

Insomnia and Daytime Sleepiness

ABSTRACTS

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- Blaicher W., 2000. Melatonin in postmenopausal females.
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Guidelines for prescribing melatonin.

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Ann Med. 1998 Feb;30(1):122-30.

Although compelling logic suggests that melatonin may be effective for a variety of disorders, there are few empirical clinical studies. The optimal dose of melatonin is not clear; most studies have used doses that produce supraphysiological blood levels. The timing of melatonin administration is important. Melatonin has few immediate side-effects except drowsiness, but the effects of chronic administration are unclear. Melatonin may be effective in reducing jet lag. In elderly patients with poor sleep and documented low melatonin production, melatonin may be helpful. In several studies, melatonin has been shown to shorten sleep latency. Further studies are needed to clarify the efficacy and safety of melatonin.

5-Hydroxytryptophan: a clinically-effective serotonin precursor.

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Altern Med Rev 1998 Aug;3(4):271-80

5-Hydroxytryptophan (5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of serotonin. Intestinal absorption of 5-HTP does not require the presence of a transport molecule, and is not affected by the presence of other amino acids; therefore it may be taken with meals without reducing its effectiveness. Unlike LT, 5-HTP cannot be shunted into niacin or protein production. Therapeutic use of 5-HTP bypasses the conversion of LT into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. 5-HTP is well absorbed from an oral dose, with about 70 percent ending up in the bloodstream. It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. In the CNS, serotonin levels have been implicated in the regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behaviour, and pain sensation. Therapeutic administration of 5-HTP has been shown to be effective in treating a wide variety of conditions, including depression, fibromyalgia, binge eating associated with obesity, chronic

headaches, and insomnia.

Melatonin in postmenopausal females.

Blaicher W, Speck E, Imhof MH, Gruber DM, Schneeberger C, Sator MO, Huber JC. w.blaicher@akh-wien.ac.at

Arch Gynecol Obstet. 2000 Feb;263(3):116-8.

There is little information about the interaction between melatonin, sexual steroids and neuroendocrine system in postmenopausal females, even if former research showed that melatonin is clearly involved in human physiology and pathophysiology. We evaluated the overnight urinary excretion of 6-sulfatoxymelatonin (6-SMT) using a radioimmunoassay in 60 postmenopausal women. The group has been divided into patients with insomnia (10), hyperprolactinemia (7), depression (9), obesity (7) and controls (27). Compared to controls 6-SMT values were significantly higher in depressive females. Patients with hyperprolactinemia showed a trend toward a significantly elevated average nocturnal melatonin concentration. Melatonin levels were significantly lower in patients with insomnia and obese postmenopausal females than in controls. Since previous studies described lower melatonin levels in postmenopausal than in premenopausal women, the indication of melatonin therapy, especially for sleep disorders in this collective, can be handled more generously. Melatonin should be prescribed restrictively in patients with depression and in those with hyperprolactinemia. The role of melatonin in obese females remains unclear.

Neurologic disorders responsive to folic acid therapy.

Botez MI, Cadotte M, Beaulieu R, Pichette LP, Pison C

Can Med Assoc J 1976 Aug 7;115(3):217-23

Six women aged 31 to 70 years had folate deficiency and neuropsychiatric disorders. The three with acquired folate deficiency were depressed and had permanent muscular and intellectual fatigue, mild symptoms of restless legs, depressed ankle jerks, diminution of vibration sensation in the legs, stocking-type hypoesthesia and long-lasting constipation; D-xylos absorption was abnormal. The bone marrow was megaloblastic in only one patient, and she and one other had atrophy of the jejunal mucosa. The third was a vegan. All three recovered after folic acid therapy. The other three were members of a family with the restless legs syndrome, fatigability and diffuse muscular pain. One also had subacute combined degeneration of the spinal cord and kidney disease but no megaloblastosis; she improved spectacularly after receiving large daily doses of folic acid. The other two also had minor neurologic signs, controlled with 5 to 10 mg of folic acid daily. Unrecognized and treatable folate deficiency (with low serum folic acid values but normal erythrocyte folate values) may be the basis of a well defined syndrome of neurologic, psychiatric and gastroenterologic disorders, and the restless legs syndrome may represent the main clinical expression of acquired and familial (or inborn) folate deficiency in adults.

Light, melatonin and the sleep-wake cycle

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J. Psychiatry Neurosci. (Canada), 1994, 19/5 (345-353)

Blood levels of the pineal hormone melatonin are high at night and low during the day. Its secretion is regulated by a rhythm-generating system located in the suprachiasmatic nucleus of the hypothalamus, which is in turn regulated by light. Melatonin is regulated not only by the circadian oscillator but acts as a darkness signal, providing feedback to the oscillator. Melatonin has both a soporific effect and an ability to entrain the sleep-wake rhythm. It also has a major role in regulating the body temperature rhythm. Melatonin rhythms are altered in a variety of circadian rhythm disorders. Melatonin treatment has been reported to be effective in treatment of disorders such as jet lag and delayed sleep phase syndrome.

Effect of melatonin in selected populations of sleep-disturbed patients.

Brusco LI, Fainstein I, Marquez M, Cardinali DP. Departamento de Fisiologia, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina.

Biol Signals Recept. 1999 Jan-Apr;8(1-2):126-31.

In an open pilot study on the efficacy of melatonin in the treatment of sleep disorders, patients with sleep disturbances alone, patients with sleep disturbances and signs of depression and patients with sleep disorders and dementia received 3 mg melatonin p.o. for 21 days, at bed time. After 2-3 days of treatment, melatonin significantly augmented sleep quality and decreased the number of awakening episodes in patients with sleep disturbances associated or not with depression. Estimates of next-day

alertness improved significantly only in patients with primary insomnia. Agitated behavior at night (sundowning) decreased significantly in dementia patients. In a second retrospective study, 14 Alzheimer's disease (AD) patients received 9 mg melatonin daily for 22-35 months. A significant improvement of sleep quality was found, while there were no significant differences between initial and final neuropsychological evaluation (Functional Assessment Tool for AD, Mini-Mental). The results indicate that melatonin can be useful to treat sleep disturbances in elderly insomniacs and AD patients.

Poisoning due to an over-the-counter hypnotic, Sleep-Qik (hyoscine, cyproheptadine, valerian).

Chan TY, Tang CH, Critchley JA. Department of Clinical Pharmacology, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin NT.

Postgrad Med J 1995 Apr;71(834):227-8

The clinical features and risk of hepatotoxicity of 'Sleep-Qik' (valerian dry extract 75 mg, hyoscine hydrobromide 0.25 mg, cyproheptadine hydrochloride 2 mg) were determined in 23 patients treated in our hospital between 1988 and 1991. The main clinical problems were central nervous system depression and anticholinergic poisoning. There was no clinical evidence of acute hepatitis in the 23 patients after taking an average of 2.5 g of valerian (range 0.5 to 12 g). There was no evidence of subclinical liver damage in 12 patients who had routine liver function tests performed approximately 6-12 hours after ingestion. Delayed onset of severe liver damage was excluded in 10 patients in whom a telephone follow-up was possible. However, subclinical liver dysfunction in the acute stage (onset after 12-24 hours) and in the intervening period after discharge from hospital could not be excluded. To establish the risk of hepatotoxicity in long-term users and in those taking an overdosage of valerian, a much larger study of longer duration with serial liver function tests is clearly needed.

Effects of intravenously administered vitamin B12 on sleep in the rat.

Chang HY; Sei H; Morita Y Department of Physiology, School of Medicine, University of Tokushima, Japan.

Physiol Behav (United States) Jun 1995, 57 (6) p1019-24

Vitamin B12 (VB12) has been reported to normalize the entrainment of circadian rhythms in the non-24-h sleep wake cycle and delayed sleep phase insomnia in humans. The purpose of this work was to clarify whether the peripheral administration of VB12 has any sleep-promoting effect on the sleep-wake rhythm in freely moving rats. After a baseline day of saline infusion, VB12 (500 micrograms/kg/day) was administered continuously for 4 days via the jugular vein. Polysomnographic recordings were carried out concurrently. In both the light and the 24-h periods, the amount of non-rapid eye movement (NREM) sleep increased significantly on VB12-days 2 and 3, while the amount of REM sleep increased significantly on VB12-day 2. In the light period, the increase in NREM sleep was due to increased duration of the episode, while the tendency to an increase in REM sleep was due to an increased number of episodes. Changes in the diurnal sleep-wake rhythm tended to appear in the earlier light period. The serum B12 concentrations in the VB12 group were 40 times higher than in controls. These findings suggest that peripherally infused VB12 has promoting effects on the rat's sleep, especially in the light period.

Rapid reversal of tolerance to benzodiazepine hypnotics by treatment with oral melatonin: A case report

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European Neuropsychopharmacology (Netherlands), 1997, 7/2 (157-160)

A 43 year old woman had suffered from insomnia for the past 11 years and was being treated with benzodiazepines. All attempts to stop benzodiazepine treatment resulted in withdrawal symptoms and a renewal of the insomnia. Treatment with 1 mg of controlled release melatonin enabled the patient to completely cease any benzodiazepine use within two days, with an improvement in sleep quality and no side effects. Examination of urinary 6- sulphatoxymelatonin levels before the melatonin treatment indicated that the levels were very low and lacked the typical circadian rhythm of excretion. Reexamination of 6-sulphatoxymelatonin levels during melatonin treatment revealed the existence of a normal circadian rhythm of excretion. This case may suggest that some of the people suffering from insomnia and addicted to benzodiazepines may successfully undergo withdrawal from these drugs and improve their sleep by means of treatment with melatonin. The results of this single case study warrant further investigation of a larger population by means of a double-blind placebo-drug study.

Use of slow-release melatonin in treatment-resistant depression.

Dalton EJ, Rotondi D, Levitan RD, Kennedy SH, Brown GM. Depression Clinic, Centre for Addiction and Mental Health (CAMH-Clarke), Toronto, Ont.

OBJECTIVE: To examine antidepressant augmentation with and hypnotic effects of slow-release melatonin (SR-melatonin) in patients with treatment-resistant depression. **DESIGN:** Open-label trial. **SETTING:** Tertiary care outpatient depression clinic. **PATIENTS:** Nine outpatients who had failed to respond to 2 or more 8-week trials of antidepressant medication. **INTERVENTIONS:** Patients received SR-melatonin 5 mg per day for the first 2 weeks and 10 mg per day for the final 2 weeks, in addition to their antidepressant medication. **OUTCOME MEASURES:** Structured Clinical Interview for DSM-IV, Axis 1 Disorders, Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory, Response Style Questionnaire, sleep and fatigue measures. **RESULTS:** One patient was excluded after 1 week because of the development of a mixed affective state. In the remaining 8 patients there was a 20% mean decrease in HRSD scores after 4 weeks of treatment, with no individual achieving an improvement of 50% or more. There was a 36% decrease on the 3-item HRSD related to insomnia, with 4 of 8 patients showing at least a 50% improvement on this measure. The greatest decrease in insomnia occurred during the last 2 weeks of the study, following the increase in dosage to 10 mg per day of SR-melatonin. Patients also reported significantly lower levels of fatigue post-treatment. **CONCLUSIONS:** SR-melatonin may be a useful adjunct for sleep, but does not substantially augment existing antidepressant therapies in some patients with treatment-resistant depression.

Effect of sustained nocturnal transbuccal melatonin administration on sleep and temperature in elderly insomniacs.

Dawson D, Rogers NL, van den Heuvel CJ, Kennaway DJ, Lushington K. Centre for Sleep Research, Faculty of Humanities and Social Sciences, University of South Australia, Queen Elizabeth Hospital, Woodville, Australia.

J Biol Rhythms. 1998 Dec;13(6):532-8.

Previous research has suggested a role for the pineal hormone melatonin in the control of the body's sleep-wake and thermoregulatory systems. In the elderly population, there have been reports of decreased nighttime secretion of melatonin and suggestions that this may, in turn, be responsible for the increased incidence of sleep disorders reported by this age group. On this basis, it has been suggested that augmented nocturnal melatonin levels may improve sleep quality in age-related sleep disorders. Following screening assessments, 12 elderly (> 55 years) subjects with sleep maintenance insomnia were treated with either 0.5 mg transbuccal melatonin or a placebo for two sessions of 4 consecutive nights, at least 3 days apart. Subjects self-selected lights-out times, and sleep was assessed using standard polysomnographic (PSG) measures. Body temperature was measured continually from 2100 to 0700 h, and sleep quality was assessed from PSG variables measured. Nightly urine samples were assayed for the melatonin metabolite 6-sulfatoxy-melatonin (aMT.6S). Compared to the placebo, transbuccal melatonin administration significantly increased mean nocturnal aMT.6S excretion (mean \pm SEM: 194.2 \pm 16.5 vs. 42.5 \pm 7.7 nmol). In addition, there was a significant reduction in core body temperature relative to the placebo condition ($p < .05$). However, sustained transbuccal melatonin treatment had no positive significant effect on any PSG measure of sleep quality. The results from the present study suggest that sustained nocturnal administration of melatonin, in the low pharmacological range, might be of limited clinical benefit in this subject population.

[Melatonin in sleep rhythm disorders after cerebral stroke] [Article in Polish]

Domzal TM, Kaca-Orynska M, Zaleski P. Kliniki Neurologicznej CSK WAM w Warszawie.

Pol Merkuriusz Lek. 2000 Jun;8(48):411-2.

Small doses of melatonin were administered to 30 patients with day/night rhythm disorders, after cerebral stroke. Psychotropic drugs administered before did not bring any clinical improvement. In evaluation of melatonin the time till falling asleep, sleep duration, anxiety and the following day activity were taken into account. Good results were observed in majority of patients, concerning falling asleep and sleep were obtained continuity. The melatonin is a safe and worth drug in sleep rhythm disorders in patients after cerebral stroke.

Critical evaluation of the effect of valerian extract on sleep structure and sleep quality.

Donath F, Quispe S, Diefenbach K, Maurer A, Fietze I, Roots I. Institute of Clinical Pharmacology, Charite University Medical Center, Humboldt University of Berlin, Germany.

Pharmacopsychiatry 2000 Mar;33(2):47-53

A carefully designed study assessed the short-term (single dose) and long-term (14 days with multiple dosage) effects of a valerian extract on both objective and subjective sleep parameters. The investigation was performed as a randomised, double-blind, placebo-controlled, cross-over study. Sixteen patients (4 male, 12 female) with previously established psychophysiological insomnia (ICSD-code 1.A.1.), and with a median age of 49 (range: 22 to 55), were included in the study. The main inclusion criteria were reported

primary insomnia according to ICSD criteria, which was confirmed by polysomnographic recording, and the absence of acute diseases. During the study, the patients underwent 8 polysomnographic recordings: i.e., 2 recordings (baseline and study night) at each time point at which the short and long-term effects of placebo and valerian were tested. The target variable of the study was sleep efficiency. Other parameters describing objective sleep structure were the usual features of sleep-stage analysis, based on the rules of Rechtschaffen and Kales (1968), and the arousal index (scored according to ASDA criteria, 1992) as a sleep microstructure parameter. Subjective parameters such as sleep quality, morning feeling, daytime performance, subjectively perceived duration of sleep latency, and sleep period time were assessed by means of questionnaires. After a single dose of valerian, no effects on sleep structure and subjective sleep assessment were observed. After multiple-dose treatment, sleep efficiency showed a significant increase for both the placebo and the valerian condition in comparison with baseline polysomnography. We confirmed significant differences between valerian and placebo for parameters describing slow-wave sleep. In comparison with the placebo, slow-wave sleep latency was reduced after administration of valerian (21.3 vs. 13.5 min respectively, $p < 0.05$). The SWS percentage of time in bed (TIB) was increased after long-term valerian treatment, in comparison to baseline (9.8 vs. 8.1% respectively, $p < 0.05$). At the same time point, a tendency for shorter subjective sleep latency, as well as a higher correlation coefficient between subjective and objective sleep latencies, were observed under valerian treatment. Other improvements in sleep structure - such as an increase in REM percentage and a decrease in NREM1 percentage - took place simultaneously under placebo and valerian treatment. A remarkable finding of the study was the extremely low number of adverse events during the valerian treatment periods (3 vs. 18 in the placebo period). In conclusion, treatment with a herbal extract of *radix valerianae* demonstrated positive effects on sleep structure and sleep perception of insomnia patients, and can therefore be recommended for the treatment of patients with mild psychophysiological insomnia.

Melatonin and aging: relevance for clinical approach?

Fauteck JD, Dittgen M, Farker K, Hoffmann A, Hoffmann H, Lerchl A, Wittkowski W.

J. Endocrinol. Invest. 1999; 22(10, Suppl): 90-1.

No abstract available.

Improvement of sleep quality by controlled-release melatonin in benzodiazepine-treated elderly insomniacs

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Archives of Gerontology and Geriatrics (Ireland), 1997, 24/2 (223-231)

Benzodiazepines are widely used in the elderly population for the initiation of sleep. However, very frequently, complaints about poor sleep maintenance persist despite benzodiazepine treatment. Melatonin, a hormone produced by the pineal gland at night, is involved in the regulation of the sleep/wake cycle. Melatonin production decreases with age and can also be inhibited by benzodiazepines. We have recently reported on the association between insomnia and impaired melatonin output in the elderly. In the present study we have investigated the efficacy of melatonin replacement therapy in improving sleep in 21 elderly subjects who have been taking benzodiazepines and had low melatonin output. In a randomized, double-blind, crossover designed study the subjects were treated for three weeks with 2 mg per night of controlled-release melatonin and for 3 weeks with placebo, 2 h before desired bedtime with a 1-week washout period between treatment periods. Subjects' sleep was assessed by wrist actigraphy. Melatonin treatment significantly increased sleep efficiency and total sleep time and decreased wake after sleep onset, sleep latency, number of awakenings and fragmental index, as compared to placebo. The results of our study indicate that melatonin replacement therapy can improve sleep quality in the elderly and that the beneficial effects are augmented in the presence of benzodiazepines.

Improvement of sleep equality in elderly people by controlled-release melatonin

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Lancet (United Kingdom), 1995, 346/8974 (541-544)

Melatonin, produced by the pineal gland at night, has a role in regulation of the sleep-wake cycle. Among elderly people, even those who are healthy, the frequency of sleep disorders is high and there is an association with impairment of melatonin production. We investigated the effect of a controlled-release formulation of melatonin on sleep quality in 12 elderly subjects (aged 76 (SD 8) years) who were receiving various medications for chronic illnesses and who complained of insomnia. In all 12 subjects the peak excretion of the main melatonin metabolite 6-sulphatoxymelatonin during the night was lower than normal and/or delayed in comparison with non-insomniac elderly people. In a randomised, double-blind, crossover study the subjects were treated for 3 weeks with 2 mg per night of controlled-release melatonin and for 3 weeks with placebo, with a week's washout period. Sleep quality was objectively

monitored by wrist actigraphy. Sleep efficiency was significantly greater after melatonin than after placebo (83 (SE 4) vs 75 (3)%, $p < 0.001$) and wake time after sleep onset was significantly shorter (49 (14) vs 73 (13) min, $p < 0.001$). Sleep latency decreased, but not significantly (19 (5) vs 33 (7) min, $p = 0.088$). Total sleep time was not affected. The only adverse effects reported were two cases of pruritus, one during melatonin and one during placebo treatment; both resolved spontaneously. Melatonin deficiency may have an important role in the high frequency of insomnia among elderly people. Controlled-release melatonin replacement therapy effectively improves sleep quality in this population.

Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach.

Garfinkel D, Zisapel N, Wainstein J, Laudon M. Aging Research and the Department of Internal Medicine, The E. Wolfson Medical Center, Holon, Israel.

Arch Intern Med. 1999 Nov 8;159(20):2456-60.

BACKGROUND: Benzodiazepines are the most frequently used drug for the treatment of insomnia. Prolonged use of benzodiazepine therapy is not recommended. However, many patients, particularly older patients, have difficulties discontinuing therapy. Melatonin, a hormone that is produced at night by the pineal gland, promotes normal sleep in humans and augments sleep induction by benzodiazepine therapy. **OBJECTIVE:** To assess whether the administration of melatonin could facilitate the discontinuation of benzodiazepine therapy in patients with insomnia. **METHODS:** Thirty-four subjects receiving benzodiazepine therapy were enrolled in the 2-period study. In period 1, patients received (double-blinded) melatonin (2 mg in a controlled-release formulation) or a placebo nightly for 6 weeks. They were encouraged to reduce their benzodiazepine dosage 50% during week 2, 75% during weeks 3 and 4, and to discontinue benzodiazepine therapy completely during weeks 5 and 6. In period 2, melatonin was administered (single-blinded) for 6 weeks to all subjects and attempts to discontinue benzodiazepine therapy were resumed. Benzodiazepine consumption and subjective sleep-quality scores were reported daily by all patients. All subjects were then allowed to continue melatonin therapy and follow-up reassessments were performed 6 months later. **RESULTS:** By the end of period 1, 14 of 18 subjects who had received melatonin therapy, but only 4 of 16 in the placebo group, discontinued benzodiazepine therapy ($P = .006$). Sleep-quality scores were significantly higher in the melatonin therapy group ($P = .04$). Six additional subjects in the placebo group discontinued benzodiazepine therapy when given melatonin in period 2. The 6-month follow-up assessments revealed that of the 24 patients who discontinued benzodiazepine and received melatonin therapy, 19 maintained good sleep quality. **CONCLUSION:** Controlled-release melatonin may effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality.

The therapeutics of melatonin: a paediatric perspective.

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Brain Dev. 2000 Jun;22(4):213-7.

The production of melatonin by the pineal gland and its functions are considered, and then its possible uses in the treatment of children. Institutionalized children, and those with severe learning disorders, often have irregular sleep-wake patterns, and there is evidence that melatonin can result in improvement to the benefit of both the child and the carers. The affected children can become less irritable, calmer, happier, and content. Also they may socialize better and become more attentive, with an improvement in their cognitive abilities. Another group of children who are likely to suffer from disturbed sleep are those who are visually handicapped. Melatonin given in the evening can improve their sleep patterns, and often their performance. No important side-effects have been reported. It is generally accepted that if a child is liable to epileptic seizures sleep deprivation may well exacerbate them. There is some evidence from clinical trials that in that event melatonin can be helpful. There are many other problems in which it is claimed that treatment with melatonin is justifiable. These are mentioned, but further confirmatory studies are needed in most of them. There is no doubt that melatonin can effect the circadian system, and shift the sleep-wake cycle; and that there are situations in which this can be desirable.

[Effectiveness of nasal CPAP-treatment (continuous positive airway pressure)]. [Article in German]

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Ther Umsch 2000 Jul;57(7):444-8

Nasal continuous positive airway pressure (n-CPAP) is an effective treatment for the obstructive sleep apnea syndrome (OSAS). It is currently regarded as the first line therapy for OSAS. The principal indication for n-CPAP treatment is daytime sleepiness. Nasal-CPAP improves daytime sleepiness dramatically in severe cases and the effect is objectively measurable with the multiple sleep latency test (MSLT). It is noteworthy that n-CPAP also improves symptoms, subjective daytime sleepiness, cognitive function, IQ, mood, quality of life and driving ability already in patients with mild sleep apnea with an apnea/hypopnea index (AHI) between 5 and 15 per hour of sleep during overnight polysomnography. Although not yet 100% robust, there is clear evidence that patients with

OSAS have an increased frequency of systemic hypertension. Some early and imperfect studies suggest that CPAP reduces cardiovascular and cerebrovascular outcomes; however unequivocal evidence that n-CPAP reduces mortality is still awaited. There is now good evidence that treatment with n-CPAP reduces the two- to sevenfold increased risk of road accidents of untreated patients with OSAS. In summary, there exists abundant evidence today that n-CPAP is an efficient therapy for symptomatic patients with the obstructive sleep apnea syndrome. A trial with n-CPAP is therefore justified in all symptomatic patients. Based on the large number of randomized controlled trials of n-CPAP a therapeutic trial is indicated even in only mildly symptomatic patients with OSAS. Nasal-CPAP use and outcomes of therapy can be improved by provision of an intensive CPAP-education and support program.

Melatonin - a chronobiotic and soporific hormone

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Archives of Gerontology and Geriatrics (Ireland), 1997, 24/2 (167-173)

In this report we review evidence that melatonin, a hormone produced by the pineal gland during the hours of darkness, plays a major role in the synchronization of the sleep/wake cycle. The production of melatonin is regulated by a structure located in the hypothalamus called the suprachiasmatic nucleus (SCN). The activity of the SCN is strongly affected by changes in illumination and, as a consequence, melatonin levels are high during darkness and low in the light and it, therefore, reflects the cycle. Changes in sleep/wake patterns are among the hallmarks of biological aging. Complaints of difficulty in initiating and maintaining sleep, and daytime drowsiness, are more common in the elderly than in any other age group. In this report, we review evidence that impaired melatonin secretion is associated with sleep disorders in old age. Circulating melatonin levels have been found to be significantly lower in elderly insomniacs than in age-matched controls, and their onset and peak times delayed. In view of these findings, we investigated the effects of melatonin treatment on melatonin-deficient insomnia in the elderly. From the results of our study, it seems likely that melatonin replacement therapy may be beneficial in the initiation and maintenance of sleep in this population.

Melatonin replacement therapy of elderly insomniacs

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Sleep (USA), 1995, 18/7 (598-603)

Changes in sleep-wake patterns are among the hallmarks of biological aging. Previously, we reported that impaired melatonin secretion is associated with sleep disorders in old age. In this study we investigated the effects of melatonin replacement therapy on melatonin-deficient elderly insomniacs. The study comprised a running-in, no-treatment period and four experimental periods. During the second, third and fourth periods, subjects were administered tablets for 7 consecutive days, 2 hours before desired bedtime. The tablets were either 2 mg melatonin administered as sustained-release or fast-release formulations, or an identical-looking placebo. The fifth period, which concluded the study, was a 2-month period of daily administration of 1 mg sustained-release melatonin 2 hours before desired bedtime. During each of these five experimental periods, sleep-wake patterns were monitored by wrist-worn actigraphs. Analysis of the first three 1-week periods revealed that a 1-week treatment with 2 mg sustained-release melatonin was effective for sleep maintenance (i.e. sleep efficiency and activity level) of elderly insomniacs, while sleep initiation was improved by the fast-release melatonin treatment. Sleep maintenance and initiation were further improved following the 2-month 1-mg sustained-release melatonin treatment, indicating that tolerance had not developed. After cessation of treatment, sleep quality deteriorated. Our findings suggest that for melatonin-deficient elderly insomniacs, melatonin replacement therapy may be beneficial in the initiation and maintenance of sleep.

Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study.

Hornyak M, Voderholzer U, Hohagen F, Berger M, Riemann D. Department of Psychiatry and Psychotherapy, Albert-Ludwigs-University, Freiburg, Germany.

Sleep 1998 Aug 1;21(5):501-5

Periodic limb movements during sleep (PLMS), with or without symptoms of a restless legs syndrome (RLS), may cause sleep disturbances. The pharmacologic treatments of choice are dopaminergic drugs. Their use, however, may be limited due to tolerance development or rebound phenomena. Anecdotal observations have shown that oral magnesium therapy may ameliorate symptoms in patients with moderate RLS. We report on an open clinical and polysomnographic study in 10 patients (mean age 57 +/- 9 years; 6 men, 4 women) suffering from insomnia related to PLMS (n = 4) or mild-to-moderate RLS (n = 6). Magnesium was administered orally at a dose of 12.4 mmol in the evening over a period of 4-6 weeks. Following magnesium treatment, PLMS associated with arousals (PLMS-A) decreased significantly (17 +/- 7 vs 7 +/- 7 events per hour of total sleep time, p < 0.05). PLMS without arousal were also moderately reduced (PLMS per hour of total sleep time 33 +/- 16 vs 21 +/- 23, p = 0.07). Sleep efficiency improved from

75 +/- 12% to 85 +/- 8% ($p < 0.01$). In the group of patients estimating their sleep and/or symptoms of RLS as improved after therapy ($n = 7$), the effects of magnesium on PLMS and PLMS-A were even more pronounced. Our study indicates that magnesium treatment may be a useful alternative therapy in patients with mild or moderate RLS-or PLMS-related insomnia. Further investigations regarding the role of magnesium in the pathophysiology of RLS and placebo-controlled studies need to be performed.

Sleep-promoting and hypothermic effects of daytime melatonin administration in humans.

Hughes RJ, Badia P. Bowling Green State University, Ohio, USA.

Sleep. 1997 Feb;20(2):124-31.

Sleep-promoting and hypothermic effects of orally administered melatonin during the daytime were assessed using a placebo-controlled, double-blind, cross-over design. Following a 7-hour nighttime sleep opportunity, healthy young male subjects ($n = 8$) were given either a placebo or one of three doses of melatonin (1 mg, 10 mg, and 40 mg) at 1000 hours. Sleep was polygraphically assessed in a 4-hour sleep opportunity from 1200 to 1600 hours. All doses of melatonin significantly shortened the latency to sleep onset. Melatonin also significantly increased total sleep time and decreased wake after sleep onset (WASO). Sleep following melatonin administration contained significantly more stage 2 and less stage 3-4, while stage 1 and rapid eye movement (REM) sleep were unaffected. In addition to the sleep-promoting effects, melatonin completely suppressed the normal diurnal rise of core body temperature. These data suggest that melatonin may be an effective method of promoting sleep for individuals attempting to sleep during their subjective day, such as shiftworkers and individuals rapidly traveling across multiple time zones.

Melatonin treatment of chronic sleep disorders.

Jan, J.E., Espezel, H.

Dev. Med. Child Neurol. 1995 Mar; 37(3): 279-80.

No abstract available.

Use of melatonin in the treatment of paediatric sleep disorders.

Jan JE, O'Donnell ME. University of British Columbia, Developmental Paediatrics, and Visually Impaired Program, Sunny Hill Health Centre, Vancouver, Canada.

J Pineal Res. 1996 Nov;21(4):193-9.

A group of Vancouver health professionals, including the authors, have studied the use of oral melatonin in the treatment of chronic sleep disorders in children with disabilities since the Fall of 1991. This review article is based on the first 100 patients, half of whom were visually impaired or blind. Children with neurological, neuropsychiatric, and developmental disabilities are predisposed to chronic sleep-wake cycle disturbances. Disorders such as blindness, deaf-blindness, mental retardation, autism, and central nervous system diseases, among others, diminish the ability of these individuals to perceive and interpret the multitude of cues for synchronizing their sleep with the environment. Melatonin, which benefitted slightly over 80% of our patients, appears to be a safe, inexpensive, and a very effective treatment of sleep-wake cycle disorders. The oral dose of fast release melatonin taken at bed-time ranged from 2.5 mg to 10 mg. Side effects or the development of tolerance have not been observed. Since the causes of sleep difficulties are extremely variable, not all children are candidates for treatment. For successful melatonin treatment, clinical experience is required, and the influences of other health problems and medications need to be considered. Further clinical and laboratory research in this field is imperative because melatonin treatment offers enormous health, emotional, social, and economic benefits to society, especially since multidisabled children with chronic sleep difficulties do not respond well to current therapeutic regimes.

Melatonin effects on sleep, mood, and cognition in elderly with mild cognitive impairment.

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J Pineal Res. 1998 Oct;25(3):177-83.

The effects of immediate-release melatonin on circadian rest-activity profiles, cognition, and mood were investigated in ten elderly individuals with self-reported sleep-wake disturbances. Melatonin (6 mg), administered 2 hr before habitual bedtime, enhanced the rest-activity rhythm and improved sleep quality as observed in a reduction in sleep onset latency and in the number of transitions from sleep to wakefulness. However, total sleep time was not significantly increased nor was wake within sleep significantly reduced. The ability to remember previously learned items improved along with a significant reduction in depressed moods. No side

effects or contraindications were reported by any of our participants during the 10 day trials. These data suggest that melatonin can safely improve some aspects of sleep, memory, and mood in the elderly in short-term use.

Does exogenous melatonin improve day sleep or night alertness in emergency physicians working night shifts?

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Ann Emerg Med 1998 Jun;31(6):699-704

STUDY OBJECTIVE: To determine whether exogenous melatonin improves day sleep or night alertness in emergency physicians working night shifts. **METHODS:** In a double-blind, placebo-controlled crossover trial, emergency physicians were given 10 mg sublingual melatonin or placebo each morning during one string of nights and the other substance during another string of nights of equal duration. During day-sleep periods, subjective sleep data were recorded. During night shifts, alertness was assessed with the use of the Stanford Sleepiness Scale. Key outcome comparisons were visual analog scale scores for gestalt night alertness and for gestalt day sleep for the entire string of nights. **RESULTS:** We analyzed data from 18 subjects. Melatonin improved gestalt day sleep ($P = .3$) and gestalt night alertness ($P = .03$) but in neither case was the improvement statistically significant. Of 13 secondary comparisons, 9 showed a benefit of melatonin over placebo; none showed a benefit of placebo over melatonin. **CONCLUSION:** Exogenous melatonin may be of modest benefit to emergency physicians working night shifts.

Melatonin treatment for rhythm disorder.

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Psychiatry Clin Neurosci. 1998 Apr;52(2):262-3.

We tried melatonin treatment in two patients with non-24 h sleep-wake syndrome, who did not respond to treatments by vitamin B12, bright light therapy, or hypnotics. In one patient, melatonin 5-10 mg improved difficulty in falling asleep and in waking, although it failed to improve the sleep-wake rhythm. In another patient, melatonin 3 mg successfully changed the sleep-wake rhythm from free-running pattern to delayed sleep phase pattern. However, melatonin re-administration after a 4-month drug-free interval failed to improve his free-running sleep-wake rhythm. These results suggest that melatonin acted as a sleep inducer in one patient and as a phase setter in the other, although the effect on the latter patient was transient.

Folates: supplemental forms and therapeutic applications.

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Altern Med Rev 1998 Jun;3(3):208-20

Folates function as a single carbon donor in the synthesis of serine from glycine, in the synthesis of nucleotides from purine precursors, indirectly in the synthesis of transfer RNA, and as a methyl donor to create methylcobalamin, which is used in the re-methylation of homocysteine to methionine. Oral folates are generally available in two supplemental forms, folic and folinic acid. Administration of folinic acid bypasses the deconjugation and reduction steps required for folic acid. Folinic acid also appears to be a more metabolically active form of folate, capable of boosting levels of the coenzyme forms of the vitamin in circumstances where folic acid has little to no effect. Therapeutically, folic acid can reduce homocysteine levels and the occurrence of neural tube defects, might play a role in preventing cervical dysplasia and protecting against neoplasia in ulcerative colitis, appears to be a rational aspect of a nutritional protocol to treat vitiligo, and can increase the resistance of the gingiva to local irritants, leading to a reduction in inflammation. Reports also indicate that neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome.

[Non-24-hour sleep-wake syndrome]. [Article in Japanese]

Kohsaka M. Sapporo Hanazono Hospital.

Nippon Rinsho 1998 Feb;56(2):410-5

The sleep-wake cycle in non-24-hour sleep-wake syndrome is longer than 24 hours. Patients go to bed a little bit later each day and then can not fall asleep and wake up at the usual time. The same sleep patterns and free running rhythms in healthy subjects have been seen in temporal isolation. The mechanism of this syndrome has not been clarified, but several factors have been proposed as follows: 1) the weakness of Zeitgeber 2) decrease of sensitivity to Zeitgeber 3) the period of the circadian system is much longer

than 24 hours. Vitamin B12 and melatonin were reported to be effective in treating this syndrome.

Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation.

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Mov Disord. 1999 May;14(3):507-11.

REM sleep behavior disorder (RBD) is clinically impressive by virtue of its vigorous sleep behaviors usually accompanying vivid, striking dreams. The main feature of the disorder, REM sleep without muscle atonia, has been shown in a variety of diseases; therefore, the disorder might possibly be underestimated. In an open-labeled trial, we treated six consecutive RBD patients over a 6-week period with 3 mg melatonin given within 30 minutes before bedtime. There was a dramatic clinical improvement in five of the six patients within a week which extended beyond the end of treatment for weeks or months. A second polysomnogram performed 6 weeks after the beginning of treatment showed a significant tendency toward normalization of the percentage of REM sleep, a significant reduction of 30-second epochs, scored as REM sleep without muscle atonia, a significant reduction of stage-shifts in REM, and a significant reduction in epochs considered as movement time in REM. All other sleep parameters were not changed consistently. We hypothesize that internal desynchrony might be a part of the underlying pathophysiology in RBD. Our data might give first evidence to the hypothesis that exogenous melatonin, administered to patients with internal desynchrony at the time of the maximal rise of melatonin secretion, might increase the overall amplitude of the circadian pacemaker by reentraining the suprachiasmatic nucleus and thereby restore circadian driven rhythms, one of them being the circadian modulation of REM sleep.

Melatonin effects in a patient with severe REM sleep behavior disorder: case report and theoretical considerations.

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Neuropsychobiology. 1997;36(4):211-4.

REM sleep behavior disorder (RBD) is so far a possibly underestimated yet well-described sleep disorder. Its major impact is the vigorous sleep behavior that often results in injuries to the patient himself or to people sleeping nearby. We treated a 64-year-old male with a clinically and polysomnographically confirmed diagnosis of RBD with 3 mg melatonin, which led to a significant reduction of motor activity during sleep, as measured by actigraphy ($p < 0.0001$ in all analyzed movement parameters), and a full clinical recovery over a 5-month treatment period. RBD phenomena gradually returned after melatonin administration was stopped. After 2 months' treatment, polysomnography showed no major changes except an increase of REM sleep (13 vs. 17% of sleep period time) and a better preservation of REM-sleep-associated muscle atonia. Our results suggest that melatonin might be able to reinforce REM sleep in RBD patients by enhancing its active inhibition of motor activity.

Daytime melatonin administration in elderly good and poor sleepers: effects on core body temperature and sleep latency.

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Sleep. 1997 Dec;20(12):1135-44.

Melatonin has been shown to have hypnotic and hypothermic effects in young adults and has been proposed as treatment for insomnia. However, the hypnotic and thermoregulatory effects of melatonin remain to be simultaneously investigated for aged good and poor sleepers. The aim of this study was to explore the short-term effects of exogenous oral daytime melatonin on core body temperature, sleep latency, and subjective vigor and affect in aged women. Twelve sleep maintenance insomniacs and 10 good sleeping postmenopausal female subjects [mean (SD) age = 65.2 (7.4) years] participated in a double-blind, crossover study in which they received a capsule containing either melatonin (5 mg) or a placebo at 1400 hours. Continuous core body temperature and hourly multiple sleep latency tests (MSLT) were collected from 1100-2030 hours. Self-reported estimates of global vigor (sleepiness) and affect were collected prior to each MSLT using visual analog scales. Comparison of good and poor sleepers failed to reveal any significant differences in core body temperature, sleep latency, or subjective vigor and affect. However, for both groups combined, melatonin administration [absolute postadministration mean (SEM) = 36.9 (0.05) degrees C] significantly lowered core body temperature compared with placebo [37.1 (0.05) degrees C]. Similarly, melatonin administration significantly reduced latency to stage 1 (SOL1) and stage 2 (SOL2) [absolute postadministration mean SOL1 = 20.1 (1.7) and SOL2 = 20.7 (1.6) minutes] compared with placebo [SOL1 = 24.3 (1.2) and SOL2 = 25.2 (1.1) minutes]. Treatment had no significant effect on either vigor or affect. Overall, our results suggest that although short-term exogenous oral daytime melatonin has significant hypothermic and hypnotic effects in aged women, the size of the effects is modest.

The hypnotic effects of melatonin treatment on diurnal sleep in humans.

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Psychiatry Clin Neurosci. 1999 Apr;53(2):243-5.

This study investigated the hypnotic effects of 10 mg melatonin and placebo, which were administered at 10.00 h, according to a single-blind crossover design, on an 8-h diurnal sleep from 11.00 to 19.00 h, following a full night of sleep. The subjects were six healthy male students, each of whom underwent polysomnography and rectal temperature monitoring. Melatonin treatment significantly increased total sleep time in diurnal sleep (403.2 ± 72.8 min and 258.5 ± 118.3 min, $P < 0.001$). As to changes in rectal temperature during diurnal sleep, however, there were no significant differences between the melatonin and placebo conditions. Thus, these results indicated that melatonin administered at 10.00 h had direct hypnotic effects on diurnal sleep.

Complex effects of melatonin on human circadian rhythms in constant dim light.

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J Biol Rhythms. 1997 Oct;12(5):467-77.

In humans, the pineal hormone melatonin can phase shift a number of circadian rhythms (e.g., "fatigue", endogenous melatonin, core body temperature) together with the timing of prolactin secretion. It is uncertain, however, whether melatonin can fully entrain all human circadian rhythms. In this study, the authors investigated the effects of daily melatonin administration on sighted individuals kept in continuous very dim light (< 8 lux) with attenuated sound and ambient temperature variations but with knowledge of clock time for two periods of 30 days. In these circumstances, the majority of individuals free run with a mean period of 24.3 h. In a double-blind, randomized crossover design, subjects received 5 mg melatonin at 20:00 h on Days 1 to 15 (Melatonin 1st) followed by placebo on Days 16 to 30 (Placebo 2nd) or vice versa (Placebo 1st, Melatonin 2nd) during Leg 1 with treatment reversed in Leg 2. The variables measured were melatonin (as 6-sulphatoxymelatonin), rectal temperature, activity, and sleep (actigraphy and logs). In the experiment, 9 of the 10 subjects free ran with Placebo 1st, whereas Melatonin 1st stabilized the sleep-wake cycle to 24 h in 8 of 10 individuals. In addition, 2 individuals showed irregular sleep with this treatment. In some subjects, there was a shortening of the period of the temperature rhythm without synchronization. Melatonin 2nd induced phase advances (5 of 9 subjects), phase delays (2 of 9 subjects), and stabilization (2 of 9 subjects) of the sleep-wake cycle with subsequent synchronization to 24 h in the majority of individuals (7 of 9). Temperature continued to free run in 4 subjects. Maximum phase advances in core temperature were seen when the first melatonin treatment was given approximately 2 h after the temperature acrophase. These results indicate that melatonin was able to phase shift sleep and core temperature but was unable to synchronize core temperature consistently. In the majority of subjects, the sleep-wake cycle could be synchronized.

Serum melatonin kinetics and long-term melatonin treatment for sleep disorders in Rett syndrome.

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Brain Dev. 1999 Jan;21(1):59-62.

We studied the circadian rhythm of serum melatonin levels in two patients with classical Rett syndrome having severe sleep disorders; serum melatonin levels were measured before and during melatonin treatment using radioimmunoassay. Patient 1 had a free-running rhythm of sleep-wake cycle from 3 years of age. At the age of 4 years, the peak time of melatonin was delayed 6 h compared to normal control and the peak value was at the lower limit. Patient 2 had a fragmented sleep pattern accompanied by night screaming from 1 year and 6 months of age. At the age of 10 years, the peak time of melatonin secretion was normal but the peak value was at the lower limit. These patients were given 5 mg melatonin orally prior to bedtime. Exogenous melatonin dramatically improved the sleep-wake cycle in patient 1. In patient 2, exogenous melatonin showed a hypnotic effect but early morning awakenings occurred occasionally. When melatonin treatment was stopped, the sleep disorders recurred and re-administration of 3 mg melatonin was effective in both patients. The effect was maintained over 2 years without any adverse effects. These findings suggest that sleep disorders in patients with Rett syndrome may relate with an impaired secretion of melatonin.

Dehydroepiandrosterone sulfate (DHEA-S) and psychiatric and laboratory measures of frailty in a residential care population.

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Previous reports have found low levels of dehydroepiandrosterone sulfate (DHEA-S) in association with frailty in elderly patients. The mechanisms underlying these associations are not known. Therefore, psychiatric symptoms and disorders that are common in frail elderly patients were correlated with DHEA-S levels in a convenience sample selected from a nursing home population. Low DHEA-S levels were associated with high degrees of self-rated disability and insomnia. In women, low DHEA-S levels were also associated with increased numbers of pain sites. However, cognitive impairment was associated with higher DHEA-S levels in women. Thus, in frail elderly patients, there are contradictory relationships between DHEA-S and neuropsychiatric measures of frailty (cognitive impairment, disability, insomnia, and number of pain sites), and there may also be gender differences in these relationships.

Daily melatonin intake resets circadian rhythms of a sighted man with non-24-hour sleep-wake syndrome who lacks the nocturnal melatonin rise

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Psychiatry and Clinical Neurosciences (Japan), 1997, 51/3 (121-127)

Effects of daily melatonin intake on the circadian rhythms of sleep and wakefulness, rectal temperature and plasma cortisol were examined in a sighted man who had suffered from the non-24-hour sleep-wake syndrome. The subject lacked the nocturnal melatonin rise in plasma, but showed robust circadian rhythms in rectal temperature and plasma cortisol. The sleep-wake rhythm free-ran with a period longer than 24 hours. Daily melatonin intake at 21:00 h concentrated sleep episodes in the nocturnal period (24:00-8:00 h), and increased the length of the episodes. A single oral dose (3 mg) of melatonin increased plasma melatonin levels to about 1300 pg/mL within one hour and remained at pharmacological levels for approximately 6 hours. The trough of rectal temperature and the circadian rise of plasma cortisol were fixed to the early morning. A higher dose of melatonin (6 mg) did not improve the general feature. After the cessation of melatonin intake, the sleep-wake rhythm began to free-run together with the circadian rhythms in rectal temperature and plasma cortisol. It is concluded that daily intake of melatonin at early night time resets the circadian rhythms in a sighted man who lacked the nocturnal melatonin rise and showed free running circadian rhythms in routine life.

Melatonin treatment for circadian rhythm sleep disorders.

Okawa M, Uchiyama M, Ozaki S, Shibui K, Kamei Y, Hayakawa T, Urata J. Department of Psychophysiology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Chiba, Japan.

Psychiatry Clin Neurosci. 1998 Apr;52(2):259-60.

We administered 1-3 mg melatonin to 11 patients (eight men, three women, aged 16-46 years) with circadian rhythm sleep disorders; nine with delayed sleep phase syndrome and two with non-24-hour sleep-wake syndrome. Sleep logs were recorded throughout the study periods and actigraph and rectal temperature were monitored during treatment periods. Melatonin was administered 1-2 h before the desirable bedtime for expected phase-shifting, or 0.5-1 h before habitual bedtime for gradual advance expecting an hypnotic effect of the melatonin. Melatonin treatments were successful in 6/11 patients. Timing and dose of melatonin administration, together with its pharmacological properties for circadian rhythm sleep disorders, should be further studied.

Physical activity and personal characteristics associated with depression and suicide in American college men.

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Acta Psychiatr Scand Suppl 1994;377:16-22

Among Harvard alumni aged 35-74 in 1962 or 1966, incidence rates of physician-diagnosed depression, together with suicide rates, were examined during a 23-27-year follow-up period, by antecedent physical activity habits and other personal characteristics. A total of 387 first attacks of depression developed among 10,201 alumni who survived through 1988; 129 suicides occurred among 21,569 alumni during follow-up through 1988. Depression rates were lower among the physically active and sports players, higher among cigarette smokers, unrelated to alcohol consumption, and higher among alumni reporting such personality traits as insomnia, exhaustion, cyclothymia, and self-consciousness. Suicide rates were largely unrelated to antecedent physical activity and alcohol consumption, higher among smokers, and substantially higher among men reporting the personality traits that predicted increased rates of depression.

Relationship of mood disturbance to cigarette smoking status among 252 patients with a current mood disorder.

J Clin Psychiatry 2001 May;62(5):319-24

BACKGROUND: The relationship between cigarette smoking and mood has received increasing attention. This retrospective study evaluated the relationship between mood disturbance and cigarette smoking status among patients with a current mood disorder. The association between level of nicotine dependence and severity of mood disturbance was also evaluated among current smokers. **METHOD:** Retrospective data for 252 patients (63.5% male, 85.0% white) admitted for treatment of a mood disorder at the San Diego Veteran Affairs Mental Health Clinical Research Center between November 1988 and June 1997 were studied. All current cigarette smokers at admission (N = 126) were matched with nonsmokers (N = 126) on the primary DSM-IV Axis I mood disorder diagnosis, admission status (inpatient or outpatient), gender, age (+/- 5 years), and ethnicity. The Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory, and the Profile of Mood States (POMS) were administered to patients on admission. Conditional logistic regression analysis for matched sets with a backward elimination was used to identify factors independently predictive of current smoking status. **RESULTS:** A greater number of cups of coffee consumed per day ($p = .002$), a history of alcoholism ($p = .004$), and higher POMS fatigue subscale scores ($p = .007$) were predictive of current smoking status. Among current smokers, the HAM-D terminal insomnia item was positively associated with mean number of cigarettes smoked per day ($p = .012$). **CONCLUSION:** Cigarette smoking should be addressed in the treatment of patients with a current mood disorder. Smokers experience greater levels of fatigue than nonsmokers. In addition, higher cigarette consumption levels are associated with mild-to-severe symptoms of terminal insomnia.

Melatonin treatment in an institutionalised child with psychomotor retardation and an irregular sleep-wake pattern.

Pillar G, Etzioni A, Shahar E, Lavie P. Pediatrics Department A, Rambam Medical Center, Haifa, Israel.

Arch Dis Child. 1998 Jul;79(1):63-4.

An institutionalised 13 year old girl with psychomotor retardation suffered from an irregular sleep-wake pattern. Multiple measurements of urinary sulphatoxy-melatonin (aMT6) concentrations were abnormally low, without any significant day-night differences. Administration of exogenous melatonin (3 mg) at 18:00 resulted in increased nocturnal urinary aMT6 concentrations and improvements in her sleep-wake pattern. Melatonin may help disabled children suffering from sleep disorders.

Effect of melatonin on tinnitus.

Rosenberg SI, Silverstein H, Rowan PT, Olds MJ. Ear Research Foundation, Sarasota, Florida 34239, USA.

Laryngoscope. 1998 Mar;108(3):305-10.

OBJECTIVE: Evaluate melatonin as a treatment for subjective tinnitus. **STUDY DESIGN:** Randomized, prospective, double-blind, placebo-controlled crossover trial. Patients were given 3.0 mg melatonin, which was taken nightly for 30 days followed or preceded by a placebo nightly for 30 days, with a 7-day washout period between medications. **SETTING:** Outpatient, private, neurotology practice. **PATIENTS:** Thirty patients with subjective tinnitus. **MAIN OUTCOME MEASURES:** Tinnitus matching, Tinnitus Handicap Inventory (THI), patient questionnaire and interview. **RESULTS:** The average pretreatment THI score was 33.91 as compared with 26.43 after the placebo and 26.09 after melatonin. The difference in the THI scores between melatonin and placebo treatment were not statistically significant. The average pretreatment THI score for patients who reported overall improvement with melatonin was statistically higher ($P = 0.02$) than the average pretreatment THI score for patients who reported no improvement with melatonin. Among subjects reporting difficulty sleeping attributable to their tinnitus, 46.7% reported an overall improvement after melatonin compared with 20.0% for placebo ($P = 0.04$). There was also a statistically significant difference in improvement with melatonin for those patients with bilateral tinnitus compared with those with unilateral tinnitus ($P = 0.02$). **CONCLUSION:** Melatonin has been shown to be useful in the treatment of subjective tinnitus. Patients with high THI scores and/or difficulty sleeping are most likely to benefit from treatment with melatonin. In light of its minimal side effects, melatonin should be a part of the physician's armamentarium in the treatment of tinnitus.

Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms?

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Sleep. 1997 Oct;20(10):908-15.

Differing conclusions regarding the sleep-promoting effects of melatonin may be the result of the broad range of doses employed

(0.1-2000 mg), the differing categories of subjects tested (normal subjects, insomniac patients, elderly, etc.), and the varying times of administration (for daytime vs. nighttime sleep). We conclude that melatonin may benefit sleep by correcting circadian phase abnormalities and/or by a modest direct soporific effect that is most evident following daytime administration to younger subjects. We speculate that these effects are mediated by interactions with specific receptors concentrated in the suprachiasmatic nucleus (SCN) that result in resetting of the circadian pacemaker and/or attenuation of an SCN-dependent circadian alerting process.

[Melatonin--a natural hypnotic?] [Article in German]

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Wien Klin Wochenschr. 1997 Oct 3;109(18):714-21.

The hypnogenic effects of melatonin are well documented in human pharmacological studies in normal volunteers after daytime parenteral and oral administration of pharmacological, supraphysiological and physiological doses. The findings after evening administration are not so unequivocal. From the clinical point of view, melatonin proved effective in double-blind, placebo-controlled trials in 2 types of sleep disorder: 1) as a chronobiotic in circadian rhythm sleep disorders such as jet lag-syndrome, shift-worker sleep disorder, delayed sleep phase syndrome and non-24-hour sleep-wake disorder; 2) as a hypnotic for insomnia in elderly patients with a relative melatonin deficit. Interactions with other psychotropic drugs are described and a potential indication in polymorbid patients with concomitant insomnia and sleep-related breathing disorders is suggested. More controlled studies are necessary on the effects, therapeutic efficacy and tolerability of melatonin in the treatment of the many different sleep disorders.

Melatonin--the key to the gate of sleep.

Shochat T, Haimov I, Lavie P. Sleep Laboratory, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa.

Ann Med. 1998 Feb;30(1):109-14.

This article reviews the evidence that melatonin, a hormone produced by the pineal gland during the dark hours, plays a major role in the regulation of the sleep-wake cycle. In recent years, our laboratory has been involved in a large-scale project aimed at investigating the role of endogenous melatonin in sleep-wake regulation and the effects of nonpharmacological levels of melatonin on sleep. Based on our finding on the precise coupling between the endogenous nocturnal increase in melatonin secretion and the opening of the nocturnal sleep gate, we propose that the role of melatonin in the induction of sleep does not involve the active induction of sleep, but is rather mediated by an inhibition of a wakefulness-producing mechanism in the central nervous system. Our studies also suggest that exogenously administered melatonin may be beneficial in certain types of insomnia that are related to disturbances in the normal secretion of the hormone.

Behavioural effects of *Passiflora incarnata* L. and its indole alkaloid and flavonoid derivatives and maltol in the mouse.

Soulimani R, Younos C, Jarmouni S, Bousta D, Misslin R, Mortier F. Laboratoire d'Ethnobotanique et de Pharmacologie, Université de Metz, France.

J Ethnopharmacol 1997 Jun;57(1):11-20

Lyophilised hydroalcoholic and aqueous extracts of the aerial parts of *Passiflora incarnata* L. (Passifloraceae) (Passion-flower), as well as chemical constituents of the plant, indole alkaloids (harman, harmine, harmaline, harmol, and harmalol) maltol and flavonoids (orientin, isoorientin, vitexin and isovitexin) were assessed for behavioral effects in mice. The accordance with the traditional use of *P. incarnata*, psychotropic properties were confirmed by some behavioral tests in mice. The anxiolytic properties of hydroalcoholic extract were confirmed at 400 mg/kg by the increase of rears and steps climbed in the staircase test (non-familiar environmental test), and the increase in locomotion and time spent in light side in the light/dark box choice test (non-familiar environmental test). The sedative properties of aqueous extract were confirmed at 400 g/kg by decrease of rears and steps climbed in the staircase test and the decrease of rears and locomotion in the free exploratory test. Moreover, the aqueous extract induced sleep in mice after treatment with a sub-hypnotic dose of pentobarbital.

Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag.

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Chronobiol Int 1998 Nov;15(6):655-66

To compare the impact of various dosage forms of melatonin and placebo on jet lag symptoms, 320 volunteers who had flights over

6 to 8 time zones were recruited for a double-blind, randomized, placebo-controlled study. The volunteers received either melatonin 0.5-mg fast-release (FR) formulation, melatonin 5-mg FR formulation, melatonin 2-mg controlled-release (CR) formulation, or placebo. The study medication was taken once daily at bedtime during 4 days after an eastward flight. The volunteers completed the Profile of Mood States (POMS), sleep log, and symptoms questionnaires once daily and the Karolinska Sleepiness Scale (KSS) three times daily prior to departure and during the 4 days of medication intake postflight. A total of 234 (73.1%) participants were compliant and completed the study. The FR melatonin formulations were more effective than the slow-release formulation. The 5-mg FR formulation significantly improved the self-rated sleep quality ($p < .05$), shortened sleep latency ($p < .05$), and reduced fatigue and daytime sleepiness ($p < .05$) after intercontinental flight. The lower physiological dose of 0.5 mg was almost as effective as the pharmacological dose of 5.0 mg. Only the hypnotic properties of melatonin, sleep quality and sleep latency, were significantly greater with the 5.0-mg dose. **Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes.**

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Int J Gynaecol Obstet. 1999 Dec;67(3):169-74.

OBJECTIVE: To evaluate the degree of psychological dysfunction and levels of stress hormones in postmenopausal women with climacteric syndromes and effect of Korean red ginseng (RG) on them. **METHODS:** ACTH, cortisol and DHEA-S in peripheral blood from 12 postmenopausal women with climacteric syndromes or 8 postmenopausal women without any climacteric syndrome were measured before and 30 days after treatment with daily oral administration of 6 g RG. Blood samples were collected in the early morning on the bed-rest. In postmenopausal women with climacteric syndromes such as fatigue, insomnia and depression, psychological tests using the Cornell Medical Index (CMI) and the State-Trait Anxiety Inventory (STAI) were performed before and 30 days after treatment with RG. **RESULTS:** CMI score as well as anxiety (A)-state in STAI score in postmenopausal women with climacteric syndromes was significantly higher than that without climacteric syndrome, while DHEA-S levels in postmenopausal women with climacteric syndromes were about a half of those without climacteric syndrome. Consequently, cortisol/DHEA-S (C/D) ratio was significantly higher in postmenopausal women with climacteric syndromes than in those without climacteric syndrome. When postmenopausal women with climacteric syndromes were treated with daily oral administration of 6 g RG for 30 days, CMI and STAI A-state scores decreased within normal range. Although the decreased DHEA-S levels were not restored to the levels in postmenopausal women without climacteric syndrome, the C/D ratio decreased significantly after treatment with RG. **CONCLUSIONS:** Improvement of CMI and STAI scores in postmenopausal women suffering climacteric syndromes, particularly fatigue, insomnia and depression, by RG seemed to be brought about in part by effects of RG on stress-related hormones as shown by a decrease in C/D ratio.

Role of magnesium sulfate in postoperative analgesia.

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Anesthesiology 1996 Feb;84(2):340-7

BACKGROUND: N-methyl-D-aspartate antagonists may play a role in the prevention of pain. An assessment was made of the effect of the physiologic N-methyl-D-aspartate antagonist magnesium on analgesic requirements, pain, comfort, and quality of sleep in the postoperative period.

METHODS: In a randomized, double-blind study, 42 patients undergoing elective abdominal hysterectomy with general anesthesia received 20% magnesium sulfate or saline (control) 15 ml intravenously before start of surgery and 2.5 ml/h for the next 20 h. Postoperative morphine requirement was assessed for 48 h using patient-controlled analgesia. Maximum expiratory flow (peak flow), pain at rest and during peak flow, and discomfort were evaluated up to the 48th postoperative hour, and 1 week and 1 month after surgery. Insomnia was evaluated after the first and second postoperative nights.

RESULTS: Compared to control subjects, magnesium-treated patients consumed less morphine during the first 48h ($P < 0.03$), which was most pronounced during the first 6 h ($P < 0.004$), and experienced less discomfort during the first and second postoperative days ($P < 0.05-0.005$). The magnesium-treated group revealed no change in postoperative sleeping patterns when compared to preoperative patterns. Control patients showed an increase in insomnia during the first and second postoperative nights ($P < 0.002$ and $P < 0.005$, respectively) compared to preoperative values.

CONCLUSIONS: This is the first clinical study showing that the perioperative application of magnesium sulfate is associated with smaller analgesic requirement, less discomfort, and a better quality of sleep in the postoperative period but not with adverse effects. Magnesium could be of interest as an adjuvant to postoperative analgesia.

Circadian interleukin-6 secretion and quantity and depth of sleep.

Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, Kales A, Prolo P, Wong ML, Licinio J, Gold PW, Hermida RC, Mastorakos G, Chrousos GP. Sleep Research and Treatment Center, Department of Psychiatry, Pennsylvania State University, Hershey 17033, USA. axv3@psu.edu

J Clin Endocrinol Metab. 1999 Aug;84(8):2603-7.

Patients with pathologically increased daytime sleepiness and fatigue have elevated levels of circulating interleukin-6 (IL-6). The latter is an inflammatory cytokine, which causes sickness manifestations, including somnolence and fatigue, and activation of the hypothalamic-pituitary-adrenal axis. In this study, we examined: 1) the relation between serial measurements of plasma IL-6 and quantity and depth of sleep, evaluated by polysomnography; and 2) the effects of sleep deprivation on the nyctohemeral pattern of IL-6 secretion. Eight healthy young male volunteers were sampled for 24 h twice, at the baseline state, after a normal night's sleep and after total overnight sleep deprivation. At the baseline state, IL-6 was secreted in a biphasic circadian pattern with two nadirs at 0800 and 2100 and two zeniths at 1900 and 0500 ($P < 0.01$). The baseline amount of sleep correlated negatively with the overall daytime secretion of the cytokine ($P < 0.05$). Also, depth of sleep at baseline correlated negatively with the postdeprivation increase of daytime secretion of IL-6 ($P < 0.05$). Sleep deprivation changed the temporal pattern of circadian IL-6 secretion but not the overall amount. Indeed, during the post-deprivation period, the mean daytime (0800-2200 h) levels of IL-6 were significantly higher ($P < 0.05$), whereas the nighttime (2200-0600 h) levels were lower than the predeprivation values. Thus, sleep-deprived subjects had daytime oversecretion and nighttime under-secretion of IL-6; the former might be responsible for their daylong somnolence and fatigue, the latter for the better quality (depth) of their sleep. These data suggest that a good night's sleep is associated with decreased daytime secretion of IL-6 and a good sense of well-being and that good sleep is associated with decreased exposure of tissues to the proinflammatory and potentially detrimental actions of IL-6. Sleep deprivation increases daytime IL-6 and causes somnolence and fatigue during the next day, whereas postdeprivation decreases nighttime IL-6 and is associated with deeper sleep.

Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications.

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J Clin Endocrinol Metab. 2001 Aug;86(8):3787-94.

Although insomnia is, by far, the most commonly encountered sleep disorder in medical practice, our knowledge in regard to its neurobiology and medical significance is limited. Activation of the hypothalamic-pituitary-adrenal axis leads to arousal and sleeplessness in animals and humans; however, there is a paucity of data regarding the activity of the hypothalamic-pituitary-adrenal axis in insomniacs. We hypothesized that chronic insomnia is associated with increased plasma levels of ACTH and cortisol. Eleven young insomniacs (6 men and 5 women) and 13 healthy controls (9 men and 4 women) without sleep disturbances, matched for age and body mass index, were monitored in the sleep laboratory for 4 consecutive nights, whereas serial 24-h plasma measures of ACTH and cortisol were obtained during the fourth day. Insomniacs, compared with controls, slept poorly (significantly higher sleep latency and wake during baseline nights). The 24-h ACTH and cortisol secretions were significantly higher in insomniacs, compared with normal controls (4.2 ± 0.3 vs. 3.3 ± 0.3 pM, $P = 0.04$; and 218.0 ± 11.0 vs. 190.4 ± 8.3 nM, $P = 0.07$). Within the 24-h period, the greatest elevations were observed in the evening and first half of the night. Also, insomniacs with a high degree of objective sleep disturbance (% sleep time < 70), compared with those with a low degree of sleep disturbance, secreted a higher amount of cortisol. Pulsatile analysis revealed a significantly higher number of peaks per 24 h in insomniacs than in controls ($P < 0.05$), whereas cosinor analysis showed no differences in the temporal pattern of ACTH or cortisol secretion between insomniacs and controls. We conclude that insomnia is associated with an overall increase of ACTH and cortisol secretion, which, however, retains a normal circadian pattern. These findings are consistent with a disorder of central nervous system hyperarousal rather than one of sleep loss, which is usually associated with no change or decrease in cortisol secretion or a circadian disturbance. Chronic activation of the hypothalamic-pituitary-adrenal axis in insomnia suggests that insomniacs are at risk not only for mental disorders, i.e. chronic anxiety and depression, but also for significant medical morbidity associated with such activation. The therapeutic goal in insomnia should be to decrease the overall level of physiologic and emotional arousal, and not just to improve the nighttime sleep.

Alterations in nocturnal serum melatonin levels in humans with growth and aging.

Waldhauser F, Weiszenbacher G, Tatzer E, Gisinger B, Waldhauser M, Schemper M, Frisch H. Department of Pediatrics, University of Vienna, Austria.

J Clin Endocrinol Metab. 1988 Mar;66(3):648-52.

The available data on potential alterations in serum melatonin (MLT) levels during a human lifetime are fragmentary and inconsistent. We, therefore, measured day- and nighttime serum MLT concentrations in 367 subjects (210 males and 157 females), aged 3 days

to 90 yr. Blood samples were collected between 0730 and 1000 h and between 2300 and 0100 h. Serum MLT levels were measured by RIA. The mean nighttime serum MLT concentration was low during the first 6 months of life, i.e. 27.3 +/- 5.4 (+/- SE) pg/mL (0.12 +/- 0.02 nmol/L). It then increased to a peak value at 1-3 yr of age [329.5 +/- 42.0 pg/mL; (1.43 +/- 0.18 nmol/L)], and it was considerably lower [62.5 +/- 9.0 pg/mL; (0.27 +/- 0.04 nmol/L)] in individuals aged 15-20 yr. During the following decades serum MLT declined moderately until old age (70-90 yr of age), i.e. 29.2 +/- 6.1 pg/mL (0.13 +/- 0.03 nmol/L). This biphasic MLT decline follows 2 exponential functions with different slopes (from age 1-20 yr: $r = -0.56$; P less than 0.001; $y = 278.7 \times e^{-0.09x}$; from age 20-90 yr: $r = -0.44$; P less than 0.001; $y = 84.8 \times e^{-0.017x}$). The decrease in nocturnal serum MLT in children and adolescents (1-20 yr) correlated with the increase in body weight ($r = -0.54$; P less than 0.001) and body surface area ($r = -0.71$; P less than 0.001). At a later age (20-90 yr) there was no correlation among these variables. Daytime serum MLT levels were low and no age-related alterations were found. This study revealed major age-related alterations in nocturnal serum MLT levels. The negative correlation between serum MLT and body weight in childhood and adolescence is evidence that expansion of body size is responsible for the huge MLT decrease during that period. The moderate decline at older ages must derive from other factors.

Age-related decreases in melatonin secretion--clinical consequences.

Wurtman, R.J.

J. Clin. Endocrinol. Metab. 2000 Jun; 85(6): 2135-6.

No abstract available

Clinical features of circadian rhythm sleep disorders in outpatients.

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Psychiatry Clin Neurosci 1998 Jun;52(3):311-6

The clinical data of 86 cases of primary circadian rhythm sleep disorder (primary CRSD) were retrospectively examined and compared to 40 cases of secondary circadian rhythm sleep disorder (secondary CRSD), who had presented with some kind of psychiatric or medical disorder, and had exhibited sleep-wake rhythm disorders that were judged to be secondary CRSD based on sleep logs. The comparison of cases found that: (i) the mean age at first presentation to the clinic was significantly younger for primary CRSD compared to secondary CRSD; (ii) more secondary CRSD cases were unemployed than were Primary CRSD cases; (iii) more cases in the secondary CRSD group had a clear trigger for sleep-wake rhythm disorder onset than cases in the primary CRSD group; and (iv) the types of sleep-wake rhythm disorders in the primary CRSD group consisted of delayed sleep phase syndrome (DSPS), 72 (83.7%), non-24 pattern, 11 (12.8%), and irregular, 3 (3.5%). In the secondary CRSD group there were 25 (62.5%) cases of DSPS pattern, 1 (2.5%) of non-24 pattern and 14 (35.0%) with irregular pattern. The 56 (65.1%) cases with primary CRSD showed good response to vitamin B12 and bright light therapy; however, 28 (70.0%) cases with secondary CRSD did not respond to such therapies.

Is carbonyl detoxification an important anti-aging process during sleep?

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Med Hypotheses 2000 Apr;54(4):519-22

Organisms living on the earth may undergo inevitable toxification by biological 'garbage', a variety of bio-metabolites. Such garbage includes a particularly large number of toxic carbonyls, such as alpha,beta-unsaturated carbonyls created by free radicals, glycation, and other post-translational side-reactions during various stresses and diseases. The accumulation of these toxic substances and their crosslinking products leads to the formation of different age pigments, such as lipofuscin, lens cataracts, and crosslinked collagen. The diurnal fluctuation in the concentration of the pineal gland hormone, melatonin, may be responsible for the 'cleaning activities' that reverse the covalently-bound semi-toxified proteins and nucleic acids. This toxification-cleaning cycle may explain the biochemical necessity for sleep of human and animals during aging. Copyright 2000 Harcourt Publishers Ltd.

Do plasma melatonin concentrations decline with age?

Zeitzer JM, Daniels JE, Duffy JF, Klerman EB, Shanahan TL, Dijk DJ, Czeisler CA. Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.

Am J Med. 1999 Nov;107(5):432-6.

PURPOSE: Numerous reports that secretion of the putative sleep-promoting hormone melatonin declines with age have led to suggestions that melatonin replacement therapy be used to treat sleep problems in older patients. We sought to reassess whether the endogenous circadian rhythm of plasma melatonin concentration changes with age in healthy drug-free adults. **METHODS:** We analyzed the amplitude of plasma melatonin profiles during a constant routine in 34 healthy drug-free older subjects (20 women and 14 men, aged 65 to 81 years) and compared them with 98 healthy drug-free young men (aged 18 to 30 years). **RESULTS:** We could detect no significant difference between a healthy and drug-free group of older men and women as compared to one of young men in the endogenous circadian amplitude of the plasma melatonin rhythm, as described by mean 24-hour average melatonin concentration (70 pmol/liter vs 73 pmol/liter, $P = 0.97$), or the duration (9.3 hours vs 9.1 hours, $P = 0.43$), mean (162 pmol/liter vs 161 pmol/liter, $P = 0.63$), or integrated area (85,800 pmol x min/liter vs 86,700 pmol x min/liter, $P = 0.66$) of the nocturnal peak of plasma melatonin. **CONCLUSION:** These results do not support the hypothesis that reduction of plasma melatonin concentration is a general characteristic of healthy aging. Should melatonin replacement therapy or melatonin supplementation prove to be clinically useful, we recommend that an assessment of endogenous melatonin be carried out before such treatment is used in older patients.

Sleep-inducing effects of low doses of melatonin ingested in the evening

Zhdanova I.V.; Wurtman R.J.; Lynch H.J.; Ives J.R.; Dollins A.B.; Morabito C.; Matheson J.K.; Schomer D.L. Dept. of Brain/Cognitive Sciences, Massachusetts Inst. of Technology, Carleton St., Cambridge, MA 02142 USA

Clinical Pharmacology and Therapeutics (USA), 1995, 57/5 (552-558)

We previously observed that low oral doses of melatonin given at noon increase blood melatonin concentrations to those normally occurring nocturnally and facilitate sleep onset, as assessed using an involuntary muscle relaxation test. In this study we examined the induction of polysomnographically recorded sleep by similar doses given later in the evening, close to the times of endogenous melatonin release and habitual sleep onset. Volunteers received the hormone (oral doses of 0.3 or 1.0 mg) or placebo at 6, 8, or 9 PM. Latencies to sleep onset, to stage 2 sleep, and to rapid eye movement (REM) sleep were measured polysomnographically. Either dose given at any of the three time points decreased sleep onset latency and latency to stage 2 sleep. Melatonin did not suppress REM sleep or delay its onset. Most volunteers could clearly distinguish between the effects of melatonin and those of placebo when the hormone was tested at 6 or 8 PM. Neither melatonin dose induced 'hangover' effects, as assessed with mood and performance tests administered on the morning after treatment. These data provide new evidence that nocturnal melatonin secretion may be involved in physiologic sleep onset and that exogenous melatonin may be useful in treating insomnia.

The use of melatonin for the treatment of insomnia.

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Biol Signals Recept 1999 Jan-Apr;8(1-2):84-9

The pineal product melatonin is involved in the regulation of the sleep/wake cycle in humans. In blind individuals and in people travelling through time zones, melatonin rhythms are sometimes unsynchronized with the diel cycle, and nocturnal sleep may be disturbed. Low or distorted melatonin rhythms have repeatedly been reported in middle aged and elderly insomniacs. Melatonin administration effectively synchronized the sleep wake cycle in blind individuals and in subjects suffering from jet lag and advanced sleep onset in subjects suffering from delayed sleep phase syndrome. In elderly insomniacs, melatonin replacement therapy significantly decreased sleep latency, and/or increased sleep efficiency and decreased wake time after sleep onset. In addition, melatonin substitution facilitated benzodiazepine discontinuation in chronic users. These data show an association between melatonin rhythm disturbances and difficulties to promote or maintain sleep at night. Specific melatonin formulations may be useful to treat circadian-rhythm-related sleep disorders and age-related insomnia.

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Inhibition of melatonin secretion onset by low levels of illumination

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Journal of Sleep Research (United Kingdom), 1996, 5/2 (77-82)

Melatonin is a hormone released during darkness under the control of the hypothalamic circadian pacemaker. It has been shown that melatonin is suppressed by light as a function of intensity, with low levels of illumination producing small effects and more intense light greater, but not complete inhibition. The studies which lead to these conclusions administered light subsequent to the secretion pattern being well established. Light as low as 250 lux administered during the normal onset of secretion can reduce melatonin to below detectable levels. The onset of melatonin secretion was delayed for at least an hour during 250 lux exposure and did not rise until termination of light exposure (two hours after control melatonin onset) with higher illumination (500, 1000 and 2500 lux). This tentatively indicates that duration of the inhibition is intensity dependent. It is suggested that the experimental paradigm used in the present study may be a more realistic representation of the effect of normal light exposure (both natural and artificial) on the circadian system, and that findings may be pertinent to the aetiology of certain sleep onset insomnias, which would include delayed sleep phase syndrome (DSPS) and adaptation to shift work.

Melatonin replacement corrects sleep disturbances in a child with pineal tumor

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Neurology (USA), 1996, 46/1 (261-263)

A child with a germ cell tumor involving the pineal region had marked suppressed melatonin secretion associated with severe insomnia. Exogenous melatonin (3 mg in the evening) for 2 weeks restored sleep continuity, as demonstrated by objective monitoring of rest-activity cycles. This case report provides direct evidence of the essential role of melatonin in normal sleep.

Use of melatonin in circadian rhythm disorders and following phase shifts

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Acta Neurobiologiae Experimentalis (Poland), 1996, 56/1 (359-362)

Following abrupt phase shifts (real or simulated time zone changes, night shift work) there is desynchronisation between the internal circadian rhythms (including melatonin) and the external environment with consequent disturbances in sleep, mood and performance. In humans the pineal hormone melatonin has phase-shifting and resynchronising properties with regard to a number of circadian rhythms. Suitably timed melatonin administration hastened adaptation to phase shift and significantly improved self-rated jet lag in large numbers of time zone travellers. Preliminary results in night shift workers showed improved daytime sleep and night-time alertness. In simulated experiments, appropriately timed melatonin improved subjective sleep, alertness and performance and facilitated the readaptation of the melatonin rhythm following a rapid 9 h advance phase shift. Melatonin has also been assessed in circadian rhythm disorders with disturbed sleep (blindness and delayed sleep phase insomnia). Compared with placebo, melatonin significantly improved sleep and synchronised the sleep wake cycle in some blind subjects. Melatonin treatment significantly advanced the sleep onset time in delayed sleep phase insomnia. Taken together these findings suggest that melatonin is of benefit in facilitating adaptation to forced phase shifts and in conditions of circadian rhythm disturbance.

Current and future strategies for insomnia management

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European Psychiatry (France), 1996, 11/Suppl. 1 (31S-33S)

Different forms of insomnia are present as symptoms of many psychiatric and other disorders. The first step for a treatment strategy is therefore a correct diagnosis. As insomnia is more common in patients with psychiatric disorders than in the general population, a careful consideration should be given, depressive and anxiety disorders should especially be carefully investigated. There are reasons to believe that even in so-called insomnia not obviously related to psychiatric disorders, stressful life situations may play a role. Therefore a co-morbidity with emotional disorders which may follow these events is worth considering. Insomnia should always be considered as part of a sleep-wake schedule disturbance and this has an impact on the importance of the pharmacological properties of the drugs used to treat insomnia. The recent trend for more specific agents both on receptor sub-populations and on relevant sites of the GABA receptor complex will help very much in selecting the most appropriate drug for treating patients.

Physiological and therapeutic effects of high frequency electrical pulses.

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Integr Physiol Behav Sci (United States) Apr-Jun 1996, 31 (2) p88-95

The results of stimulating human subjects with the LISS Cranial Stimulator (LCS) and the LISS Body Stimulator (LBS) include an increase or decrease in the activities of certain neurotransmitters and neurohormones and the reduction of associated pain, insomnia, depression, and spasticity. The effects were documented in human subjects with measurements of the serum concentration of the various agents and assessments of the symptoms being performed before and after stimulation. The stimulators had a carrier frequency of 15,000 hz, which utilizes the bulk capacitance of the body, and a 15 hz modulating bioactive frequency. The second modulating frequency presently used, 500 hz, reduces the energy input to the patient by half. Significant increases in levels of CSF serotonin and beta endorphin were recorded post stimulation. There were also elevations in the levels of plasma serotonin, beta endorphin, GABA and DHEA together with diminished levels of cortisol and tryptophan. Concomitant with these changes were significant improvements in the symptoms of pain, insomnia, spasticity, depression, and headache.

Melatonin replacement therapy of elderly insomniacs

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Sleep (USA), 1995, 18/7 (598-603)

Changes in sleep-wake patterns are among the hallmarks of biological aging. Previously, we reported that impaired melatonin secretion is associated with sleep disorders in old age. In this study we investigated the effects of melatonin replacement therapy on melatonin-deficient elderly insomniacs. The study comprised a running-in, no-treatment period and four experimental periods. During the second, third and fourth periods, subjects were administered tablets for 7 consecutive days, 2 hours before desired bedtime. The tablets were either 2 mg melatonin administered as sustained-release or fast-release formulations, or an identical-looking placebo. The fifth period, which concluded the study, was a 2-month period of daily administration of 1 mg sustained-release melatonin 2 hours before desired bedtime. During each of these five experimental periods, sleep-wake patterns were monitored by wrist-worn actigraphs. Analysis of the first three 1-week periods revealed that a 1-week treatment with 2 mg sustained-release melatonin was effective for sleep maintenance (i.e. sleep efficiency and activity level) of elderly insomniacs, while sleep initiation was improved by the fast-release melatonin treatment. Sleep maintenance and initiation were further improved following the 2-month 1-mg sustained-release melatonin treatment, indicating that tolerance had not developed. After cessation of treatment, sleep quality deteriorated. Our findings suggest that for melatonin-deficient elderly insomniacs, melatonin replacement therapy may be beneficial in the initiation and maintenance of sleep.

Improvement of sleep equality in elderly people by controlled-release melatonin

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Melatonin, produced by the pineal gland at night, has a role in regulation of the sleep-wake cycle. Among elderly people, even those who are healthy, the frequency of sleep disorders is high and there is an association with impairment of melatonin production. We investigated the effect of a controlled-release formulation of melatonin on sleep quality in 12 elderly subjects (aged 76 (SD 8) years) who were receiving various medications for chronic illnesses and who complained of insomnia. In all 12 subjects the peak excretion of the main melatonin metabolite 6-sulphatoxymelatonin during the night was lower than normal and/or delayed in comparison with non-insomniac elderly people. In a randomised, double-blind, crossover study the subjects were treated for 3 weeks with 2 mg per night of controlled-release melatonin and for 3 weeks with placebo, with a week's washout period. Sleep quality was objectively monitored by wrist actigraphy. Sleep efficiency was significantly greater after melatonin than after placebo (83 (SE 4) vs 75 (3)%, $p < 0.001$) and wake time after sleep onset was significantly shorter (49 (14) vs 73 (13) min, $p < 0.001$). Sleep latency decreased, but not significantly (19 (5) vs 33 (7) min, $p = 0.088$). Total sleep time was not affected. The only adverse effects reported were two cases of pruritus, one during melatonin and one during placebo treatment; both resolved spontaneously. Melatonin deficiency may have an important role in the high frequency of insomnia among elderly people. Controlled-release melatonin replacement therapy effectively improves sleep quality in this population.

Sleep-inducing effects of low doses of melatonin ingested in the evening

Zhdanova I.V.; Wurtman R.J.; Lynch H.J.; Ives J.R.; Dollins A.B.; Morabito C.; Matheson J.K.; Schomer D.L.
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Clinical Pharmacology and Therapeutics (USA), 1995, 57/5 (552-558)

We previously observed that low oral doses of melatonin given at noon increase blood melatonin concentrations to those normally occurring nocturnally and facilitate sleep onset, as assessed using an involuntary muscle relaxation test. In this study we examined the induction of polysomnographically recorded sleep by similar doses given later in the evening, close to the times of endogenous melatonin release and habitual sleep onset. Volunteers received the hormone (oral doses of 0.3 or 1.0 mg) or placebo at 6, 8, or 9 PM. Latencies to sleep onset, to stage 2 sleep, and to rapid eye movement (REM) sleep were measured polysomnographically. Either dose given at any of the three time points decreased sleep onset latency and latency to stage 2 sleep. Melatonin did not suppress REM sleep or delay its onset. Most volunteers could clearly distinguish between the effects of melatonin and those of placebo when the hormone was tested at 6 or 8 PM. Neither melatonin dose induced 'hangover' effects, as assessed with mood and performance tests administered on the morning after treatment. These data provide new evidence that nocturnal melatonin secretion may be involved in physiologic sleep onset and that exogenous melatonin may be useful in treating insomnia.

Light, melatonin and the sleep-wake cycle

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J. Psychiatry Neurosci. (Canada), 1994, 19/5 (345-353)

Blood levels of the pineal hormone melatonin are high at night and low during the day. Its secretion is regulated by a rhythm-generating system located in the suprachiasmatic nucleus of the hypothalamus, which is in turn regulated by light. Melatonin is regulated not only by the circadian oscillator but acts as a darkness signal, providing feedback to the oscillator. Melatonin has both a soporific effect and an ability to entrain the sleep-wake rhythm. It also has a major role in regulating the body temperature rhythm. Melatonin rhythms are altered in a variety of circadian rhythm disorders. Melatonin treatment has been reported to be effective in treatment of disorders such as jet lag and delayed sleep phase syndrome.

Melatonin rhythms in night shift workers

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Sleep (USA), 1992, 15/5 (434-441)

For some time, it has remained uncertain whether the circadian rhythms of permanent night shift workers are adapted to their night-active schedule. Previous studies of this question have often been limited by 'masking' (evoked) effects of sleep and activity on body temperature and cortisol, used as marker rhythms. In this study, the problem of masking was minimized by measuring

the timing of melatonin production under dim light conditions. Nine permanent night shift workers were admitted to the Clinical Research Center (CRC) directly from their last work shift of the week and remained in dim light while blood samples were obtained hourly for 24 hours. Melatonin concentrations were measured in these samples using a gas-chromatographic mass-spectrometric method. Sleep diaries were completed for two weeks prior to the admission to the CRC. Overall, the onset of the melatonin rhythm was about 7.2 hours earlier (or 16.8 hours later) in the night workers compared to day-active controls. It was not possible to know whether the phase of the melatonin rhythm was the result of advances or delays. In night shift workers, sleep was initiated (on average) about three hours prior to the onset of melatonin production. In contrast, day-active subjects initiated sleep (on average) about three hours after their melatonin onset. Thus, the sleep times selected by night shift workers may not be well-synchronized to their melatonin rhythm, assumed to mark the phase of their underlying circadian pacemaker.

Effect of melatonin replacement on serum hormone rhythms in a patient lacking endogenous melatonin

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Brain Res. Bull. (USA), 1991, 27/2 (181-185)

A potentially confounding variable inherent in studies designed to examine the effect of melatonin administration in humans is the presence of an endogenous melatonin rhythm in the experimental subjects. The effects of exogenous melatonin administration on serum hormone rhythms was recently examined in a male patient who lacked detectable circulating levels of endogenous melatonin. The patient's pineal gland had been destroyed five years previously in the course of treatment for a pineal astrocytoma. On three separate occasions, over approximately a one-year period, the patient was given daily oral melatonin replacement (2 mg/day, 1 mg/day and 0.5 mg/day). These experiments were designed to assess the effects of exogenous melatonin on serum growth hormone, prolactin, cortisol and testosterone rhythms. Analysis of blood samples collected every 2-4 hours for 24-hour periods both before and during melatonin replacement revealed that the exogenous melatonin rhythm was associated with improvements in self-reported sleep and mood ratings. Melatonin administration produced robust nocturnal peaks in serum growth hormone and prolactin levels immediately following ingestion of the hormone, while serum cortisol and testosterone rhythms were not influenced. These results suggest that melatonin may modulate the coordination and enhancement of selected biological rhythms in man.

Melatonin administration in insomnia

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Neuropsychopharmacology (USA), 1990, 3/1 (19-23)

Ten patients with persistent insomnia were randomized in a double-blind design and the effects of 1-mg and 5-mg oral dosages of melatonin on the electroencephalogram-recorded sleep were examined. Subjects showed no changes in either the onset or duration of sleep, nor any effect on mood or alertness the following day. A significant increase in rapid-eye movement (REM) latency was noted at the 1-mg dose, though no other parameter of REM sleep was affected. The patients reported less sleep on both melatonin conditions. Despite this perception of decrease, overall subjective quality was reported to be improved.

Treatment of delayed sleep phase syndrome

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General Hospital Psychiatry (USA), 1995, 17/5 (335-345)

Delayed sleep phase syndrome (DSPS) is a common but little reported cause of severe insomnia. Affected individuals complain of difficulty falling asleep and difficulty awaking at socially acceptable hours. It results from a dysregulation of the circadian sleep-wake cycle. DSPS presents in clinically heterogeneous ways as modulated by motivation, psychopathology, drug status, and treatment compliance factors. Patients respond variably to the range of possible treatments. Bright light treatment potentially corrects the circadian abnormality of DSPS. Other treatments reported to relieve some DSPS patients include schedule shifts, drugs, and vitamin and hormone treatments. The safety and efficacy of light treatment have not been conventionally defined, but available information suggests that it is ophthalmologically safe. At present, DSPS must be managed empirically by various methods.

Nutritional factors in the etiology of the premenstrual tension syndromes.

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J Reprod Med (United States) Jul 1983, 28 (7) p446-64

The premenstrual symptom complex many women experience in a moderate to severe form can be divided into four subgroups. Because there is more than one syndrome and nervous tension is one of the most common symptoms, the term premenstrual tension syndromes (PMTS) is used. The most common subgroup, PMT-A, consists of premenstrual anxiety, irritability and nervous tension, sometimes expressed in behavior patterns detrimental to self, family and society. Elevated blood estrogen and low progesterone have been observed in this subgroup. Administration of vitamin B6 at doses of 200-800 mg/day reduces blood estrogen, increases progesterone and results in improved symptoms under double-blind conditions. Women in this subgroup consume an excessive amount of dairy products and refined sugar, and progesterone may be of value in them. The second-most-common subgroup, PMT-H, is associated with symptoms of water and salt retention, abdominal bloating, mastalgia and weight gain. The severe form of PMT-H is associated with elevated serum aldosterone. Vitamin B6 at high dosage suppresses aldosterone and results in diuresis and clinical improvement. Vitamin E helps the breast symptoms. Methylxanthines and nicotine should be curtailed and sodium limited to 3 gm/day. PMT-C is characterized by premenstrual craving for sweets, increased appetite and indulgence in eating refined sugar followed by palpitation, fatigue, fainting spells, headache and sometimes the shakes. PMT-C patients have increased carbohydrate tolerance and low red-cell magnesium. Adequate magnesium replacement results in improved glucose tolerance tests and decreased PMT-C symptoms. Deficiency of the prostaglandin PGE1 may also be involved in PMT-C. PMT-D is the least common but most dangerous because suicide is most frequent in this subgroup. The symptoms are depression, withdrawal, insomnia, forgetfulness and confusion. In ten PMT-D patients the mean blood estrogen was lower and the mean blood progesterone higher than normal during the midluteal phase. Elevated adrenal androgens are observed in some hirsute PMT-D patients. Two PMT-D patients with normal blood progesterone and estrogens had high lead levels in hair tissue and chronic lead intoxication. This subgroup needs careful medical attention when the symptoms are severe. Therapy should be individualized according to the results of the evaluation.

Effects of intravenously administered vitamin B12 on sleep in the rat.

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Physiol Behav (United States) Jun 1995, 57 (6) p1019-24

Vitamin B12 (VB12) has been reported to normalize the entrainment of circadian rhythms in the non-24-h sleep wake cycle and delayed sleep phase insomnia in humans. The purpose of this work was to clarify whether the peripheral administration of VB12 has any sleep-promoting effect on the sleep-wake rhythm in freely moving rats. After a baseline day of saline infusion, VB12 (500 micrograms/kg/day) was administered continuously for 4 days via the jugular vein. Polysomnographic recordings were carried out concurrently. In both the light and the 24-h periods, the amount of non-rapid eye movement (NREM) sleep increased significantly on VB12-days 2 and 3, while the amount of REM sleep increased significantly on VB12-day 2. In the light period, the increase in NREM sleep was due to increased duration of the episode, while the tendency to an increase in REM sleep was due to an increased number of episodes. Changes in the diurnal sleep-wake rhythm tended to appear in the earlier light period. The serum B12 concentrations in the VB12 group were 40 times higher than in controls. These findings suggest that peripherally infused VB12 has promoting effects on the rat's sleep, especially in the light period.

Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (vitamin B12).

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Sleep (United States) Oct 1991, 14 (5) p414-8

Two adolescent patients suffering from persistent sleep-wake schedule disorders appear to have responded to treatment with vitamin B12 (methylcobalamin). A 15-year-old girl with delayed sleep phase syndrome (DSPS) and a 17-year-old boy with hypnnycthemeral syndrome complained of not being able to attend school despite many trials of medication. The improvement of the sleep-wake rhythm disorders appeared immediately after the administration of high doses (3,000 micrograms/day) of methylcobalamin. Neither patient showed any laboratory or clinical evidence of vitamin B12 deficiency or hypothyroidism (which can cause B12 deficiency). Serum concentrations of vitamin B12 during treatment were in the high range of normal or above normal. The duration of the sleep period of the DSPS patient decreased gradually from 10 hours to 7 hours, and the time of sleep

onset advanced from 2 a.m. to midnight. The period of the sleep-wake cycle of the hypernycthemeral patient was 24.6 hours before treatment and 24.0 hours after treatment. The relationship between the circadian basis of these disorders and vitamin B12 and its metabolites is discussed.

Vitamin B12 treatment for sleep-wake rhythm disorders.

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Sleep (United States) Feb 1990, 13 (1) p15-23

Vitamin B12 (VB12) was administered to two patients suffering for many years from different sleep-wake rhythm disorders. One patient was a 15-year-old blind girl suffering from a free-running sleep-wake rhythm (hypernycthemeral syndrome) with a period of about 25 h. In spite of repeated trials to entrain her sleep-wake cycle to the environmental 24-h rhythm, her free-running rhythm persisted for about 13 years. When she was 14 years old, administration of VB12 per os was started at the daily dose of 1.5 mg t.i.d. Shortly thereafter, her sleep-wake rhythm was entrained to the environmental 24-h rhythm, and her 24-h sleep-wake rhythm was maintained while she was on the medication. Within 2 months of the withholding of VB12, her free-running sleep-wake rhythm reappeared. The VB12 level in the serum was within the normal range both before and after treatment. The other patient was a 55-year-old man suffering from delayed sleep phase syndrome since 18 years of age. After administration of VB12 at the daily doses of 1.5 mg, his sleep-wake rhythm disorder was improved. The good therapeutic effect lasted for more than 6 months while he was on the medication.

[Folate and the nervous system (author's transl)]

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Sem Hop (France) Sep 18-25 1979, 55 (31-32) p1383-7

The responsibility of the folate deficiency in some neuropsychiatric disorders is recent knowledge. The role of the folate on the nervous system is not yet well definite, but the action on the metabolism of the amino-acids, on the purine and the pyrimidine synthesis and on the metabolism of the catecholamins are certainly essential. The neuropsychiatric diseases secondary to the folate deficiency are numerous: dementia, schizophrenia like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, puerperal psychosis, peripheral neuropathy, myelopathy (spinal cord syndrome and/or pyramidal tract damage), restless legs syndrome. Clinically the diagnosis may be difficult with sub acute combined degeneration secondary to the pernicious anaemia, and the dosage of the folate (in serum, in red-cells and in cerebrospinal fluid) is necessary. The congenital defects in the uptake or utilization of the folate are associated with neuropsychiatric disturbances. The treatment is easy and safe if the vitamin B12 deficiency is eliminated and if employed with caution in epileptic patients because folate can induced seizures.

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