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Assessment of onset, duration, sleep efficiency and quality of sleep through SleepRite™ combination product(s) on adult subjects with difficulties in falling asleep

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Abstract

Background: Sleep is a basic requirement of the human body as is eating or breathing. Time and again it has been demonstrated how sleep deficiency are detrimental to general metabolism and bio-systems of the body. Sleep disorders affecting significant populations are a global phenomenon reported across both, advanced and emerging economies. Sleep inadequacy has a direct tangible impact on health and also on the quality of life. Poor sleep by research, has been consistently linked to metabolic pathologies, cognitive productivity, physical performance, cardiac and Immunological health.

In this study, the objectives predominantly were to determine the safety and efficacy of SleepRite™ combination product(s) through measures of onset, duration, sleep efficiency and quality of sleep. The active investigational product (SleepRite™) as a combination of chamomile, melatonin, valerian, L-tryptophan and passion flower extracts. Further to this, to analyze the effects of the combination product(s) on the mean improvement in onset, duration, sleep efficiency and quality of sleep in comparison with the placebo.

Methods: The study was a randomized, single-blind (subject), two center, crossover, placebo-controlled study to evaluate safety and efficacy of SleepRite™ (consisting of chamomile, valerian, melatonin, L-tryptophan and passion flower extracts) supplement on mean improvement in onset, duration and quality of sleep in adult literate subjects (n=24). There were two dosages of the combination product of SleepRite™ evaluated in the study, one 66% concentration and another with 100% concentration, both in comparison with the placebo. Study was conducted through four visits over a period of about thirty days. Subjects who had received a combination product of SleepRite™ 66% received a SleepRite™ 100% and vice-versa. At each visit, the mean improvement in onset, duration, sleep efficiency and quality of sleep were deduced by means of subjective and objective assessments with subject diaries, Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) throughout the study. The secondary efficacy variables included assessments of study products on day-time functioning by recording ISI, PSQI scoring across the study, summarized by visits and treatments. The secondary variables of safety and tolerability were estimated by way of adverse events reporting and subject diaries. The investigational study products were consumed in several flavours and subjects' preferences to these were also evaluated.

Conclusions: Consumption of SleepRite™ (combination of active products) has shown significant improvement of sleep in standard and subjective measures of sleep onset, latency and sleep efficiency. It has been found that there is considerable reduction in mean onset of sleep for subjects with SleepRite™ 100% (17.25 minutes) administration as compared to SleepRite™ 66% (22.08 minutes) when compared against Placebo arm (32.13 minutes). This clearly shows that both active strengths in SleepRite™ study have shown substantial improvement in the onset of the sleep. There is appreciable increase in duration of sleep when subjects were under SleepRite™ 100% (7.9 hrs) administration as compared to SleepRite™ 66% (6.8 hrs) as compared to the Placebo arm (6.1 hrs). It has been found that there is substantial increase in sleep efficiency for subjects on SleepRite™ 100% (by 91%) administration as compared to the SleepRite™ 66% (by 86%) administration when compared to placebo arm (by 80%). However, there were no significant changes noted in the quality of sleep as the sample population was small and the sample size did not adequately justify the above objective. However, trends showed some positive changes were observed amongst people with SleepRite™ in the quality of sleep.

Keywords: SleepRite™, clinical study, placebo, sleep onset, sleep duration, sleep quality, sleep efficiency, subject diary

Introduction

There is growing ignorance amongst general public with respect to the awareness, understanding and significance of sleep and its impact on the well-being of humans. Even amongst the medical professionals and content in standard medical textbooks are not tuned enough into sleep disturbances and their morbid consequences [1, 2]. It has been estimated that more than half of the working population in India have experienced some form or other form of sleep deprivations or alterations during their lifetime [13]. These lead to challenges to the professionals involved in public safety from drivers causing accidents, shift workers, fire safety, health care professionals and other emergency service providers to mention a few instances where cognitive vigilance is paramount [19]. Our literature survey looked at some of the ingredients in SleepRite™ from its historic use and state of the literature for these agents in its effect on sleep metabolism. Several studies [3-7] conducted with individual

ingredients and their nocturnal administration have been shown to reduce sleep latency, increased sleep time and overall quality of sleep.

Previous research studies suggests that supplementation with melatonin may help increase total sleep time in individuals suffering from sleep restriction or altered sleep schedules, relieve daytime fatigue associated with jet lag, reset the body's sleep-wake cycle and reduce the time it takes to fall asleep in people with delayed sleep phase syndrome [4]. In contrast to most available sleep medications, melatonin has little dependence potential, is not associated with habituation and typically produces no hangover [16]. In examining the effects on sleep latency, the nocturnal administration of L-tryptophan is compounded by the usually shortened sleep latency at bedtime. It has been suggested that L-tryptophan simply lowers the arousal threshold during the waking state to permit more rapid sleep onset and it indirectly increases levels of melatonin and serotonin levels [3, 17].

Chamomile did not demonstrate a statistically significant benefit over placebo in the predetermined primary sleep endpoints, specifically, sleep diary metrics [5, 14]. However, there is a growing literature of chamomile on its effect on GABA (gamma-aminobutyric acid) and its indirect action on sleep synergistically with other products that makes it more of a supplement to sleeping aides. Valerian is the most commonly used herbal product to induce sleep and systematic reviews conducted suggests that valerian could improve sleep quality and may have adequate power to assess changes on subjective measures of sleep quality and overall quality of life [5, 6, 15]. Oral premedication with passion flower extracts reduced preoperative anxiety without inducing sedation or changing psychomotor function. Some studies have shown small changes in sleep efficiency and onset of sleep but not on total sleep time [7].

Methods

A randomized, two-center, single-blind, crossover, involving twenty-four adult literate subject clinical study was conducted using test and placebo. The study was conducted at two medical centers and the study was approved by an Independence Ethics Committee (IEC) which is constituted and functions as per the Good Clinical Practice (GCP) guidelines and is registered with the local regulatory authorities. The study was conducted over four visits through a duration of thirty-two days. Study design comprised a crossover of two active treatment arms (subjects receiving combination SleepRite™ 66% received combination SleepRite™ 100% and vice-versa).

Selection of Subjects

Twenty-four subjects (24) were men and women aged from 20 to 60 years and those subjects who willingly gave informed consent participated in the study. Subjects with any psychiatric disorders by standard Beck Depression Index (BDI) and uncontrolled metabolic disorders and/or unstable medical illness were excluded by clinical examination and history. Women who were pregnant, breast feeding, and planning pregnancy were also excluded from the study.

Study Design

This was a randomized, single-blind, cross-over, placebo-controlled study to evaluate safety and assess the efficacy of SleepRite™ (chamomile, valerian, melatonin, L-tryptophan and passion flower extracts) supplement on mean improvement in onset, duration and quality of sleep. As per the plan, twenty-four subjects were enrolled into the study after being screened for compliance to eligibility criteria, subjects underwent clinical physical exam, medical and concomitant medications history to rule out medical and substance-related causes of sleep deprivation. All participating subjects were blinded to the study products and all completed the study. All subjects received the three study investigational products that includes two concentrations of the SleepRite™ and placebo.

The primary objectives of the study were to assess mean improvement in onset, duration, sleep efficiency and quality of sleep. Subjects who complied with entry eligibility criteria were randomized into two treatment arms to receive SleepRite™ 100% and 66% at Visit 1, followed by placebo, with one day wash-out period at visit 2 and cross-over of the treatments as scheduled at visit 3. Further, subjects received an initial five days with either or amongst two active treatments (SleepRite™100 % / 66%) as per randomization schedule and then followed by placebo with one day wash-out period and cross-over of the active treatments at the scheduled visit 3. Hence each subject consumed the study investigational products over fifteen days, where three products were assessed by each subject in the subject diaries provided to them. Washout period was followed by crossover of treatments arms (subjects received combination SleepRite™ of 66% first and later 100% or vice-versa with the placebo product administered in between active products). The primary outcomes were evaluated to changes from baseline in SleepRite™ (combination of chamomile, valerian, melatonin, L-tryptophan and passion flower extracts) on sleep measures. The secondary outcomes entailed changes from baseline of SleepRite™ on daytime functioning measures. The active and placebo investigational products were provided with several flavors and preferences to which were determined by subjects. During the scheduled visits Insomnia Severity Index (ISI) and Pittsburg Sleep Quality Index (PSQI) were recorded to help assess the primary and secondary outcomes of the study.

Study Research Tools

Insomnia Severity Index (ISI) is a clinically useful screening and measuring tool used to evaluate insomnia/sleep disorders to therapy and evaluating treatment response outcomes. ISI's total score from 0 to 28 is reliable and sensitive to detect changes in sleep difficulties. ISI scores can be compared to subjects' entries into the study diaries and that total ISI scores could positively correlate with subjective sleep estimates. Change in ISI scores in the same subject and between subjects over time draws a good map to indicate efficiency of the interventions treating sleep disorders [8, 9].

Pittsburg Sleep Quality Index (PSQI) is a self-rated screening and clinometric questionnaire which assesses sleep quality and disturbances. It is specifically designed to measure sleep quality in clinical populations and measure intervention outcomes. The nineteen individual items generate seven composite scores to sleep issues and help understand subject's sleep disorders and patterns. With ISI and PSQI scoring(s) alongside subject diaries recurrently addressing any adverse experiences, enabled Investigators to comprehensively review efficacy and safety of study investigational products through the study [10].

Beckman Depression Inventory (BDI): The BDI questionnaire ensured that psychiatric depression was ruled

out in subjects enrolled for the study. BDI is a 21-item self-report rating inventory that measures characteristic attitudes and symptoms of depression [11, 12].

Investigational Products

The Investigational products (IP) are proprietary products of Nutrite Healthcare Pvt. Ltd. Mumbai contains SleepRite™ 66% /100 % (chamomile, valerian, melatonin and L-tryptophan and passion flower extracts) and placebo. A volume of 60 ml of each of the three study Investigational products on study in sealed containers were manufactured by Nutrite Healthcare Pvt. Ltd, Mumbai. These products were supplied to the research team for research purpose without any commercial binding or subjected to any bias during the conduct of the study.

Table 1: Composition of SleepRite™

Ingredients
Valerian Root [*Valeriana wallichii*] extract (0.25%),
Chamomile [*Matricaria chamomilla*] extract (0.083%),
Passion flower [*Passiflora foetida*] extract (0.083%),
L-Tryptophan (0.066%)
Melatonin (0.003%),

Sixty milliliters (60 ml) of each of the three investigational products were provided to subjects in containers that were returned in subsequent visits. Study products were provided appropriately to randomized subjects at specific visits as per protocol. Subjects self-administered, the three study products at nights (as per the instructions provided by the study team and randomisation) on specific days. Onset (latency) and duration of sleep were recorded accordingly in the subject diaries provided to them during the course of the study. Study was planned as a single-blind study and subjects were unaware of contents received as per study products, depending on the arm the subject was randomized using randomization chart provided to the clinical sites. The dosage and volume of all three investigational products were determined as sufficient as per most subjects in study.

Statistical analysis

Study was analysed using SPSS 20.0 by a biostatistician to measure the outcome of the study. Onset of sleep (mins), duration of sleep (mins) and sleep efficiency (proportions) are summarized by days and treatment. Mean values of these among treatments are compared using non-parametric test Mann-Whitney U test with 5% level of significance. Quality of sleep is summarized by treatments and days (key days 1, 5, 7, 11, 13 and 17). Shift in quality of sleep is summarized to assess the impact of treatment arms. Insomnia Severity Index (ISI) total score and PSQI component scores are summarized by visits and treatment. Respective scores among treatments are compared using non-parametric method Mann-Whitney tests. No statistical assumptions regarding population were made as non-parametric methods were applied.

Results

Total of 24 subjects were enrolled for the study with twenty male and four female subjects across two clinical centers (Table 2). This study enrolled subjects from age group of 20 to 60 years with an average age group of 31 years.

- **Onset of Sleep:** With p-value = 0.001, we can infer that there is a difference between SleepRite™ 100% subjects and placebo subjects change from baseline in onset of sleep. With p-value = 0.005, we can infer that there is a difference between SleepRite™ 100% subjects and SleepRite™ 66% subjects change from baseline in onset of sleep (Figure 1). Onset of Sleep by visit and treatment of mITT population, with p-value = 0.0170, we could conclude that there is a significant difference between SleepRite™ 100% subjects and SleepRite™ 66% subjects on onset of sleep. Onset of Sleep by visit and treatment of mITT population, with p-value = 0.0381, we can conclude that there is a significant difference between SleepRite™ 66% subjects and placebo subjects of onset of sleep. And, with a p-value = 0.0001, we can infer that there is a difference between SleepRite™ 100% subjects and placebo subjects of onset of sleep.
- **Duration of Sleep:** With p-value = 0.0002, we can conclude that there is a significant difference between SleepRite™ 100% subjects and placebo subjects duration of sleep. With p-value = 0.0392, we can conclude that there is a significant difference between SleepRite™ 66% subjects and placebo subjects duration of sleep. With p-value = 0.0489, we can conclude that there is a difference between SleepRite™ 66% subjects and SleepRite™ 100% subjects duration of sleep. On an average, there is considerable increase in duration of sleep when subjects are under SleepRite™ 100% administration. 476.50 mins (7.94 h) while in SleepRite™ 100% administration when compared to 362.25 mins (6.03 h) while under placebo (Figure 2). For duration of sleep, with a p-value = 0.0002, we could conclude that there is a significant difference between SleepRite™ 100% subjects and placebo subjects. With a p-value = 0.0392, we could conclude that there is a significant difference between SleepRite™ 66% subjects and placebo subjects for duration of sleep. With a p-value = 0.0489, we could conclude that there is a significant difference between SleepRite™ 66% subjects and SleepRite™ 100% subjects in duration of sleep.
- **Sleep Efficiency:** There was significant enhancement of sleep efficiency when subjects were under SleepRite™ administration. i.e., Sleep efficiency was found to be 91% while on SleepRite™ 100% administration, 86% under SleepRite™ 66% when compared to 80% in placebo. Sleep efficiency and its change from baseline is summarized by assessment days and compared using Mann-Whitney U test between SleepRite™ (100%), SleepRite™ (66%) and placebo (combined). For sleep efficiency, with p-value = 0.0001, we could conclude that there is a significant difference between SleepRite™ 100% subjects and placebo subjects' sleep efficiency. With a p-value = 0.0046, we could conclude that there is a significant difference between SleepRite™ 100% subjects and SleepRite™ 66% subjects sleep efficiency (Figure 4).
- **Quality of Sleep:** is summarized by key assessment days by categories. There is an improvement in quality if sleep for three subjects while under SleepRite™ 100% administration. Whereas, improvement was seen for one subject under SleepRite™ 66% and two subjects in placebo subjects (Figure 3).
- **Insomnia Severity Index (ISI):** It's found that there is considerable decrease in ISI total score during subjects are under SleepRite™ administration. i.e., ISI total score is found to be 1.91 while in SleepRite™ 100% administration, 5.33 while under SleepRite™ 66% when

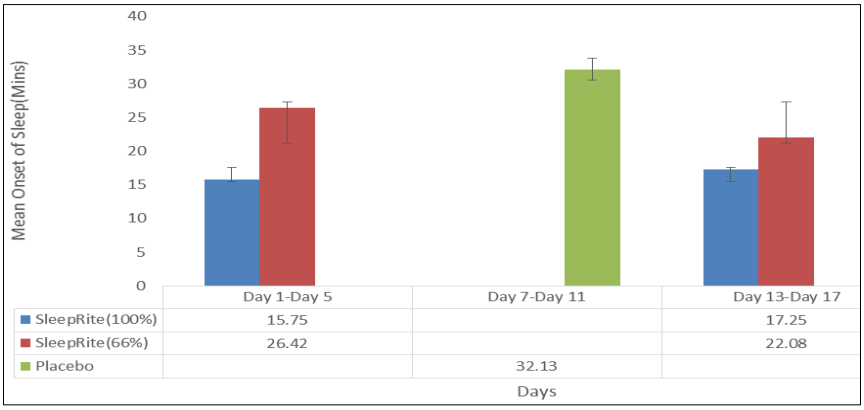
compared to 7.75 while in placebo. With obtained significant p-values, we conclude that there is a significant difference between SleepRite™ 66% and placebo subjects ISI total score of sleep and it's change from baseline (Figure 5). Insomnia Severity Index (ISI) component scores by visit and treatment of mITT population with a p-value of 0.002, we can infer that there is a significant difference between SleepRite™ 100% subjects and placebo subjects change from baseline in ISI total score. With a p-value of 0.077, we can infer that there is no difference between SleepRite™ 100% subjects and SleepRite™ 66% subjects change from baseline in ISI total score (Figure 5).

- **Pittsburg Sleep Quality Index (PSQI):** It's found that there is considerable decrease in PSQI component score when subjects were under SleepRite™ administration. i.e., PSQI component score is found to be 2.25 while in SleepRite™ 100% administration, 4.16 while under SleepRite™ 66% when compared to 5.29 while in placebo. With obtained significant p-values, we conclude that there is a significant difference between SleepRite™ 66% and placebo subjects with PSQI total score of sleep and it's change (Figure 6). Pittsburgh Sleep Quality Index (PSQI) component Scores by visit and treatment with mITT Population, that with p-value of 0.0127, we could conclude that there is a significant difference between SleepRite™ 100% subjects and placebo subjects PSQI score. With a p-value of 0.0270, we could conclude that there is a significant difference between SleepRite™ 66% subjects and placebo subjects PSQI score (Figure 6).

Table 2: Summary of Demographic and Baseline Characteristics

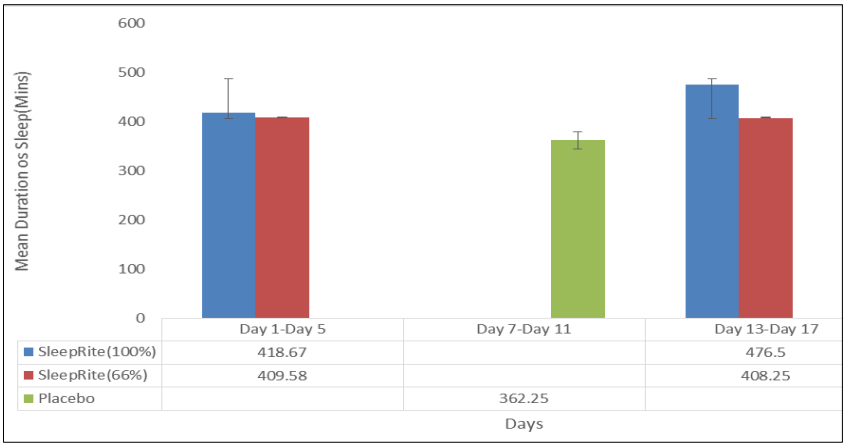
Parameters	Category/ Statistic	Overall (N=24)
Sex, n (%)	Male	20 (83.3%)
	Female	4(16.7%)
Age (years)	N	24
	Mean±SD	31.08 ± 9.28
	Min, Max	20.00, 60.00
Height (cm)	Mean±SD	167.47 ± 8.17
	Min, Max	150.00, 188.00
Weight (kg)	Mean ± SD	68.14±22.92
	Min, Max	30.40,135.00
BMI (kg/m2)	Mean ± SD	23.980±7.050
	Min, Max	13.51,46.00
Waist Circumference (cm)	Mean± SD	83.38 ± 11.99
	Min, Max	66.04, 116.00

Note: Sequence 1: SleepRite™ (100%) + Placebo + SleepRite™ (66%); Sequence 2: SleepRite™ (66%) + Placebo + SleepRite™ (100%); N = Number of subjects in Randomized Population; SD = standard deviation; BMI = Body Mass Index. Percentages are based on N.



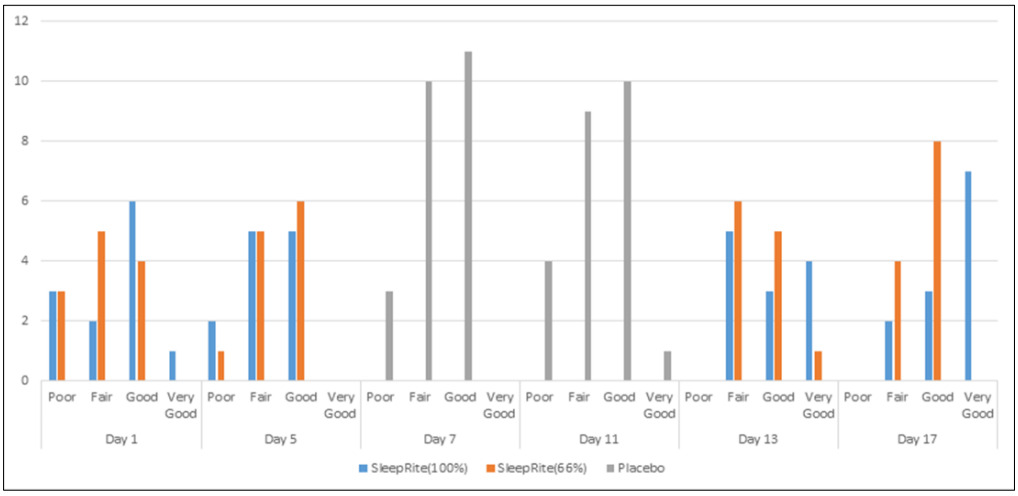
P-value obtained by comparing mean value of 100% SleepRite™ with Placebo using Mann-Whitney U Test. **P-value obtained by comparing mean value of 66% SleepRite™ with Placebo using Mann-Whitney U Test. n = Number of subject(s) with non-missing assessment at particular visit.

Fig 1: Mean (+/-) SD for Onset of Sleep by Days and Treatment



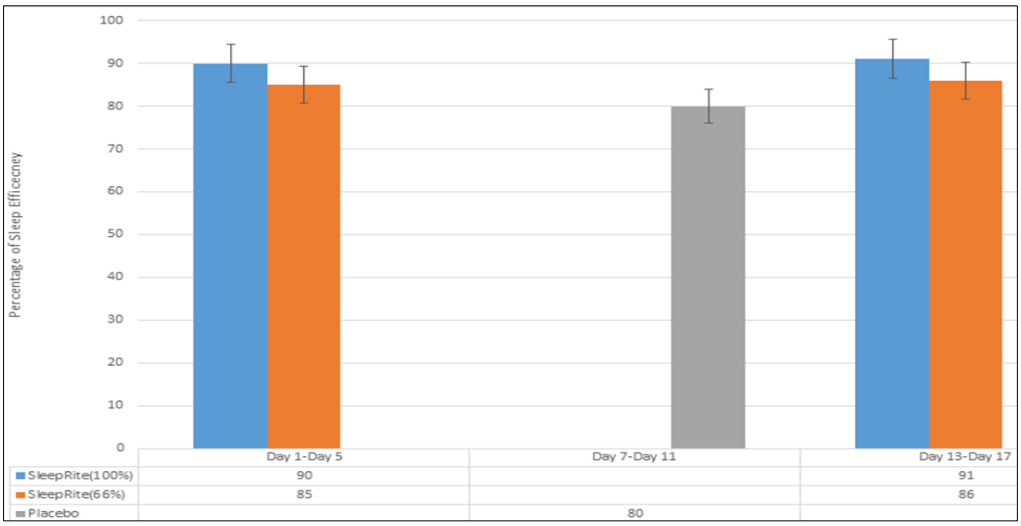
n = Number of subjects with non-missing assessment at particular visit. *P-value obtained by comparing mean value of 100% SleepRite™ with Placebo using Mann-Whitney U Test.**P-value obtained by comparing mean value of 66% SleepRite™ with Placebo using Mann-Whitney U Test.

Fig 2: Mean (+/-) SD of Duration of Sleep by Days and treatment



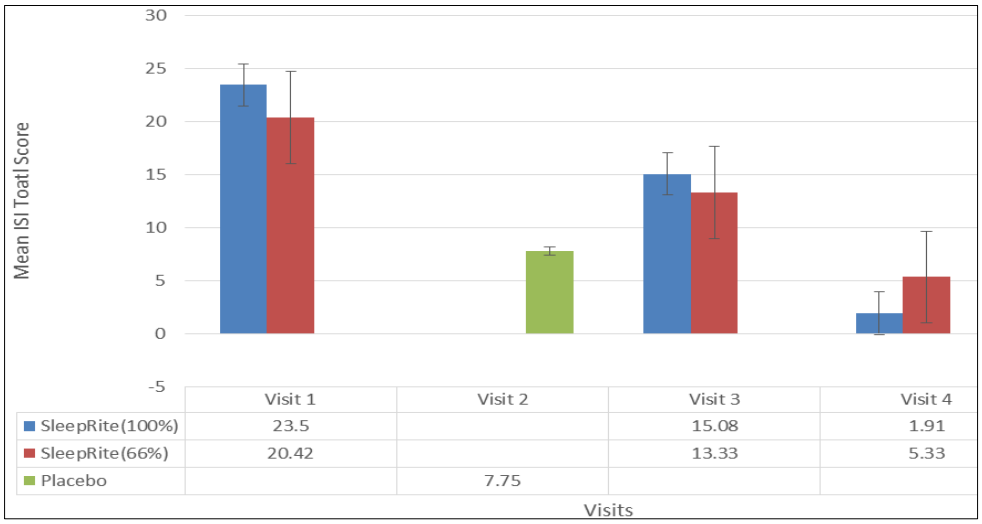
P-value obtained by comparing mean value of 100% SleepRite™ with Placebo using Mann-Whitney U Test. P-value obtained by comparing mean value of 66% SleepRite™ with Placebo using Mann-Whitney U Test. n = Number of subject with non-missing assessment at particular visit.

Fig 3: Figure for Quality of Sleep over period of treatment



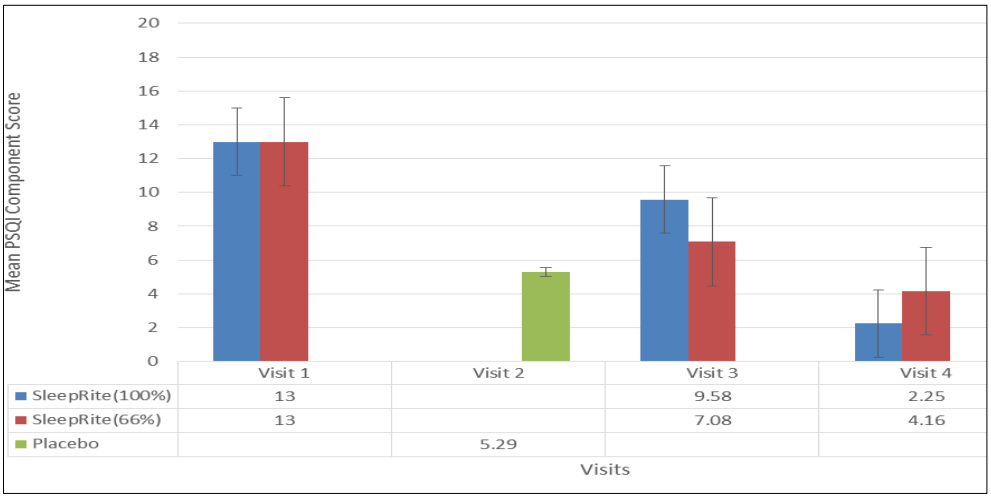
P-value obtained by comparing mean value of 100% SleepRite™ with Placebo using Mann-Whitney U Test. P-value obtained by comparing mean value of 66% SleepRite™ with Placebo using Mann-Whitney U Test. n = Number of subject with non-missing assessment at particular visit.

Fig 4: Percentage of Sleep Efficiency across treatment groups



P-value obtained by comparing mean value of 100% SleepRite™ with Placebo using Mann-Whitney U Test. P-value obtained by comparing mean value of 66% SleepRite™ with Placebo using Mann-Whitney U Test. n = Number of subjects with non-missing assessment at particular visit.

Fig 5: Mean (+/-SD) for Insomnia Severity Index (ISI) total Scor



P-value obtained by comparing mean value of 100% SleepRite™ with Placebo using Mann-Whitney U Test. P-value obtained by comparing mean value of 66% SleepRite™ with Placebo using Mann-Whitney U Test. N = Number of subjects with non-missing assessment at particular visit.

Fig 6: Mean + SD of PSQI Component Scores

Discussion & Conclusion

Epidemiology of circadian pattern and sleep have been elucidated in long- and short-term research with Indian populations with relation to etio-pathogenesis and their related metabolic and cardiovascular, neurological health challenges especially in those industries related with travel, business process outsourcing, medical care and public transport that could lead to unnecessary repercussions[19]. However, obtaining adequate and good quality sleep are continual challenges for the active human population. The purpose of this study was to a) determine improvement in onset, duration, efficiency and quality of sleep b) evaluate the safety of all the ingredients as combined products c) assess outcomes and dosing structure most applicable for these products based on the possible two dosage strengths envisaged in comparison with placebo d) generalize results to those who suffer from issues related to sleep disturbances and sleep hygiene based on the inclusion and exclusion criteria laid out in the clinical study. There is an abundance of interest in health or dietary supplements for these conditions where one can supplement poor sleep with these aides which can directly or indirectly improve onset, duration and sleep efficacy without interfering or having adverse events. Many naturally occurring products are manufactured and marketed for a variety of sleep symptoms across the world and it is used over the years as over the counter products. Comprehensive research on these natural products for sleep-related indications is in its adolescence; however there is a spectrum of evidence supporting the efficacy of these agents [18].

The analyses of sleep disorders are multidimensional and include a clinical evaluation by physicians that are complemented by self-report questionnaires (ISI and PSQI) and daily sleep diaries. As sleep disorders are also often arduous to evaluate clinically and reliably, these brief and valid questionnaires facilitate initial screening and aid formal evaluation of sleep conditions [10-12]. Subjects were instructed to complete subject diaries to record changes to specific sleep components and subjective feeling of sleep is essential to assess the quality and quantum of sleep. Lack of sleep as diagnosed by Investigators were indicated by shortened sleep duration at night, an increased sleep latency or onset, and history of tiredness post awakening for inclusion into study. Subjects with history of psychiatric illness on medications and therapy, substance abuse and uncontrolled medical illness were excluded as these were tested more on subjects who genuinely had a problem to get sleep without any organic cause. It is interesting to note subjects on SleepRite™ has shown improvement with sleep onset and duration of sleep compared to placebo. Objectively, subjects' interpretation is critical to monitor progress and evaluate sleep outcomes after initiating treatment and that is the foundation of any measure for sleep aides that can have positive impact on day to day life. Regulatory perspectives to subject-reported outcomes are increasingly used to substantiate evidence of treatment effectiveness in clinical trials [10]. Total ISI scores were correlated and compared with subjective sleep estimates in subject diaries and with PSQI total scores, indicating good convergent validity with subject-reported measures of sleep and this was shown positively in the current study wherein SleepRite™ at two different doses has shown improvement in subject reported outcomes compared to placebo. Based on the above rationale ISI and PSQI were recorded by every eligible randomized subject across four visits planned in the study.

It has been evaluated from the study that this combination product helps to initiate sleep, increase duration and improve sleep effectiveness amongst individuals suffering from sleep restrictive or altered sleep schedules. This may further help reduce the time taken to fall asleep in subjects with delayed sleep phase or in improving the overall sleep improvement. Literature has shown that individual ingredients improve one of the components of sleep and in combination may produce a synergistic or additive effect. From systematic review conducted during this study, suggests that the combination of active products may help improve sleep disturbances and has adequate power to assess changes in standard, subjective measures of sleep onset, latency and sleep efficiency.

There were no significant changes noted in the quality of sleep as the sample population was small and the sample size did not adequately justify the claim. However, trends showed some changes amongst subjects with SleepRite™ improving the quality of sleep. It has been statistically projected that SleepRite™ 100% was found to be superior to SleepRite™ 66% for the three primary assessments of onset of sleep,

duration of sleep and sleep efficiency. SleepRite™ 66% was found to be superior to placebo for the three primary assessments of onset of sleep, duration of sleep and sleep efficiency. SleepRite™ was not associated with habituation and produced no hangover as noted in study.

There were four natural ingredients in SleepRite™ and the study helped evaluate the combined actions of these active ingredients. However, the weakness in the study is that the actions and evaluations of individual ingredients was not possible. However, a long term larger population study should answer the quality of sleep in subjects who has difficulty in getting sleep. Clinical safety data evaluated from the study both from SleepRite™ 66%, SleepRite™ 100% arms and placebo arm were found to be safe and well tolerated in the sample population of the study. This study further appends to evidence-based research methodologies that benefits from adequate good sleep and a balanced twenty four hour approach goes a long way in ensuring overall health and fitness in human lives.

References

1. Charles Morin. The Oxford handbook of sleep and sleep disorders. Oxford University, 2012.
2. Theodore Baker L. Introduction to sleep and sleep disorders. Medical Clinics of North America. 1985; 69(6):1123-52.
3. Pandi-Perumal SR, Srinivasan V, Spence DW, Cardinali DP. Role of the melatonin system in the control of sleep: therapeutic implications. CNS drugs. 2007; 21:995-1018.
4. George CF, Millar TW, Hanly PJ, Kryger MH. The effect of L-tryptophan on daytime sleep latency in normals: correlation with blood levels. Sleep. 1989; 12(4):345-353.
5. Amsterdam JD, Li Y, Soeller I, Rockwell K, Mao JJ, Shults J. A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (chamomile) extract therapy for generalized anxiety disorder. J Clin Psychopharmacol. 2009; 29(4):378-382.
6. Stephen Bent, Amy Padula, Dan Moore, Michael Patterson, Wolf Mehling. Valerian for Sleep: A systematic review and meta-analysis., Am J Med. 2006; 119(12):1005-12.
7. Akhondzadeh S, Nhaghavi H, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. Journal of Clinical Pharmacy and Therapeutics. 2001; 26:363-367.
8. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001; 2(4):297-307.
9. Charles Morin M, Geneviève Belleville, Lynda Bélanger, Hans Ivers. The Insomnia Severity Index: Psychometric Indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011; 34(5): 601-608.
10. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2):193-213.
11. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of General Psychiatry. 1961; 4:561-571.
12. García-Batista ZE, Guerra-Peña K, Cano-Vindel A, Herrera-Martínez SX, Medrano LA. Validity and reliability of the Beck Depression Inventory (BDI-II) in general and hospital population of Dominican Republic. PLoS ONE. 2018; 13(6):e0199750. https://doi.org/ 10. 1371/ journal.pone.0199750.
13. Shah N, Bang A, Bhagat A. Indian research on sleep disorders. Indian Journal of psychiatry. 2010; 52(1):S255-9.
14. Shao-Min Chang, Chung-Hey Chen. Effects of an intervention with drinking chamomile tea on sleep quality and depression in sleep disturbed postnatal women: a randomized controlled trial. J Adv Nurs. 2016; 72(2):306-315.
15. Nunes A, Sousa M. Use of valerian in anxiety and sleep disorders: what is the best evidence. 2011; 24(4):961-966.
16. Buscemi N, Vandermeer B, Pandya R, Hooton N, Tjosvold L, Hartling L, *et al*. Melatonin for Treatment of Sleep Disorders. Evid Rep Technol Assess (Summ). 2004; 108:1-7.
17. Schneider-Helmert D, Spinweber CL. Evaluation of L-tryptophan for treatment of insomnia: a review. Psychopharmacology (Berl). 1986; 89(1):1-7.
18. Kapalka George M. Nutritional and herbal therapies for children and adolescents: a handbook for mental health clinicians. Amsterdam: Elsevier/ AP, 2010, http://public. eblib.com/choice/publicfullrecord. aspx?p=569285.
19. Lockley SW1, Cronin JW, Evans EE, Cade BE, Lee CJ, Landrigan CP, *et al*. Harvard Work Hours, Health and Safety Group. Effect of reducing interns' weekly work hours on sleep and attentional failures. N Engl J Med. 2004; 351(18):1829-37.