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The Effects of Magnesium – Melatonin - Vit B Complex Supplementation in Treatment of Insomnia

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Abstract

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Abbreviations: APA- American Psychiatric Association; DSM-5- Diagnostic Criteria from Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ACP- The American College of Physicians; CBT- Cognitive behavioral therapy; 5-HT₂- Serotonergic receptors type 2; GABA-A- Gamma-aminobutyric acid receptors type A; H₁- Histamine receptors type 1; D₂- dopamine receptors type 2; OR1- orexin receptors type 1; OR2- orexin receptors type 2; Mel 1- melatonin receptors type 1; Mel 2- melatonin receptors type 2; 5-HT- Serotonin receptor system; DA- Dopamine receptor system

Insomnia means difficulty in falling asleep and/or stays asleep. Insomnia commonly leads to daytime sleepiness, lethargy, and a general feeling of being unwell. The most common treatment of insomnia includes GABAA receptor positive allosteric modulators or Melatonin agonists. Our study aimed to evaluate the efficacy of Magnesium- melatonin-vitamin B complex supplement in the treatment of insomnia. The study included 60 patients diagnosed with insomnia. The patients were randomly divided into study group (N = 30), and control group (N = 30), and study group was treated with Magnesium-melatonin-vitamin B complex (one dose contains 175 mg liposomal magnesium oxide, 10 mg Vit B6, 16 µg vit B12, melatonin 1 mg, Extrafolate-S 600 µg) once a day 1 hour before sleep, during the 3 months. The severity of insomnia symptoms was measured by self-reported Athens insomnia scale (AIS), with a cut-off score by Soldatos (AIS score ≥ 6). Mean AIS score at zero points was 14.93 ± 3.778 in the study group and 14.37 ± 4.081 in the control group (p = 0.476), indicating the compatibility of the groups, and both scores correspond to mild to moderate insomnia. Mean AIS score after 3 months of the Magnesium- melatonin- vitamin B complex supplementation was 10.50 ± 4.21 corresponding to mild insomnia, while median AIS score in the control group was 15.13 ± 3.76 which is referred to moderate insomnia, and difference among groups was significant (p = 0.000). Our findings indicating that 3 months of the Magnesium-melatonin-vitamin B complex supplementation has a beneficial effect in the treatment of insomnia regardless of cause.

Introduction

Insomnia is a sleep disorder with difficulties to fall asleep or stay asleep or both. It is the most common sleep disorder, according to the American Psychiatric Association (APA), with approximately

30% of all adults and 6-10% of those who have severe symptoms diagnosed as insomnia disorder [1].

Diagnostic Criteria from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) include:

- Difficulty in initialisation or maintaining sleep

or early-morning awakening that leads to low quantity or quality of sleep.

- Sleep disturbance that leads to impairment in social, occupational, educational, academic, behavioural, or other important areas of functioning.

- Patients experience this even with adequate opportunity to sleep, at least 3 nights per week, and for at least 3 months.

- Insomnia is not explained by the presence of mental disorders or medical conditions and is not associated with another sleep disorder [2].

Pharmaceutical and nonpharmaceutical treatments are recognisable for insomnia. The American College of Physicians (ACP) advised cognitive-behavioural therapy (CBT) as a first-line treatment for chronic insomnia in adults. Sleep hygiene training (avoiding caffeine, exercise near bedtime, watching TV or surfing the internet from the bed) can help you change some of these disruptive behaviours [1].

Medications that have insomnia as an approved indication are:

- Benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)-eszazolam, eszopiclone, flunitrazepam, flurazepam, lormetazepam, nitrazepam, quazepam, temazepam, triazolam, zaleplon, zolpidem (alpha 1 subunit selective benzodiazepine receptor agonist).

- Norepinephrine and serotonin reuptake inhibitor and 5-HT₂ receptor antagonist doxepine in very low doses 3mg and 6mg for insomnia in the USA

- H₁ and D₂ receptor antagonist promethazine

- OR₁ and OR₂ receptor antagonist suvorexant

- Mel₁ and Mel₂ receptor agonist ramelteon and melatonin [3].

The hormone melatonin is produced during the sleep cycle. Studies are inconclusive regarding whether melatonin can help treat insomnia in adults, but melatonin could promote sleep by helping to regulate the body's bio clock and sleep-wake cycles and to adhere to more healthful sleep patterns. Research indicates that melatonin may shorten the time it takes to fall asleep, increase overall sleep amounts, and may increase REM sleep [4], [5], [6].

Few sleep-promoting nutrients enhance sleep and relaxation. Magnesium is a muscle relaxant and inducer of the deeper sleep. Circadian rhythms dysregulation and compromised lifestyle also increase magnesium excretion, leading to deficiency [7]. Magnesium supplementation improves sleep efficiency, sleep time and sleep onset latency, early morning awakening, and insomnia objective measures such as the concentration of serum renin, melatonin,

and serum cortisol, in older adults [8]. Dietary magnesium intake may have long-term benefits in reducing the likelihood of daytime falling asleep in women [9]. Anxiety can cause insomnia, and vice versa which can result in a self-perpetuating cycle, which leads to chronic insomnia. According to Australia's Sleep Health Foundation, anxiety and worrying are leading causes of insomnia [1]. Existing evidence is suggestive of a beneficial effect of Mg on subjective anxiety in anxiety vulnerable samples, and for mild-to-moderate depression in adults within 2 weeks [10], [11]. According to the National Sleep Foundation, insomnia promotes depression and depression-induced insomnia. A meta-analysis of 34 studies concluded that insomnia is significantly associated with an increased risk of depression, which has implications for the prevention of depression in non-depressed individuals with insomnia symptoms [12]. Melatonin and the nonselective MT₁ / MT₂ receptor agonist agomelatine have displayed anxiolytic-like action and have been used in the elderly, but exact mechanisms of action are still unknown [13], [14]. Recent studies suggest that the MT₂ receptor is implicated in the antidepressant-like effects of melatonin [15], [16].

The recent results showed mixed effects of vitamin B₁₂ on sleep patterns [17] and promoting an effect of vitamin B₆ on the reduction of psychological distress, which could induce sleep disturbance [18]. Contrary to that, there is clear evidence on the antidepressant effect of vitamin B₁₂ [19] and vitamin B₆ for therapy of hormone-related depression in women [20].

Our study aimed to evaluate the efficacy of Magnesium-melatonin-vitamin B complex supplement in the treatment of insomnia.

Material and Methods

The study included 60 patients diagnosed with insomnia who refused to take drugs for insomnia and have a positive attitude towards the supplements. The patients were randomly divided (bias coin randomization) into study group (N = 30), and control group (N = 30), and study group was treated with Magnesium-melatonin-vitamin B complex (one dose contains 175 mg liposomal magnesium oxide, 10 mg Vit B₆, 16 µg vit B₁₂, melatonin 1mg, Extrafolate-S 600 µg) once a day 1 hour before sleep, during the 3 months. The manufacturer advertises it as mild rapid-acting natural sleep medicine containing magnesium, melatonin, and vitamin B complex. It is recommended to use one capsule daily, evening dose, an hour before sleep. We followed the manufacturer's recommendation regarding the supplement intake. The severity of insomnia symptoms was measured by self-reported Athens insomnia scale (AIS), with

Gamma-aminobutyric acid score by Soldatos (AIS score ≥ 6). The severity of insomnia measured by AIS was graded according to Morin's criteria: AIS score 7-14- mild insomnia; AIS score 15-21- moderate insomnia; AIS score 22-28- severe insomnia. AIS and CGI-S scores were evaluated at zero points and after 3 months of supplement consumption.

Statistical analysis

All collected data were analysed using the IBM SPSS Statistics for Windows (IBM SPSS, IBM Corp., Armonk, NY, USA) software, version 22.0. The descriptive statistics are presented as a central tendency (means) and variability (standard deviation and variation interval). Means were compared with the independent samples t-test, while for testing data of different categories, we used Pearson's χ^2 test and Mann-Whitney test. We used repeated-measures analysis of covariance (RM ANCOVA) for the assessment on t0 and t90 between and within the groups. The level of statistical significance was set at $p < 0.05$.

Results

Gender distribution was 67% male and 33% female in the study group and 77% male and 23% female in the control group. The average age in the study group was 51.40 ± 14.61 years, and 44.93 ± 14.40 years in the control group, the age distribution of subjects indicating the comparability of the studied groups ($p = 0.090$). Mean AIS score at zero points was 14.93 ± 3.778 in the study group and 14.37 ± 4.081 in the control group ($p = 0.476$), indicating the compatibility of the groups, and both scores correspond to mild to moderate insomnia. Mean AIS score after 3 months of the Magnesium-melatonin-vitamin B complex supplementation was 10.50 ± 4.21 , corresponding to mild insomnia, while the median AIS score in the control group was 15.13 ± 3.76 which refers to moderate insomnia, and difference among groups was significant ($p = 0.000$) (Table 1).

Table 1: AIS score at zero and endpoint

| | T0 | | T90 | | p** |
|---------------|-------------------------------|-------|------------------------------|-------|-------|
| | X \pm SD; Med (min-max) | p* | X \pm SD; Med (min-max) | p* | |
| Study group | 14.93 \pm 3.78; 15 (9-24) | 0.476 | 10.50 \pm 4.21; 9 (3-20) | 0.000 | 0.000 |
| Control group | 14.37 \pm 4.08; 13.5 (9-24) | | 15.13 \pm 3.76; 14 (10-24) | | |

*Mann-Whitney test; **Wilcoxon test.

Mean CGI-S at zero point was 3.57 ± 0.568 in study group, and 3.43 ± 0.58 in control group ($p = 0.328$). Difference became significant at the end point visit ($p = 0.05$) with mean CGI-S score 2.97 ± 0.77 in the study group, and 3.53 ± 0.63 in control group (Table 2).

Table 2: CGI-S at zero and endpoint

| | T0 | | T90 | | p** |
|---------------|-----------------------------|-------|-----------------------------|-------|-------|
| | X \pm SD; Med (min - max) | p* | X \pm SD; Med (min - max) | p* | |
| Study group | 3.57 \pm 0.57; 4 (3-5) | 0.328 | 2.97 \pm 0.77; 3 (1-4) | 0.005 | 0.005 |
| Control group | 3.43 \pm 0.57; 3 (3-5) | | 3.53 \pm 0.63; 3 (3-5) | | |

*Mann-Whitney test; **Wilcoxon test.

Mean CGI-I score after 3 months was 3.23 ± 0.73 (minimally improved), which is significantly different in comparison with mean CGI-I score in control group 4.07 ± 0.25 (no change) ($p = 0.000$) (Table 3).

Table 3: CGI-I at the endpoint

| | T90 | | p* |
|---------------|-----------------------------|--|-------|
| | X \pm SD; Med (min - max) | | |
| Study group | 3.23 \pm 0.73; 3 (2-4) | | 0.000 |
| Control group | 4.07 \pm 0.25; 4 (4-5) | | |

*Mann-Whitney test.

Discussion

The results of this study demonstrate that supplementation with Magnesium-melatonin-vitamin B complex for 3 months has a significant positive effect on sleep disturbances and is highly effective for the treatment of patients with insomnia. Regardless of the insomnia aetiology, Magnesium-melatonin-vitamin B complex supplementation reduces insomnia symptoms, as well as its consequences, thus improving the patients' quality of life and preventing potential unwanted clinical, social, economic, or emotional repercussions.

Magnesium is one of the most important minerals in the human body. It is involved in more than 300 enzyme systems responsible for the maintenance of normal homeostasis [9]. One of the more recently discovered functions of magnesium is its effect on cellular timekeeping and regulation of circadian rhythm. Studies that back up this theory have shown that inadequately low levels of serum magnesium are associated with low quality sleep and insomnia [17]. Lack of magnesium intake seems to be involved in the development of depression, which increases the risk of insomnia [12].

A study performed by Abbasi et al. [8] examined the independent role of magnesium in the treatment of insomnia. After 8 weeks of magnesium supplementation, the patients had increased sleep time, as well as sleep efficiency. The results demonstrate that magnesium supplementation brings significant improvement, both subjective and objective, to the patients who have insomnia. These results are consistent with the results of our study, which demonstrates that magnesium, isolated or as a part of a combination supplement, is successful in treating insomnia. Interestingly, a statistically significant increase in serum melatonin concentration was recorded in the experimental group that received

dietary magnesium supplementation compared to the placebo group. This finding suggests the complicated interaction between these two elements that are both important for the regulation of sleep and the day-night cycle.

Melatonin is a hormone produced and secreted by the pineal gland. It has an important role in the maintenance of the organism circadian rhythm, which is being expressed through a wide range of different physiologic, neuroendocrine, and behavioural functions. Its plasma concentrations reach a peak during nighttime, while during the daytime, they are barely measurable [15]. Animal and human studies have demonstrated that melatonin binds to the receptors in the central nervous system, producing an effect on sleep promotion and sleeping phase shifts [13], [16].

Pharmacological agents that are prescribed for insomnia cannot reproduce the properties of physiological sleep and are associated with adverse effects like sedation, anxiety, tremor, tolerance to the drug or dependence [13]. The research conducted by Ochoa-Sanchez et al., [21] revealed that melatonin receptor agonists had much more favourable pharmacological properties in terms of sleep promotion and regulation when compared to prescribed benzodiazepines. Also, melatonin and its agonists did not produce adverse effects commonly attributable to benzodiazepines.

The study of Grima et al. [5], which dealt with melatonin administration for sleep disturbances after traumatic brain injury, reported a significant improvement in sleep quality and sleep efficiency, as well as a reduction in fatigue and anxiety symptoms, after only 4 weeks of melatonin treatment. This result is consistent with our study, although patients in our experimental group did not receive isolated melatonin, as a part of the Magnesium-melatonin-vitamin B complex supplement, and they received it for a substantially longer period as well.

From the B vitamins group, the best examined in terms of sleeping interactions is vitamin B12. The direct relationship between insomnia and vitamin B12 levels is yet to be established. However, vitamin B12 deficiency is known to be involved in the pathophysiology of depression, which can commonly be associated with insomnia [19].

Lichstein et al. [18] examined the influence of different vitamin supplementation on sleep quality and duration. The results suggest that the use of combined multivitamin supplements, as well as single vitamins, including vitamin B complex, hurts sleep maintenance, causes a higher rate of insomnia, and requires greater use of sleep medicine. In contrast to this study, our results show that vitamin B complex, in combination with magnesium and melatonin, has a positive effect on sleep regulation and can be used to treat insomnia. This could be attributed to the combined additive effect of the three components of

the prescribed supplement, in contrast to the single effects of isolated molecules that were previously tested.

Although there are studies that investigated the effect of different combined supplements for the treatment of insomnia, to the best of our knowledge, this is the first study that investigated the particular combination of Magnesium-melatonin-vitamin B complex supplement. The research conducted by Rondanelli et al. [22] investigated the influence of the supplement consisting of melatonin, magnesium, and zinc on insomnia in the elderly.

Their results showed that these elements were effective in managing sleep disorders after 2 months of treatment. This finding is consistent with our study, which shows that common elements from both studies – magnesium, and melatonin have a significant effect on sleep regulation.

Our findings indicate that 3 months of the Magnesium-melatonin-vitamin B complex supplementation has a beneficial effect in the treatment of insomnia regardless of cause. According to our results, Magnesium-melatonin-vitamin B complex augmentation improves AIS and CGI-S score with statistical significance relative to the control group. The global improvement according to the CGI-I score, was minimal but significant different compared with the control group where there was no change.

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