors which to some extent can also influence the synthesis⁵⁹. The enzymes which are

largely responsible for the day–night rhythm of MLT production are arylalkylamine N-acetyltransferase (AA-NAT) and hydroxyindole-O-methyltransferase (HIOMT).

$2\text{-}^{125}\text{I}$ -iodomelatonin has been used extensively to locate MLT receptors. Two distinct groups have been identified: ML1 (high-affinity) and ML2 (low-affinity). The ML1 binding sites are membrane-associated proteins linked to the guanine nucleotide-binding protein (G-protein). Their activation results in the inhibition of adenylate cyclase activity. The ML2 receptors are coupled to the stimulation of phosphoinositide hydrolysis^{60,61}. The ML1 binding sites have been noted in numerous areas of the brain, with the highest concentrations in the suprachiasmatic nucleus^{62,63}. Three receptor subtypes have been identified: ML1a, ML1b, and ML1c^{64,65}. There are also receptors in the visual system⁶⁶, the heart and lungs⁶⁷, arteries⁶⁸, the adrenal gland⁶⁹, and other peripheral tissues⁷⁰, and their density can vary from location to location. The widespread distribution of these binding sites suggests that MLT may have many actions. The binding sites are more widespread and more abundant in foetuses, which may suggest a role of maternal MLT in prenatal development⁷¹.

Normally the pineal gland begins to produce MLT in the evening and MLT is rapidly released into the blood stream. The blood level reaches a peak at around 3 am, after which it declines until morning, and during the day the secretion is insignificant. MLT can be found in saliva, cerebrospinal fluid, amniotic fluid, the anterior chamber of the eye, and other tissues⁷². It is one of the few lipid-soluble hormones. Due to its high lipophilicity, the endogenous MLT levels are 3 to 10 times higher in the brain than in the serum and there is even a possibility that the brain tissue itself is capable of selective uptake⁵⁵. Exogenous oral daytime administration of MLT rapidly changes the waking EEG power density in the theta–alpha range (an EEG sign of sedation), significantly before sleepiness clinically becomes apparent⁷³.

Interindividual and age variations in MLT pharmacokinetics are significant^{74,75}. Newborn infants produce little or no MLT until about 3 months of age⁷⁶. Then the levels increase for the next 9 to 10 months and remain stable. There is a higher secretion rate in prepubertal children and metabolites are excreted faster than in adults⁷⁷. Just before puberty the levels decline and there appears to be a strong correlation with the onset of sexual maturity^{78–80}. With advancing age, MLT secretion is reduced, sometimes to undetectable levels^{75,81,82} and the timing of the decrease is so reliable that blood MLT levels have been proposed as a measurement of biological age⁸³.

The pineal gland can only store MLT for a short time and the half-life of this hormone is 30 to 53 minutes⁸⁴. It is metabolized in the liver to its hydroxylated 6-sulfatoxymelatonin form which is then excreted in the urine. The pineal gland, MLT synthesis, physiology, roles, and mechanisms of action and disorders of secretion were described in detail by Arendt in 1994⁸⁵.

Circadian rhythms, melatonin, and sleep

Circadian rhythms are a fundamental adaptation to the solar changes of light and dark. The term originates from the Latin words 'circa' meaning 'around' and 'dies' meaning 'day'. It is the suprachiasmatic nucleus (SCN) of the anterior hypothalamus immediately above the optic chiasm which is responsible for this function⁸⁶. The SCN is a relatively small structure containing about 10 000 neurons. It exhibits spontaneous

cycles of metabolic and electrical activity *in vivo*, and when isolated *in vitro*. The tissue, even *in vitro*, responds to MLT which can inhibit neurons and cause phase-shifting⁶⁴. Experimental and pathological lesions of the SCN in animals and humans block the ability to express circadian rhythms^{87,88}.

Pineal MLT secretion depends on light being transmitted to the retina which, through the retinohypothalamic tract influences the function of the SCN, the anterior hypothalamic region, the paraventricular nucleus, and the lateral hypothalamic area. Some blind individuals without a pupil response have light-induced suppression of MLT secretion⁸⁹. This supports the concept that the retinohypothalamic pathway is separate from the retinogeniculostrate visual system. There may be a second visual pathway from the lateral geniculate body which ends entirely in the SCN⁹⁰. 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 (through the reticular system, the spinal cord, cervical ganglia, and postganglionic sympathetic fibres) is responsible for initiating or inhibiting the production of MLT in the pineal gland. Blood MLT levels are higher in darkness and lower in light. Thus, the eye of adult primates, by mediating the effects of visible light (400 to 700 nm), plays a major role in the secretion of MLT^{91,92} and in immunological and neuroendocrine rhythms⁹³. Although the retinohypothalamic pathways are the most important in the control of the endogenous rhythm-generating system, both the SCN and the pineal gland appear to receive additional input from the brain. Furthermore, the pineal MLT through the SCN modulates circadian rhythmicity and other neurometabolic processes⁹⁴. Thus, MLT is a chronobiotic because it is able to phase shift and reset the endogenous rhythm-generating system. In addition, MLT has rapid sedative properties⁷³ and a hypothermic effect⁹⁵. All of these appear to play a role in sleep–wake regulation. It appears that MLT induces sleep by inhibiting the 'wakefulness generating system'^{96,97}. This inhibitory effect, in mice, has recently been shown to be mediated by a common subtype of MLT receptor, ML1a, while the phase-shifting effect is mediated by the much rarer ML1b receptors^{64,98}.

The nocturnal sleep onset correlates well with the onset of MLT secretion^{10,47}. Appropriately timed administration of exogenous MLT can result in earlier onset of endogenous night-time secretion, i.e. 'phase advance'⁹⁹. Thus, exogenous MLT can participate in the regulation of sleep–wake cycle disorders and endogenous MLT secretion¹⁰⁰ but the timing of administration is important. The treatment is most effective when the dose coincides with the onset of endogenous MLT secretion¹⁰¹ and when it falls within the 'phase advance window'¹⁰². When MLT is inappropriately administered it may even have deleterious effects on sleep¹⁰³. MLT, given during the day is physiologically unsound and may produce tiredness, irritability, and impaired intellectual functioning^{17,47,73}.

Recent developments in our understanding of the molecular basis of circadian rhythms demonstrate a relation between individual genes and the execution of complex patterns of biological behaviour, including sleep^{104,105}.

Causes of sleep–wake cycle disorders

The more-or-less regular hours of sleep are due to the so-called 'zeitgebers' or entraining factors. Entraining means

adjusting the function of the SCN and the endogenous rhythm-generating system of the brain by means of environmental stimuli. The light–dark cycle is the strongest zeitgeber but other inputs are also important. For falling asleep, the brain requires a decrease or cessation of vigilance and of environmental stimuli such as noise, strong light, or movements. The process is also influenced by variations in temperature, by cerebral functions such as established habits, knowledge of the clock time, and by numerous behavioural,

social, and nutritional cues¹⁰⁶. These complex cerebral regulatory systems are modulated and integrated in the prefrontal cortex¹⁰⁷. Circadian disturbances can result from a wide variety of causes such as pathological lesions of the brain, psychiatric and neurological disorders, environmental changes, decreased understanding of many zeitgebers, aging, and the use of drugs which interfere with MLT secretion^{108,109}.

Lesions of the endogenous rhythm-generating system in the brain, such as SCN ablation, result in random distribution

Table 1: Paediatric sleep–wake cycle disorders treated with MLT: literature review

<i>Authors</i>	<i>Nr of subjects</i>	<i>Age (y)</i>	<i>Dose (mg)</i>	<i>Associated diagnosis</i>	<i>Type of study</i>	<i>MLT secretion studied</i>	<i>Response</i>
Palm et al. 1991 ²⁵	1	9	0.5	Blind and ND	Case report	+	Good
Dahlitz et al. 1991 ³	1	14	5	Educational difficulties	Double-blind placebo-controlled	+	Good
Tzischinsky et al. 1992 ²⁶	1	18	5	Blind	Case report	+	Good
Jan et al. ^a 1994 ²⁷	15	0.5–14	2–10	Blind/ND; normal	Double-blind crossover	–	Moderate to good
Tomoda et al. 1994 ²⁸	1	18	5	Depression, school failure	Case report	–	Good
Jan et al. ^a 1994 ²⁹	4	5.5–13	2.5–10	ND and blind; all with refractory bipolar disorders	Case report	–	Minimal to moderate
Nagtegaal et al. 1994 ³⁰	1	12	5	Delayed sleep onset	Double-blind	–	Good
Lapierre and Dumont 1995 ³¹	1	5	0.5	Blind and ND	Case report	–	Good
Etzioni et al. 1996 ³²	1	14	3	Pineal tumour	Case report	+	Good
Jan and O'Donnell ^a 1996 ³³	100	0.3–21	2.5–10	ND/blind	Uncontrolled clinical trial	–	82% ^b
Zhdanova et al. 1996 ³⁴	13	2–10	0.3	Angelman syndrome	Uncontrolled clinical trial	+	Good
Espezel et al. ^a 1996 ³⁵	7	0.3–17	2.5–10	Blind/ND	Prevalence study	–	Good
Camfield et al. 1996 ³⁶	6	3–13	0.5–1	Blind and ND	Double-blind placebo	–	Poor
Palm et al. 1997 ³⁷	8	3–23	1–4	Blind and ND	Uncontrolled clinical trial	+	Good
Robertson and Tanguay 1997 ³⁸	1	10	6–12	Refractory bipolar disorder	Case report	–	Good
Horrigan and Barnhill 1997 ³⁹	1	17	3	Asperger's disorder	Case report	–	Good
Tanaka et al. 1997 ⁴⁰	1	9	5	ND	Case report	–	Good
Schmitt-Mechelke et al. 1997 ⁴¹	36	1–16	2–10	ND/blind	Uncontrolled clinical trial	–	94% ^b
Hung et al. 1998 ⁴²	37	1.3–19.5	2–10	ND/blind	Uncontrolled clinical trial	–	86% ^b
Jan et al. ^a 1998 ⁴³							
Vancouver Study	90	0.3–21	2.5–20	ND/blind	Uncontrolled clinical trial	–	87% ^b
Edmonton Study	16	3.5–15	2.5–10	ND/blind	Placebo controlled	–	79% ^b
Ross et al. 1997 ⁴⁴	16	Not known	7.5–10	Neurological or psychiatric difficulties	Uncontrolled clinical study	–	44% ^b
McArthur and Budden 1998 ⁴⁵	9	4–17	2.5–7.5	Rett syndrome	Double-blind placebo-controlled crossover	–	Significant decrease in sleep-onset latency
Pillar et al. 1998 ⁴⁶	1	13	3	ND	Case report	+	Good

ND, neurodevelopmental disorders; blind, severe visual loss due to brain damage or ocular causes – the visual loss is most often not complete; + MLT levels done; – MLT levels not done.

^a Overlapping database.

^b Percentage of individuals who improved.

(fragmentation) of sleep and waking states throughout the 24-hour period¹¹⁰. Tumours and other lesions of the hypothalamus or optic chiasm which destroy the SCN, as in optic-nerve gliomas in children, do the same³³. Disorders of the sympathetic nervous system, as in spinal-cord injury blocking the central innervation of the superior cervical ganglia, can inhibit pineal MLT secretion¹¹¹. Tumours can destroy the pineal gland^{112,113} and result in diminished or absent endogenous MLT together with delayed sleep onset and fragmented sleep patterns. Exogenous MLT rapidly corrects such a sleep-wake cycle disorder^{32,114}. Disorders of the prefrontal cortex may also lead to sleep difficulties¹⁰⁷. In 1996 McArthur and colleagues¹¹⁵ described a sighted man who had had a free-running sleep-wake cycle syndrome since childhood. Investigation revealed decreased sensitivity to bright light during light-induced MLT tests, suggesting that his visual subsystem may have been defective. Exogenous MLT stabilized his MLT secretion and his sleep rhythm.

Examples of environmental changes resulting in sleep disorders are jet lag, shift work, and delayed sleep-phase syndrome, sensory deprivation experiments¹¹⁶, and even living in unusual climates, such as in Antarctica¹¹⁷. Astronauts are likely to have similar sleep-wake disorders in space¹¹⁸. Oren and coworkers¹¹⁹ (1997) described a man with a free-running sleep-wake cycle disorder who lived in a dimly lit environment. His serum MLT levels were undetectable. Light therapy corrected his sleep difficulties and restored the normal MLT rhythm.

Lack of appreciation of environmental zeitgebers also commonly gives rise to sleep disorders in people with severe multiple disabilities, low intellectual functioning, and blind or deaf-blind children^{35,85}. Clinical experience strongly suggests that neurological, neurodevelopmental, and neuropsychiatric disabilities predispose children to sleep-wake rhythm disturbances^{33,37}. Disorders such as blindness, deaf-blindness³⁵, mental retardation, cerebral palsy²⁹, autism¹²⁰, head injury, central nervous system diseases, and depression^{121,122} diminish the ability of these individuals to perceive and interpret a multitude of cues for synchronizing their sleep with the environment⁸⁵. Therefore, the development of sleep-wake cycle disorders is more likely when the perception of zeitgebers is weaker or absent. Adults are also predisposed to disorders of MLT secretion when affected by some neurological and psychiatric disorders^{19,76,123}. In elderly people, MLT deficiency appears to be a major reason for chronic sleep difficulties^{20,123}. In contrast, in chronic primary insomnia, MLT deficiency is not present¹²⁵.

Studies with healthy adult volunteers indicate that the primary synchronizer of human circadian rhythms is the light-dark cycle rather than social cues, food intake, various activities, and knowledge of clock time^{126,127}. As the light-dark cycles are powerful zeitgebers, blind subjects provide an excellent model to study sleep-wake cycle disorders. Indeed, they have received a great deal of attention in the research on biological rhythms^{7,25-27,35,128-138}. The abnormal endogenous MLT secretion in blind children with sleep-wake cycle disorders was an important finding¹³⁶. Sasaki in 1992¹³⁷ showed that in children with diminishing vision the prevalence of sleep-wake-rhythm disorders tends to increase. Similar findings have been noted in adults¹³⁹. This seems to emphasize the influence of the retinal input on the SCN. However, children with cortical visual impairment and intact

retinohypothalamic pathways experience far more frequent and more severe sleep-wake cycle disorders than those with ocular visual loss³⁵. These patients not only have visual loss due to brain damage but various severe neurodevelopmental deficits, and as a result of the lack or markedly diminished appreciation of all the zeitgebers, including light and darkness, they have more difficulties in synchronizing their sleep-wake cycles with the environment.

Effect of sleep deprivation on children and their caregivers

Reluctance to go to bed and night awakenings affect about 20% of the general population. Such difficulties tend to be age-related, mild, and transient¹⁴⁰, and readily respond to treatment¹⁴¹. In contrast, in children with severe neurodevelopmental difficulties, the prevalence of sleep disorders is up to 80%. Their sleep disorders tend to be chronic, resistant to sedatives, and may be difficult or impossible to correct by enforcing strict sleep habits²⁷. Resistant sleep difficulties in a child with multiple disabilities can be such an enormous socioeconomic and health burden on the parents that they become unable to offer continuous care¹⁴². Caregivers' sleep deprivation, due to repeated arousals night after night, is a major reason for the breakdown of families and for giving up the child's care³⁵. It results in degradation of performance and can cause increased accidents at work, at home, and during travelling^{143,144}.

Chronic sleep disorders can adversely affect the child's development, as sleep plays a major role in the early maturational process of the brain¹⁰⁷. Sleep deprivation leads to reduced attention span, low frustration threshold, mood changes, impaired social interactions, difficulties with memory formation and recall, loss of ability to learn, and health problems¹⁴⁵. Therefore, appropriate treatment of sleep disorders in children is imperative.

Diagnosis of sleep-wake cycle disorders

Sleep-wake cycle disorders in children could be confirmed by clinically useful sleep charting (somnology) recorded by the parents. During the night the caregivers are repeatedly awakened by their children's crying and demands, and so these somnology records represent the disturbed sleep of one or both parents^{146,147}.

Polysomnographic recordings are not readily available for children because of few paediatric sleep-disorder clinics. The studies are expensive and also difficult to perform in people with multiple disabilities because of the subject's lack of cooperation. Computerized actigraphs, which measure movements during the night by a small solid-state movement detector strapped to an arm or leg, may be a suitable alternative⁴⁵. Sleep-wake cycle disturbances are often associated with disturbed MLT secretion, and so MLT measurements are valuable. MLT levels can be obtained from plasma¹⁴⁸ and saliva by ¹²⁵I radio-immunoassay¹⁴⁹ and the major MLT metabolite, 6-sulfatoxymelatonin, can be measured in urine¹⁵⁰. Some investigators caution about the inconsistent ratio between serum and salivary MLT⁷⁷. The difficulty at present is that MLT levels are measured mainly in research laboratories, and a series of blood, saliva, and/or urine collections is needed.

The most common sleep-wake cycle disorder in children appears to be sleep fragmentation³⁵. Most patients with this problem experience difficulties in both sleep induction and

maintenance, and their endogenous MLT levels tend to be lower²¹. Delayed sleep onset alone, from various causes, is also common³³ and here the onset of MLT secretion may or may not be delayed^{3,34,151}. It could be speculated that some individuals may require higher blood levels of MLT to fall asleep, especially when their state of arousal is higher, as for example in children with attention-deficit-hyperactivity disorder who frequently have delayed sleep onset^{152,153}. Laurant and coworkers (1997)¹⁵⁴ showed that MLT treatment can be very effective in these patients.

Free-running sleep rhythms are associated with a daily delay of sleep onset and of MLT secretion. The delay can vary but is usually approximately 1 hour. (Several weeks of sleep charting is necessary for diagnosis.) This type of sleep-wake cycle disorder is common in totally blind people^{10,37,136}. In blind individuals, daytime napping is not compensation for sleep lost during the night but the result of increased daytime endogenous MLT secretion¹⁵⁵. Day-night reversals and variable sleep onset are less frequent in children. In these subjects MLT secretion has not been studied. Sleep-wake cycle disorders often present as a mixture of the above patterns. More research is still required to understand the relation between sleep disturbance and MLT secretion.

Melatonin treatment of sleep-wake cycle disorders^a

MLT treatment of sleep-wake cycle disorders is related to its chronobiotic, sedative, and hypothermic effects but it is still unclear how much benefit is derived from each of these properties¹⁰². Once patients are appropriately selected for treatment by an experienced physician, oral synthetic MLT is prescribed. For sleep induction, fast-release MLT is the best, whereas for sleep maintenance, in view of the short half-life of this hormone, the slow-release form is more useful^{84,124}. The authors' clinical experience suggests that the fast-release MLT is effective for about 5 hours. Slow- or time-release MLT tablets can be effective for 8 to 9 hours but unfortunately the data on the formulation of these tablets are not readily available. Sublingual MLT is absorbed slightly more quickly, but offers no practical advantage over the other forms. MLT should be prescribed without added substances, such as a mixture of vitamins.

In most children, MLT is given 20 to 30 minutes before the desired bedtime, which is decided according to individual needs, and sleep induction occurs within half an hour. Each dose should be given at approximately the same time every day. The sleep environment also needs to be well structured with strong reinforcement of healthy sleep habits in order to reset the circadian rhythm. It is important to note that most people with multiple disabilities, when their zeitgebers have been strengthened and taught from infancy, can develop healthy sleep habits.

The absorption of oral MLT may be delayed when taken with large meals, therefore, it is better to administer MLT on an empty stomach, or with minimal fluids. Drugs, as for example anticonvulsants, also appear to interfere with the absorption of MLT and could be given 1 or more hours earlier. There are no absorption studies to support these clinical impressions.

^aThis section is based on the review of the literature and on the clinical experience of the authors of this paper with MLT in the treatment of sleep-wake cycle disorders in almost 200 children since 1991.

The most effective dose of fast-release MLT depends on the type of sleep disorder being treated. For sleep induction, smaller amounts can be used. In one study, healthy volunteers received either 0.3 mg or 1 mg and the smaller dose was as effective for sleep induction as the larger one²¹. It should be noted, however, that these adult volunteers were healthy and did not have chronic sleep disorders. Furthermore, there are significant interindividual variations in MLT pharmacokinetics and children metabolize MLT more quickly than adults⁷⁷. Low doses (0.3 to 0.5 mg) have been used successfully by some researchers to correct sleep-wake cycle disorders^{25,31,34}. Nevertheless, the literature review and clinical experience based on large paediatric populations suggest that children, depending on age, may require 2.5 to 10 mg and on rare occasions, more^{27,33,37}. Such pharmacological doses are more effective in inducing temperature suppression⁹⁵, phase shift¹⁵⁶, and sedation⁷³. As the half-life of MLT is slightly below 1 hour, large doses of fast-release MLT may be required to promote longer sleep. It is sensible to start with a low dose, as for example 1 to 3 mg in infants and toddlers and 2.5 to 5 mg for older children. Depending on the response during the first few days or weeks, the dose can be adjusted to the optimal amount. There are reports on the use of slow-release MLT in adults^{20,124}, but not, as yet, in children. However, the authors' paediatric experience indicates that the dose may be close to that of the regular fast-release MLT.

The caregivers can be allowed to increase or reduce the amount of MLT slightly from time to time, because sleep is so readily influenced by illness, anxiety, travelling, medications, and changes in routine.

In some children, the sleep difficulties disappear after the first dose, while in others the improvement takes days and occasionally weeks. This may be because the endogenous rhythm-generating system must be entrained, not only by the administration of exogenous melatonin but also by establishing and strengthening the environmental zeitgebers⁸⁵. In some patients, MLT does not have the desired effect.

The duration of treatment is variable. The aim is to establish healthy sleep habits, with both the lowest, most effective dose of MLT, and with entrainment. Once improved circadian control is established, it may be possible to successfully withdraw the treatment after several months, especially in higher-functioning children with multiple disabilities. Thus, MLT treatment can assist in learning better sleep habits. There has been no report of deleterious effects following discontinuation of MLT. In some of these children, periodic administration of night-time MLT may be useful during illness, trips or changes in routines such as vacations. For some individuals, especially those whose understanding of the environment is so impaired that they can not perceive any of their zeitgebers, treatment may be necessary throughout their lives. For them exogenous MLT administration serves as a zeitgeber.

Anecdotal reports of adverse acute side effects, such as headache, sedation, restlessness, confusion, nausea, tachycardia, and pruritus have been attributed to the use of MLT¹⁵⁷. These may have been caused by impurities in some MLT products because with pharmacologically regulated MLT no significant side effects, other than sedation, have been reported in children^{33,37} or, with very large doses, in adults^{16,158}. Theoretically, it is possible that MLT administration may exacerbate certain immunological diseases because

of its multiple immunological effects¹⁵⁹, but there is still no scientific evidence for this. Pregnant women should not receive exogenous MLT until much more is known about the effect of this hormone on the foetus. Preliminary animal studies with MLT have not shown teratogenic effects¹⁶⁰. Vivid dreaming is often noted, but this is likely to be due to improved sleep architecture^{161,162}. A common concern is possible adverse endocrine effects but there are no published reports on this. Because long-term follow-up studies in humans who are on continuous MLT therapy do not exist beyond 7 to 10 years^{33,37,139} presently unknown side effects may still emerge with time.

The relation between sleep, mood, depression, and MLT is complex^{163,164}. MLT is known to have a direct effect on certain mood disorders^{121,165}. Some adults with depression and sleep difficulties may benefit from MLT treatment¹⁶⁶, while others deteriorate¹⁶⁷. Controlled studies are still not available¹⁹. Approximately 75% of depressed children and adolescents complain of insomnia¹⁶⁸ but there are no published reports of MLT treatment in these patients. Shafii and his colleagues in 1996¹⁶⁹ showed that depressed children without psychosis have elevated nocturnal MLT levels. Sleep problems may also predispose to depression¹⁷⁰, yet numerous studies have shown that adult patients with depression may improve with sleep deprivation¹⁷¹.

MLT is not a blanket treatment for every sleep disturbance and its indiscriminate use is not recommended. Paediatric sleep disorders have many causes, as children can be aroused by pain, gastroesophageal reflux, excessive noise, illnesses, seizures, and emotional and other endogenous or environmental factors. People with multiple disabilities, on occasion, may have even more than one reason for their disturbed sleep. In fact, the treatment of sleep disorders in people with multiple disabilities requires considerable clinical experience. It is, therefore, important to diagnose the cause of sleep difficulties accurately. Thus, MLT treatment is most effective when the physician first carefully obtains a history, examines the child, carries out a number of basic investigations, obtains appropriate sleep studies, and uses carefully tested MLT products.

There is no evidence in the literature that large exogenous doses of MLT can desensitize MLT receptors. The development of tolerance has not been reported, perhaps due to the lack of long-term human studies or because all living creatures secrete endogenous MLT. However, physicians who use MLT treatment should be aware that there are many medications which interfere with its metabolism. For example, benzodiazepines and propranolol block MLT production, tryptophan raises it, while marijuana causes a dramatic increase in MLT levels^{108,109}. GABAergic anticonvulsant drugs may suppress nocturnal plasma MLT levels^{172,173}. Drug interactions with MLT are very important, but are complex and beyond the scope of this article^{85,174}.

Benefits of melatonin treatment

The literature review and experience of the authors of this paper show that establishment of normal sleep patterns dramatically changes the children as they soon become less irritable, calmer, happier, more playful, and more affectionate. Cognitive functioning, speed of learning, memory, and problem-solving abilities tend to improve. They are able to socialize better and may have less self-injurious behaviour.

Successful MLT treatment has been noted to result in improved health, fewer infections^{27,33}, and occasionally improved growth rates which could be secondary to stimulation of growth-hormone secretion by MLT¹⁷⁵. MLT may have immunological and endocrine roles^{72,159,176} and it is a potent antioxidant¹⁷⁷. The role of MLT in cancer treatment is also being studied¹⁷⁸⁻¹⁸⁰.

Some children with incompletely controlled epilepsy may experience fewer seizures following MLT treatment once they are no longer sleep deprived^{33,35}. The relation between the circadian rhythm, sleep, and epilepsy is complex¹⁸¹. It is well known that better sleep results in improved seizure control. Increased seizures following MLT treatment were reported by Sheldon in 1998¹⁸². Jan and coworkers in 1998¹⁸³, who reviewed the literature on the anticonvulsant action of MLT, felt that this is most likely due to interference with some antiepileptic medications because MLT does have a mild anticonvulsant action¹⁸⁴ as shown by numerous animal¹⁸⁵⁻¹⁸⁸ but very few human studies^{2,189-191}. The general use of MLT for children with epilepsy cannot be recommended until more research data are available.

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