

Insomnia treatment: a new multitasking natural compound based on melatonin and cannabis extracts

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Abstract

Objectives. Our main aim was to investigate the short-term therapeutic effects, safety/tolerability of natural compound, composed of melatonin (1.5 mg) and cannabis extracts (2.5 mg CBD) in patients with sleep disorders

Methods. In this spontaneous, anecdotal, retrospective, “compassionate-use,” observational, open-label study, 20 patients (age 43-96 years) were appealed to our “Second Opinion Medical Consulting Network” (Modena, Italy), because of a variable pattern of sleep disorders and anxiety and were instructed to take sublingually the compound (20 drops) overnight for 3 months of treatment. Tolerability and adverse effects were assessed monthly during the treatment period through direct contact (email or telephone) or visit if required.

Results. PSQI and HAM-A scores evidenced reduction in mood alterations, including anxiety, panic, paranoia, depression ($P < 0.03$), in pain ($P < 0.02$) and good general health perceptions.

Conclusions. These data suggest that the formula CBD-melatonin could be competitive with the classic hypnotic synthetic drugs, the antioxidant activity of melatonin offers a further benefit to the brain network, restoring the biological clock functions, while CBD, reducing chronic pain perception, helps to complete the neuromuscular relaxation and to relieve anxiety fulfilling a very balanced sensation of wellbeing during the sleep. *Clin Ter 2022; 173 (1):91-96. doi: 10.7417/CT.2022.2399*

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Introduction

Insomnia is a common disorder affecting quality of sleep and daily productivity. One-third of the general adult population reports the presence of insomnia at some time, with primary insomnia being the most common diagnosis. Insomnia is associated with an increased risk for mental disorders, including depression, anxiety, and alcoholism.

It also is associated with an increased risk for metabolic syndrome, acute coronary syndrome, and hypertension. The economic impact of insomnia is substantial. In the United States, alone, direct annual costs of insomnia reached \$13.9 billion during the 1990s and indirect costs ranged from \$77 to \$92 billion (1). Thus, insomnia treatment is expected to provide benefits from an individual and social perspective: several drugs have been registered and marketed in the last 20 years to normalize the sleep or increase sleep quality with different indications and success (Table 1). Furthermore, the drugs addiction subsequent to their chronic use very often causes switch off one to another and another one along the time. Chemical compounds and many herbal extracts are offered to the consumer accordingly whether his preference might be natural or synthetic formulation (2, 3).

In this study we have clinically verified quite an intriguing hypothesis, administering in the same liquid two “natural” compounds, melatonin and cannabis extracts, in order to take control both most common neuropsychological and physical distressing symptoms disturbing the regular sleep and causing multiple awakenings.

Cannabis Sativa and *Indica* are the most widespread plant species worldwide, they contain more than 80 cannabinoids mainly tetrahydrocannabinol (THC) and cannabidiol (CBD), the former has definite psycho activity, the latter is provided of other neurological effects through the CBD receptors network, modulating especially chronic pain and other central and peripheral nervous disorders (4). Production of CBD oil is achieved from hemp plants seeds harboring less than 0.3% THC (5, 6). Anxiolytic effects reach with dose between 1 mg/kg and 100 mg, so a low dose is more effective, probably due to specific CB1 and 5-HT1A brain receptors. In the insomnia setting, nitrazepam has been challenged in a clinical crossing over trial with 160 mg CBD showing a more effective sleeping recovery. Cortisol level is reduced by higher doses of CBD reducing in parallel anxiety and insomnia, achieving moderate mental sedation. The utmost interesting property of CBD administration is the absolute safety of the compound even for very high dosages (1600 mg or more) without any reported mortality.

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Table 1. List of synthetic drugs and natural hypnotic herbs.

SYNTHETIC HYPNOTIC DRUGS	NATURAL HYPNOTIC HERBS
Ambien (zolpidem)	Piper methysticum L.f. (Piperaceae)
Belsomra (suvorexant)	Zizyphus jujuba Mill var. spinose (Rhamnaceae)
Butisol (butabarbital)	Valeriana officinalis L. (Caprifoliaceae)
Doral (quazepam)	Hypericum montbretii Spach (Hypericaceae)
Edluar (zolpidem)	Pinus massoniana Lamb. (Pinaceae)
Estazolam	Scutellaria baicalensis Georgi (Lamiaceae)
Flurazepam	Atractylodes macrocephala Koidz. (Compositae)
Halcion (triazolam)	Ipomoea orizabensis (Pelletan) Ledeb. ex Steud. (Convolvulaceae)
Hetlioz (tasimelteon)	Ternstroemia lineata DC. (Pentaphylacaceae)
Intermezzo (zolpidem)	Rhus parviflora Roxb. (Anacardiaceae)
Lunesta (eszopiclone)	Dimocarpus longan Lour. (Sapindaceae)
Restoril (temazepam)	Crassocephalum bauchiense (Hutch.) Milne-Redh. (Compositae)
Rozerem (ramelteon)	Chrysanthemum morifolium Ramat. (Compositae)
Seconal (secobarbital)	Dorstenia arifolia Lam. (Moraceae)
Silenor (doxepin)	Magnolia officinalis Rehder & E.H.Wilson (Magnoliaceae)
Sonata (zaleplon)	Glycyrrhiza glabraL. (Leguminosae)
Zolpimist (zolpidem)	Ecklonia cavaKjellman (Lessoniaceae)
Benadryl (diphenhydramine)*	Melissa officinalis L. (Lamiaceae)
Unisom (doxylamine)*	

In the recent study (2019), Shannon et al investigated the effect of CBD on anxiety and insomnia, and the compliance related, safety of its chronic use (7). 103 adult patients complaining of anxiety and sleep disturbances were recruited: patients with only primary diagnoses of schizophrenia, or post-traumatic stress disorder, and agitated depression were excluded. 72 patients fulfilled the investigation steps: 47 with relevant anxiety and 25 with sleep impairment. Psychiatric comorbidity required contemporary use of other psychotropic drugs that were not withdrawn during the trial. The administration schedule was 25 mg and 75 mg day capsules for at least one month either in the morning or in the evening time accordingly with the peak of the symptoms. Results showed definite decrease of anxiety score during the CBD administration (79.2%). A high percentage (66,7%) of patients improved sleep quality in the first month of treatment, with some fluctuating events in the follow up. The clinical evaluation was performed monthly for three months (7).

Melatonin n'acetyl-5-metoxotriptamine is produced in the pineal gland, but also in lymphocytes, bone marrow, skin, gut retina and testis, spermatozoa and ovaries (8). Melatonin has strong antioxidant activity either directly covering or indirectly through melatonin receptors 1 and 2, promoting antioxidant tissue enzymatic activity, inducing glutathione synthesis, stabilizing the mitochondrial electronic chain to prevent electric charges leakage; conversely it can also display pro-oxidant activities. It has a key role in synchronizing circadian rhythms, namely the sleep-wake cycle (9).

It has been and currently is successfully prescribed to treat a wide range of sleep disorders, such as jet lag, primary insomnia, sleep-wake cycle disruption and sleep problems in children with neuro-developmental disorders.

Even if there is not a specific registration of melatonin in the treatment of insomnia, in 2007 a slow release 2 mg dosage has been licensed in Europe (EMA-EU) as short-term treatment of primary insomnia and poor sleep quality in patients 55 years old or over. Further claims for melatonin administration were: -reduced sleep latency like hypnotics,

-improvement of sleep quality, -next day alertness improvement, -no evidence of impairing cognitive and psychomotor skills. The life quality superiority of melatonin challenged against placebo. We fairly demonstrated while other aspects, such as rebound dependence, abuse or minor untoward effects were overlapping with placebo.

Conclusively, melatonin can be prescribed aside many other drugs and it can potentiate GABA A receptor modulators.

Our Second Opinion Medical Consulting Network was founded by one of us (B. Palmieri) a few years ago at the University of Modena medical school, it is a free of charge examination and counseling service dedicated to patients with comorbidity or unresolved health problems desperately trying to achieve positive results (health recovery or at least life quality improvement), through stubborn sometimes obsessive web screening, and contacts (the classic doctor google consultation) with often self-referral Doctors or Institutions (10-12). We have named such a patient's compulsory behavior "the Web Babel Syndrome" and obviously our mission has been to release promptly proper diagnostic and effective therapeutic options, relieving this frustrating situation (13). This happens very often in co-morbidity affected old patients, when each specialist prescribes one or more remedies, on his own point of view without any contact and compliance with the other physicians to harmonize the drug prescriptions in terms of compatibility, scheduled time, side effects etc.

We tried to rearrange a rationale harmless and effective drug delivery schedule, following up with planned phone interview and/or periodical visit to our office, in order to effectively interact with to the problem-solving goal. Sometimes, when a specific supposedly effective drug not available on the market is required, or when the symptoms complexity requires a dedicated multidrug formulation, we draw a galenic prescription, either directly to the pharmacist or playing to some nutraceutical manufacturing company to prepare for us some amount of a specific molecular complex tailored for our case solving purposes.

In the case of melatonin plus CBD, the inspiring concept was to manufacture a galenic compound able to induce good mental relaxation to relieve some minor pain symptoms disturbing the quite sleep follow up during the supine postural adaptation to reduce gastroesophageal reflux and micturition episodes and to trigger the cortical EEG synchronization to start the sleep, prolonged for 5-7 hours.

We pooled progressively (from January 2016 to June 2019) a certain number (n=20) of patients unsatisfied by their sleep quality and requiring switch off their addicted hypnotics looking for some natural compounds with limited side effects. We committed to a swiss Company a specific oil formulation containing melatonin (1,5 mg) and CBD.

Materials and methods

28 patients (16 females and 12 males) aged between 37-96 years have been recruited for this investigation, but we had totally 8 drop out due lack of compliance, or no complete feedback in the follow up.

The final sample consisted of 20 adults (14 women and 6 men) presenting with primary concerns of anxiety or poor sleep. The average age for the patients with anxiety and sleep disorders was 67 years (range = 43-96 years). Most patients (n = 13) suffered from physical pain or other somatic disorders that could interfere with sleep. Half of patients (n = 10) suffered from cognitive disorders and anxiety, even these elements affect the quality of sleep. All patients completed sleep and anxiety assessments at the onset of treatment and at the third monthly follow-up. Sleep concerns

were tracked at monthly visits using the PSQI (Pittsburg Sleep Quality Index) questionnaire. Anxiety levels were monitored at monthly visits using the HAM-A (Hamilton Anxiety Rating Scale) questionnaire. Both scales are non-patented. The Hamilton Anxiety Rating Scale is a widely used and validated anxiety measure with 14 individual questions. It was first used in 1959 and covers a wide range of anxiety-related concerns. The score ranges from 0 to 56. A score under 17 indicates mild anxiety, and a score above 25 indicates severe anxiety. The Pittsburg Sleep Quality Index is a self-report measure that assesses the quality of sleep during a 1-month period. It consists of 19 items that have been found to be reliable and valid in the assessment of a range of sleep-related problems. Each item is rated 0 to 3 and yields a total score from 0 to 21. A higher number indicates more sleep-related concerns. A score of 5 or greater indicates a "poor sleeper".

The patients both sexes and their drug use are described in the following table (Table 2):

The patients were asked to stop the previous hypnotic medication with a 1 week wash out interval. The recruitment enclosed patient with comorbidities, and cardiovascular or any other metabolically active drugs for diabetes etc., was followed up without drop out. The scale for insomnia with 17 items was recorded at the beginning of the study one and three months in the follow up. The compound (CBD oil) was administered overnight.

Data were entered into an HQCD database by a researcher and analyzed using the R software, version 3.1.2 (2015, Vienna, Austria) s. Statistical tests included the Mann-Whitney test (continuous variables not normally

Table 2. List of patients undergoing treatment, symptoms and previous hypnotic drugs used

Patient	Symptoms	DRUG
C. A. 96 F	Chronic Pain Arthritis	Diazepam
T. F. 55 M	Anxiety, Shoulder Pain	Lorazepam
P. E. 48 F	Depression	Flunitrazepam
C. P. 67 M	Chronic Pain At Bed And Frequent Micturition	Zolpidem
P. P. 80 M	Spondylarthritis, BPCO And Frequent Micturition	Melatonin, Diazepam
V. A. 86 M	Early Dementia, Agitation	Flunitrazepam
S. O. 87 F	Memory Loss, Agitation,	Melatonin
P. I. 82 F	Cancer Relapse Abd Pain	Oxycodone + Tramadol
C. A. 61 F	Chronic Arth Pain.	Seroxat + Diazepam
M. P. 45 F	Atm Dysfunction Pain Trisma Bruxism	Diazepam
S. R. 82 F	Colicky Pain, Heartburn Reflux	Melatonin
D. L. 89 F	Arthritis, Night Excitability, Hypertension	Trazodone
D. G. 68 F	Anxiety, Cognitive Impairment, Tachycardia	Chlorazepam
A. A. 62 M	Prostate Cancer, Anxiety, Urinary Frequency	Nitrazepam
B. E. 47 F	Lumbar Block Sciatica.	Pregabalin
D. N. 43 M	Amputation Neurologic Bladder. Lumbar Pain	Thioridazine
D. N. 69 F	Osteoporosis, Anxiety, Arthritis. Frequent Micturition	Clorpromazina
G. S. 58 F	Restless Legs	Mirtazapine, Pregabalin
P. R. 62 F	Chronic Stress lbd.	Mixed Sedation Herbs (Valerian, Passiflora)
M.S. 52 F	Muscle Pain, Fasciculation, Cramps Insomnia Due To Charcot-Marie-Tooth Syndrome	No Drug

distributed) and the chi-squared test (categorical variables). A commonly used measure of linear correlation, the Pearson correlation coefficient, denoted by r , was reported. Statistical significance was set at a P value < 0.05 .

Results

All the recruited patients completed the treatment for three months with CBD-based compound, appearing positive therapeutic effects on symptoms and quality of sleep. The main efficacy endpoints, as assessed by the monthly PSQI and HAM-A questionnaire, administered at the end of every month treatment, are reduction in mood alterations, including anxiety, panic, paranoia, depression ($P < 0.03$), in pain ($P < 0.02$) and good general health perceptions. The results show an improvement in physical symptoms such as chronic pain (Fig. 1) and mood disorders such as anxiety (Fig. 2) that affected sleep. The red line in the graphs represents the disturbances at time 0 (without treatment), while the green line shows the disturbances found after three months of treatment.

In addition, improvements in sleep quality and anxiety have been observed, evidenced through a lowering of the average values of PSQI and HAM-A indices (Fig. 3). The following graph shows the trend of PSQI (blue columns) and HAM-A scores (orange columns) evaluated at the beginning of the study, after one and three months of treatment.

Discussion

The studies investigating the relationship between cannabis and melatonin in order to evaluate synergy or antagonism of their contemporary administration *in vivo*

are very few. Algabonsi et al. described antagonistic effect between melatonin and tetrahydrocannabinol in the rat sperm, whose genital apparatus when exposed to cannabis induced oligospermia partially neutralized by melatonin supply due to its strong antioxidant activity (1). No clinical experience on the contrary has been described in the insomnia combined treatment (melatonin plus CBD), which is quite a puzzling therapeutic option, because the long-term treatment of sleep disturbances very often requires regular periodic drugs re-prescription turnover due to the addiction of the common hypnotics drugs (generally benzodiazepines or antidepressants) or to untoward side effects.

Our results show that sleep improved for all the recruited patients, and they are still satisfied 30-60 days after the end of the trial.

The partial or total symptoms remission in terms of:

1. Chronic pain relapsing nighttime due to the resting body position, pressure upon joints and bone, involuntary movements.
2. Frequent micturition due to prostate enlargement or prostatitis, hyperactive bladder, detrusor instability.
3. Anxiety with nightmares and arms and legs involuntary movement and speech.
4. Disturbing bowel movements, reflux, bloating, with or without IBD.

A quite remarkable continuity and quality of the sleeping time restored the patients with a good energy and daily activity feedback the morning after.

In conclusion, the physician, prescribing natural compounds; to optimize the night rest and relieve at the same time a series of troublesome symptoms, usually increasing with age namely neurological musculoskeletal, urogenital, abdominal, which awake the patients even several times in the night; could consider the formula CBD (2,5 mg) and melatonin (1,5 mg) as definitely competitive with the classic hypnotic synthetic drugs.

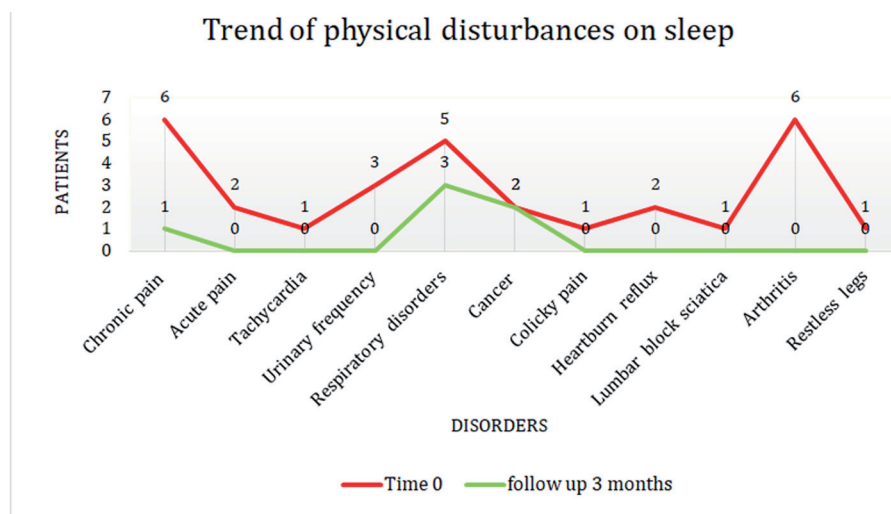


Fig. 1. Trend in sleep disorders over the study period of three months

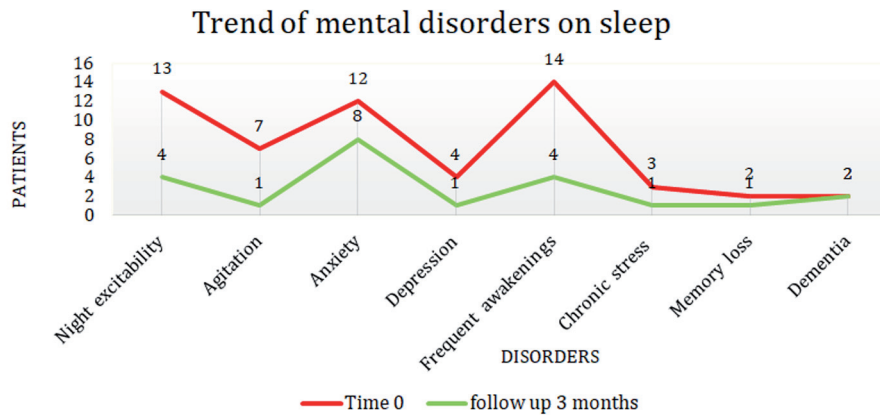


Fig. 2. Trend in emotional disorders over the study period

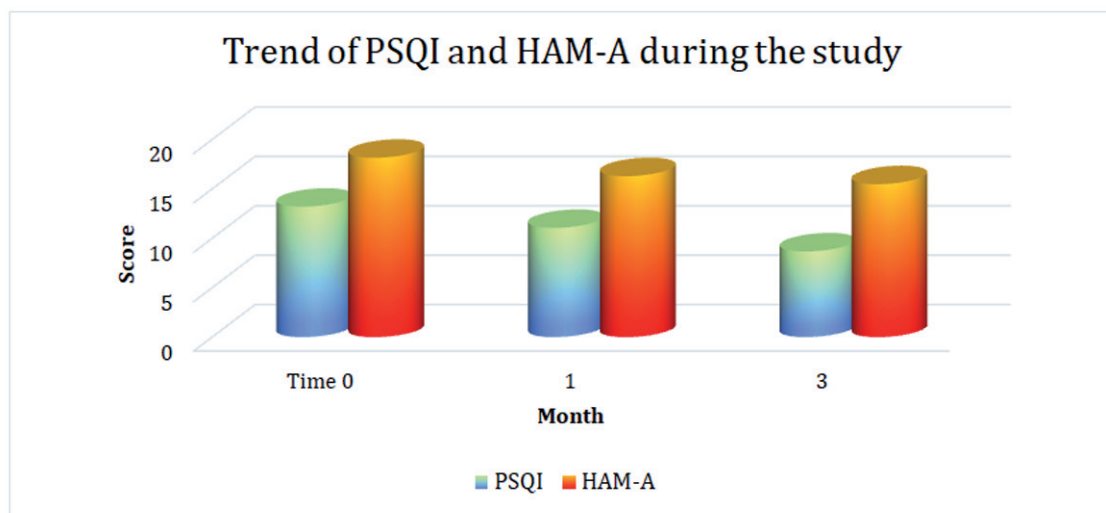


Fig. 3. Average values of PSQI and HAM-A indices during the study period

The strong antioxidant activity of melatonin offers a further benefit to the brain network, restoring the biological clock functions, while CBD, reducing chronic pain perception helps to complete the neuromuscular relaxation and to relieve anxiety fulfilling a very balanced sensation of wellbeing during the sleep.

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