The Effect of Melatonin, Magnesium, and Zinc on Primary Insomnia in Long-Term Care Facility Residents in Italy: A Double-Blind, Placebo-Controlled Clinical Trial

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OBJECTIVES: To determine whether nightly administration of melatonin, magnesium, and zinc improves primary insomnia in long-term care facility residents.

DESIGN: Double-blind, placebo-controlled clinical trial.

SETTING: One long-term care facility in Pavia, Italy.

PARTICIPANTS: Forty-three participants with primary insomnia (22 in the supplemented group, 21 in the placebo group) aged 78.3 ± 3.9.

INTERVENTION: Participants took a food supplement (5 mg melatonin, 225 mg magnesium, and 11.25 mg zinc, mixed with 100 g of pear pulp) or placebo (100 g pear pulp) every day for 8 weeks, 1 hour before bedtime.

MEASUREMENTS: The primary goal was to evaluate sleep quality using the Pittsburgh Sleep Quality Index. The Epworth Sleepiness Scale, the Leeds Sleep Evaluation Questionnaire (LSEQ), the Short Insomnia Questionnaire (SDQ), and a validated quality-of-life instrument (Medical Outcomes Study 36-item Short Form Survey (SF-36)) were administered as secondary end points. Total sleep time was evaluated using a wearable armband-shaped sensor. All measures were performed at baseline and after 60 days.

RESULTS: The food supplement resulted in considerably better overall PSQI scores than placebo (difference between groups in change from baseline PSQI score = 6.8; 95% confidence interval = 5.4–8.3, $P < .001$). Moreover, the significant improvements in all four domains of the LSEQ (ease of getting to sleep, $P < .001$; quality of sleep, $P < .001$; hangover on awakening from sleep, $P = .005$; alertness and behavioral integrity the following morning, $P = .001$), in SDQ score ($P < .001$), in total sleep time ($P < .001$), and in SF-36 physical score ($P = .006$) suggest that treatment had a beneficial effect on the restorative value of sleep.

CONCLUSION: The administration of nightly melatonin, magnesium, and zinc appears to improve the quality of sleep and the quality of life in long-term care facility residents with primary insomnia. **J Am Geriatr Soc 59:82–90, 2011.**

Key words: dietary supplement; elderly; insomnia; melatonin; zinc; magnesium

Insomnia is a condition characterized by difficulty in initiating or maintaining sleep or by chronic nonrestorative and poor-quality sleep, despite adequate opportunities and conditions for sleep.[1] The prevalence of insomnia increases with age and in particular results in poor subjective sleep quality.[2–4] Approximately 50% of older adults complain of insomnia and are generally dissatisfied with the quality of their sleep.[2–5] A survey conducted as part of the National Institute on Aging Established Populations for Epidemiologic Studies of the Elderly (EPESE) found that 42% of community-dwelling elderly people reported difficulties in falling and staying asleep,[6] but more than two-thirds of insomnia cases are undiagnosed, and physicians are seldom trained to detect or enquire about symptoms of insomnia.[7] Although the total amount and type of sleep varies throughout the life cycle, and the prevalence of insomnia is higher in older adults, insomnia is not necessarily an inevitable consequence of aging.[8] Insomnia is particularly challenging for clinicians because of the lack of treatment guidelines, especially regarding the elderly population, and because of different methods used in clinical trials. Poor sleep is correlated with morbidity and mortality in older adults.[9] In addition to daytime dysfunction, insomnia is associated with various adverse effects such as poorer quality of life in

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institutionalized individuals[10] and public health concerns that are related, but not limited, to the associated direct and indirect costs.[11] For example, epidemiological studies have indicated that people with sleep disturbance are much more likely to require health care, which imposes a substantial economic burden on individuals and healthcare systems.[10,12] Moreover, accumulating evidence suggests that sleep problems are related to slips and falls in older adults.[13]

Insomnia also impairs normal daytime functioning as a result of sleep insufficiency. These impairments generally include fatigue, irritability, poorer memory and concentration, and malaise.[14] A greater incidence of depressive symptoms correlates with poor sleep quality or chronic insomnia, disturbances that appear to be major risk factors for depression.[15]

Hence, an understanding of the physiological mechanisms of sleep regulation, and especially of the consequences of their breakdown, can help to unravel the complexities of the pathophysiology of depressive disorders.[15] Melatonin plays an important role in this context. Disturbances in the rhythm and amplitude of melatonin secretion may account for symptomatic disturbances to sleep and mood. Moreover, the close association between sleep and mood disorders suggests that melatonin may be important in mood management.[16,17] Melatonin treatment not only improved total sleep time, but also reduced depressive symptoms,[17] indicating a relationship between sleep disturbance and symptoms of depression.

The pineal hormone melatonin (N-acetyl-5-methoxytryptamine) acts as a neuroendocrine transducer of the light–dark cycle. It plays an important role in regulating human circadian rhythms and may have sleep-inducing effects in humans.[18,19] Melatonin production declines with age and is lower in middle-aged and elderly adults with insomnia than in good sleepers.[20]

Long-term use of sedative-hypnotics for insomnia lacks an evidence base and has traditionally been discouraged for reasons that include concerns about potential adverse drug effects, such as cognitive impairment (anterograde amnesia), daytime sedation, motor incoordination, and risk of motor vehicle accidents and slips and falls. In addition, the effectiveness and safety of long-term use of these agents remain to be determined.[21] Moreover, several studies have been conducted to assess the effects of sleep hygiene interventions and various nonpharmacological interventions, such as physical activity, bright light exposure, and noise abatement, but no definite effect on night time sleep has been reported.[22] Many people seek treatment for insomnia using alternative and complementary medicine.[23] Generally, the main goal of nonpharmacological remedies in the treatment of primary insomnia is to correct behavior patterns that are not conducive to a good quality sleep, and nutrients might play a significant role in this setting, but no evidence is available as to the preferred alternative treatment of insomnia, and in particular, controlled clinical trials are lacking in this field. In addition to melatonin, other micronutrients such as zinc and magnesium may play a role in facilitating sleep. Zinc exhibits an antidepressant-like activity, as stated in a preclinical model of depression[24–26] and in two other clinical trials.[25,26] Significant clinical correlates were shown[27] related to its action as an antagonist of the glutamate/N-methyl-D-aspartate receptor. Magnesium has beneficial effects on mood and is crucial, together with zinc, in the endogenous synthesis of melatonin.[28]

The purpose of this double-blind, placebo-controlled clinical trial was to assess the efficacy and safety of the combination of melatonin (5 mg), magnesium (225 mg), and zinc (11.25 mg), conveyed in pear pulp (100 g), in improving quality of sleep and morning alertness in adults aged 70 and older who met the criteria for primary insomnia.

PARTICIPANTS AND METHODS

Participants

The study was performed under the approval of the Ethics Committee of the Department of Internal Medicine and Medical Therapy, University of Pavia. Participants gave their written consent to take part in the study. The participants were recruited from a long-term care facility in Pavia and were enrolled after at least 3 months of institutionalization. The F. Pertusati long-term care facility (Azienda di Servizi alla Persona, Pavia) has 250 inpatients divided into nine care units (one special care unit with 20 patients presenting serious memory problems). The facility employs seven doctors: five geriatricians, a neurologist, a nutritionist, a psychologist, and two dietitians. Each medical care unit also has its own specially trained staff members, on hand 24 hours a day, to provide medical care, as well as physical, speech and occupational services. Admission to the F. Pertusati facility depends on physical and mental health status, especially when disorders are so numerous and severe as to cause disability. Some individuals are admitted for other reasons, such as social factors: very old adults with no family, older adults without economic support. The residents remain institutionalized until they die. Eligible individuals were aged 70 and older and were diagnosed as with primary insomnia as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)[1] for at least 1 month.

Primary Insomnia

Exclusion criteria were breathing-related sleep disorder, circadian rhythm sleep disorder, sleep disorder due to a general medical condition, significant psychiatric or neurological disorder (anxiety, depression, dementia), restless leg syndrome, and intake of any medication that affects the central nervous system or sleep—wake cycle 2 weeks before the first day of the placebo run-in period. Individuals taking beta-blockers were also excluded. Beta-blockers, widely used in the treatment of hypertension and heart disorders, may be associated with sleep impairment because they inhibit melatonin production by binding to pineal beta-adrenoreceptors.[29] Primary insomnia was initially diagnosed using a sleep history questionnaire (SHQ) recommended by Clinical Practice Guideline—Adult Insomnia.[30] The SHQ characterizes the primary sleep complaints according to the different diagnostic criteria (DSM-IV and *International Classification of Diseases, Tenth Revision*). The questionnaire also helps to differentiate primary from secondary insomnia caused by medical and psychiatric disorders (including depression and anxiety) and specific insomnia disorders, such as circadian rhythm disorders, movement

disorders, parasomnias, and breathing-related sleep disorders. Primary insomnia was defined, according to the DMS-IV, as difficulty in initiating or maintaining sleep over more than a 1-month period with no sign of any other sleep or mental disorder, general medical condition, drug use, or abuse. A geriatrician screened potential participants and administered a physical examination, which has an important role in evaluating people with insomnia with medical symptoms.[30] To exclude psychiatric disorders, including depression and dementia, participants underwent a detailed psychological assessment that included the Geriatric Depression Scale (GDS)[31] and the Mini-Mental State Examination (MMSE)[32] during their first visit. Potential participants who scored 15 or more on the GDS and those with a score less than 24 on the MMSE (adjusted for the socioeducational level of the individual) were not considered eligible for the study. In addition, history of severe psychiatric disorders, especially psychosis, anxiety, and depression, were exclusion criteria. Participants' ability to care for themselves was assessed using the Katz index of independence in activities of daily living (ADLs)[33] before enrolment. Last, long-term care facility residents who had undergone psychotropic treatments (neuroleptics, antiepileptics, barbiturates, antidepressants, anxiolytics, or lithium) within 3 months before the study were excluded. During the second visit, a drug screen for benzodiazepines, barbiturates, sedating antihistamines, hydroxyzine, doxylamine, zaleplon, zopiclone, and zolpidem was administration and, if positive, led to exclusion. Other forms of medication were continued as prescribed by the attending physician.

Endpoints of the Study

Primary Outcome

The main outcome measure was the effect of a food supplement consisting of melatonin, magnesium, and zinc, conveyed in pear pulp, on the quality of sleep. This was assessed according to mean change from baseline to Week 8 in Pittsburgh Sleep Quality Index (PSQI) total score and was compared between the two groups.

Secondary Outcomes

Secondary outcomes were changes in the quality of sleep and daily activity, measured according to other questionnaires as detailed below: changes in mood, as measured according to the GDS; changes in quality of life, as measured according to the physical and mental components of the Medical Outcomes Study 36-item Short-Form Survey (SF-36); and nutritional status changes. All of the changes were evaluated at baseline and after 8 weeks of treatment. The occurrence and severity of any adverse effects were recorded. Individuals were also asked whether they were happy with pear pulp as a vehicle for administering the food supplement.

Assessment Measures

Pittsburgh Sleep Quality Index

The PSQI[34] is a seven-component scale, each component dealing with a major aspect of sleep: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. These components are weighted equally on a 0 to 3 scale, with a global score ranging from 0 to 21. A global PSQI score greater than 5 has been found to have a sensitivity of 89.6% and a specificity of 86.5% in differentiating good from poor sleepers.

Leeds Sleep Evaluation Questionnaire

The Leeds Sleep Evaluation Questionnaire (LSEQ)[35] is an instrument that measures subjective evaluation of sleep and daytime effects. It includes 10 visual analogue scales (VASs) that measure four domains of sleep and morning behavior: ease of getting to sleep (GTS), quality of sleep (QOS), hangover on awakening from sleep (AFS), and alertness and behavioral integrity the following morning (BFW). The LSEQ has been validated in a number of studies involving the target population of people with insomnia aged 55 and older.[36]

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a questionnaire that measures an individual's expectation of dozing in eight hypothetical situations. Dozing probability ratings range from 0 (none) to 3 (high probability). A total score of 10 or more is considered to be indicative of excessive daytime sleepiness. An Italian translated version of the ESS was administered.[37]

Sleep-Wake Activity Inventory

The Sleep-Wake Activity Inventory[38] consists of 59 items that provide six subscale scores: excessive daytime sleepiness, nocturnal sleep, ability to relax, energy level, social desirability, and psychic distress. Each item is rated on a 1 to 9 semicontinuous Likert-type scale from always to never, based on the previous 7 days.

Short Insomnia Questionnaire

The Short Insomnia Questionnaire (SDQ)[39] is a short self-rating questionnaire with 18 questions on different sleep problems and five questions concerning sleep habits. The first group of questions requires participants to evaluate whether they have had any sleep disorder in the past month. The first three questions in this group concern symptoms of insomnia. The other questions investigate the presence of excessive sleepiness, sleep apnea, and parasomnias. A subsequent set of questions investigates the duration, frequency, and consequences of the problem and is used to evaluate the severity of the sleep disturbances reported. Question 18 concerns possible snoring problems.

Wearable Armband-Shaped Sensor

Total sleep time, total steps taken, and total time in bed were evaluated according to detected rollover movements during sleep using a wearable armband-shaped sensor (SenseWear Pro2 Armband, Sensormedics Italia, Milan, Italy).[40] The sensor was worn consecutively for 72 hours on the nondominant upper arm during the 2 weeks before starting the study and the last 2 weeks of the study.

Medical Outcomes Study 36-Item Short-Form Survey

The SF-36[41] is a valid generic instrument for rating health-related quality of life in several research fields, with a recognized validity, high internal consistency, and high test—retest reliability. Response items are arranged in eight domains reflecting physical and mental health-related quality of life. Participants are asked to rate their general health status and to compare it with the previous year. The eight scales were scored from 0 to 100 (worst to best possible health status) according to the scoring manuals and combined into two dimensions: the physical (PCS) and mental (MCS) component subscale scores, normalized for the Italian population.

Geriatric Depression Scale

The GDS is a routine scale for a comprehensive geriatric assessment (0–9 normal, 10–19 mildly depressed, 20–30 severely depressed).[31]

Participants completed the questionnaires in three stages over 3 consecutive days.

Nutritional Status

Nutritional status was assessed using anthropometric measurements. Body weight and height were measured, and body mass index (BMI) (kg/m^2) was calculated. The Mini Nutritional Assessment (MNA) was administered in all participants.[42] Participants ate three daily meals: breakfast between 7:00 a.m. and 8:00 a.m., lunch between noon and 1:00 p.m., and dinner between 6:00 p.m. and 7:00 p.m. Food intake was based on a well-balanced diet (with standard calories and macro and micronutrients) provided by the hospital kitchen.

The appointed care givers (the same two dietitians) collected data regarding adverse effects daily after participants had taken the supplement, 1 hour before bedtime.

Study Design

This was a parallel-group, randomized, double-blind, placebo-controlled clinical trial to assess the efficacy of a food supplement consisting of melatonin, magnesium, and zinc, conveyed in pear pulp, in reducing sleep disorders as measured according to the PSQI questionnaire in older adults. All measures were performed at baseline and after 60 days of treatment. Treatment consisted of a food supplement of melatonin, magnesium, and zinc (Mezinat, Difass, Republic of San Marino) conveyed in 100 g of pear pulp, with the following nutritional values: 60 kcal/252 kJ, 0.5 g of protein, 14 g of carbohydrates, 0.2 g of fat, 5 mg of melatonin, 225 mg of magnesium, and 11.25 mg of zinc. The decision to administer 5 mg of melatonin was based on the "melatonin replacement hypothesis,"[43] according to which insomnia in older adults is partly due to an age-

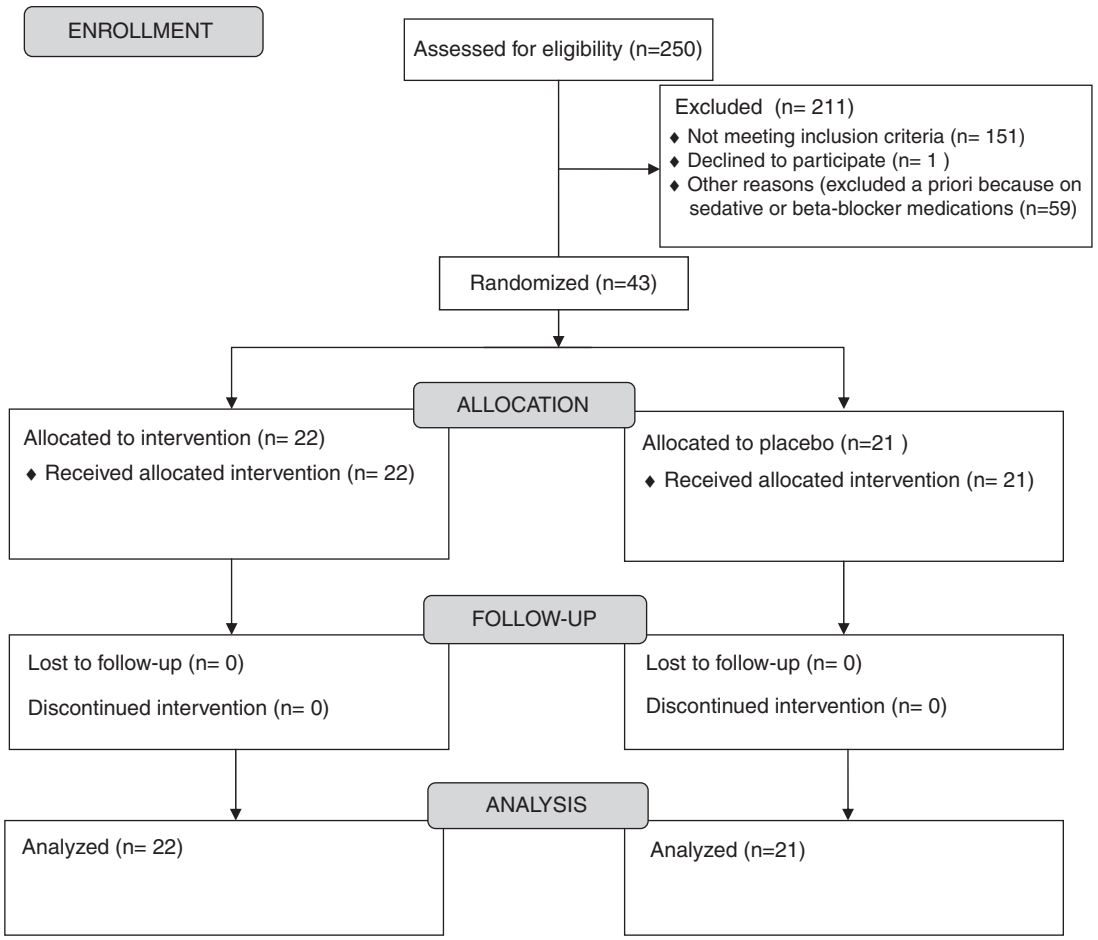

Figure 1. Study flow diagram.

related decline in melatonin, so that replacement therapy with high doses of melatonin is expected to improve insomnia in these people. Considering potential malabsorption and the poorer sensitivity of melatonin receptors in elderly adults, it was decided to administer melatonin in the upper limit of the range of doses applied in experimental studies in the literature. Recently, an oral dose of 5 mg of melatonin proved to be effective in improving insomnia and behavioral disorders and in facilitating the discontinuation of hypnotic drugs in a community-living elderly population.[17]

Controls were given 100 g of pear pulp. Participants were randomized to receive one serving of the food supplement, orally, once a day, 1 hour before bedtime (between 9.00 p.m. and 9.30 p.m.) or an identical serving of placebo for 8 weeks. Each portion of the same product assigned to each treatment group was labelled with a participant number and code (A or B) according to a block randomization list prepared by an independent statistician. Both preparations were identical in appearance, smell, and taste. Investigators were blinded to the randomization table, code assignments, and procedure. At the time of enrollment, each participant was assigned a progressive participant number. The CONSORT guidelines (http://www.consort-statement.org) for the study design and report were followed.

Sample Size

Based on evidence in the literature,[44] PSQI score was expected to decrease 0.84 points in the placebo group and 3.20 (difference 2.36) in the treated group. A common standard deviation (SD) of 2.50 was considered in the computations. A sample size of 19 participants per group has 80% power to detect such a difference (effect size of 1 SD) with a Student *t*-test for independent samples and a significance level of 5% (two-sided). To adjust for an expected drop-out rate of 10%, approximately 42 participants (21 per group) needed to be enrolled in the study. nQuery 4 (Statistical Solutions, Cork, Ireland) was used for computations.

Statistical Analysis

Continuous data were described as means and SDs and categorical data as counts and percentages. All analyses were based on the intention-to-treat principle. None of the participants were lost to follow-up, and no protocol deviation was observed.

The analysis of the primary outcome was based on the intention-to-treat principle. The primary outcome measure was change in PSQI from baseline. The Student *t*-test was used to compare changes in the placebo with those in the treated group. The mean differences between changes and their 95% confidence intervals (CIs) were computed. Within each treatment group, alterations from baseline to the end of the study were assessed using the paired Student *t*-test. Mean changes and 95% CIs were reported. The Fisher exact test supported the analysis of the primary endpoint, comparing the proportion of participants who reached a PSQI less than 5 in each group. The difference in proportion and its 95% CI were calculated. Results were confirmed according to a sensitivity analysis of the primary endpoint, which compared changes in PSQI with the Mann Whitney *U* test and a general linear regression model, also including baseline values, and by calculating Huber-White robust standard errors.

The analysis of secondary outcomes was conducted using the same algorithms as for the main analysis of the primary outcome.

Stata 10.1 (StataCorp, College Station, TX) was used for computation. A two-sided *P*-value $<.05$ was considered statistically significant.

Table 1. Baseline Characteristics of Participants

Characteristic	Treatment Group	Placebo Group
Male, n (%)	7 (32)	9 (43)
Female, n (%)	15 (68)	12 (57)
Age, mean ± SD	78.6 ± 4.1	78.1 ± 3.8
Geriatric Depression Scale score (0–9 normal, 10–19 mildly depressed, 20–30 severely depressed), mean ± SD	11.7 ± 4.3	9.6 ± 2.2
Mini-Mental State Examination score <24 (cognitively impaired), mean ± SD	26.3 ± 2.9	26.2 ± 3.0
Activity of daily living score (0 = dependent to 6 = independent), mean ± SD	4.2 ± 1.0	4.2 ± 1.1
Pittsburgh Sleep Quality Index (≥5 indicates poor sleeper), mean ± SD	12.7 ± 2.6	12.3 ± 3.6
Leeds Sleep Evaluation Questionnaire (visual analogue scale: −5 (negative aspects) to +5 (positive aspects)), mean ± SD		
Getting to sleep	−7.3 ± 4.5	−6.0 ± 4.3
Quality of sleep	−4.1 ± 3.2	−5.1 ± 2.7
Hangover on awakening from sleep	−1.0 ± 4.1	−1.5 ± 3.9
Alertness and behavioral integrity the following morning	−4.9 ± 5.6	−1.8 ± 4.8
Epworth Sleepiness Scale (≥10 = excessive daytime sleepiness), mean ± SD	10.9 ± 5.1	11.0 ± 3.9
Sleep-Wake Activity Inventory (≤40 indicates excessive daytime sleepiness, 40–50 possible daytime sleepiness, ≥50 no daytime sleepiness), mean ± SD	82.5 ± 17.1	82.0 ± 10.8
Short Insomnia Questionnaire score, mean ± SD	3.2 ± 1.3	3.0 ± 1.4
Total time in bed, minutes, mean ± SD*	3,065.9 ± 88.0	3,041.6 ± 152.4
Total sleep time, minutes, mean ± SD*	1,297.0 ± 78.7	1,293.8 ± 37.1
Total steps, mean ± SD*	1,068.6 ± 126.1	1,089.8 ± 232.4
Medical Outcomes Study, 36-item Short-Form Survey score, mean ± SD		
Physical Component Subscale	32.1 ± 6.7	35.1 ± 5.9
Mental Component Subscale	49.5 ± 10.0	47.8 ± 9.4
Body mass index, kg/m^2, mean ± SD	23.1 ± 2.4	21.9 ± 2.3
Mini Nutritional Assessment score (≥24 = well nourished, 23.5–17 = at risk of malnutrition, <17 = malnourished), mean ± SD	22.4 ± 2.7	22.3 ± 1.9

* SenseWear Pro2 Armband worn for 72 hours.
SD = standard deviation.

RESULTS

Fifty-nine of the 250 long-term care facility residents, institutionalized in F. Pertusati (Azienda di Servizi alla

Table 2. Primary End Point: Comparison of Change Over Time in Pittsburgh Sleep Quality Index (PSQI) Scores of Treated and Untreated Participants

PSQI	Treatment Group	Placebo Group	*P*-Value
Treatment effect: Difference in change (95% CI)	6.8 (5.4–8.3)		<.001
Score			
Baseline, mean ± SD	12.7 ± 2.6	12.3 ± 3.6	
After 60 days, mean ± SD	5.5 ± 1.9	12.0 ± 4.4	
Change over time (95% CI)	−7.1 (–8.1 to −6.2)*	−0.3 (−1.5–0.8)°	
Success: score ≤5, n (%)	13 (59)	3 (14)	.004
Incidence of success, % (95% CI)	45 (20–70)		

$P <$ *.001, °.58 vs baseline. CI = confidence interval; SD = standard deviation.

Persona in Pavia) were excluded a priori because they were receiving sedative–hypnotic medication, antidepressant medication, or a beta-blocker at the time of the interview. Forty-four of the remaining 191 participants fulfilled the diagnostic criteria of primary insomnia according to DSM-IV Text Revision. All of them had been institutionalized for more than 3 months before enrollment. One eligible participant refused to take part in the study, leaving a final number of randomized participants of 43, as shown in Figure 1. All participants were fully informed about other treatment options but chose to participate. Twenty-two participants were randomly included in the intervention group and 21 in the placebo group. Population characteristics were similar in both groups (Table 1).

Primary Outcome

Table 2 summarizes the primary outcome evaluations. The food supplement conveyed in pear pulp significantly improved overall PSQI scores by 7 points in the treated group but not in the placebo group (Figure 2), with a difference of 6.8 points between groups (95% CI = 5.4–8.3) ($P < .001$). Moreover 59% of intervention group participants reached a PSQI of 5 or less, versus 14% of controls—a difference of 45 percentage points (95% CI = 20–70).

Secondary Outcomes

A significant treatment benefit of melatonin, magnesium, and zinc in the supplement group was also reached in most secondary outcomes, as shown in Table 3. This was observed in all four domains of the LSEQ and in the SDQ score, both evaluating quality of sleep, as well as in GDS score and SF-36 PCS, evaluating mood and quality of life, respectively. Mean changes in total sleep time and total steps taken, evaluated according to the wearable armband-shaped sensor, were significantly higher in the treated group. The nutritional parameters (BMI, MNA) were found to be similar in the treated and placebo groups.

Adverse Effects and Acceptability

All of the participants tolerated the treatment well, with excellent adherence, with good palatability of the pear pulp. Only two participants in the treatment group reported mild headache. One participant in the placebo group complained of epigastric pain during the study period. None of the participants dropped out of the study, further indicating that the treatment was well tolerated. Adverse events were monitored during all of the follow-up visits, but none were reported. None of the participants complained about smells or commented on the contents of the supplement or revealed a perception of having been included in one of the two groups.

DISCUSSION

This double-blind, placebo-controlled clinical trial is the first study, to the knowledge of the authors, to show that a food supplement containing melatonin, magnesium, and zinc, conveyed in pear pulp, taken 1 hour before bedtime, results in significantly better quality of sleep than a placebo treatment in long-term care facility residents aged 70 and older experiencing primary insomnia. The benefits of this supplementation in primary insomnia in long-term care facility residents appears to have significant clinical importance because insomnia is common in late life.[2–5] Insomnia

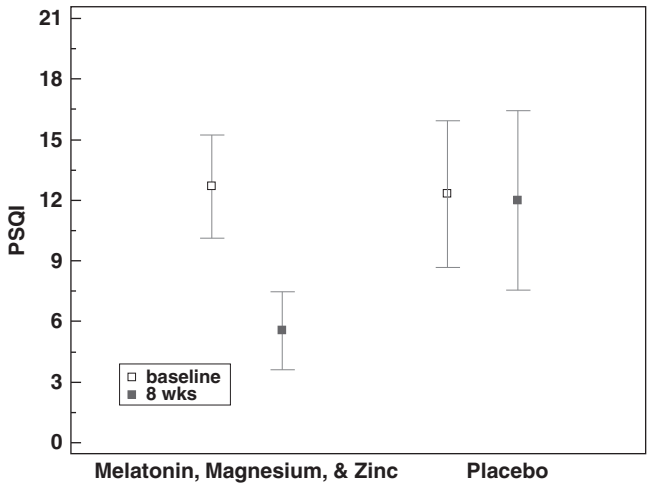

Figure 2. Effects of treatment of the primary end point. Mean Pittsburgh Sleep Quality Index (PSQI) (marker) are reported at baseline and at 8 weeks for the melatonin, magnesium, and zinc (left) and placebo (right) participants, together with their standard deviations (whiskers).

Table 3. Secondary End Points: Comparison of Change Over Time of Treated and Untreated Participants

Parameter	Change from Baseline (95% Confidence Interval)			
	Treatment Group	Placebo Group	Treatment Effect (Treated–Untreated)	*P*-Value
Geriatric Depression scale	− 3.16 (− 4.42 to −1.9)	− 0.59 (− 1.65–0.47)	2.57 (0.97–4.16)	.002
Mini-Mental State Examination	0 (0–0)	0.05 (− 0.05–0.14)	0.05(− 0.05–0.14)	.32
Activities of daily living	0 (− 0.14–0.14)	0.05 (− 0.05–0.14)	0.05 (− 0.12–0.21)	.57
Leeds Sleep Evaluation Questionnaire				
Getting to sleep	13.45 (10.74–16.17)	1.00 (− 0.97–2.97)	− 12.45 (− 15.71 to − 9.20)	< .001
Quality of sleep	6.5 (4.2–8.8)	0.77 (− 0.47–2.02)	− 5.73 (− 8.27 to −3.19)	< .001
Hangover on awakening from sleep	4.23 (− 2.17–6.28)	0.27 (− 1.58–2.13)	− 3.95 (− 6.64 to −1.27)	.005
Alertness and behavioral integrity the following morning	6.77 (3.68–9.86)	− 1.09 (− 3.24–1.05)	− 7.86 (− 11.51 to − 4.21)	.001
Epworth Sleepiness Scale	− 2.91 (− 5.36 to − 0.46)	− 0.76 (− 2.39–0.87)	2.15 (− 0.73–5.03)	.14
Sleep–Wake Activity Inventory	7.05 (0.59–13.5)	1.41 (− 2.2–5.02)	− 5.64 (− 12.81–1.54)	.12
Short Insomnia Questionnaire	4.45 (3.82–5.09)	1.95 (1.37–2.54)	− 2.5 (− 3.34 to − 1.66)	< .001
Total time in bed, minutes*	5.82 (− 53.5–65.13)	− 41.09 (− 115.2–33.02)	− 46.91 (− 139.03–45.21)	.31
Total sleep time, minutes*	182.18 (160.02–204.34)	− 4.64 (− 23.29–14.02)	− 186.82 (− 214.93 to − 158.71)	< .001
Total steps*	49.55 (6.11–92.98)	− 76.36 (− 199.07–46.35)	− 125.91 (− 252.23–0.41)	.05
Medical Outcomes Study, 36-item Short-Form Survey				
Physical Component Subscale	2.48 (0.48–4.49)	− 1.06 (− 2.62–0.49)	− 3.55 (− 6.02 to − 1.07)	.006
Mental Component Subscale	2.03 (− 0.04–4.11)	0.02 (− 2.27–2.3)	− 2.02 (− 5.00–0.97)	.18
Body mass index, kg/m^2	− 0.33 (− 0.89–0.22)-	0.06 (− 0.28–0.39)	0.39 (− 0.24–1.02)	.22
Mini Nutritional Assessment	0.18 (− 0.33–0.7)	0.36 (− 0.05–0.78)	0.18 (− 0.46–0.82)	.57

* SenseWear Pro2 Armband worn for 72 hours.

is not a natural part of aging and is often reversible with prompt and appropriate treatment, but if left untreated, chronic insomnia may have clinical, economic, and human consequences for the individual and society.[9,11,13,14] Because insomnia is associated with significant daytime distress, improvement in sleep is only of value if it enhances well-being or performance in the individual the following day. The efficacy of melatonin, magnesium, and zinc improved self-reported morning alertness significantly more than placebo treatment, as demonstrated by the significant improvements in all four domains of the LSEQ. The significant increase in total steps taken during the day also represents an indirect sign of morning alertness. Another important advantage observed in this study is that melatonin, magnesium, and zinc supplementation is significantly associated with better mood and quality of life. The results of this study confirm various intervention studies already published in this field demonstrating that improvement in quality of sleep seems to be associated with better performance on attention tests, concentration, fine motor activity, and reaction time, which results in a feeling of better daytime well-being.[45] After 2 months of treatment, physical and mental function in participants who received the supplement improved significantly, as demonstrated by SF-36 score, as well as mood, as demonstrated by the GDS. This observation has never been made before and is of great value from a clinical point of view, because of the relevance of these aspects in the elderly population. The concept of quality of life is defined as perceived global achievement and satisfaction within a number of key domains, with special emphasis on well-being.[46] These results appear to confirm the close relationship between sleep disturbances and mood and behavioral disorders. The strength of the dietary supplement lies in the rational combination of these three nutrients given the potent synergy between the effect of melatonin, magnesium, and zinc.[28,47] Moreover, the melatonin, magnesium, and zinc supplement conveyed in pear pulp appears to be safe. No significant unwanted side or adverse effects were observed in the treated group, as reported in previous studies.[48] Sedation is an expected but not invariably reported side effect considering the high doses of melatonin used in this study. At variance with this expectation, participants did not show excessive sleepiness as measured according to the ESS. Daytime sleepiness is a complex phenomena, and the ESS investigates just one of its subjective components. It is possible that better nighttime sleep quality made participants more alert during the day, making up for the potential melatonin sedative effect. Furthermore, improved mood and well-being may have positively influenced the subjective evaluation of daytime sleepiness in the participants. Finally, the potential inadequacy of this scale in measuring daytime sleep propensity in older institutionalized people may truly have limited sleepiness evaluation in this investigation.

Among the limits of this investigation are the small size of the sample examined, the particular group of elderly adults studied, and the methods used to investigate sleep. Most of the sleep parameters in this investigation were based on standardized sleep questionnaires and scales and are subjective measures. Objective measures of sleep or daytime sleepiness were not obtained. Although sleep quality is a readily accepted clinical construct, it is a complex

phenomenon. Because of its largely subjective nature, sleep quality correlates with sleep laboratory measures even if not accurately defined. It has been reported that subjective criteria are more effective than polysomnography in differentiating individuals with insomnia from control participants and that sleep laboratory recordings provide little relevant information to confirm or exclude the presence of insomnia.[49] The only objective findings were those that the wearable armband-shaped sensor provided, which evaluated total sleep time, total steps taken, and total rest time. This method is a novel economical alternative to traditional medical measurement equipment, with a competitive edge in monitoring sleep-related activity and sleep quality measurements. A further limit of the study is that long-term care facility residents are a particular class of people, because their life rhythms (mealtimes, sleep, physical activity) are planned differently than those of older people living alone, but if confirmed by further studies, the findings of the present investigation might be of great value, considering that insomnia is particularly disruptive of physical and mental health in older adults and that treatment options are limited. Benzodiazepines and nonbenzodiazepine medications are poorly tolerated in elderly people,[21] and studies regarding the efficacy of nonpharmacological interventions and sleep hygiene interventions in nursing home residents have been reported to have no definite effect on nighttime sleep quality, even though they have been shown to improve daytime alertness, physical and mental activity, and quality of life.[22]

In conclusion, the melatonin, magnesium, and zinc supplement used in this study may become a useful instrument in managing sleep disorders in long-term care facility residents, which could also be extended as a helpful aid to the general elderly population.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Each author contributed intellectually or practically to this research. MR, FM, and AO recruited the participants, conducted the intervention study at the clinic, analyzed the data, and wrote the study. RM, NA, and MR designed the study and provided supervision. CK was responsible for statistical issues and provided advice on interpretation of results.

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REFERENCES

1. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington, DC: American Psychiatric Association, 2000.
2. Richardson GS, Carskadon MA, Orav EJ et al. Circadian variation of sleep tendency in elderly and young adult subjects. Sleep 1982;5:82–94.
3. Ohayon MM, Zulley J, Guilleminault C et al. How age and daytime activities are related to insomnia in the general population: Consequences for older people. J Am Geriatr Soc 2001;49:360–366.
4. Roth T, Costa e Silva JA, Chase MH. Sleep and cognitive (memory) function: Research and clinical perspectives. Sleep Med 2001;2:379–387.
5. Maggi S, Langlois JA, Minicuci N et al. Sleep complaints in community-dwelling older persons: Prevalence, associated factors, and reported causes. J Am Geriatr Soc 1998;46:161–168.
6. Foley DJ, Monjan A, Simonsick EM et al. Incidence and remission of insomnia among elderly adults: An epidemiologic study of 6,800 persons over three years. Sleep 1999;22:366–372.
7. Sateia MJ, Doghramji K, Hauri PJ et al. Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. Sleep 2000;23:243–308.
8. Mathews D. Review of insomnia: The sleep cycle and treatment options. Pharm Times 2003;69:75–87.
9. Weissman MM, Greenwald S, Nino-Murcia G et al. The morbidity of insomnia uncomplicated by psychiatric disorders. Gen Hosp Psychiatry 1997;19:245–250.
10. Hatoum HT, Kong SX, Kania CM et al. Insomnia, health-related quality of life and healthcare resource consumption. A study of managed-care organisation enrollees. Pharmacoeconomics 1998;14:629–637.
11. Sateia MJ, Nowell PD. Insomnia. Lancet 2004;364:1959–1973.
12. Kapur VK, Redline S, Nieto FJ et al. The relationship between chronically disrupted sleep and healthcare use. Sleep 2002;25:289–296.
13. Brassington GS, King AC, Bliwise DL. Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64–99 years. J Am Geriatr Soc 2000;48:1234–1240.
14. National Institutes of Health. National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults, June 13–15, 2005. Sleep 2005;28:1049–1057.
15. Lustberg L, Reynolds CF. Depression and insomnia: Questions of cause and effect. Sleep Med Rev 2000;4:253–262.
16. Srinivasan V, Smits M, Spence W et al. Melatonin in mood disorders. World J Biol Psychiatry 2006;7:138–151.
17. Garzón C, Guerrero JM, Aramburu O et al. Effect of melatonin administration on sleep, behavioral disorders and hypnotic drug discontinuation in the elderly: A randomized, double-blind, placebo-controlled study. Aging Clin Exp Res 2009;21:38–42.
18. Scheer FA, Czeisler CA. Melatonin, sleep, and circadian rhythms. Sleep Med Rev 2005;9:5–9.
19. Buscemi N, Vandermeer B, Hooton N et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: Meta-analysis. BMJ 2006;332:385–393.
20. Haimov I, Laudon M, Zisapel N et al. Sleep disorders and melatonin rhythms in elderly people. BMJ 1994;309:167.
21. Bain KT. Management of chronic insomnia in elderly persons. Am J Geriatr Pharmacother 2006;4:168–192.
22. Schnelle JF, Alessi CA, Al-Samarrai NR et al. The nursing home at night: Effects of an intervention on noise, light, and sleep. J Am Geriatr Soc 1999;47:430–438.
23. Chung KF, Lee CK. Over-the-counter sleeping pills: A survey of use in Hong Kong and a review of their constituents. Gen Hosp Psychiatry 2002;24:430–435.
24. Kroczka B, Zieba A, Dudek D et al. Zinc exhibits an antidepressant-like effect in the forced swimming test in mice. Pol J Pharmacol 2000;52:403–406.
25. Nowak G, Siwek M, Dudek D et al. Effect of zinc supplementation on antidepressant therapy in unipolar depression: A preliminary placebo-controlled study. Pol J Pharmacol 2003;55:1143–1147.
26. Siwek M, Dudek D, Paul IA et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: A double blind, placebo-controlled study. J Affect Disord 2009;118:187–195.
27. Sowa-Kućma M, Legutko B, Szewczyk B et al. Antidepressant-like activity of zinc: Further behavioral and molecular evidence. J Neural Transm 2008;115:1621–1628.
28. Laires MJ, Monteiro CP, Bicho M. Role of cellular magnesium in health and human disease. Front Biosci 2004;9:262–276.
29. Arendt J, Bojkowski C, Franey C et al. Immunoassay of 6-hydroxymelatonin sulphate in human plasma and urine: Abolition of the urinary 24-hour rhythm with atenolol. J Clin Endocrinol Metab 1985;60:1166–1173.
30. Chesson A Jr, Hartse K, Anderson WM et al. Practice parameters for the evaluation of chronic insomnia. An American Academy of Sleep Medicine report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 2000;23:237–241.
31. Yesavage JA, Brink TL, Rose TL et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 1982-1983;17:37–49.
32. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
33. Katz S, Downs TD, Cash HR et al. Progress in development of the index of ADL. Gerontologist 1970;10:20–30.
34. Buysse DJ, Reynolds CF III, Monk TH et al. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.

35. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations - a review. Psycopharmacology 1980;71: 173–179.
36. Tarrasch R, Laudon M, Zisapel N. Cross-cultural validation of the Leeds Sleep Evaluation Questionnaire (LSEQ) in insomnia patients. Hum Psychopharmacol 2003;18:603–610.
37. Vignatelli L, Plazzi G, Barbato A et al. Italian version of the Epworth Sleepiness Scale: External validity. Neurol Sci 2003;23:295–300.
38. Rosenthal L, Roehrs TA, Roth T. The Sleep-Wake Activity Inventory: A self-report measure of daytime sleepiness. Biol Psychiatry 1993;34:810–820.
39. Violani C, Devoto A, Lucidi F et al. Validity of a short insomnia questionnaire: The SDQ. Brain Res Bull 2004;63:415–421.
40. Miwa H, Sasahara S, Matsui T. Roll-over detection and sleep quality measurement using a wearable sensor. Conf Proc IEEE Eng Med Biol Soc 2007;2007:1507–1510.
41. Ware JE, Snow KK, Kosinski M et al. SF-36 Health Survey: Manual and Interpretation Guide. Boston: The Health Institute, 1993.
42. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. Nutr Rev 1996;54:59–65.
43. Hughes RJ, Sack RL, Lewy AJ. The role of melatonin and circadian phase in age-related sleep-maintenance insomnia: Assessment in a clinical trial of melatonin replacement. Sleep 1998;21:52–68.
44. Nunes DM, Mota RM, Machado MO et al. Effect of melatonin administration on subjective sleep quality in chronic obstructive pulmonary disease. Braz J Med Biol Res 2008;41:926–931.
45. Waldhauser F, Saletu B, Trinchard-Lugan I. Sleep laboratory investigations on hypnotic properties of melatonin. Psychopharmacology 1990;100:222–226.
46. Hörnquist JO. Quality of life: Concept and assessment. Scand J Soc Med 1990;18:69–79.
47. Oztürk G, Akbulut KG, Afrasyap L. Age-related changes in tissue and plasma zinc levels: Modulation by exogenously administered melatonin. Exp Aging Res 2008;34:453–462.
48. Holliman BJ, Chyka PA. Problems in assessment of acute melatonin overdose. South Med J 1997;90:451–453.
49. Vgontzas AN, Bixler EO, Kales A et al. Validity and clinical utility of sleep laboratory criteria for insomnia. Int J Neurosci 1994;77:11–21.