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Bibliographic Data	
Authors	Rondanelli M, Opizzi A, Monteferrario F, and et al.
Title	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
PMID	
Citation	J Am Geriatr Soc 59:82–90, 2011.
Other information if relevant	

Methods	
Aim of study	To determine whether nightly administration of the combination of melatonin, magnesium, and zinc improves primary insomnia in long-term care facility residents.
Design	Double-blind placebo controlled randomized clinical trial

Participants	
Population from which participants are drawn	The participants were recruited from one long-term care facility in Pavia, Italy.
Setting (location and type of facility)	The study was conducted at the F. Pertusati long-term care facility in Pavia.
Age	Adults aged 70 and older, mean age 78.3 years
Sex	27 females, 16 males
Total number of participants for whom outcome data were reported	The number of participants was 43. Intention to treat analysis was performed.
Inclusion criteria	Ages 70 years or older, a minimum of 3 months of institutionalization, diagnosed with primary insomnia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)1 for at least 1 month.
Exclusion criteria	Exclusion criteria were breathing-related sleep disorder, circadian rhythm sleep disorder, sleep disorder due to a general medical condition, history of or current significant psychiatric or neurological disorder (anxiety, depression, dementia, psychosis), movement disorders, parasomnias, restless leg syndrome, and intake of any medication (includes beta-blockers) that affects the central nervous system or sleep/wake cycle 2 weeks before the first day of the placebo run-in period. A score of 15 or more on the Geriatric Depression Scale (GDS) or a score less than 24 on the Mini-Mental State Examination (MMSE), or use of psychotropic treatments within 3 months of the study or a positive drug screen for several medications also resulted in exclusion.
Other information if relevant	Baseline characteristics did not differ between groups.

Intervention Groups

Group 1	
Group name	Supplement or Intervention group

Number in group	22
Description of intervention	Participants took a food supplement containing 5 mg melatonin, 225 mg magnesium, and 11.25 mg zinc mixed with 100 g of pear pulp every day for 8 weeks, 1 hour before bedtime.
Duration of treatment period	8 weeks
Co-interventions if reported	none
Additional information if relevant	

Group 2	
Group name	Control group
Number in group	21
Description of intervention	Participants took a placebo containing only 100 g of pear pulp every day for 8 weeks, 1 hour before bedtime.
Duration of treatment period	8 weeks
Co-interventions if reported	none
Additional information if relevant	The preparations for both the intervention group and the control group were identical in appearance, smell, and taste.

Primary outcomes	
Outcome name and criteria for definition	Primary outcome was quality of sleep assessed using the Pittsburgh Sleep Quality Index (PSQI) total score comparing the mean change from baseline to week 8 between the two groups. The PSQI 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. The PSQI is a global score ranging from 0 to 21. A global PSQI score greater than 5 defines a poor sleeper.
Time points measured and/or reported	Assessments were conducted at baseline before the first treatment and after 8 weeks of treatment.
Differences between groups	Baseline PSQI scores were similar for both groups (supplementation group = 12.7, control = 12.3). For within group results, the mean PSQI score decreased 7.1 points (P<.001) for the supplementation group and 0.3 points (P = .58) for the control group after 8 weeks of treatment. This was a significant overall improvement in the PSQI score in the supplementation group, but not in the placebo group. The mean difference between groups in change from baseline after 60 days of treatment was 6.8 points (95% CI 5.4–8.3) (P<.001).Moreover 59% of the supplementation group participants reached a PSQI of 5 or less, versus 14% of controls which is a difference of 45 percentage points (95% CI 20–70).
Additional information if relevant	Follow-up rates were excellent. None of the participants were lost to follow-up, and no protocol deviation was observed. Intention-to-treat analysis was conducted.

Secondary outcomes	
Outcome name and criteria for definition	Secondary outcomes were the Epworth Sleepiness Scale, the Leeds Sleep Evaluation Questionnaire (LSEQ), the Short Insomnia Questionnaire (SDQ), a validated quality-of-life instrument, the Medical Outcomes Study 36-item Short Form Survey (SF-36), and total sleep time evaluated using a wearable armband-shaped sensor.
Time points measured	Assessments were conducted at baseline before the first treatment and after 8 weeks of treatment.
Differences between groups	There were significant improvements for the supplementation group 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 the SDQ score (P<.001), in total sleep time (Po<.001), and in the SF-36 physical score (P=.006). These results suggest that treatment had a beneficial effect on the restorative value of sleep.
Additional information if relevant	None of the participants dropped out of the study. All of the participants tolerated the treatment well with excellent adherence, and 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.
Conclusions	
Key conclusions of study authors	- This double-blind, placebo-controlled clinical trial is the first study 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 for primary insomnia in long-term care facility residents, appears to have significant clinical importance because insomnia is common in late life. - A significant treatment benefit of melatonin, magnesium, and zinc in the supplement group was also reached in most secondary outcomes. The efficacy of the supplement improved self-reported morning alertness significantly more than placebo treatment, as demonstrated by the significant improvements in all 4 domains of the LSEQ, and was also significantly associated with better mood and quality of life. Physical and mental function improved significantly, as demonstrated by the SF-36 score, as well as mood, as demonstrated by the Geriatric Depression scale. - These study 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 3 nutrients given the potent synergy between the effect of melatonin, magnesium, and zinc. - No significant unwanted side or adverse effects were observed in the treated group. - In conclusion, the melatonin, magnesium, and zinc supplement used in this study may become a useful treatment in managing sleep disorders in long-term care facility residents, which could also be extended as a helpful aid to the general elderly population.

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	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.
Allocation concealment *(selection bias)*	Low	Investigators were blinded to the randomization table, treatment code assignments, and procedure.
Blinding of participants and personnel *(performance bias)*	Low	Patients were not aware of which group they were in. Both pear pulp preparations were identical in appearance, smell, and taste.
Blinding of outcome assessment *(detection bias)*	Low	All outcome assessments were collected by an assessor blinded to intervention assignment.
Incomplete outcome data *(attrition bias)*	Low	Participant follow-up was excellent with no drop-outs. Results of all outcomes were reported.
Selective outcome reporting? *(reporting bias)*	Unclear	The trial was not registered with clinicaltrials.gov
Other bias		

Sponsorship if reported		
Study funding sources if reported	Not reported. This research was conducted under the approval of the Department of Internal Medicine and Medical Therapy, University of Pavia.	
Possible conflicts of interest for study authors	The authors have no financial or any other kind of personal conflicts with this study.	
Notes:		

Comments by DOWC staff

- The results of this study support that a dietary supplement containing melatonin, magnesium, and zinc, conveyed in pear pulp, taken 1 hour before bedtime, results in significantly better quality of sleep and quality of life than a placebo treatment in long-term care facility residents aged 70 and older experiencing primary insomnia. Between-group differences were statistically significant and clinically meaningful.
- Strengths of the study included a designated primary outcome, a placebo control group, blinded participants, and an objective measure of total sleep time.
- The fact that there were no drop-outs and no adverse effects in either group is indicative of a well-tolerated, safe intervention.
- It is difficult to attribute the results of the study to either the combination of the dietary supplement (melatonin, magnesium, and zinc) or simply one or 2 ingredients of the supplement. It is not known which components of the supplement, or if all, contributed the most beneficial effects.
- Most of the sleep parameters used in this study were self-reported subjective measures based on standardized sleep questionnaires and scales. Objective measures of sleep or daytime sleepiness were not obtained from the questionnaires, but the results on total sleep time and total rest time from the wearable armband-shaped sensor provided objective findings that supported the results of the subjective measures.
- Since the study included only elderly residents in one long-term care facility, the results may not be generalizable to the general population. It is not known if this treatment would be effective on chronic pain patients, younger adults, the working population, community dwelling adults, or people with secondary insomnia. If other similar studies were conducted on different populations and confirmed the results of this study, that would add great value to the conclusions of this study.
- Limitations of the study included no clinical trial registration, small sample size, and the inclusion of only elderly residents in one long-term care facility.

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	This study is adequate for some evidence that a dietary supplement containing melatonin, magnesium, and zinc, conveyed in pear pulp, taken 1 hour before bedtime, results in significantly better quality of sleep and quality of life than a placebo treatment in long-term care facility residents aged 70 and older with primary insomnia.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant