Effect of melatonin administration on sleep, behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-blind, placebo-controlled study

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*ABSTRACT. **Background and aims:** The aim of the study was to evaluate the effect of melatonin administration on sleep and behavioral disorders in the elderly and the facilitation of the discontinuation of regular hypnotic drugs. **Methods:** This was a prospective, randomized, double-blind, placebo-controlled, crossover trial in a community-living population. Participants were 22 older adults (7 men, 15 women over 65) with a history of sleep disorder complaints. Fourteen of these subjects were receiving hypnotic drug therapy. Participants received 2 months of melatonin (5 mg/day) and 2 months of placebo. Sleep disorders were evaluated with the Northside Hospital Sleep Medicine Institute (NHSMI) test, discarding secondary insomnia and evaluating sleep quality. Behavioral disorders were evaluated with the Yesavage Geriatric Depression Scale (GDS) and Goldberg Anxiety Scale (GAS). Patients discontinuing hypnotic drugs were also recorded. **Results:** Melatonin treatment for two months significantly improved sleep quality scores measured by the NHSMI test (1.78±0.40) when compared with both basal (3.72±0.45; p=0.001) and placebo (3.44±0.56; p=0.025) groups. Depression measured by GDS and anxiety measured by GAS also improved significantly after melatonin administration (p=0.043 and p=0.009, respectively). Nine out of 14 subjects receiving hypnotic drugs were able to discontinue this treatment during melatonin but not placebo administration; one discontinued hypnotic drugs during both melatonin and placebo administration, and four were unable to discontinue hypnotic therapy. **Conclusions:** The results of this study suggest that melatonin administration significantly improves sleep and behavioral disorders in the elderly and facilitates discontinuation of therapy with conventional hypnotic drugs.*
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INTRODUCTION

Insomnia and transient sleep disorders are common health problems in the elderly (1). These alterations are frequently associated with behavioral disorders (sometimes as a cause and at other times as a consequence) (2, 3). Benzodiazepines are the most commonly used drug in the treatment of sleep disorders, but when used for prolonged periods in older people, may be associated with impaired (mental and physical) functional status, increasing the risk of falls and fractures (4-6).

Several studies have shown progressive alterations in the circadian time-keeping system with age (7, 8). The pineal hormone melatonin, secreted mostly at nighttime in humans, plays a major role in sleep induction and regulation. Thus, the sharp increase in sleep propensity at night usually occurs two hours after the onset of endogenous melatonin production in humans (9, 10). Administration of melatonin during the day, when it is not present endogenously, results in induction of fatigue and sleepiness in humans (11, 12). The beneficial effects of melatonin in improving night sleep have been reported, particularly in elderly patients with insomnia who do not produce sufficient amounts of this hormone (13-17). Actually, melatonin production decreases with age, and older adults have very low plasma levels of this hormone (18, 19). Previous studies have shown that discontinuation of benzodiazepines and alternative therapy with melatonin for sleep disorders in the elderly improves sleep quality, preserving functional status (20, 21).

Key words: Behavioural disorders, elderly, melatonin, sleep disorders.

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Since there are few data concerning the effect of melatonin on sleep in elderly patients, the purpose of our study, unlike previous ones, was to evaluate the effect of melatonin administration on sleep and behavioral disorders in the elderly and the facilitation of the discontinuation of regular hypnotic drugs.

METHODS

The institutional review board of Seville University approved the study. Written informed consent was obtained before enrolment from an authorized representative empowered to make health-related decisions for the potential study participant.

Design

The study was an 18-week, placebo-controlled, randomized, double-blind crossover design. The procedure was double blind; participants and investigators were unaware of which participants were in which phase. Participants were administered melatonin for 8 weeks and placebo for 8 weeks, with order determined at random. Since melatonin has a very short haf-life (40-60 min), a 2-week washout period between phases was considered sufficient (Fig. 1). An 18-week trial was considered long enough to demonstrate sleep and behavior changes, given the acting nature of melatonin, daily dosing schedule, and high frequency of the observational outcome assessment.

Setting and participants

Participants were recruited from several community health centers in the metropolitan area of Seville, Spain. Inclusion criteria included healthy men and women aged 65 and older, with insomnia (defined with DSM-IV diagnostic criteria) or transient sleep disorders related to emotional stress. Subjects could be receiving hypnotic drug therapy.

Exclusion criteria included secondary sleep disorder, autoimmune diseases, tumors, dementia, psychosis or other severe mental disorder; advanced, severe, or unstable medical disease; and current enrolment in another experimental protocol.

Intervention

Melatonin (purity >99.5%) was provided by Helsinn Chemicals SA (Biasca, CH). During the intervention phase, participants were administered 5-mg melatonin capsules, with lactose as excipient, at bedtime (approximately 23.00 h) 7 days per week for 8 weeks. This dosing is consistent with the therapeutic efficacy and safety data of previous research on melatonin use in older people (22, 23). During the placebo phase, capsules containing lactose, identical in all ways to the active capsules, were administered on the same schedule. There was a 2-week washout period between the two phases. Participants receiving hypnotic drug therapy were encouraged to reduce their dosage 25% during week 1, 50% during week 2, 75% during week 3, and to discontinue hypnotic therapy completely during week 4.

Measurement and procedure

The Northside Hospital Sleep Medicine Institute Test (NHSMI) was the primary measure of participant sleep disorders (24). It evaluates 38 items which either discard secondary sleep disorders (1-10; 19-38) or evaluate sleep quality (11-18). After discarding secondary sleep disorders, the total score ranges from 0 to 8.

Another primary outcome was to assess the ability of participants to discontinue hypnotic drug treatment during melatonin or placebo administration.

Secondary outcome measures were the Yesavage Geriatric Depression Scale (GDS) (25) and Goldberg Anxiety Scale (GAS) (26) to evaluate behavioral disorders. The GDS is scored on a scale of 1 to 30, and represents a basic screening measure for depression in older adults. The GAS is scored by summing the ratings on 9 items, representing an efficient interview guide for the detection of psychologic distress. The total score ranges from 0 to 9.

A study investigator (CG) conducted NHSMI, GDS and GAS in basal conditions and after the first and second study phases as described in Figure 1.

Although no significant side-effects of melatonin administration have been described (22, 23), study investigators monitored for possible side-effects by immediate discontinuation of participation. Hematological, biochemical (liver, kidney and endocrine functions) and immune parameters were monitored by blood tests before and after participation.

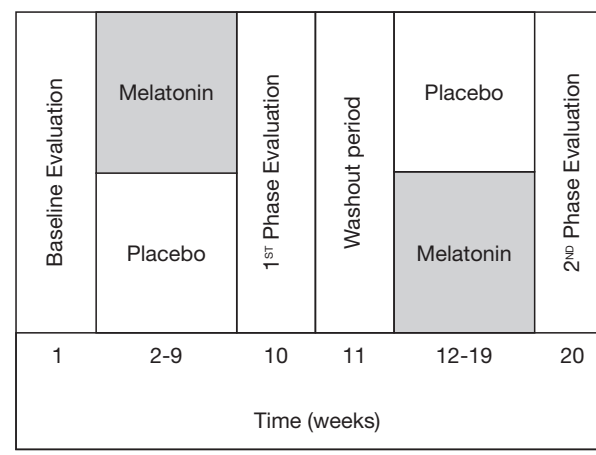

Fig. 1 - *Design of crossover trial, schedule of melatonin and placebo administration, and time-points of evaluation.*

Table 1 - *Clinical characteristics of study participants.*

	Men	Women
Cases (n)	7	15
Age (mean)	75.8	74.3
Body Mass Index* (kg/m^2, mean)	29.6	29.2
Chronic Sleep Disorders (n)	6	14
Transient Sleep Disorders (n)	1	1
Hypnotic Drug Users (n)	4	10
Type 2 Diabetes Mellitus (n)	3	2
Hypertension (n)	4	8

*Normal range 18-24.9; overweight 25-29.9; obese ≥30.

Data analysis

All analyses were performed with SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL). Repeated measures analysis of variance (ANOVA) was used for continuous data. Outcomes (NHSMI, GDS, GAS) were compared across intervention and placebo study phases. Where applicable, Student's paired *t*-test was used to compare groups. All results were reported as statistically significant at $p<0.05$. Score values were expressed as means ± standard error. Cochran's Q-test was used to evaluate the contrast of hypnotic drug therapy discontinuation during placebo and melatonin administration.

RESULTS

Participant characteristics

Twenty-two adults (7 men, 15 women) older than 65 were recruited from several community health centers in the Seville metropolitan area. Participants were randomly assigned either to melatonin-placebo or placebo-melatonin groups.

The clinical characteristics of participants are listed in Table 1. Six of the 7 men and 14 of the 15 women had diagnoses of chronic sleep disorders (insomnia). The remaining participants had a history of transient sleep disorders related to emotional stress. Four men and 10 women were habitual hypnotic drug users (benzodiazepines). Lastly, 5 and 12 participants had been diagnosed with type 2 diabetes mellitus and hypertension, respectively.

Of the 22 participants, 18 completed both study phases. Three of the 4 non-completers were removed during the placebo phase, after completing melatonin treatment. The other non-completer was removed during the melatonin phase. The causes for study discontinuation involved missing more than two days of participation (n=2), an adverse event that was determined to be unrelated to the study (n=1), and diagnosis of a severe disease (n=1).

Primary outcomes

Sleep quality scores measured by the NHSMI test, after the placebo period did not differ significantly from baseline values. However, the melatonin treatment improved sleep quality (1.78±0.40) significantly ($F=7.505$; $p<0.005$) when compared with both baseline (3.72±0.45; $p<0.001$) and placebo (3.44±0.56; $p<0.025$). Moreover, the benzodiazepine therapy discontinuation rate during melatonin treatment significantly exceeded that of the placebo group. Thus, nine out of 14 subjects receiving hypnotic drugs were able to discontinue this treatment during melatonin but not placebo administration; one discontinued hypnotic drugs during both melatonin and placebo administration, and four were unable to discontinue hypnotic therapy, although they did not suffer a more severe sleep disorder or anxiety/depression (Cochran's $Q= 18.200$; $p<0.001$).

Secondary outcomes

Depression and anxiety were also evaluated after melatonin treatment, as shown in Table 2. Depression measured by GDS improved significantly after the melatonin period when compared with baseline or placebo conditions ($F=3.44$; $p=0.043$). Similarly, anxiety measured by GAS also improved significantly after melatonin administration ($F=5.36$; $p=0.009$).

Safety and adverse events

The treatment was well tolerated. No definitive adverse effects of melatonin were reported. Hematological, bio-

Table 2 - *Behavioral evaluation scores: baseline, placebo, and melatonin phase comparisons.*

n=18	Mean Score	Standard Error	F-value	*p*-value
GDS*				
Baseline	7.33	1.03		
Placebo	7.06	1.16	3.44	0.043
Melatonin	5.61	1.15		
GAS†				
Baseline	2.28	0.56		
Placebo	1.50	0.62	5.36	0.009
Melatonin	0.50	0.42		

*Yesavage Geriatric Depression Scale (Normal range score ≤10); †Goldberg Anxiety Scale (Normal range score ≤2).

chemical (liver, kidney and endocrine functions), and immune parameters were monitored by blood tests before and after participation, with no significant modifications (data not shown). The causes for discontinuation in a patient by adverse events were determined to be unrelated to melatonin administration, i.e., palpitations in a woman with a pacemaker.

DISCUSSION

This study shows that, in a placebo-controlled, randomized, double-blind crossover design, melatonin treatment significantly improved sleep quality when compared with both baseline and placebo conditions. Melatonin has been described as a time cue to various organs, including the suprachiasmatic nucleus, and is therefore able to shift the endogenous circadian clock and to entrain sleep-wake and neuroendocrine rhythms (12). It is also an important physiological sleep regulator, increasing sleep propensity at night after the onset of its endogenous production (27). In elderly patients with insomnia and deficient production of melatonin (18, 19), exogenous administration of the hormone improves night sleep (13, 14, 16, 17). In one clinical trial, melatonin appeared to shorten sleep latency, without improving total sleep time, sleep efficiency, or wake after sleep onset (15). Other trials which have examined the efficacy of melatonin in people with sleep disorders have shown considerable heterogeneity in results (28-32). Recent meta-analyses reviewing the efficacy and safety of melatonin in the management of sleep disorders have shown that melatonin is not effective in treating most primary and secondary sleep disorders with short-term use (22, 23) but significantly reduces sleep onset latency, and increases sleep efficiency and total sleep duration (33). Many factors may contribute to this heterogeneity, such as variations in product quality, different formulations (slow or fast release), the wide range of doses used, and length of treatment. The presence of comorbid conditions and age in the study population may also contribute to heterogeneity (22). In our study, participants were administered 5-mg melatonin capsules at bedtime (approximately 23.00 h) 7 days per week for 8 weeks. This dosing is consistent with the therapeutic efficacy and safety data of previous research on melatonin use in older people (22, 23). The dose of melatonin used in our study (5 mg/day) in the upper limit of the doses used in most of the previous clinical trials, the relatively long period of study (8 weeks) when compared with other trials, and the use of a sleep quality test rather that somnography, may have contributed to our results. In our participants with insomnia (defined by DSM-IV diagnostic criteria) or transient sleep disorders related to emotional stress, melatonin was able to improve quality sleep as assessed by the NHSMI test.

Our results also show that nine out of 14 subjects receiving hypnotic drugs were able to discontinue this treatment during melatonin but not placebo administration. Similar results were found by Garfinkel et al. using 2 mg/day melatonin in a controlled-release formulation (20) and Siegrist et al. using 3 mg/day of regular gelatin melatonin capsules (21). These authors found that melatonin can effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality. In contrast, a similar dose of melatonin (3 mg/day) with a fast-release formulation failed to show effectiveness in reducing benzodiazepine consumption (34). The results found in our study are especially interesting since benzodiazepines are the most frequently used drug for the treatment of insomnia and their prolonged use is not particularly recommended in older patients because of the possibility of iatrogenic-functional limitations (4) and the increased risk of falls (35, 36).

There is a close relationship between insomnia, depression and anxiety (2, 3). Improving sleep quality may be accompanied by improvements in behavioral disorders and, conversely, improvements in behavioral disorders may improve sleep quality. We evaluated the effects of melatonin on depression and anxiety with the well-validated GDS and GAS tests, showing that both improved significantly after melatonin treatment when compared with baseline and placebo conditions. Melatonin therapy has been evaluated in sleep disturbances associated with behavioral and psychiatric disorders, showing that it is effective in improving sleep quality and vitality in such patients (30, 32, 37). We cannot conclude that improvements in depression or anxiety symptoms were due to the direct effect of melatonin treatment or to the secondary effect of melatonin *via* the improvement in sleep quality.

Lastly, treatment with melatonin was well tolerated in all patients, with no adverse clinical, hematological or biochemical events after 8 weeks. These results in elderly patients, as in previous studies in younger patients (33, 38), show that melatonin is also an effective and safe substance at the doses and during the period of time evaluated.

CONCLUSIONS

Melatonin administration may be safe and useful in improving sleep and behavioral disorders in elderly patients and can facilitate discontinuation of therapy with conventional hypnotic drugs. However, since the number of participants in this study was rather limited, and since various doses of melatonin should also be tested, further studies are necessary to establish the optimal dose of melatonin needed, the length of treatment and the long-term safety of the hormone.

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