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A PROSPECTIVE, OPEN-LABEL, NON-RANDOMISED STUDY TO ASSESS THE EFFICACY AND SAFETY OF ZERO TENSION TABLETS IN PATIENTS WITH STRESS, ANXIETY AND INSOMNIA DISORDERS

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ABSTRACT

Introduction: *Passiflora incarnata*, *Valeriana wallichii* and *Withania somnifera* are known to have psychotropic effects. These plants have been reported to alleviate stress, anxiety, and insomnia. This study aimed to evaluate the safety and efficacy of Zero Tension tablets in patients with mild to moderate stress, anxiety, and insomnia disorders. Methods: This study was a prospective, open-label, non-randomised study on patients (n = 100) with mild to moderate stress, anxiety, and insomnia disorders. All participants received two tablets with lukewarm water daily at night for 56 days. Primary outcomes were changes in the Hamilton anxiety scale (HAM-A), perceived stress scale (PSS), insomnia severity index, general health scores, serum levels of cortisol and dehydroepiandrosterone (DHEA) from day 0 to day 56. Secondary outcomes included adverse effects, changes in vital signs, haematological parameters, and serum biochemistry. Datasets were analysed at different assessment points using a t-test and one-way analysis of variance (ANOVA), as applicable. Results: Consumption of Zero Tension tablets significantly ($p<0.001$) reduced HAM-A, PSS, insomnia severity, and general health scores. Most participants experienced reduced stress, anxiety, and insomnia symptoms after 56 days of treatment. The serum cortisol and DHEA levels were also mildly reduced. No significant adverse effects or changes in vital signs, haematological, or blood biochemistry parameters were observed. Conclusion: The results suggested that the Zero Tension tablet is safe and could be an effective alternative to improve stress, anxiety and sleep disorders.

Keywords: Zero Tension Tablet, Clinical Study, Stress, Anxiety, Insomnia

INTRODUCTION

Stress, anxiety, and insomnia are the most common mental health disorders, with a recent global prevalence of 25.18%, 29.57%, and 23.50%, respectively.[1] Clinical evidence suggests that these conditions are often comorbid in three pairs: stress and anxiety, stress and insomnia, and anxiety and insomnia in the complexity of mental health disorders.[2] According to studies, stress can cause anxiety and insomnia;[3,4] furthermore, 24-36% of people with anxiety disorders also have insomnia.[5] The overall impact of stress, anxiety, and insomnia is not limited to increased risk of major depression, immune dysfunction, neurological, cardiovascular, and cerebrovascular diseases,[6,7] but also lowers the quality of life and perceived well-being.[8] Anxiolytics or somatic agents, antipsychotics, sedatives, and selective serotonin reuptake antagonists are used as everyday stress, anxiety, and insomnia treatments.[9,10] However, these medications are frequently associated with drug dependence, tolerance, withdrawal symptoms, cognitive issues, tremors, and cardiovascular symptoms.[11,12] Therefore, alternative therapies are constantly being sought to mitigate the effects of these widespread health risks.

Considering the problems mentioned above, herbal products can be a safe and effective alternative to managing stress, anxiety and sleep disorders. In recent years, the use of herbal remedies to treat chronic stress-related conditions has grown in Western societies. Herbal medicines are now one of the most widely used alternative treatments for stress, sleep disorders, depression, and anxiety. Numerous clinical studies have shown that herbal medicine can help patients with stress, anxiety, and insomnia and improve their quality of life.[13-15] *Passiflora incarnata* (flower), *Valeriana wallichii* (root), and *Withania somnifera* (root) are examples of phytotherapeutic interventions that have been reported to alleviate stress, anxiety, and insomnia by regulating the GABA system.[16-18] In clinical studies, Passiflora flower extract effectively reduced anxiety.[19,20] Valerian root extract was reported to be effective in treating sleep disorders, but the results were inconsistent.[21,22] Systemic reviews and meta-analyses of clinical studies revealed that *W. somnifera* extract effectively improves sleep quality and prevents stress, anxiety, depression, and other psychiatric disorders.[23-25] In this regard, the Zero Tension tablet, a poly-herbal formulation of *P. incarnata*, *V. wallichii*, and *W. somnifera*, was developed and promoted in India to manage stress, anxiety, and insomnia. This study aimed to assess the efficacy and safety of the Zero Tension tablet in patients suffering from stress, anxiety, and insomnia.

MATERIALS AND METHODS

Participants and Study Criteria

This was an open-label, non-randomised post-marketing monitoring study on the Zero Tension Tablet. This study enrolled 100 individuals with mild-moderate stress, anxiety, and insomnia. The study was conducted in 2022 at Campbell Hospital in Bangalore, India. No statistical criteria have been used to estimate the sample size. Male and female subjects 18–60 years of age with mild to moderate stress, anxiety and insomnia had Hamilton-A scale (HAM-A) and perceived stress scale (PSS) scores of 17–24

and 14–26, respectively, were eligible to participate in this study. Subjects were excluded if they had a history of allergies, polycystic ovary, thyroid disorders, uncontrolled hypertension, diabetes, mental disorders (e.g., schizophrenia, Alzheimer's disease), acute or chronic illnesses (e.g., cardiovascular, respiratory, gastrointestinal, immunological, metabolic, endocrinology, neurological), past or current users of psychoactive medicines or supplements, drug abuse, smoking, alcoholism, and pregnant women.

Study Design

This study was a 56-day, non-randomised, open-label, prospective, phase IV post-marketing surveillance study evaluating the efficacy and safety of a polyherbal Zero Tension tablet on subjects with stress, anxiety, and insomnia. The study was conducted between March 2022 and September 2022 at Campbell Hospital, Bangalore. Potential subjects were screened after obtaining signed informed consent and based on inclusion and exclusion criteria, 100 eligible subjects were enrolled in the study. The total 56-day study duration consisted of three scheduled clinic visits, including a screening visit (V1, days 0), baseline visit (V2, day 2), final visit (V4, day 56) and a telephonic follow-up visit (V3, day 28). During the screening visit, data related to demographics, physical examinations, medical history, vital signs, pregnancy, concomitant medications, blood parameters, HAM-A score, PSS score, insomnia severity index, general health status, serum cortisol, and dehydroepiandrosterone (DHEA) levels were collected. At the baseline visit, a review of inclusion-exclusion criteria, medical history, concomitant medications, and enrolment of subjects, followed by the dispense of investigational products, was undertaken. During the telephonic follow-up, an assessment of the insomnia severity index was performed, and information related to general health status, the occurrence of adverse events, and the use of concomitant medications were collected. At the final visit, physical examinations, vital signs, concomitant medications, blood parameters, HAM-A score, PSS score, insomnia severity index, general health status, serum cortisol, DHEA levels, and adverse events data were collected.

Intervention

Zero Tension tablet's study intervention comprised *P. incarnata*, *V. wallichii*, and W. *somnifera* extracts. All subjects were instructed to consume two Zero Tension tablets (500 mg) with lukewarm water at night before bed for 56 days.

Outcome Measures

Primary Outcomes
The primary outcome was the clinical improvement in stress, anxiety, and insomnia conditions as measured by the changes in the HAM-A and PSS scale scores, insomnia severity index, and serum levels of cortisol and DHEA from visit 1 (day 0) to visit 4 (day 56). In addition, the change in the overall mental health condition of the subjects was assessed by evaluating their general health questionnaire at visits 1, 3, and 4.

Hamilton Anxiety Rating Scale (HAM-A)
The HAM-A is a well-validated, most commonly used tool consisting of 14 items to assess an individual's somatic and psychic anxiety.[26] Each item is rated on a 5-point scale (0–4) and rated as 0 = not present, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. The total score ranges from 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity, and 25–30 moderate to severe.

Perceived Stress Scale-14 (PSS-14)
The PSS is the most widely used tool for stress assessment in clinical psychology. PSS-14 contains a self-reporting questionnaire of 14 items to evaluate a subject's perceived stress level. Each item is rated on a 5-point Likert scale of 0–4, where 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, and 4 = very often. The total score ranges from 0-40, with higher scores indicating higher levels of perceived stress.[27]

Insomnia Severity Index
The insomnia severity index was assessed using a self-administered questionnaire (7 items) on sleep quality using a five-point scale. The summed-up total score of 7 items estimates the sleep quality of subjects. The higher the scores, the worse the sleep quality. Insomnia severity has been classified based on total scores (range 0-28): 0–7 = no insomnia; 8–14 = mild; 15–21 = moderate; and 22–28 = severe.

Serum Cortisol and DHEA Levels
The most commonly used serum indicators of physiological stress are cortisol and DHEA. Both biomarkers were used to assess the effects of the Zero Tension tablet on stress. The serum cortisol and DHEA levels were measured during the screening visit (V1) and at the follow-up visit (V3) and at the end of the study (V4).

General Health Status
The subjects' general health status was evaluated using a self-administered questionnaire of 12 items. The total score of 12 items ranging from 0–12 was used to determine the mental health status of the subject. A score of >6 indicates poor mental health, suggesting depression, anxiety, and social dysfunction.

Secondary Outcomes

Assessment of Safety
As part of the safety assessment, changes in laboratory parameters such as complete blood count (CBC), random blood sugar (RBS), thyroid function, serum levels of SGPT and creatinine were assessed at the screening visit (V1) and the end of the study (V4). The occurrence of any adverse effects related to study intervention was evaluated at the end of the study. In addition, the occurrence of any adverse or serious adverse events was recorded throughout the study period.

Ethical Considerations
The study was conducted following the principles of the Helsinki Declaration, ICH-GCP guidelines, and the ICMR ethical standards for biomedical research involving human subjects (2017). The ACE Independent Ethics Committee approved the trial protocol to conduct the study at the Campbell Hospital, Bangalore. The study was prospectively registered with the Clinical Trial Registry-India (www.ctri.nic.in) with the no: CTRI/2022/04/042212.

Statistical Analysis
Statistical analysis was done using SPSS software version 23.0 (SPSS Inc., USA). Changes in the mean scores of the study parameters from visit one to visit four were assessed by t-test. Descriptive statistics were used for presenting demographic data as mean ± standard deviation (SD) and percentages. The insomnia severity index was evaluated at three assessment points using one-way analysis of variance (ANOVA) analysis. The P value, 0.05, was considered statistically significant.

Table 1: Demographic and baseline characteristics of the study subjects (n = 100).

Variable	Results
Age (yrs), mean, SD	34.07 ± 10.22
Age groups	
18 yrs, (%)	3
19-30 yrs, (%)	38
31-40 yrs, (%)	37
41-50 yrs, (%)	13
51-60 yrs, (%)	9
Male, (%)	55
Female, (%)	45
Systolic Blood Pressure (mmHg), mean, range	120.90 (105.0 – 134.0)
Diastolic Blood Pressure (mmHg), mean, range	79.57 (70.0 – 86.0)
Body Temperature (°F), mean, range	97.42 (97.0 – 97.80)
Pulse Rate (beats/min), mean, range	68.01 (57.0 – 78.0)

Table 2: Effect of Zero Tension tablet on vital signs and laboratory parameters.

Laboratory parameters	Visit 1 (n = 100) (mean ± SD)	Visit 4 (n = 100) (mean ± SD)	p-value
Haemoglobin (g/dL)	13.56 ± 2.14	13.32 ± 2.23	0.438
Random blood sugar (mg/dL)	76.94 ± 22.66	77.60 ± 19.29	0.825
SGPT (U/L)	24.30 ± 15.38	24.19 ± 14.77	0.960
Serum creatinine (mg/dL)	0.74 ± 0.20	0.96 ± 1.25	0.077
T3 (ng/mL)	1.17 ± 0.22	1.12 ± 0.21	0.135
T4 (µg/dL)	9.58 ± 1.68	8.89 ± 1.74	0.005**
TSH (µIU/mL)	2.24 ± 1.39	2.54 ± 1.83	0.191
Systolic blood pressure (mmHg)	120.90±6.14	122.10±6.02	0.064
Diastolic blood pressure (mmHg)	79.57±3.42	79.71±3.23	0.732
Body temperature (°F)	97.42±0.27	97.34±0.37	0.084
Pulse Rate (beats/min)	68.01±6.26	69.42±4.35	0.063

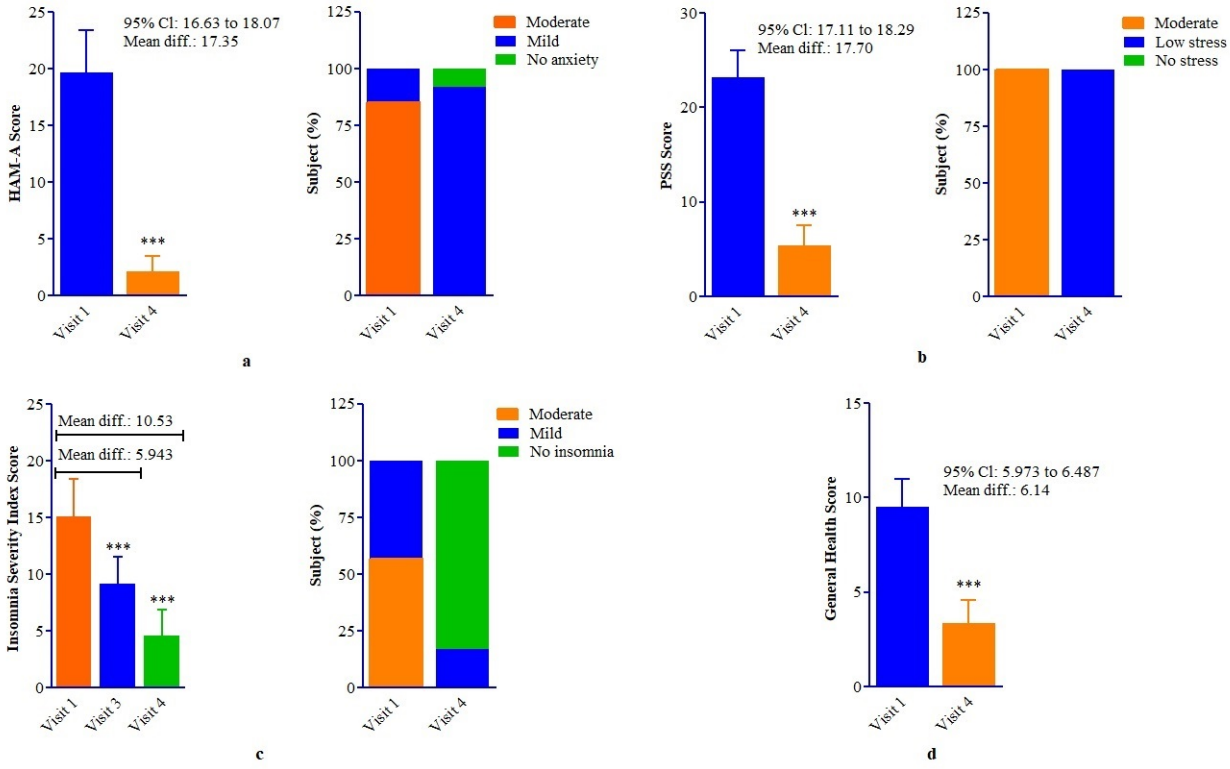

Figure 1: Assessment of a) HAM-A score, b) PSS score, c) Insomnia Severity Index and c) general health status at different assessment visits.

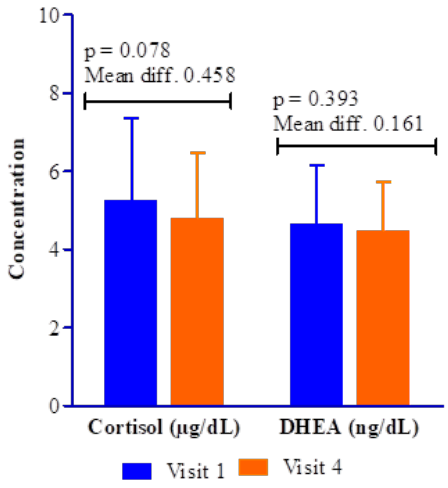

Figure 2: Serum cortisol levels and DHEA at visits one and four.

RESULTS

Demographic Data

A total of 107 subjects were screened, and seven of them failed to meet the eligibility criteria. Hence, 100 subjects were enrolled in this treatment, of which 55 were males and 45 were females, with a mean age of 34.07 ± 10.22 years. At the onset of the study, the vital signs, including systolic and diastolic blood pressure, body temperature, pulse rate, and respiratory rate, are shown in Table 1.

Primary Outcome Measures

HAM-A Score

As illustrated in Figure 1A, consumption of the Zero Tension tablet significantly decreased the HAM-A score from day 0 (19.86 ± 3.78) to day 56 (2.19 ± 1.39). The reduction was statistically significant ($p<0.001$) compared to the baseline, with a mean difference of 17.35 and 95% CI of 16.63 to 18.07. At visit 1, 85% and 15% of subjects had moderate or mild anxiety, but after 56 days of treatment with the Zero Tension tablet, 92% of subjects had mild anxiety, and 8% of subjects had reported no anxiety.

PSS Score

The PSS score was measured on day 0 and at the end of the study. After consuming the Zero Tension tablet for 56 days, the PSS score significantly declined compared to day 0. The reduction in PSS score was statistically significant ($p<0.001$; mean diff. 17.70; 95% CI: 17.11 to 18.29) (Figure 1B). After 56 days of treatment, all patients' moderate stress levels decreased from moderate to low.

Insomnia Severity Index

Over the 56 days of treatment with the Zero Tension tablet, there was a significant reduction in insomnia severity index scores at day 28 (from 15.09 ± 3.34 to 10.25 ± 2.36; mean diff. 5.94; 95% CI: 5.026 to 6.861; $P<0.001$) and at the end of the study (from 15.09 ± 3.34 to 5.45 ± 2.35; mean diff. 10.53; 95% CI: 9.616 to 11.45; $P<0.001$) compared to day 0 (Figure 1C). On day 0, 57% and 43% of subjects had moderate and mild insomnia, respectively, and after treatment with the Zero Tension tablet, 17% of subjects reported mild insomnia, while no insomnia was reported by 83% of subjects.

General Health Status

At day 0, the total mean score on the general health questionnaire was 9.51 ± 1.45. After treatment with the Zero Tension tablet, there was a significant ($P<0.001$) reduction in the general health score at day 56 compared to day 0 (from 9.51 ± 1.45 to 3.1 ± 1.2; mean diff. 6.14; 95% CI: 5.97 to 6.49) (Figure 1D).

Serum Cortisol and DHEA Levels

After treatment with the Zero Tension tablet, the serum cortisol and DHEA levels were reduced from 5.23 ± 1.96 to 4.84 ±1.67 (mean diff. 0.458; 95% CI: -0.04894 to 0.9646) and 5.20 ± 1.22 to 4.80 ± 1.230 (mean diff. 0.161; 95% CI: -0.208 to 0.531), respectively, from visit 1 to visit 4 (Figure 2). However, the serum cortisol and DHEA levels reduction were not statistically significant.

Secondary Outcome Measures

Assessment of Safety

After 56 days of treatment, there were no significant changes in the vital signs and laboratory parameters, such as Hb (haemoglobin) levels, random blood sugar, SGPT, serum creatinine, T3, T4, and TSH, compared to day 0 (Table 2). The participants reported no adverse events.

DISCUSSION

Herbal medicines are most commonly used to treat stress, anxiety, depression, insomnia, and other psychological disorders. However, scientific evidence for the efficacy of such treatments is limited. Several over-the-counter (OTC) herbal psychotropic medications are available in the market that is safer than conventional pharmacotherapies, such as antidepressants and benzodiazepines.[28,29] Polyherbal formulations comprised a variety of plants and were typically used to achieve a synergistic therapeutic effect. Several studies have found that polyherbal formulations synergistically affect stress, anxiety, depression, and insomnia.[30-32] GABA receptors play an important role in physiological and neuropathological conditions [33]. Valerian roots, passion flowers, and ashwagandha roots are said to benefit patients with stress, anxiety, depression, and insomnia by modulating the GABA system [34,35], which is one of the main mechanisms of action on anxiety and related neurological disorders.[36,37] Valerian root contains more than 150 chemical components, of which actinidin, valerianin, valerene, valerenic acid, and valeranone are the most important active components that interfere with the GABA neurotransmitter receptor[38]. Passion flower contains several pharmacologically active flavonoids such as chrysin, vitexin, isovitexin, orientin, and isoorientin, and chrysin has been shown to modulate the GABA system[39]. The primary active phytoconstituents in ashwagandha roots are steroidal alkaloids and lactones such as withanolides and withaferins, which have been suggested to activate GABAergic signalling[33]. Systemic reviews revealed that these plants have a wide range of pharmacological activities, including anti-inflammatory, immunomodulatory, antipsychotic/anxiolytic, antioxidant, cytoprotective, sedative, and neuroprotective properties.[40-42] Considering the benefits of polyherbal formulations and based on current evidence, valerian roots, passion flowers and ashwagandha roots are used in the Zero Tension tablet, a polyherbal preparation for the treatment of stress, anxiety and insomnia.

In this non-randomised, open-label, phase IV post-marketing surveillance trial, 56 days of intake of the Zero Tension tablet by patients with stress, anxiety, and insomnia resulted in significant improvements over time. The intake of the Zero Tension tablet was associated with a statistically significant reduction ($p<0.001$)

in HAM-A, PSS, insomnia severity, and general health scores. Based on the HAM-A, PSS, and insomnia severity scores, most participants experienced positive improvements in stress, anxiety, and insomnia symptoms after taking the Zero Tension tablet. Changes in the stress hormones cortisol and DHEA were measured to understand the Zero Stress tablet's mechanisms. Hypothalamic-pituitary-adrenal (HPA) axis activity increases in response to a stressor, increasing cortisol[43] and DHEA[44] concentrations. This study showed that taking the Zero Tension tablet for 56 days was associated with a mild reduction in serum cortisol and DHEA levels. This could be due to the synergistic modulation of the GABA system by the active components of valerian root, passion flower and Ashwagandha. Therefore, improving these parameters would probably have required a large or very prolonged dose of Zero Tension tablet.

Assessing a product's safety is an integral part of any clinical study. Plant-based herbal products are generally considered safe, but they are not always free of the risk of toxicity or adverse effects.[45] This study also demonstrated the safety and tolerability of the Zero Tension tablet. The findings of this study indicated that the Zero Tension tablet was well tolerated, with no significant adverse effects or changes in laboratory parameters over time. Finally, the treatment duration of the current study was limited to 56 days, and future studies of longer duration on a larger scale are required to more fully evaluate the durability of the Zero Tension tablet in the treatment of stress, anxiety, and insomnia.

CONCLUSION

In preclinical investigations, extracts of *P. incarnata*, *V. wallichii*, and *W. somnifera* reduced stress, anxiety, and insomnia. Such an effect may have been caused by the active ingredients of these plants that modulate the GABA system. In this study, Zero Tension Tablet, a polyherbal formulation of these plants, was found to reduce HAM-A, PSS, and insomnia severity index scores, as well as serum cortisol and DHEA levels among participants. The general state of health also improved. After 56 days of treatment with the Zero Tension Tablet, all vital signs, haematological and serum markers of blood sugar, thyroid, liver, and renal function parameters were within the normal range. During the study period, no adverse events were reported. These results indicate that the Zero Tension tablet is highly effective for clinical use in reducing stress, anxiety, and insomnia and that it is also well-tolerated and safe. Therefore, it might have a greater chance of acceptance in the general medical community as an alternative treatment for managing stress, anxiety, and insomnia.

LIMITATIONS

The trial has the disadvantage of being non-randomised, single centre and open-label. Further randomised studies are needed to compare the impact of the Zero Tension Tablet with that of standard medication or a placebo.

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