ChronoPhysiology and Therapy

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CORRIGENDUM

New developments in the treatment of primary insomnia in elderly patients: focus on prolonged-release melatonin [Corrigendum]

Cardinali DP, Vidal MF, Vigo DE.
ChronoPhysiology and Therapy 2012, 2:67–79.

Some of the references listed in Table 1 are incorrect. The correct referencing is included in the table below.

Table 1 Relevant clinical studies on prolonged-release melatonin in primary insomnia

Condition	Type of study	n	Daily melatonin dose	Duration of treatment
Primary insomnia outpatients aged 76 ± 8 (68–93) years who took BZP and had low urinary 6-sulfatoxymelatonin levels	Randomized, double-blind, placebo-controlled, crossover study	12	2 mg	3 weeks with melatonin or placebo, followed by one-week washout, and then crossed over for another 3 weeks
Primary insomnia outpatients aged 79 ± 5.2 (68–93) years under BZP treatment and having low urinary 6-sulfatoxymelatonin levels	Randomized, double-blind, placebo-controlled, crossover study	21	2 mg	3 weeks with melatonin or placebo, followed by one-week washout, and then crossed over for another 3 weeks
Primary insomnia outpatients aged 40–90 years who took BZP and had low urinary 6-sulfatoxymelatonin levels	Randomized, double-blind, placebo-controlled study followed by a single-blind period	34	2 mg	Patients received melatonin or placebo for 6 weeks. They were encouraged to reduce BZP dose 50% during week 2, 75% during weeks 3 and 4, and to discontinue BZP during weeks 5 and 6. Then melatonin was administered (single-blind) for 6 weeks and attempts to discontinue BZP therapy were resumed; follow-up reassessment was performed 6 months later
Primary insomnia outpatients aged ≥55 years	Double-blind, placebo-controlled trial	170	2 mg	3 weeks
Primary insomnia outpatients aged ≥55 years	Double-blind, placebo-controlled trial	354	2 mg	3 weeks
Healthy volunteers aged ≥55 years	Randomized, double-blind, placebo-controlled, single-dose, four-way crossover study	16	2 mg, zolpidem 10 mg, and their combination	Subjects were tested one and 4 hours and next morning after dosing
Primary insomnia outpatients aged 55–68 years	Double-blind, placebo-controlled trial	40	2 mg	3 weeks
Primary insomnia outpatients aged 18–80 years	Randomized, double-blind, parallel-group, clinical trial	791	2 mg	3-week double-blind treatment, followed by a 26-week, double-blind, extension period with patients randomized to receive melatonin or placebo, followed by a 2-week, single-blind, placebo withdrawal period
Community-dwelling adults with primary insomnia of mean age 55.3 years	Prospective open-label study	244	2 mg	6–12 months
Perimenopausal women with insomnia aged 45–52 years	Open-label, case series	11	2 mg	Treated with mirtazapine 15 mg for 2–4 weeks. Melatonin was then added on, and mirtazapine was tapered off for another 1–3 months

Outcome measures	Response	Ref
Sleep quality was objectively monitored by wrist actigraphy.	Sleep efficiency was greater after melatonin than after placebo and wake time after sleep onset was shorter. Trend to decrease sleep latency. Total sleep time remained unaffected	78
Sleep assessed by wrist actigraphy. Urinary 6-sulfatoxymelatonin measurement	Melatonin increased sleep efficiency and total sleep time and decreased wake after sleep onset, sleep latency, number of awakenings and fragmental index	79
Sleep diary and recording of BZP use	14 of 18 subjects who had received melatonin, but only 4 of 16 in the placebo group, discontinued BZP therapy. Sleep-quality scores were higher in the melatonin group. Six additional subjects in the placebo group discontinued BZP after 6 months of treatment. At the follow-up, 19 of 24 patients who discontinued BZP kept good sleep quality	82
Quality of sleep and morning alertness assessed by Leeds Sleep Evaluation Questionnaire. Sleep quality reported on five categorical scales. Presence of rebound insomnia or withdrawal effects	Significant improvement in quality of sleep and morning alertness. The improvements in quality of sleep and morning alertness were strongly correlated. No rebound insomnia or withdrawal effects were seen	87
Responder rate in Leeds Sleep Evaluation Questionnaire, Pittsburgh Sleep Quality Index global score, Quality of Night and Quality of Day derived from a sleep diary, Clinical Global Improvement scale and quality of life (WHO-5 well being index)	Significant improvements in quality of sleep and morning alertness and in quality of life. Shortening of sleep latency	88
Psychomotor functions, memory recall, and driving skills	No impairment of performance after melatonin. Zolpidem impaired psychomotor and driving performance one and 4 hours post-dosing, and early memory recall. Melatonin coadministration exacerbated zolpidem effect	108
Polysomnography and EEG spectral analysis. Psychomotor performance assessed by the Leeds Psychomotor Test battery	Shorter sleep onset latency as compared to placebo. Significantly better scores in the Critical Flicker Fusion Test. 50% of patients reported substantial improvement in sleep quality at home. No rebound insomnia or withdrawal effects	91
Sleep diary, Pittsburgh Sleep Quality Index, Quality of Life (World Health Organzaton-5) Clinical Global Impression of Improvement assessment, urinary 6-sulfatoxymelatonin and adverse effects and vital signs	In patients aged ≥65 years (n = 281) melatonin decreased sleep latency regardless of 6-sulfatoxymelatonin excretion. Effect in patients with low urinary 6-sulfatoxymelatonin levels regardless of age did not differ from placebo. Improvement of sleep and daytime parameters maintained or enhanced over a 6-month period with no signs of tolerance. Most adverse events were mild in severity with no clinically relevant differences with placebo, including endocrine parameters	89
Sleep diary, adverse events, vital signs, laboratory tests, and withdrawal symptoms. Nocturnal urinary 6-sulfatoxymelatonin excretion assessed upon discontinuing treatment	Of the 244 patients, 36 dropped out, 112 completed 6 months of treatment, and 96 completed 12 months of treatment. The mean number of nights reporting sleep quality as "good" or "very good" was significantly higher during treatment. There was no evidence of tolerance and discontinuation was not associated with rebound insomnia or withdrawal symptoms. No suppression of endogenous melatonin production	90
Body weight data. Subjective assessment of sleep quality and well-being (Pittsburgh Sleep Quality Index and Well-Being Index, WHO-5)	Significant improvement in sleep quality and well-being during combined mirtazapine and melatonin intake and during subsequent intake of melatonin alone or together with very low doses of mirtazapine, 5 of 7 women demonstrating weight gain following mirtazapine intake started to reduce weight after melatonin treatment	107

(*Continued*)

Table 1 (*Continued*)

Condition	Type of study	n	Daily melatonin dose	Duration of treatment
Type 2 diabetic patients with insomnia aged 46–77 years	Randomized, double-blind, placebo-controlled, crossover study	36	2 mg	3 weeks with melatonin or placebo, followed by one-week washout, and then crossed over for another 3 weeks. Extension period of 5 months giving melatonin to all patients in an open-label design
Healthy volunteers, aged 55–64 years	Randomized, double-blind, placebo-controlled, single-dose, three-way crossover study	24	2 mg, zolpidem 10 mg was used as active control	Subjects were tested 30 minutes before and 1.5 and 4 hours after dosing
Patients classified according to their use of hypnotic BZP or BZP-like drugs	Retrospective study from a longitudinal database	112	2 mg	Varied intervals

Outcome measures	Response	Ref
Sleep monitoring by actigraphy. Measuring of fasting glucose, fructosamine, insulin, C-peptide, triglyceride, total cholesterol, high-density and low-density lipoprotein cholesterol, antioxidants and glycosylated hemoglobin levels	Sleep efficiency, wake time after sleep onset, and number of awakenings improved significantly. No significant changes in blood parameters after 3 weeks of melatonin treatment. After 5 months of treatment, glycosylated hemoglobin levels decreased	92
Body sway tested by the area of the 95% confidence ellipse enclosing the center of pressure (A95) and its path length	No effect of melatonin on A95. It increased path length at 4 hours post-dose in open but not closed eyes condition. Zolpidem significantly increased the A95 and path length	109
Discontinuation rate of BZP	31% of patients discontinued BZP after melatonin initiation. The discontinuation rate was higher in patients receiving two or three melatonin prescriptions	86

Abbreviations: BZP, benzodiazepine; EEG, electroencephalography.