Health Library

Melatonin

Uses

Principal Proposed Uses

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- Jet Lag and Other Sleep Disorders

Oral Uses

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Melatonin is a natural hormone that regulates sleep. During daylight, the pineal gland in the brain produces an important neurotransmitter called serotonin. (A neurotransmitter is a chemical that relays messages between nerve cells.) But at night, the pineal gland stops producing serotonin and instead m akes melatonin. This melatonin release helps trigger sleep.

The production of melatonin varies according to the amount of light you're exposed to; for example, your body produces more melatonin in a completely dark room than in a dimly lit one.

Melatonin supplements appear to be helpful for people whose natural sleep cycle has been disturbed, such as travelers suffering from jet lag. The hormone may also be helpful in various other sleep disorders.

Based on early reports that melatonin levels decline with age, the hormone was briefly marketed as a kind of fountain of youth. However, newer evidence suggests that melatonin levels do not decline with age after all. 65

Other potential benefits of melatonin remain largely speculative. Very weak evidence hints that melatonin might be helpful for functional dyspepsia (chronic indigestion of unknown cause). 113

Sources

Melatonin is not a nutrient. However, travelers and workers on rotating or late shifts can experience sleep disturbances that seem to be caused by changing melatonin levels.

You can boost your melatonin production naturally by getting thicker blinds for the bedroom windows or wearing a night mask. You can also take melatonin tablets.

Therapeutic Dosages

Melatonin is typically taken half an hour before bedtime for the first 4 days after traveling.

For ordinary insomnia, melatonin is usually taken about 30 minutes to 1 hour before bedtime. To fall asleep on Sunday night after staying up late Friday and Saturday, one study suggests using melatonin 5.5 hours before the desired bedtime.

The optimum dose of melatonin is not clear, but it is probably in the 1 to 5 mg range.

Melatonin is available in two forms: immediate-release (just plain melatonin, also called "quick-release") and slow-release (a special preparation, also called "controlled-release," designed to spread melatonin absorption over many hours). It seems reasonable to suppose that quick-release melatonin helps in falling asleep, while slow-release melatonin helps in staying asleep, but study results are inconsistent on this issue. 1

Therapeutic Uses

Reasonably good evidence tells us that melatonin can help people with jet lag adjust to a new schedule. 46 Although it probably works in part by resetting the biological clock, it also appears to decrease or block wakefulness-promoting circuits in the nervous system 86 and may have other direct sedative effects. Based on this, melatonin has been tried for insomnia of various types, but results have been inconsistent 87.

Three small double-blind studies suggest that use of melatonin might reduce symptoms of irritable bowel syndrome. 89-90,111 It has been suggested that melatonin might work through effects on the nervous system in the digestive tract.

Four double-blind studies performed by Saudi researchers reported that melatonin was useful for reducing anxiety prior to surgery, presumably due to its sedative effects. 2,3,95,102 However, other researchers have been unable to confirm these results. 99-100

Three, small, double-blind, placebo-controlled studies found evidence that melatonin may slightly reduce nighttime blood pressure. 67,88,101

Two preliminary double-blind trials hint that use of melatonin at a dose of 10 mg/day may reduce symptoms of tardive dyskinesia. 45,68

A preliminary double-blind study suggests that melatonin may improve quality of life in children with epilepsy, perhaps by improving sleep and reducing medication side effects. 69

One surprising double-blind study suggests that topical application of melatonin may increase hair growth in women with thinning hair, for reasons that are entirely unclear. 70

Oral melatonin has shown some potential for treating seasonal affective disorder , cluster headaches , 47-50,71 and irritable bowel syndrome.

Highly preliminary studies, including unblinded controlled trials, suggest that melatonin may enhance the effectiveness of standard therapy for breast cancer, prostate cancer, brain glioblastomas, non-small-cell lung cancer, and other forms of cancer. 4-6,51-53 (For information on why such studies are unreliable, see Why Does This Database Rely on Double-blind Studies?) Melatonin has also shown some promise in animal studies for reducing side effects (specifically, cardiac toxicity) of the chemotherapy drug doxorubicin ; however, the only human trials supporting this use fall considerably beneath modern scientific standards. 103-110

Weak evidence supports a role for melatonin in reducing nicotine withdrawal symptoms. 91

On the basis of one uncontrolled trial, melatonin has been promoted as a treatment for fibromyalgia. 72

Based on theoretical reasoning and scant evidence, it has been suggested that melatonin can boost the immune system , prevent heart disease , and fight aging in general. 8-11

Evidence to date suggests that melatonin is *not* helpful for menopausal symptoms , 73chronic fatigue syndrome , 74 or migraines. 118

What Is the Scientific Evidence for Melatonin?

Sleep Disorders

Melatonin appears to produce sedation comparable to that of conventional pharmaceuticals used for inducing sleep 75 without impairing mental function. 76 Melatonin has shown promise as a treatment for a variety of sleep disorders, of which the best studied is jet lag.

Jet Lag

There is good evidence that melatonin can help you fall asleep when your bedtime rhythm has been disturbed by travel (jet lag). 46,77

For example, one double-blind, placebo-controlled study enrolled 320 people and followed them for 4 days after a long plane trip. 12 The participants were divided into four groups and given a daily dose of 5 mg of standard melatonin, 5 mg of slow-release melatonin, 0.5 mg of standard melatonin, or placebo. 12 The group that received 5 mg of standard melatonin slept better, took less time to fall asleep, and felt more energetic and awake during the day than the other three groups.

Another small double-blind trial found that airplane crews experienced improved rest when using melatonin (10 mg) as compared to placebo, and equivalent benefits as compared to the drug zopiclone. 44 Neither group experienced any impairment in mental function the following morning.

According to one review of the literature, melatonin treatment for jet lag is most effective for those who have crossed a significant number of time zones, perhaps eight. 13

Shift Work

Studies of melatonin for the treatment of insomnia related to shift work have yielded mixed results. 15,19,20,42-44,92,117 Researchers have been surprised by these findings, but suggest that perhaps working at night upsets the biological rhythm even more profoundly than traveling over many time zones, too profoundly for melatonin to help.

Sleep in the Elderly

Mixed results have been seen with the use of melatonin for treating insomnia in the elderly. 14-18,21,57,78,115 Not only have many studies failed to find melatonin helpful, those studies with positive results found widely varying benefits; for example, some studies found a decreased time to falling asleep, but no change in sleep throughout the night, while others found the reverse. These differences have not followed dose or type of melatonin in any obvious way, making them somewhat suspect.

General Insomnia

One small study failed to find benefit for general insomnia in healthy people. 79

Sleep Problems in Children

A 4-week, double-blind trial evaluated the benefits of melatonin for children with difficulty falling asleep. 22 A total of 40 children who had experienced this type of sleep problem for at least 1 year were given either placebo or melatonin at a dose of 5 mg. The results showed that use of melatonin significantly helped participants fall asleep more easily. Similar results were seen in a double-blind, placebo-controlled study of 62 children 80 and in a study of 20 developmentally disabled children with sleep problems. 23

Researchers have also focused on sleep problems in children and teens with autism spectrum disorders. In a systematic review of 5 randomized trials and 13 observational studies, melatonin was associated with faster sleep onset and longer sleep duration. 120

Delayed Weekend Sleep Pattern (Monday Morning Fatigue)

Many individuals stay up late on Friday and Saturday nights, and then find it difficult to get to sleep at a reasonable hour on Sunday. A small double-blind, placebo-controlled study found evidence that taking melatonin 5.5 hours before the desired Sunday bedtime improved the ability of participants to fall asleep. 24

Sleep in Hospitalized Patients

Benefits were seen in a small, double-blind trial of patients in a pulmonary intensive care unit. 25 It is famously difficult to sleep in an ICU, and the resulting sleep deprivation is not helpful for those recovering from disease or surgery. In this study of 8 hospitalized individuals, 3 mg of controlled-release melatonin "dramatically improved" sleep quality and duration.

Other Sleep Problems and Sleep Problems Among People With Specific Medical Problems

Small double-blind trials have found benefits for improving sleep in people with diabetes , 26asthma (however, see Safety Issues), 81 head injury, 82schizophrenia , 27Alzheimer’s disease , 83 and Parkinson's disease. 94 Melatonin has also shown benefit for improving sleep in people with attention deficit disorder ; 93,112 it has failed, however, to show benefit for the symptoms of ADHD per se. 112

Blind people often have trouble sleeping on any particular schedule, because there are no "light cues" available to help them get tired at night. A small double-blind, placebo-controlled, crossover trial found that the use of melatonin at a dose of 10 mg per day was able to resynchronize participants' sleep schedules. 28

Some individuals find it impossible to fall asleep until early morning, a condition called delayed sleep phase syndrome (DSPS). Melatonin may be beneficial for this syndrome. 29

Individuals trying to quit using sleeping pills in the benzodiazepine family may find melatonin helpful. A double-blind, placebo-controlled study of 34 individuals who regularly used such medications found that melatonin at a dose of 2 mg nightly (controlled-release formulation) could help them discontinue the use of the drugs. 30 Interestingly, another study failed to find melatonin helpful for reducing benzodiazepine use among people taking drugs in that family for anxiety. 58

Note: There can be risks in discontinuing benzodiazepine drugs. Consult your physician for advice.

Cancer Treatment

Melatonin has been used with conventional anticancer therapy in more than a dozen clinical studies. Results have been surprisingly good, although this research must be considered preliminary. For example, a double-blind study on 30 people with advanced brain tumors suggested that melatonin might prolong life and also improve the quality of life. 33 Participants received standard radiation treatment with or without 20 mg daily of melatonin. After 1 year, 6 of 14 individuals in the melatonin group were still alive, compared with just 1 of 16 from the control group. The melatonin group also had fewer side effects due to the radiation treatment—a notable improvement in their quality of life.

Improvements in symptoms and a possible reduction of mortality were also seen in other studies. 34,35 Melatonin appears to work by increasing levels of the body's own tumor-fighting proteins, known as cytokines. 36

Headaches

Some evidence suggests that individuals with cluster headaches have lower than average levels of the hormone melatonin. 47-50 In a double-blind, placebo-controlled study of 20 individuals with cluster headaches, use of melatonin (10 mg daily) for 14 days appeared to reduce headache severity and/or frequency in about half the participants. 59 Overall, use of melatonin produced better effects than placebo.

In a small randomized, crossover study, 48 men and women who suffered from migraines took melatonin (2 mg) every night for 8 weeks. The supplement did not decrease the number of migraine attacks. 118

Seasonal Affective Disorder

One study found that people with seasonal affective disorder (SAD) have higher levels of melatonin than those without the condition. 60 On this basis, it would seem that supplemental melatonin should worsen SAD symptoms. However, the evidence for such an effect is inconsistent. 61 Some researchers have proposed that interaction between SAD and melatonin might be more complex than merely high or low levels, and that, when taken at certain times of day, melatonin might help the condition. A very small study found that when melatonin was given in the afternoon, it produced some benefit for people with SAD. 62 However, a study of melatonin used in the early morning or the late evening failed to find any benefit. 63

Melatonin has shown equivocal effects for two conditions related to SAD: subsyndromal seasonal affective disorder (S-SAD) and weather associated syndrome (WAS). According to the one reported study, use of melatonin improved some symptoms but worsened others. 84

Dementia

In a sizable Danish trial, researchers investigated the effects of melatonin on mood, sleep, and cognitive decline in elderly patients, most of whom suffered from dementia. 115 They found that melatonin (2.5 mg) given nightly for an average of 15 months, slightly improved sleep, but it worsened mood. The latter effect was reversed by adding light therapy during the day. Melatonin

apparently had no significant effect on cognition. In a systematic review of 5 randomized trials including 323 people with dementia, researchers failed to find evidence that melatonin is helpful in enhancing memory and other cognitive abilities. 119 In 2 of the trials, however, melatonin was associated with short-term improvement in mood and behavior.

Safety Issues

A safety study found that melatonin at a dose of 10 mg daily produced no toxic effects when given to 40 healthy males for a period of 28 days. 37 However, this does not prove that melatonin is safe when taken on a regular basis over the long term. Keep in mind that melatonin is not truly a food supplement but a hormone. As we know from other hormones used in medicine, such as estrogen and cortisone, harmful effects can take years to appear. Hormones are powerful substances that have many subtle effects in the body, and we're far from understanding them fully. While in one small study, use of melatonin over an 8-day period by healthy men did not affect natural release of melatonin or levels of pituitary or sex hormones, 85 another study found effects on testosterone and estrogen metabolism in men and possible impairment of sperm function. 66 Also, a small study in women found possible effects on the important female hormone called LH (luteinizing hormone). 96

Melatonin appears to cause drowsiness and decreased mental attention for about 2 to 6 hours after using it and may also impair balance. 38,39,64 For this reason, you should not drive or operate machinery for several hours after taking melatonin. In a study of healthy middle-aged and older adults, however, an extended release version of melatonin, which is said to more closely mimic natural fluctuations of the hormone in the body, did not impair mental ability or driving skills 1 to 4 hours later compared to placebo. 116 In either case, melatonin does not appear to have any "hangover" effects the following day. 44

Based on theoretical ideas of how melatonin works, some authorities specifically recommend against using it in people with depression, schizophrenia, autoimmune diseases, and other serious illnesses. One study in postmenopausal women found evidence that melatonin might impair insulin action and glucose tolerance, suggesting that people with diabetes should not use it. 40 However, another study found melatonin safe and effective for people with diabetes. 41 Because of these contradictions, we suggest that individuals with diabetes seek physician supervision before using melatonin.

Two exceedingly preliminary studies reported by one research group has led to publicized concerns that use of the supplement melatonin might increase night-time asthma. 97 However, one double-blind study of melatonin in people with asthma found evidence of improved sleep without worsening of symptoms. 98 Again, at the current state of knowledge, caution must be advised for people with night-time asthma who wish to try melatonin.

There is some evidence that melatonin may interfere with the ability of blood to clot normally, at least in healthy volunteers, 114 though the clinical significance of this finding is at yet unknown.

Maximum safe dosages for young children, pregnant or nursing women, or those with serious liver or kidney disease have not been established.

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Melatonin for Treatment of Sleep Disorders in Children With Developmental Disabilities

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Abstract

This study explored the safety and efficacy of synthetic melatonin in the treatment of sleep problems in 20 children with developmental disabilities, in a randomized, double-blind, placebo-controlled 6-week trial of melatonin versus placebo. All but 2 children fell asleep more quickly when receiving melatonin than placebo. Overall, the greater the sleep latency (time to fall asleep) was at baseline or when receiving placebo, the more pronounced was the decrease in sleep latency with melatonin. The effect of melatonin on sleep latency was significant ($P < .05$). The duration of sleep while receiving melatonin was significantly greater than baseline ($P < .007$) but was not significantly different from placebo, and no difference in the number of awakenings was noted. No side effects were reported. Eleven of 18 parents (61%) correctly identified the weeks their child received melatonin. This study suggests that synthetic melatonin reduces sleep latency in children with developmental disabilities. (J Child *Neurol* 2001;16:581-584).

Melatonin in the treatment of insomnia in children and adolescents *The Psychiatrist June 1, 2004 28: 222-224* Abstract Full Text Full Text (PDF)
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Melatonin in Children and Adolescents with Insomnia: A Retrospective Study *CLIN PEDIATR January 1, 2003 42: 51-58* Abstract Full Text (PDF)
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Insomnio

Términos Relacionados
- Desvelo

Principales Tratamientos Naturales Propuestos
- Melatonina, Valeriana (Sola o Combinada con Lúpulos o Melisa o Toronjil)

Otros Tratamientos Naturales Propuestos
- 5-HTP (5-Hidroxitriptófano), Acupuntura o Acupresión , Ashwagandha, Astrágalo, Biorretroalimentación, Manzanilla, He Shou Wu, Lúpulo, Kava, Zapatito de la Virgen, Pasiflora, Terapias de Relajación, Hierba de San Juan, Escutelaria

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De acuerdo a reportes recientes, muchas personas hoy en día tienen un serio problema para obtener una buena noche de sueño. Nuestras vidas simplemente están muy ocupadas como para que podamos tener las 8 horas de sueño que necesitamos. Para empeorar las cosas, muchos de nosotros sufrimos de insomnio. Cuando vamos a la cama, podemos estar despiertos pensando durante horas. El dormir en sí puede ser menos descansado en lugar de refrescante.

La mayoría de las personas que duermen sustancialmente menos de 8 horas en una noche experimentan una variedad de síntomas desagradables. Los más comunes son dolores de cabeza, confusión mental, irritabilidad, malestar, deficiencias inmunológicas, depresión y fatiga. La falta total de sueño puede causar alucinaciones y un colapso mental.

La mejor forma de mejorar el sueño implica hacer cambios en el estilo de vida; eliminando la cafeína y el azúcar de su dieta, evitando actividades estimulantes antes de acostarse, adoptando un horario regular para dormir y apagando gradualmente las luces. También se pueden adoptar propuestas de conducta más complejas para mejorar los hábitos de sueño.

Muchos medicamentos también pueden ayudar con el sueño. Tales medicamentos como Sonata, Ambien, Restoril, Ativan, Valium, Xanax e hidrato de cloro son usados ampliamente para los problemas de sueño. Sin embargo, estos medicamentos pueden fomentar la dependencia de estos.

Recientemente, los doctores han venido a referirse a algunas formas de insomnio como una variación de la depresión. Esta conclusión viene de un tipo de razonamiento inverso. Sabemos que la depresión casi siempre perturba el sueño, y que los antidepresivos frecuentemente ayudan al insomnio. Por lo tanto, quizás algunos casos de insomnio realmente sean una depresión disfrazada.

Los antidepresivos se pueden usar de dos maneras para corregir los problemas de sueño. Dosis bajas de ciertos antidepresivos provocan el sueño de inmediato debido a que sus efectos secundarios incluyen somnolencia. Sin embargo, este efecto tiende a desvanecerse con el uso repetido.

Para los problemas crónicos de sueño, dosis completas de antidepresivos a veces pueden ser útiles. Se cree que los antidepresivos funcionan realmente alterando la química cerebral, lo que produce un efecto benéfico en el sueño. Desyrel (trazodona) y Serzone (nefazodona) son dos de los antidepresivos recetados más comúnmente cuando se desea mejorar el sueño, pero la mayoría de los otros antidepresivos también pueden ser útiles.

Principales Tratamientos Naturales Propuestos

A pesar de que la evidencia científica aún no es definitiva, la hierba valeriana y la hormona melatonina son ampliamente aceptadas como tratamientos para ciertas formas de insomnio.

Valeriana: Parece Mejorar el Sueño Gradualmente

La valeriana ha tenido un uso tradicional de mucho tiempo para el insomnio y hoy es aceptada como un medicamento sin receta médica para el insomnio en Alemania, Bélgica, Francia, Suiza e Italia.

La valeriana es la más recomendada como auxiliar para el insomnio ocasional. Sin embargo, los resultados del estudio más grande y mejor diseñado sugieren que puede ser más útil para el mejoramiento a largo plazo del sueño. [1]

Este estudio doble ciego controlado por placebo de 28 días de duración, observó a 121 personas con antecedentes de trastorno significativo del sueño. [5] Este estudio observó la efectividad de 600 mg de un extracto de valeriana hecho a base de alcohol tomado una hora antes de acostarse.

La valeriana no funcionó de inmediato. Durante el primer par de semanas, la valeriana y el placebo estaban avanzando de forma pareja. Sin embargo, para el día 28 la valeriana se había adelantado bastante. La efectividad fue considerada como buena o muy buena por la evaluación de los participantes en un 66% del grupo de la valeriana y en un 61% por la evaluación médica, mientras que en el grupo del placebo, sólo el 29% fue considerada así por los participantes y los médicos.

Este estudio proporciona una buena evidencia de que la valeriana es efectiva para el insomnio. Sin embargo, tiene un aspecto confuso: La demora de 4 semanas antes de que sus efectos fueran notados. En otro estudio, la valeriana produjo efectos notables inmediatos en el sueño, [6] y esto es lo que la mayoría de los profesionales creen que es típico. El porqué a la valeriana le tomó tanto tiempo para funcionar en este estudio no ha sido explicado.

Otros estudios de la valeriana sola, o en combinación con el lúpulo o la melisa , han arrojado resultados mixtos. [7 - 18,84]

Para más información, incluyendo la dosis y las cuestiones de seguridad, consulte el artículo completo de la valeriana .

Melatonina: Efecto Rápido en el Sueño

El cuerpo utiliza la melatonina como parte de su ciclo normal de sueño-vigilia. La glándula pineal produce la serotonina y luego la convierte en melatonina cuando la exposición a la luz disminuye. Una luz fuerte (como la luz solar) reduce la producción de melatonina más de lo que lo hace una luz débil, y un cuarto completamente obscuro aumenta la cantidad de producción de melatonina más de lo que un cuarto parcialmente obscuro lo hace. [39]

Tomar melatonina como un complemento parece estimular el sueño cuando el ciclo natural es perturbado.

Aunque no todos los estudios fueron positivos, una evidencia razonablemente buena indica que la melatonina es útil para el insomnio relacionado con el desajuste de uso horario , de acuerdo a una revisión mayor publicada en el 2001. [85] Uno de los mejores estudios de apoyo fue uno doble ciego controlado con placebo que abarcó 320 viajeros que cruzaron de 6 a 8 husos horarios. [47] Los participantes fueron divididos en cuatro grupos y se les dio una dosis diaria de 5 mg de melatonina estándar, 5 mg de melatonina de liberación prolongada, 0.5 mg de melatonina estándar o un placebo. El grupo que recibió 5 mg de melatonina estándar durmió mejor, le tomó menos tiempo quedarse dormido y se sintió con más energía y más despierto durante el día que los otros tres

grupos.

Resultados mixtos se han visto en estudios que implican el uso de la melatonina para los trabajadores que cambian de turno y para los individuos ancianos con insomnio. [52,54 - 62,79,81,82,86]

Una prueba doble ciego de 4 semanas evaluó los beneficios de la melatonina en niños con dificultad para dormirse. [63] A un total de 40 niños que habían experimentado este tipo de trastorno del sueño por lo menos durante un año se les dio o un placebo o melatonina en una dosis de 5 mg. Los resultados mostraron que el uso de la melatonina ayudó de manera significativa a los participantes a dormir considerablemente de manera más fácil. Los beneficios también se notaron en un estudio con 20 niños discapacitados en su desarrollo con problemas de sueño. [80]**Nota: La seguridad en el consumo a largo plazo de la serotonina no ha sido establecido. No les de a sus hijos melatonina excepto bajo supervisión médica.**

Muchos individuos se quedan despiertos hasta tarde las noches del viernes y del sábado, y luego encuentran difícil ir a dormir a una hora razonable el domingo. Un pequeño estudio doble ciego controlado con placebo, encontró evidencia de que el uso de la melatonina 5.5 horas antes de la hora deseada para acostarse el domingo mejoró la habilidad de los participantes para quedarse dormidos. [64]

Los beneficios fueron observados en una pequeña prueba doble ciego de pacientes en una unidad de cuidados intensivos pulmonares. [65] Tiene fama la dificultad para dormir en una ICU (siglas en inglés para, unidad de cuidados intensivos), y el resultado de la falta de sueño no es útil para aquellos que se están recuperando de alguna enfermedad o cirugía. En este estudio de 8 individuos hospitalizados, 3 mg de melatonina de liberación prolongada controlada mejoraron significativamente la calidad y duración del sueño.

Las personas ciegas con frecuencia tienen problemas para dormir en cualquier horario en particular, debido que no hay pistas de luz disponibles para ayudarlos a que se sientan cansados por las noches. Una pequeña prueba cruzada doble ciego controlada por placebo descubrió que, el uso de la melatonina en dosis de 10 mg al día era capaz de sincronizar los horarios de sueño de los participantes. [68]

Algunos individuos encuentran imposible dormirse hasta temprano por la mañana, una enfermedad llamada síndrome de la fase retardada del sueño (DSPS, por sus siglas en inglés). La melatonina puede ser benéfica para este síndrome. [69]

Además, las personas que están tratando de dejar de tomar pastillas para dormir de la familia de la benzodiazepina pueden encontrar útil la melatonina. Un estudio doble ciego controlado con placebo, de 34 individuos que utilizaban regularmente dichos medicamentos encontró que la melatonina en dosis de 2 mg cada noche (fórmula de liberación prolongada) podría ayudarlos a descontinuar el uso de los medicamentos. [70]

Nota: Puede haber riesgos en descontinuar los medicamentos de benzodiazepina. Consulte con su médico para que le aconseje.

Para más información, incluyendo dosis y temas de seguridad, consulte el artículo completo de la melatonina .

Otros Tratamientos Naturales Propuestos

Acupresión o acupuntura puede ser útil para el insomnio, pero la evidencia de apoyo permanece débil. Un estudio doble ciego controlado con placebo que abarcó 84 residentes de asilos, encontró que la acupresión real fue superior a la acupresión falsa para mejorar la calidad del sueño. [77] Los participantes tratados se durmieron más rápido y durmieron más profundamente. Otro estudio sencillo controlado doble ciego reportó beneficios con la acupuntura, pero falló en incluir un

análisis estadístico propio de los resultados. [87] Por esta razón, no se pueden sacar conclusiones del reporte. En un tercer estudio, 98 personas con enfermedad renal grave fueron divididas en tres grupos; sin tratamiento extra, 12 sesiones de acupresión falsa (no usando puntos de acupuntura en realidad) o 12 sesiones de acupresión verdadera. [88] Los participantes que recibieron acupresión real experimentaron una mejoría significativa en el sueño en comparación con aquellos que no recibieron tratamiento extra. Sin embargo, la acupresión falsa fue tan efectiva como la acupresión real.

Varios estudios controlados han evaluado las terapias de relajación para el tratamiento del insomnio. [89] Estos estudios son difíciles de resumir porque muchos implican terapia combinada con otros métodos como la biorretroalimentación , la restricción del sueño y, paradójicamente su intento (tratar de no dormir). El tipo de terapia de relajación usado en la mayoría de estas pruebas fue una relajación progresiva de los músculos (PMR, por sus siglas en inglés). La evidencia total indica que las terapias de relajación pueden ser, de alguna manera, útiles para el insomnio, aunque no de manera dramática. Por ejemplo, en un estudio controlado con 70 personas con insomnio, los participantes que utilizaron la relajación progresiva no mostraron una mejoría significativa en el tiempo que les tomó quedarse dormidos o en la duración del sueño, pero reportaron sentirse más descansados por la mañana. [90] En otro estudio, se requirieron 20 minutos de prácticas de relajación para mejorar el tiempo del sueño en 30 minutos. [91]

La hierba de San Juan y el complemento 5-HTP han mostrado se prometedores como tratamientos para la depresión . Debido a que los antidepresivos recetados pueden ayudar al sueño, estas substancias naturales han sido sugeridas también para el insomnio. Sin embargo, no existe evidencia directa de que sean efectivas. Una prueba doble ciego con 12 personas que no padecen insomnio, no encontró un beneficio para fomentar el sueño con la hierba de San Juan. [78]

De manera similar, las hierbas y los complementos utilizados para la ansiedad, como la kava o la pasionaria , podrían ser útiles para el insomnio, pero no hay evidencia directa en dónde comenzar.

Muchas otras hierbas tienen reputación de ofrecer beneficios sedantes o relajantes, incluyendo la ashwagandha , astrágalo , manzanilla , He shou wu , zapatito de la virgen y la escutelaria . Sin embargo, de nuevo no hay evidencia de apoyo para indicar que éstas realmente funcionen.

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The Psychiatrist

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Drug information quarterly

Melatonin in the treatment of insomnia in children and adolescents

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- **Declaration of interest**
- None.

Next Section

Abstract

AIMS AND METHOD

To review the efficacy and safety of melatonin in the treatment of insomnia in children and adolescents, through a Medline search covering the years 1966 to November 2003.

RESULTS

Five placebo-controlled studies and several case series were identified. Melatonin reduces sleep latency, but does not consistently improve other aspects of sleep disturbance. Safety, particularly in the medium- and longterm, is poorly evaluated; short-term concerns include exacerbation of epilepsy and asthma.

CLINICAL IMPLICATIONS

Melatonin might be effective in the short-term treatment of sleep onset insomnia. The optimal dose is unknown. It cannot currently be recommended for the treatment of other forms of sleep disturbance or for routine long-term use. Melatonin is not a licensed medicine in the UK.

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From early childhood onwards, the cycle of wakefulness and sleepiness is regulated by a circadian 'clock' in the suprachiasmatic nucleus (SCN) of the hypothalamus. This clock is regulated (reset) by various cues, including that of the light-dark cycle of day and night.

In the neonate, there is little entrainment of the sleep-wake cycle to the light-dark cycle (Garcia *et al*, 2001). By the age of 6 months, circadian rhythms have become established and sleep patterns have taken on a roughly 24 hour cycle of nocturnal sleep plus daytime naps. By the age of 6 years, most children sleep only at night. Total sleep time gradually decreases with age and by adolescence has stabilised to a daily average of about 8 hours and the sleep-wake cycle to slightly more than 24 hours. This cycle is reset daily by the SCN.

Insomnia is a common problem in children with sensory deficits and some learning disability

syndromes. It is also a symptom of childhood psychiatric disorders such as depression and attention-deficit hyperactivity disorder. Persistent sleep disturbance in a young child can adversely affect family life. Mothers of learning-disabled children with severe sleep problems have been reported to be more irritable and less affectionate towards their children than mothers of such children without sleep problems (Quine, 1992). Successful treatment of the child's sleep problems generally leads to improvements in the mother's mental state, confidence and relationship with the child, as well as in the child's behaviour (Minde *et al*, 1994).

In adolescence, delayed sleep phase syndrome, in which the sleep-wake cycle may be particularly prolonged, is common. About 10% of otherwise normal children (Smits *et al*, 2001) and up to 80% of children with developmental disorders (Jan & O'Donnell, 1996) are affected.

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The role of melatonin

Melatonin is an endogenous hormone chemically related to serotonin. It is produced by the pineal gland in the midbrain. Body levels follow a circadian course, being stimulated by the evening onset of dim light and suppressed by bright light. The evening rise in melatonin precedes the rise in sleepiness by about 1.5-2 hours (Tzischinsky & Lavie, 1994). The circadian rhythm of sleep consolidation (the ability to stay asleep) may also be related to melatonin levels, but this has yet to be demonstrated. Melatonin acts by resetting any disruption of SCN rhythms. Given its association with circadian rhythms, oral melatonin could be expected to treat sleep disturbances. Many case studies, case series, open and controlled studies have been published. These are summarised below.

Case series

Jan & O'Donnell (1996) gave melatonin (2.5-25 mg) to 100 children with developmental disorders, half of whom were visually impaired or blind. Benefits including fewer tantrums, better attention and improved socialisation were noted in 80%. In a further case series, Palm *et al* (1997) gave melatonin (0.5-4 mg) 30-60 min before the scheduled bedtime to eight children and young adults. All the children were learning-disabled and blind, and four also had hearing impairments. All improved in terms of sleep-wake timings.

In a case series of two children with Rett syndrome, a dramatically beneficial effect on the regulation of the sleep-wake cycle was seen in one child, with the other child showing marginal benefit (Miyamoto *et al*, 1999). Jan (2000) gave melatonin (3 mg) to 10 children with developmental disorders and severe sleep disorders: 8 of the 10 improved with respect to delay of sleep onset, early morning waking, duration of unbroken sleep and total duration of sleep. In the most recent case series, Ivanenko *et al* (2003) gave melatonin (average dose 2 mg) an hour before bedtime to 32 children with chronic sleep problems. Partial or complete resolution of sleep problems was achieved in 29. Some children (number unstated) were receiving other unspecified medical and behavioural interventions.

Controlled studies

Five placebo-controlled studies have been published. Camfield *et al* (1996) gave melatonin (0.5 mg or 1mg) or placebo in 2-week alternating phases at 18.00 to six children with fragmented sleep and developmental disorders, none of whom showed any significant improvement in sleep patterns. McArthur & Budden (1998) gave nine children with Rett syndrome variable doses of melatonin or placebo for a 4-week period with a 1-week drug wash-out period between the treatment and placebo phases. Sleep latency was reduced significantly in the treatment phase, although individual response varied greatly. Dodge & Wilson (2001), in a 6-week double-masked, placebo-controlled study, compared melatonin with placebo in 20 children with developmental disorders. Significant reductions in sleep latency were observed, but sleep duration and number of awakenings did not

change.

Smits *et al* (2001) gave 40 children with sleep onset insomnia either 5 mg melatonin or placebo once daily at 18.00 for 4 weeks. Children with developmental disorders were excluded. Melatonin was significantly better than placebo with respect to lights-off time, sleep onset and sleep duration, but not sleep latency or wake-up time. Two children had mild headache during the first 2 days of treatment with melatonin, and one child developed mild generalised epilepsy while taking open-label melatonin 4 months after the start of the trial. On 18-month follow-up, 13 children were able to stop taking melatonin without further sleep disturbance.

In a further similar study (Smits *et al*, 2003), 62 children with idiopathic chronic sleep-onset disorder were given melatonin 5 mg or placebo for 4 weeks after a 1-week baseline period. The active group improved significantly in measures of general health, sleep onset time and sleep offset time. There was no change in lights-off time or total sleep time. Children with comorbid psychiatric illness were excluded from this study, with the exception of those treated with methylphenidate. The active and placebo groups contained markedly different numbers of children prescribed methylphenidate (22% v. 54%). This could have biased the result, as methylphenidate is independently associated with insomnia.

Melatonin is widely prescribed by child psychiatrists in the UK, although it is not a licensed medicine.

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Side-effects

Since melatonin is a natural substance, it is often assumed that its side-effect profile is benign. However, most other endogenous hormones produce considerable adverse effects in high or inappropriately phased doses and it should be anticipated that melatonin might behave similarly. Many of the published reports involved children with developmental abnormalities, which limited the scope for detection of subtle adverse effects. Most studies involved short-term use of melatonin and did not systematically inquire about side-effects.

Sheldon (1998) reported that melatonin increased seizure frequency in neurologically disabled children, an effect that disappeared when melatonin was discontinued and reappeared on further challenge. Also, Smits *et al* (2001) reported the development of mild epilepsy in one child. Whether seizure threshold is affected in the general population is unknown.

Melatonin raises levels of inflammatory cytokines such as interleukins 1 and 6 and tumour necrosis factor alpha (Maestroni, 1993), and this effect may have adverse consequences for people with inflammatory-mediated conditions such as asthma. Sutherland *et al* (2003) and Sutherland *et al* (2002) reported that peak endogenous levels of melatonin were elevated in people with nocturnal asthma and were inversely correlated with measures of respiratory function; they concluded that the ‘avoidance of exogenous melatonin supplementation by persons with asthma might be warranted’.

Melatonin has contraceptive properties and can affect the onset of puberty (Weaver, 1997). It also has antioxidant (Pieri *et al*, 1994) and cytostatic (Brzezinski, 1997) properties. These effects are minimal at physiological levels, but may become more apparent when synthetic melatonin is taken in supraphysiological doses: the cut-off point between physiological and pharmacological levels in adults is estimated to be produced by doses of 500 μg, and this is likely to be less in children.

In clinical depression in adults, there is evidence that the risk-benefit ratio for melatonin may be adverse. Carman *et al* (1976) found that melatonin exacerbated symptoms of dysphoria, reduced sleep and led to weight loss in a small, double-blind, cross-over study in moderately to severely depressed adult patients. It has been suggested that seasonal affective disorder might respond to propranolol through the suppression of endogenous melatonin production (National Institute of Mental Health USA, 2003).

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Overview

Five placebo-controlled trials in children have been identified. Most of the published literature consists of case reports and case series, which used a variety of doses and formulations of melatonin. The nature of the populations treated is diverse, and most studies report shortterm use in which the placebo effect would be highest. Oral melatonin may reduce sleep latency, but its effects on other aspects of sleep are inconsistent between studies. The optimal dosages and duration of treatment are unknown. Side-effects have been poorly evaluated to date, although worsening of seizures and asthma have been reported in the short term. Long-term side-effects are not established, although melatonin is known to have significant effects on many body systems. Melatonin is not a licensed medicine in the UK and the prescriber is fully accountable for any problems that might result from its use.

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Responses to this article

- Sumudu H Chandraratne

Melatonin: prescribing practice in child and adolescent mental health service *The Psychiatrist published online January 8, 2007* Full text

Articles citing this article

- Reflections on melatonin: focus on child mental health *The Psychiatrist December 1, 2008 32:444-448* Abstract Full text PDF

By squideast | Sep 06, 2011

2 Comments

My 8 year old son was diagnosed with ADD over a year ago, and prescribed Concerta. His mother and I are divorced. I learned that she is giving him Melatonin at night to 'help him sleep'. This was not prescribed by the pediatrician; it is over-the-counter. I do not give him any sleep aids when he is with me. He has no sleep issues in my home. He falls asleep within 15 minutes of being put to bed. I have researched and see that some pediatricians recommend Melatonin to help with sleeplessness in children with certain neurological disorders. That is fine and well, but I do not agree with giving my child a medication that I don't see he needs and his pediatrician has not ordered.

So here's my question: is it unsafe for a child to *intermittently* take Melatonin? There are many drugs out there that are not OK to 'start and stop'. Is Melatonin one of them? If it's 'harmless', my ex and I can just agree to disagree. If this is harmful to him, however, we cannot continue to have this 'difference' in each home.

Thanks for your time.

Watch this discussion

Related Discussions

- 10yr old with trouble falling asleep (6 replies):
  My son is having alot of problems falling asleep. He se...[more]
- My 8 year old can't sleep! He on Concerta (12 replies):
  My 8 year old has ADD and is taking 36mg of concerta, it...[more]
- is melatonin is safe for toddler? (5 replies):
  i have a problem w/ my two yrs old, she cant sleep w/ ou...[more]

- Sleep Problems (2 replies):
  My son is 11 years old and has been having trouble falli...[more]
- Sleeplessness (6 replies):
  My 3yo son does not sleep but maybe 3-4hrs a night if th...[more]

2 Comments

Sandman2

Sep 06, 2011

Well, it certainly should help him fall asleep sooner - which may be her idea. It sounds like you have researched this pretty well. I don't think our opinion is going to matter much to your ex. I think you will need to find a professional for that.

I was able to find one report from consumers union which I am posting here as you need the paid subscription to read it. (don't tell). Hope this helps.

Melatonin
Natural therapy
Hormone that controls your body clock.
Treatment Rating
(Do benefits outweigh harms?)
Likely
More info

Benefits likely outweigh harms

Giving your child a pill or capsule of melatonin before bedtime may help them sleep sooner and for longer. But there's a risk of side effects. Also, because melatonin is not sold as a medication, it's hard to know how pure and safe the melatonin you buy may be.
Melatonin is a hormones
Hormones are chemicals that are made in certain parts of the body. They travel through the bloodstream and have an effect on other parts of the body. For example, the female sex hormone estrogen is made in a woman's ovaries. Estrogen has many different effects on a woman's body. It makes the breasts grow at puberty and helps control periods. It is also needed to get pregnant.

hormone. Hormones are chemicals your body makes naturally to control some of the things it does. For example, hormones can tell your body how to use energy, or when to go to sleep.
Melatonin is the hormone that controls your body clock. Normally, your brain produces melatonin during the night to help you sleep. Your body starts to make melatonin when it gets dark, and stops when it gets light. The melatonin that's sold as a treatment is a man-made version of this hormone.
We found one good-quality study a
randomized controlled trial), which looked at how well melatonin worked for children ages 6 through 12 years who had sleep problems. The children took melatonin before going to bed.

Source:
Smits MG, Nagtegaal EE, van der Heijden J, et al.
Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial.
Journal of Child Neurology. 2001; 16: 86-92.

The study found that the children:

* Went to bed one hour earlier on average
* Slept about half an hour longer.

But the study also found that the children:

* Took just as much time to get to sleep after going to bed
* Woke up just as early.

Another study found children slept better if they took 5 milligrams of melatonin before bedtime.

Source:
Smits MG, van Stel HF, van der Heijden K, et al.
Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial.
Journal of the American Academy of Child and Adolescent Psychiatry. 2003; 42: 1286-1293.

But this research may not be reliable because there were problems with how the study was done. There hasn't been much research on the best dose of melatonin for children to take. For some children, high doses of melatonin don't help. Melatonin may be more helpful if your child has only a low dose.

Source:
Brzezinski A, Vangel MG, Wurtman RJ, et al.
Effects of exogenous melatonin on sleep: a meta-analysis.
Sleep Medicine Reviews. 2005; 9: 41-50.

Source:
Jan JE, Freeman RD.
Melatonin therapy for circadian rhythm sleep disorders in children with multiple disabilities: what have we learned in the past decade?
Developmental Medicine and Child Neurology. 2004; 46: 776-782.

We found two small studies that looked at children with epilepsy, and one study that looked at children with attention deficit hyperactivity disorder (ADHD for short). Taking melatonin didn't make much difference to how well the children slept overall.
Source:
Gupta M, Aneja S, Kohli K.
Add-on melatonin improves sleep behaviour in children with epilepsy: randomized, double-blind, placebo-controlled trial.
Journal of Child Neurology. 2005; 20: 112-115.

Source:
Gupta M, Gupta YK, Aneja S, et al.
Effects of add-on melatonin on sleep in epileptic children on carbamazepine monotherapy: a randomized placebo controlled trial.
Sleep and Biological Rhythms. 2004; 2: 215-219.

Source:
Weiss MD, Wasdell MB, Bomben MM, et al.
Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia.
Journal of the American Academy of Child and Adolescent Psychiatry. 2006; 45: 512-519.

We don't know how safe melatonin is for children, or how safe it is to take it regularly for a long time. There hasn't been enough research to say.
The studies we looked at found that children did have some side effects. Some of the children who took melatonin felt cold or dizzy or they had a low mood. Some children also didn't feel hungry and had mild headaches.
Source:
Smits MG, Nagtegaal EE, van der Heijden J, et al.
Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial.
Journal of Child Neurology. 2001; 16: 86-92.

Source:
Smits MG, van Stel HF, van der Heijden K, et al.
Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial.
Journal of the American Academy of Child and Adolescent Psychiatry. 2003; 42: 1286-1293.
There's also some evidence that children may get epilepsy or worse
seizures if they take melatonin, but we don't know this for sure. In one study we looked at, one child had mild epilepsy after four months of taking melatonin.
Source:
Smits MG, Nagtegaal EE, van der Heijden J, et al.
Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial.
Journal of Child Neurology. 2001; 16: 86-92.

In another study, 4 in 6 children with epilepsy had more seizures when they took melatonin.
Source:
Sheldon SH.
Pro-convulsant effects of oral melatonin in neurologically disabled children.
Lancet. 1998; 351: 1254.

And they got seizures less often when they stopped taking the supplement.
Some studies also suggest melatonin could delay the start of puberty

Source:
Arendt J.
Safety of melatonin in long-term use.
Journal of Biological Rhythms. 1997; 12: 673-681.

Source:
Weaver DR.
Reproductive safety of melatonin: a 'wonder drug' to wonder about.
Journal of Biological Rhythms. 1997; 12: 682-689.

You can buy melatonin from pharmacies and health food stores. But melatonin isn't sold as a medication. It's sold as a supplement, a bit like vitamin pills and cod liver oil. This means that, like all supplements, it may not be made to the same standards as medications. You can't be sure how good-quality it is. Because melatonin may cause harm, it's important to speak with your child's pediatrician before giving melatonin to your child.

This information was last updated on Jan 07, 2011

 squideast

Sep 07, 2011
To: Sandman2
Thanks for the info (and I won't tell! lol).

I can't even discuss with the ex whether or not he should be taking it *at all*. It's like talking to a brick wall. I'm firmly of the belief he does not need it, and am none too thrilled that he's taking it at any time unnecessarily.

My concern is the intermittent administration of it. While I do *not* want to administer this supplement to him in the absence of a need for it or doctor's order, I also don't want to cause our son any medical harm, or discomfort from withdrawals, by *not* giving it to him in my home. I just want to do what's best for him on my end.

I did find the following, which leads me to not worry, since I know our son doesn't have 'sleep disturbances' to begin with:

http://www.healthy.net/scr/article.aspx?Id=1233

"When deciding to stop the use of melatonin or any sleeping medicine, it is best to taper off over a period of 1 to 2 weeks to avoid any sleep disturbances...Only a small percentage of people feel any withdrawal symptoms."

But I thought I'd ask the question on this site to double check.

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Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT

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Abstract

Rationale

Pharmacokinetics of melatonin in children might differ from that in adults.

Objectives

This study aims to establish a dose–response relationship for melatonin in advancing dim light melatonin onset (DLMO), sleep onset (SO), and reducing sleep onset latency (SOL) in children between 6 and 12 years with chronic sleep onset insomnia (CSOI).

Methods

The method used for this study is the randomized, placebo-controlled double-blind trial. Children with CSOI ($n = 72$) received either melatonin 0.05, 0.1, and 0.15 mg/kg or placebo during 1 week. Sleep was assessed with log and actigraphy during this week and the week before. Outcomes were the shifts in DLMO, SO, and SOL.

Results

Treatment with melatonin significantly advanced SO and DLMO by approximately 1 h and decreased SOL by 35 min. Within the three melatonin groups, effect size was not different, but the circadian time of administration (TOA) correlated significantly with treatment effect on DLMO ($r_s = -0.33$, $p = 0.022$) and SO ($r_s = -0.38$, $p = 0.004$), whereas clock TOA was correlated with SO shift ($r = -0.35$, $p = 0.006$) and not with DLMO shift.

Conclusions

No dose–response relationship of melatonin with SO, SOL, and DLMO is found within a dosage range of 0.05–0.15 mg/kg. The effect of exogenous melatonin on SO, SOL, and DLMO increases with an earlier circadian TOA. The soporific effects of melatonin enhance the SO shift. This study demonstrates that melatonin for treatment of CSOI in children is effective in a dosage of 0.05 mg/kg given at least 1 to 2 h before DLMO and before desired bedtime.

Keywords: Melatonin treatment, Elementary school-aged children, Chronic sleep onset insomnia, Randomized placebo controlled, Dose finding

Go to:

Introduction

Prevalence of chronic sleep onset insomnia in the nondisabled school-aged population is approximately 10% (Blader et al. 1997). A chronically reduced sleep due to insomnia may induce various cognitive and behavioral problems in children as well as more widespread difficulties within their families (Dahl 1996; Blader et al. 1997; Ring et al. 1998). It has even been suggested that the current attention-deficit hyperactivity disorder (ADHD) epidemic might partly be attributable to delayed sleep phase disorder, due to a shared underlying pathophysiology or to misinterpretation of daytime consequences of insomnia as ADHD symptoms (Szeinberg et al. 2006).

Chronic sleep onset insomnia in children is often associated with a delayed time at which endogenous melatonin concentration starts to rise in dim light (DLMO) indicating that the biological clock rhythm in these children is set at a later clock time than desired (Van der Heijden et al. 2005). The DLMO is a convenient parameter, as it can usually be obtained before—instead of during—sleep time and is more reliable than many other endocrine or temperature markers of the circadian pacemaker (Klerman et al. 2002). Administration of exogenous melatonin in children with insomnia shifts DLMO as well as sleep onset to an earlier time in the evening, thereby ameliorating the insomnia problems (Smits et al. 2001, 2003; Van der Heijden et al. 2007). The direction, a phase advance or phase delay, and the magnitude of the response of the circadian pacemaker to exogenous melatonin depends on the timing of administration of melatonin relative to the rhythm phase of the pacemaker, the so-called phase response curve. The phase response curve illustrates that the largest phase-advancing therapeutic effects of melatonin can be expected when administration occurs approximately 5 to 6 h before the individual DLMO. Lewy et al. (2004) were the first to describe this in blind people with a free-running sleep–wake rhythm. Van der Heijden et al. (2005) demonstrated that the earlier (within a window of 3/4–6 h before DLMO) melatonin is administered in children with sleep onset insomnia and normal vision, the larger the phase advance of sleep onset is.

Since melatonin administration in the afternoon has the potential to cause undesired direct soporific effects, administration in children usually takes place in the early evening, preferably not earlier than 18 h. Most studies apply a melatonin dosage of 5 mg, although melatonin plasma concentrations in children are generally higher than in adults due to the fixed size of the pineal gland in humans during development, while the body volume increases (Waldhauser et al. 1988; Schmidt et al. 1995; Griefahn et al. 2003). Children metabolize melatonin, however, more quickly than adults (Cavallo and Dolan 1996; Cavallo and Ritschel 1996). Consequently, the dose–response relationship of melatonin in children may differ from that in adults.

Several small studies and case reports on the efficacy of melatonin for childhood insomnia have been published, with pharmacological doses of 2–12 mg. These studies showed that melatonin treatment is effective and safe in children with sleep onset disorders with or without co-morbidity (Jan et al. 1994, 2000; McArthur and Budden 1998; Jan 2000; Smits et al. 2001, 2003; Coppola et al. 2004; Weiss et al. 2006; Van der Heijden et al. 2007; Wasdell et al. 2008). The applied dosage of

melatonin in these studies is very diverse, and—except in one study (Van der Heijden et al. 2007)—not adjusted to age or bodyweight. This is at least exceptional, in comparison to other drug regimens in children. Most drugs are dosed in children in relation to their bodyweight.

Recently, several reviews concluded that melatonin is effective and safe in children irrespective of the dosage (Pandi-Perumal et al. 2007; Owens and Moturi 2009; Bendz and Scates 2010). So, a knowledge gap remains as to the dosage of melatonin in children. The aim of the present trial was to assess the dose–effect relationship of melatonin in advancing the sleep–wake rhythm in elementary school children aged 6–12 years suffering from chronic sleep onset insomnia and to find the most appropriate dosage with the largest effect and least adverse events.

With the results of a trial of short length and noninvasive measurements, we intend to contribute to evidence-based medicine and, therefore, to rational drug prescription in children (Sutcliffe and Wong 2006; Vitiello 2007) suffering from insomnia, finding the appropriate dosage of melatonin.

Methods and materials

Study design

The trial consisted of two consecutive periods: a 1-week qualification period and 1 week of treatment, in which participants were randomly and evenly allocated to one of the doses of melatonin or to placebo.

The trial was performed according to the 1997 European Guidelines for Good Clinical Research Practice in children and followed the 1983 revised provisions of the 1975 Declaration of Helsinki.

The protocol was approved by the institutional review board as a mono-center trial by the Central Committee on Research Involving Human Subjects and registered in the International Standard Randomized Controlled Trial Number Register (ISRCTN20033346).

Participants

Children who suffered from chronic sleep onset insomnia were referred by their general practitioner, pediatrician, or child psychiatrist to the Centre for Sleep–Wake Disorders and Chronobiology of the Hospital Gelderse Vallei Ede. Children were eligible if they were 6–12 years old, suffering from sleep onset insomnia more than four nights a week for more than 1 year, and insufficiently responded to sleep hygiene improving measures based on parental reports. Sleep onset insomnia was defined as sleep onset later than 8:30 p.m. in children aged 6 years and for older children 15 min later per year until age 12 (10:00 p.m.). Furthermore, the latency between lights-off time and sleep onset (sleep onset latency) had to be more than 30 min on average. Their sleep onset had not been advanced sufficiently with the usual sleep hygiene improving measures (Lam and Mason 2007). Further inclusion criteria were normal sleep architecture as indicated by a normal hypnogram, performed within 2 months prior to participation, and written informed consent obtained from parents. Exclusion criteria were chronic sleep onset insomnia due to psychiatric or pedagogic problems, known intellectual disability, pervasive developmental disorder, chronic pain, known disturbed hepatic or renal function, epilepsy, prior use of melatonin, and use of stimulants, neuroleptics, benzodiazepines, clonidine, antidepressants, hypnotics, or beta-blockers within 4 weeks before enrollment.

Finally, DLMO was determined by saliva measurements before inclusion as described elsewhere (Nagtegaal et al. 1998) to validate the diagnosis of DSPD.

Interventions

During the treatment week, all participants took medication on nights 1–6 between 17:30 and 19:30, placebo or melatonin 0.05 or 0.1 or 0.15 mg/kg (constituting four treatment groups). The children

and their parents were instructed to administer the trial medication every day at the same time, depending on age and designated bedtime. For practical reasons, we aimed at 1.5–2 h before bedtime. This way, we ensured to be in the previously mentioned timeframe of preferred time of administration (TOA). The time of administration was recorded in the sleep diary every evening.

Participants were not allowed to have their co-medication changed. Both weeks had to be regular school weeks, at least 2 weeks after time-shift weeks (summertime/wintertime), and preferably without parties, school camps, holidays, etc.

Compliance of the medication was assessed by counting the number of capsules returned.

Outcomes

Sleep: sleep onset, sleep onset latency, wake-up time, and total sleep time

During the baseline and treatment periods, the parents recorded lights-off time, sleep onset, and wake up time daily in a sleep log (on paper or online in a specialized internet software application (Medsys/De Nieuwe Coster/2004)); additional information on mood and adverse events were also recorded.

During all 14 days of the trial, participants were instructed to wear an actigraph (Cambridge Neurotechnology) from the moment they went to bed until the moment they got up in the morning (get-up time). This motion-sensing device—the size of a normal wristwatch—was attached to the non-dominant wrist. Actigraphic monitoring measured movements in 30-s periods. It is a validated method to assess sleep patterns in children (Morgenthaler et al. 2007; Werner et al. 2008). Actigraphic data were converted into sleep parameters by the validated automatic Actiwatch scoring algorithm, combined with subsequent manual verification based on sleep log-derived bedtime and get-up time (Kushida et al. 2001). Sleep onset (SO) and wake-up time, as derived from the wrist activity records, averaged over three to seven nights of each week and were estimated as described elsewhere (Littner et al. 2003). Sleep onset latency (SOL) and total sleep time (TST) were calculated (SOL = SO − bed time and TST = wake up time − SO). Sleep log data were used to validate the actigraphy data; in case of discrepancy, the actigraphy data prevailed.

Dim light melatonin onset

On the last nights of the baseline and the treatment week, five saliva samples were collected by chewing on a cotton plug during 1 min (Salivetten, Sarstedt Nümbrecht, Germany) at 19:00, 20:00, 21:00, 22:00, and 23:00 h. In the treatment week, at this night, no trial medication was used. Salivary melatonin concentrations were measured as described elsewhere (Nagtegaal et al. 1998). To prevent suppression of melatonin secretion by bright light (Bojkowski et al. 1987) during the collection period, the children were instructed to stay in bed or in the living room, with closed curtains and only dim light allowed, 40 lx (Brainard et al. 2000). DLMO was defined as the time at which salivary melatonin concentration reaches 4 pg/ml and was calculated by linear interpolation between the two samples just below and just above 4 pg/ml.

Sample size

Based on results of a previous study of melatonin in a similar population (Smits et al. 2001), sample size calculation with the SPSS Sample Power 2.0 program showed that 26 subjects in the melatonin-treatment group and 26 subjects in the placebo-treatment group are needed to find a significant ($p < 0.05$; power 0.90; one tailed) advance (SD) sleep onset of 67 (85) min compared to an advance (SD) of 10 (46) min in the placebo group. When four subjects have to be excluded in each treatment group, 30 subjects can be considered to be enough to find a significant advance of sleep onset time. For four treatment groups, the planned sample size was 120 participants to be

recruited within 3 years.

Randomization

For this trial, a specialized internet software application (Medsys/De Nieuwe Coster/2004) was developed for randomization of participants, for calculation of the assigned dose (based on body weight), and for collection of sleep log data.

Patients were randomized in blocks of eight to keep possible seasonal time effects to a minimum.

During a visit with the neurologist, eligible patients were invited to participate in Meldos and, if willing, added to the database Medsys. Afterwards, the hospital pharmacist made a telephone call to check willingness, to make an appointment, and to randomize participants in Medsys. For this appointment, the hospital pharmacy prepared the appropriate trial medication and programmed the actigraph. During the visit, the hospital pharmacist handed over all materials (actigraph, salivettes, medication, and sleep log) and gave instructions.

Blinding

The assigned dose of melatonin was ad hoc prepared by one of the hospital pharmacy technicians in capsules, containing only microcrystalline cellulose (Bufa, Haarlem, The Netherlands) as placebo or containing melatonin (melatonin supplied by Pharma Nord, Denmark) in the appropriate calculated dosage and microcrystalline cellulose. The capsules were packed in unit dose strips, labeled with "Melatonine × mg" masked with an X to keep participants blind to the treatment allocation and subject number.

All participants, care providers, and investigators involved in the study were unaware of the treatment allocation.

Data analysis

The time measurements bed-, sleep onset, wake-up, and get-up time was expressed in 24 h/min.

The difference (shift) between baseline and treatment week for DLMO and mean sleep measures (SO, SOL, and TST) was calculated for each participant individually.

This way, we assessed individual responses to one of the treatments. These shifts were expressed in hours minute or minutes alone and the means per treatment group (mean (±SD)) were compared.

Comparisons of demographic and clinical characteristics between treatment groups were conducted using independent samples Student's *t* test for continuous variables with a normal distribution and Mann–Whitney *U* test when distribution was not normal, using SPSS 15.0 for Windows (SPSS Inc. 2006).

We wanted to differentiate between dosing effects and timing effect in the observed baseline-treatment week shifts of DLMO, SO, and SOL. Second-degree polynomial trend line estimation in Microsoft Office Excel 2003 (Microsoft Inc 1985–2003) and quadratic curve fit and two-tailed correlation analysis (Pearson and Spearman's r_s; SPSS 15.0) were used to assess timing effect. We studied all shifts as function of clock TOA and as function of circadian TOA. The circadian TOA is determined by defining DLMO as CT14 (Lewy et al. 1999); a clock TOA 2 h before DLMO means a circadian TOA of CT12.

Additionally, shifts of DLMO, SO, and SOL were studied in relation to the baseline individual circadian alignment, characterized by the phase angle difference (PAD). PAD reflects the time distance between baseline DLMO and baseline mid-time of sleep measured by actigraphy (Lewy et al. 2006).

We first analyzed the effect of melatonin treatment (different dosages) compared to placebo. Then,

we analyzed the differences between the different melatonin dosages. The latter analyses required exclusion of the placebo group as a considerable part of the correlation between dosage and outcome parameters is due to the difference between placebo and melatonin and not to differences between the different dosages of melatonin.

Wake-up time and total sleep time data are not analyzed since those data were found to be strongly influenced by fixed wake-up time.

Results

Baseline demographic and clinical characteristics

Initially, 88 children were found eligible to participate in this study. Due to several reasons (logistic problems due to shortage of actigraphs, holidays, social activities, attending high school, winter/summertime shift, unexpected family circumstances, and not allowed-co medication), 16 children were excluded before randomization (Fig. 1).

Fig. 1
Randomization scheme and justification of obtained outcome data (per group actigraphy and DLMO data obtained within the same group of included participants)
Based on the results of interim analyses of data of the 72 included children during a period of almost 3 years, the decision was made to finish recruitment instead of extending the trial over a longer period of time. The trial was conducted between May 2004 and February 2007.

Table 1 shows demographic characteristics of participants per treatment group, including bed and medication times; the participants were encouraged not to change bedtime and get-up time during the 2 weeks.

Table 1
Demographic characteristics of participants

Group		1	2	3	4
Dose (mg/kg)		0.05	0.1	0.15	0
n		16	19	18	17
Bodyweight	Mean	32	31	29	27
	Min	18	16	16	20
	Max	45	49	42	35
	SD	8	8	7	4
Dose	Mean	1.60	2.91	4.39	0
	Min	0.9	1.4	2.4	0
	Max	2.2	4.9	6.3	0
	SD	0.39	0.91	0.98	0

The mean (±SD) bedtime, measured by actigraphy, averaged over the four treatment groups was 20:41 (±0:41) h in the baseline week and 20:33 (±0:33) h in the treatment week. Mean get-up time was 07:40 (±0:23) h at baseline and 07:39 (±0:25) h in the treatment week. Both weeks are comparable in events (ordinary [school] weeks, no special days or activities); observed effects on sleep parameters can, therefore, be attributed to the melatonin administration. Get-up time was for most days, and most children clearly restricted due to school times and, therefore, excluded from evaluation as a treatment result. At baseline, there were no significant between-group differences in demographic variables.

Seventy-two children were randomized to one of the four treatment arms. Actigraphic data were collected from 67 participants, and DLMO was determined in 62 participants. Two children ended

participation after randomization but before the start with the trial medication: one boy because his mother was concerned that he would see the actigraph as a challenge to stay awake as long as possible, the second child because of diagnosis of mononucleosis infectiosa, just prior to starting.

Three children forgot to wear the actigraph the second week and were, for that reason, excluded from actigraphic data analysis.

The analysis was based on 5.3 (±0.87) nights (mean (±SD)).

Two children forgot to collect saliva samples and were, for that reason, excluded from DLMO analysis. Additionally, in six children, the DLMO could not be calculated because the first salivary level at 19:00 h was already higher than 4 pg/ml (DLMO reached), resulting in blank values. The five collected saliva samples were not suitable for determination of individual thresholds like Voultsios and Burgess did (Voultsios et al. 1997; Burgess et al. 2008) as the timing was aimed at determination of DLMO. For this reason, we adhered to the traditional definition of DLMO (saliva 4 pg/ml).

The parents of 25 (35%) children did report most results online; the other parents filled in the print out. These data were added to the database afterwards.

Seventy-two children received seven capsules each. Two children returned the medication unused. One child returned two capsules because his mother decided to advance the second DLMO test due to bedwetting (three nights in a row). Eight children returned zero capsules: five because of postponing the final DLMO test for social reasons, three because the remaining capsule was used afterwards because its effect was much appreciated.

TOA, as daily recorded in the sleep diary, was related to age and varied between 17:58 and 20:42 h (mean 19:08 ± 0:34 (SD); Table 1).

Co-medication

Ten participants reported use of co-medication during the trial, two in groups 1 and 4 and three in groups 2 and 3. Four participants used anti-histaminics: desloratadine, ketotifen, levocetirizine, hydroxyzine; five participants used methylphenidate. One participant used fluticason and salbutamol by inhalation, and one participant used valproic acid, trimethoprim, and lactitol.

DMLO, SO, and SOL results

DLMO was delayed by 16 min in the placebo group and was advanced by 50–90 min in the melatonin treatment groups. SO was advanced by 9 min in the placebo group and 51–66 min in the melatonin treatment groups. SOL was reduced by 12 min in the placebo group and by 43–54 min in the melatonin treatment groups.

Table 2 shows the comparison of three melatonin treatments (0.05, 0.1, and 0.15 mg/kg) with placebo.

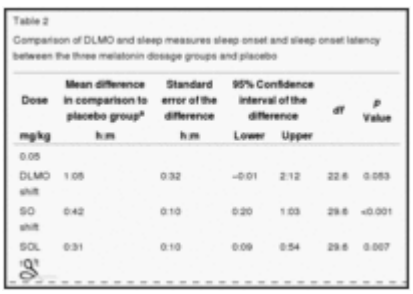

Table 2

Comparison of DLMO and sleep measures sleep onset and sleep onset latency between the three melatonin dosage groups and placebo

Dose	Mean difference in comparison to placebo group[a]	Standard error of the difference	95% Confidence interval of the difference		df	p Value
mg/kg	h:m	h:m	Lower	Upper		
0.05						
DLMO shift	1:05	0:32	−0:01	2:12	22.6	0.053
SO shift	0:42	0:10	0:20	1:03	29.6	<0.001
SOL	0:31	0:10	0:09	0:54	29.6	0.007

The DLMO advance in the 0.1 and 0.15 mg/kg treatment group was significantly ($p < 0.001$) different from placebo; the 0.05 mg/kg group did not reach significance ($p = 0.053$).

SO advanced in all three melatonin groups compared to placebo; the SO shift difference between melatonin treatment and placebo treatment is 42–56 min, which is significant ($p < 0.001$) for all melatonin groups.

SOL was reduced in all three melatonin groups compared to placebo. The difference between placebo treatment and melatonin treatment for SOL shift was 31–42 min, and the reduction of SOL differed significantly in all three treatment groups from placebo ($p = 0.007$, $p = 0.001$, and $p < 0.001$).

Dose–response relationship versus time–response relationship

The shifts of DLMO, SO, and SOL are visualized in Fig. 2a–c.

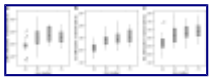

Fig. 2
a DLMO (threshold = 4 pg/ml) advance (individual differences between baseline and treatment week) in the four treatment groups. **b** SO shift (individual differences between baseline and treatment week) in the four treatment groups. **...**
Because no clear dose–response relationship was detected in all groups, the individual time of administration of melatonin relative to baseline DLMO were calculated (circadian TOA). Shifts of DLMO, SO, and SOL in the three groups with melatonin were plotted as function of clock TOA (Fig. 3a) and as function of circadian TOA (Fig. 3b). These figures demonstrate the relationship of the DLMO shift with circadian TOA and not with clock TOA. On the contrary, for SO and SOL shifts, the TOA relationship does not show distinct differences between clock TOA and circadian TOA.

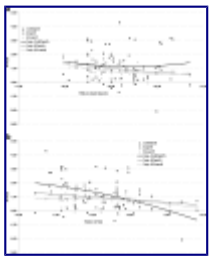

Fig. 3
a DLMO, SO, and SOL shifts with clock TOA in the three melatonin-treatment groups. **b** DLMO, SO, and SOL shifts with circadian TOA in the three melatonin-treatment groups
PAD was significantly correlated to the DLMO shift, but not to the SO and SOL shift (Fig. 4).

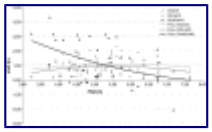

Fig. 4
DLMO, SO, and SOL shifts with PAD in the three melatonin-treatment groups
Curve fitting of DLMO shift (of the three melatonin groups) with TOA expressed in relative Circadian Time, with DLMO (CT14) as reference point = 0 according to Burgess et al. (2008) resulted in the small part of the expected PRC of melatonin ($R^2 = 0.175$, $p = 0.015$; Fig. 5a). Dosage differentiation did not result in distinct curves due to the small number of subjects per dose ($n = 16$–19).

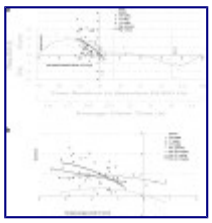

Fig. 5

a DLMO shift (individual differences between baseline and treatment week) with TOA related to baseline DLMO, for all groups, plotted on top of a 24-h phase response curve adapted from Burgess et al. (2008). **b** SO shift (individual differences between baseline **...**

Curve fitting of SO shift versus TOA in relation to baseline DLMO resulted in distinct curves for all groups (Fig. 5b). For the higher doses, a bigger shift was noted with an early TOA; for the TOA closer to the DLMO, this dose relationship disappeared.

In the bivariate correlation analysis, the dose was significantly correlated with all outcome parameters (DLMO, SO, and SOL shift), as was the circadian TOA, when tested in all treatment groups.

DLMO shift was correlated with SO shift and SOL shift as well (Spearman correlation $r_s = 0.38$, $p = 0.003$ and $r_s = 0.36$, $p = 0.05$). None of the sleep outcome parameters appeared to be significantly related to clock TOA, in contrast to the circadian TOA.

After exclusion of the placebo group from analysis, correlation of all sleep parameters with dosage disappeared, as did the previous association of the DLMO shift with SO shift and SOL shift (Table 3). After exclusion of placebo, correlation between SO shift and clock TOA became significant, in addition to the relation with circadian TOA. For SOL shift, exclusion of the placebo group resulted in an additional correlation with clock TOA and in disappearance of the correlation with the circadian TOA. All correlations with TOA are negative, indicating a larger shift when medication is taken earlier.

Table 3

Results of bivariate correlation analysis for dosage, PAD, TOA in clock time and in circadian time, and shifts of DLMO, SO, and SOL, tested for melatonin treatment groups 1–3 ($n = 46–53$)

	Dosage	PAD	Clock TOA	Circadian TOA	DLMO shift	SO shift
PAD	0.16 $p = 0.13$					
Clock TOA	−0.05 $p = 0.37$	−0.18 $p = 0.11$				
Circadian TOA	−0.10 $p = 0.26$	−0.65 $p < 0.001$	−0.32 $p = 0.012$			
DLMO shift	0.15 $p = 0.16$	0.37 $p = 0.005$	−0.09 $p = 0.28$	−0.33 $p = 0.022$		
SO shift	0.17	0.17	−0.35	−0.38	0.03	

Table 3

Results of bivariate correlation analysis for dosage, PAD, TOA in clock time and in circadian time, and shifts of DLMO, SO, and SOL, tested for melatonin treatment groups 1–3 ($n = 46–53$)

DLMO shift was significantly correlated to PAD and circadian TOA, and not to clock TOA (Table 3).

Adverse effects

The most common adverse events were red cheeks, red earlobes, and red eyes and yawning within an hour after administration ($n = 15$); pale looks, dizziness, and cold feelings (eight); headache (two); nausea and stomachache (one); and dizziness and nausea (one). Most of the adverse events wore off during the treatment week. Headache and stomachache were reported in the placebo group, not in the melatonin-treatment groups. The sleep-related adverse events (red cheeks or rather pale looks, cold feelings) and dizziness were reported in the three melatonin groups; the frequency was related to dosage (0.15:0.1:0.05 = 5:4:3). One participant ended the treatment period early due to bedwetting, attributed to the medication by his mother (0.05 mg/kg). Two other participants

reported enhanced urination during the evening and night (0.1 and 0.15 mg/kg).

Discussion

In children with chronic sleep onset insomnia, 1-week treatment with melatonin significantly advanced sleep onset and dim light melatonin onset by approximately 1 h and reduced sleep onset latency by approximately 35 min, compared to placebo. Surprisingly, there was, within the dosage range of 0.05–0.15 mg/kg, no dose–response relationship of melatonin and shifting of the sleep parameters or DLMO.

It is unlikely that the treatment duration of 1 week was too short to show differences in the efficacy between dosages. Data from earlier studies of melatonin effects on sleep parameters with duration of 5 weeks showed that as early as after the first treatment night, robust treatment effects emerged and that the effects remained stable during the following weeks (Van Geijlswijk et al. 2010).

There may be a point of diminishing returns at a dosage lower than the tested lowest dosage of 0.05 mg/kg. Hence, each additional increase in dosage beyond this dosage yields less and less additional response, until reaching a "ceiling effect," like the upper right part of a traditional dose–response curve. Another possibility is that the dose–response relationship reflects an "all-or-nothing" principle. That is, all dosages above a certain threshold dose induce similar magnitudes of responses, like the acetylcholine receptor-mediated innervations of motor cells (Ruff 1998). The absence of a dose–response relationship in this study is in line with findings in a sleep–EEG study where melatonin was administrated at 18:00 h in the dose range of 0.5–10 mg in six healthy adults (Stone et al. 2000).

In contrast, the timing of drug administration seems to have substantial influence on the treatment effect. TOA was recorded daily; the naturalistic design of this study allowed for some flexibility on this aspect. As a result of this, the average TOA on Friday and Saturday was later than the TOA on weekdays. When correcting for circadian TOA, the differences between the 0.05 mg/kg group and the other two dosing groups for mean DLMO shift disappear. This is at least partly due to the considerably wider range of DLMO–TOA interval values in the 0.05 mg/kg group that can be attributed to the extreme minimum and maximum results of the DLMO shift ([−2.04]–4.18) within this group.

From a pharmacokinetic point of view, one could argue that the lower the dosage, the shorter the interval between TOA and DLMO should be since melatonin has a very short elimination half-life in most individuals (between 35 and 45 min). Recently, the association between time of administration and dosage in relation to endogenous melatonin onset is made (Burgess et al. 2008). It is plausible that very low dosages (0.5 mg or less) given early (5 h before DLMO) are already cleared to below physiological levels before endogenous melatonin onset occurs, and we expect that no shift of DLMO will be observed (Burgess et al. 2008). This phenomenon might also have contributed to the nonsignificant DLMO shift observed in the 0.05 mg/kg group, since the maximum of DLMO–TOA interval was similar (low dosage to high dosage 3.27, 3.55, and 3.17 h) in all melatonin groups.

SO was significantly advanced by administration of exogenous melatonin. The magnitude of effect was not predicted by dosage but was significantly related to clock TOA and to circadian TOA. Especially, the correlation with clock TOA could imply that the effects on SO and SOL that we measured were induced by the direct soporific effects of melatonin rather than by a chronobiotic effect, comparable to the way traditional sedatives act.

There is a methodological difference between measuring the DLMO shift and measuring SO and SOL shifts. Post-treatment DLMOs are determined after a period of melatonin administration; but on the night of melatonin measurements, no exogenous melatonin is administrated. The DLMO shift is, therefore, not influenced by direct effects of administrated melatonin. This is in contrast to the effects on SO shift and SOL shift, which are influenced by melatonin administration on the

measurement nights. This might explain the relationship of PAD with DLMO shift, and not with SO and SOL shift, the DLMO shift reflecting exclusively chronobiotic effects. The soporific effect of melatonin improves SO and reduces SOL, which is why individuals with a PAD ≥6 still experience a SO and SOL shift, without a DLMO shift.

The children included all had late DLMOs. A long TOA–DLMO interval in this population will result in a large response to melatonin therapy, in DLMO shift, which is a demonstration of the chronobiotic mechanism, and in SO and SOL shift. In addition to the chronobiotic effect, soporific effects of melatonin will add to the size effect on SO and SOL. The effect of the same dosage of exogenous melatonin on SO in a normal population can be completely different since this DLMO–TOA interval will be shorter when taken at the same clock TOA. Melatonin administration at the TOA of traditional hypnotics confers risk for the TOA being later than DLMO, thus minimizing the potential for phase advancing the rhythm (Fig. 5a). This may be the mechanism behind the inefficacy of melatonin as an ordinary hypnotic. When timing is correct, the magnitude of effect on SO, SOL, and DLMO is not related to the dose in the threefold dose range we have studied. This supports earlier findings stressing the importance of measuring DLMO before starting melatonin treatment (Hoebert et al. 2009).

A number of potential limitations need to be noted. First, this trial assessed the effects of only 1-week treatment with melatonin. In children with sleep onset insomnia using melatonin, drug-holiday breaks during 1 week result in return of the former sleep pattern in more than 90% of the users (Hoebert et al. 2009). This implies that the chronobiotic effect can only be sustained with chronic treatment, although in children, the need for advancing sleep onset disappeared in 8% of the children after 4 years of treatment (Hoebert et al. 2009). For the report of adverse events, long-term studies need to be done. In fact, we did readdress the participants of this trial 1.5–4.6 years after inclusion and evaluated their experiences with prolonged therapy. We will report on this soon.

Second, the groups are small, 16–19 observations per group. Additionally, third, we should interpret all outcomes after correction for the multiple statistical comparisons of DLMO, SO, and SOL with the standard Bonferroni procedure. This procedure is under discussion for its usefulness and limitations, especially in small-numbered studies like this (Nakagawa 2004).This is why we finally decided to report all *p* values instead of reporting significance categories. Fourth, TOA in this study neither depended on applied dosage nor DLMO; TOA was determined in a naturalistic way instead. This caused a wide range of DLMO–TOA intervals, which might have hampered the effects, especially of the lowest dosage. Due to the double-blind dose assigning, a dose-related TOA was not even possible. In future study design, this relationship should be taken into account; for instance with lower doses, a smaller DLMO–TOA interval is strived for.

Strength of the present study is that we studied individual responses. This differs from most melatonin trials, where response consisted of the shift of means of the different treatment groups. We applied a naturalistic design for timed melatonin administration, related to desired bedtime, but with focus on maximizing the DLMO–TOA interval.

The current finding, that the effects of melatonin treatment on sleep–wake rhythm are not related to the dosage in the pharmacologic dosing range (>0.05 mg/kg) but rather to the time of administration relative to the endogenous melatonin rhythm, is highly suggestive of melatonin's chronobiotic properties instead of primarily hypnotic pharmacological properties.

In conclusion, we do not expect that dosages higher than 0.15 mg/kg will exert larger shifting effects (based on the present data and our clinical experience). On the contrary, we recommend that dosages higher than 0.05 mg/kg for children with chronic insomnia are not necessary and probably should be avoided. Whether clinically effective dosages should be expected in the range achieving physiological serum levels or at least in dosages lower than 0.05 mg/kg cannot be inferred from the present data. Further dose–response studies should be performed in order to find the lowest possible dosage of melatonin in children, in combination with the most appropriate time of administration. The issue of bioavailability should be taken into account in further studies, with the sublingual

tablet with ultralow dosages as an interesting candidate. Furthermore, additional long-term studies are needed to verify the safety of melatonin in children in the long run.

This study demonstrates that melatonin for treatment of chronic sleep onset insomnia in children is effective in a dosage of 0.05 mg/kg given 1–2 h before DLMO and before desired bedtime, resulting in 1-h shifts of DLMO and SO and a SOL reduction by 35 min.

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Toma de decisiones clínicas basadas en pruebas científicas

EVIDENCIAS EN PEDIATRÍA

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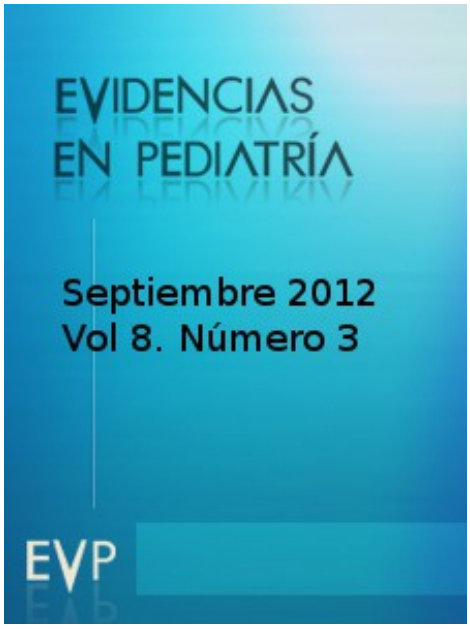

Marzo 2012. Volumen 8. Número 1

Tratamiento con melatonina en niños mayores y adolescentes con retraso del inicio del sueño

Autores: Barroso Espadero D, Ugarte Libano R.

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AAP | Del artículo al paciente:

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Palabras clave: terapia; niño; metaanálisis; melatonina; adolescente; trastornos del sueño del ritmo

circadiano; trastornos del sueño

Keywords: therapy; child; meta-analysis; melatonin; adolescent; sleep disorders, circadian rhythm; sleep disorders

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Escenario Clínico

Consultan unos padres porque su hijo de 12 años tiene problemas para quedarse dormido a una hora apropiada. No suele dormirse hasta la una de la madrugada, aunque se acueste sobre las diez de la noche. Es un niño sano sin antecedentes médicos relevantes (adenoidectomía a los tres años), le va bien en el colegio, no tiene problemas de comportamiento y es deportista. Exploración física sin nada llamativo: tensión arterial normal, índice de masa corporal en percentil 45, estadio de Tanner P2-3/G3. Tras evaluar los hábitos relacionados con horarios e higiene del sueño y realizar seguimiento durante tres semanas con agenda del sueño, nos encontramos con que al niño le cuesta quedarse dormido a la hora que le indican, pero una vez dormido el sueño nocturno no muestra problemas. Tiene que madrugar los días de colegio para acudir a un centro escolar emplazado a 70 km de su casa (hora de levantarse: 06:30) y es frecuente que presente síntomas de falta de sueño en la primeras horas de la mañana, pero solo los días de colegio. Por la tarde tiene dos horas diarias de actividades extraescolares. Suele pasar las horas previas a quedarse dormido conectado a Internet. Los padres creen que su hijo “necesita medicamentos para ayudarle a dormir”. Han oído hablar de la melatonina y han visto en Internet “que se está usando para el insomnio en los niños”.

Pregunta Clínica

¿Es eficaz la melatonina para el tratamiento del insomnio por retraso del inicio de sueño, en niños y adolescentes sanos?

Búsqueda Bibliográfica

Fecha de la búsqueda: 30/7/2011.

1. MEDLINE (PubMED/MEDLINE). Descriptores: Child; Female; Humans; Male; Melatonin/administration & dosage/therapeutic use/adverse effects; Sleep/drug effects/drug therapy/therapeutic use/therapy; Sleep Disorders/drug therapy; Sleep Initiation and Maintenance Disorders/drug therapy; Randomized Controlled Trials as Topic; Clinical Trials as Topic; Circadian Rhythm/drug therapy/ therapy; Sleep Deprivation/drug therapy.
2. Metabuscador TRIP. Estrategia de búsqueda: (sleep OR insomnia) AND (child* OR adolescen* OR peidatri*) AND melatonin, seleccionando la opción "title" y aplicando los siguientes filtros: "*systematic reviews*" y "*guidelines*".
3. EMBASE (1980-2011). Estrategia de búsqueda: (sleep disorders OR insomnia OR sleep) AND melatonin AND (children OR pediatric OR adolescent).
4. The Cochrane Library Plus (Register of Systematic Reviews): (MELATONIN OR MELATONINA) AND (SLEEP OR SLEEP DISORDER* OR INSOMNIA) AND (CHILD* OR PEDIATRI* OR ADOLESCEN*):TI.

Tras revisar las referencias recuperadas, se encuentran de interés para responder a nuestra pregunta, los siguientes artículos[1,2]:

- Van Geijlswijk IM, Korzilius HPLM, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. Sleep. 2010;33:1605-14[1].
- Van Geijlswijk IM, van der Heijden KB, Egberts AC, Korzilius HP, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT.

Psychopharmacology (Berl). 2010;212:379-91[2].

Resumen estructurado de los artículos seleccionados

Estudio 1: van Geijlswijk IM, Korzilius HPLM Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. SLEEP. 2010;33:1605-14[1].

Objetivo: valorar la eficacia y la seguridad de la melatonina exógena para adelantar el ritmo sueño-vigilia en pacientes con insomnio por retraso de fase de sueño.

Diseño: metaanálisis (MA) de ensayos clínicos aleatorizados (ECA) y controlados con placebo.

Fuentes de datos: PubMed, Embase y resúmenes de sociedades de sueño y cronobiología (1990-2009). No se aportaron los descriptores y estrategias de búsqueda empleados y se empleó el límite por idioma (inglés). Se revisaron las listas de referencias de los artículos. No se buscaron estudios no publicados.

Selección de los estudios: ECA, con doble cegamiento y controlados con placebo.

Criterios de inclusión: estar realizados en individuos con retraso de fase de sueño (SRF; *delayed sleep phase disorder* [SPD]) y reunir los siguientes requisitos: a) comparación de melatonina con placebo; b) resultados en salud expresados en, al menos, uno de los siguientes parámetros: inicio del ascenso de melatonina con la atenuación vespertina de la luz (d*im light melatonin onset* [DLMO]), hora de inicio del sueño (s*leep onset time* [SOT], hora de despertar (w*ake-up time* [WUT]), latencia de inicio de sueño (*sleep onset latency* [SOL], definida como el tiempo que transcurre desde que se acuesta y apaga la luz, con intención de dormir, hasta el momento en que realmente se inicia el sueño nocturno) y el tiempo total de sueño (TTS, tiempo transcurrido entre el SO y el WUT), y c) mención expresa de la relación entre momento de administración de la melatonina exógena y la hora correspondiente del ciclo del reloj interno circadiano. Se excluyeron estudios en pacientes con insomnio secundario y con patologías de base (salvo TDAH), estudios que investigaban otros resultados clínicos o que únicamente estudiaron parámetros bioquímicos.

Se aceptaba la presencia de medidas no medicamentosas habituales (higiene del sueño…) como cointervención. No se permitía el uso de otros medicamentos para el tratamiento del insomnio. De 182 estudios, se incluyeron nueve.

Extracción y síntesis de datos: realizada por alguno de los investigadores por separado, siendo revisadas posteriormente por otro distinto. La validez interna fue evaluada mediante la aplicación de la escala de Jadad y la puntuación obtenida en el cuestionario QA. De cada uno de los estudios se extrajeron datos correspondientes a variaciones tras intervención en los siguientes parámetros de sueño: DLMO, hora de inicio del sueño nocturno SO, WUT, SOL y TTS. Las diferencias de medias (DM) e intervalos de confianzas del 95% (IC 95%) extraídos para cada parámetro se presentan en figuras del metaanálisis. Otros datos seleccionados fueron los efectos adversos, dosis de melatonina, hora de administración del fármaco y duración del periodo de tratamiento.

La variable principal fue la medición de cambios obtenidos, antes/después de la intervención, para al menos uno de los parámetros de sueño enumerados anteriormente. Se calcularon las medias de las diferencias combinadas y sus correspondientes IC 95%. Para combinar los resultados se empleó un modelo estadístico de tipo aleatorio. Tanto en los estudios en paralelo como en los estudios cruzados se valoraron los cambios respecto al valor basal.

Evaluación de la validez interna: los nueve estudios incluidos en el MA estuvieron por encima del punto de corte de calidad (> 3) en la escala de Jadad. Las puntuaciones medias fueron: 4 sobre 5 en la escala de Jadad (intervalo 3-5) y 26 sobre 32 (intervalo 19-31) en la escala QA. La puntuación en la escala QA para los ECA pediátricos (ECAp) fue siempre ≥ 28 (intervalo: 28-31).

Resultados principales: cinco ECA solo incluyeron adultos, los otros cuatro fueron ECAp. Los ECAp[3,6] incluyeron 226 pacientes entre 6 y 14 años. Los tamaños de las muestras oscilaron entre 19 y 105. Los porcentajes de pérdidas variaron un 0-5%, si bien un ECAp[4] mostró un 11,4%. Cinco de los ECA del metaanálisis eran estudios cruzados (cuatro en adultos y un ECAp). En el ECAp, con un diseño cruzado, los participantes recibían melatonina o placebo durante dos periodos de diez días separados por un periodo de blanqueo de cinco días. Los otros tres ECA pediátricos fueron diseños en paralelo, con periodos de duración de la intervención de cuatro semanas. La cifra total de pacientes en los ECA pediátricos del metaanálisis con TDAH fue de ≥ 160 de los 226. El intervalo de horas de administración de melatonina fue muy amplio, y las dosis de este medicamento que se usaron fueron muy diversas.

Todos los ECAp mostraron que la melatonina conseguía mejores resultados que el placebo. Para la combinación de los ECAp, todos los parámetros menos uno (WUT) mostraron resultados estadísticamente significativos. Para la combinación de los estudios en adultos, los resultados de los siguientes parámetros no alcanzaron significación estadística: WUT, SOL y TTS. Los resultados promedios fueron: DLMO: acortamiento de 1,18 horas, SOT: acortamiento de 0,67 horas, WUT: acortamiento de 0,28 horas, SOL: acortamiento en 23,27 minutos, y TTS: incremento en 16,23 minutos (tabla 1).

Tabla 1. Los autores muestran en el metaanálisis los resultados de los parámetros consistentes en periodos de tiempo, expresados como horas decimales Mostrar/ocultar

La melatonina exógena en niños adelantó el comienzo del sueño (SO) una media de 38,4 minutos (IC 95%: 28,8 a 59,9) y disminuyó la latencia hasta el comienzo del sueño (SOL) una media de 23,27 minutos (IC 95%: 4,83 a 41,72).

El principal efecto adverso fue la aparición de cefalea. Otros fueron sensación de disminución de apetito y mareo[4,5].

Conclusión de los autores: la melatonina exógena resulta efectiva en trastornos por retraso de fase para lograr adelantos tanto en los ritmo de sueño-vigilia como en los ritmos de secreción de la melatonina endógena.

Conflicto de intereses/financiación: los autores declaran que el metaanálisis no estaba financiado por la industria y afirman no presentar ninguno de ellos conflicto de intereses.

Estudio 2: Van Geijlswijk IM, van der Heijden KB, Egberts AC, Korzilius HP, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. Psychopharmacology (Berl). 2010;212:379-91[2].

Objetivo: establecer, en niños con insomnio crónico de tipo de inicio de sueño (SOI crónico), la relación dosis-respuesta entre la administración de melatonina y las modificaciones en el sueño (adelantando el tiempo de SO/reduciendo el SOL).

Diseño: ECA, controlado con placebo y doble cegamiento.

Emplazamiento: centro de referencia especializado en trastornos del sueño-vigilia y de cronobiología del sueño (hospital de referencia) en Holanda.

Población de estudio: 72 niños con intervalo de 6 a 12 años y SOI crónico. Los pacientes fueron referidos desde consultas de Pediatría o Psiquiatría. No se explica con detalle el modo de selección.

Intervención: placebo frente a melatonina. Periodo de tratamiento de una semana (diseño paralelo).

Mediciones para las variables de resultado: los resultados valorados fueron la mejoría del insomnio de inicio del sueño: adelantamiento logrado para el SO, y acortamiento conseguido en la SOL. Se estudiaron otros aspectos adicionales como la repercusión de la mejora del sueño en el estado de ánimo.

Resultados: la melatonina logró adelantar el SO en los tres grupos con melatonina; el adelanto en la hora del SO fue de 42 a 56 minutos ($p < 0,001$). En cuanto al acortamiento del periodo de SOL, fue de 31 a 42 minutos (35 minutos cuando la melatonina se administró dos horas antes de la hora deseada para irse a dormir). En cuanto a la diferencia de efecto-dosis, con las tres dosis usadas en el estudio se encontraron reducciones, que fueron siempre significativas ($p = 0,007$, $p = 0,001$, y $p < 0,001$). La interrupción de los tratamientos durante una semana tuvo como resultado la desaparición de las mejoras, con retorno al patrón previo de SO y SOL hasta en el 90% de los pacientes tratados.

Conclusiones de los autores: el tamaño del efecto, adelantando el SO y acortando la SOL, logrado con el tratamiento con melatonina, aumenta con una hora de administración más temprana (en relación con el reloj circadiano).

Conflicto de intereses/financiación: melatonina fue proporcionada por Pharma Nord, Dinamarca.

Comentario Crítico

Justificación: se ha descrito la eficacia de la melatonina en el insomnio crónico (de inicio del sueño o de otra clase) en niños y adultos afectos de diferentes tipos de problemas médicos (trastornos del neurodesarrollo, trastornos psiquiátricos y déficits cognitivos). Sin embargo, hay pocos estudios acerca de la utilización de la melatonina en niños sanos, para tratar los trastornos crónicos de insomnio de inicio del sueño/SRF. A pesar de ello, su uso se ha extendido, incluso en niños. Por ello es necesario evaluar la eficacia y delimitar el papel terapéutico de la melatonina en niños y adolescentes con estos tipos de problemas de sueño.

Validez o rigor científico: aunque ninguno de los cuatro ECAp utilizó el diagnóstico de SRF como criterio de inclusión, se podía presuponer que muchos de los participantes incluidos podrían cumplir los requisitos diagnósticos de este trastorno. Por el contrario, en el ECA de Van Geijlswijk, sí se refleja el criterio de inclusión que se utilizó.

Para el MA solamente se analizaron los estudios que describieron la relación entre la hora de administración de la melatonina y el reloj interno circadiano (esto deja la duda de que podrían haberse ignorados estudios con información válida). Dos de los cuatro ECAp eran investigaciones en pacientes con SOI crónico y TDAH, en los otros dos ECAp se incluyeron porcentajes altos de participantes diagnosticados de TDAH: alrededor del 27 y el 50%, respectivamente.

Los autores del MA no ofrecen en el artículo la estrategia de búsqueda empleada ni los descriptores. La restricción por idioma, buscando solo artículos publicados en inglés, y la ausencia de intento de búsqueda para trabajos no publicados constituyen limitaciones claras del artículo.

El total de niños[3,6] del MA fue de 226 pacientes, lo que supone un número total de participantes más bien bajo. También era bajo el número de pacientes del ECA del segundo artículo[2].

En el MA, tres de los cuatro ECAp estuvieron realizados por un mismo grupo investigador y el primer autor de dos de los ECA[3,4] fue también uno de los autores del propio MA. Esto puede traducirse en un sesgo de selección.

Aunque la elección de estudios que usaban parámetros de evaluación directa del sueño parece adecuada para una investigación inicial de melatonina frente a placebo, también creemos que esos parámetros podrían considerarse como resultados subrogados o parciales. Los verdaderos efectos finales importantes, que sería necesario investigar también, deberían ser aquellos que correspondiesen a mejoría en las horas diurnas de vigilia obtenidas al mejorar el sueño (cognición, progreso en el aprendizaje y rendimiento escolar; mejora de la calidad general de vida; atención; comportamiento; desaparición de la somnolencia diurna…).

En los dos ECA de Smits, que incluyeron un número significativamente elevado de participantes diagnosticados con TDAH (la gran mayoría de ellos medicados con fármacos estimulantes), hubiera sido necesario haber realizado un análisis por subgrupos. Especialmente en el ECA de Smits 2003[4],

la falta de homogeneidad de los grupos arroja todo género de dudas sobre la validez externa de los resultados. La notable diferencia en los porcentajes de participantes con metilfenidato que presentaron los grupos (aproximadamente el doble en el grupo placebo) podría haber tenido como consecuencia la alteración de los resultados en una dirección: sobrestimar el efecto de la melatonina.

Es llamativa, en los ECA de niños con TDAH, la elevada frecuencia de comorbilidad. Como consecuencia de esto, las muestras de estos estudios no resultan representativas de la población real de niños con TDAH.

En el MA, las diferentes dosis fueron recogidas, pero no se realizó un análisis separado de su influencia en el efecto. No hay constancia de que se realizara un estudio de sensibilidad en el MA y no se ofrece información sobre estudio de homogeneidad.

Importancia clínica: los niños que recibieron melatonina en comparación con placebo tuvieron 26,9-63 minutos de adelanto del SO, y 8-42 minutos de reducción de la SOL. Este pequeño tamaño del adelanto obtenido en la hora de sueño deja dudas sobre la significancia clínica de este efecto.

El SO/SOT y la SOL son los parámetros válidos y útiles para responder a la pregunta clínica. El DMLO se puede considerar un valor útil en el laboratorio. El WUT o el TTS son medidas que dependen más de factores externos (horarios estrictos de levantarse por la mañana) que del propio efecto directo de la intervención.

Los resultados, en términos de mejoría en los parámetros de sueño, desaparecen después de finalizar periodos de tratamientos de corta duración (1-4 semanas).

Estos resultados también pueden conseguirse con medidas no farmacológicas habituales. Los ECA analizados, por lo general aportan los datos numéricos para conocer la dimensión de los retrasos reales de los participantes en la hora de SOT (únicamente Weiss *et al.*[6] informan en su ECA de una media 91,7 minutos de retraso en la SOL), pero es muy probable que la mayoría de los niños y adolescentes, por lo demás sanos, que nos consulten por SRF/SOL crónico, presenten retrasos superiores a dos o tres horas en días normales de colegio. Teniendo esto en cuenta, la melatonina parece perfilarse más bien como una herramienta opcional para estos insomnios, capaz de "aportar algo de ayuda" más que como "la solución" definitiva al problema. En realidad, alguno de estos ECA sirve para poder mostrar, para el caso de las medidas de higiene del sueño, un efecto de mayor tamaño que el de la intervención con melatonina[6], y el tamaño del efecto (por ejemplo, 30 minutos de adelanto del SO) puede ser algo estimable para la situación de algún niño concreto.

Aplicabilidad a la práctica clínica: el tratamiento con melatonina plantea interrogantes en cuanto la duración prolongada (EA, prolongación del efecto tras el periodo de tratamiento), pero también, para los periodos cortos. Entre las dudas no resueltas están:

1. El efecto beneficioso demostrado para la melatonina no parece permanecer en el tiempo. Desaparece cuando se retira el fármaco después de periodos de tratamiento de corta duración (< 1 mes)[2]. Un estudio posterior (sin control con grupo placebo) encuentra esto nuevamente[7].
2. En el MA se comenta la hipótesis de que la adecuación del momento de administración del fármaco (la hora administración apropiada) se relaciona con un mejor efecto logrado por la melatonina, en términos de adelanto del inicio del sueño (aunque no lo evidencian los resultados)[2]. En el ECA de Van Geijlswijk, esta correlación queda incluso demostrada por sus resultados. Como consecuencia de ello, los autores se postulan a favor de una administración más temprana del medicamento. Esta propuesta de administración temprana genera preocupación sobre la posibilidad, no descartada hasta ahora, de aparición de sopor y somnolencia como efecto indeseado de la melatonina, lo cual podría interferir con la capacidad de concentración adecuada que los niños mayores y adolescentes pueden requerir en las últimas horas de vigilia del día para estudiar y realizar tareas escolares. En los niños

diagnosticados con TDAH y tratamiento con metilfenidato, el adelanto propuesto en la hora de administración podría dar lugar a más solapamiento en el tiempo de la acción de ambos medicamentos.

Otro punto no resuelto es el de si la melatonina consigue lo mismo, en términos de adelanto del SOT, en escolares y adolescentes con retrasos pequeños, que en aquellos con retrasos mucho mayores. Dar respuesta a este interrogante tendría consecuencias clínicas decisivas, puesto que lo que realmente necesitamos saber los pediatras clínicos es qué resultado sería esperable en el subgrupo de pacientes que presenta retrasos más marcados (que son los que de verdad tienen el problema, y que son los que probablemente acudan a nuestras consultas preguntando por medicamentos para el insomnio). En los ECA pediátricos aquí valorados, el punto de corte en los criterios de inclusión se situó bastante bajo (a partir de 30 minutos de retraso del SOT). Cabe preguntarse, en aquellos que ya lograron con estrategias no farmacológicas correctas dejar reducido su retraso del inicio del sueño a solo media hora: ¿tienen estos pacientes un problema merecedor de tratar con fármacos? En futuros ECA será imprescindible investigar en aquellos niños, sanos por lo demás, pero con retrasos marcados en el SOT (lo que se podría conseguir elevando el umbral en los criterios de admisión, o realizando luego análisis de subgrupos).

El diagóostico del DSPD/SRF es debatido. El SRF basa en parte su descripción en elementos externos al individuo, en relación con exigencias del entorno (“incapacidad para dormirse a las horas que sería deseable para poder adaptarse a exigencias externas, poder despertarse a una hora matinal establecida como adecuada por horarios derivados de obligaciones”). Este hecho ha dado lugar a controversia sobre si, en realidad, en la mayoría de los casos de adolescentes con problemas de retraso de inicio del sueño, estos presentan una verdadera anormalidad biológica de los ciclos circadianos, o si se trata, áas bien, de la manifestación de la dificultad de niños y adolescentes, sanos por lo demás, para poder ponerse al día en la “deuda acumulada de sueño” contraída por situaciones, prologadas en el tiempo, de privación de las necesidades diarias de dormir. En la pubertad tiene lugar un retraso de sueño fisiológico; y también es frecuente durante la pubertad la aparición de retrasos del inicio del sueño relacionados con estilos de vida.

Las estimaciones de la prevalencia de niños (< 6 años) y adolescentes con dificultad para dormirse a las horas esperadas son tan elevadas como del 27%. Se informa de frecuencias de SOL > 30 minutos en al menos un 11%[8]. Otros autores comunican cifras estimadas alrededor del 7-10% de SRF en adolescentes[9]. La relativa falta de cifras y las diferencias entre estimaciones en la literatura puede que reflejen el solapamiento y la mezcla de problemas y definiciones diferentes (SOI crónico; retraso de fase fisiológico del adolescente; verdaderas alteraciones cronobiológicas del ritmo circadiano de la melatonina correspondiente al SRF; consecuencias de la privación prolongada por normas sociales impuestas…).

Para conocer el efecto de la melatonina en los niños adolescentes con retraso de inicio del sueño, son necesarios ECA bien diseñados y de un tamaño muestral apropiado. De esta forma, se podría responder a preguntas acerca de qué población podría beneficiarse, durante cuánto tiempo, y qué hora y dosis serían las más adecuadas.

Los resultados de estos estudios respaldan la posibilidad de usar la melatonina exógena, junto a otras medidas no farmacológicas, en escolares y adolescentes con SOI/SRF crónicos. Su uso puede plantearse, en determinados casos, durante menos de un mes, siempre que no se haya logrado un resultado suficientemente favorable después de aplicar de forma correcta las medidas no farmacológicas. Hay que informar del relativamente pequeño efecto demostrado.

La melatonina exógena debe restringirse a un pequeño subgrupo de pacientes. Su uso generalizado y masivo (teniendo en cuenta que la melatonina es una hormona con efectos multiorgánicos) no está justificado y, por este motivo, sería aconsejable mantener la clasificación de este fármaco como de dispensación obligatoria con receta médica. Los tratamientos con melatonina exógena deberían mantenerse bajo estricto control y supervisión médica, del pediatra de Atención Primaria o del

médico experto en sueño.

Resolución del Escenario

Se le recomienda usar las siguientes medidas no farmacológicas: a) evitar la exposición lumínica antes de acostarse (luces fuertes, ordenador, aparato de televisión, teléfonos móviles, videoconsolas, etc.); b) evitar ejercicio físico en las últimas horas de la tarde; c) técnicas de relajación antes de dormir; d) eliminar alguna actividad extracurricular prescindible (agenda sobrecargada); e) evitar en la tarde y noche la ingesta de bebidas que contengan cafeína. El baloncesto y las clases particulares finalizarán dentro de una semana (final de curso). En el próximo curso están de acuerdo en reducir las actividades extracurriculares (siempre antes de las 19:00 horas). Un colegio más cercano, o con un inicio de actividades escolares no tan temprano, modificaría la situación. Se informa del tamaño del beneficio que puede aportar la melatonina, de los puntos aún no aclarados, y de que actualmente no está disponible en España como fármaco bajo prescripción con receta. Los padres creen que puede interesarles añadir un ciclo de un mes con melatonina a las medidas recomendadas, si después del periodo de prueba aún el niño no se duerme antes de las 23:30. (un mes de tratamiento es suficiente para ellos durante los exámenes finales, aunque luego se restablezca la situación previa). Consideran que 30 minutos de adelanto del inicio del sueño puede suponer un incremento del 10% en el tiempo total de sueño. Se acuerdan seguimientos y controles.

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