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EFFECTS OF MELATONIN IN ELDERLY PATIENTS WITH SLEEP DISTURBANCE: A PILOT STUDY

ISIDORO FAINSTEIN,[1] ALBERTO J. BONETTO,[1] LUIS I. BRUSCO,[2] AND DANIEL P. CARDINALI[2]

[1]Centro Médico Ing. A. Rocca, Hospital Italiano de Buenos Aires, and [2]Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

ABSTRACT

This open-label, short-term pilot study was designed to assess the efficacy and tolerability of melatonin in the treatment of sleep disturbances in elderly patients. The 41 patients (28 women and 13 men; mean age [±SD], 74 ± 12 years) were separated into three groups: (1) patients with sleep disturbances alone (n = 22); (2) patients with sleep disturbances and signs of depression (n = 9); and (3) patients with sleep disturbances and dementia of the degenerative or vascular type (n = 10). All patients received 3-mg gelatin capsules of melatonin orally 30 minutes before expected sleep time for 21 days. Overall sleep quality and daytime alertness were assessed by means of structured clinical interviews and sleep logs completed by the patients (or their caregivers in the case of dementia patients). Starting from day 2 or 3 of treatment, melatonin significantly improved sleep quality and decreased the number of awakenings in patients with sleep disturbances with or without associated depression. Patients with dementia did not show significant improvement of sleep quality. Estimates of next-day function (ie, alertness in the morning and during the day) improved significantly only in patients exhibiting sleep disturbances alone. Clinical assessment indicated that symptoms improved in 16 (73%) of the patients with sleep disturbances alone and 4 (44%) of those with sleep disturbances associated with depression, and that agitated behavior at night (sundowning) decreased significantly in 7 (70%) of the patients with dementia. This was reflected by the coefficient of variation of bedtime, which averaged 58% in patients with dementia compared with 27% and 33% in nondepressed and depressed patients, respectively, on days 0 to 2 of treatment, and which decreased significantly only in dementia patients when reassessed on days 19 to 21. Four (31%) of the 13 patients with primary insomnia who were receiving benzodiazepines concomitantly reduced their benzodiazepine use (by 50% to 75% of initial doses) and 4 (31%) discontinued use of these agents; of the 7 patients with depression and 7 with dementia who were receiving benzodiazepines concomitantly, 2 (29%) in each group reduced benzodiazepine use by up to

Address correspondence to: D. P. Cardinali, MD, PhD, Departamento de Fisiologia, Facultad de Medicina, UBA CC 243, 1425 Buenos Aires, Argentina.
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50%. No side effects considered to be attributable to treatment were reported. The results of this trial suggest that melatonin may be useful for the treatment of primary sleep disturbances in elderly patients. ***Key words:*** **melatonin, sleep disturbance, aging, dementia, depression.**

INTRODUCTION

Aging is characterized by changes in sleep quality.[1] The stereotypes of diminished daytime alertness and early morning awakening of elderly persons (older than 65 years of age) are reflections of these changes and are reported by approximately one third of elderly patients visiting a physician.[2] Although amplitude attenuation is the most marked change, advances in phase, shortening of periods, and desynchronization of circadian rhythms are also apparent.[3]

Neuronal degeneration at the suprachiasmatic nucleus[4] and decreases in both the number of pinealocytes[5] and the amplitude of melatonin rhythm[6–10] have been identified as consequences of aging and may cause age-related insomnia and behavioral changes (eg, decreased physical activity and photic stimulation). Other circadian rhythms, including body temperature and the secretion of cortisol, are also altered with age.[2,11,12] Because changes in circadian rhythms among elderly persons are associated with a reduction in nighttime sleep quality, a decrease in daytime alertness, and attenuation in cognitive performance, reversing such changes could enhance quality of life for a large, rapidly increasing population.

Chronic insomnia is defined as insomnia that lasts at least 21 consecutive nights.[13,14] In elderly patients it can be associated with mental disorders, psychophysiologic conditions (primary insomnia), neurologic disorders (dementia or Parkinson's disease), inadequate sleep hygiene, or drug dependency.[15] The most prevalent association is with psychiatric disorders and the second most prevalent is primary insomnia.[15]

Melatonin has shown promise in the treatment of sleep disturbances in elderly patients. Reversal of symptoms appears to be possible by increasing melatonin levels with appropriately timed exposure to photic stimulation or administration of exogenous melatonin.[8,9,16] Among elderly persons, including healthy individuals, sleep disorders are often associated with impairment of melatonin production.[6–10] The sleep-promoting action of melatonin in humans has been known for more than 20 years.[17,18] Recent studies have identified a beneficial effect of melatonin in elderly patients with sleep disturbances. For example, Haimov et al[9] reported that in melatonin-deficient elderly patients with insomnia, replacement therapy with 2 mg of a sustained-release melatonin preparation was effective for sleep maintenance, whereas sleep initiation was improved with a fast-release melatonin preparation. Sleep quality deteriorated after cessation of treatment.

The present study is part of a project designed to evaluate the efficacy of 3-mg gelatin melatonin* capsules administered orally as a physiologic regulator of sleep in humans. This paper describes the results of the initial open-label, short-term pilot study of the efficacy and tolerability of melatonin in the treatment of sleep disturbances in elderly patients.

PATIENTS AND METHODS

Forty-one patients (28 women and 13 men) 56 to 96 years of age (mean age, 74 ± 12 years) were included in the study. The patients (or their legal caregivers in the case of patients with dementia) gave written informed consent for participation. A patient was considered to have insomnia if, in a structured interview[19] with the patient or caregiver, at least one of the following criteria was identified as having occurred daily for the past 30 days: (1) sleep latency longer than 30 minutes; (2) more than three episodes of sleep interruption lasting at least 5 minutes each; or (3) sleep efficiency (sleep time/bedtime × 100) lower than 85%. Patients were excluded from the study if they had any of the following, as assessed in the structured interview; an organic disorder; a psychiatric disorder other than depression or dementia; a history of neurologic disorder; alcohol abuse, or addiction to other drugs; or a heavy smoking habit (more than 15 cigarettes a day).

Patients were separated into the following three groups for purposes of analysis: (1) patients with sleep disturbances alone (n = 22); (2) patients with sleep disturbances and signs of depression (n = 9); and (3) patients with sleep disturbances and dementia of the degenerative (Alzheimer's disease, senile dementia of the Alzheimer type) or vascular type (n = 10) (Table I). Patients in the latter two groups were institutionalized. Depressed patients met *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition[14] criteria for major depression (melancholic type) and did not have any other current or past psychiatric illness.

Patients or their caregivers were initially interviewed by a physician and then given a questionnaire[19] dealing with demographics, sleep environment, sleep pattern, bedtime, wake time, number of awakenings, and general sleep information. Patients were treated for 21 days with 3-mg gelatin melatonin capsules administered orally 30 minutes before expected sleep time (as estimated from the clinical interview of the patients or their caregivers). Data on melatonin purity, as provided by the supplier, indicated that it was more than 97% pure by infrared and ultraviolet spectra and by high-performance liquid chromatography (total impurities, ≤1.0%; individual impurities, ≤0.3%). Only one dosage (3 mg/d) was used in the study, because this is the only dosage approved for medicinal use in Ar-

* Trademark: Melatol® (Elisium S.A., Buenos Aires, Argentina).

Table I. Demographic data.

Patient No.	Age (y)	Sex	Clinical Diagnosis	Other Psychopharmacologic Treatment
1	68	F	Primary insomnia	Clonazepam 2 mg
2	82	F	Primary insomnia	Alprazolam 1 mg
3	91	M	Primary insomnia	Alprazolam 1.5 mg
4	62	F	Primary insomnia	Alprazolam 1 mg
5	58	F	Primary insomnia	Bromazepam 3 mg
6	58	F	Primary insomnia	Clonazepam 0.5 mg
7	63	M	Primary insomnia	Clonazepam 0.25 mg
8	82	F	Primary insomnia	
9	79	F	Primary insomnia	Clonazepam 0.5 mg
10	60	F	Primary insomnia	
11	94	F	Primary insomnia	
12	86	M	Primary insomnia	Alprazolam 1 mg
13	66	M	Primary insomnia	
14	62	F	Primary insomnia	Clonazepam 0.25 mg
15	96	F	Primary insomnia	
16	69	F	Primary insomnia	Alprazolam 1.5 mg
17	70	F	Primary insomnia	
18	72	F	Primary insomnia	
19	73	F	Primary insomnia	Alprazolam 1.5 mg
20	60	F	Primary insomnia	
21	62	F	Primary insomnia	Bromazepam 2 mg
22	56	F	Primary insomnia	
23	67	F	Insomnia + depression	Clomipramine 15 mg, clonazepam 2 mg
24	77	M	Insomnia + depression	Paroxetine 20 mg
25	80	F	Insomnia + depression	Amitriptyline 75 mg, alprazolam 1.5 mg
26	86	M	Insomnia + depression	Paroxetine 40 mg, clonazepam 3 mg
27	60	F	Insomnia + depression	Amitriptyline 100 mg
28	64	F	Insomnia + depression	Fluoxetine 20 mg, alprazolam 2 mg
29	74	F	Insomnia + depression	Amitriptyline 100 mg, alprazolam 1.5 mg
30	86	M	Insomnia + depression	Amitriptyline 75 mg, clonazepam 1 mg
31	96	F	Insomnia + depression	Sertraline 40 mg, clonazepam 1 mg
32	79	M	Insomnia + Alzheimer-type dementia	Thioridazine 25 mg, clonazepam 1 mg
33	84	M	Insomnia + vascular-type dementia	Thioridazine 25 mg, clonazepam 1.5 mg
34	84	F	Insomnia + vascular-type dementia	Promazine 50 mg
35	86	M	Insomnia + Alzheimer-type dementia	Thioridazine 15 mg
36	79	M	Alzheimer's disease	Thioridazine 10 mg, bromazepam 3 mg
37	64	M	Insomnia + vascular-type dementia	Thioridazine 50 mg, alprazolam 1 mg
38	80	M	Insomnia + vascular-type dementia	Bromperidol 2 mg
39	85	F	Insomnia + vascular-type dementia	Thioridazine 25 mg, alprazolam 1 mg
40	62	F	Insomnia + Alzheimer-type dementia	Clonazepam 1 mg
41	84	F	Insomnia + Alzheimer-type dementia	Thioridazine 10 mg, bromazepam 2 mg

F = female; M = male.

gentina. No relationship was noted between patient body weight (range, 56 to 94 kg) or sex and the observed response to melatonin treatment.

Assessments of overall sleep quality and daytime alertness, as well as the changes observed after treatment, were based on the structured clinical interviews[19] and sleep logs completed by the patients or their caregivers. Data from the sleep logs on sleep patterns, bedtimes, wake time, number of awakenings, and general sleep information were analyzed. The patients or their caregivers were asked to assess the quality of sleep, morning alertness, and daytime alertness graphically on a visual analogue scale from 0 to 10.

As an indirect estimate of agitated behavior at the beginning of the night, the coefficient of variation ([SD/mean]100) of bedtime was computed on days 0 to 2 and on days 19 to 21 of treatment. It was postulated that the degree of day-to-day variation in bedtime would differ between patients with and without dementia and could give an indirect evaluation of sundowning and its changes after melatonin administration.

In this open-label study, patients continued to receive their usual medication until day 11 of treatment, when an attempt was made by the physician in charge to discontinue or decrease benzodiazepine administration, as suggested by the findings on clinical examination. Concomitant psychopharmacologic medication included benzodiazepines (clonazepam, alprazolam, or bromazepam), antidepressants (clomipramine, amitriptyline, fluoxetine, paroxetine, or sertraline), and antipsychotic drugs (promazine, thioridazine, or bromperidol) (Table I). None of the patients had received melatonin or any other sleep aid (prescription or nonprescription) before the study. Caffeine-containing beverages and alcohol were prohibited during the study.

Adverse effects were monitored throughout the study. The withdrawal period was not monitored.

Statistical Analysis

Results were analyzed statistically by nonparametric repeated-measures analysis of variance followed by Friedman's test or by paired nonparametric Wilcoxon's test.

RESULTS

Figure 1 shows the effect of melatonin treatment on sleep quality. Starting from days 2 and 3 of treatment, melatonin augmented subjective evaluations of sleep quality in patients with sleep disturbances with or without symptoms of depression; the change reached statistical significance on days 9 and 10 of treatment ($P < 0.05$). Patients with sleep disturbances and dementia did not exhibit significant changes in sleep quality, as evaluated by their caregivers.

The effect of melatonin treatment on the number of awakenings is shown in Figure 2. Melatonin significantly diminished the number of sleep interruptions in patients with sleep disturbances alone and in those with sleep disturbances associated with symptoms of depression; the change was statistically significant from day 3 through day 21 of treatment in patients with sleep disturbances alone ($P < 0.01$) and on days 19 and 20 in patients with sleep disturbances and depression ($P < 0.05$). The decrease in the number of awakenings during melatonin treatment in patients with dementia did not reach statistical significance.

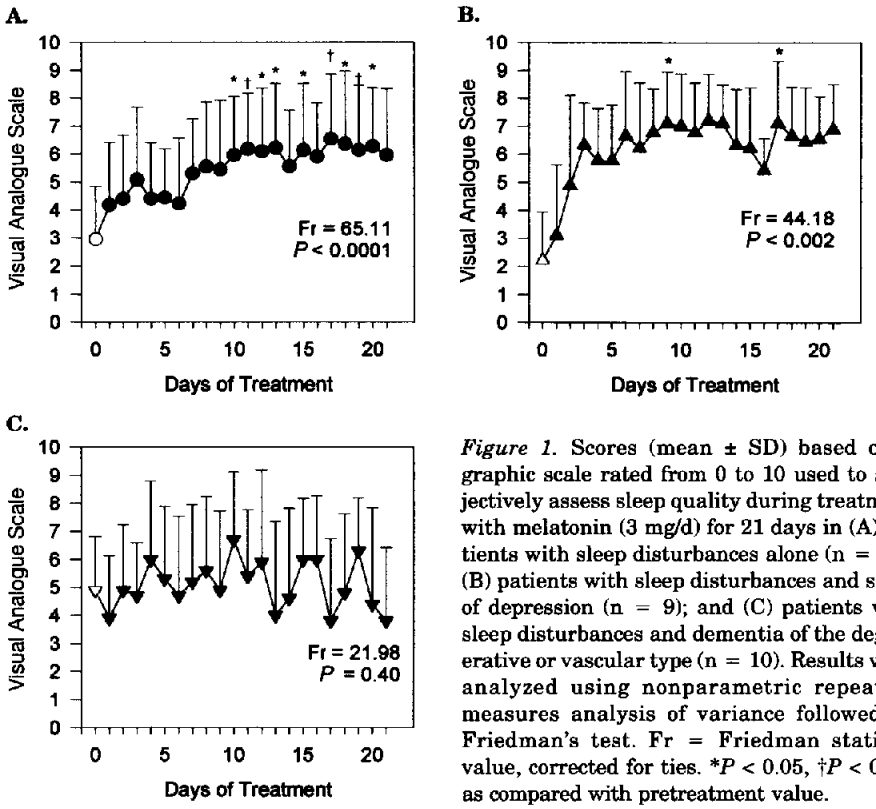

Figure 1. Scores (mean ± SD) based on a graphic scale rated from 0 to 10 used to subjectively assess sleep quality during treatment with melatonin (3 mg/d) for 21 days in (A) patients with sleep disturbances alone (n = 22); (B) patients with sleep disturbances and signs of depression (n = 9); and (C) patients with sleep disturbances and dementia of the degenerative or vascular type (n = 10). Results were analyzed using nonparametric repeated-measures analysis of variance followed by Friedman's test. Fr = Friedman statistic value, corrected for ties. *$P < 0.05$, †$P < 0.01$, as compared with pretreatment value.

Figures 3 and 4 show the consequences of melatonin treatment on self-rated estimates of next-day function (ie, alertness in the morning and during the day). In patients with sleep disturbances only, melatonin augmented morning alertness (Figure 3) and daytime alertness (Figure 4); these changes reached statistical significance ($P < 0.05$) starting on day 10 and day 13 of treatment, respectively. Patients with depression or dementia did not exhibit significant improvement of morning or daytime alertness during melatonin treatment.

Table II summarizes the effect of melatonin treatment on the coefficient of variation of patient bedtime. As an indirect estimate of agitated behavior at the beginning of the night, the coefficient of variation was computed on days 0 to 2 and on days 19 to 21 of treatment. On days 0 to 2, the coefficient of variation averaged 58% in patients with dementia; in patients not exhibiting signs of dementia, the coefficient of variation averaged 33% for those with sleep disturbances alone and 27% for those with sleep disturbances and depression. A significant decrease was detected on days 19 to 21 of treatment in the patients with dementia.

Clinical evaluation on day 21 of treatment indicated that 16 (73%) of

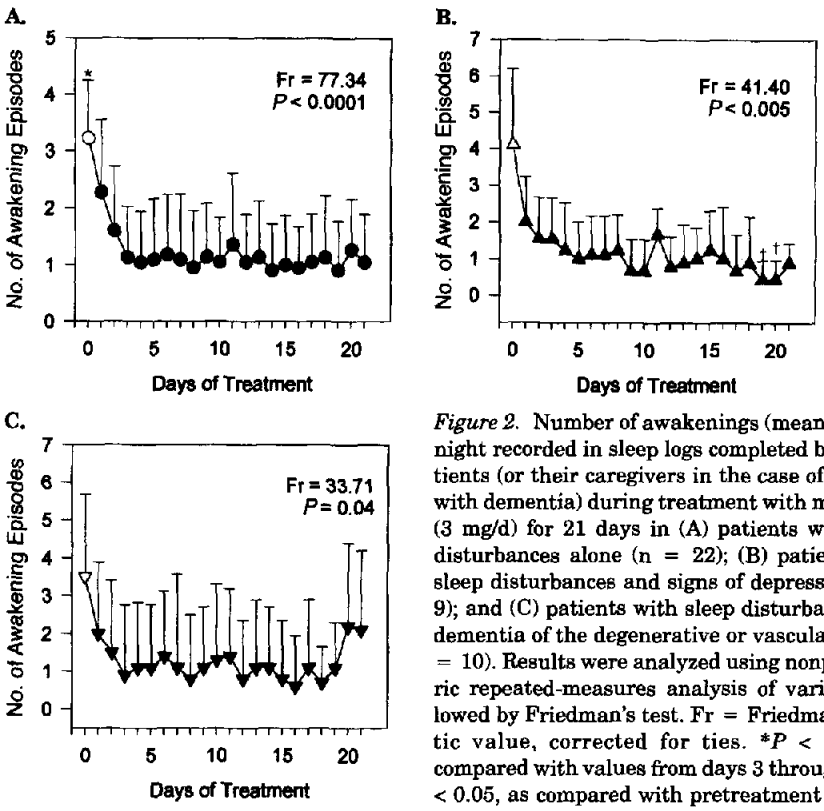

Figure 2. Number of awakenings (mean ± SD) at night recorded in sleep logs completed by the patients (or their caregivers in the case of patients with dementia) during treatment with melatonin (3 mg/d) for 21 days in (A) patients with sleep disturbances alone (n = 22); (B) patients with sleep disturbances and signs of depression (n = 9); and (C) patients with sleep disturbances and dementia of the degenerative or vascular type (n = 10). Results were analyzed using nonparametric repeated-measures analysis of variance followed by Friedman's test. Fr = Friedman statistic value, corrected for ties. *$P < 0.01$, as compared with values from days 3 through 21; †$P < 0.05$, as compared with pretreatment value.

the patients with sleep disturbances only and 4 (44%) of the patients with sleep disturbances plus depression experienced symptomatic improvement. In patients with dementia, significant improvement of sundowning was reported in 7 (70%) of the 10 patients with dementia. With regard to concomitant benzodiazepine treatment, 4 (31%) of 13 patients with primary insomnia reduced concomitant benzodiazepine use (by 50% to 75% of initial doses) and 4 (31%) discontinued use, whereas in patients with depression or dementia, 2 (29%) of 7 patients in both groups reduced their benzodiazepine dose by up to 50%.

No treatment-related side effects were reported.

DISCUSSION

Changes in sleep-wake patterns are among the hallmarks of aging; the number and duration of waking episodes increase, the nondreaming phases of sleep decrease in number and duration, the first rapid-eye-movement phase occurs earlier in the night, and the tendency to fall asleep

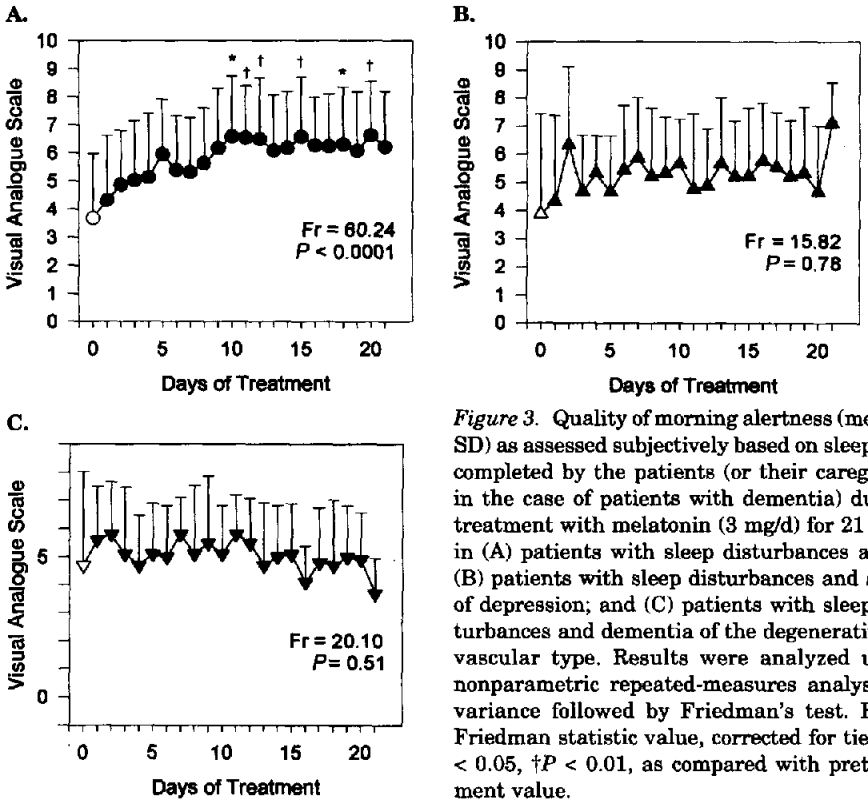

Figure 3. Quality of morning alertness (mean ± SD) as assessed subjectively based on sleep logs completed by the patients (or their caregivers in the case of patients with dementia) during treatment with melatonin (3 mg/d) for 21 days in (A) patients with sleep disturbances alone; (B) patients with sleep disturbances and signs of depression; and (C) patients with sleep disturbances and dementia of the degenerative or vascular type. Results were analyzed using nonparametric repeated-measures analysis of variance followed by Friedman's test. Fr = Friedman statistic value, corrected for ties. $^*P < 0.05$, $^\dagger P < 0.01$, as compared with pretreatment value.

during the day increases.[1–3,20] Complaints of difficulty in initiating and maintaining sleep and of daytime drowsiness are more common among elderly patients than among patients in any other age group, and evidence indicates that impaired melatonin secretion is associated with sleep disturbances in the elderly.[6–10]

In the present open-label, short-term pilot study, the sleep-promoting action of melatonin (3 mg orally for 21 days) was explored in a small, heterogeneous group of elderly patients with psychophysiologic insomnia and insomnia associated with depression or dementia. Overall sleep quality and daytime alertness were assessed by means of structured clinical interviews and sleep logs completed by the patients or their caregivers. The results suggest that melatonin therapy may be beneficial in the initiation and maintenance of sleep in patients with insomnia alone or insomnia associated with symptoms of depression. Estimates of next-day function (ie, alertness in the morning and during the day) showed significant improvement after melatonin therapy in elderly patients with sleep disturbances alone but not in those with depression. Hence, the efficacy of

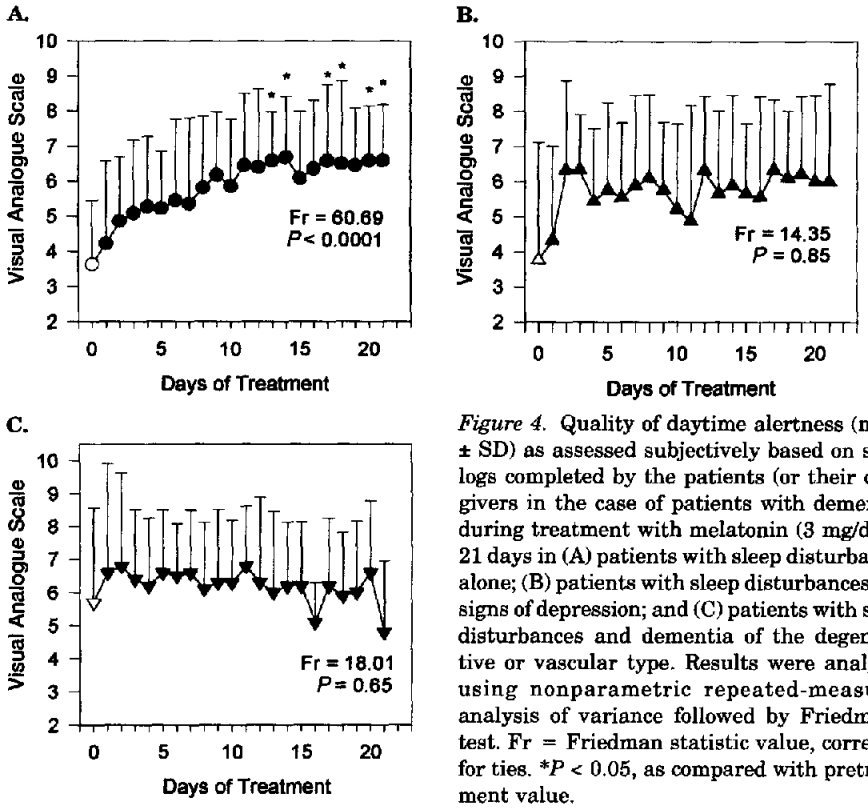

Figure 4. Quality of daytime alertness (mean ± SD) as assessed subjectively based on sleep logs completed by the patients (or their caregivers in the case of patients with dementia) during treatment with melatonin (3 mg/d) for 21 days in (A) patients with sleep disturbances alone; (B) patients with sleep disturbances and signs of depression; and (C) patients with sleep disturbances and dementia of the degenerative or vascular type. Results were analyzed using nonparametric repeated-measures analysis of variance followed by Friedman's test. Fr = Friedman statistic value, corrected for ties. *$P < 0.05$, as compared with pretreatment value.

melatonin in improving sleep may not correlate with a similar beneficial effect on mood in depressed patients.

Patients with sleep disturbances and dementia of the degenerative or vascular type did not show signs of improvement in sleep quality or alertness. However, they exhibited less variability of bedtime as treatment progressed, and the overall clinical assessment indicated amelioration of sundowning episodes in 7 (70%) of the 10 patients examined. This was

Table II. Effect of melantonin treatment on coefficient of variation of bedtime in patients with sleep disturbances. Values are percent variation ([SD/mean]100) of bedtime in time interval quoted.

Sleep Disturbances Alone (n = 22)		Sleep Disturbances and Depression (n = 9)		Sleep Disturbances and Dementia (n = 10)	
Days 0–2	Days 19–21	Days 0–2	Days 19–21	Days 0–2	Days 19–21
32.6 ± 14.9	31.5 ± 10.8	27.1 ± 14.1	24.5 ± 13.5	58.0 ± 24.7	41.5 ± 20.9*

* $P < 0.03$, as compared with days 0 to 2 of treatment.

reflected by a significant decrease in the percentage of variation in bedtime when the initial versus the final period of treatment was analyzed.

Four (31%) of 13 patients with primary insomnia who were receiving benzodiazepines concomitantly reduced their doses by 50% to 75%, whereas 4 other patients discontinued benzodiazepine treatment. Two (29%) of 7 patients with depression and an equal number with dementia reduced benzodiazepine use by up to 50%.

Our findings support those of Garfinkel et al,[21] which indicate that melatonin treatment increases sleep quality and quantity and decreases wakefulness after sleep onset, sleep latency, and the number of awakenings in elderly patients who have been taking benzodiazepines. Thus melatonin therapy may be an effective tool for decreasing benzodiazepine use in patients with sleep disturbances.

CONCLUSION

The results of this open-label, short-term pilot study suggest that melatonin may be useful for the treatment of primary sleep disturbances in elderly patients. Results in patients with depression or dementia were more ambiguous. It should be stressed that the long-term efficacy and tolerability of melatonin treatment remain to be determined in randomized, double-masked trials in a variety of populations of elderly patients.

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