Nutrafoods (2022) 1:324-330 DOI 10.17470/NF-022-0041

Original Research

Treatment of insomnia in individuals undergoing diet therapy: nutraceutical approach vs pharmacological approach, a retrospective evaluation

Abstract

Nutritional modulation can be a factor in sleep quality, with the potential to cause insomnia. Insomnia has negative consequences both on the outcomes of treatment and on health in general. In this retrospective case–control evaluation, individuals with insomnia likely induced by diet therapy treatment and with a reduced tolerance to Bromazepam therapy, were evaluated on the effects obtainable with the administration of a multi-layered, differentiated release nutraceutical formulation containing highly standardized and titrated extracts of valerian (*Valeriana officinalis* L.), passionflower (*Passiflora incarnata* L.) and hawthorn (*Crataegus oxyacantha* L.) distributed under the commercial name of Neurofast®.

A double-check was carried out against individuals with insomnia likely induced by diet therapy who were tolerant to Bromazepam therapy or who, by personal choice, preferred the use of nutraceuticals from the outset. The results demonstrate how the use of the nutraceutical product both as a first solution therapy and as a replacement for Bromazepam therapy significantly reduces insomnia and psychosomatic and autonomic symptoms. The Bromazepam therapy participants showed significantly effective, rapid results leading to complete remission of insomnia.

When Bromazepam therapy was replaced with the nutraceutical product clinical remission was maintained, demonstrating a potentially comparable effect in the complete absence of rebound effect. Notably, the symptom 'morning sleepiness', which can be considered an adverse effect of Bromazepam, was detectable at a severe level in the Bromazepam therapy group but completely absent in nutraceuticals groups. The modified release multilayer nutraceutical formulation distributed under the trade name of Neurofast® proves to be a safe and effective solution in the management of insomnia symptoms even in the presence of autonomic and psychosomatic symptoms. Further studies, more structured and carried out on a larger and selected sample with more stringent criteria, will be necessary to further clarify the aspects taken into consideration.

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Keywords: Overweight, obesity, diet, insomnia, valerian, passionflower, hawthorn, differentiated release, Neurofast®, nutraceuticals

Introduction

Overweight and obesity are pathological manifestations in constant growth worldwide, so much so that they can be classified as pathologies with a real pandemic impact. It is predicted that by 2025 at least 175 million adults will be affected by severe outcomes of morbid obesity, 1 billion will be obese and well over 2.5 billion will be overweight [1, 3]. This projection constitutes a particularly serious picture considering that, in the absence of interventions, the evolutionary nature of these pathologies shows a worsening dynamic [4, 5]. Many nutritional approaches for the treatment of overweight and obesity include quantitative modulation in the consumption of carbohydrates, a factor documented as capable of altering the dynamics of sleep. Research by Vlahoyiannis *et. al.* (2021) analyses how the quality and quantity of carbohydrates consumed influences the latency time for the onset of sleep, while a greater carbohydrate intake in quantitative terms is associated with the depth of sleep and its prolongation, particularly in the REM phase [6]. Nutritional modulation can therefore be an influencing factor in sleep quality, with the potential to cause insomnia, which in this case can be properly classified as secondary insomnia as it can be correlated to nutritional treatment [7]. When this occurs, it is important to consider how insomnia has negative consequences on treatment outcomes and on health in general, being related to autonomic and/or psychosomatic disorders in the absence of organ pathology (anxiety; feeling of tightness in the throat, chest and abdomen; muscle disorders; tachycardia; palpitations, etc.), blood pressure, metabolic, immune changes [8, 9]. These negative factors are of considerable importance both for the success of the nutritional plan and for the protection of the individual's health.

When hygiene and health measures for sleep management are not sufficient, pharmacological approaches are often recommended under medical supervision and for limited periods, which may include taking sedatives, antidepressants, and anxiolytics. These approaches are generally effective but are characterized by potential side-effects including drug tolerance, withdrawal rebound, and/or morning sleepiness [10]. Before resorting to a pharmacological approach, it is worth considering the use of botanicals, which is generally characterized by a lower incidence of side-effects, a reduced risk of real drug interactions, and consequently, greater ease of use [11]. The aim of this work is to consider the effects obtainable with the administration of a nutraceutical formulation made with valerian, passionflower and hawthorn with dynamic, differentiated and optimized release versus conventional therapy in participants with diet therapy-induced insomnia.

Materials and methods

Participants

A total of 75 participants were involved in the trial: 60 women and 15 men, aged between 25 and 60 years in diet therapy, with adherence to the proposed nutritional prescription of more than 75% who began to manifest sleep disturbances accompanied by psychosomatic and/or autonomic disturbances that cannot be resolved with behavioural measures relating to sleep hygiene. Of the total participants, 25 were currently being treated with Bromazepam therapy 1.5 mg as a single evening administration but with poor tolerance to the therapy, so much so that therapy was interrupted. This group was evaluated against 25 participants currently being treated with Bromazepam therapy 1.5 mg as a single evening administration with good tolerance and 25 participants who, by personal choice, preferred

a nutraceutical approach from the outset.

The following groups were excluded from the trial: pregnant women; individuals with ongoing pathologies; individuals taking other therapeutic drugs except Bromazepam or taking any other nutraceutical product; individuals diagnosed with psychiatric/behavioural disorders; individuals who consumed alcohol, drugs, tobacco or their derivatives; individuals who practised intense physical activity after 4pm.

Evaluated products and evaluation scheme

In this retrospective case-control evaluation, participants with insomnia, likely induced by diet therapy treatment, and with reduced tolerance to Bromazepam therapy were evaluated on the effects obtainable with the administration of a multi-layered, differentiated release nutraceutical formulation containing highly standardized and titrated extracts of Valeriana officinalis L., *Passiflora incarnata* L. and *Crataegus oxyacantha* L. distributed under the commercial name of Neurofast®.

Obtainable effects were double-checked against participants with insomnia, likely induced by diet therapy treatment, who were tolerant of Bromazepam therapy or who, by personal choice, preferred the use of nutraceuticals from the outset. Retrospective data studies and analysis were conducted in accordance with good clinical practice rules fixed by the Declaration of Helsinki and in accordance with the European Union Directive 2001/20/EC [12]. Each patient signed a consent form and privacy policy documents and approved data analysis and publishing. The nutraceutical product used is a multilayer tablet suitably made to provide three different nutraceutical principles with modified release dynamics produced by SIIT (Trezzano sul Naviglio, Milan, Italy), and notified to the Italian Ministry of Health as a food supplement by Pharmextracta SpA (Pontenure, PC, Italy) complying with Law no.169/2004 (notification number 26), marketed under the name Neurofast®. The first layer contains 100 mg standardized extract titrated with valeric acids (0.8%) from the rhizome and roots of Valeriana officinalis L. and formulated with fast-release layer technology to release its content in five minutes. This is with the aim of speeding up the plasma peak of valerenic acids to maximize the anxiolytic and hypnotic effects related to the GABA-ergic potential (increase in synthesis and release, reduction in agonistic catabolism for the receptor) [13–16]. The second layer contains 100 mg standardized extract titrated with flavonoids [3.5%] from aerial parts of *Passiflora incarnata* L. and formulated with slow-release layer technology to release its content in eight hours. This is with the intention of promoting prolonged contact with the intestinal mucosa and prolonged and uniform absorption, with the potential to reduce the hepatic first-pass effect, favouring a prolonged and lasting action on psychosomatic symptoms [17–20]. The third layer contains 100 mg standardized extract titrated with vitexin-2-rhamnoside (1.8%) from the flowering tops of *Crataegus oxyacantha* L. and formulated with normal-release layer technology to release its content in 45 minutes. This is with the intention of favouring its positive inotropic, negative chronotropic, positive dromotropic and negative bathmotropic action [21–26].

The group of participants with reduced tolerance to Bromazepam (BN) was asked to take the nutraceutical preparation at a daily dosage of one tablet before bedtime and a second tablet 12 hours apart, amounting to two tablets/day from t0 and continuing for three weeks. This group were also asked to cease taking their Bromazepam therapy after the first day of the trial, with an overall drug/nutraceutical overlap of one day. After three weeks the BN group then took a reduced nutraceutical dosage of one tablet per day before bedtime for the remainder of the trial.

The group being treated with the nutraceutical product only (N) took the same dosage with the same dynamics. The group being treated with Bromazepam only (B) continued their current therapy with the prescribed dosage. Each of the three groups was composed of 25 participants and the overall evaluation period was six weeks. The scores relating to the symptoms were detected at the start of evaluation (t=0), after 3 weeks (t=1) and after 6 weeks (t=2) as shown in **Fig. 1**. Symptoms taken into consideration include those listed in **Table 1**.

Symptoms were recorded on a scale of 0–2 where 0 represents the absence of symptoms, 1 represents a moderate symptomatology and 2 represents severe symptoms. At the time of enrolment, each participant had to show a score of at least 13 points (>80% on the scale considered), assigned by the evaluating doctors. Morning sleepiness was considered as a potential adverse effect and was therefore considered individually.

Table 1 Symptoms considered and evaluation scale

Symptom	Absent	Moderate	Severe
Difficulty in falling asleep	0	1	2
Difficulty in maintaining sleep	0	1	2
Tachycardia and/or palpitations	0	1	2
Anxiety	0	1	2
Throat and/or chest oppression	0	1	2
Abdominal cramp	0	1	2
Muscular pain	0	1	2
Morning sleepiness	0	1	2

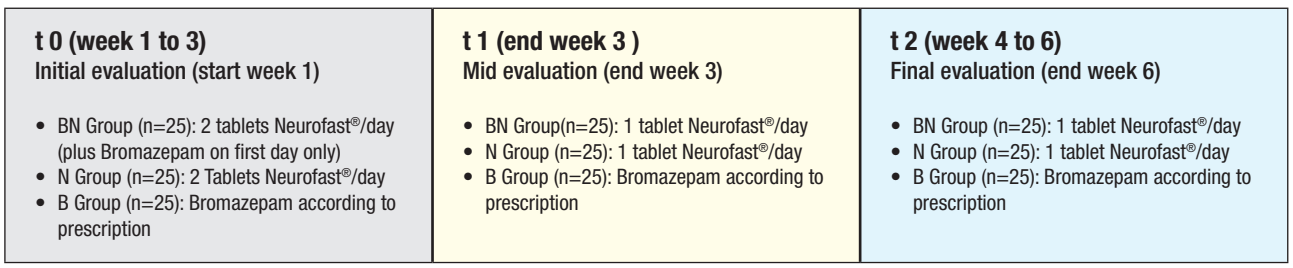
Results

The results collected demonstrate how the use of the nutraceutical product both as a first solution and as a replacement for Bromazepam significantly reduces insomnia and psychosomatic and autonomic symptoms, with significant improvements already detectable at t1 (after three weeks of treatment) including the disappearance of symptoms such as tachycardia, tightness in the throat and chest, anxiety and muscle pain. Particularly interesting is the fact that clinical remission was maintained when Bromazepam therapy was replaced with the nutraceutical product, demonstrating a potentially comparable effect in the complete absence of rebound effect. Bromazepam therapy was significantly effective, leading rapidly to complete remission of the clinical condition. However, it is notable that the symptom 'morning sleepiness', which can be considered an adverse effect of the drug, is completely absent in groups N and BN, while it is detectable at a severe level in the B group (**Table 2**).

Discussion

Insomnia induced by diet therapy and associated with autonomic and psychosomatic symptoms is a factor potentially capable of compromising the effectiveness of the diet therapy intervention and more broadly of compromising the health of the person concerned. In this context, the extractive derivatives of

Figure 1 Clinical trial design



Valeriana officinalis L. standardized and titrated in valerenic acids (0.3% – 0.8% in the different pharmacopoeias) are considered active against insomnia with a GABA-ergic mechanism as previously described and are used in numerous nutraceuticals and dedicated drugs for this purpose. Extract of *Passiflora incarnata* L. is considered useful by virtue of peripheral mechanisms of action able to act at the level of the smooth muscles with a spasmolytic effect, therefore able to act at the level of psychosomatic manifestations in particular at the level of the digestive system, limiting its impact on sleep. Extract of *Crataegus oxyacantha* L. is characterized by the presence of a procyanidolic oligomeric fraction. It has been extensively studied for its ability to intervene on cardiac dynamics as described above and is used in numerous drugs and nutraceuticals. Based on these characteristics, the release and absorption dynamics were created to optimize the activity of the multicomponent nutraceutical formulation under consideration. The results showed that the multicomponent nutraceutical formulation shows a clinical action when used directly as a first approach (in participants with more severe symptoms) and when used as a substitute for Bromazepam. Unlike the drug, the nutraceutical formulation prevents (and does not show) the onset of any rebound effect related to benzodiazepine withdrawal. At the end of the six-week evaluation period, the symptom pictures of the three groups proved to be superimposable, suggesting the non-inferiority of the multicomponent nutraceutical formulation with the advantage of not causing the marked morning sleepiness generally related to the intake of Benzodiazepines. A further future development could be to evaluate the time window following the interruption of treatment with the multicomponent nutraceutical formulation within which complete symptomatic remission is maintained.

Table 2 Clinical activity (M±SD) of the multicomponent preparation group (N), Bromazepam group (B) and Bromazepam→Neurofast® group (BN) in treatment for insomnia complicated by autonomic and psychosomatic symptoms

Symptom	t0	t1 (3 weeks)	t2 (6 weeks)
Group Neurofast® (N)			
Difficulty in falling a sleep	2±0	0.5±0.5	0.12±0.5
Difficulty in maintaining sleep	2±0	0.5±0.5	0
Tachycardia and/or palpitations	2±0	0	0
Anxiety	2±0	0.5±0.5	0
Throat and/or chest oppression	2±0	0	0
Abdominal cramp	2±0	0.5±0.5	0.25±0.5
Muscular pain	2±0	0.5±0.5	0
Morning sleepiness	0±0	0±0	0±0
Group Bromazepam (B)			
Difficulty in falling a sleep	1±0	0	0
Difficulty in maintaining sleep	1±0	0	0
Tachycardia and/or palpitations	2±0	0	0
Anxiety	1±0	0	0
Throat and/or chest oppression	2±0	0	0
Abdominal cramp	2±0	0.12±0.5	0.12±0.5
Muscular pain	2±0	0.12±0.5	0
Morning sleepiness	2±0	2±0	2±0
Group Bromazepam→Neurofast® (BN)			
Difficulty in falling a sleep	2±0	0	0
Difficulty in maintaining sleep	2±0	0	0
Tachycardia and/or palpitations	2±0	0	0
Anxiety	2±0	0	0
Throat and/or chest oppression	2±0	0	0
Abdominal cramp	2±0	0.25±0.5	0.25±0.5
Muscular pain	2±0	0.25±0.5	0.25±0.5
Morning sleepiness	2±0	0±0	0±0

^ Each of the eight symptoms assessed with scores 0 = absent; 1 = moderate; 2 = severe

Conclusions

Based on the findings, the modified release multilayer nutraceutical formulation distributed under the trade name of Neurofast® proves to be a safe and effective solution in the management of insomnia symptoms even in the presence of autonomic and psychosomatic symptoms. Further studies, more structured and carried out on a larger and selected sample with more stringent criteria, will be necessary to further clarify the aspects taken into consideration.

Author contributions All authors contributed equally to writing of the manuscript; all authors read and approved the final version of the manuscript.

Funding This research received no external funding.

Conflict of Interest A Bertuccioli works as a scientific consultant for the company responsible for developing Neurofast®.

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