

# Melatonin in sleep disorders and jet-lag

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## Abstract

In elderly insomniacs, melatonin treatment decreased sleep latency and increased sleep efficiency. This is particularly marked in Alzheimer's disease (AD) patients. Melatonin is effective to reduce significantly benzodiazepine use. In addition, melatonin administration synchronizes the sleep-wake cycle in blind people and in individuals suffering from delayed sleep phase syndrome or jet lag. Urinary levels of 6-sulphatoxymelatonin decrease with age and in chronic diseases like AD or coronary heart disease. The effect of melatonin on sleep is probably the consequence of increasing sleep propensity (by inducing a fall in body temperature) and of a synchronizing effect on the circadian clock (chronobiotic effect).

## Exogenous melatonin induces sleep in healthy subjects

The promoting effect of melatonin on sleep and sedation has been known since long. Such effect of melatonin is probably the consequence of increasing sleep propensity (by inducing a fall in body temperature) and of a synchronizing effect on the circadian clock (chronobiotic effect). Initial studies addressing the effect of melatonin on sleep made use of the i.v. or the intranasal route [1-3] or administered very large doses of the methoxyindole by the oral route [1, 4]. From these early studies it was concluded that melatonin reduces sleep latency and induces sleepiness and fatigue.

More recently, the effect of lower doses of melatonin were examined. These studies included young normal volunteers and patients with insomnia of different origins including Alzheimer's disease patients exhibiting sundowning syndrome [see 5]. In most instances melatonin significantly improved subjective and/or objective sleep parameters.

Exogenous oral or intravenous melatonin has a short metabolic half-life (from 20 to 60 min in humans) with a large hepatic first-pass effect and a biphasic elimination pattern [6, 7]. Very large individual variation in peak plasma concentrations (25-fold) after a given oral dose of melatonin are seen and attributed to differences in absorption. About 60-70% of melatonin in plasma is bound to albumin [8]. The lipophilicity of melatonin contributes to its easy passive diffusion across cell membranes as well as through cell layers. Most of melatonin in the general circulation is converted to 6-hydroxymelatonin in the liver, which clears 92-97% of circulating melatonin on a single pass [9]. The 6-hydroxymelatonin formed is conjugated and excreted into urine. The sulfate derivative of 6-hydroxymelatonin amounts for 50-80% and the glucuronide for 5-30% of the excreted melatonin. The remaining melatonin is excreted either unchanged (less than 1%), as 5-methoxyindoleacetic acid (0.5%), or as the non-indolic metabolite N-acetyl-5-methoxykynurenamine (15%). A new melatonin metabolite cyclic 3-hydroxymelatonin

could be an indicator of the endogenous hydroxyl radical scavenging properties of melatonin [10].

Melatonin 0.3 or 1 mg p.o. significantly reduced sleep latency and increased sleep efficiency in normal volunteers [11, 12]. In contrast, a 5 mg dose did not modify sleep induction or maintenance [13]. In healthy nocturnal young subjects oral administration of exogenous melatonin before going to bed increased stage 2 sleep significantly, with few hypothermic action [14]. The effect of a high melatonin dose (80 mg p.o.) was tested in subjects with situational insomnia induced by exposure to recorded traffic noise. In this study, melatonin reduced sleep latency and the number of awakening episodes and increased stage 2 sleep and sleep efficiency [15].

Melatonin was also administered during the day to normal volunteers. In doses of 1–40 mg significantly reduced sleep latency and increased total sleep time [16–18]. Administration of melatonin previous to the nap in subjects who were partially sleep deprived and allowed a 4-h nap starting at 13:00 h did not significantly modify sleep induction or maintenance [19]. In addition, sleep-onset latency, oral temperature and the number of correct responses on the Wilkinson vigilance task decreased significantly [20]. After the administration of a 5 mg dose of melatonin p.o. at either 13:00 or 18:00 h sleepiness increased significantly as well as theta/alpha frequencies of waking EEG [21]. Alertness and performance decreased after melatonin administration in the morning to healthy young individuals, an effect that lasted for 6 h [22]. Melatonin (0.1, 0.5 and 5 mg p.o.) decreased wake time after sleep onset and increased feelings of sleepiness and fatigue in the late afternoon (17:00–21:00 h) in healthy volunteers [23]. When melatonin (0.1–10 mg) was administered at 1145 h all doses increased significantly sleep duration and self-reported sleepiness and fatigue.

Assessment of the hypnotic action of melatonin during daytime administration and its comparison with triazolam indicated that a 6 mg dose of melatonin demonstrated hypnotic effects that were nearly equal to those of triazolam at 0.125 mg. Rectal temperature was significantly decreased by melatonin [24]. In another placebo-controlled and double-blind with a cross-over design including temazepam (20 mg), the hypnotic activity of melatonin at early evening (presumably in the absence of endogenous melatonin) was similar to 20 mg temazepam [25, 26]. These data in humans reproduced previous findings in rodents [27].

It has been contended that high pharmacological doses of melatonin are needed to improve sleep of normal volunteers during nighttime [28]. However, an important question, not yet solved, concerns as to what “physiological” means in terms of intracerebral melatonin levels. The levels of a lipophilic substance like melatonin reaching neurons under physiological conditions may differ considerably from circulating hormone concentration. Indeed, in early studies using HPLC [29] or RIA [30, 31] hypothalamic melatonin concentrations were found to be about 50 times greater than in plasma and a recent study demonstrated that third ventricle CSF melatonin levels were 20-fold higher than nocturnal plasma concentrations in sheep [32].

### **Exogenous melatonin is useful to improve sleep in aged subjects suffering insomnia**

The effect of melatonin on the polysomnographic sleep of insomniac patients was assessed in several studies. Melatonin (1 or 5 mg, 15 min before bedtime for 1 night) did not modify variables related to sleep induction and maintenance [33, 34]. It must be noted that in these studies subject population under placebo showed low sleep efficiency (about 85%); hence any possible effect of melatonin could have been limited by a ceiling effect.

In middle-aged and elderly insomniacs who made use of immediate-release (0.5 mg) and controlled release (0.5 mg) preparations of melatonin 30 min before bedtime, polysomnographic recordings and sleep actigraphy showed that melatonin shortened latencies to persistent sleep [35]. There was no correlation between prior melatonin production and responsiveness to melatonin replacement. Administration of a 3 mg dose of melatonin during 14 nights to elderly patients with chronic primary insomnia brought about a significant reduction in wake time after sleep onset while total sleep time and sleep efficiency increased, with an increase of stage 2 sleep [36]. No correlation was found between prior 6-sulphatoxymelatonin levels in urine and subsequent sleep improvement after receiving melatonin.

In studies monitoring sleep quality by wrist actigraphy in elderly insomniacs, controlled-release melatonin (2 mg) taken 2 h before the desired bedtime during 3 weeks reduced sleep latency and wake time after sleep onset and increased total sleep time and sleep efficiency [37]. Melatonin (3 mg) administered 30 min before the expected bedtime for 21 nights to patients with chronic insomnia significantly improved sleep quality and decreased the number of awakenings from day 2–3 of treatment [38]. A sustained-release preparation of melatonin (2 mg) improved sleep initiation, with further improvement of sleep initiation and sleep maintenance after 2 months [39]. Insomniac patients receiving 75 mg melatonin at 22:00 h for 7 consecutive nights reported improved subjective sleep time and subjective daytime alertness [40]. Low amounts of melatonin (0.3 mg) given during 3 nights to middle-aged and elderly patients with chronic insomnia reduced sleep latency, the number of nocturnal awakenings and body movements per night, whereas core temperature remained unchanged [41]. In medically ill persons with initial insomnia receiving 5.4 mg melatonin or placebo, double-blind assessments of aspects of sleep indicated that melatonin significantly hastened sleep onset, improved quality and depth of sleep, and increased sleep duration [42].

Administration of melatonin (3 mg p.o.) for up to 6 months did not affect circulating PRL, FSH, TSH or estradiol, nor were any indications of hematological or blood biochemistry alteration found, in elderly insomniac females [43]. In a study assessing the acute effect of melatonin (1 mg) on serum PRL, LH, FSH, GH and TSH, only levels of PRL were stimulated [44]. Melatonin augmented sleep quality and duration, and decreased sleep latency and the number of awakening episodes; estimates of next-day function also improved significantly [43]. The urinary excretion of 6-sulphatoxymelatonin

before starting administration of melatonin correlated negatively and significantly with age but not with intensity of sleep disorder or outcome of treatment. In another study blood parameters were not affected by a dose of 10 mg of melatonin for 28 days [45].

It is interesting to note that melatonin can effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality. A number of animal studies indicated that several behavioral effects of melatonin can be suppressed by inhibiting central benzodiazepine receptors [46, 47]. Indeed melatonin and benzodiazepines share several properties, remarkable anxiolytic effects, and therefore melatonin could be useful to help patients to discontinue benzodiazepine treatment. In one study 14 out of 18 subjects under benzodiazepine therapy receiving melatonin (2 mg in a controlled-release formulation) discontinued benzodiazepine therapy and after a 6-month follow-up assessment of the 24 patients who discontinued benzodiazepine and received melatonin therapy, 19 maintained good sleep quality [48]. In another study, 13 of 20 patients taking benzodiazepines together with melatonin, benzodiazepine use could be stopped, and in another four patients, benzodiazepine dose could be decreased to 25–66% of the initial dose [43].

Although there have been reports on a correlation of low melatonin levels and insomnia in aged individuals, a recent study demonstrated that older people with age-related sleep maintenance problems do not have lower melatonin levels than older people reporting normal sleep [49]. Diminished melatonin secretion in the elderly is associated with insufficient environmental illumination [50].

A remarkable exception to the lack of correlation of melatonin levels and severity of sleep disorders is Alzheimer's disease (AD). Melatonin levels are greatly suppressed in these patients [51]. Cross-sectional studies report that about 40% of AD patients have disruptions in their sleep [52, 53]. Increased duration and frequency of awakenings and daytime napping and decreased non-REM and to a less extent REM sleep, characterize the sleep of AD patients [54]. Another phenomenon related to the sleep disturbances is "sundowning" [see 5]. We reported that melatonin (9 mg melatonin daily for 22 to 35 months) is effective to treat sleep disorders and sundowning in AD patients [55, 56]. Similar results were reported by others [57, 58].

### **Melatonin is useful in other types of insomnia**

Although insomnia is one of the main complaints in elderly people inducing benzodiazepine abuse, other sleep disturbances, e.g. restless legs syndrome, are also frequent in this group of age. Melatonin was found helpful in restless legs syndrome [59] and parasomnia like REM sleep behavior disorder [60, 61]. Typically, circadian sleep disorders like delayed sleep phase syndrome and non-24 h sleep-wake syndromes can be treated with melatonin [62–65].

Melatonin improves sleep quality of patients with treatment-resistant depression [66]. However, as it was observed previously [38], depression itself is not modi-

fied by melatonin treatment. Melatonin is also useful for sleep disturbances in manic patients with treatment resistant insomnia [67] and in patients with fibromyalgia [68]. Melatonin improved sleep in intensive care patients [69], a finding that can be correlated with data indicating that patients with coronary disease had a low melatonin production rate, with higher decreases in those with higher risk of cardiac infarction [70].

Another promising field of application for melatonin is that of sleep disorders in children. Observations included patients with childhood sleep onset insomnia [71–73] as well as children with sleep disorders linked to developmental disabilities [74–77].

### **Melatonin as a treatment for jet-lag**

With few exceptions [78], published evidence indicates that melatonin is useful for ameliorating "jet-lag" symptoms in air travelers [79–89]. A recent meta-analysis on the efficacy of melatonin to prevent and treat jet-lag indicated that melatonin, taken close to the target bedtime at the destination, decreased effectively jet-lag from flights crossing five or more time zones [90].

Athletes often ingest melatonin in an attempt to improve sleep quality or alleviate symptoms of jet-lag. Recently we addressed the subject in professional soccer players and their coaches who traveled from Buenos Aires to Tokyo to play the final game of the Intercontinental Cup (12 time-zone westerly transmeridian flight) [91]. To carry out this study a compromise had to be achieved to disturb minimally the players' own schedules and habits. A multifactorial approach to hasten the resynchronization in this group of elite sports competitors was used. First, we employed exposure to outdoors light as an attempt to cover symmetrically the phase delay and the phase advance portions of the phase-response curve reported for light in humans [92]. Conceivably this would lead to a suppression of circadian rhythmicity and to the sensitization the circadian clock for additional chronobiological manipulation. Second, we administered non-photoc stimulation (i.e., physical exercise) that practically coincided with outdoor light exposure as another manipulation tending to mask the circadian oscillator. Third, we gave the athletes melatonin at local bedtime to resynchronize the circadian oscillator to the new time environment. Twenty-two male subjects were included in the study. The day prior to departure, urine was collected from each subject from 18:00 h to 06:00 h to measure the melatonin metabolite 6-sulphatoxymelatonin. Participants were asked to complete sleep log diaries from day 0 (pre-flight) to the day before returning to Buenos Aires (day 8). All subjects received 3 mg of melatonin p.o. daily at expected bedtime at Tokyo immediately after leaving Buenos Aires. Upon arrival at Tokyo the subjects performed a daily physical exercise routine outdoors at two restricted times of the day (from 08:00 h to 11:00 h in the morning and from 13:00 h to 16:00 h in the afternoon). Exposure to sunlight or physical exercise at other times of the day was avoided. Except for the number of awakenings (which increased on days 1 and 3) and sleep latency (which decreased on days 2, 6 and 8), there was an absence of significant

changes in subjective sleep parameters as compared to pre-flight assessment. Sleep quality and morning alertness at Tokyo correlated significantly with pre-flight 6-sulphatoxymelatonin excretion. Mean resynchronization rate of sleep-wake cycle to the 12 h-time shift was  $2.13 \pm 0.88$  days, significantly different from the minimal resynchronization rate of 6 days expected after a 12-time zones flight. The results indicated that the combination of melatonin treatment, an appropriate environmental light schedule and timely applied physical exercise is useful to

help elite athletes to overcome the consequences of jet-lag [91].

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