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A combination of melatonin, vitamin B6 and medicinal plants in the treatment of mild-to-moderate insomnia: A prospective pilot study

Patrick Lemoine[a,*], Jean-Christophe Bablon[b], Christèle Da Silva[b]

[a] Clinique Lyon Lumière, Meyzieu, Lyon, France
[b] Medical Department, Sanofi Consumer Health Care, Paris, France

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ABSTRACT

Objectives: Currently available pharmaceutical therapies for sleep disorders have significant side effects and dependence potential, thus necessitating the need for alternative treatment approaches. This study investigated the effect of a combination of melatonin, vitamin B6 and medicinal plants in patients with mild-to-moderate sleep disorders.

Design and setting: This was a 4-week, single-center, single-arm, open-label study conducted in 40 participants with mild-to-moderate insomnia, in Poland.

Intervention: Participants received Novanuit® Triple Action (melatonin, vitamin B6, California poppy extract, passionflower extract, and lemon balm extract) capsules per day for two weeks.

Outcomes: Using a daily electronic sleep diary, information was collected on sleep quality (assessed on a 0–10 scale), total sleep duration, sleep onset latency, sleep-related daytime impairment, and safety of the study medication.

Results: There was a statistically significant ($p < 0.001$) improvement in sleep quality by the end of the 2-week treatment period, with mean sleep quality score increasing by 1.9 points from pre-treatment (5.4 points) to post-treatment (7.3 points). Similarly, statistically significant improvements were observed following treatment completion in sleep onset latency, total sleep duration, and sleep-related daytime parameters ($p < 0.01$ for all outcomes). Administration of the combination of melatonin, vitamin B6, and medicinal plants was associated with high compliance (39/40; 97.5%). No serious adverse events were reported.

Conclusions: This pilot study suggests that the combination of melatonin, vitamin B6, and medicinal plants may be beneficial in mild-to-moderate insomnia.

1. Introduction

Sleep disorders comprise various dysfunctions, including difficulty initiating sleep, poor sleep quality, circadian rhythm disorders, parasomnias, sleep-related movement disorders, and sleep-related breathing disorders [1]. This can be associated with adverse short- and long-term health, social, and economic outcomes [2,3]. Insomnia is defined as the subjective perception of difficulty with sleep initiation, or inadequate sleep duration, consolidation, or quality, despite adequate sleep opportunity and resulting in some form of daytime impairment. It is the most prevalent sleep disorder, accounting for > 5.5 million outpatient visits/year in the United States alone [4]. Between 20 and 42% of the general population is estimated to suffer from lack of sleep [5].

A variety of pharmacological treatments are available to address sleep disorders, including chloral hydrate, barbiturates, benzodiazepines, benzodiazepine agonists, antidepressants, and anxiolytics [1]. However, these medications have important side effects, including memory loss, dizziness, gastrointestinal upset, and hallucinations [6]. In addition, these agents carry a risk of tolerance to sedating effects, rebound worsening of sleep problems at discontinuation, and addiction [6,7]. Consequentially, there has been an increased interest in finding alternative effective treatment approaches for sleep disorders with fewer side effects [1].

Novanuit® Triple Action is a dietary supplement, commercially available in Europe since 2013, containing melatonin, vitamin B6, and extracts of lemon balm (*Melissa officinalis*), passionflower (*Passiflora incarnata*), and California poppy (*Eschscholzia californica*). Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized by the pineal

Abbreviations: ABR, auditory brainstem response; AE, adverse event; BMI, body mass index; CI, confidence interval; GABA, gamma-aminobutyric acid; IQR, interquartile range; ISI, Insomnia Severity Index; min, minutes; SCN, suprachiasmatic nucleus; SD, standard deviation; SEM, standard error of the mean

* Corresponding author at: 33 bis rue du 8 mai, 69330, Meyzieu, Lyon, France.
E-mail address: patrick.lemoine99@free.fr (P. Lemoine).

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gland, with a key role in regulating the circadian rhythm and sleep-wake cycle [6,8]. Disruption to the timing in its release or production may contribute to insomnia.[6] Due to its reported hypnotic properties, relatively benign side-effect profile, and over-the-counter availability, melatonin has become a commonly used sleep aid [9–11], marketed to help increase total sleep time, aid with fatigue from jet lag, and balance circadian rhythms [12]. Vitamin B6 (pyridoxine) acts as a coenzyme in the biosynthesis of melatonin, and its deficiency has been implicated in sleep disturbances [13]. Traditional botanical extracts (e.g., valerian, lime blossoms, passiflora, California poppy, and lemon balm) possess sedative and anxiolytic effects mediated via the gamma-aminobutyric acid (GABA)ergic system, with few known side effects [14–17].

Considering the sedative properties of each active ingredient in the product, Novanuit® Triple Action may potentially offer an alternative to the currently available pharmaceutical therapies for sleep disorders. This pilot study examined the effect of combined melatonin, vitamin B6, and medicinal plants on self-reported sleep disturbances and sleep quality in participants with mild-to-moderate insomnia.

2. Methods

2.1. Study design

This study was a prospective, single-center, single-arm, open-label trial (Fig. 1) conducted in Gdansk, Poland, between March and July 2017. The study protocol was approved by the Bioethics Committee of the Regional Chamber of Physicians in Gdansk. This study was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable Polish laws and regulations. All participants provided written informed consent prior to study enrolment. The trial was registered on ClinicalTrials.gov (NCT03514732).

2.2. Participants and recruitment

This study recruited 20–75-year-old male and female participants with a body mass index (BMI) of 18.5–29.9 kg/m^2 and affected by mild-to-moderate insomnia (as defined by the Insomnia Severity Index [ISI]; total score range, 8–21). The ISI is a 7-item self-reporting questionnaire assessing the severity of day- and night-time components of insomnia over the past month. A 5-point Likert scale was used to rate each item of the questionnaire (0, no problem; 4, very severe problem), yielding a total score ranging from 0 to 28. The total score was interpreted as follows: absence of insomnia (0–7), sub-threshold insomnia (8–14), moderate insomnia (15–21), and severe insomnia (22–28) [18]. Only low-level smokers (≤10 cigarettes/day) or non-daily smokers and those with low habitual intake of alcohol (< 21 units/week) were included in the study.

Exclusion criteria included: pregnancy or lactation; known sleep disorders, such as dyssomnias, parasomnias, and circadian rhythm sleep disorders; neuropsychiatric disorders or any other medical condition causing sleep problems; eating disorders; or use of hypnotics, sedatives, or opioids within 6 months or dietary supplements for insomnia within 3 months before the start of the study. Participants with irregular working hours or with children experiencing significant night-time sleep disturbances were also excluded from the study.

Subjects were recruited via the study-center participant database, and via social media outlets.

2.3. Procedures

Participants underwent a 1-week pre-screening period wherein they completed an electronic sleep diary; adhered to a fixed sleep schedule; and avoided caffeinated drinks, nicotine, and alcohol. This was followed by a 2-week treatment period in which participants received the study medication. Each participant received two capsules of Novanuit® Triple Action/day to be taken at the same time 30–60 min before their fixed bedtime. Each daily dose (comprising two capsules) contained 1 mg melatonin, 0.42 mg vitamin B6, 8.4 mg California poppy extract, 150 mg passionflower extract, and 240 mg of lemon balm extract. The selection of melatonin dose (1 mg) was based on a previous placebo-controlled study conducted in 8 healthy males, wherein there was no difference in the improvements in sleep latency or sleep efficiency across the dose range of 0.5–5 mg melatonin [19]. After 2 weeks, patients stopped receiving the study drug, and were followed for an additional week to assess sleep parameters during the week after product discontinuation.

In total, there were 3 study visits: at the start of the trial (screening), and on the first and last day of the 2-week treatment period. Following the last visit, participants completed a 5-item post-treatment dependency questionnaire over the phone; this questionnaire was mainly used to investigate the occurrence of any withdrawal symptoms in participants following treatment discontinuation.

Throughout the 4-week study period, data were collected using a daily electronic sleep diary. To reduce recall bias, participants completed the sleep diary each morning to record sleep patterns for the previous night. They reported on the time they got into bed, time they

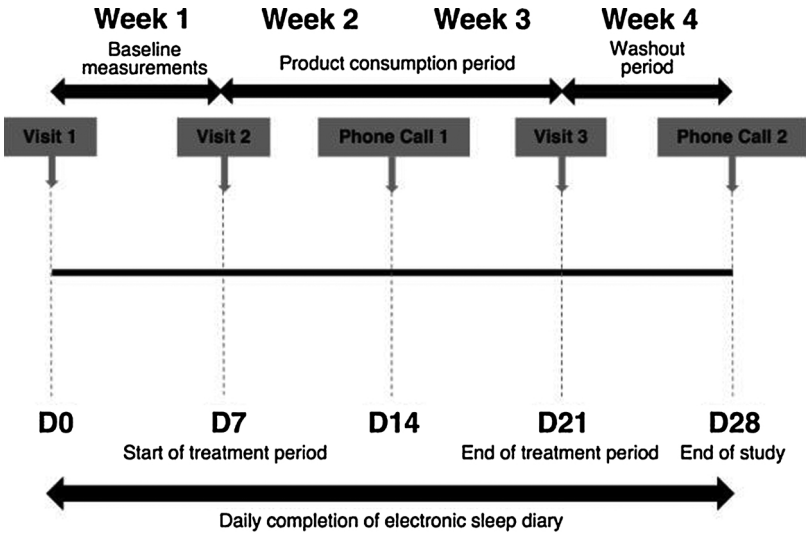

Fig. 1. Overview of study timeline.
D, day.

fell asleep, number and duration of night awakenings, number of nightmares, time they woke up to start the day, and number and duration of daytime naps. Across each 7-day assessment period, average total sleep duration, sleep onset latency, number of night-time awakenings and their duration, number of nightmares/night, and number of daytime naps and their duration were extracted for analyses. Sleep quality, awakening quality, and daytime fatigue were also subjectively assessed by the participants in their sleep diary on a 0–10 Likert scale (0: bad sleep, bad awakening quality or no daytime fatigue; 10: very good sleep, very good awakening quality or extreme fatigue).

Participants recorded adverse events (AEs) in their sleep diary; at the final study visit at Week 3, AEs were recorded by directly asking participants if they had experienced any AE or illness. To assess compliance with the study medication, participants were asked to return the unused capsules following treatment completion, and pill count was performed.

2.4. Outcomes

The primary study outcome was the change in the mean sleep quality score from Week 1 to Week 3. Secondary outcomes included the change in the mean sleep quality score from Week 1 to Week 4 and the change in the mean value of other sleep parameters, including total sleep duration, sleep onset latency, number of night-time awakenings, number of nightmares/night, number and duration of daytime naps, daytime fatigue, and awakening quality from Week 1 to Weeks 3 and 4 of the study. AES were reported throughout the study period. Compliance with the treatment protocol and the dependence potential of the study medication were also assessed.

2.5. Statistical analysis

For sample size calculation, we considered an increase of 2.0 points in the mean sleep quality score from Week 1 to Week 3 of the study to be significant, and assuming a standard deviation (SD) of 3, 26 participants were required to achieve 90% power at a 0.05 significance level. Assuming a 40% likelihood of screening failure or withdrawal, a minimal sample size of 44 patients was required.

For descriptive analysis, categorical variables were summarized as counts and percentages, whereas continuous and interval variables were reported as mean, SD, standard error of the mean (SEM), median, range, interquartile range (IQR), and 95% confidence interval (CI). A paired Student's *t*-test was used to compare the mean of normally distributed quantitative data. The Wilcoxon signed-rank test was used for non-normally distributed quantitative data. No missing value imputation or substitution was performed, and no statistical adjustment was made for the multiplicity of endpoints, as the secondary outcomes were considered as informative only.

All statistical tests were two-sided and were performed at a 0.05 significance level. Statistical analyses were conducted using SAS version 9.3.

3. Results

3.1. Study participants

Of 65 volunteers that were recruited and pre-screened, 40 met the eligibility criteria and were enrolled in the study. Demographic and clinical characteristics of the study participants are presented in Table 1. The study population was predominantly female (87.5%), relatively young (median age: 28 years), with a normal BMI. Moderate insomnia was reported in the majority of participants (median ISI score: 16.0). All 40 participants completed the study, with no withdrawals or major protocol deviations.

Table 1
Baseline demographic and clinical characteristics.

Baseline characteristic		Study population (N = 40)
Male/female, n (%)		5 (12.5)/35 (87.5)
Age (years)	Mean ± SD	33.2 ± 11.6
	Median (IQR)	28.0 (24.5 – 39.5)
	Range	22.0 – 65.0
BMI (kg/m^2)	Mean ± SD	23.3 ± 3.2
	Median (IQR)	23.4 (20.2 – 25.7)
	Range	18.5 – 28.6
ISI total score	Mean ± SD	15.5 ± 2.6
	Median (IQR)	16.0 (13.5 – 17.0)
	Range	9.0 – 21.0

Percentages are calculated as n/N.
BMI, body mass index; IQR, interquartile range; ISI, Insomnia Severity Index; SD, standard deviation.

3.2. Compliance and safety

Almost all participants (39/40; 97.5%) complied with the treatment protocol (two capsules/day taken at the same time 30–60 min before bedtime). Only one participant accidentally took an additional dose of two capsules on Day 9 of the study. However, the patient remained asymptomatic throughout the remainder of the study.

Treatment was well-tolerated by the study population; no serious AEs were reported and no participants discontinued the study medication due to AEs. Overall, 6 participants (15.0%) experienced 7 AEs, including headaches (3 events), abdominal pain (2 events), neck pain (1 event), and accidental overdose (1 event detailed above). All AEs resolved spontaneously, and were deemed not related or unlikely to be related to the study treatment.

3.3. Sleep assessment

Statistically significant improvements from pre-treatment (Week 1) to post-treatment (end of Weeks 3 and 4) were detected for all self-reported sleep outcomes ($p < 0.01$ or < 0.005 or < 0.001 for all sleep parameters; Table 2).

There was a statistically significant ($p < 0.001$) improvement in sleep quality by the end of the 2-week treatment period, with the mean ± SD sleep quality score increasing by 1.9 ± 1.5 points from Week 1 (5.4 ± 1.1 points) to Week 3 of the study (7.3 ± 1.5 points). Improvement in quality of sleep was sustained until Week 4 of the study (mean ± SD sleep quality score: 7.0 ± 1.5 points; $p < 0.001$ compared to Week 1). Mean sleep quality score did not change significantly between study Weeks 3 and 4 ($p = 0.13$). Fig. 2 illustrates the mean ± SEM weekly score of sleep quality through the 4-week study period.

Similarly, statistically significant improvements were observed from Week 1 to Weeks 3 and 4 of the study in sleep onset latency, total sleep duration, number of nightmares, and number of nocturnal awakenings (Table 2). There was a mean ± SD decrease by 15.1 ± 22.2 min in sleep onset latency from Week 1 (39.0 ± 29.7 min) to Week 3 of the study (23.9 ± 14.2 min; $p < 0.001$). There was also an increase in the total sleep duration from a mean ± SD of 6.9 ± 0.9 h at the end of Week 1 to 7.5 ± 0.9 h at the end of the 2-week treatment period (mean increase of 0.6 h; $p < 0.001$).

These improvements in nocturnal sleep parameters from baseline to Weeks 3 and 4 were reflected in statistically significantly improved scores for daytime parameters, including improved awakening quality ($p < 0.001$), reduced daytime fatigue ($p < 0.001$), and reduced daytime nap duration ($p < 0.01$ for Week 3, $p < 0.005$ for Week 4; Table 2).

Comparisons between Week3- and 4-sleep parameter scores revealed that a statistically significant difference was only detected for daytime fatigue which increased following treatment completion

Table 2
Summary of results for primary and secondary endpoints.

	Difference in means Week 1 to Week 3 [95% CI], p value	Difference in means Week 1 to Week 4 [95% CI], p value	Difference in means Week 3 to Week 4 [95% CI], p value
Quality of sleep*	1.9 [1.4; 2.3], p < 0.001	1.6 [1.2; 2.1], p < 0.001	−0.3 [−0.6; 0.08], p = 0.13
Awakening quality*	1.8 [1.3; 2.3], p < 0.001	1.5 [0.9; 2.0], p < 0.001	−0.4 [−0.7; 0.0], p = 0.052
Daytime fatigue*	−1.3 [−1.8; −0.7], p < 0.001	−0.9 [−1.4; −0.4], p < 0.001	0.4 [0.07; 0.7], p = 0.02
Sleep onset latency (minutes)	−15.1 [−22.2; −8.1], p < 0.001	−11.9 [−18.8; −4.9], p < 0.001	3.3 [−0.4; 6.9], p = 0.09
Nocturnal sleep duration (hours)	0.6 [0.4; 0.9], p < 0.001	0.5 [0.3; 0.7], p < 0.001	−0.1 [−0.3; 0.04], p = 0.13
Daytime nap duration (hours)	−0.08 [−0.1; −0.02], p < 0.01	−0.1 [−0.2; −0.04], p < 0.005	−0.02 [−0.05; 0.02], p = 0.41
Number of awakenings per night	−0.5 [−0.7; −0.3], p < 0.001	−0.5 [−0.7; −0.3], p < 0.001	−0.03 [−0.1; 0.05], p = 0.4
Number of nightmares per night	−0.08 [−0.1; −0.03], p < 0.005	−0.07 [−0.1; −0.02], p < 0.005	0.01 [−0.02; 0.03], p = 0.6

* Data are expressed in arbitrary units (0–10 Likert scale). CI, confidence interval.

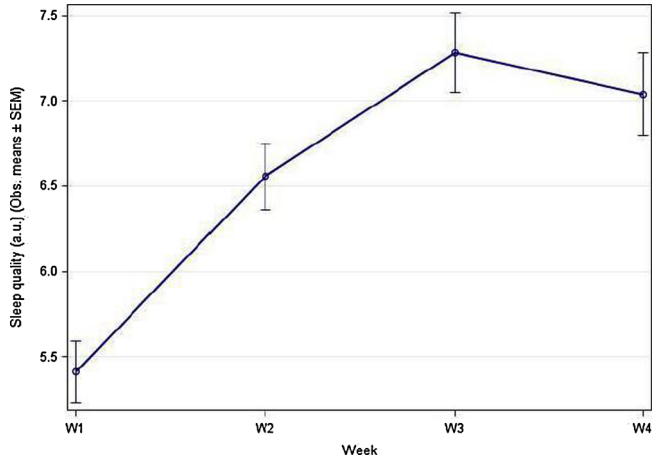

Fig. 2. Mean weekly score of sleep quality throughout the 4-week study period. a. u., arbitrary unit; Obs. means ± SEM, observed means ± standard error of the mean; W, week.

(mean ± SD daytime fatigue score: 3.3 ± 1.5 points at Week 3 versus 3.6 ± 1.5 points at Week 4; p = 0.02).

3.4. Post-treatment dependency questionnaire

At the end of the 4-week study period, when participants were contacted for a post-treatment assessment, almost all (37/40; 92.5%) felt that they slept better during the 2-week treatment period; of these, 25 (67.6%) felt that the study medication was associated with improved sleep outcomes even after 1 week of treatment completion.

None of the participants reported occurrence of AEs or withdrawal symptoms following treatment completion, and only one patient reported drug craving or feeling in a state of lack in the week following product discontinuation.

4. Discussion

This single-arm open-label pilot study showed that in otherwise healthy adults diagnosed with mild-to-moderate insomnia, the combination of melatonin, vitamin B6, and medicinal plants led to improvements from baseline in sleep onset latency, sleep quality, and daytime functional disability. The absence of any control arm means that a treatment effect has not been proven, but the results are suggestive of a potential benefit. To our knowledge, this is the first study to qualitatively explore this combination in the management of sleep disorders.

Insomnia is one of the most common complaints in primary care, with a > 30% symptom prevalence in adults [18,19]. Several large-scale studies have highlighted an ongoing increase in occasional insomnia-related symptoms in the general adult population across different countries [4,19–21]. This is a cause for concern since insomnia is known to be associated with various psychosocial and behavioral problems, and chronic physical illnesses [3,21,22] Thus, a natural sleep aid with limited AEs may offer advantages in the management of sleep disorders over prescription sleep drugs with well described AEs [12].

Except melatonin and a few popular herbal medicines like valerian, there is a paucity of clinical trial data for alternative remedies for the management of sleep disorders [18]. A 2013 meta-analysis of 19 randomized, placebo-controlled trials found that melatonin administered at daily doses of 0.1 mg–5 mg decreased sleep latency by 7.1 min, increased total sleep time by 8.3 min, improved overall sleep quality, and had a favorable adverse effect profile.[10] The primary physiological function of melatonin in humans is to reinforce darkness-related behaviors, such as sleep propensity [23]. Three mechanisms of action have been associated with melatonin administration in patients with sleep disturbances: (1) promotion of sleep onset (by impairing the activity of the suprachiasmatic nucleus [SCN], and the consequent inhibition of the circadian wake signal, thereby operating via the specific sleep-circuit pathway); (2) sleep maintenance; and (3) phase-shifting of circadian rhythms (mediated by MT2 melatonin receptors in the SCN) [12,24].

A study determining the effect of vitamin B6 (single dose, 100 mg) on serum melatonin levels, core body temperature, and sleep patterns in healthy adult men found that participants receiving vitamin B6 subsequently spent 33% more time in rapid eye movement sleep compared with those given a placebo; however this difference was not statistically significant (possibly because of the small study population [N = 12]) [25]. In another study evaluating sedation for auditory brainstem response assessment of hearing impairment in children aged 1–4 years, administration of melatonin, tryptophan, and vitamin B6 for 7 days before the assessment substantially reduced the need for repeated examinations as well as the need to use sedative drugs compared with melatonin alone or placebo, suggesting that Vitamin B6 and tryptophan have some efficacy in inducing sleep in this setting [13].

Limited clinical data are available for herbal extracts in sleep disorders. Administration of lemon balm extract for 15 days was associated with an improvement of associated symptoms of insomnia and anxiety.[14] Based on a study in mice, two mechanisms have been postulated for the action of lemon balm extract on anxiety-like reactivity and on circadian and exploratory activities: through its cholinergic properties, as measured by acetylcholinesterase inhibition and cholinergic receptor-binding capacity (nicotinic and muscarinic receptors), and through its GABAergic properties, by GABA transaminase inhibition [26]. Although anxiolytic and hypnotic activities of passionflower have been evaluated previously, limited information is available about its mechanism of action [15,27]. A pharmacological study in rats showed that passionflower acts in a concentration-dependent manner by binding to $GABA_A$ and $GABA_B$ receptors and inhibiting GABA uptake into rat cortical synaptosomes [27]. Similarly, the sedative and anxiolytic effects of California poppy extract have been linked to benzodiazepine receptor activation [17].

Melatonin, vitamin B6, and medicinal plants have all individually demonstrated a favorable safety profile, with minimal reported AEs,

and no reported concerns about addiction or withdrawal [14,28–30]. A meta-analysis of 17 studies and 651 participants, evaluating the effects of exogenous melatonin on people with secondary sleep disorders or sleep disorders accompanying sleep restriction found that the most commonly reported AEs of headache, dizziness, nausea, and drowsiness, were similar for melatonin and placebo [28]. The findings of this meta-analysis are consistent with our study, in which no serious AEs were observed and headache was the most commonly reported AE. In a more recent meta-analysis, it was found that higher melatonin doses and longer duration trials were related to significantly greater improvement in sleep latency and total sleep time in subjects with primary sleep disorders, suggesting that there is low risk for developing tolerance to melatonin [10]. The results of the current study are consistent with these results, with no participants reporting withdrawal symptoms following treatment completion and only one patient (1/40; 2.5%) reporting drug craving. However, larger, controlled studies with longer treatment and follow-up periods are required to investigate the dependence potential of this combination treatment.

The current study has several limitations. Most importantly, the absence of a control group severely limits the interpretation of the significance of the study findings, potentially leading to an overestimation of treatment effects, since it is unknown to what extent a 'placebo'-like effect is being observed. Furthermore, it is possible that there may be a selection bias of participants due to the uncontrolled nature of the study design. The sample size was small, with participation restricted to healthy, young, and predominantly female patients, thereby limiting the generalizability of these study findings to broader populations. Another limitation is the inability to isolate effects of individual active components of the combination product. Whilst this study was based on self-reported sleep assessments by the participants, future studies should include objective assessments using polysomnography or actigraphy to increase the validity and reliability of findings.

5. Conclusions

This preliminary, single-arm, open-label study suggests that a combination of melatonin, vitamin B6, and extracts of California poppy, passionflower, and lemon balm may be beneficial in improving sleep quality and daytime function in participants with mild-to-moderate insomnia. To test this hypothesis, further research is needed to examine the long-term safety and efficacy of this combination in large randomized controlled trials.

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Conflicts of Interest

Patrick Lemoine has received travel, advisory board, and research funding from Sanofi-Aventis, France. Christèle Da Silva and Jean-Christophe Bablon are employees of Sanofi-Aventis, France.

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