Evaluation of Efficacy of Novel Formulation E-In-05 (DreemzOn) Capsules in Treatment of Insomnia

Dr. Shalini Srivastava[*], Dr. Sachin R. Dighe[**]

[*] PG, Clinical Research (Cranfield University)
[**] C.C.H. (Mum), C.G.O. (Mum), M.B.A. (Mum)

***Abstract*:**

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines insomnia as a complaint regarding the quantity, quality, or sleep timing at least 3 times a week for at least 1 month.

In spite of presence of several treatment modalities, it possesses significant challenge in the development of effective treatment protocol of insomnia. The varied presentation of the disorder as well as uncertainty in efficacy and safety profile of treating agents complicates the scenario for physicians.

There is an unmet medical need to develop an effective yet safe treatment option to address these multiple factors contributing to several aspects of insomnia.

Materials and Methods:

Twenty four subjects, diagnosed as case of insomnia as per "The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)". Guidelines were enrolled in case study. Nine subjects who completed the study were assessed to evaluate efficacy of the proprietary formulation E-IN-05 on improving the sleep quality; Sleep Onset Latency; Sleep Efficiency; Sleep Duration and Day Enthusiasm level.

Result:

Six weeks administration of E-IN-05 yielded an overall improvement. The mean sleep quality improved from 2.4 (0.52) on Day-0 to 0.89(0.78) on Day-42.Sleep efficiency increased to 69.48(. 9.22) Day-42 as compared to that of 46.6(10.76) on Day-0. The mean sleep latency reduced from 81.1(18.83) mins at Day 0 to 40(14.79) mins at Day 42.The initial sleep duration score of 3(0) at Day 0 gradually improved to 1.78(1.3) at Day 42. The mean enthusiasm level in the study population on Day – 0 was calculated as 0.66 (0.5) which increased to 2.22 (0.97)at the end of the study.

Conclusion:

Six weeks administration of E-IN-05 yielded a significant improvement in several aspects of "Pittsburgh Sleep Quality Index" score namely Sleep quality, Sleep efficiency, sleep latency and day enthusiasm level.

***Keywords*:** *Primary Insomnia; Sleep onset latency; sleep efficiency; Pittsburgh sleep quality index*

BACKGROUND

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) defines insomnia as a complaint regarding the quantity, quality, or sleep timing at least 3 times a week for at least 1 month[i]. In a study comprising of adult samples from different countries, 30% of the subjects reported one or more of the symptoms of insomnia: difficulty initiating sleep, difficulty maintaining sleep, waking up too early and in some cases, non-restorative or poor quality of sleep[ii].Although the disorder has been discussed and written about since at least last 2000 years, it possesses significant challenge in the development of effective treatment protocol of insomnia. This complication is majorly attributed to the varied presentation of the disease, as well as the large side effect profile of the treatment modalities. Hyperarousal i.e. a state of increased psychological and physiological tension, circadian dysrhythmia i.e. disturbance in sleep-wake pattern, and homeostatic dysregulation of sleep i.e. disturbance in basic metabolic process of sleep are said to be the major factors attributed to the pathophysiology of insomnia. These factors are responsible for different elements of insomnia e.g. hyperarousal contributes to increased sleep latency, circadian disturbances contribute to the disturbed sleep initiation and maintenance and dysregulation of sleep homeostasis largely impacts the overall quality of sleep. However a definite and conclusive relationship between these factors and impact is challenging. Therefore it is an unmet medical need to develop an effective yet safe treatment option to address these multiple factors contributing to several aspects of insomnia.

Therapies for insomnia:

As sleep complaints are not only common but also debilitating, self-medication as well as experts' prescriptionis usual. Depending on the comorbid conditions as well as the affected sleep elements, as much as 19 agents are commonly loosely prescribed. Benzodiazepine receptor agonists, such as flurazepam, triazolam, quazepam, estazolam, and temazepam, and the non-benzodiazepine agents such as zolpidem, zaleplon and eszopiclone are some of the most common therapeutic agents used for treatment of insomnia. Eszopiclone, extended release formulations of zolpidem, and ramelteon, a melatonin receptor agonist are approved for prolonged use in patient with

chronic insomnia. However most of them lack well-established effectiveness and safety data for use beyond brief intervals in situational insomnia, or as part of a combined approach using cognitive behavioral therapy (CBT) and brief pharmacological therapy[iii].

Meta-analysis of the therapeutic benefits of various pharmacological agents has showed limited correction of various sleep endpoints, with mean differences in sleep latency being about 15 minutes, wake after sleep onset improving by about 26 minutes and total sleep time improving by about 40 minutes[iv],[v],[vi].Though these agents are able to provide some degree of subjective improvement of the symptoms, the associated risk factors such as residual hypersomnia, dizziness, lightheadedness, impaired mental status hold great challenge in prescribing them. Clearly, better options to improve sleep are still needed.

Several unconventional therapy tried have failed to be proven as conclusive treatment modality due to several concerns. One of the well accepted herbal supplements, valerian extracts has been observed to cause both CNS depressions by inhibiting enzyme-induced GABA (Gamma-Aminobutyric Acid) breakdown in the brain[vii].In humans, Valerian withdrawal appeared to mimic the withdrawal syndrome of benzodiazepines and several cases of delirium and cardiac complications was reported. Kava-Kava and Ginseng also are hypothesized to have similar mechanism of action thereby potentiating inhibitory effect on CNS. In a study, administration of passion flower to group of rats extended the sleeping time[viii] however absence of well-designed randomized control study in human population makes the result non conclusive. Concerns have been raised regarding habituation related to usage of synthetic melatonin leading to intermittent incremental dosage increases or drug holidays[ix].The possibility of important side effects has been highlighted by Sheldon[x], who reported increased seizure activity in four out of six children treated with melatonin.

E-IN-05 is a proprietary herbo-mineral composition designed with the intention of effectively yet safely addressing together the different components of sleep-wake system. The formulation has been proven to improve various aspects of this system which includes sleep onset latency, sleep efficiency, sleep quality as well as enthusiasm level on awakening. The strategically selected ingredients of the formulation complement each other to maintain the sleep architecture by regulating the mediators of sleep.

METHODS AND MATERIALS

Subjects recruited in the case study were diagnosed as case of insomnia based on presence of one or more of the following complaints:

- ✓ History of sleep duration of less than 4.5 hrs/ night
- ✓ History of sleep latency of ≥ 60 min
- ✓ History of tiredness post awakening

The duration of complain was considered to be not less than one month in order to comply the definition of insomnia as laid by "The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)".

The subjects were enrolled in a 42 days open label case study and were followed up as per the study design (*Figure 1 Appendix*)

The primary purpose of the study was to evaluate efficacy of the proprietary formulation E-IN-05 on improving the sleep quality as assessed by:

- Participant's subjective assessment of sleep quality over last 3 weeks in terms of very good, fairly good, fairly bad or very bad;
- Secondary endpoint of the study was to evaluate the improvement of individual elements of sleep architecture as assessed by the improvement of following parameters of "Pittsburgh Sleep Quality Index" at the end of 6 weeks duration as compared to the baseline scores:
  - ✓ Sleep Onset Latency defined by the time taken to accomplish the transition from full wakefulness to sleep during last 3 weeks;
  - ✓ Sleep Efficiency defined as the ratio of time spent asleep i.e. total sleep time to the amount of time spent in bed during last 3 weeks;
  - ✓ Sleep Duration as assessed by the number of hours that actually subject perceives to sleep at night during the last 3 weeks.
  - ✓ Day Enthusiasm level defined by level of problem that patient faced in keeping up enthusiasm in routine activities for last 3 weeks. The responses were graded as no problem at all; only slight problem, somewhat problem and Very big problem;

The individually standardized ingredients were used for the preparation of the formulation after appropriate quality control testing. The formulation was supplied in a bottle of 50 gelatin capsules and was stored at the investigational sites. The 50 capsules pack was supplied to cover the product supply for 3 weeks (42 capsules) ±4 days of window period (08 capsules).

The study subjects were divided into two subgroups:

I. Group A: Subjects diagnosed as case of primary insomnia as defined by the study protocol without any underlying psychiatric conditions. This group was included in the study with the intention to assess the effect of investigational product in cases with primary insomnia.
II. Group B: Subjects diagnosed as case of insomnia with underlying psychiatric conditions and currently on one or more than one medication for such condition.

The subjects were included in the study on the basis of following criteria:

- Male and female subjects in the age group of 24-60 years who are diagnosed as case of insomnia by the investigator.
- Having sleep disorder indicated by one or more of the following:
  - ✓ History of sleep duration of less than 4.5 hrs/ night.
  - ✓ History of sleep latency of ≥ 60 min.
  - ✓ History of tiredness post awakening.
  - ✓ History of presence of above symptoms for not less than 1 month duration.
- Able and willing to give informed consent.
- Able and willing to follow all study related instructions and to make all required visits.

The patients fulfilling all above criteria were enrolled in the study and were dispensed the investigational product to receive 2 capsule at bedtime daily. During study proper accountability record with regards to investigational product was maintained individually for each patient. The subjects enrolled in the study were followed up for 6 weeks of duration with two consecutive visits at the gap of 3 weeks each. A window period of 4 days was allowed for each follow up visit. 24 subjects were enrolled in the study to provide the total of 14 completed patients (n=14). "*Pittsburg Sleep Quality Index"* was used as tool to evaluate the various outcomes of the study. Each subject filled the PSQI questionnaire three times during the study i.e. on each visit. The index was scored by the investigators according to the guidance provided by **Sleep Medicine Institute, University of Pittsburgh**. The completed patients included both the groups of the patient i.e. subjects who did not had any underlying psychiatric conditions (Group A: n= 9) and subjects with underlying psychiatric conditions (Group B: n=5). Both the groups completed the study following the same protocol.

RESULTS

A total of 24 patients were enrolled onto this study to have completed 14 patients. The data received from the 14 patients was evaluated for the primary as well secondary endpoint.

Sleep Quality Rating:

The overall sleep quality as assessed by the patient's rating of sleep quality as per *Pittsburg Sleep Quality Index* with 3 being worst and 0 being the best. The data analysis of both the group collectively (Group A+ B) indicated good improvement resulting in very good sleep quality in 3 patients, 6 patients showed fairly good sleep quality, 3 patients had fairly bad sleep even after consuming IP for 6 weeks whereas 2 patients did not show any improvement in the sleep quality. The sleep quality score showed a reduction of 49% from Day-0 to Day-42. The mean sleep quality improved from 2.5 (0.51) on Day-0 to 1.28(0.99) on Day 42 (*Fig 2, Appendix*).

The individual group analysis was also performed.

Group A (n=9) showed remarkable improvement in the sleep quality. The sleep quality score showed a decrease of approximately 63% with the mean score being 2.4 (0.52) at Day-0 which improved to 0.89(0.78) at Day- 42. (*Fig: 3, Appendix*)

Group B (n= 5) subjects showed slower response as individual group. The sleep quality score showed lowering of approximately 20% with mean sleep quality improving from 2.6(1.0) on Day-0 to 2.0(0.54) on Day – 42.(*Fig 4, Appendix*)

Sleep Efficiency Rating:

The sleep efficiency as assessed by *Pittsburg Sleep Quality Index is* defined as the ratio of total sleep time to the amount of time spent in bed. The sleep efficiency score in the overall study population demonstrated an improvement of 36% with sleep efficiency increasing to 64.4(10.32) Day-42 as compared to sleep efficiency of 47.28(9.09) on Day-0. (*Fig 5, Appendix*)

After administration of the investigational product in Group A (with 94.7% compliance to investigational product), the mean sleep efficiency improved to 69.5(9.22) on Day-42 as compared to 46.6(10.76) on Day-0, demonstrating a mean improvement of approximately 50% The sleep efficiency showed a better improvement in the subjects with lower sleep at Day-0. (*Fig 6, Appendix*)

In the group of subject with underlying psychiatric conditions and currently on psychotropic medication (Group – B), the investigational product could improve the sleep efficiency score by 14.4%. The mean sleep efficiency improved to 55.26(3.74) on Day-42 as compared to 48.3(5.88) on Day-0. The product compliance in this group was approximately 96%. (*Fig 7, Appendix*)

The lesser improvement in sleep efficiency score is mainly hypothesized to be attributed to the underlying comorbid psychiatric condition as well as the effect of psychotropic drugs used by the subjects. A larger study in the sub group is further required to substantiate the hypothesis.

Sleep Onset Latency:

In sleep science, sleep onset latency (SOL) is the length of time that it takes to accomplish the transition from full wakefulness to sleep. Sleep onset latency was measured in the study for both the study groups using "*Pittsburgh Sleep Quality Index*". The sleep latency showed a reducing trend in most of the subjects. The mean sleep latency reduced from 78.9(17.22) mins at Day0 to 47.8 mins (21.18) at Day42 for the Group A+B demonstrating a 39.4% improvement in sleep onset latency. (*Fig 8, Appendix*)

Group A demonstrated more than 50% reduction in sleep onset latency time and the mean sleep onset latency of the group at Day 42 was 40(14.79) mins. Two out of the nine subjects of group A showed excellent reduction of 73.3% and achieved sleep onset latency of 20 mins which is considered to be normal. (*Fig 9, Appendix*)

The sleep onset latency showed a weaker response in Group B with the mean sleep latency reduction of 17.3% reducing to 62(25.14) mins from 75(15) mins (*Fig 10, Appendix*).

Sleep Duration:

In the study, the sleep duration was assessed using "*Pittsburgh Sleep Quality Index*", by subjects' response to the question "During the past three weeks, how many hours of actual sleep did you get at night". As per the tool, the answer in hours was further coded as:

≥ 7 hours of sleep – 0;
< 7 and ≥ 6 hours of sleep – 1;
< 6 and ≥ 5 hours of sleep – 2;
< 5 – 3.

The study population conjointly scored the average score of 3(0) at Day 0, which gradually improved to 1.78(1.12) at Day 42: Sleep duration score showed a reduction of 41% from Day-0 to Day-42. (*Fig 11, Appendix*).

Although there was a progressive improvement of approx. 40% observed during the study, a study of the longer duration is warranted to confirm the statistically significant improvement in the sleep duration.

Both the groups when assessed individually showed similar response. Individually Group A when analyzed, also demonstrated an improvement of approximately 40% with sleep duration score of 1.77(1.3) on Day – 42 (0.02) from 3(0) on Day – 0 (*Fig 12, Appendix*).

Group B also demonstrated improvement of approximately 40% with score improving to 1.8(0.83) on Day 42 to from 3(0) on Day 0 (*Fig 13, Appendix*).

Day enthusiasm level:

Several studies have concluded that despite controlling the risk factor of short sleep duration, enthusiasm is the strongest independent risk factor for reporting to a doctor with an insomnia complaint[xi].Reduced enthusiasm is also indicative of depression which is commonly associated with progressing insomnia.

The study subjectively evaluated enthusiasm level of study population as well as individual groups using "*Pittsburgh Sleep Quality Index"*. The tool assessed the enthusiasm level by subjects' response of problem level in keeping up enough enthusiasm to get things done in last three weeks duration. The response was answered in terms of: No problem at all (3), only very slight problem (2), somewhat a problem (1) and a very big problem (0). Hence 0was considered as worst and 3was considered best for the purposes of the study evaluation. The mean baseline (Day 0) enthusiasm level in the study population was calculated as 0.7(0.46). After 42 days of investigational product intake with 95% of compliance, the mean enthusiasm level of the study population increased to 1.7(1.12) making it closer to the response "Only very slight problem" (*Fig 14, Appendix*).

The mean enthusiasm level of Group A, when calculated discretely on Day 42 improved to the score of 2.2(0.97) from initial level of 0.7(0.5) (*Fig 15, Appendix*).

After the same level of investigational product compliance by Group B, improvement in mean enthusiasm level was lower as compared to Group A. The mean enthusiasm level on calculated on Day 42 for Group B was 1.0(1.0) from 0.8(0.4) at Day 0 (*Fig 16, Appendix*).

CONCLUSION

Several studies suggest a relationship between sleep quality and quality of life and eventually quantity and risk of cognitive decline, and also indicate that interventions to normalize sleep duration and correct sleep disorders may not only improve quality of life, but have potential to reduce or prevent cognitive decline.

The ingredients of E-IN-05 have been known traditionally to improve different aspects of sleep wake cycle. Reported effects of the herbs coupled with the results of this this case study demonstrate efficacy of the formulation in primary insomnia.

Six weeks administration of E-IN-05 yielded a significant improvement in several aspects of "*Pittsburgh Sleep Quality Index"* score namely Sleep Quality, Sleep efficiency, Sleep latency and day enthusiasm level. Insomnia is generally associated with daytime fatigue as well as mood disorders such as depression[xii]. The outstanding effect of the product in

improving the day enthusiasm level indicates towards distinguishable efficacy profile of the formulation in correction of these fatigue and mood disorder thereby improving the overall sleep architecture. The safety profile of the formulation is well appreciated as no side effects related to conventional sedatives and hypnotics was reported in the study.

LIMITATIONS

Although due to small number of participants and short observation period, it was difficult to get a statistically significant outcome, this case study serves as base for investigating the effect of E-IN-05 in clinical study with a larger group. It is also warranted that improvement in total "*Pittsburgh Sleep Quality Index"* score is perceived as standard endpoint however the same could not be used for this study due to small sample size as well as diverse study population. To achieve the statistically significant results a comparator controlled randomized study with bigger sample size is recommended.

APPENDICES

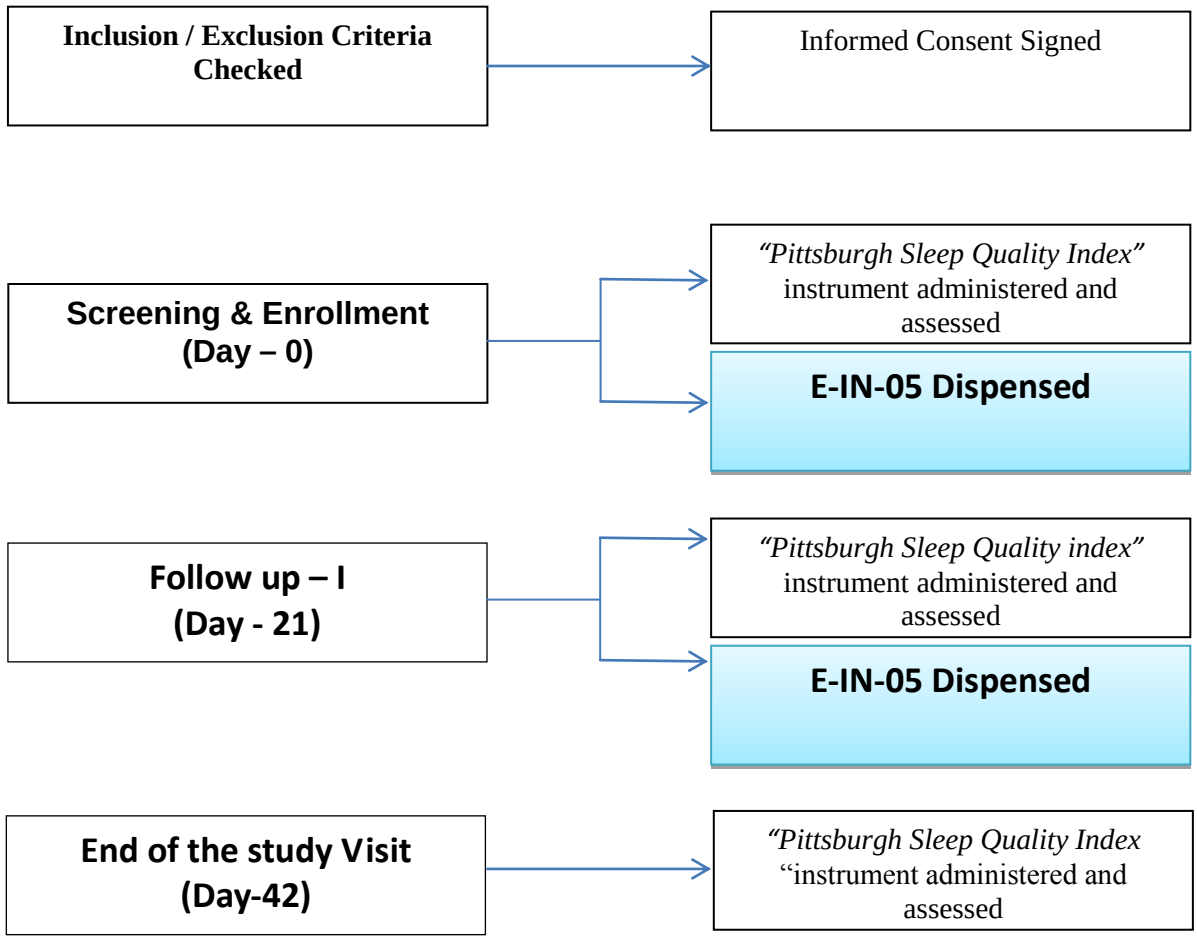

Figure 1: Study design to demonstrate screening, enrollment, follow up, treatment assignment and follow up of the patients

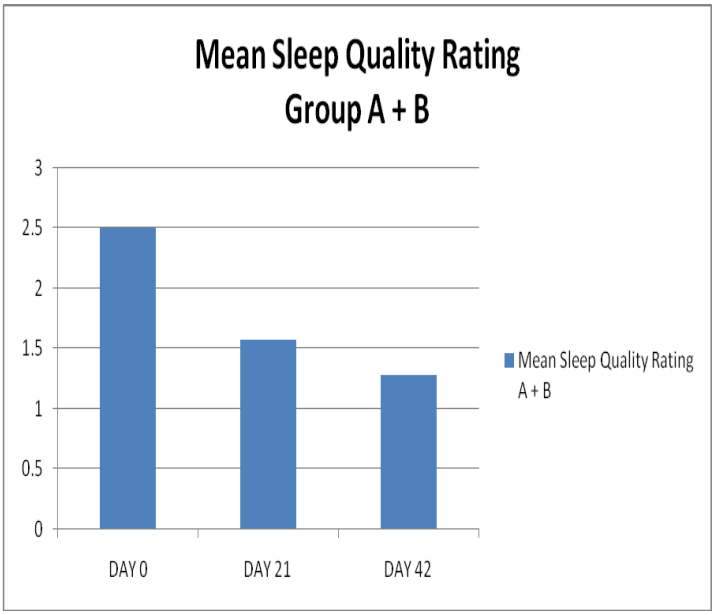

Figure 2: Graphical representation of "Mean Sleep Quality Rating" in subjects of Group A+ Group B.

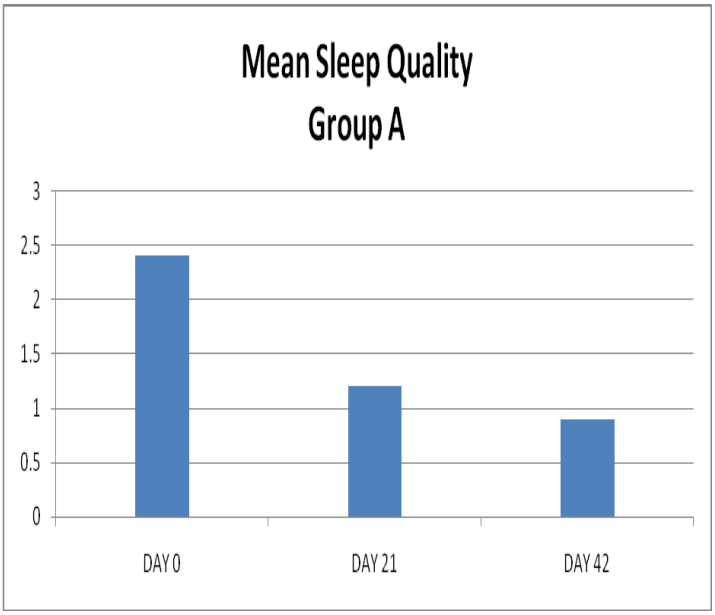

Figure 3: Graphical representation of "Mean Sleep Quality Rating" in subjects of Group A.

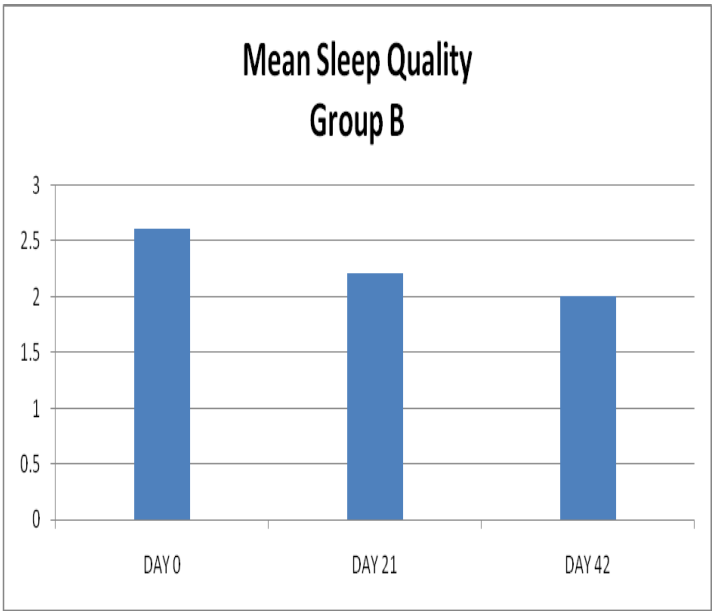

Figure 4: Graphical representation of "Mean Sleep Quality Rating" in subjects of Group B.

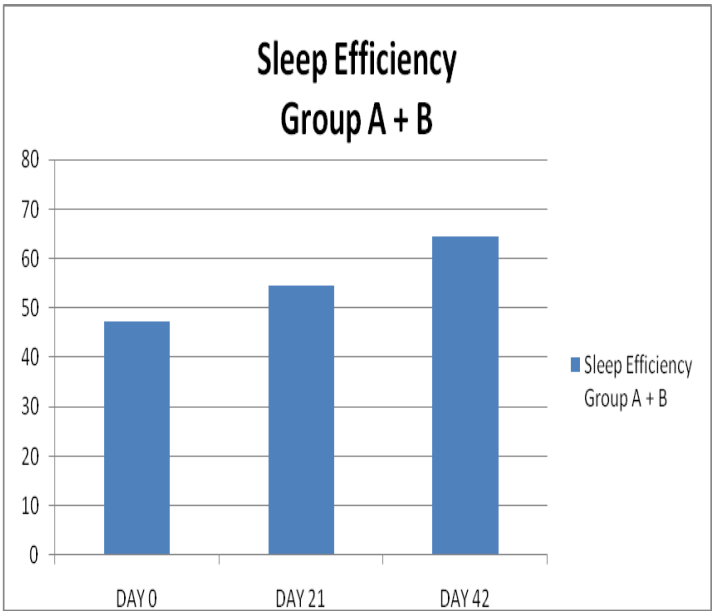

Figure 5: Graphical representation of "Sleep Efficiency Rating" in subjects of Group A+ Group B.

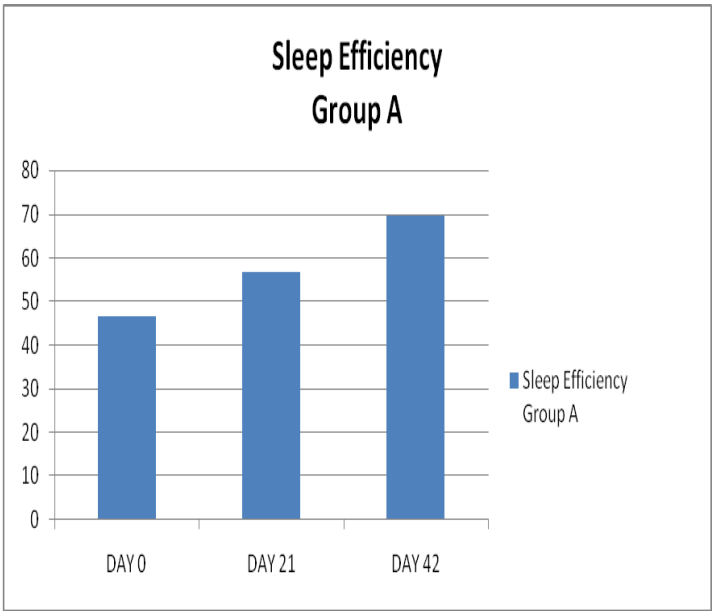

Figure6: Graphical representation of "Sleep Efficiency Rating" in subjects of Group A.

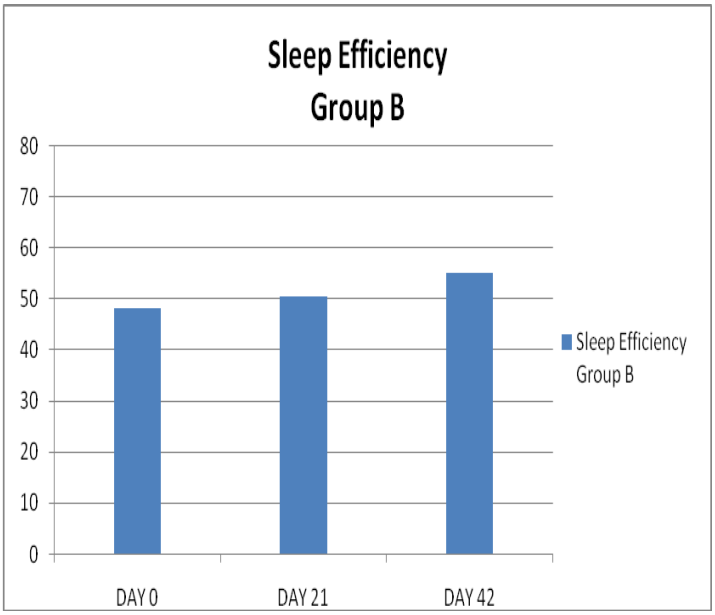

Figure 7: Graphical representation of "Sleep Efficiency Rating" in subjects of Group B.

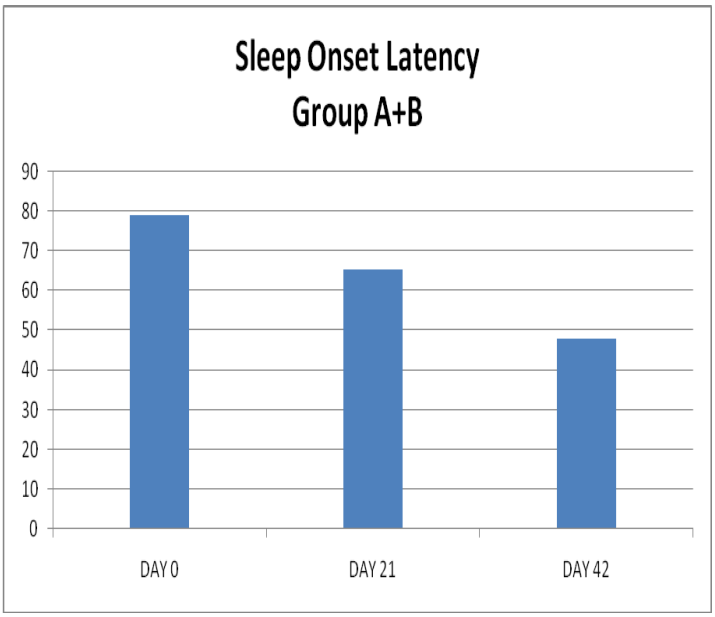

Figure 8: Graphical representation of "Sleep Onset Latency Time" in subjects of Group A+ Group B.

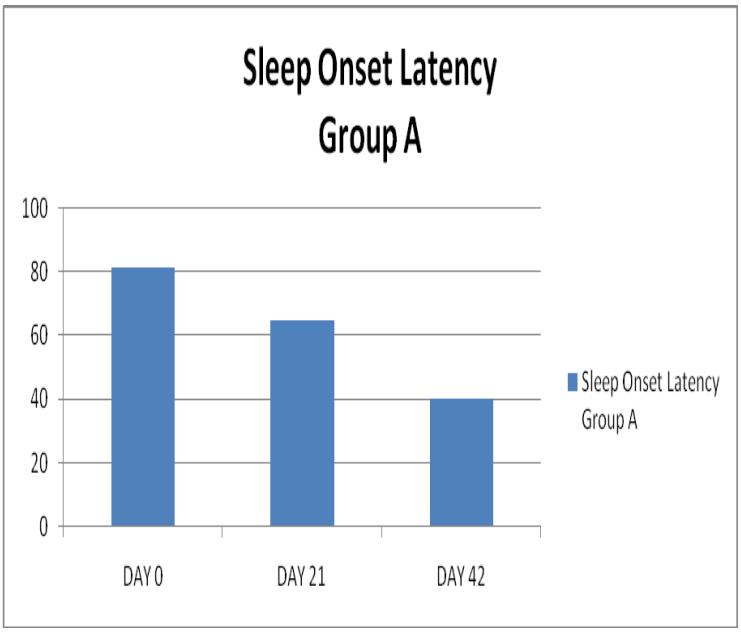

Figure 9: Graphical representation of "Sleep Onset Latency Time" in subjects of Group A.

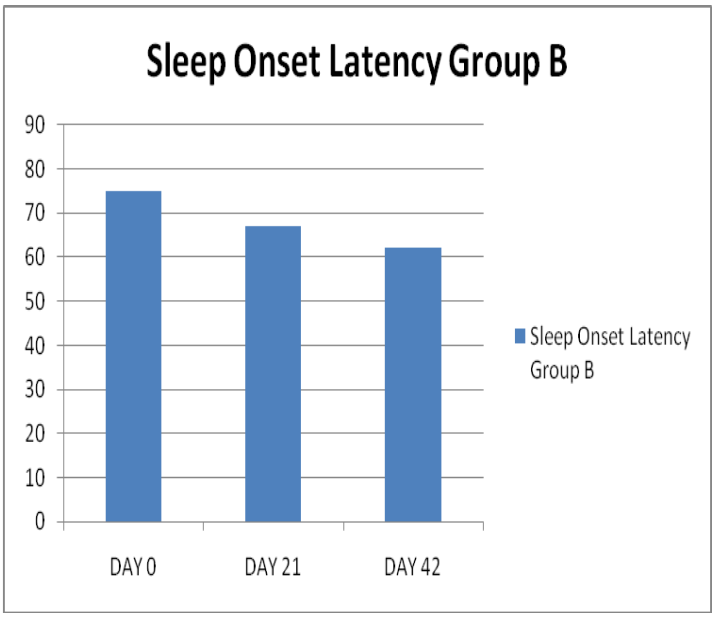

Figure 10: Graphical representation of "Sleep Onset Latency Time" in subjects of Group B

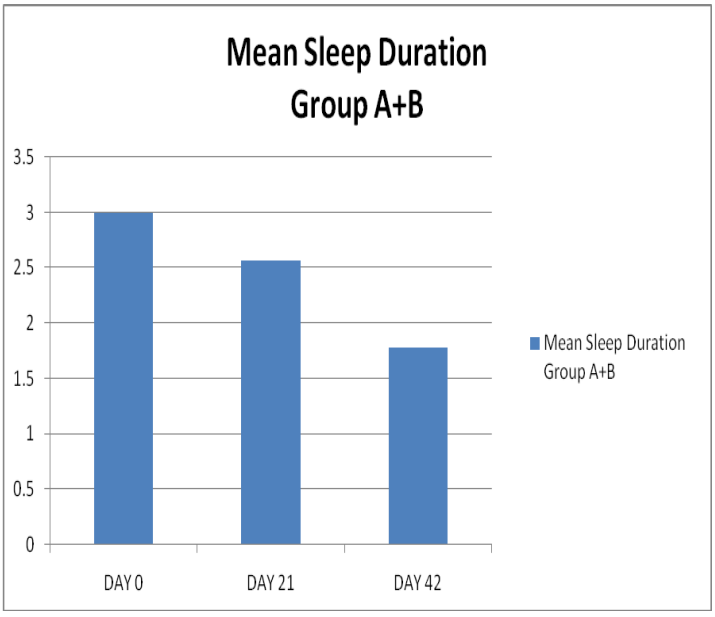

Figure 11: Graphical representation of "Sleep Duration" in subjects of Group A + B

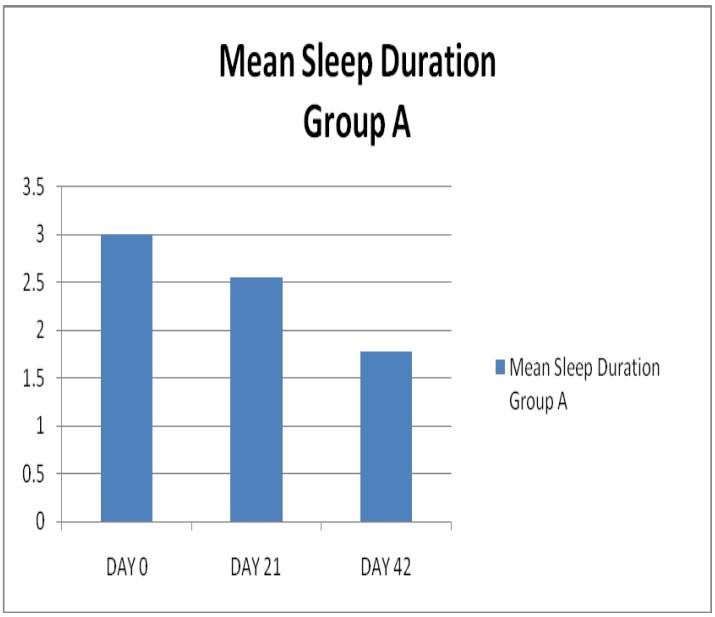

Figure 12: Graphical representation of "Sleep Duration" in subjects of Group A

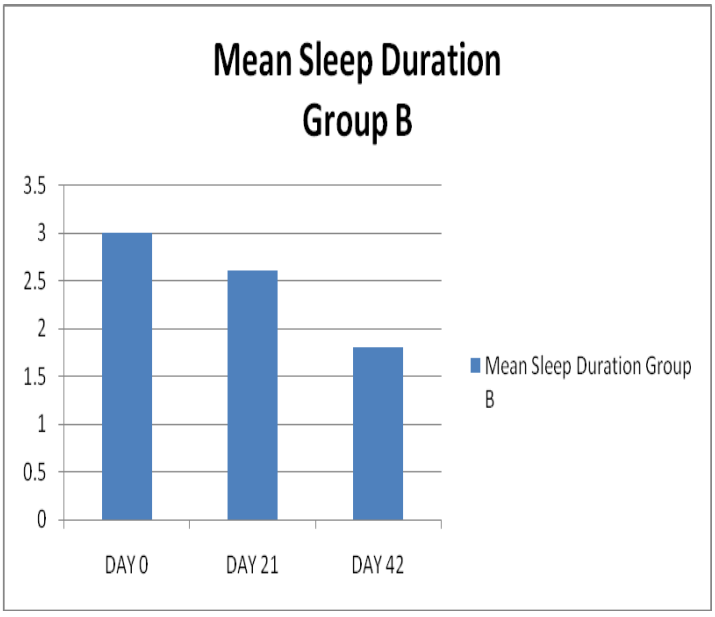

Figure 13: Graphical representation of "Sleep Duration" in subjects of Group B

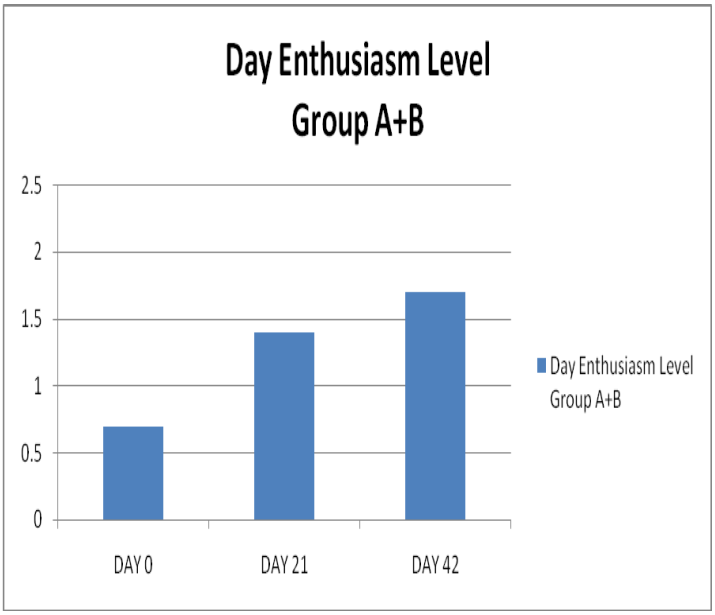

Figure 14: Graphical representation of "Enthusiasm Level" in subjects of Group A + B

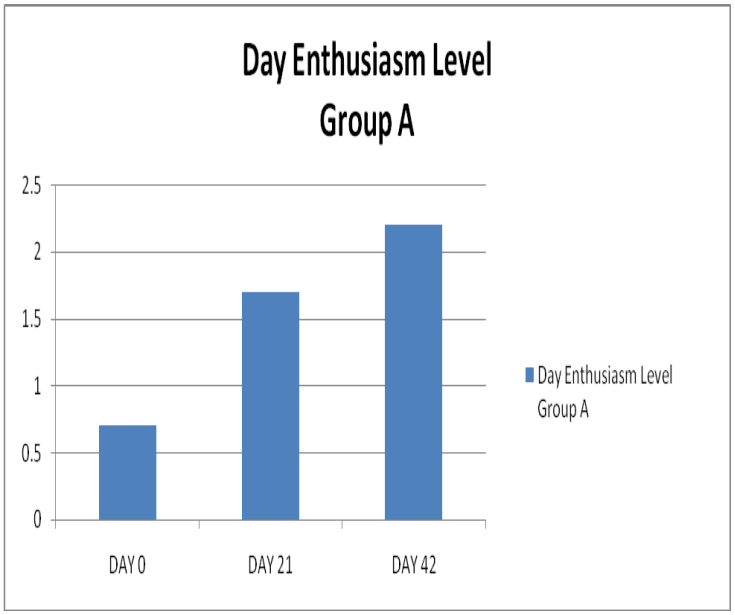

Figure 15: Graphical representation of "Enthusiasm Level" in subjects of Group A

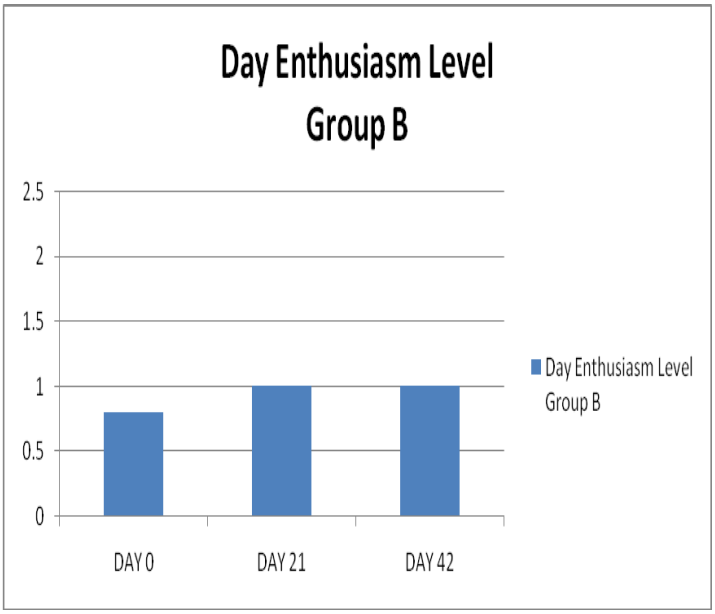

Figure 16: Graphical representation of "Enthusiasm Level" in subjects of Group B

ACKNOWLDGMENT

We sincerely thank Mr. Jayesh Chaudhary and Mrs. Latha Chaudhary for their financial and technical support rendered for the project.

REFERENCES

[i] Erika N. Ringdahl, Susan L. Pereira, and John E. Delzell Jr; Treatment of Primary Insomnia; The Journal of the American Board of Family Medicine; May 1, 2004 vol. 17 no. 3 212-219

[ii] Thomas Roth; Insomnia: Definition, Prevalence, Etiology, and Consequences; Journal of Clinical Sleep Medicine; 2007 August 15; 3(5 Suppl): S7–S10

[iii] Debra L. Barton, Pamela J. Atherton, Brent A. Bauer, Dennis F. Moore, Jr, Bassam I. Mattar, Beth I. LaVasseur, Kendrith M. Rowland, Jr, Robin T. Zon, Nguyet A. LeLindqwister, Gauri G. Nagargoje, Timothy I. Morgenthaler, Jeff A. Sloan, and Charles L. Loprinzi: The Use of Valeriana Officinalis (Valerian) in Improving Sleep in Patients Who Are Undergoing Treatment for Cancer: A Phase III Randomized, Placebo-Controlled, Double-Blind Study: NCCTG Trial, N01C5; J Support Oncol. 2011 JANUARY–FEBRUARY; 9(1): 24–31.

[iv] Barbera J, Shapiro C. Benefit-risk assessment of zaleplon in the treatment of insomnia. Drug Saf005;28:301–318. [PubMed: 15783240]

[v] Bellon A. Searching for new options for treating insomnia: are melatonin and ramelteon beneficial? J PsychiatrPract 2006;12:229–243. [PubMed: 16883148]

[vi] Bootzin RR, Buysse DJ, et al. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). Sleep 2006;29:1398–1414. [PubMed: 17162986] 23 Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry 1994;151:1172–1180. [PubMed: 8037252] 24 Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002;159:5–11. [PubMed: 11772681]

[vii] Skidmore-Rose L. (2001) Mosby's hand book of herbs and natural supplements. St Louis, MO: Mosby Inc. 10. Harkness R, Bratman S. (2000) Drug-Herb–Vitamin Interactions Bible. Rockline, CA: Prima Publishing.11. Heck AM, DeWitt BA, Lukes AL. (2000) Potential interactions between alternative therapies and warfarin. American Journal of Health System Pharmacy, 57, 221–227.12. Lininger SW, Gaby AR, Batz F, Yarnell E, Brown DJ, Constantine G. (1999) A-Z Guide to Drug-Herb–Vitamin
Interactions.Rockline, CA: Prima Publishing

[viii] Speroni, E. and Minghetti, A. (1988), Neuropharmacological activity of extracts from *Passiflora incarnata*. Planta Med., 54, 488-491

[ix] J Turk; Melatonin supplementation for severe and intractable sleep disturbance in young people with genetically determined developmental disabilities: short review and commentary

[x] Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. Lancet1998;351:1254

[xi][xi] Delwyn J. Bartlett, Nathaniel S. Marshall, Anthony Williams and Ron R. Grunstein; Predictors of primary medical care consultation for sleep disorders; Sleep Medicine Volume 9, Issue 8 , Pages 857-864, December 2008

[xii] Kales A, Kales JD.Evaluation and treatment of insomnia 1984

AUTHORS

First Author – Dr. Shalini Srivastava, MD (Phy) Russian State Medical University (Moscow); MSc in Clinical Research (Cranfield University), email: shalini@enovatebiolife.com drshalinee@gmail.com

Second Author –Dr. Sachin R. Dighe, B.A.M.S.; Sion Ayurvedic Medical College Sion Mumbai, C.C.H.; Wadia Children Hospital and Research Center Mumbai, C.G.O.; Wadia Maternity Hospital and Research Center Mumbai, M.B.A.; National Institute of Management Mumbai sachin@enovatebiolife.com, drsachin.dighe@gmail.com

Correspondence Author – Dr. Shalini Srivastava; MD (Phy); Russian State Medical University); MSc in Clinical Research (Cranfield University), email: shalini@enovatebiolife.com , drshalinee@gmail.com